

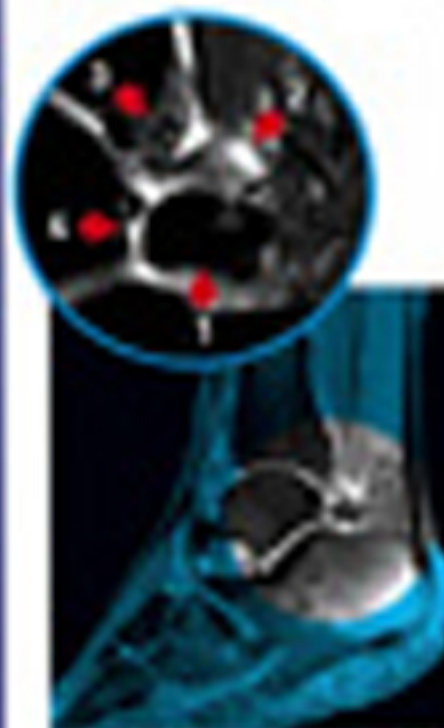
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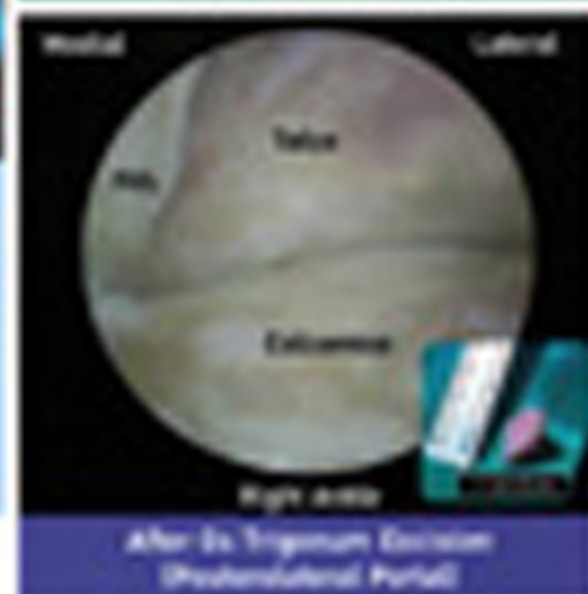
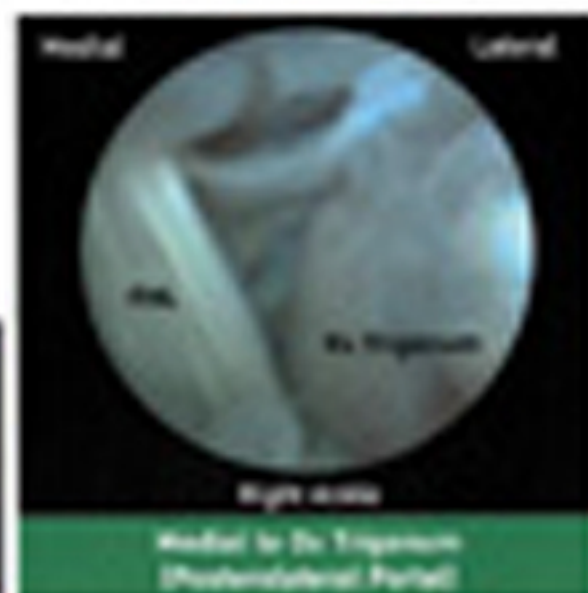
Highlights

- Successful Outcomes of Pediatric Hematopoietic Cell Transplantation for Thalassemia and Leukemia Cell Diseases
- The Development of Nurse Residency Program
- A Case Report of Surgical Treatment of Symptomatic Aberrant Right Subclavian Artery Aneurysm Treated at Bangkok Hospital Phuket, Thailand
- Exploring Inside a Uracilone by Magnetic Resonance Imaging
- Acute Fulminant Hepatitis due to Herpes Simplex Type 1 Infection
- All Events Courses
- A Brief History of Development of the Cyclotron and PET Center at Moolamoonh Cancer Hospital

Os Trigonum Syndrome Posterior Ankle Impingement (PAI)



- 1 Os trigonum
- 2 Surrounding Soft Tissue Edema
- 3 Bone Marrow Edema of Posterior Tibia
- 4 Synchondrosis Edema



This, our seventh volume of the Bangkok Medical Journal, delivers a wide range of contributions from the field of investigative and clinical medicine sourced from Bangkok Hospital practitioners and guest authors. We draw your attention to a very rare case of ‘The Infant and the Snowman’ and ‘Jejunal tubulovillous adenomas’. The edition also covers our pioneering work in the use of endobronchial ultrasound to evaluate downstaging of lung cancer after combined chemotherapy and radiotherapy.

We also highlight a special report from Suthorn Bavonratanavech MD, President Elect AO Foundation, on the AO Davos courses, a hallmark of knowledge exchange and transfer of expertise among surgeons Dr. Suthorn Wongsiri is our specialist orthopaedic surgeon, and is the current AO Foundation president elect (2012-2014). He will be confirmed as President of the AO Foundation from June 30, 2014 until 2016. Bangkok Hospital is the only hospital in Thailand to be certified as a clinical site for the AO Foundation.

We would like to draw your attention to the report from guest authors from Mahidol University, Bhoom Suktitipat MD PhD and Chayanon Peerapittayamongkol MD PhD. They provide an insightful opinion editorial on genome-wide association study (GWAS) and the next-generation sequencing (NGS) and why many groups of scientists are ready to switch from GWAS to NGS.

Bangkok Hospital is the first hospital in Thailand to offer diagnostics with Cyclotron and PET/CT scans. We are deeply appreciative of the vision of Dr. Prasert Prasarttong-Osoth who saw the immediate and long-term benefits of developing the Cyclotron and PET/CT Center at Wattanosoth Cancer Hospital. We express our sincere thanks to Mr. Kamthorn Kanchananwatee, Mr. Thanakit Senapaeung and Ms. Sritrang Panpitpat, as distributor PET/CT and technical support. We are particularly proud to have Dr. Ananya in our institution. We thank the team for their ongoing dedication and efforts.

The Center has been in operation since 2005, and has helped in the diagnosis of patients with cancer, Alzheimer’s disease, and Parkinson’s disease.

We remain dedicated to bringing the reader a valuable, insightful and informative journal with features on ground-breaking medical procedures and updates on ongoing programmes designed to improve the quality of the excellent care provided to our patients. We invite you to read on, and we trust you will find our innovative case studies and reports educational and thought-provoking.

Chirochana Suchato, MD
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Successful Outcomes of Pediatric Hematopoietic Cell Transplantations for Thalassemia and Sickle Cell Diseases



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Keywords: hematopoietic cell transplantation, thalassemia, sickle cell disease

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OBJECTIVE: To assess outcomes of hematopoietic cell transplantation (HCT) for thalassemias and hemoglobinopathies in a single medical center in Thailand.

METHODS: Case series study for thalassemia and hemoglobinopathy patients undergoing HCT at Bangkok Hospital Medical Center (BMC) from February 2009 through December 2013.

RESULTS: There were a total of 15 patients. Eleven cases were Thai, 1 was French-Thai, 1 was Bangladeshi, 1 was Lao, and 1 patient was Omani who had sickle cell disease (SCD). Thirteen cases were diagnosed as beta-thalassemia/hemoglobin E diseases, 1 as a transfusion-dependent alpha-thalassemia, and 1 as SCD. Among the 15 HCTs, 9 patients underwent bone marrow transplant (BMT), 4 patients underwent umbilical cord blood transplant (CBT), and 2 patients underwent combined cord blood and marrow transplantation (CB+BMT). All donors were related and fully-HLA-matched. The male to female patient ratio was 12:3. The patients' ages at transplant varied from 2 years to 15 years 11 months with a median of 5 years. The patient's body weight varied from 11.1 kilogram (kg) to 50kg (a median of 17.3kg). According to the Pesaro classification, among the 14 thalassemia patients there were 10 class I, and 4 class II patients. Busulfan, fludarabine, and rabbit ATG were mainly used as the myeloablative conditioning regimen. Cyclosporine and short-course methotrexate were mainly used as graft-versus-host disease (GvHD) prophylaxis in BMT and CB+BMT groups, while cyclosporine alone was used in the CBT group. CD34+ cell doses per kilogram body weight recipients ranged from 5.6 to 34.7x10⁶ (a median of 12.3x10⁶) in the BMT group (n=9), and from 1.6 to 3x10⁵ (median 2.3x10⁵) in the CBT group (n=4). Complete donor engraftments were achieved in 12 patients. Mixed-chimerism states with donor predominance were present in 2 patients from the BMT group and 1 patient from the CBT group. No patients experienced graft failure. Neutrophil recoveries were evident on days +10 to +23 (median day +14), and platelet recoveries were observed on days +19 to +64 (median day +40). No patients developed acute or chronic GvHD. There were no mortalities. Median follow-up time for all patients was 2 years 2 months (1 month to 4 years 10 months). Overall (OS) and disease-free survival (DFS) were 100% and 100% for all patients (n=15). Based on the risk class, the OS and DFS for class I thalassemia patients (n=10) were 100% and 100%, and class II patients (n=4) were 100% and 100%, respectively.

CONCLUSION: Our experience in HCT for thalassemias and hemoglobinopathies has been very favorable. HLA-matched related donor HCT yielded the best success rate. Anyhow, regular follow-up visits are encouraged to detect any possible complications and to determine long term outcomes.

Thalassemia and sickle cell disease (SCD) are the two most widely distributed inherited hemoglobinopathies in the world. Thalassemias are prevalent in Mediterranean, Middle Eastern, South and Southeast Asian countries, while sickle cell diseases originate from countries across Africa; both have become widespread globally due to modern migration patterns.¹

In beta-thalassemia disease, pathogenesis involves absent or impaired synthesis of the beta-globin chains which constitute adult hemoglobin molecules. This genetic defect causes ineffective erythropoiesis through the whole process of proliferation and maturation of the erythroid precursors, and severe apoptosis is evident due to an accumulation of excess alpha-2 chains. Hemoglobin E is abnormal hemoglobin, formed by a single nucleotide substitution: lysine replacing glutamic acid at the 26th position of the beta-globin chain of hemoglobin A.

In SCD, a single nucleotide substitution occurs: valine replaces glutamic acid at the 6th position of the beta-globin chain of hemoglobin A, forming the pathological hemoglobin called hemoglobin S. The abnormality of hemoglobin S polymerization causes an alteration of the red blood cell structure to a stable sickle shape. Consequently, episodic anemia and acute and chronic vaso-occlusion of small and large vessels in many organs occur and lead to polymorphic clinical features of the disease. Intramedullary apoptosis is also present but is generally milder than that seen in thalassemia.¹

Many thalassemic patients need continuous red blood cell replacement through a regular red blood cell transfusion program. Without adequate transfusions, thalassemic patients have remarkable skeleton deformities due to intramedullary expansion, as well as hepatomegaly and splenomegaly due to the proliferation of the hematopoietic system with extramedullary hematopoiesis. Since both thalassemia and SCD are genetic diseases in which the genetic defect is expressed in the hematopoietic system, they are both considered to be curable by allogeneic cellular gene therapy through hematopoietic the cell transplantation (HCT) method.¹

The basic rationale of allogeneic HCT in thalassemia consists of substituting thalassemic stem cells bearing ineffective erythropoiesis with healthy allogeneic stem cells capable of effective erythropoiesis.^{2,3} This cellular replacement therapy is not limited to only the diseased erythropoietic component, but also to the replacement of the entire hematopoietic system. Nevertheless, the ultimate goal is to obtain a long-lasting, possibly permanent, effective correction of chronic hemolytic anemia, subsequently avoiding any further transfusion requirements and preventing associated complications such as iron overload and major organ damage, etc.

Transfusion-dependent beta-thalassemia and alpha-thalassemia are highly prevalent hereditary hematologic disorders in Thailand.⁴ As mentioned earlier, hematopoietic stem cell transplantation is the only curative treatment of these diseases. Most of the reports worldwide are of bone marrow transplantation.⁵ Increasingly recently umbilical cord blood transplantations (CBT) have been performed in a variety of malignant and non-malignant diseases, including thalassemia.^{4,6-8}

In this study we assessed the outcomes of thalassemia and hemoglobinopathy patients undergoing allogeneic HCT in our medical center. Not only the prospects of engraftment, but our analysis also focused on the occurrence of potential complications such as acute and chronic GvHD, treatment related morbidity and mortality, overall survival (OS) and disease-free survival (DFS).

Material and Methods

All transfusion-dependent thalassemia and hemoglobinopathy patients undergoing allogeneic HCT from February 2009 through December 2013 were included in this case series study. The transplant procedures were performed at the Bangkok Blood and Marrow Stem Cell Transplantation Unit, Wattanosoth Hospital, Bangkok Hospital Group, Bangkok, Thailand. Donors were selected from HLA-identical siblings of each patient by HLA typing methods. Parents of the patients and donors signed informed consent before treatment and donation. Likewise, parents of cord blood newborn donors also signed informed consent prior to cord blood collection and cryopreservation.

Our hematopoietic cell transplantation procedures complied with standard practice and considerations. Bone marrow was considered as a first-choice source of hematopoietic cells from the existing donors, HLA-identical siblings, whereas umbilical cord blood was considered from newborn siblings if applicable. Every recipient (patient) was implanted with a double-lumen central venous catheter, namely Hickman, by a vascular surgeon, prior to starting the pre-transplant medication. We used a myeloablative conditioning regimen approach for the patients who were pre-classified as Pesaro class I or II. Pre-transplant conditioning chemotherapy was composed of busulfan^{9,10} (Bu) 4-4.8mg/m²/day for 4 days and fludarabine (Flu) 35mg/m²/day for 5 days and rabbit anti-thymocyte globulin (rATG) 1, 2, 3mg/kg/day for 3 consecutive days for thalassemia patients, while Bu (same dose) and cyclophosphamide (Cy) 50mg/kg/day for 4 days and rATG (same dose) were used for sickle cell disease patients. This preparatory regimen usually took about 8 days, and was completed at least 1 day before infusion day (transplant day = day zero).

On transplant day for bone marrow transplantation (BMT) cases, bone marrow stem cells were obtained from the donor by a bone marrow harvest under general anesthesia in the operating room. Each fresh bone marrow product was subsequently infused into the recipient's blood circulation via Hickman catheter on the same day. If there was major blood group ABO incompatibility between donor and recipient, the donor's bone marrow product had to undergo a red blood cell depletion process before infusion. In contrast, if a minor ABO incompatibility was identified, a plasma removal process of the donor's marrow product was performed before stem cell infusion.

In the case of umbilical cord blood transplant (CBT), umbilical cord blood units that had been identified were transported to the transplant unit under frozen conditions by a portable cryo-tank and thawed just before infusion into the recipient's great vein through Hickman catheter. In the case of combined cord blood and bone marrow transplant (CB+BMT), the standard cord blood infusion procedure was performed and followed soon after by a fresh marrow infusion. The CD34+ cell dose per kilogram of the recipient's body weight was considered an essential marker to determine the hematopoietic cell dose.

During the pre- and early post-transplant period, prophylactic antimicrobial medication was administered. Protective environment precautions were applied. The recipient remained in an isolated, positive-pressure, high efficient particulate aerosol (HEPA) filtration room. All packed red cell units and platelet-pheresis units were filtered and irradiated before being transfused as a supportive treatment.

After stem cell infusion, graft-versus-host disease (GvHD) prophylaxis was administered, consisting of intravenous cyclosporine and short-course, low-dose methotrexate injection for BMT recipients. GvHD prophylaxis consisted of only cyclosporine for CBT recipients. All patients were given recombinant human granulocyte colony-stimulating factor (G-CSF) 5 microgram/kg after transplantation. It was infused over a ten minute period intravenously starting from 4 hours after HCT and continuing once daily until neutrophil recovery exceeded $2 \times 10^9/l$ for 2 consecutive days.

Meanwhile, neutrophil recovery or engraftment was defined as the first day of an absolute neutrophil count (ANC) over $0.5 \times 10^9/l$ for 3 consecutive days. Platelet recovery was defined as the first day of a platelet count over $20 \times 10^9/l$ for 3 consecutive days without platelet transfusion support. Graft failure or rejection was defined if ANC did not rise, or no neutrophil engraftment within 28 days after HCT or ANC declined below $0.2 \times 10^9/l$ after initial recovery. After neutrophil engraftment, acute GvHD would be diagnosed and graded according to previously reported criteria.^{11,12} Recipients living 100 days post-transplant with sustained donor engraftment were considered to be evaluated for chronic GvHD, as described.¹³

The CMV DNA viral load was monitored weekly in all post-transplant patients when white blood cells had recovered, in order to detect any CMV activity. Patients who had reactivation of CMV were treated with pre-emptive therapy of ganciclovir at a conventional dosage and they were monitored until the viral replication became undetected.¹⁴

Results

There were fifteen thalassemia and hemoglobinopathy patients with ages ranging from 2 to 15 years 11 months old (median 5 years), all undergoing allogeneic HLA-matched sibling donor HCT. The details of patient characteristics are reported in Table 1. Thirteen patients were diagnosed with transfusion-dependent beta-thalassemia/hemoglobin E diseases, one was diagnosed with transfusion-dependent alpha-thalassemia disease (hemoglobin H Constant Spring = alpha-thalassemia 1/alpha Constant Spring), and one was diagnosed with sickle cell disease with frequently recurrent painful vaso-occlusive crises. The patients were 12 males and 3 females. Their nationalities consisted of 11 Thais, 1 French-Thai, 1 Bangladeshi, 1 Lao, and 1 Omani. The patients' body weight ranged from 11.1kg to 50kg (median 17.3kg). The fourteen thalassemia patients were classified based on Pesaro classification into class I (n=10), class II (n=4). There were no class III patients in our series.

Table 1: Clinical characteristics of enrolled patients. (n = 15).

Parameters	No. of case
Median patient age (range)	5 (2-15.9) years
Median patient weight (range)	17.3 (11.1-50) kg
Patient sex	
Male	12
Female	3
Nationalities	
Thai	11
French/Thai	1
Lao	1
Bangladeshi	1
Omani	1
Diagnosis	
Beta-thalassemia/hemoglobin E	13
Alpha-thalassemia (transfusion-dependent)	1
Sickle cell disease	1
Types of hematopoietic cell transplant	
Bone marrow	9
Cord blood	4*
Cord blood + bone marrow	2

Note: *There was one patient receiving two cord blood units collected from his two identical-twin, newborn sisters.

There were 16 related donors overall who were fully-HLA-matched with their corresponding 15 recipients. (This is because there were two identical-twin, newborn sisters whose two cord blood units were collected and later used for transplantation to one recipient, their elder brother). With regards to the status of the donors, 5 had normal typing, 6 had beta-thalassemia traits, 3 had hemoglobin E traits, 1 had alpha-thalassemia one traits, and 1 had sickle cell traits (see Table 2 and 3). The source of the donors' hematopoietic cells consisted of 9 bone marrow (BM), 5 umbilical cord blood (CB) units, and 2 cord blood plus bone marrow (CB+BM). BM donors were 6 males and 5 females, with ages ranging from 2 to 18 years old (median 4 years) (see Table 2). Five CB units were collected from 5 term neonates when they were delivered, two of whom were identical twins. There were two 2-year-old male donors who donated their cord blood units and bone marrow for their respective elder brothers who had thalassemia diseases.

Among the 9 patients to receive a transplant of BM, the median CD34+ cell dose was 12.3 (range 5.6 to 34.7) x 10⁶/kg body weight. Among the 4 patients to receive a transplant of CB stem cells, the median CD34+ cell dose was 2.3 (range 1.6 to 3) x 10⁵/kg body weight.

The probability of initial hematopoietic recovery by day 30 was equal to 100% (15 out of 15 patients). Neutrophil recoveries were evident on days +10 to +23 (median day +14), and platelet recoveries were observed on days +19 to +64 (median day +40).

Engraftment evaluations were studied by chimerism analysis using the microsatellite, short tandem repeat method. For cases of gender mismatch between recipients and donors, the techniques of fluorescent in-situ hybridization (FISH) of XX-XY chromosome were also used. In terms of engraftment, no patients experienced graft failure. Every patient was neutrophil engrafted. Twelve patients achieved complete donor engraftment. Two patients from the BMT group and one from the CBT group developed stable mixed-chimerism states with donor predominance and they were no longer blood transfusion-dependent, nor required further transfusion. The summaries are reported in Table 4.

Every recipient and donor had Rh positive blood group. Eleven recipients had same blood group ABO as their corresponding donors. There were three recipients of major blood group B-O incompatibility and their blood groups were altered from pre-HCT "O" to post-HCT "B". On the other hand, there was one case of minor blood group A-AB incompatibility and this patient's blood group was switched from pre-HCT "AB" to post-HCT "A" (see Table 5).

Table 2: Clinical characteristic of bone marrow donors [bone marrow transplant (BMT) & cord blood and marrow transplantation (CB+BMT)] (n = 11).

Parameters	No. of case
Median donor age (range)	4 (2-18) years
Donor sex	
Male	6
Female	5
Nationalities	
Thai	7
French/Thai	1
Lao	1
Bangladeshi	1
Omani	1
Status	
Normal hemoglobin typing	4
Beta-thalassemia trait	3
Hemoglobin E trait	2
Alpha-thalassemia one trait	1
Sickle cell trait	1

Table 3: Clinical characteristic of isolated cord blood newborn donors.

Parameters	No. of case (n = 5*)
Donor sex	
Male	3
Female	2*
Nationalities	
Thai	5*
Status	
Normal hemoglobin typing	1
Beta-thalassemia trait	3*
Hemoglobin E trait	1

Table 4: Outcomes of recipients after allogeneic HCT (n=15).

Parameters	No. of cases (%)
Complete donor engraftment	12 (80)
Stable mixed chimerism with donor predominance	3 (20)
Graft failure	0 (0)
Veno-occlusive disease (mild)	2 (13.3)
Acute GvHD	0 (0)
Chronic GvHD	0 (0)
Serious transplant-related morbidity (treatable)	2 (13.3)
Transplant-related mortality	0 (0)
Overall survival	15 (100)
Disease-free survival	15 (100)

HCT = hematopoietic cell transplantation

Table 5: Alteration of blood group in ABO-mismatched recipients after allogeneic HCT.

Incompatibility	Pre-HCT	Donors	Post-HCT	Cases
Major	O	B	B	3
Minor	AB	A	A	1

HCT = hematopoietic cell transplantation

No patients developed acute or chronic GvHD. The overall probability of mortality was equal to 0%. Two patients had mild veno-occlusive diseases of the liver which were later completely reversible by means of conservative treatment. There were no cases of mortalities, but some serious morbidity due to infectious complications occurred. One patient had severe but treatable pneumocystis pneumonia at 4 months post CBT. Another patient had catheter-related gram negative bacilli septicemia at 2 months post CB+BMT and recovered after receiving intravenous antibiotics after the Hickman central venous catheter removal. Both patients remain well to date. Moreover, there were two recipients who developed CMV reactivation, with no clinical manifestation, during their respective 3 and 4 months post HCT. They responded well with pre-emptive ganciclovir therapy and were able to discontinue the medicine within 2 months.

The median follow-up time for all 15 patients was 2 years 2 months (1 month to 4 years 10 months). Overall (OS) and disease-free survival (DFS) rates were 100% and 100% for all patients (n=15). Based on the Pesaro risk class, the OS and DFS for class I thalassemia patients (n=10) were 100% and 100%, and class II patients (n=4) were 100% and 100%, respectively (see Table 4).

Discussion

These globally widespread single-gene disorders: beta-thalassemia and sickle cell disease (SCD), can only be cured by means of allogeneic hematopoietic cell transplantation (HCT). Although improvements in conservative treatment have considerably improved the prognosis of non-HCT, transfusion-dependent thalassemia cases, disease- and treatment-related complications in these patients progress over time, causing inevitable morbidity and eventual shortened life expectancy.¹⁷ HCT still remains the only cure currently available for this group of patients.

Treatment outcomes by HCT for thalassemia have substantially improved over the past two decades, with the development of updated pre-transplant preparative regimens, advancement in preventive strategies, and control of transplant-related complications.¹⁷ Outcomes nowadays are much improved compared with the 1980s and 1990s, with more than 90% of patients surviving

transplantation and more than 80% of them being disease-free in several medical centers worldwide.^{2,15,16} Some studies revealed a risk class-based transplantation approach led to disease-free survival probabilities of 90%, 84%, and 78% for class I, II, and III thalassemia patients, respectively.¹ Some revealed a risk class-based approach to transplantation in thalassemia led to a disease-free survival probability of 87%, 85% and 82% in classes I, II and III patients, respectively. Adult thalassemia patients are higher risk patients for transplant-related toxicity due to an advanced phase of disease and have a cure rate of 62% with current treatment protocols.¹⁷

Based on our study results, the OS and DFS were excellent with 100% survival in both categories. However, the numbers of cases is small, only 15. We will have to gather more case enrollments and repeat the analysis in the future. Favorable factors are summarized as follows: 1) There were only class I and II patients, no class III, 2) Every patient underwent HLA-identical sibling HCT, 3) Adequate hematopoietic stem cell doses had been estimated before the actual transplantation process (CBT) started or were obtained by bone marrow harvest before stem cells infusion (BMT), 4) Peripheral blood was not used as a source of stem cells since there were several reports of enhancing incidence of GvHD after peripheral blood stem cell transplantation, 5) Our current conditioning regimen, GvHD prophylaxis, and antimicrobial prevention was effective, 6) Our transplant care team cared for the patients safely throughout pre-, during, and post-transplant periods and forestalled potentially fatal complications.

Although allogeneic HCT has such a high success rate, the major limitation to whether the patient is eligible for HCT is the lack of an HLA-identical sibling donor for most affected patients. In fact, only 25-30% of thalassemia patients have a matched sibling donor available. Therefore, there is a need to develop alternative sources of stem cell donations. To date high-resolution HLA typing tests have enabled some patients to have the chance to undergo a transplant from an HLA-matched unrelated volunteer donor, with results comparable with those undergoing an HLA-identical sibling transplantation.¹⁷

The near-future prospects of our HCT team include: dealing with good prognostic-factor patients or HLA-identical sibling donors, and at risk class III patients, and undertaking HLA-matched unrelated donor searching

and procurement. The HCT team needs to keep updating its knowledge base and keep reviewing reports and experiences from other modern medical practices. This is crucial to keep seeing good treatment results with future patients.

Conclusion

Our experience in HCT for thalassemias and hemoglobinopathies has been very favorable. The HLA-matched related donor HCT has had the best success rate. Cord blood transplantation yielded the same excellent outcomes as bone marrow transplantation. Nonetheless, we plan to regularly follow up with post-transplant patients to detect any possible complications and to determine long-term outcomes.

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Echocardiographic Parameters of Right Ventricular Dysfunction in Thalassemic Patients



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Keywords: right ventricular function, thalassemia, pulmonary hypertension, PH

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OBJECTIVE: To evaluate pulmonary hypertension (PH) in asymptomatic thalassemic patients using echocardiographic right ventricular (RV) parameters.

MATERIAL AND METHODS: This is a cross-sectional study. We assessed 32 ambulatory asymptomatic thalassemia cases both clinically and using echocardiographic parameters. PH was observed in 13 (40%) patients.

RESULTS: Unpaired two tail t-test between groups show significant difference in RV echocardiographic parameter S' ($p = 0.03$), E' ($p = 0.016$) and Tricuspid valve (TV) E/E' ($p = 0.04$). Other RV echocardiographic parameters such as the right ventricular ejection fraction (RVEF), tricuspid annular plane systolic excursion (TAPSE), A', and Tei index are insignificant.

CONCLUSION: PH was found in 40% of asymptomatic thalassemic patients. Of all echocardiographic RV parameters, we found that the tissue doppler imaging (TDI): S', E' and TV E/E' are the best tools for screening. This tool detects early RV dysfunction in asymptomatic thalassemias with PH.

Thalassemia and hemoglobinopathy are hereditary diseases that cause chronic hemolytic anemia leading to many physiological adaptations and pathological effects with multiple organ dysfunction.¹⁻⁴ Heart disease is a major source of mortality and morbidity in patients with thalassemia,⁵ despite improved prognosis with iron chelation. The common cardiac problems are cardiac hypertrophy, ventricular systolic dysfunction, pericarditis and PH.^{6,7}

Many features of cardiac disease in thalassemic patients are still poorly understood. Cardiac complications are multifactorial and may be due to chronic anemia, iron overload, and probably various other mechanisms.^{8,9} It has been noted that some patients with severe forms of thalassemia have a burden of right heart strain resulting from PH, iron overload, or small pulmonary emboli.¹⁰⁻¹⁶

Thalassemia heart disease affects mainly left ventricular (LV) dysfunctions caused by transfusion-induced iron overload. However, recent studies refer that thalassemia major and thalassemia intermedia patients have an exceptional hemodynamic pattern consistent with right ventricular cardiomyopathy and PH, in addition to the left ventricular abnormalities,¹⁷ and can be a leading cause of heart failure in these patients.

Studies in thalassemia show that adults frequently have undetected PH, with a prevalence of 60-70% reported.^{18,19} Although most of the reported thalassemic patients with PH were splenectomised,^{6,20,21} non-splenectomised patients were also found

to have PH.⁶ Advanced age and a history of splenectomy are major risk factors for PH in this population.²⁰⁻²⁵ Since strict compliance with chronic transfusion and chelation therapy to prevent iron overload cuts the condition of heart failure, and prevents PH,²⁶⁻²⁸ insufficiently transfused thalassemia patients may be at higher risk for the development of PH.

Treatment of thalassemia major consists of constant blood transfusions and iron chelation therapy, which can delay cardiac complications and improve longevity. Early studies showed notable improvement of survival rates and good prognosis from treatment with chelating agents and regular transfusion.^{29,30} even in severe cardiomyopathy, which may be due to accumulation of iron within myocytes,³¹ which may be reversed by treatment with iron chelators.^{32,33}

Frequent monitoring of cardiac function in transfusion-dependent patients may identify those at risk of developing future cardiac problems, who might then be candidates for more intensive and sustained iron chelation therapy

The development of the T2* parameter using cardiac magnetic resonance (cMR) scanning has provided a powerful tool for assessing tissue levels of iron and has contributed to the recently observed decrease in deaths from cardiac iron overload.³⁴ Despite the importance of cMR scanning and T2* assessment of tissue iron content, the scan is quite expensive and not available generally. Transthoracic echocardiography (TTE) is widely available at low cost. For many countries the backbone of assessing cardiac involvement in thalassemia has been by TTE. This technique is widely available and has the advantage of being applied at the bedside.

To the best of our knowledge, no studies exist of PH and right ventricular function in splenectomized and nonsplenectomized thalassemic patients who have supposedly received adequate treatment with blood transfusion and iron chelating agents. We speculated that there would be differences in echocardiographic indexes.

Our study aims to determine PH and right ventricular function by using conventional, tissue doppler imaging and a novel echocardiographic technique in thalassemic patients.

Material and Methods

Study population

The study population included 32 asymptomatic thalassemic patients (16 male, 16 female; mean age 40.43±14 years). Inclusion criteria: diagnosis of beta thalassemia; normal

renal function; asymptomatic; no prior history of admission with heart failure; and an absence of congenital or acquired structural heart or lung disease. All thalassemic patients received regular follow-ups at out-patient hematologic clinic department, faculty of medicine, at Ramathibodhi Hospital, Mahidol University. Cardiac evaluations of all patients were performed after they had visited the hematologic clinic. The laboratory requirements were collected at the same time. Informed consent was obtained and the study was approved by the Institutional Ethics Committee.

Echocardiography

Conventional, tissue doppler imaging and speckled tracking echocardiography (ARTIDA, Toshiba) were performed by an experienced cardiologist. Conventional echocardiographic measurements were done according to the American Society of echocardiography guidelines.³⁶

PH is defined as: a right ventricular systolic pressure (RVSP) of > 40mmHg and/or a mean pulmonary arterial pressure (mPAP) of > 25mmHg.

The two-dimensional strain is a new measurement method. This new measure uses regional and global contractility. However, normative data of the right ventricular function is not available using this method; therefore we collected the value and compared the findings with other methods.

Statistical analysis

The results were analyzed using SPSS for windows 17.0 and descriptive statistics were presented as percentage, means and SDs. Univariate analysis for group comparisons were performed using Student's *t* test and Mann-Whitney U tests, where appropriate.

Results

Clinical characteristics and laboratory results of the study group are given in Table 1. All the thalassemic patients had a normal LV systolic function. Echocardiography method; there is no significant differentiation between group and normal value (Table 2). We found a statistically significant difference between the non-pulmonary hypertension group and the PH group in E', S' and RV E/E'. In both groups, the myocardial perfusion imaging (MPI) values are abnormal but there is no statistical significance difference between groups (Table 3). A new echocardiography parameter: Global RV strain did not show significant difference between the two groups, though there was a trend of lower global strain in the PH group (Table 4).

Table 1: Clinical characteristics and laboratory parameters of the study group (n = 32).

Parameters	No. of cases
Age (year)	39.9 ± 13.4
Sex	Male 16, Female 16
Systolic blood pressure (mmHg)	114.28 ± 14.5
Diastolic blood pressure (mmHg)	64.4 ± 8.99
Ferritin	801.5
BMI (kg/m ²)	19.13 ± 2.2
Beta Thalassemia/HbE (%)	31 (96.87)
Splenectomy (%)	28 (87.5)

Ferritin: Mode, BMI = body mass index

Table 2: Conventional echocardiographic method.

Parameters	Normal	No PH	PH
LVEF	> 60%	65.07 ± 5.53	62.57 ± 7.39
RVEF	> 44%	58.55 ± 11.61	63.25 ± 10.61
TAPSE	> 16 mm	25.48 ± 5.58	24.33 ± 7.21

LVEF by modified Simpson's biplane PH = pulmonary hypertension
 LVEF = left ventricular ejection fraction RVEF = right ventricular ejection fraction
 TAPSE = tricuspid annular plane systolic excursion

Table 3: Tissue doppler echocardiography of right ventricle.

Parameters	Normal	No PH	PH	p
E'	-	14.2 ± 2.8	11.6 ± 2.42	0.0089
S'	> 10	17.9 ± 3.0	14.82 ± 4.58	0.036
A'	-	16.29 ± 5.5	14.79 ± 7.73	NS
RV E/E'	< 6	3.98 ± 0.87	5.19 ± 1.53	0.042
RV E/A	0.8-2.1	1.56 ± 0.35	1.45 ± 0.43	NS
MPI	< 0.55	0.57 ± 0.16	0.70 ± 0.3	NS

PH = pulmonary hypertension

Table 4: Speckle tracking echocardiography of right ventricle.

Parameters	No PH	PH	p
RVEF speckle	48.46 ± 12.40	53.45 ± 11.80	NS
Global RV strain	17.67 ± 4.98	15.93 ± 5.28	NS

PH = pulmonary hypertension
 RV = right ventricular
 RVEF = right ventricular ejection fraction

Discussion

Cardiopulmonary complications are the main cause of morbidity and mortality in thalassemic patients. In adults with thalassemia pulmonary hypertension is frequently undetected, with a prevalence of 60-70% reported. Thalassemia heart disease affects the left ventricular dysfunction mainly. Thalassemia major and thalassemia intermedia patients have an exceptional hemodynamic pattern consistent with right ventricular cardiomyopathy and PH, in addition to the left ventricular abnormalities that can be a leading cause of cardiopulmonary problems in these patients. Frequent monitoring of cardiac function in patients may indicate those at risk of developing symptomatic cardiac disease, and these patients might then become candidates for more intensive and sustained iron chelation therapy.

The progression of thalassemic cardiomyopathy and PH is a gradual process and the patient is often found to be asymptomatic. Magnetic resonance imaging (MRI) has been shown to quantify myocardial iron content and cardiomyopathy, however, MRI is not widely available and is expensive.

Our study shows that tissue doppler imaging E', S' and RV E/E' parameters are significantly different between those with and without PH in asymptomatic thalassemic patients. A decrease in E' and E/E' suggested that RV diastolic dysfunction would be found in those with pulmonary hypertension. S' velocity was significantly lower in the PH group though it was still in the low normal range. The MPI values in both groups fall in the abnormal range and there was no significant difference. With the speckle tracking technique, we found that the global strain rate was lower in the pulmonary hypertension group though it was not statistically significantly different.

The study's limitation includes the small sample volume, it was a cross sectional study, with no comparison to a normal age, sex match control group. If this study is to be extended, we extrapolate that we might be able to see the progress of RV diastolic and systolic function in both groups very clearly.

Conclusion

PH was found in 40% of asymptomatic thalassemic patients. Of all the echocardiographic RV parameters, we found that S', E' and TV E/E' by TDI was the best screening tool to detect early RV dysfunction in asymptomatic thalassemias with PH.

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Depression and Risk of Adverse Cardiovascular Events in Patients with Stable Coronary Artery Disease



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OBJECTIVE: Depression is known to be associated with at least doubling the risk of cardiac events over 1 to 2 years after an acute myocardial infarction (MI). However, less is known about the prevalence and prognosis of depression in outpatient samples especially in short-term follow-up studies in stable coronary artery disease (CAD) patients. The purpose of this study was to evaluate the relationship between depressive disorders and short term risk of major adverse cardiovascular events (MACEs) in stable coronary artery disease patients.

MATERIAL AND METHODS: This prospective study included 134 stable CAD patients at the cardiovascular out patient department (OPD) clinic at Bangkok Metropolitan Administration (BMA) Medical College and Vajira Hospital. The Thai equivalent of the Montgomery-Asberg Depression Rating Scale (MADRS) score was used. After 6 months, all patients were assessed for major adverse cardiovascular events (MACEs).

RESULTS: 15% of the sample had a depressive condition (MADRS score > 10), yet less than half of them (20%) had been treated with anxiolytic medications. After the 6 months follow-up period, there were no cases reported of cardiac death in either group. Myocardial infarction was seen in the normal MADRS group [Four cases (3.5%)] but none appeared in the group diagnosed with depressive conditions. Two cases (10%) of those with depressive conditions and seven cases (6.10%) of the normal MADRS group had percutaneous transluminal coronary angioplasty (PTCA); $p = 0.525$. CABG or stroke was not found in either group. There was no statistically significant different incidences of MACEs (cardiac death, MI, PTCA, CABG, stroke) in either group (10% vs. 9.6%; $p = 0.961$).

CONCLUSION: There was no statistically significant difference in the short term MACEs between the two groups (those with and without depressive conditions) in this study.

The prevalence of major depression in patients with coronary artery disease (CAD) was between 17 and 27%.^{1,2} Depression was also found to be about 3 times more common in patients after an acute myocardial infarction.³ Compared to individuals with no history of depressive conditions, patients with depressive conditions had frequently higher levels of biomarkers that predicted cardiac events or promoted atherosclerosis. In fact, several studies in depressive patients have shown reduced heart rate variability (suggesting an increased sympathetic activity and/or reduced vagal activity)⁴, evidence of increased plasma platelet factor 4 and beta thromboglobulin (suggesting enhanced platelet activation)^{5,6} impaired vascular function⁷, increased C-reactive protein, interleukin-6, intercellular adhesion molecule-1 and fibrinogen levels (suggesting enhanced inflammatory response).^{8,9}

Material and Methods

Patient population

The study was approved by the Institutional Review Board for Human Subjects' Research of the Bangkok Metropolitan Administration (BMA) Medical College and Vajira Hospital. Written informed consent was given by all the study participants and all the consent forms were collected before the study began. A total of 134 stable CAD patients who came to the cardiovascular OPD clinic at BMA medical college and Vajira Hospital between August 2011 and January 2012 took part.

Exclusion criteria were patients with: 1) acute coronary syndrome (unstable angina, myocardial infarction or revascularization) or congestive heart failure 2) a history of recent cardiovascular surgery within the preceding 3 months 3) patients who were diagnosed as having a history of depressive disorders or other psychiatric diseases before enrollment and 4) patients who did not wish to participate.

The stable CAD patients' complete medical history was evaluated. Montgomery-Asberg Depression Rating Scale (MADRS) Thai version was used to assess depressive symptoms, score of 10 or higher was diagnosed as depression. This scale was shown as acceptable for reliability and validity.¹⁵ The screening test was patient self-rated and could be completed within 5 minutes or less.

Follow-up

The sample was classified into two groups according to the MADRS score on initial enrollment: patients with a MADRS score > 10 were classified as the depressive disorder group. All patients were followed up for 6 months after their initial enrollment. The major cardiovascular end points studied were: 1) cardiac death 2) acute myocardial infarction 3) percutaneous coronary artery revascularization (PTCA) 4) coronary artery bypass graft (CABG) and 5) acute ischemic or hemorrhagic stroke. Hospital records, out-patient clinical records and interviews with the patient or primary physician were used to confirm each event.

Statistical analysis

Continuous variables were expressed as the mean value \pm SD. Categorical variables were expressed as percentages and were analyzed using Fisher's exact test. A two-tailed $p < 0.05$ was considered significant. The correlation test was analyzed using the Pearson Correlation method. The data was analyzed by statistics software, compatible with Microsoft office.

Results

The 134 cases with stable CAD that were included in this study were followed up at the OPD clinic. All the participants had stable clinical symptoms during the study period. We found that the prevalence of depressive disorders in this study was 15%. The baseline characteristic of patients was: 71% male and 29% female. Fifty-six patients (41.8%) were of normal weight, whilst 63 patients (47%) and 15 patients (11.2%) were overweight and obese respectively (see Table 1).

Table 1: Clinical characteristics and laboratory parameters of the study group (n = 134).

Baseline characteristic	No. of cases (%)
Patient	134 (100)
Gender	
Male	96 (71.60)
Female	38 (28.40)
Age (mean \pm SD)	64.90 \pm 10.05
BMI (mean \pm SD)	24.96 \pm 3.64
Normal (18.5-24.9 kg/m ²)	56 (41.80)
Overweight (25-29.9 kg/m ²)	63 (47.00)
Obesity (> 30 kg/m ²)	15 (11.20)
Education	
Never frequented school	7 (5.2)
Primary school	48 (35.80)
Secondary school	41 (30.60)
Bachelor degree or higher	38 (28.40)
Occupation	
Unemployed	74 (55.20)
Civil servant	32 (23.90)
Employee	17 (12.70)
Own business	11 (8.20)
Marriage status	
Single	15 (11.20)
Married	102 (76.10)
Divorced	17 (12.70)
Medication	
Anti-platelet drug	117 (87.31)
Anti-hypertensive drug	96 (71.64)
Lipid-lowering drug	99 (73.90)
Diuretic drug	15 (11.20)
Psychiatric drug	
Lorazepam	23 (17.10)
Alprazolam	4 (3.00)

BMI = body mass index

Table 2: Correlation between factors (age, BMI, duration of illness) and MADRS score (n =134).

Factors	MADRS score	Age	BMI	Duration of illness
MADRS score	1.00			
Age	0.084	1.00		
BMI	-0.046	-0.301*	1.00	
Duration of illness	0.002	0.037	-0.015	1.00

* $p < 0.01$

MADRS = Montgomery-Asberg Depression Rating Scale, BMI = body mass index

Data were analyzed using Pearson Correlation [Correlation is significant at the 0.01 level (2-tailed)].

Table 3: MACEs in the depressive and non-depressive group.

Major cardiac events (MACEs)	Depressive disorder (%) (MADRS score >10)	No depression (%) (MADRS score <10)	p
n	20 (15)	114 (85)	
No event	18 (90)	103 (90.4)	
Events (n = 13)	2 (10)	11 (9.60)	0.961
Cardiac death	0 (0)	0 (0)	N/A
MI	0 (0)	4 (3.50)	0.395
PTCA	2 (10)	7 (6.10)	0.525
CABG	0 (0)	0 (0)	N/A
Stroke	0 (0)	0 (0)	N/A

MI = Myocardial infarction; CABG = Coronary artery bypass graft.

PTCA = Percutaneous coronary artery revascularization;

Data are presented as the number (%) of the patients and were analyzed using Fisher's Exact Test.

Half of the patients were unemployed and received financial support from their family. Most of them were on medications such as: anti platelet and anti-hypertensive drugs and lipid lowering drugs for the treatment of their co-morbidity conditions. But only around 20% of them had received psychiatric drugs (23 patients had been administered lorazepam and 4 patients had been administered alprazolam). Of the twenty-seven patients who had been treated with psychotropic drugs we also found that only seven patients (35%) of the depressive disorder group had been given anxiolytic but not anti-depressant drugs. We found that twenty (18%) of the participants in the non-depressive disorder group had been over-treated with anxiolytic drugs. Any negative correlation between BMI and age is shown in Table 2.

During the six months of the follow-up period, neither group had a cardiac death among them. That said, myocardial infarction was seen in the normal MADRS group (Four cases (3.5%)) but none were evident in the depressive disorder group. Two cases (10%) of the depressive disorder group and seven cases (6.10%) of the non-depressive disorder group had percutaneous transluminal

coronary angioplasty (PTCA); $p = 0.525$. CABG or stroke was not found in either group (see Table 3). There was no statistically significant difference in incidences of cardiovascular events (MACEs) in both groups (10% vs. 9.6%; $p = 0.961$).

Discussion

This study shows that depression occurred in about 15% of patients with stable CAD. Only 20% of patients were treated with psychotropic medications. Surprisingly, all of them were prescribed anxiolytic medications for the treatment of depression, but none of them had received anti-depressants.

A meta-analysis of 22 prospective studies found that post-MI depression leads to two-fold increase in the risk of death, cardiovascular death, and cardiovascular events.¹⁶ Similar to previous studies, Smith NS et al.¹⁷ found that in patients with stable CAD, diagnostic and dichotomous self-report measures of anxiety and depression predicted an increased odds ratio of experiencing MACEs in the long term 2 year follow-up period. However, the results of our study are not relevant to previous ones; this might be due to the short study period. Therefore, the factor of time should be taken into consideration in future studies to allow for comparative assessments to other studies.

There are some limitations of our study. Firstly, although the range of this study was adequate, the sample size was relatively small. Secondly, the short term follow-up period might be considered as a limitation. Future efforts should focus more on assessing a larger sample size and a longer follow-up period.

The recommendation from this study is that cardiologists should be more alert to the factor of depression and should provide more appropriate treatment management protocols; this remains true regardless of whether the cardiologists treat the depression of their patients themselves, or if their patients are referred to psychiatric healthcare providers who are qualified in assessing and treating depression.

Conclusion

Though the MACEs in this study were not statistically different in both depressive and non-depressive groups, the study showed a high prevalence of depression in patients with CAD. Therefore, cardiologists need to raise their awareness of this and to administer and manage depression properly. A longer study period and a larger sample size are recommended for future studies.

Conflict of interest: There is no conflict of interest in this study.

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A Retrospective Study of the Effect of Nutritional Care



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Keywords: self-oral intake, tube feeding, nutritional status, radiation treatment planning, cancer patients

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OBJECTIVE: To compare the effectiveness of nutritional care between self-oral intake and enteral tube feeding (ETF) and/or total parenteral nutrition (TPN) on radiation treatment planning and nutritional status in head and neck cancer patients.

MATERIAL AND METHODS: This retrospective descriptive study was performed on head and neck cancer patients receiving radiation therapy at Wattanosoth Hospital between January 1, 2011 and December 31, 2011. Medical records and clinical data from the hospital's database system were reviewed.

RESULTS: Among a total of 58 patients, 58.6% had self-oral intake while 41.4% received ETF and/or TPN. There was a difference in the effect of nutritional care on radiation treatment planning and nutritional status in head and neck cancer patients between the self-oral intake group and the ETF and/or TPN group. However, this difference was not statistically significant ($p > 0.05$).

CONCLUSION: In head and necks patients, curative radiation therapy or the concurrent chemotherapy can cause side effects including sore throat, mouth sores and nutritional deficiency. Although ETF and/or TPN should be considered, some patients may refuse these types of nutritional care. Medical personnel should consider the feelings of loss in body image of an individual patient, regularly assess the patient's nutritional status and develop an appropriate nutritional plan for each patient.

Head and neck cancers are common and regarded as one of the top public health problems in Thailand. According to Public Health Statistics issued in 2011 by the Department of Medical Service of the Ministry of Public Health, the number of lip, oral and pharyngeal cancer patients was the second highest number of all cancer patients receiving medical treatment.¹ Moreover, this number is likely to increase because people tend to engage in high risk behavior such as alcohol consumption and cigarette smoking.²

Radiation therapy is an effective treatment for head and neck cancers. Although radiation therapy destroys cancer cells, it damages normal cells as well, causing side effects. The side effects of radiation vary from person to person depending on the size, location of the area being treated, and the amount of radiation. Patients with head and neck cancers, such as nasopharyngeal, oral cavity, laryngeal, and tongue cancers, may experience particular side effects because they receive radiation to the face and neck. Additionally, head and neck cancer patients treated with curative intent must be exposed to high doses of radiation. Thus, these patients may experience side effects and acute complications including sore throat, mouth sores, mucositis, dry mouth, and taste loss.³⁻⁶ The patients may develop chronic or subsequent complications

such as mouth stiffness, jaw stiffness, limited mouth opening, and stiff neck.⁷⁻⁹ These symptoms can lead to loss of appetite and malnutrition.

Besides, there will be more side effects if a patient is given chemotherapy combined with radiation therapy.¹⁰ This will affect the patient's nutritional status since the patient might not receive sufficient essential nutrients, especially during treatment. This results in weakness, weight loss, fatigue, impaired immune system, and complications during treatment such as anemia and infections. Due to these side effects, some patients have to postpone radiation therapy and some patients have to discontinue their treatment. The cancer control programs and survival rates are also affected. Therefore, nutritional care is an important factor behind the outcomes of radiation therapy in cancer patients, their recovery, and quality of life.

Nowadays, when patients receiving radiation therapy suffer from side effects which cause them not to have enough food or not be able to eat, they will receive nutritional care by TPN or ETF, which is divided into nasogastric tube feeding and gastrostomy tube feeding. The nutritional care can help patients receive treatment according to the plan without radiation dose adjustment, postponing and discontinuation of chemotherapy. A study by Naiyana P.¹¹ found that, among 20 head and neck cancer patients who received nasogastric tube feeding, 4 patients gained weight, 16 patients lost weight, and only 1 patient lost more than 10% of their body weight. However, there was no patient who discontinued treatment. This showed that nasogastric tube feeding can help improve a patient's nutritional status and it is beneficial for the doctor's treatment planning.

The radiotherapy service at Wattanosoth Hospital is a specialized department offering radiotherapy services for a private tertiary-care cancer hospital with a focus on patient-centered care. It is found that many patients refuse ETF during radiation therapy because they are distressed by the change in their body image. It also affects their lifestyle, routine activities, and quality of life. Due to an awareness of this issue and the fact that there has been no research on nutritional care of head and neck cancer patients in a private hospital, the researcher decided to conduct a comparative study of the effectiveness

of nutritional care between self-oral intake and ETF and/or TPN to find out whether the types of nutritional care have an effect on treatment planning and nutritional status in head and neck cancer patients. It is hoped that the results will be applied to provide some guidelines to nutritional care in head and neck cancer patients who are receiving radiation therapy and concurrent chemotherapy and radiotherapy in the future.

Material and Methods

This research is a retrospective descriptive study. The target population was head and neck cancer patients who received radiation therapy at Wattanosoth Hospital. The sample was 58 head and neck cancer patients who received radiation therapy at Wattanosoth Hospital between January 1, 2011 and December 31, 2011. The inclusion criteria were age > 18 years and complete medical records of radiotherapy. The exclusion criteria were death during radiation treatment.

The research instrument collected data from a medical records review. The data consisted of 3 parts:

1. Patient data including sex, age, nationality, preferential treatment of the patient, Eastern Cooperative Oncology Group (ECOG) performance score¹² (Table 1), tumor site, type and stage of cancer, concomitant disease (if any), smoking history, alcohol-drinking history, and concurrent chemotherapy.
2. Radiation therapy data comprised the number of times of postponed radiotherapy, the number of days of postponed radiotherapy, radiotherapy dose adjustment, and radiation discontinuation before completing radiation.
3. Nutritional status data, before and after receiving nutritional care - self-oral intake and ETF and/or TPN, consisted of body weight, body mass index (BMI), hemoglobin (Hb), hematocrit (Hct), white blood cell count (WBC count), platelet count.

Data collection

The hospital database system was searched for a list of head and neck cancer patients who received radiotherapy. Then, eligible patients who met the inclusion and exclusion

Table 1: Performance Eastern Cooperative Oncology Group (ECOG) Status.¹²

Grade	Detail
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted from engaging in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Deceased

criteria were enrolled in this study. The patient data, radiation therapy data and nutritional status data were acquired from medical records and the hospital database system.

Statistical analysis

The collected data were analyzed by using a statistical software package. The statistically significant difference in patient data, radiation therapy data and nutritional status data between the self-oral intake group and the ETF and/or TPN group was examined by using a chi-square test, at $p < 0.05$.

Results

There were 58 patients in total. The numbers of patients with self-oral intake and patients with ETF and/or TPN were 34 (58.6%) and 24 (41.4%), respectively. In the ETF and/or TPN group, 17 patients (29.31%) received TPN, 3 patients (5.17%) received ETF, and 4 patients (6.90%) received ETF and TPN.

Comparisons between patients with self-oral intake and patients with ETF and/or TPN show no significant statistical difference. The personal information including age, sex, BMI, tumor site, ECOG performance status, oral cavity, paranasal sinus and nasal cavity, concomitant disease, smoking history, alcohol history, and radiation complications also shows no difference (statistically significant at 0.05). Only radiation therapy combined with chemotherapy (concurrent chemotherapy) shows a significant difference at $p = 0.033$ with parenteral and/or enteral feeding outnumbering the oral feeding as shown in Table 2. There was no difference in the patient data between the self-oral intake group and the ETF and/or TPN group, except concurrent chemotherapy which differed significantly at $p = 0.033$ as shown in Table 2.

No significant differences were found in the number of times of postponed radiotherapy, the number of days of postponed radiotherapy and radiation discontinuation before completing radiation between the self-oral intake group and the ETF and/or TPN group at $p > 0.05$ (see Table 3). However, among 4 patients who postponed radiotherapy, 2 patients had to change their radiation masks in stage 2 of treatment due to side effects from concurrent chemotherapy at mild-moderate level. One patient in this group suffered from gastrointestinal (GI) side effects from concurrent chemotherapy at mild-moderate level during the last week of treatment. The last patient had side effects from concurrent chemotherapy at moderate-severe level.

There were no significant differences in body weight, BMI, Hb, Hct, WBC Count, platelet count both before and after receiving nutritional care between the self-oral intake group and the ETF and/or TPN group at $p > 0.05$ (see Table 4).

Table 2: Comparison of patient data between the self-oral intake group and the enteral tube feeding (ETF) and/or total parenteral nutrition (TPN) group.

Factor	Self-oral intake (%)	ETF and/or TPN (%)	p
Total patient (n)	34 (100.0)	24 (100.0)	NS
Age (mean \pm SD)	56.0 \pm 13.1	52.0 \pm 15.2	NS
Sex (male, female)	64.7, 35.3	79.2, 20.8	NS
Body mass index (BMI)			
Underweight	3 (8.8)	5 (20.8)	NS
Normal weight	11 (32.3)	10 (41.7)	NS
Overweight	6 (17.7)	4 (16.7)	NS
Obese	14 (41.2)	5 (20.8)	NS
Body weight (mean \pm SD)	56.0 \pm 13.1	52.0 \pm 15.2	NS
Tumor site			
Oral cavity	5 (14.7)	3 (12.5)	NS
Paranasal sinus and nasal cavity	2 (5.9)	0 (0)	NS
Nasopharynx	19 (55.9)	11 (45.8)	NS
Oropharynx	5 (14.5)	8 (33.4)	NS
Hypopharynx	3 (8.8)	1 (4.2)	NS
Stage			
Stage II	15 (44.1)	7 (29.2)	NS
Stage III	7 (20.6)	5 (20.8)	NS
Stage IV	12 (35.3)	12 (50.0)	NS
Eastern Cooperative Oncology Group (ECOG) score			
ECOG 0	24 (70.6)	18 (75.0)	NS
ECOG 1	10 (29.6)	6 (25.0)	NS
Concurrent Chemotherapy	16 (47.1)	18 (75.0)	0.033 *
Oral Cavity	5 (14.7)	3 (12.5)	NS
Paranasal sinus and nasal cavity	2 (5.9)	0 (0)	NS
Concomitant disease			
Diabetes mellitus	6 (17.6)	0 (0)	NS
Hypertension	8 (23.5)	2 (8.3)	NS
Other	6 (17.6)	4 (16.7)	NS
Coronary artery disease	1 (2.9)	0 (0)	NS
Systemic lupus erythematosus (SLE)	0 (0)	1 (4.2)	NS
Dyslipidemia	2 (5.9)	3 (12.5)	NS
Hyperthyroidism	1 (2.9)	0 (0)	NS
Depression	1 (2.9)	0 (0)	NS
Pulmonary tuberculosis	1 (2.9)	0 (0)	NS
Smoking history			
Smoking	6 (17.6)	6 (25.0)	NS
Non smoking	28 (82.4)	18 (75.0)	NS
Alcohol history			
Alcohol	3 (8.8)	7 (29.2)	NS
Non alcohol	31 (91.2)	17 (70.8)	NS
Radiation complications			
Mucositis	27 (79.1)	22 (91.7)	NS
Skin reaction	30 (88.2)	23 (95.8)	NS
Abnormal taste	12 (35.3)	12 (50.0)	NS

* $p < 0.05$ NS = not significant

Table 3: Comparison of the effect on radiotherapy between the self-oral intake group and the enteral tube feeding (ETF) and/or total parenteral nutrition (TPN) group.

Effect on radiotherapy	Self-oral intake (%)	ETF and/or TPN (%)
- Patients (n)	34 (100.0)	24 (100.0)
- Patient with postponed radiotherapy	2 (5.9)	2 (8.3)
- Total days postponed (days)	24 (6.18)	33 (12, 21)
- Total number of postponed (times)	1.5	2
- Patient with radiotherapy dose adjustment	1 (2.9)	1 (4.2)
- % of total dose adjusted (compared with planned total dose)	2.8 (200cGy)	3.0 (215cGy)
- Patient with radiation discontinuation	1 (2.9)	0 (0)

Table 4: Comparison of nutritional status before and after receiving nutritional care between the self-oral intake group and the enteral tube feeding (ETF) and/or total parenteral nutrition (TPN) group.

Nutritional status (before-after)	Self-oral intake (%)	ETF and/or TPN (%)
Patients (n)	34	24
BMI (kg/m ²)	- 1.8±1.2	- 1.8±1.8
Body weight (kg)	- 4.7±3.3	- 4.8±4.7
Hematocrit (%)	- 3.6±3.8	- 4.2±4.9
Hemoglobin (g/dl)	- 1.2±1.3	- 1.3±1.5
Total WBC (10 ³ /mm ³)	- 1.8±2.2	- 3.1±3.9
Platelet count (10 ³ /mm ³)	- 43.3±52.1	- 39.0±72.1

p value is not significant

Discussion

The study in nutritional care in head and neck cancer patients treated with curative intent or concurrent chemotherapy, both self-oral intake and enteral tube feeding (ETF) and/or total parenteral nutrition (TPN), did not affect radiation treatment planning and the patient's nutritional status. A possible explanation for this might be that most cancer patients at Wattanosoth Hospital are wealthy, and thus they enjoy good health and nutrition. This is reflected in the good to excellent performance ECOG status. There were a total of 58 patients in this study. Among the patients who had ECOG Performance Status of 0, there were 24 patients with self-oral intake and 18 patients having ETF and/or TPN (total of 42 patients, 72.4%). There were 16 patients with ECOG performance status of 1, or 27.6%. Among these were 10 patients with self-oral intake and 6 patients having ETF and/or TPN.

Also, all of the patients in Wattanosoth Hospital were assessed for oral care, cleanliness in the mouth, and prevention and relief of oral mucosa inflammation by nurses. Moreover, patients were evaluated and a nutritionist planned the patients' nutritional intake both for suitable taste and amount of nutrition received. Doctors also cared for any side effects evident in the oral cavity and throat. All of these cares were performed before, during and after radiation treatment periodically. The side effects were also reduced by the use of modern technology to minimize the unnecessary radiation dose in major organs associated with eating, especially the salivary gland and oral cavity. In addition, there were a small number of patients in this study and the data was collected over a short duration, which results in inadequate statistical accuracy.

Conclusion

The results show no significant difference in radiotherapy planning and nutritional status of head and neck cancer patients between patients with self-intake and patients having enteral tube feeding and/or total parenteral nutrition in case of ECOG scale 0-1 only. Therefore, enteral feeding or total parenteral nutrition before radiation treatment does not have sufficient supporting data. However, head and neck cancer patients receiving radiation treatment should be provided suitable and adequate nutrition. Especially those patients who have adverse reactions from radiation such as a sore throat, pain in the mouth and significant malnutrition. The consideration of applying enteral or parenteral feeding is therefore still necessary. It is recommended to take into account the potential impact on the patients' physical and psychological well-being, and to assess each patient in a holistic way.

Limitations: As this research is a retrospective descriptive study and the data is collected from medical records and the hospital database system, there is a limited amount of data and some related data is neither comprehensive nor complete. In addition, the sample size was small and the data collection period was limited. Therefore, the generalization of the findings and the ability to analyze the results of the study are limited as well.

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A 14 Weeks Prospective Pilot Study of the Headache Registry Program at Bangkok Hospital Medical Center



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OBJECTIVE: Obtain clinical information from headache patients to improve the management of headache patients at Bangkok Hospital Medical Center (BMC).

MATERIAL AND METHODS: Patients who visited the Comprehensive Headache Clinic at BMC from March to June 2013 were enrolled in this study. The follow-up period is 14 weeks, divided into 5 visits. At the first visit, patients complete an initial assessment questionnaire including rating migraine disability, headache frequency and pain score. The diagnosis by our physicians is documented. The patient receives information about headaches and a treatment plan is discussed. The patients' symptoms and any side effects are assessed from the 2nd to the 5th visits. This information, and any issues arising from taking medication, is evaluated to improve patient care delivered by the Comprehensive Headache Clinic.

RESULTS: Seventy patients were enrolled in the registry program. Eighty percent of the patients were female, with an average age of 36 ± 11 years. Migraine headache was the most common diagnosis (68.6%). Triptans were most commonly used for acute medication in 59% of the patients. Antiepileptics were most commonly prescribed as prophylactic treatment in 48% of patients. Patients with chronic migraine came in for follow up visits more regularly than patients with episodic headaches (100% vs. 71.1% on the 2nd visit, 100% vs. 65% on the 3rd visit, 100% vs. 11.1% on the 4th visit, and 94.7%, 0% on the 5th visit). The average pain score (NRS) dropped from 7 to 3 and the average headache frequency dropped from 3 to 2 times per week. These clinical outcomes showed a statistically significant improvement in patient quality of life.

CONCLUSION: The Headache Registry Program demonstrates a good adherence and compliance to treatment along with a significant reduction in the severity and frequency of headaches.

Headache is a common presenting symptom for patients who visit neurologists at the neuroscience center in at the Bangkok Hospital Medical center. The statistics from the last 5 years show that headache was a presenting symptom in 65% of the patients. The comprehensive headache clinic has been established since 2011 in order to care for this group of patients more effectively.^{1,2}

The mission of the comprehensive headache clinic is to obtain standard diagnosis according to the International Classification of Headache Disorders 2nd Edition (ICHD-2)³ and to the holistic treatment guidelines from the American Academy of Neurology and the European Federation of Neurology Society. The clinical characteristics data on the severity of headache experienced by patients is very important to help identify the appropriate treatment plan.

The Headache Registry Program is a prospective study based on patient data from March to June 2013. The data collected included demographic data, characteristic of headache, diagnosis, treatment, clinical outcome, and treatment adherence.

Materials and Methods

Materials

The headache registry program consists of a headache registry questionnaire used to evaluate the patient's experience of headache to include: a pain score assessment, the headache frequency per week, and a Migraine Disability Assessment Questionnaire (MIDAS). Once a detailed history has been collated and after the neurologist or headache specialist from the comprehensive headache clinic has completed their neurological examination, the patient will be diagnosed according to ICHD-2. Patients will then have an opportunity to discuss treatment strategies and to receive appropriate treatment consisting of headache education, trigger avoidance, pharmacological and non-pharmacological treatments on offer and also instructions in the use of a headache diary to document their symptoms and frequency of headaches.

The headache registry questionnaire is a questionnaire used to collate the patient's history of headaches. The questions cover the characteristics of headache, the duration, frequency and location of the headache, the pain score, any associated symptoms, trigger factors, and the impact the headache has on daily life, any history of past illnesses, and any medications used including analgesics.

A headache diary is used to record headache symptoms. The information includes the day the headache occurred, the pain intensity (pain score), duration, and triggers, any associated symptoms, and any analgesic used.

The pain score⁴ is a pain assessment graded on a numerical rating scale (NRS) ranging from a score of 0 to 10. The scores are divided into 4 categories:

- 0 = no pain,
- 1 - 3 = mild pain,
- 4 - 6 = moderate pain
- 7 - 10 = severe pain.

The headache frequency per week is the number of headache attacks in a week.

The Migraine Disability Assessment Questionnaire (MIDAS)⁵⁻⁷ is a disability self-assessment tool for migraineurs. The questionnaire assesses the disability ranking in daily activities of migraine patients in 3 areas including work or study, household activity, and social activity for the previous 3 months. The results can be divided into 4 grades:

MIDAS Grade	Definition	MIDAS Score
Grade I	Little or no disability	0-5
Grade II	Mild disability	6-10
Grade III	Moderate disability	11-20
Grade IV	Severe disability	21+

Statistical Analysis

1. Patient characteristics are described as absolute numbers, percentage, mean, and standard deviation (SD).
2. Inferential statistics were used with the Wilcoxon Signed Rank Test to determine each headache parameter before treatment (1st Visit) versus after treatment (5th Visit).

Methods

The data collection process is divided into 5 visits¹:

• 1st Visit

1. The headache nurse coordinators assess the patient who visits the comprehensive headache clinic giving them a headache registry questionnaire.
2. The history and physical examination is performed by either a neurologist or headache specialist in the comprehensive headache clinic.
3. Patients who met the inclusion criteria are informed about the research, and asked to participate by signing an informed consent.

Inclusion Criteria:

- Patients who are visiting the comprehensive headache clinic for the first time.
- Patients who have been diagnosed according to the ICHD-2 criteria as having primary headache disorder, secondary headache disorder, cranial neuralgias, central and primary facial pain, and other headaches.
- Patients aged 15 and above, who can communicate well.

Exclusion Criteria:

- Patients who declined taking part in the study.
 - Patients whose diagnosis changed, and was not related to the ICHD-2 criteria.
4. Pain score, headache frequency, and disability scores were obtained.
 5. A treatment plan was customized for each patient and was discussed with the patient in detail including headache education, trigger avoidance, efficacy of treatment, and adverse effects of treatment by neurologists and the headache coordinator. The headache coordinator also recommends that the patient should keep a headache diary, as well as answer any questions asked. On average, this process took 15-20 minutes per case.

- 2nd Visit (1-2 weeks), 3rd Visit (3-4 weeks), 4th Visit (5-9 weeks) and 5th Visit (10-14 weeks):
 1. Assess the progress of the disease including pain score and headache frequency per week. The MIDAS score was reevaluated at the 5th visit.
 2. Monitor the side effects of treatment.
 3. Monitor the adherence and compliance including rate the administration of medication and attending follow up visits.

Results

Population

Most patients are female (80%) with an average age of 36±11 years. The most common age range is 31-60 years (63%) followed by 15-30 years (34%) and > 60 years (3%).

The most common headache type is primary headache (82.9%), including migraine headache⁹ (68.6%) followed by tension type headache (11.4%) and other headaches (2.9%).

The second most common headache disorder is secondary headache (10.0%) including medication overuse headache (5.7%) and cervicogenic headache (4.3%). The least common type is cranial neuralgia, central and primary facial pain, and other headaches (7.1%) including occipital neuralgia (2.9%), tolosa-hunt syndrome (2.9%) and trigeminal neuralgia (1.3%). (Table 1)

Treatment

Medications for the treatment of headaches were divided into two groups: acute medications and prophylaxis medications.¹⁰⁻¹² In acute medications, triptans were the most commonly used (59%), followed by non-steroidal anti-inflammatory drugs (NSAIDs) (41%). The most commonly used prophylaxis medications were antiepileptics drugs (48%), followed by antidepressants (45%) and calcium channel blockers (7%). (Figure 1)

Minor and transient adverse effects were found in 0.7% with acute medications and 16.22% with prophylaxis medications. Two patients (0.7%) experienced adverse effects after using triptans, including 1 case of chest pain and 1 case of nausea. There were 28 patients (13.16%) who experienced adverse effects after using tricyclic antidepressants including 23 patients with drowsiness, 3 patients with dizziness, and 2 patients with constipation. Of the patients who took antiepileptic drugs, 4 patients (2.04%) had numbness in their extremities and 2 patients (1.02%) had memory difficulties. (Table 2)

The average pain score dropped from 7 (severe pain) to 3 (mild pain) ($Z = -3.488, p < 0.01$). The average headache frequency per week was reduced from 3 to 2 times per week. (Table 3)

Table 1: Patient Characteristics (n=70).

Parameters	No. of Cases (%)
Gender	
Male	14 (20)
Female	56 (80)
Age (year)	
15-30	24 (34)
31-60	44 (63)
> 60	2 (3)
Mean ± SD (Min, Max)	36 ± 11 (17, 85)
Headache Diagnosis (ICHD-2)	
• Primary Headache	58 (82.9)
- Migraine Headache	48 (68.6)
- Tension Type Headache	8 (11.4)
- Other	2 (2.9)
• Secondary Headache	7 (10.0)
- Cervicogenic Headache	3 (4.3)
- Medication Overuse Headache	4 (5.7)
• Cranial Neuralgia, Central and Primary Facial Pain and Other Headache	5 (7.1)
- Occipital Neuralgia	2 (2.9)
- Tolosa-Hunt Syndrome	2 (2.9)
- Trigeminal Neuralgia	1 (1.3)

Table 2: Types and numbers of patients with side effects.

Medication/Adverse Event	No. of Cases (%)
Acute Medications	
Triptans (n=35)	2 (0.70)
Chest pain	1 (0.35)
Nausea	1 (0.35)
Prophylaxis Medications	
Tricyclic antidepressants (n=47)	28 (13.16)
Drowsiness	23 (10.81)
Dizziness	3 (1.41)
Constipation	2 (0.94)
Antiepileptics drugs (n=51)	6 (3.06)
Numbness	4 (2.04)
Difficulty with memory	2 (1.02)

Table3: Headache parameters on 1st visit and 5th visit.

Medication/Adverse Event	Mean	SD	Z	p
Pain Score				
1 st Visit	7	1.6	-3.488	<0.01**
5 th Visit	3	2.7		
Headache Frequency per Week				
1 st Visit	3	2.4	-2.581	<0.01**
5 th Visit	2	2.1		

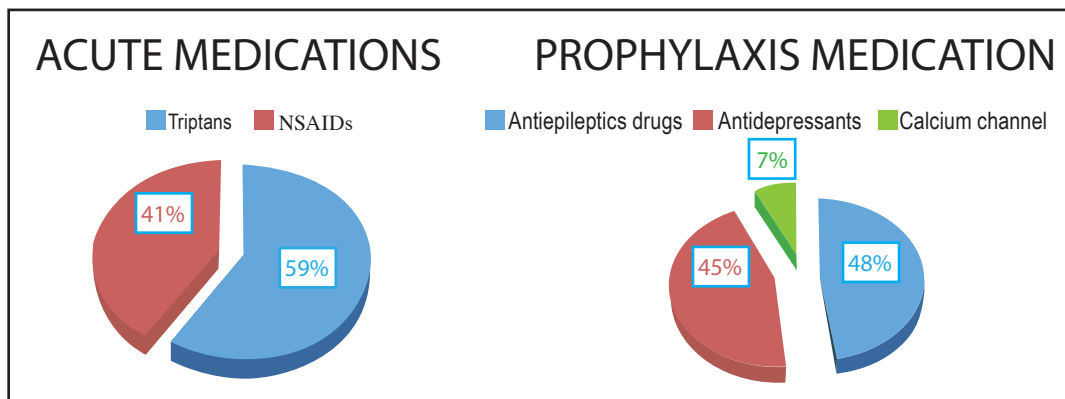


Figure 1: Medications used

Patients' Adherence

Patients' adherence to treatment was evaluated as the percentage of patients that came to their appointment. Patients were divided into two groups according to their headache frequency as either episodic headache (headache frequency < 15 days per month) or chronic headache (headache frequency ≥ 15 days per month).

Most of the patients with episodic headaches came to their 2nd visit (71.1%) and 3rd visit (65%), but most of these patients were not present at their 4th and 5th scheduled visit (11.1% and 0% respectively). The reason for not showing up for the appointment was evaluated via phone and it was found that 89% reported a dramatic improvement in symptoms, 8% were unavailable on the appointed date, and 3% were unreachable by phone.

Chronic headache patients scored a 100% attendance rate at the 1st, 2nd, 3rd, and 4th visit. However, 94.7% came to their 5th visit. The reason for not showing up for the appointment was also asked via phone, and the reason given was that the symptoms had improved and the follow-up visit was not seen as necessary.

Patients' compliance to the medication was assessed by counting the leftover pills at each follow up visit. It was found that the compliance rate was 100%.

Discussion

The results show that most patients who attended the comprehensive headache clinic suffered from migraine headache with a severe degree of symptoms (average pain score = 7, headache frequency per week = 3, MIDAS = 27.1). The first-line medication was triptans for acute treatment, and antiepileptic drugs for prophylaxis treatment. This is consistent with the guidelines from the American Academy of Neurology and the European Federation of Neurology Society.¹²⁻¹⁵

Most patients with episodic headache came in for follow-up during the first 2 visits, and when the symptoms

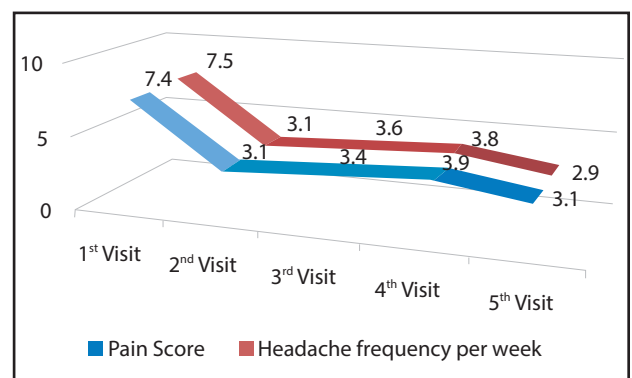


Figure 2: The average pain score and headache frequency per week

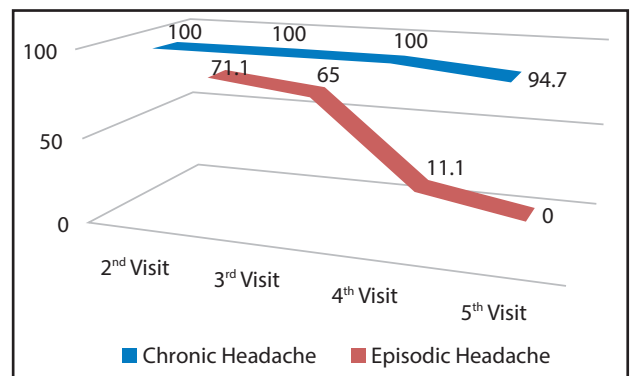


Figure 3: Patient adherence in episodic and chronic headache

improved, most of these patients were not coming back for their later scheduled visits. Since none of these patients were present at the 5th visit, we could not compare the pain score, headache frequency per week, and MIDAS of the 1st versus 5th visit in this group. However, 63% of these patients said they would visit the comprehensive headache clinic should their symptoms relapse. This was a marked difference from their view prior to taking part in the program. Before, these patients would only have considered a visit to the clinic if their symptoms had been unbearable.

In patients with chronic headache, almost 100% of patients showed good compliance and adherence to the treatment resulting in a statistically significant reduction in pain score and headache frequency per week. Furthermore, we also found that these patients had received several headache treatments from other hospitals or clinics with unsatisfactory results due to: inadequate patient education about disease progression, the treatment plan, and the side effects of medication.

A challenge for the headache registry program was patient tracking for MIDAS evaluation at the 5th visit. This was because some patients changed their appointment

and the alert for MIDAS evaluation disappeared from the computer system. In order to solve this problem, the nurse coordinator will monitor each patient on the appointment schedule to see who still needs to be assessed with the MIDAS questionnaire and make a note in the computer system to notify the team.

Conclusion

The Headache Registry Program provides patient education and encourages patients to take part in planning their treatment. This approach has resulted in good adherence and compliance to treatment accompanied by a significant reduction in the severity and frequency of headache.

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The Development of Nurse Residency Program



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Keywords: nurse residency program, NRP, mentoring program for new graduate nurses

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OBJECTIVE: To study new graduate nurses' work problems; to design training program courses as well as the experimental evaluation of the effectiveness of the courses after the nurses have been trained.

MATERIAL AND METHODS: Studying work problems of new graduate nurses through a research survey. The questionnaires were given to the sample group of 168 new nurses who have at least one year of experience in a 200-bed size private hospital in the Bangkok area. The result of the survey led to the development of two training programs. They were the Nurse Residency Program (NRP) and Mentoring for new graduate nurses. The activities and teaching methods were on the job training (OJT) for 20 new graduate nurses and 20 mentors in intensive care units (ICU). The NRP was analyzed after one group was trained for pre-test, and post-test design as well as three months later. The mentoring program was analyzed for pre-test, and post-test design. T-test statistics were used for these programs.

RESULTS: The work problems of new graduate nurses were: 1) clinical knowledge competency for nurse's notes; 2) nursing intervention for the procedure of intravenous administration; 3) anxiety adjustment; 4) and leadership and communication for lack of self-confidence to perform the task at hand. After the NRP training it was found that the clinical knowledge competency was significantly higher than before training and three months after training it was higher still except for the area of critical care nursing of gastrointestinal and endocrine patients as well as patients with shock. These remained the same. The competency of nursing interventions was found to be higher after training and after three months of training the competency was found to be higher than after training at the statistically significant level of 0.05. Anxiety adjustment before, after and after three months of training was not statistically different. The leadership and communication, before, after and after three months of training were not statistically different either. When the courses finished, there were 16 remaining new graduate nurses, and the retention rate was 80% in a year.

CONCLUSION: These training courses, the NRP and Mentoring program, were appropriate and suitable, and were successful in solving work problems faced by new graduate nurses.

Nowadays, almost all health organizations do not have sufficient registered nurses (RNs) taking care of patients. This problem occurs around the world, not only in Thailand, and affects the efficacy of nursing services because RNs are an important staff component for the delivery of hospital services. As a result, the lack of RNs impacted the economy negatively because it is necessary to fund and train new graduate nurses to become a RN. A RN is then able to care for patients while keeping safety as a first priority.

With regard to jobs of new graduate nurses, they have to face an ever-changing atmosphere of a new workplace, the hospital's systems, rules and policies. These all affect the work of new graduate nurses. Some of the nurses may be able to adapt to the new workplace but many find it difficult. As a result, the latter are likely to quit in their first year of work.^{1,2} The role transition from a student nurse to a RN is a challenge. In a hospital context, this transition is the first step of their duties. Being a RN is recognized as being more stressful than being a student nurse working under the supervision of a nurse instructor. Therefore, student nurses who become RNs have to adapt themselves to a nursing society and adjust their minds in order to work as RNs efficiently.

In addition, RNs are required to follow the rules and regulations of their new workplace. If they fail to do so, they will be worried and stressed as well as run the risk of losing their self-confidence. In other words, if they are not able to perform work tasks assigned to them by senior nurses or if they cannot manage to provide adequate care to patients under their own authority, they will lose self-esteem. This in turn will affect the quality of care for patients. After a bad attitude about being a RN emerges, this might result in the nurses taking a day off, quitting, transferring, abandoning their posts or even resigning from their jobs. This problem can become an obstacle for the advancement of their nursing career as well as affecting them negatively both physically and mentality. 'Reality Shock' at the beginning of a nursing career is important to recognize because it impacts a nurse's confidence, job stability, willingness to work and can lead to interpersonal conflict.³ In addition, a new workplace can be a shock to new graduate nurses. If new graduate nurses compare their expectations of a workplace and their actual reality, they will be more likely to quit their job.⁴ 'Reality Shock' is a transition period when a student nurse becomes a RN which can be divided into 4 periods³ which are: the Honeymoon Phase, the Shock Phase, the Recovery Phase and the Resolution Phase. The transition can be exemplified as a step in becoming a RN, divided into 3 phases⁴: Doing, Being and Knowing (see Figure 1).

Although a large number of new graduate nurses are recruited, many other nurses will quit in their first year of a career too.⁵ Even though some organizations arrange preceptor nurses to assist new graduate nurses in their first 3 months, it negatively impacts on the organization's budget for training and diminishes the workforce that drives the organization forward. Preceptorship programs or mentoring programs help new graduate nurses to work and it increases the staff retention rate from 62% to 92%.⁷ In contrast, some organizations do not have this program and hence new graduate nurses cannot do their work efficiently and they eventually quit. To sum up, preceptor nurses are crucial to the training of new graduate nurses because they help the apprentices to overcome obstacles in the beginning of their career.^{6,7}

The way to overcome 'Reality Shock' is to establish a program that helps new graduate nurses to be able to enter the nursing career, reducing stress (see Figure 1) and, especially, preventing them from resigning.^{2,4,8-11} The program is called "Nurse Residency Program" or "NRP". The researcher works in the human resources development department of the nursing division, and states that the turnover rate of new graduate nurses in private tertiary level hospitals is more than 50% in the first year of the nurses' career. Moreover, in Thailand, there is still no NRP and this is the reason why the researcher intends to establish a training NRP as part of the pathway of a student nurse to becoming a registered nurse.

Material and Methods

1. The study of the work problems of new graduate nurses working in a 200-bed private hospital in the Bangkok area with under a year's work experience were included in the research survey. The work problems cover four perspectives: clinical knowledge; nursing skills; anxiety adjustment in a new workplace; and leadership and communication skills.
2. The analysis from the result of the research survey and the interview of private hospitals' executives to design a NRP and a mentoring program.
3. A sample group of 20 new graduate nurses and another 20 experienced nurses who have worked in an ICU.
4. The course consisted of a NRP and a Mentoring program.
5. The NRP test and the course evaluation from four perspectives immediately before and after training, as well as three months after training.
6. One group pre-test and post-test design.

Example	Before	Object	After	3-month after
A	O ₁	X	O ₂	O ₃

Methodology

First: To study the work problems of new graduate nurses.

1. Conduct a literature review interviewing seven new nurses about how to work in a new workplace, selected four work problem areas; clinical knowledge; nursing skills; anxiety adjustment; leadership and communication.
2. Gathering information from questionnaires. Then, submitting the gathered information to five expert reviewers to analyze, find, and index each item objective's congruence and later to adjust the questionnaire in accordance with experts and advisors' recommendations.
3. Testing the questionnaire with 30 new graduate nurses with work experience of less than a year in a 200-bed private hospital in Bangkok in order to find the item-total correlation and reliability by alpha coefficient.

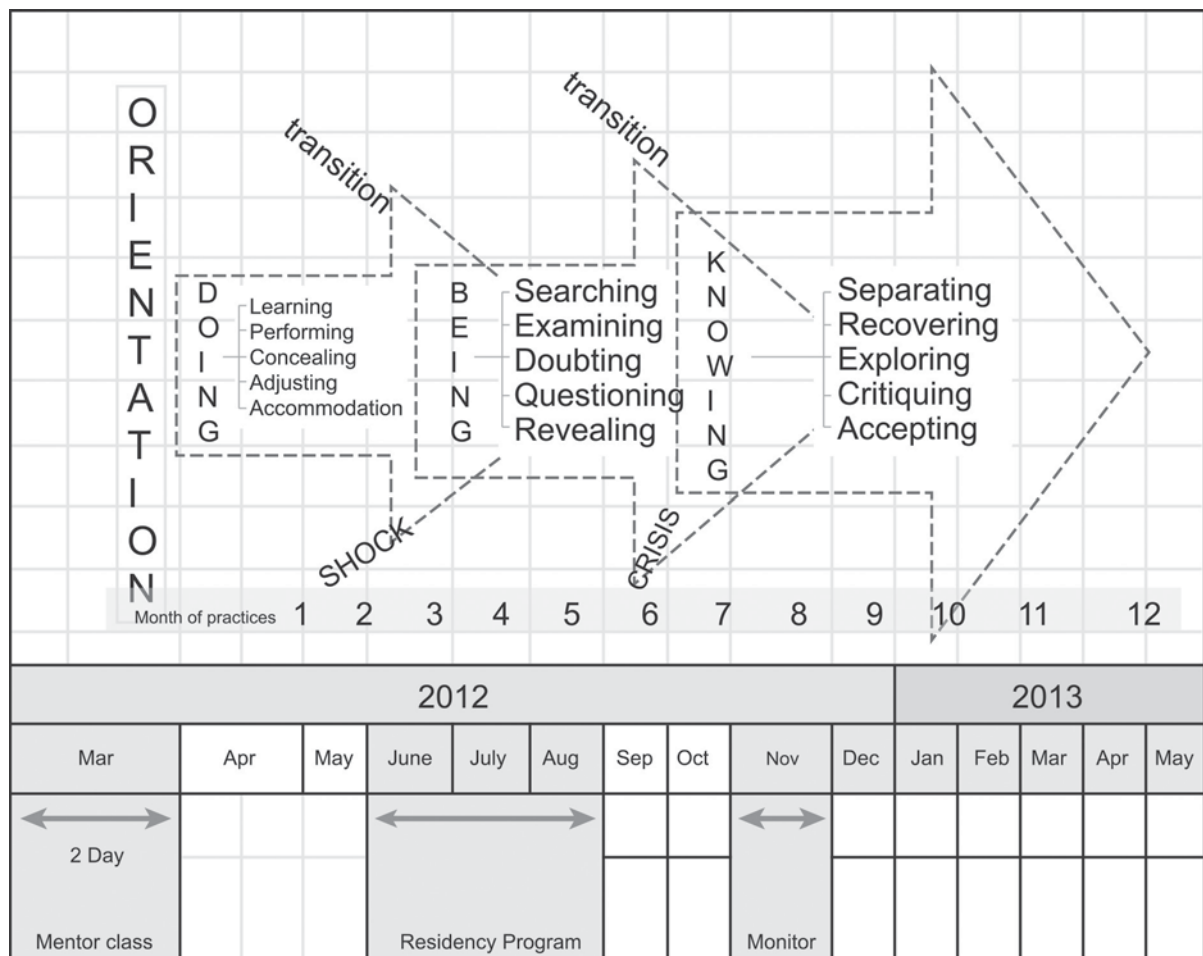


Figure 1: Shows period of nurse residency program (NRP) and related mentoring program.

4. Using the approved questionnaire. Distributing to 168 new graduate nurses or 93.3% and analysis using descriptive statistics, such as mean and standard deviation.

Second: Design the Nurse Residency Program to train new graduate nurses.

1. Synthesize the data gathered from the study of new graduate nurses' work problems, interviews with hospital executives and the ICU manager to create the Nurse Residency Program and Mentoring program.

1.1. Mentoring program for preceptor nurses:

- New graduate nurses' work problems.^{12,13}
- Preceptor nurses' role.^{12,13}
- Methods to manage stress, roles and duty of preceptor nurses, apply to on the job training (OJT), encourage leadership and communication and evaluation of new graduate nurses' work performance.
- Game to encourage new graduate nurses.
- Activity and training of preceptor nurses' training program consisting of lectures, brainstorming activities, clinical teaching in bedside care using the OJT method.
- Preceptor nurses' evaluation and aptitude testing.

1.2. Nurse Residency Program: NRP for new graduate nurses:

- New graduate nurses' problems on clinical knowledge, nursing skills, anxiety adjustment, leadership and communication. Integrated course:^{2,4,9-11}
- Increase new graduate nurses' ability to solve their work problems.
- Increase new graduate nurses' development of clinical knowledge, nursing skills, success in adjusting themselves to new work environments, improved stress management, leadership and communication.
- Course description consists of six fields of clinical knowledge such as: nursing for intensive care patients of cardiovascular, respiratory, cerebrovascular, renal patient and balancing in body, gastrointestinal and endocrine system as well as shock-phase intensive care patients for 64 hours or eight days and seven fields of nursing skills such as use of ventilator, suctioning, and intravenous interventions. This training for nursing skills takes 56 hours or seven days. In addition, there is 24 hours (3 days') training for new graduate nurses to help them to adjust to new work environments and

improve their stress management. Then, new graduate nurses have to train to improve their leadership and communication skills. For example, they need to know how to write nurses' notes, and how to work collaboratively as well as learning from case studies.

- Activities include lectures, OJT, games, brain storming activities, discussions, learning from case studies through media such as handouts, slides, video clips, medical devices and patients' files.
 - Evaluation for the program is carried out by observing new graduate nurses' working problems from four perspectives using four tools:
 - Clinical knowledge: A 60-question test in 6 subjects before and after training and also 3 months after training.
 - Nursing skills: competency assessment skills checklist, before and after training and also 3 months after training.
 - New graduate nurses' skills for adjusting themselves to the work environment: Pagana's Clinical Stress Questionnaire¹⁷ and Spielberger's State-Trait Anxiety Inventory¹⁸, before and after training and also three months after training.
 - Leadership and Communication: Casey-Fink graduate nurse survey¹, before and after training and also three months after training.
2. Present the program's structure to five experts in order to approve the structure and verify that it is relevant and appropriate.
 3. Use comments from the experts to improve the program.

Third: test the program:

1. Test the approved program through the:
 - 1.1. Mentoring program tested by 20 ICU nurse volunteers. There were two days of pre-test and post-tests.
 - 1.2. Nurse Residency Program tested by 20 new graduate nurses who work full-time in the ICU. The training took place every Thursday and Friday, over nine weeks, for a total of 21 days. There were pre-tests and post-tests as well as a post-test three months after the training finished.

The four tools used for research were:

1. The tools for new graduate nurses' working problems synthesized from the literature and an interview with new graduate nurses. Then, find internal consistency by using Cronbach's Alpha statistic.
2. Three tools used were Pagana's Clinical Stress Questionnaire-CSQ¹⁷ for clinical stress test, Spielberger state-trait anxiety inventory¹⁸ for the anxiety¹ test and the Casey-Fink graduate nurse survey¹ for leadership and communication evaluation. Three tools are in English and the researcher translated these from English to Thai. Then, three experts

validated the correlation between the source text and the translated text. After that, the text was edited and tested on 30 non-example new graduate nurses who work in a private hospital in order to find item-total correlation and reliability by alpha coefficient. Finally, this tool was used along with the pre-test, post-test and post-test again three months after the end of the training.

3. A tool for the clinical knowledge test was a 60-question test in 6 subjects. The test for new graduate nurses is produced by lecturers. First, the test is used along with the pre-test, post-test and post-test again three months after the end of the training.
4. A tool for nursing competency assessment skills test was seven checklists from the ICU.

Results

The research results showed new graduates nurses' work problems from four perspectives:

1. **Clinical knowledge perspective** was found in the top three scores; 1) new graduate nurses cannot write nurses' notes 2) competency of nursing assessment is relevant as well as being unable to predict a patients' symptoms and 3) changing in accordance with patients' current symptoms.
2. **Nursing skills perspective** was found in the top three scores; 1) nursing intervention for the procedure of intravenous administration 2) nursing services for the discharge process 3) nursing competency about steps of cardiopulmonary resuscitation (CPR) or basic life support.
3. **Anxiety adjustment perspective** was found in the top three scores; 1) new graduate nurses' work performance was affected by their temperamental colleagues, 2) feeling of failure caused by working inefficiently and 3) difficulty in adjusting themselves to the work environment.
4. **Leadership and communication perspective** was found in the top three scores; 1) lack of confidence to work as a nurse 2) lack of confidence to give information to other nurses and colleagues and 3) inability to solve unexpected problems.

The NRP and Mentoring training programs were found to be appropriate and at a high level and the highest level and congruence for all factors. The results after the Mentoring training program compared to before and after participating in the program was found to be a statistically significant level of 0.05 and the NRP training program was found to significantly increase clinical knowledge when compared between levels before training and three months after training, apart from critical care nursing of Gastro-intestinal and Endocrine patients as well as the patients with shock (Table 1). These remained the same. The competency of nursing interventions was found to be higher after training. After three months of training this competency was higher than after training at the statistically

The Development of Nurse Residency Program

significant level of 0.05 (Table 2). Anxiety adjustment before, after and after three months of training remained the same (Table 3). The leadership and communication, before, after and after three months of training remained the same as well (Table 4). After new graduate nurses have been trained in the Nurse Residency Program, they

have more clinical knowledge, better skills than before and are able to adjust their anxiety about their workplace. During the research period, there were four of 20 new graduate nurses who resigned. So, in the first two months, there were 16 new graduate nurses who were still eligible for the study.

Table 1: Result of clinical knowledge test compared before and after, after and after 3 months program implementation (n = 16).

Clinical knowledge	After		Before		<i>t</i>	After 3-month		After		<i>t</i>
	\bar{X}	SD	\bar{X}	SD		\bar{X}	SD	\bar{X}	SD	
1. Critical care nursing of cardiovascular patients	8.75	0.93	3.93	0.99	15.73*	9.06	0.97	8.75	0.93	2.61*
2. Critical care nursing of respiratory patients	8.62	1.02	4.56	1.20	10.96*	9.37	0.61	8.62	1.02	2.53*
3. Critical care nursing of cerebrovascular patients	7.56	0.89	4.12	1.02	8.88*	8.93	0.77	7.56	0.89	6.21*
4. Critical care nursing of renal patient and balancing in body	7.31	0.70	3.06	0.77	17.00*	8.50	0.96	7.31	0.70	4.84*
5. Critical care nursing of gastrointestinal and endocrine patients	9.56	0.62	5.75	0.68	20.33*	9.62	0.71	9.56	0.62	0.56
6. Critical care nursing patient of shock	8.87	0.80	3.87	0.71	18.25*	9.37	0.71	8.87	0.80	2.07

* $p < .05$

Table 2: Result of nursing practice skill compared before and after, after and after 3 months program implementation (n = 16).

Nursing practice skill	After		Before		<i>t</i>	After 3-month		After		<i>t</i>
	\bar{X}	SD	\bar{X}	SD		\bar{X}	SD	\bar{X}	SD	
1. Ventilator use	48.56	2.09	26.87	8.93	9.71*	82.06	1.34	48.56	2.09	51.89*
2. Airway suctioning	68.50	3.05	42.93	2.29	25.46*	86.87	3.09	68.50	3.05	21.00*
3. Intravenous administration	60.31	3.82	34.12	3.15	20.07*	68.18	2.40	60.31	3.82	9.59*
4. Nursing care of invasive	46.62	2.27	25.06	1.28	28.65*	85.50	1.89	46.62	2.27	83.71*
5. Nursing care of intercostal drainage	47.93	3.08	31.62	2.41	16.26*	71.68	3.19	47.93	3.08	33.17*
6. Nursing care of nasogastric tube	78.37	3.96	43.37	5.43	17.42*	82.31	3.13	78.37	3.96	7.34*
7. Nursing care of Foley' catheter	73.31	2.12	50.68	7.43	11.36*	89.37	2.27	73.31	2.12	17.82*

* $p < .05$

Table 3: Result of clinical stress and anxiety test compared before and after, after and after 3 months program implementation (n = 16).

Test	After		Before		<i>t</i>	After 3-month		After		<i>t</i>
	\bar{X}	SD	\bar{X}	SD		\bar{X}	SD	\bar{X}	SD	
Clinical stress test										
Threat	2.21	0.44	2.18	0.35	.517	2.31	0.47	2.21	0.44	1.006
Challenge	3.11	0.29	3.02	0.24	.906	3.02	0.27	3.11	0.29	-1.962
Harm	1.86	0.27	1.80	0.27	.892	2.04	0.26	1.86	0.27	2.907*
Benefit	3.03	0.45	3.04	0.44	-.148	2.67	0.51	3.03	0.45	-3.286*
State & Trait Anxiety										
State Anxiety -Positive	2.65	0.48	2.59	0.37	.530	2.36	0.42	2.65	0.48	-2.853*
State Anxiety -Negative	2.12	0.34	2.00	0.32	1.319	2.28	0.42	2.12	0.34	1.835
Trait Anxiety -Positive	2.54	0.42	2.55	0.28	-.154	2.34	0.40	2.54	0.42	-2.118*
Trait Anxiety -Negative	1.84	0.32	1.73	0.30	1.119	2.00	0.53	1.84	0.32	1.324

* $p < .05$

Table 4: Result of leaderships and communication competency compared before and after, after and after 3 months program implementation.

Competency	n	After		Before		t	After 3-month		After		t
		\bar{X}	SD	\bar{X}	SD		\bar{X}	SD	\bar{X}	SD	
Leadership	16	3.26	0.28	3.24	0.20	0.159	3.11	0.24	3.26	0.28	-1.838
Communication	16	2.93	0.42	2.77	0.43	1.282	2.91	0.33	2.93	0.42	-0.192

* $p < .05$

Discussion

This research found that most new graduate nurses felt a profound lack of preparation for their new role. Problems included: being able to write nurses' notes, nursing practices and other issues. When student nurses were incorrect, their nurse instructor would remedy the errors and explain. Preceptor nurses are needed to supervise new graduate nurses at the beginning of their registered nurses' career. As a registered nurse, they may get someone to review, coach on critical thinking, improving clinical judgment, nursing processes and many other areas in order to prepare for their role. Although they had a preceptor assigned to them for coaching for a time, they need more supervision. They also feel worried and insecure^{13,14} that they will not be able handle pressure. So, they always have to consult their preceptor nurses.¹²⁻¹⁵

This aspect of training was a simulator for new graduate nurses to find solutions if they feel stressed. A new job in a new environment can make people stressed and each person will have a different reaction when they are stressed.¹⁶ Hence, each nurse should eliminate stress in their own way and try to understand problems they have to encounter.

Furthermore, it was found that new graduate nurses have a problem about leadership and communication. Sometimes they lack the confidence to work collaboratively and to solve unexpected problems. Most of them cannot make others understand them even though communication is a way to make friends among colleagues. They should be friends with their colleagues. There were some group activities for new graduate nurses to help them to get to know each other. They cannot communicate efficiently because they do not have much work experience and hence they may feel nervous to communicate with others. New graduate nurses' problems might be solved by the supervisor of their preceptor nurses. A new graduate nurse's ability to adjust to the work environment is also

important. Being a nurse in an ICU requires an understanding of the needs of their patients and their families.

Also their stress levels did not change after the end of the training. Actually, the moment that new graduate nurses felt the most stressed was when they have taken care of patients and the patients' symptoms change. Therefore, the program has simulated activities for new graduate nurses, aiming for them to be able to deal with stress well.⁹⁻¹¹ The stress of new graduate nurses in the 3 periods assessed remained the same. Actually, they are mostly generation Y people who like to learn new things and are very confident. In the 'being' period, new graduate nurses will try their best to adjust themselves to the work environment, and deal with their intrapersonal conflict and have positive thinking and try to accomplish their goals.⁴

Evaluation of this program showed that new graduate nurses have more clinical knowledge in the six aspects after they received training. They also improved more in four aspects (except for caring for patients who need care in gastrointestinal and endocrine as well as patients who were in shock phase) after the training program ended for 3 months because their intensive care unit did not assign these 2 tasks to new graduate nurses because it was too dangerous for them to take care of patients with severe conditions. It showed that training and assigning work tasks for them can improve new graduate nurses' clinical knowledge after they have been trained in this program.

Conclusion

This research suggested the program's length should be six months in order to cover the 'reality shock' period of new graduate nurses. Before training in this program, new graduate nurses should have work experience of 3-6 months. Moreover, the program's length should be one year in order to maximize the quality of training. Elements in the training program should be in accordance with problems that happen in the real lives of new graduate nurses.

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Sleep Apnea: A Novel Risk Factor in Acute Stroke and Transient Ischemic Attack



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Obstructive sleep apnea (OSA) is a prevalent disease and has been increasingly recognized as an independent risk factor for hypertension, diabetes, cardiovascular disease, and stroke. Stroke is a frequent disease, a second leading cause of death worldwide which generates high healthcare costs. Recent studies suggest that sleep apnea is common after stroke with the prevalence of 50-94%. OSA is emerging as one of the important risk factors for stroke.

Untreated OSA contributes to poor stroke outcome and also is a risk factor for subsequent cardiovascular diseases including recurrent stroke. Treating sleep apnea improves recovery from stroke and decreases cardiovascular morbidity & mortality.

Nonetheless, the under-diagnosis of OSA in stroke patients is still common. Considering that typical symptoms of OSA are not often found in stroke, as well as none of the predictors regarding stroke characteristics can identify the presence of sleep apnea in stroke patients. These findings support the implementation of routine OSA screening in stroke patients.

Obstructive sleep apnea (OSA), the most common form of sleep disordered breathing (SDB), is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) airway obstruction during sleep despite respiratory effort resulting in repeated arousals, sleep fragmentation and hypoxia during sleep. Classic symptoms of OSA include snoring, witnessed apnea, choking during sleep, excessive daytime sleepiness or fatigue. OSA is common in the general adult population and may occur in up to 24% of men and 9% of women.¹ It becomes more prevalent with increasing age; approximately 70% of older men and 56% of older women.² Regarding underlying diseases, its prevalence seems to be even higher among patients with neurological diseases such as Parkinson's disease, Alzheimer's disease, myotonic dystrophy, epilepsy as well as stroke.

OSA is common after stroke, and stroke appears to be more common in those with OSA. Moreover, there are shared risk factors for both. So the question remains, stroke causes sleep apnea, or sleep apnea leads to stroke, or are they both caused by the same risk factors? This is important because it may have implications for prevention, acute treatment, and rehabilitation of patients with acute stroke. There is actually extensive research over the past 2 decades. In this review, the accumulating evidence of sleep apnea and stroke is summarized, regarding prevalence, predictors, causative relationship, and consequences of untreated OSA in stroke patients as well as possible mechanisms responsible for OSA leading to stroke.

Case Report

A 52-year-old male was transferred to the Bangkok Hospital Pattaya from an outside hospital for evaluation of recurrent transient ischemic attacks (TIAs) and acute ischemic stroke. He has presented to an outside hospital one day prior with acute onset weakness and numbness of left upper and lower extremities. Initial computed tomography of the brain was performed which failed to reveal any evidence of cerebral infarction or hemorrhage. His past medical history was significant for hypertension, hypercholesterolemia and recurrent TIAs. One year prior to his current presentation, the patient had a transient episode of right-sided numbness and slight weakness on the right for two hours and six months ago the patient had reported an episode of left-sided weakness and numbness lasting for four hours for which he has been treated in the outside hospital. He denied regular alcohol drinking, tobacco or illicit drug use. His medication included Diovan, Prevacid, Crestor and Aspirin. After the second episode of TIA, Aspirin was subsequently switched to Plavix.

On initial presentation at our hospital, the patient had a blood pressure of 130/82 mmHg, heart rate of 80 beats per minute, respiratory rate of 14 per minute and oxygen saturation of 98% at room air. His body mass index (BMI) was 28. His lungs were clear to auscultation. Cardiac auscultation did not reveal any murmurs or gallops. Neurological examination was significant for left facial palsy as well as grade 4/5 weakness of the left upper and lower extremities. He was then admitted to the stroke unit of our hospital. Magnetic resonance imaging of the brain was performed which revealed acute infarction in the right thalamus. Even though all of the symptoms had completely recovered within 8 hours after admission, we had tried to identify the mechanism of stroke and recurrent TIAs in his case by various tests. Magnetic resonance imaging of the carotid and intracranial arteries were unremarkable. Ultrasonography of bilateral carotid arteries and transcranial doppler ultrasound (TCD) were reported to be normal. Trans-esophageal echocardiogram with bubble test was unremarkable for intracardiac mass, valvular defects and patent foramen ovale (PFO). There was mild left ventricular hypertrophy and left ventricular ejection fraction was 74%. Routine laboratory work up including of fasting blood sugar, protein C, protein S and antithrombin III were normal. Cholesterol was 140 and LDL was 60mg/dL.

At this point, we were aware that sleep apnea was one of the risk factors of stroke. Based on sleep history collected from the patient and his wife, there was no history of typical clinical features of OSA such as loud snoring, witnessed apneas or excessive daytime sleepiness. However, he mentioned occasional morning headaches which usually resolved within 2-3 hours after waking which could be one of the manifestations of sleep apnea. An ear nose throat examination revealed normal uvula and tonsils.

Friedman tongue position was grade II. A polysomnogram was done which revealed severe obstructive sleep apnea associated with severe oxygen desaturation to the nadir of 64%. The apnea-hypopnea index (AHI) was 70. Apnea was defined as an episode of > 90% reduction in amplitude of the nasal pressure signal lasting > 10 seconds. The hypopnea definition was > 50% reduction in amplitude for > 10 seconds associated with an arousal or > 3% oxygen desaturation. The total number of apneic and hypopneic episodes per hour of sleep represented the AHI. The diagnosis of sleep apnea was made when an AHI \geq 5. Sleep apnea severity was defined as mild: AHI 5 - <15, moderate: AHI 15 - < 30 and severe: AHI > 30. CPAP titration study was also performed which revealed that at the CPAP setting of 10 cmH₂O, the AHI was normalized and oxygen saturation was maintained at or above 95%. After using CPAP, the patient felt more refreshed in the morning and no longer had morning headache. Moreover, after the regular use of CPAP during sleep for 2 years, without any change in medication, he had no further episode of recurrent stroke or TIA.

Prevalence of sleep apnea following stroke

Several studies have reported that sleep apnea is common after stroke with the prevalence of 50-94% from the first day to 5 weeks after acute stroke or TIA.³⁻¹⁶ One study revealed the sleep apnea prevalence of 62% during the first night after cerebral infarction (62%).⁹ Recently, a meta-analysis of 29 studies of sleep apnea in stroke patients revealed that the frequency of sleep apnea (determined by apnea-hypopnea index: AHI > 5) was 72%.¹⁷ The prevalence was reported to be 61% among ischemic stroke, 71% among hemorrhagic stroke and 52% in TIA. However, this prevalence was possibly underestimated given that most studies excluded patients with severe medical conditions and who were unable to sign informed consent.

Furthermore, there were several important limitations to these studies, for example, patient selection (age, gender, BMI), the criteria diagnosis of SDB regarding the AHI cut-off, various types of polysomnogram (PSG) monitoring, and co-existing cardiovascular diseases.

OSA as a risk factor of stroke

Treatment of stroke include antiplatelet, thrombolysis, anticoagulants for patients with cardiac embolism, statin, blood pressure control, glucose control in patients with diabetes mellitus, carotid endarterectomy or stenting in patients with significant ipsilateral carotid stenosis along with lifestyle changes. Considering that despite aggressive treatment of stroke, up to 43% of stroke patients will have a progression of neurological deficit, with 87% occurring within the first 48 hours and the relative reduction in the risk of recurrent stroke is not greater than 10 to 30%, reflecting that these traditional risk factors do not fully

explain the occurrence of stroke.^{18,19} A better understanding of the risk factors for stroke is warranted in order to develop additional preventive strategies. In this sense, sleep apnea is being increasingly recognized as an important risk factor for stroke.

Initially, several articles focused on snoring. They demonstrated that snoring was an independent risk of stroke even when adjusted for confounding factors.²⁰⁻²⁵ There was a two-fold increase in relative risk for the combined outcome of stroke and ischemic heart disease in habitual snorers versus nonsnorers.²⁶ Later, when the AHI was used as a gold standard for OSA diagnosis, several large prospective studies had demonstrated that OSA increases the risk of stroke independently of known risk factors and the strength of the increase in the risk of stroke in OSA is similar to that of the traditional risk factors of stroke, such as hypertension, hypercholesterolemia and smoking.^{3,5,6,8}

The relationship between OSA and stroke is complex. There are shared risk factors that may lead to a high co-occurrence of these disorders. Additionally, OSA may be an independent risk factor for stroke, as it is thought to promote atherosclerosis due to repeated hypoxemia, and also may promote hypercoagulability through platelet activation. Conversely, OSA or CSA (central sleep apnea) can be a consequence after stroke, in other words, stroke may be a risk factor for OSA/CSA. There is evidence suggesting that OSA is likely to be a risk factor for stroke. First, several prospective studies demonstrated that sleep apnea had preceded stroke. Secondly, if sleep apnea were the result of stroke, the prevalence of sleep apnea in stroke would be expected to exceed the prevalence in TIA given that there is no lasting neurological damage in TIA. But recent studies showed that the prevalence of sleep apnea was the same in both stroke and TIA. This suggests that sleep apnea is likely to have preceded stroke. Thirdly, likewise, if sleep apnea were the consequence of stroke, it would likely improve following stroke, as do other stroke-related symptoms. Nonetheless, a study of patients with acute stroke demonstrated that sleep apnea persisted despite neurologic recovery, suggesting that it may have occurred before the development of stroke. And lastly, the lack of association between different stroke locations and prevalence of sleep apnea favor sleep apnea causing stroke given that if stroke is the cause of sleep apnea, sleep apnea may be more prevalent in brainstem stroke which can affect respiratory neurons.

As mentioned above, several large prospective studies have demonstrated that OSA (defined as $AHI \geq 5$) increases the risk of stroke independent of known risk factors. Marin et al. recruited more than 1,000 male OSA patients from sleep lab compared with simple snorers, and healthy men, matched for age and BMI. After a mean follow-up of 10.1 years, patients with untreated severe OSA had a higher incidence of cardiovascular events including stroke

than patients with mild to moderate OSA and OSA of any severity treated with CPAP, snorers, and healthy controls. And severe OSA had 3-fold increase in the risk of cardiovascular events and death from cardiovascular events including stroke compared to controls after adjusting for potential confounders; hypertension, diabetes, cardiovascular diseases, lipid disorders, smoking status.²⁷ Another prospective study stratified over 1,000 patients admitted to a sleep laboratory into groups with an $AHI \geq 5$ or < 5 and followed up over 6 years. OSA was found in 68% and was associated with a stepwise increased in the risk for stroke, TIA and death from any cause even when adjusted for confounding factors (such as age, gender, BMI, HT diabetes, AF, hyperlipidemia, and smoking habits). The risk of stroke or death in patients in the most severe quartile of sleep apnea ($AHI > 36$) was three times that in the controls and even the mild OSA increased the risk almost 2 times.²⁸ However, the major limitation of these 2 studies is that vascular risk was examined in patients who came to see doctors with some sleep complaints, and therefore their risk profile may not represent the general population. There are some population-based studies which overcame this limitation. The Wisconsin sleep cohort, which followed up 1,500 persons, initial age of 48 ± 8 years, over 18 years, found that SDB patients (defined as $AHI \geq 5$) had an increased risk for overall and cardiovascular mortality including stroke when compared with those without sleep apnea after adjustment for age, sex, BMI, smoking, and hypercholesterolemia.²⁹ Moreover, the mortality increased with the severity of sleep apnea in which severe sleep apnea ($AHI \geq 30$) have an increased risk for overall (OR 3.8) and cardiovascular mortality (OR 5.2) when compared with those without sleep apnea. Most studies focused on a middle-aged population, whereas it is well-known that the greatest incidence of stroke is found in older people. So Munoz recruited an elderly population aged from 70 to 100 years old, stroke-free at base line, and followed up for 6 years. The subjects with severe sleep apnea without CPAP treatment had an increased risk of first-ever ischemic stroke by 2.5 fold independent of known confounding factors.³⁰

Recently, the Sleep Heart Health Study which is an 8 year-follow-up of prospective data from a large community based cohort of 5,422 enrolled patients of middle-aged and older adults, which specifically addressed stroke as an endpoint rather than a composite endpoint as had been reported before, provided compelling evidence that in men, stroke risk increases across the mild to severe range of AHI.³¹ Moreover, men with moderate to severe OSA had an almost 3 fold increase risk of ischemic stroke. In the mild to moderate range ($AHI 5-25$), the risk of stroke increased 6% with every unit increase in AHI. Moreover the effect size for stroke for AHI levels in the upper quartile ($AHI > 20$) was comparable to that for a 10-year increase in age or atrial fibrillation. However, in women, the increased risk was observed at an $AHI > 25$.

Mechanisms of OSA leading to stroke

There are two major types of stroke; hemorrhagic stroke and ischemic stroke which accounts for 80% of all stroke. Determining the causes of stroke does influence choices for management. The causes of stroke include embolism from the heart, aorta, or paradoxical via PFO, small vessel occlusion, extracranially or intracranially large-artery atherosclerosis or coagulation abnormalities.

OSA may directly or indirectly increase the risk of stroke by increasing the odds of developing risk factors for stroke (for example hypertension and diabetes mellitus) or provokes cardiac arrhythmias. In clinical practice, OSA and hypertension (HTN) are tightly linked. HTN was observed in more than 50% of patients with OSA and conversely 25% of HTN patients had OSA.³²⁻³⁶ The prevalence of OSA was particularly higher in patients with drug-resistant HTN found in up to 83%.³⁷ OSA is an independent risk factor for hypertension and AHI is an independent predictor of HTN.^{34,36,38,39} Adults with AHI of 15 or more had three times the risk of developing HTN in the next 4 yrs. The risk increased with a higher AHI. Moreover, even mild OSA increased risk of HTN. Among OSA patients, the risk of developing diabetes was increased by 5.5-fold and there was some evidence that OSA contributes to insulin resistance, by the effect of tumor necrosis factor alpha.²⁹ The Sleep Heart Health Study has also shown that moderate to severe OSA increases the risk of atrial fibrillation (AF) by fourfold and there was a 17-fold increase in odds of an arrhythmia, including AF and non-sustained ventricular tachycardia, occurring after apnea/hypopnea than an arrhythmia occurring after normal breathing during sleep.⁴⁰

The main acute consequences of OSA linking to stroke are intermittent hypoxias, sympathetic activation with blood pressure swings, cardiac arrhythmias, and cerebral blood flow (CBF) fluctuations. During the apnea event there is significant reduction in blood pressure, pulse, cardiac output and CBF which increase suddenly at apnea termination.^{41,42} Large fluctuations in CBF velocity in OSA could result in repetitive episodes of cerebrovascular shearing stress which likely contributes to cerebral vascular endothelial dysfunction. One study, using Transcranial Doppler Ultrasound (TCD) in severe sleep apnea patients compared with age-matched control during sleep and on awakening adjusted for the major physiologic variables which impact on CBF such as age, hematocrit and PCO₂, found that blood flow velocities, which reflects CBF, of the patient with sleep apnea were reduced at all times during sleep as well as during wakefulness when compared to control subjects. This reflected an impaired cerebral autoregulation which may result in the progression over time of the infarct core at the expense of the irreversible damage of the ischemic penumbra.⁴³ When the cerebral circulation is already compromised, such as with patients with carotid stenosis, a further reduction in CBF

during an apnea event may raise the risk of stroke especially in regions with poor hemodynamic reserve particularly border-zone areas between the junction of the distal fields of two arterial systems and terminal arterial territories.

Chronic intermittent hypoxia resulting from OSA has been shown to promote generalized atherosclerosis, hypertension and glucose intolerance through systemic inflammation, oxidative stress and impaired endothelial function. Several inflammatory markers such as C-reactive protein, interleukin-6 and soluble E-selectin were found elevated in OSA.⁴⁴ In animal models, intermittent hypoxia also has been shown to induce the hepatic enzyme leading to dyslipidemia and atherosclerotic lesions.⁴⁵ One animal model even suggested that mechanical energy transmission to the carotid artery from snoring could also be involved in intimal injury leading to atherosclerosis or even initiate plaque rupture.⁴⁶

Another possible mechanism for increased risk of stroke among OSA patients is linked to Patent Foramen Ovale (PFO). PFO reopening or increased shunt while straining can cause paradoxical embolization leading to ischemic stroke. The prevalence of PFO by TCD has been shown to be 2 times higher in OSA patients than controls (27 vs. 15%) suggesting that the shunt may be open from right to left during brief Valsalva effect at the termination of sleep apneas.⁴⁷

Types of sleep apneas in acute stroke patients

The most common form of sleep apnea in stroke patients is OSA. However, central sleep apnea (CSA) and Cheyne-Stokes breathing (CSB) may be present in up to 7%.¹⁷ The contribution of brain damage to the pathophysiology of OSA and CSA in stroke remains poorly understood. In one study, from the acute (within 72 hours) to the subacute (at 3 months) phase of stroke, sleep apnea tended to improve, but this was due to an improvement in central apneas not in OSA in which more than half of patients still exhibited an AHI > 10.⁶ These results suggested that OSA likely exists prior to the stroke; on the other hand CSA or CSB is a consequence of stroke. The presence of bilateral strokes, heart failure, and profound disturbances of consciousness, traditionally described in stroke patients with CSB, is not always necessary.⁴⁸

OSA and outcome of stroke

Previous studies have reported that almost half of stroke patients will have a neurological progression. This typically occurs early after stroke onset, with almost 90% occurring within the first 48 hours despite standard treatment.^{49,50} This may, in part, be due to uncorrected factors including sleep apnea which could contribute to poor stroke outcome and also be a risk factor for subsequent cardiovascular diseases including recurrent stroke.⁵¹⁻⁵⁴

Short term outcomes of stroke with sleep apnea includes an early neurological worsening, more depression, delirium and longer hospitalization.^{55,56} Long term outcomes include a poorer clinical outcome of stroke and a higher mortality rate.^{3,52-54} One study even showed that the mortality risk increased 5% for each additional unit of AHI.⁵⁴

Significance of treating OSA post-stroke

Treatment strategies of OSA in stroke patients include prevention, early recognition and treatment of aspiration pneumonia along with avoidance of alcohol and sedative-hypnotic drugs, which may all negatively affect breathing during sleep. Side sleeping position can also improve OSA.⁵⁷ Continuous positive airway pressure (CPAP) should be prescribed for patients with OSA and oxygen/adaptive servo-ventilator (ASV) in patients with CSA and CSB.

Treatment of sleep apnea in acute stroke patients is important. CPAP has been shown to improve stroke recovery, subjective well-being and mood in stroke patients.⁵⁵ Based on the blood pressure-lowering effects of CPAP, treatment of sleep apnea may lead to a stroke risk reduction of 20%.⁵⁸ Furthermore, CPAP reduced cardiovascular events after stroke and reduced 5-year mortality from stroke and all-cause mortality in severe sleep apnea (defined as an AHI > 20 in this study) compared to patients intolerant to CPAP.^{59,60} There was evidence that CPAP decreased the level of surrogate markers of vascular diseases, reversed the inflammatory changes and endothelial dysfunction.⁶¹⁻⁶³ Moreover, the CPAP treatment decreased carotid intima-media thickness (IMT), a validated marker of atherosclerosis.⁶⁴

Predictors of OSA in stroke

Given that sleep apnea has been identified as a risk factor of stroke (JNC7) and contributes to poor stroke outcome, exploring the predictors of sleep apnea in stroke is clinically compelling. Among several studies,⁴⁻⁹ apart from some traditional OSA risk factors (high BMI and neck circumference), nothing can predict stroke patients likely to have sleep apnea. Most patients did not have the typical clinical features of OSA (excessive daytime sleepiness, snoring, nocturnal choking or un-refreshed sleep). Thus, approximately 30% of stroke patients with severe OSA would be missed if only clinical history of typical symptoms of sleep apnea alone were used for screening. Moreover, sleep apnea was not related to infarct volume or neurologic severity. A recent meta-analysis

of 29 studies of stroke and sleep apnea¹⁷ revealed that a significant number of patients will be missed if sleep history alone is used for screening given that > 25% of sleep apnea patients did not snore while > 50% of those without sleep apnea did snore. Sleep apnea was more common in male patients and there was a trend toward increasing frequency of AHI > 10 with increasing age but not with increasing BMI. Moreover, the frequency of sleep apnea was not significantly related to any stroke characteristics including stroke types (61% in ischemic stroke, 71% in hemorrhagic stroke, 52% in TIA), locations (83% in brain stem stroke and 73% in hemispheric stroke) or timing of sleep study after stroke onset (within 1 week, 1-4 weeks, > 4 weeks). Sleep apnea was more common in those with recurrent strokes and stroke of unknown etiology. The reason why the patients with an unknown cause of stroke had increased rate of sleep apnea could be that sleep apnea may be responsible for the cause in some of these patients. One study showed the high prevalence of nocturia in OSA and demonstrated that nocturia was an independent predictor for severe OSA in ischemic stroke.⁶⁵ This association between OSA and nocturia has further been confirmed by the significant improvement of nocturia after CPAP treatment.⁶⁶

Conclusions

In conclusion, the prevalence of SDB, particularly OSA, is very high in patients with acute stroke. OSA appears to be an independent risk factor for stroke, and, conversely, stroke is a risk factor for OSA, CSA and CSB. Untreated OSA contributes to worse outcomes of stroke and is also a risk factor for coronary artery disease, arrhythmia and recurrent stroke. Patients with acute stroke with co-morbid OSA should certainly be treated with CPAP which can improve recovery from stroke and decrease cardiovascular morbidity & mortality.

At the present time, there are no guidelines whether stroke patients should be routinely screened for the presence of OSA. Thus, OSA is still under-diagnosed among stroke patients. This review supports that OSA should be viewed as an important modifiable risk factor for stroke and the systematic screening of OSA in all stroke patients is needed given its high prevalence, its implications for acute treatment and rehabilitation as well as prevention of further cardiovascular diseases and recurrent stroke. Further well-designed prospective studies are needed to determine the clinical effect of CPAP on stroke and cardiovascular outcome.

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Endobronchial Ultrasound to Evaluate Downstaging of Lung Cancer After Combined Chemotherapy and Radiation Treatment



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Chemotherapy and radiotherapy, separately or sequentially, are established protocols in the management of lung malignancy. However, as early as 1999 a study in Osaka, Japan concluded that the concurrent approach yielded a significantly increased response rate and enhanced median survival duration when compared with the sequential approach [as applied to selected patients with unresectable stage III non-small cell lung cancer (NSCLC)].¹

Several other studies and clinical trials that were subsequently published validated the efficacy of concomitant chemotherapy and radiotherapy in the management of NSCLC.²

While previous studies did indeed advance novel treatment methods for NSCLC, the team in Bangkok Hospital found it curious that even in a recent study published in April 2012,³ the most advanced staging evaluation methods used were mediastinoscopy or mediastinotomy (following bronchoscopy, bone scan, computed tomography (CT) scan of the chest) to acquire biopsy samples from lymph nodes. A randomized trial in 2010 of two-hundred and forty one patients revealed that a staging strategy combining endosonography and surgical staging showed a higher sensitivity rate for mediastinal nodal metastases when compared to surgical staging alone among patients with (suspected) NSCLC.⁴ A minimally-invasive procedure, endobronchial ultrasonography is currently considered the gold standard in the evaluation of mediastinal lymph nodes and lung lesions along with its other usage in the clinical set-up.

We designed a study that will explore the efficacy of concomitant use of chemotherapy and radiotherapy by using endobronchial ultrasound (a low-risk method), as an evaluation tool for downstaging of lung cancer patients not limited to NSCLC.

Eligibility Criteria

The patients who were selected for this study were histologically or cytologically confirmed as newly diagnosed and untreated for lung cancer. They were aged 18 and above, without intake of aspirin or any blood thinners 7 days prior to procedure and signed a written consent for treatment in the hospital and for receiving the EBUS procedure in the operating room.

Exclusion Criteria

Patients who were excluded were pregnant or nursing, or fertile patients who aren't using effective contraception; had previous thoracic radiotherapy, chemotherapy, immunotherapy or biologic therapy for lung cancer; or blood thinner intake 7 days prior to procedure.

Endosonography

A combination of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endobronchial ultrasound with guide sheath (EBUS-GS) was used to obtain sample specimens for biopsy. During endobronchial ultrasound (EBUS) procedures, the lungs and mediastinum were visualized for possible pathology or lesions through a flexible scope. Ultrasonic waves enabled the operator to see structures through the wall of the airway. Samples of the lymph nodes and any masses were taken as necessary. Biopsy specimens underwent On-site pathology/Rapid on-site evaluation (ROSE). The remaining tissue samples were sent to the laboratory for further cytological and immunohistochemistry testing. Tumor gene mutation deficiencies were also investigated via Anaplastic lymphoma kinase (ALK) and the epidermal growth factor receptor (EGFR) tests.

Chemotherapy and Radiotherapy

The patients with definite diagnosis of lung cancer were referred to oncologists who prescribed patient-specific chemotherapy and radiotherapy drug combination.

Case Report #1

A 72-year-old male patient was previously being treated for chronic obstructive pulmonary disease (COPD) when chest x-ray revealed left lower lung mass. Carcinoembryonic antigen (CEA) was 108.90ng/ml and positron emission tomography and computed tomography (PET/CT) Scan showed there was a 3.5x4.0cm speculated mass in the superior segment of the left lower lobe with radiating strands to the hilum and the fissure. Another tiny subpleural nodule was present at the posterior gutter of the left lower lobe. There are a few 0.6-0.9cm nodes at the interlobar station of the left hilum. There was another 1.0cm pleural based nodule at the posterior segment of the right upper lobe with retraction of the fissure. No pleural effusion was seen. There are a few 0.5-0.7cm nodes in the lower paratracheal and AP window regions. The finding of positron emission tomography (PET) scan in the thorax was a left lower lobe lung mass showing markedly increased the foundations of digital Games (FDG) uptake with maximum standardized uptake value (SUV) of 6.1. Hypermetabolic hilar node was also noted with SUV of Faint metabolic activity of nodule in right upper lobe and right hilar region was noted with SUV of 0.8 and 1.1 respectively. Bronchoscopy and biopsy were done which revealed small sheets of tumor cells found with highly pleomorphic enlarged hyperchromatic nuclei, occasional small nucleoli and abundant vacuolated cytoplasm. He was then diagnosed of non-small cell carcinoma.

The patient underwent sessions of radiation and chemotherapy treatment. He was able to tolerate the medications and therapy until 6 months later, when he

developed left lung atelectasis. His chest x-ray showed retrocardiac left lower lobe atelectasis appearing slightly increased. Small amounts of bilateral pleural effusion, more on the left side were noted. The CT scan of chest revealed right pneumothorax, measuring about 0.7 cm in thickness. Pulmonary infiltration, more on the superior segment of left lower lobe, where atelectasis was increased. Fluid in left bronchi was observed.

Fiberoptic bronchoscopy was done and revealed endobronchial obstruction of the medial and lateral segment of left lower lobe. A tumor at the medial segment was completely removed but the lateral segment tumor was hard as stone. Biopsy was done instead and bleeding was managed by electrocautery. Cytopathology report was acute and chronic bronchitis with mild squamous metaplasia. Necrotic tissue with fibrinopurulent exudate was also found. Microscopic investigation showed that two pieces of necrotic tissue, with fibrinous material and areas of acute inflammation and one cluster of a few tiny fragments of bronchial mucosa showing mild acute and chronic inflammation with areas of mild squamous metaplasia. No epithelioid granuloma or malignancies were observed.

He was then treated for atelectasis and bronchitis. The cytopathology results from bronchoscopy confirmed no recurrence of lung cancer.

Case Report # 2

A 60-year-old male, was diagnosed with limited small cell lung cancer post chemo, thoracic radiation therapy and prophylactic whole brain radiation therapy (WBRT). His last dose was given 3 months prior to consultation.

Three months prior to consult, the patient complained of dysphagia, body weight loss of 8 kilograms (kg) for the past 2 months, chest discomfort that radiates to the abdomen and voice hoarseness.

Physical examination revealed that he appeared thin, had diminished breath sounds upon auscultation, no coughing, no sputum, and had no fever episodes. PET/CT scan revealed there is a 3.0x3.5cm speculated mass with scattered punctuate calcifications at the posterior segment of the right upper lobe with extension to the hilum, broad attachment to the fissure and volume loss of the right hemithorax (Figure 1). There are scattered foci of reticulonodular opacities in the upper lobe, superior segment right lower lobe and the right middle lobe, possibly representing underlying or superimposed infection. A few nonspecific tiny subpleural nodules were also found in both lungs. There was no pleural effusion. A 0.7cm right hilar node and 0.6cm subcarinal and right lower paratracheal nodes were observed. PET scan revealed speculated mass in the posterior segment of right upper lung and showed faint uptake of the FDG with SUV of 1.3. Opacities in right upper and right lower lung also showed minimally increased

FDG uptake with SUV of 1.6. The metabolic activity of each hilum or mediastinum was not increased. EBUS-GS and EBUS-TBNA were done to investigate if there was evidence of recurrence of lung cancer.

Brushing slide specimen revealed therapy-induced atypia and mediastinal lymph node was negative for granuloma and malignancy. Fluid and brush showed benign reactive bronchial cells along with some foamy macrophages, lymphocytes and neutrophils. Some atypical cells were seen with enlarged cells, vacuolated cytoplasm, multinucleated nuclei and prominent nucleoli. There was no evidence of granuloma or malignancy. Smears contain mature lymphocytes which have small dark nuclei and scanty cytoplasm. The polymorphous population of lymphocytes was also seen. The background shows numerous red cells and benign bronchial epithelial cells. There was no evidence of tumor or granuloma. Bronchial biopsy revealed hyalinized fibrosis, no evidence of granuloma or malignancy.

With the provided results, the tumor panel concluded at that moment, there was no evidence of recurrence of small cell lung cancer.

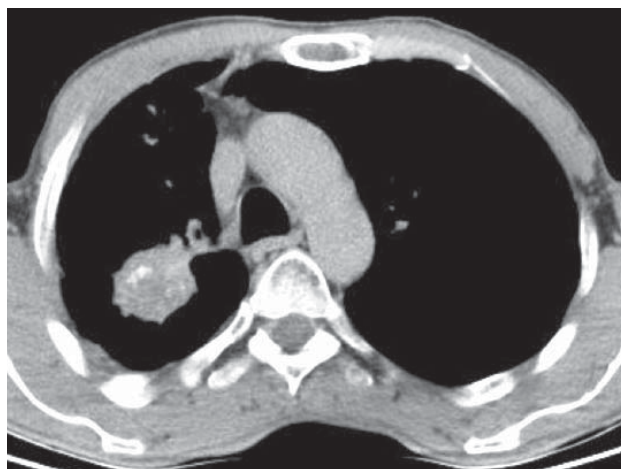


Figure 1: A picture of the CT scan result as described in case study # 2

Case Report # 3

A 50-year-old male caucasian patient was diagnosed with adenocarcinoma stage II. He was a former smoker for 6 years and has family history of lung cancer.

Three months prior to consultation, he developed fever, cough, anorexia, body weight loss of 13kg and pain in with his bones. He was then diagnosed with giardiasis and gastritis but was subsequently treated. He regained his appetite but his cough still persisted. One month prior to consultation, he had had several episodes of febrile (temperature 39.8°C), sweating, and cough. He went for a

medical consultation in Chiang Mai, Thailand where he was tested for tuberculosis which came back negative. CT scan of chest revealed mass at the right upper lobe with mediastinal node enlargement.

Initial assessment revealed diminished lung breath sounds at right upper lobe lung. PET/CT scan was done and revealed an irregularly outlined soft tissue mass at the posterior segment of the right upper lobe with a broad attachment to the fissure. The mass measures about 8.2x4.0 cm. There was central necrosis at the main component of the mass and cavitation at the peripheral aspect, and at the medial extension behind the right main bronchus. There was no abnormality in the rest of the lungs or pleural effusion. A 0.9cm node was seen at the precarinal space and a few 0.5-0.7cm nodes in the right lower paratracheal space. PET scan findings of density in the right upper lung showed increased FDG uptake with SUV max of 5.3. The cavitating postbronchial component showed a hypermetabolic activity with SUV of 1.8. CEA was 1.70ng/mL and Quantiferon TB result was negative.

EBUS-GS and EBUS-TBNA were advised for further assessment and evaluation. The onsite pathologist revealed that the specimen obtained from the upper lobe mass revealed adenocarcinoma. However, the two slides from right paratracheal nodes were negative for malignancy. Post operatively, the patient did not manifest pneumothorax, bleeding, and infection.

The official cytopathology report revealed that the first smear contained mature lymphocytes which have small dark nuclei and scanty cytoplasm. The polymorphous population of lymphocytes was also seen. The background showed numerous benign bronchial epithelial cells. The second, showed more bloody background. There is no evidence of tumor or granuloma. The second smear contains some clusters of atypical cells which have enlarged vesicular nuclei, prominent nucleoli and foamy cytoplasm. The background showed benign bronchial epithelium and numerous neutrophils. Bronchial biopsy revealed a section of a small piece infiltrated of malignant glandular epithelium with nuclear enlargement, hyperchromicity, small nucleoli and moderate amount of pink foamy cytoplasm. The larger piece showed only benign bronchial mucosa with numerous neutrophils and fibrin material. Tumor mutation from EGFR and ALK results were both negative.

In cooperation with Dr. Lodi, the patient was treated under two protocols. First, was the combination of Taxotere 10mg and Carboplatin 50mg alternating every other week with the second protocol was Cisplatin 10mg, Etoposide 10mg and Vinorelbine 10mg.

After the treatment, the patient decided to go back to his home country, underwent lobectomy which revealed no presence of malignancy in lung tissue.

Discussion

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a mediastinal staging modality that has been developed in the last decade. High sensitivities and specificities have been reported in a large number of studies.⁴

The procedure is well tolerated, safe and has a high diagnostic accuracy (89-95%) for the analysis of mediastinal lymph node (LN). So far, no complications of EUS-FNA in the analysis of mediastinal LN have been reported. The advantages of this technique are multiple: tissue samples are obtained (in contrast to the imaging technique of CT) and the procedure itself is minimally invasive, is performed in an out-patient setting and can be repeated a number of times without technical difficulties (in contrast to mediastinoscopy).⁵

A similar study published in 2008 investigated the accuracy and sensitivity of EBUS-TBNA for restaging the mediastinum after induction chemotherapy in patients with NSCLC. The team from the University of Heidelberg concluded that despite EBUS-TBNA being a sensitive, specific, accurate, and minimally invasive test for mediastinal restaging of patients with NSCLC, tumor-negative findings should still be confirmed by surgical staging before thoracotomy.⁶

A study in Japan, on the other hand, stated that for mediastinal staging in lung cancer, the diagnostic yield of EBUS-TBNA is comparable to surgical staging in patients with enlarged lymph nodes.⁷

The above studies are important contributions to the development of EBUS. However, their research does not include analysis and evaluation of the downstaging of lung cancer after combined chemotherapy and radiation treatment. To our knowledge, this study in Bangkok Hospital is the pioneering report with which combined EBUS-TBNA and EBUS-GS has been used as an evaluation tool to measure downstaging of lung cancer after combined chemotherapy and radiation treatment.

Conclusion

Endobronchial Ultrasonography (EBUS) is an effective tool in evaluating downstaging in patients with lung cancer after combined chemotherapy and radiotherapy.

EBUS-GS provides a pathway to peripheral pulmonary lesions, enabling the operator to obtain short-axis bronchial views. It is a useful method for collecting samples from peripheral pulmonary lesions, including those which are too small to be visualized under fluoroscopy. The use of EBUS-TBNA is known for increasing diagnostic yield in obtaining a specimen for biopsy. It can be used for collecting both cellular and tissue specimen collection. With this capability, administering these procedures in tandem can effectively diagnose lung cancer as well as other diseases such as sarcoidosis and malignant lymphoma. The two procedures, complementing each other in many ways, are both safe for the patient: minimally invasive, relatively low risk and avoiding possible unnecessary thoracotomies.⁸

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Fatal Penetrating Aortic Ulcer and Aorto-iliac Occlusion Mimics Acute Coronary Syndrome: A Case Report and Literature Review



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A case of penetrating aortic ulcer (PAU) with an aorto-iliac occlusion from aortic dissection (AD) is a rare condition. The patient's condition can develop swiftly and deteriorate rapidly leading to multiple organ failure causing metabolic acidosis and delayed diagnosis.

Case Report

A 56-year-old man, a cigarette smoker, with a known history of hypertension, gout and kidney disease, presented with cardiac arrest. According to a friend, he had been receiving medication from a private clinic and had been experiencing exertion dyspnea for several months. On admission day, he complained of chest pains when lying down, breathing was hard and he fell unconscious. It took about 30 minutes to transfer the patient, and he stopped breathing on arrival at the hospital. The initial electrocardiography (ECG) showed asystole and cardiopulmonary resuscitation was promptly started. After two doses of intravenous adrenaline, the sinus rhythm returned and BP was 150/90 mmHg. A physical examination showed an overweight man with a coma score of E1M4VT. The pupils were 3mm dilated and sluggishly reacted to light and were slightly deviated to the left. A computed tomography (CT) of the brain showed generalized brain atrophy, and a probable small lacuna infarct. In addition, non-obstructive atherosclerotic changes of intra-cranial arteries were noted with no explainable causes of coma. He had Kussmaul breathing with rhonchi, crepitation in both lungs, and a bronchodilator and furosemide were given. All extremities were cold and femoral pulses were not palpable. The chest film revealed a cardiomegaly with bilateral pulmonary edema. The arterial blood gas showed metabolic acidosis (pH 7.32, pCO₂ 33, pO₂ 85 mmHg, HCO₃ 17 mmol/L) and sodium bicarbonate was given. The post-resuscitation ECG revealed a sinus rhythm with a complete right bundle branch block (RBBB), ST elevation in the aVR, J point ST depression in V2-4 and a QT segment of 400 msec (see Figure 1). The echocardiogram showed hypokinesia of the mid-distal septum, with impaired left ventricular systolic function and an ejection fraction of 0.35. The cardiac TnT was elevated at 45ng/L. These findings suggested acute coronary syndrome from the proximal left anterior descending coronary artery, so the patient was referred for an emergent coronary angiography. Informed consent was obtained by relatives.

It was found that both common iliac arteries were occluded, so a coronary angiogram was performed via the rightbrachial artery. The left coronary angiogram showed an unobstructed left main trunk, left anterior descending (LAD) artery, circumflex (Cx) artery which supplied the postero-descending artery (PDA), (see Figure 2B).

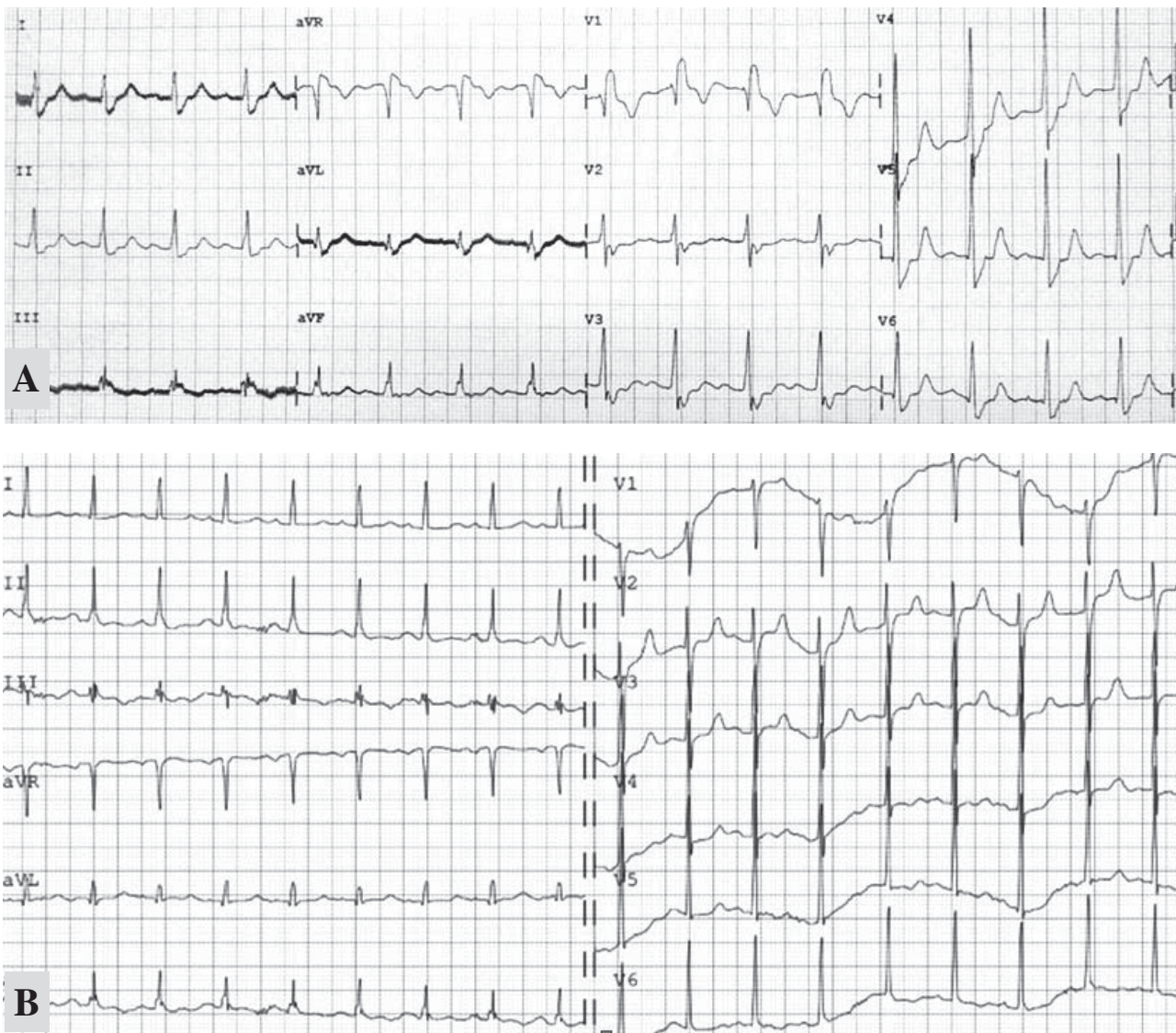


Figure 1A: Post-arrest ECG showed a sinus rhythm rate of 100/min, complete RBBB, J point ST depression in V2-4, ST elevation in leads aVR and lead III.
1B: the RBBB pattern disappeared on the following day.

We could not engage the non-dominant right coronary artery (RCA). An aortogram was performed by hand injection and revealed a totally occluded abdominal aorta below the renal arteries (Figure 2C). Both renal arteries were unobstructed. The aortic CAT scan showed an unobstructed RCA, multiple penetrating ulcers (PAU) from the aortic arch to the abdominal aorta with an intramural hematoma (Figure 3A-C, 4A). There were large intraluminal thrombi obstructing the infra-renal aorta (Figure 3D, 4B) and the inferior mesenteric and bilateral common iliac arteries. There was minor collateral supply to the right common, external, internal iliac arteries and the distal part of the left external iliac artery.

Heparin, anti-platelet medication and hemodialysis were started but the patient remained in a coma with severe metabolic acidosis. The blood ketone was negative and the serum lactate was rising (Table 1). The RBBB ECG pattern disappeared the next day (see Figure 1B). After 24 hours, his condition deteriorated and bluish feet were noted (Figure 5). Vascular surgeons were consulted and it was concluded that it was too late to save him. The serum creatinine rose from 2.39 to 3.78mg/dl without urine output. The liver enzyme and creatinine phosphate were elevated (Table 1). The patient passed away 48 hours after admission from multi-organ failure and uncorrected metabolic acidosis. An autopsy was not authorized by family members.

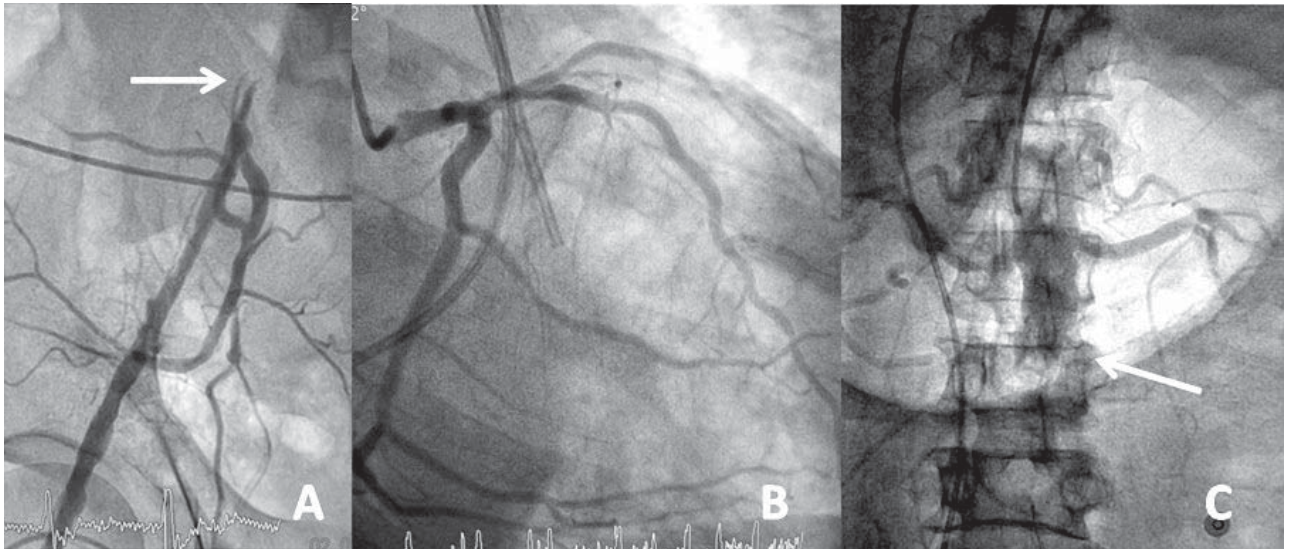


Figure 2: An occluded iliac artery (A), non-obstructive left dominant coronary angiogram (B) and occluded infra-renal aorta (C).

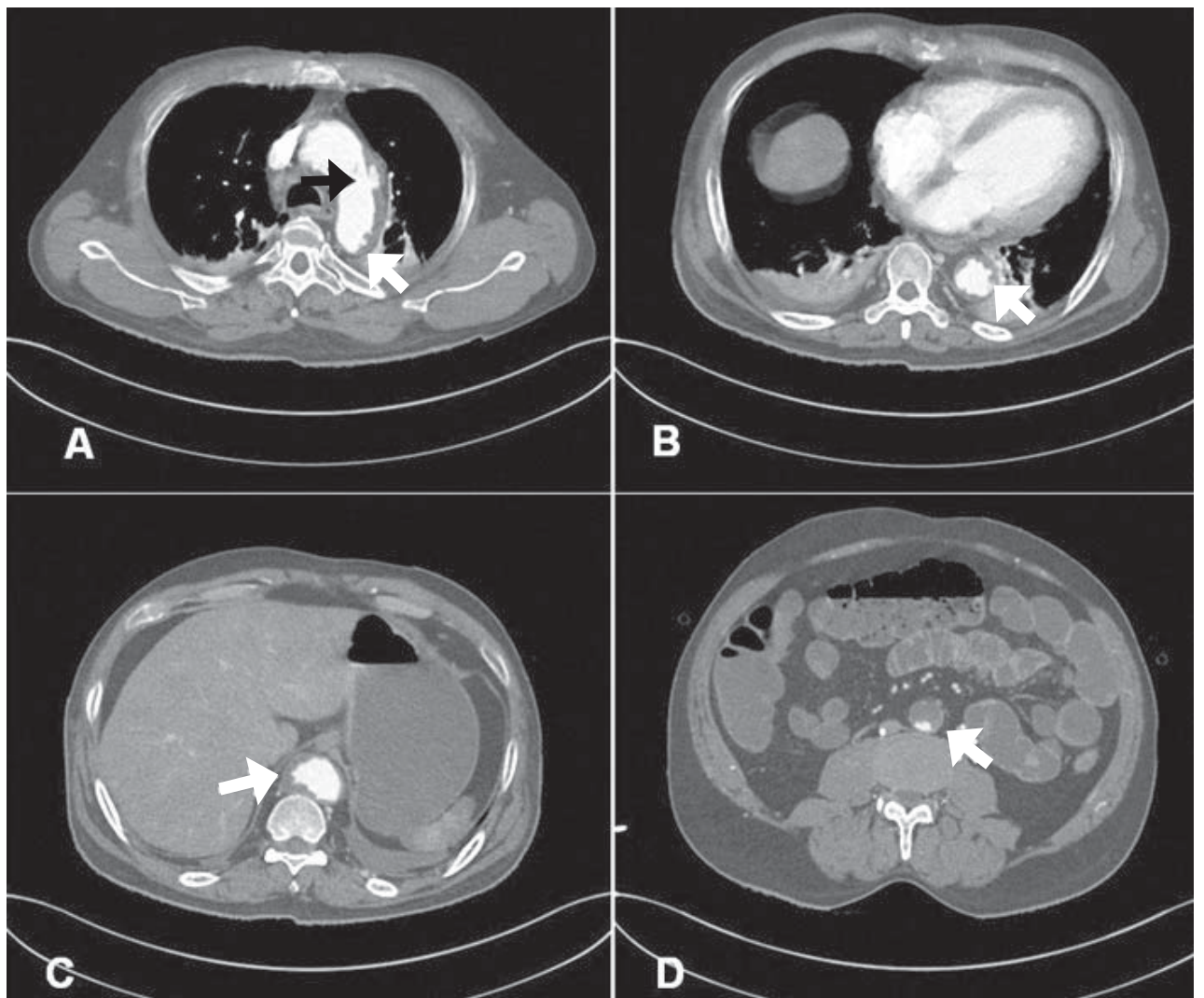


Figure 3: CT shows a large penetrating aortic ulcer (PAU) at the lateral wall of the aortic arch (A, black arrow), multiple small PAU along the abdominal aorta with intramural and mural thrombus (white arrow, A-C). The inferior renal abdominal aorta is occluded with thrombus. Bilateral pleural effusion and atelectasis are also noted (Figure 3A-B).

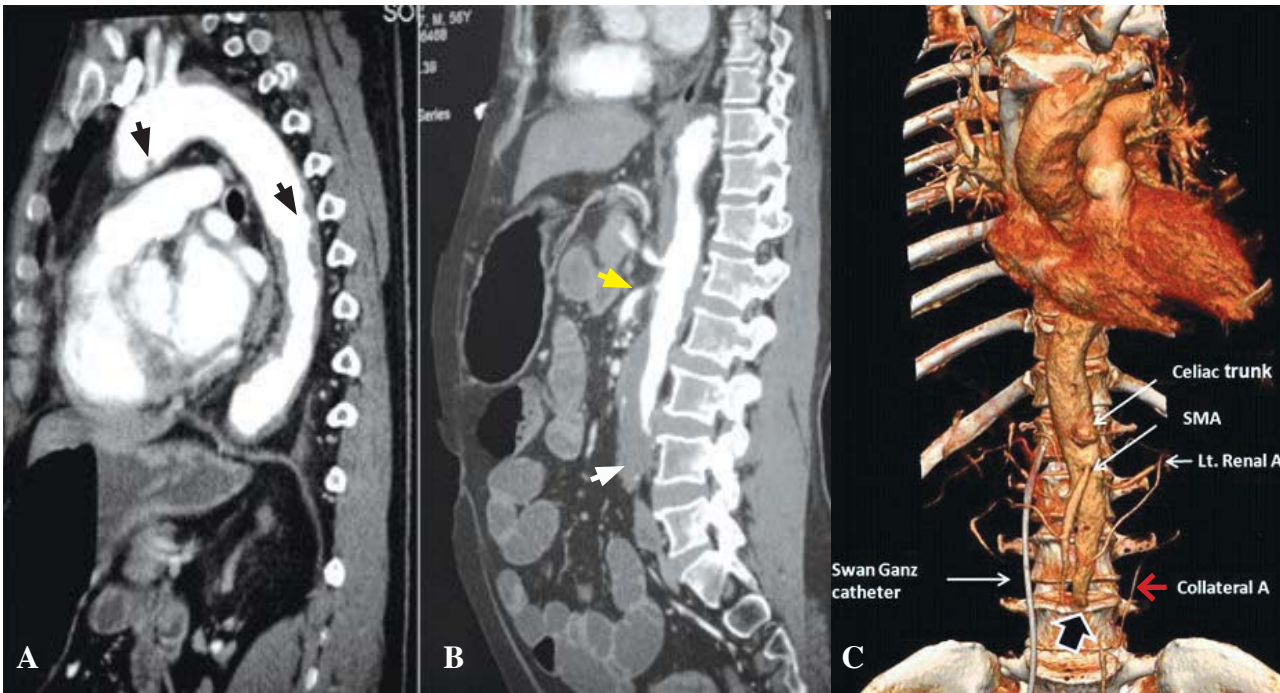


Figure 4: The sagittal CT image shows multiple aortic ulcers (black arrow, A) extending from the arch along the descending aorta and mural thrombi occluded distal abdominal aorta (white arrow, B). The inferior mesentery is occluded. The celiac artery is patent; the superior mesenteric artery is marked as narrow at its origin (yellow arrow, B). The volume-rendered CT image (4C) shows an abdominal aortic occlusion (black arrow) with minimal collateral circulation from the retroperitoneal artery (red arrow, C).



Figure 5: After 24 hours, the patient presented bluish feet caused by vascular occlusion.

**Fatal Penetrating Aortic Ulcer and Aorto-iliac Occlusion Mimics
Acute Coronary Syndrome: A Case Report and Literature Review**

Table 1: Laboratory tests from day 1 to day 3.

Laboratory test	30/12/2013	31/12/2013	01/01/2014
WBC (cell/mm ³)	16,940	17,280	16,260
Neutrophils, Lymphocytes, Monocytes (%)	38, 51, 6	82, 6, 3	80, 7, 3
Hemoglobin (gm/dl)	7.4	9.9	9.6
MCV (fl)	63.4	64	63.5
Platelet (cell/ul)	392,000	318,000	337,000
pH	7.32	7.44	-
pCO ₂	33	21	-
pO ₂	85	171	-
HCO ₃	17	14.3	-
BE			-
O ₂ saturation (%)	95%	100%	-
Glucose (mg/dl)	387	-	108
BUN (mg/dl)	22	-	55
Creatinine (mg/dl)	2.39	-	3.78
GFR (ml/min)	28.3	-	16.6
Sodium (mM/L)	141	-	140
Potassium (mM/L)	4.8	-	5.8
Chloride (mM/L)	107	-	102
Carbonate (mM/L)	8	-	13
Magnesium (mM/L)	2.58	-	2.0
Serum Lactate (0.5-2.2mmol/L)	-	-	5.1
Hs-Troponin T (<14 ng/L)	45.3	-	-
Prothrombin time	13.5	-	239
INR	1.19	-	16.9
PTT	47.1	34.8	37.7
Albumin/Globulin (g/dl)	-	-	2.9/2.8
Direct/total bilirubin (mg/dl)	-	-	0.17/0.29
SGOT (U/L)	-	-	685
SGPT (U/L)	-	-	367
CPK (U/L)	-	-	12,727
CPK-MB (ng/ml)	-	-	204

Discussion

Acute aortic syndrome

Acute aortic syndrome is a highly fatal aortic disease comprising aortic dissection (AD), intramural hematoma (IMH) and penetrating aortic ulcer (PAU¹). AD resulted from a tear in the intima which resulted in blood entering the media, creating a false lumen and mal-perfusion. Unlike intramural thrombus, IMH is located inside the intima and is caused either by spontaneous bleeding of the vasa vasorum in the aortic media or by a PAU.¹ PAU is an ulcerated atheromatous plaque that extends from the intima into the aortic media². The pulsatile blood flow in the wall then creates a medial hemorrhage which causes IMH.^{1,3} The propagating IMH along the aortic media further

weakens the aortic wall leading to AD⁴, an aortic rupture¹ or an inwardly disrupted intima causing a communicating AD.⁵

Causes of cardiac arrest

Our patient experienced chest pain before collapsing. The cause of asystolic arrest remains unclear. The potassium concentration was normal and there was no significant coronary artery stenosis, no pericardial tamponade and no other explainable cerebral cause identified from the brain scan. A subsequent ECG showed that the RBBB pattern had disappeared (see Figure 1B). His microcytic anemia was caused by a combination of iron deficiency and hemoglobin E trait. There was no evidence of blood loss during admission and the serial hematocrit was stable.

His main CT findings were a large PAU in the lateral wall of the aortic arch (Figure 3A), multiple small PAUs along the descending and abdominal aorta (Figure 3B-C) with diffuse IMH and intramural thrombus occluding the infra-renal abdominal aorta, the inferior mesenteric and the bilateral common iliac arteries. Minor collateral supply (Figure 4C) suggested an acute thrombosis on top of chronic atheromatous disease at a relatively young age. Although PAU could be an incidental finding, in the Mayo clinic study, most PAU cases (75%) were symptomatic, mostly from back pain, and 30% had pleural effusion.⁶ The majority of cases in the Mayo clinic study had a history of hypertension (92%) and tobacco smoking (77%).⁶ Our case also shared these characteristics. Although the CT of chest showed a small pleural effusion and atelectasis (Figure 3B), these findings could also have occurred after cardiac arrest. On very rare occasions, PAU patients present with hemoptysis from an oozing hematoma located outside the aorta.⁷ It is known that PAU and IMH are not benign conditions. Both of these conditions are predominantly located in the descending aorta, associated with hypertension and are a potential cause of AD.^{1,8-10} Evangelista and colleagues followed 68 IMH cases for 45 months and found that most IMH cases (54%) progressively worsened to become either true (30%) or pseudo-aortic aneurysms (24%). Classic AD and spontaneous regression were observed in 8% and 34% of cases respectively.¹¹ Although our case had several features for developing AD, i.e. long-standing hypertension, smoking, abrupt pain, pulse deficiency and kidney failure, we could not find definitive evidence of either AD or any aneurysm in the multi-plan CT images.

Metabolic acidosis and aorto-iliac occlusion

Most successfully resuscitated cardiac arrest victims do not have persisting metabolic acidosis after spontaneous circulation has been restored. In this case, severe metabolic acidosis was detected throughout and the blood ketone was negative. Table 1 shows increasing levels of serum lactate, liver and muscle enzymes. After 24 hours, ischemic feet became apparent (Figure 5). In 1965, Johnstone and colleagues reported metabolic changes after infra-renal aorto-iliac clamping in six patients who had received reconstructive surgery for aorto-iliac disease. There was a profound fall in oxygen tension in lower limbs causing anaerobic production of lactate and metabolic acidosis.¹² In 1993, Whalley and colleagues reported the same findings during the application and removal of aortic cross clamps of the infra-renal aorta in 20 patients who had undergone aneurysmal repairs or procedures to reconstruct

occlusive arteries.¹³ It was noted that the mixed venous blood lactate concentration positively correlated with the time of aortic cross clamp ($r = 0.717$, $p = 0.0297$) emphasizing the role of collateral circulation in the development of metabolic acidosis during aortic surgery. Therefore, it is quite possible that the hypo-perfusion stage from prolonged aorto-iliac occlusion caused an over-production of lactic acid and severe metabolic acidosis in our case. In addition, Yamamoto and colleagues reported four patients with acute aortic occlusion and concomitant internal iliac occlusion who had undergone bypass surgery or thrombectomy. All of them were elderly (ages ranged from 63 to 82 years) and presented with lower limb weakness and ischemia. Despite thrombectomy and axillo-bifemoral bypass operations, two patients (age 72 and 85 years) had insufficient re-perfusion of the bilateral internal iliac arteries and died on day three (mortality rate of 50%) from hyperkalemia and multi-organ failure¹⁴. An autopsy of one of the cases showed patent superior mesenteric and celiac arteries but occluded bilateral iliac arteries with severe intestinal ischemia. Elevated CPK and myoglobinuria were observed in all patients but this was more prominent in the fatal cases.¹⁴ The other possible contributing factor in this case was thrombo-embolism from the athero-thrombotic aorta to the superior mesenteric or celiac arteries. Abdominal distension and leukocytosis strongly supported the manifestation of acute ischemic bowel.¹⁵ Unfortunately, these findings were only detected after 24 hours when his condition had already worsened considerably. Liver and kidney failure were noted with a prolonged prothrombin time of 239 seconds (INR of 36.9), an elevated SGOT, a SGPT of 685,367U/L respectively and a creatinine increase from 2.39 to 3.78mg/dl (Table 1). Rhabdomyolysis occurred with CPK of 12,727U/L. Cause of death was severe acidosis and multi-organ failure.

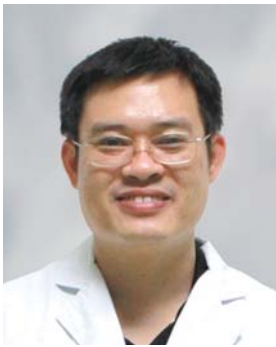
Conclusion

We reported on a relatively young man who presented with cardiac arrest, acute aortic syndrome (PAU and IMH) and severe metabolic acidosis. Initial ECG mimicked anterior myocardial ischemia but no significant coronary artery lesion was found. CT scan revealed multiple penetrating aortic ulcerations, intramural hematoma, mural thrombus occluding infra-renal aorta, inferior mesenteric and bilateral common iliac arteries causing lower limbs and possible intestinal ischemia. The patient's condition rapidly deteriorated and the cause of death was severe metabolic acidosis and multi-organ failure. This was a very high risk patient presenting a fatal aorto-iliac occlusion case which required early diagnosis and intervention.

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A Case Report of Surgical Treatment of Symptomatic Aberrant Right Subclavian Artery Aneurysm (ARSA) at Bangkok Hospital Phuket, Thailand



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Keywords: aberrant right subclavian artery aneurysm, ARSA, Kommerell's diverticulum, KD, arterial lusoria, dysphagia lusoria

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Aberrant right subclavian artery (ARSA), also called arteria lusoria, is one of the most common intrathoracic arterial anomalies. Although most of the patients are asymptomatic, the retroesophageal and retrotracheal course of the lusorian artery might result in non-specific chest pain, dysphagia, dyspnea, arterioesophageal or arteriotracheal fistula with hematemesis or hemoptysis, and aneurysmal formation with relevant risk of rupture. The first case report of dysphagia from ARSA was reported by David Bayford in 1794.¹ The prevalence of this rare congenital anomaly is around 0.5-2%.² Normally the right subclavian artery (RSA) develops from the fusion of the persistent right proximal dorsal aorta with the right seventh intersegmental artery distally. The abnormal origin of the RSA is caused by the involution of the right fourth vascular arch and proximal right dorsal aorta and the persistence of the seventh intersegmental artery originating from the proximal descending thoracic aorta, forming the aberrant course of the lusorian artery.³ The arteria lusoria arises from an aortic arch diverticulum at the proximal descending aorta, first described by Kommerell.⁴ According to variables of underlying vascular pathology, various surgical procedures were chosen for appropriate cases. The operative procedures could be done via median sternotomy, supraclavicular approach, and transaxillary thoracotomy approach, with or without heart-lung machine support. Recently, endovascular surgery has been chosen as an alternative procedure in some cases.^{5,6}

Case Report

A 73-year-old female patient had clinical symptoms of dysphagia in association with an ARSA; her body weight dropped from 60kg to 31kg in 6 months. She also had symptoms of bronchospasm from time to time and needed broncodilators for treatment. The chest radiography showed a prominent aortic knob (Figure 1).

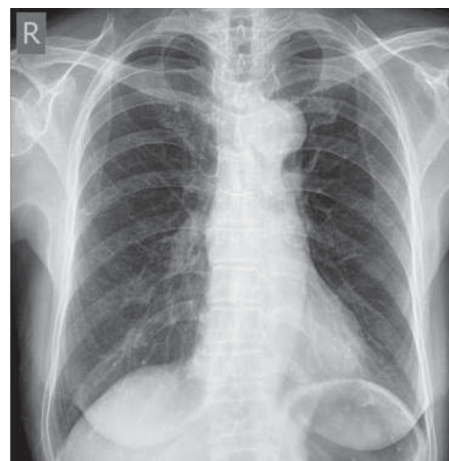


Figure 1: Chest x-ray on pre-operative day.

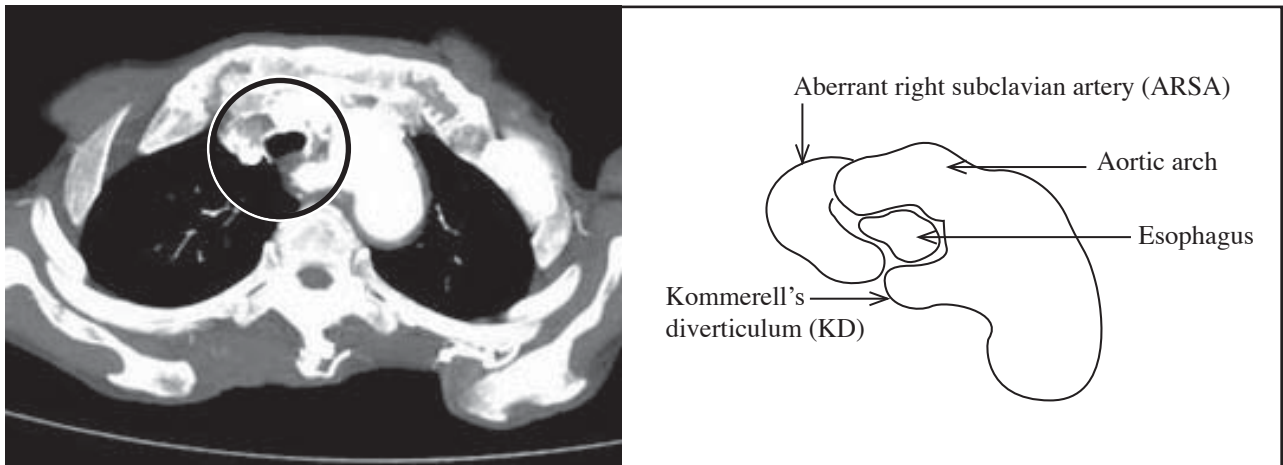


Figure 2: The computer tomography shows the esophagus being trapped between Kommerell's diverticulum (KD) and the trachea (in the circle).

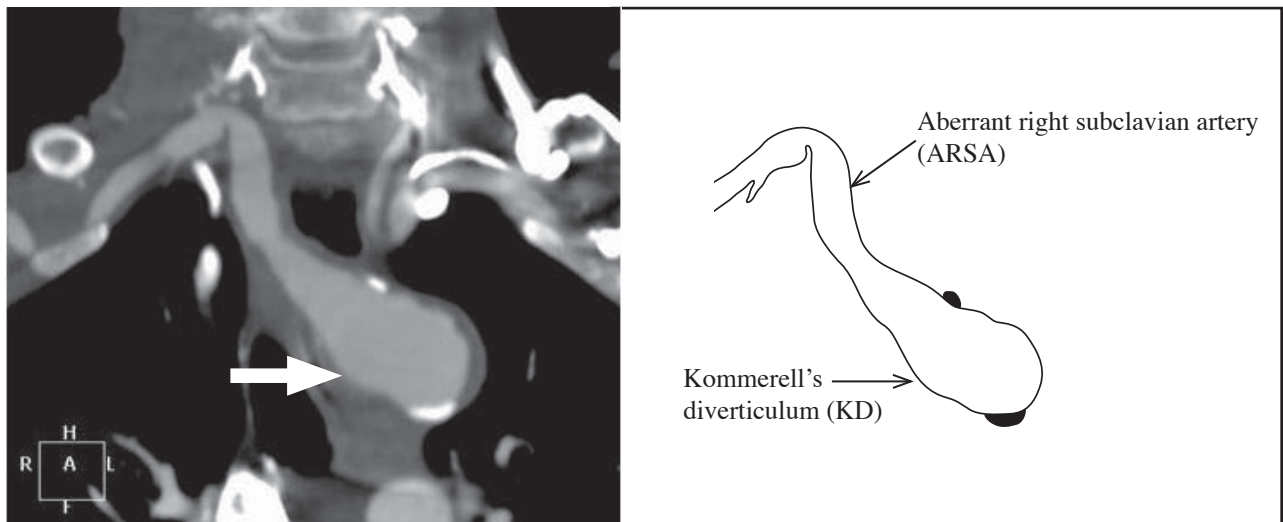


Figure 3: The computer tomography shows Kommerell's diverticulum (KD) (white arrow).

The computer tomography showed the ARSA with Kommerell diverticulum (KD) compressing the esophagus (Figure 2-4). An open surgery and endovascular procedure were proposed to the patient's family as options and they chose the open surgery option.

Result

The patient was prepared under general anesthetic and put in a left lateral decubitus position and bilateral radial artery monitoring was performed. The right transaxillary approach was undertaken via the 3rd intercostal space. The ARSA was mobilized and divided; both ends of the artery were closed with No.4-0 polypropylene suture and reinforced with pledgeted (Figure 5). The esophagus was moved away from the surrounding tissue. The right radial mean arterial pressure was 45 mmHg, while the right index

pulse oxygenation was around 70%. The reanastomosis of the right subclavian artery was abandoned. A No. 28 drainage tube was inserted in the right pleural space. The patient was extubated immediately post operation. The oxygen saturation on the right hand increased to 95%, while the mean arterial pressure was around 70 mmHg, with a normal wave form.

The patient had a liquid diet on postoperative day 1 and a soft diet on day 3. The intercostal drainage tube was removed. She was discharged home on postoperative day 7. She gained around 3kg in weight in the first month after being discharged and had only one episode of a mild bronchospasm attack. She resumed her normal daily activities in the 2nd month after surgery, without clinical signs of bronchospasm. By the 3 months follow-up, the patient had gained a further 3kg.

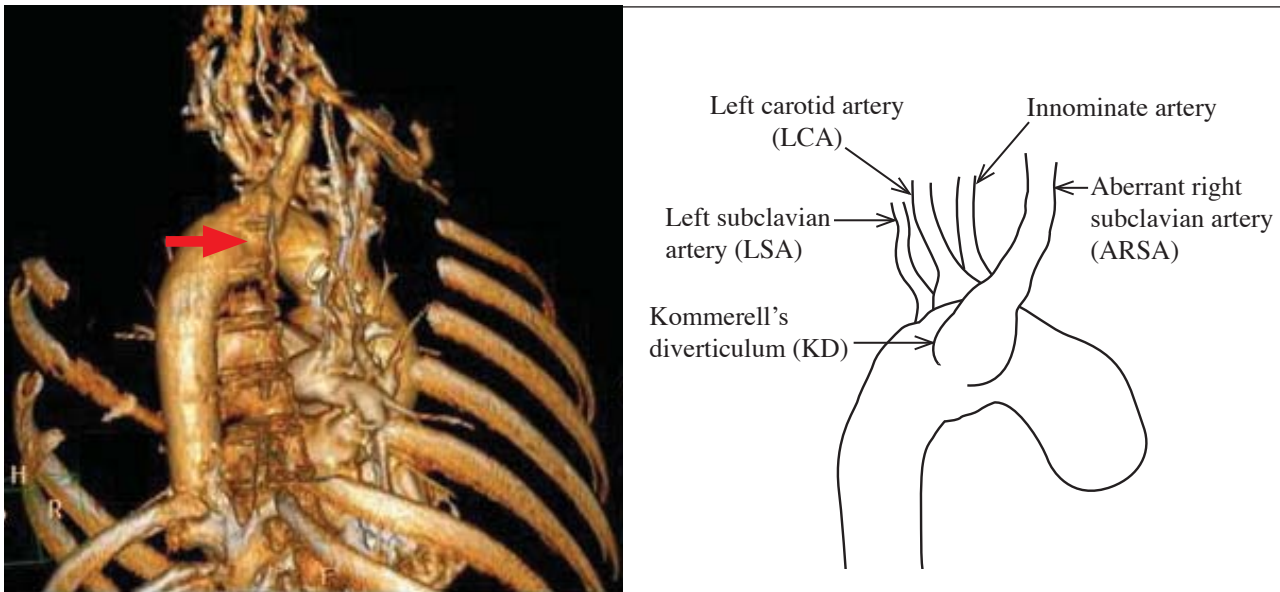


Figure 4: The 3D reconstruction computer tomography shows Kommerell's diverticulum (KD), the back view (red arrow).

Discussion

Aberrant right subclavian artery (ARSA) diverticulum is an extremely rare occurrence. Due to the extremely rare nature of the disease, the mortality and morbidity rates of its surgical treatment are still unclear. Some case reports on the surgical treatment of ARSA aneurysms have been published, but it is very difficult to ascertain the mortality and morbidity associated with this operation from these as it is likely that only successful cases have been published.

The first successful repair of an ARSA was reported by Gross.⁷ However, the best surgical approach to treat patients with pathologies of the lusorian artery is still a point of discussion. The division of the proximal part of the ARSA is the recommended surgical procedure in symptomatic patients. For patients with an aneurysm of ARSA or Kommerell's diverticulum, exclusion is performed by the right or left thoracotomy, sternotomy, or transaortic repair with extracorporeal circulation according to the underlying pathology and the site of the aortic arch. Kieffer and colleagues reported the largest single-center series with 33 patients treated for asymptomatic or aneurysmal of ARSA.⁸ According to their data, the perioperative mortality rate in the group of patients with aneurysmal disease of the ARSA was 23.5%. Nowadays, the endovascular surgery or combined surgical and endovascular treatment of patients with symptomatic pathologies of ARSA is an alternative treatment and used worldwide. Based on the reports in the literature, the combined endovascular occlusion of the aortic origin of the ARSA with subclavian artery transposition and distal prevertebral occlusion seems to be a safe and effective alternative for elective treatment, with no perioperative deaths so far. However, there is no report of long-term results.⁹⁻¹⁴

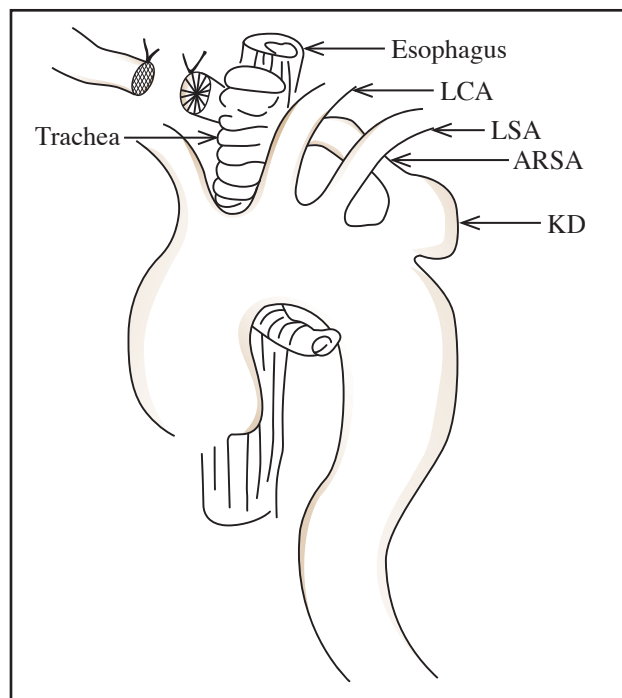


Figure 5: A drawing of the operative procedure for this patient.

Occlusion of the proximal ARSA without subclavian artery reconstruction might cause right arm ischemia or symptoms described as subclavian steal syndrome. The RSA transposition in cases of combined surgical and endovascular treatment for ARSA aneurysms are believed to be increasingly necessary to prevent reduction in cerebrobasilar blood flow. That said, the experience with the thoracic stent graft implantation in the proximal descending aorta with occlusion of the left subclavian artery (LSA) suggests sufficient blood supply to the left arm without transposition of the LSA.¹⁵

Conclusion

An ARSA can cause relevant symptoms due to compression of the esophagus or the trachea in association with or without an ARSA aneurysm. Operative repair by open surgery or in combination with an endovascular procedure is recommended to treat these symptoms and to reduce the risk of aneurysm rupture. Symptomatic patients can be treated by either a supraclavicular or transthoracic repair or an extrathoracic cervical-endovascular approach with a transbrachial proximal stent graft occlusion. Our experience suggests that a proximal descending aortic endovascular implantation without a left subclavian bypass causes no limb ischemia. The technique of dividing the ARSA without subclavian transposition which has been used in some cases produced no ischemic complications.

For patients with an ARSA aneurysm or an aneurysm of the proximal descending aorta, a thoracic aortic stent graft implantation to occlude the origin of the ARSA in combination with a distal occlusion of the ARSA and a subclavian artery transposition is the alternative treatment which is a minimally invasive approach with promising mid-term results. However, as there have only been a few cases of patients being treated with endovascular procedures so far, long-term results of a larger group of patients should be studied.

We report our successful surgical experience in a case of aberrant right subclavian artery (ARSA) aneurysm.

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Exploring Inside a Snowman by Magnetic Resonance Imaging



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Keywords: snowman, TAPVR, heterotaxy, isomerism, MRI

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The snowman sign is a sign on a chest x-ray image that indicates a supra-cardiac type total anomalous pulmonary venous return (TAPVR).¹ TAPVR is a serious congenital heart disease which occurs due to an abnormal development of the fetal heart. This leads to an inappropriate connection of all four pulmonary veins.¹ TAPVR is a congenital left to right shunt disease where all four pulmonary veins are gathered into a vertical vein behind the left atrium. The vertical vein plays a role as a reservoir of oxygenated blood that drains into the right side system directly or via the left innominate vein. TAPVR causes neonatal death if there is no oxygenated blood shunting from the pulmonary venous circulation system to the systemic circulation system. Thus TAPVR is considered a critical congenital heart disease because an infant with TAPVR needs surgical correction early after birth to survive.² The incidence of TAPVR accounts for 1-5% of all cardiovascular congenital heart disease.^{3,4} TAPVR is classified into four types according to the location (level) of the target organ of blood drainage from the vertical vein. The four types of TAPVR are: 1) supra-cardiac type, 2) cardiac type, 3) infra-cardiac type and 4) mixed type.¹

The target organ of blood drainage in the supra-cardiac type is the right superior vena cava (SVC) which is at the supra-cardiac level. The head of the snowman sign is composed of a dilated vertical vein on the left, a dilated right SVC on the right and, in addition, there is sometimes a left innominate vein on the top. The body of the snowman is the dilated right atrium.¹ The target organs of pulmonary venous drainage of the other types of TAPVR are shown in Table 1. The essential factor in keeping TAPVR patients alive is a right to left shunt pathway to facilitate oxygenated blood flow through systemic circulation. The most common right to left shunt pathway in TAPVR is a patent foramen ovale (PFO) and an atrial septal defect (ASD) and the least common is a patent ductus arteriosus (PDA).⁴ The specific treatment for TVPVR is the reconnection of all four pulmonary veins to the left atrium and the closing of cardiovascular defects. However, as a TAPVR infant grows up, the reconnection sites of pulmonary veins to the left atrium may be in stenosis which generally accounts for 40% of cases; therefore, a stent placement may be needed to permanently re-dilate the narrow venous port.⁵

Case Report

A 15-month-old boy with TAPVR, heterotaxy syndrome and with status post bilateral Blalock Taussig (BT) shunts implantation in 2009 (with a status post stenting for PDA correction in the neonatal period) was admitted for a Fontan operation. During the admission process, the patient still had cyanosis with no worsening progression. A Pre-Fontan operation evaluation was ordered by the pediatrician.

Table 1: Type of total anomalous pulmonary venous return (TAPVR).

Sequential segmental analysis steps	Differentiation 30/12/2013
I. Cardiac position and apex orientation	Levocardial (heart in the left side of chest), Dextrocardial (heart in the right side of chest), mesocardia (heart in the middle of chest)
II. Atrial arrangement	Situs solitus (usual atrial arrangement), Situs inversus (morphologic left atrium on the right, morphologic right atrium on the left) or right isomerism (bilateral left to right atrial morphologies)
III. Atrioventricular connection	Normal; left atrium connects to the left ventricle and the right atrium connects to the right ventricle
IV. Ventriculoarterial connections	Concordant (appropriate connection between the great vessels and ventricles; the aorta connects to the left ventricle, the pulmonary artery connects to the right ventricle), discordant (inappropriate connection), double outlet, single outlet
V. Associated malformations and function of segments	i.e., common atrium

A twelve leads electrocardiogram (ECG) and an echocardiography was performed. The twelve leads ECG showed tachycardia (heart rate of 114 beats per minute), regular rhythm, complete right bundle branch block and large P wave amplitude which indicated an enlargement of the right atrium. The echocardiography examination revealed right isomerism heterotaxy syndrome and TAPVR supra-cardiac type, and a well patency of the right BT shunt (shunt connection between the right pulmonary artery and the right innominate artery) and a left BT shunt (shunt connection between the left pulmonary artery and the left subclavian artery) with preserved left ventricular function. The abnormal obstruction of the venous vessel was not shown on the echocardiogram. The echocardiographic result did not explain the cause of dyspnea. Thus the patient was sent to undergo a magnetic resonance imaging (MRI) study with and without a gadolinium-contrast injection to confirm the diagnosis. The gradient echo CINE MRI images demonstrated the following:

- I. mesocardia
- II. common atrium with bilateral right atrial morphology (right isomerism), the liver was in the middle
- III. common right morphologic atrium connected to the common right morphologic ventricle, common atrio-ventricular valve
- IV. double outlet connection of the aorta and pulmonary artery with the single ventricle, the right SVC and left sided IVC drained into the common atrium. All four pulmonary veins are confluence into the vertical vein and are connected to the left innominate vein on the left side, the left innominate vein is the connection vessel of the right SVC and the vertical vein
- V. well patency of both Blalock Taussig shunts as reported in the echocardiography result (using the gradient echo CINE MRI and MR angiography with gadolinium contrast injection technique).

The stenosis of the left vertical vein at the emptying port to the left innominate vein, however, caused a high jet flow into the left innominate vein. This stenotic lesion was also seen on the coronal view of the gradient echo CINE MRI images and of the MR angiogram with gadolinium-contrast injection. This abnormal finding was not shown in the echocardiogram. This was an inconclusive result therefore a right heart catheterization was proposed and performed to obtain the final conclusion. The angiogram of the right heart catheterization study showed the stenosis at the junction area of the vertical vein to the left innominate vein and a well patency of both BT shunts. The results of the right heart catheterization were compatible with the MRI result. Finally the patient was discharged and instructed to continue their current treatment. The patient will undergo a Fontan operation as planned.

Discussion

Theory discussion

The case presented in this article is a supra-cardiac type total anomalous pulmonary venous return (TAPVR) with a right isomerism heterotaxy. The TAPVR case in this article is specified as a supra-cardiac type because the target organ of the pulmonary venous drainage, the right SVC, is found at the supra-cardiac level. TAPVR is a left (pulmonary veins-vertical vein) to right (SVC) shunt congenital heart disease. No pure oxygenated blood was emptying directly into the left atrium. The existing common atrium and common ventricle, including the connection between the vertical veins to the left innominate vein, were vital to the survival of this patient by increasing the flow of oxygenated blood flowing through the systemic circulation. The common atrium acts as a mixing tank of deoxygenated and oxygenated blood. The oxygenated blood travels from the vertical vein through the innominate

vein and the right SVC to reach the common atrium. This baby has been admitted for a Fontan operation. The Fontan procedure is a palliative surgical procedure designed to divert the venous blood from the right atrium to the pulmonary artery bypassing the morphologic right ventricle. It has been used for infants with a single ventricle. It helps the single ventricle to work less hard.⁶ During the admission period while this patient was waiting for the Fontan operation; the patient received a bilateral Blalock Taussig (BT) shunts implantation. In theory, the Blalock Taussig shunt is a surgical connection shunt between the systemic artery and pulmonary artery and is used with the objective to increase pulmonary blood flow. It is an interim palliative treatment when waiting for specific surgical treatment in the future.⁷ The BT shunts of this patient are the connection between the right pulmonary artery and the right brachiocephalic artery on the right side and between the left pulmonary artery and the left subclavian artery on the left. A single ventricle with a double outlet caused an insufficiency of blood volume supply to the pulmonary system. The MRI study and a right heart catheterization revealed the stenosis of the vertical vein to the innominate vein. The obstruction of the pulmonary venous drainage can occur in any type of TAPVR. It is uncommon in type I but it is the most common obstruction in infra-cardiac type with an incidence of about 78%. In infants with TAPVR, cyanosis and congestive heart failure typically develop in the early neonatal period. Around 30% of the patients with TAPVR have other associated cardiac lesions such as heterotaxy syndrome with asplenia¹ as did this patient.

Heterotaxy or isomerism or situs ambiguous are the arrangement disorder of the organs in the chest and abdominal cavities in an unformed fashion. Hetero-means different and -taxy means arrangement. The mal-formation and mal-position of the organs in heterotaxy are more complex than in situs inversus. In theory, the clinical pathologies of the heterotaxy are a discordance of the cardiac apex from the liver and stomach and include cardiac chamber malformations, with a common atrium, single ventricle, and transposition of the great vessels. A total anomalous pulmonary venous return occurs in the majority of cases, with asplenia or polysplenia. Situs inversus is defined as the mal-position of the organs in the chest and abdominal cavities as a mirror image with no presence of body organ malformation. For the heterotaxy, the discordant character of the thoracic and the abdominal organs lie between the situs solitus and situs inversus.⁸ The heterotaxy is also called situsinversus ambiguous. Atrial isomerism as mentioned in echocardiography and MRI results can be left or right isomerisms. The left and right isomerism mean the morphology of the two atria are left and right morphologies respectively. In this case, the patient has a right isomerism with asplenia (lack of spleen). In general, asplenia syndrome is the same as right atrial isomerism or Ivemark syndrome.⁹ The hallmark of heterotaxy is bilateral isomerism, left or right.¹⁰

Imaging discussion

TAPVR/heterotaxy is a good complex case to show how to approach a complex congenital heart disease with imaging tools. A thorough knowledge of the disease core pathology and imaging techniques is important to diagnose congenital heart disease. Good imaging protocol planning comes from good clinical and technical knowledge of the operator. In this article, the key to diagnose TAPVR is:

- a) to document that none of the pulmonary veins drain into the left atrium,
- b) to localize the common venous reservoir (vertical vein) that is the confluence of all pulmonary veins, and the target organ of the vertical venous drainage
- c) to define any associated condition.

TAPVR is a complex congenital heart disease. In addition, a congenital heart disease approach by using imaging tools should be done in a systematic fashion to prevent a misdiagnosis and to prevent overlooking any information. The sequential segmental analysis principle has been proposed as an approach to evaluate congenital heart disease.¹¹ Synchronization of the sequential segmental analysis principle with our clinical and technical knowledge to diagnose congenital heart disease using imaging tools has been proposed as a good comprehensive method for congenital heart disease approach.⁷ The steps in this sequential segmental analysis include an analytic method to assess and to report the diagnosis of congenital heart disease in a sequential order as shown in Table 2 and the MRI report result (step I-V). A sequential segmental analysis method involves a differentiation of cardiac tissue morphology of all chambers and a characterization of the cardiac chambers and great vessels' connection including any associated conditions. Hence, a good application of sequential segmental analysis principle on imaging to approach congenital heart disease needs a modality with a high resolution, a widening field of view and a no limit window scan. The MRI seems to be the ideal modality for the application of the sequential segmental analysis approach principle. According to the steps of sequential segmental analysis approach, the tissue morphology differentiation is the most important. Tissue morphology analysis is the first step of this analysis approach technique to identify the components of the heart and the information results are described in sequential steps as shown in Table 2.

Well tissue characterization and differentiation are the strengths of MRI. A gradient echo white blood, CINE pulse sequence is the major pulse sequence used to perform tissue morphology differentiation. Cardiac anatomy and physiology can be assessed simultaneously on a gradient echo CINE MRI. To diagnose isomerism in cases of heterotaxy syndrome, the information about the anatomical structure arrangement and orientation of thoracic and abdominal organs is needed. As in this case, the patient was diagnosed as a bilateral right atrial morphology isomerism with asplenia, related to bilateral morphologic right bronchi or bilateral tri-lobar lungs.⁹ Therefore, the

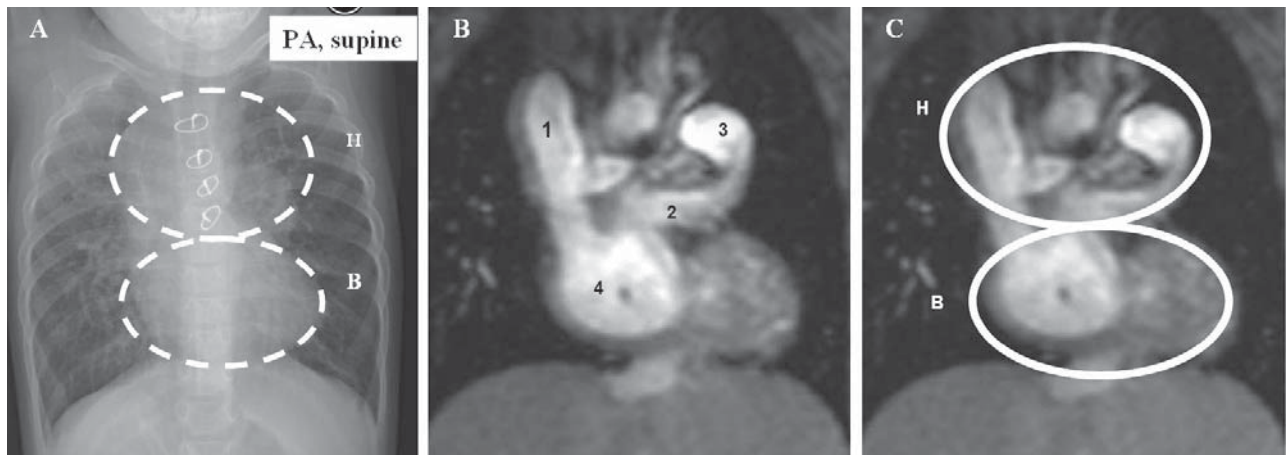


Figure 1: Chest x-ray image on PA-supine view and magnetic resonance imaging (MRI) using gradient echo CINE pulse sequence on coronal view show the Snowman sign of TAPVR supra-cardiac type.

1A: Snowman sign on chest x-ray image. 1B: Demonstration of the components of the snowman sign on a gradient echo CINE MRI image on the coronal view, 1 = Dilated right SVC, 2 = Dilated vertical vein, 3 = Dilated left SVC, 4 = Dilated right atrium. 1C: H = Head of snowman, B = Body of snowman.

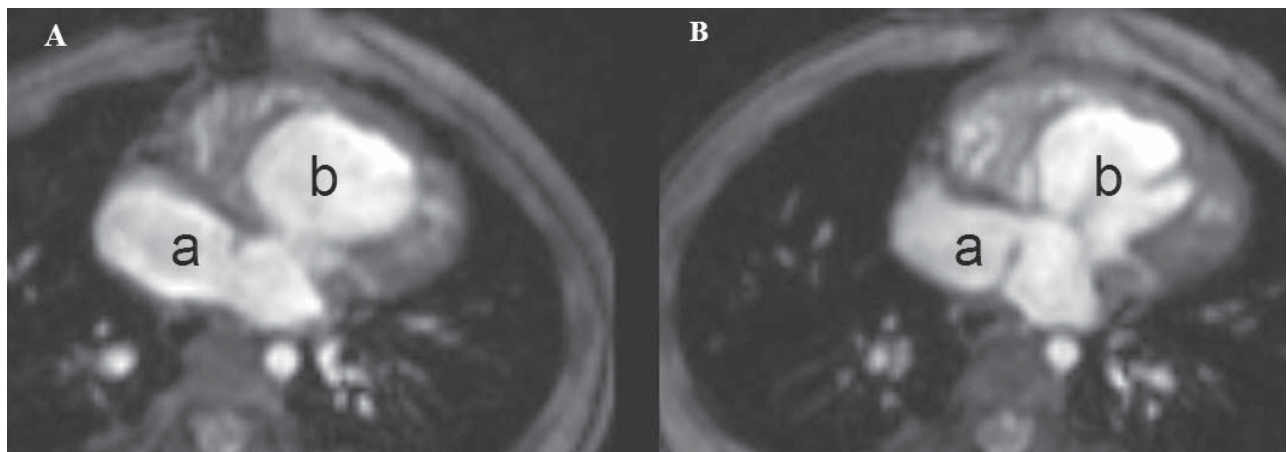


Figure 2: Sequential segmental demonstration approach steps I, II, III (see Table 1) are applied to MRI with a gradient echo CINE pulse sequence in an axial view. A and B show: mesocardia, common right atrium morphology (see atrial appendage character) (a) and common right morphology right ventricle (b), concordance of atrio-ventricular connection, right isomerism (bilateral atrial morphology).

imaging of bilateral morphologic right bronchial structure can be used to indicate right isomerism. The morphology of the bronchi can be seen simply by using a spin echo and gradient echo MRI pulse sequences on coronal and axial views. The hypo-signal of air in the trachea and bronchus are seen in both spin echo and gradient echo MRI images. This helps to strengthen the anatomical morphologic structure of these. Although sequential segmental analysis approach is used for cardiovascular anatomical analysis, it cannot be perfectly applied to every single imaging modality image in a one stop shop fashion. However, it can be used as a guide to approach congenital heart disease in a simple sequence of steps and can be applied completely in any combination on different modality images. Figures 1-5 show the inside of a snowman sign of TVPVR with right isomerism heterotaxy on MRI images and the synchronizing of the sequential segmental approach principle on MRI to assess a TAPVR /heterotaxy case.

Table 2: Type of TAPVR.

Type of TAPVR	Common receiving venous reservoir from all pulmonary veins
Supracardiac	Superior Vena Cava
Cardiac	Coronary sinus, right atrium
Infracardiac	Systemic vein -IVC, hepatic vein, azygos system, portal system
Mixed	Brachiocephalic vein, SVC, azygos vein, coronary sinus, right atrium, or below the diaphragm.

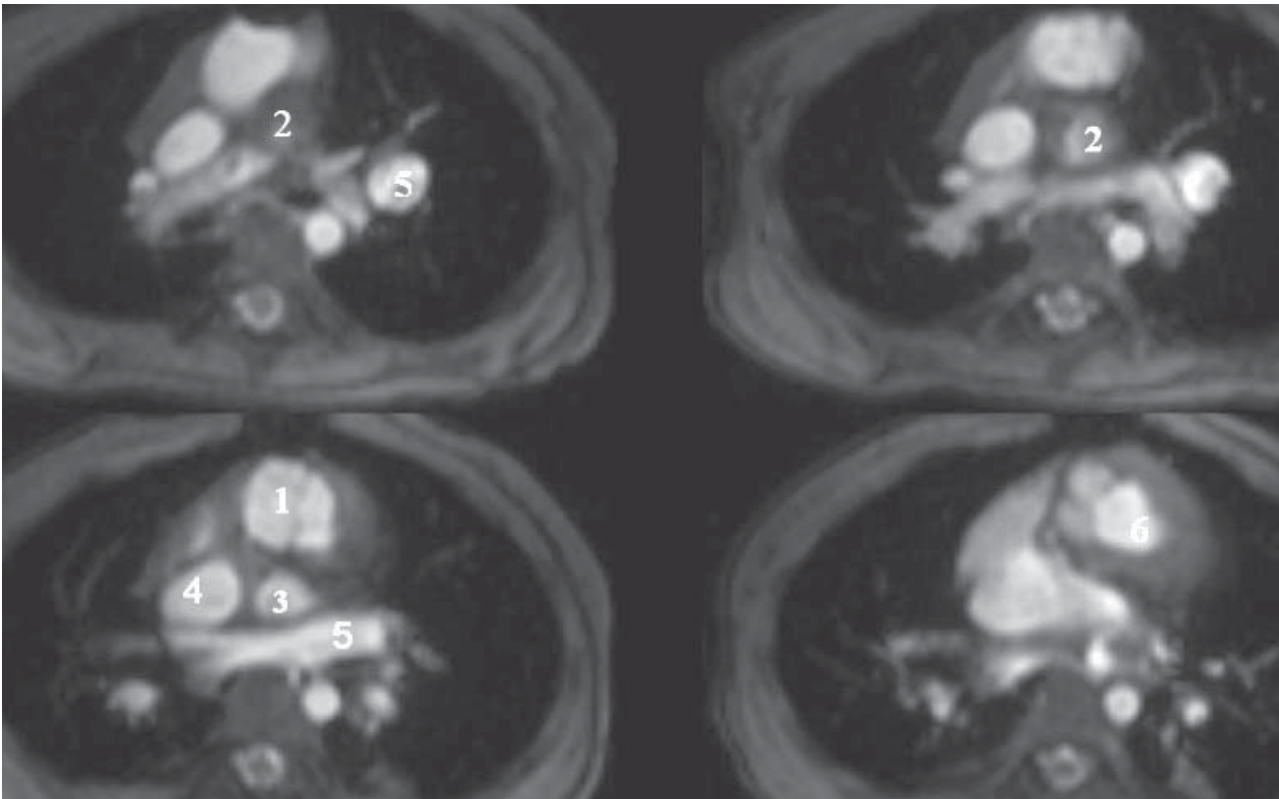


Figure 3: Sequential segmental demonstration approach step IV is applied to an MRI with a gradient echo pulse sequence in an axial view. A-D show concordant ventriculoarterial connection, with double outlet morphology. 1 = Aortic valve, 2 = Pulmonic valve, 3 = Pulmonary viens, 4 = Superior vena cava, 5 = Vertical vein (confluence of four pulmonary arteries).

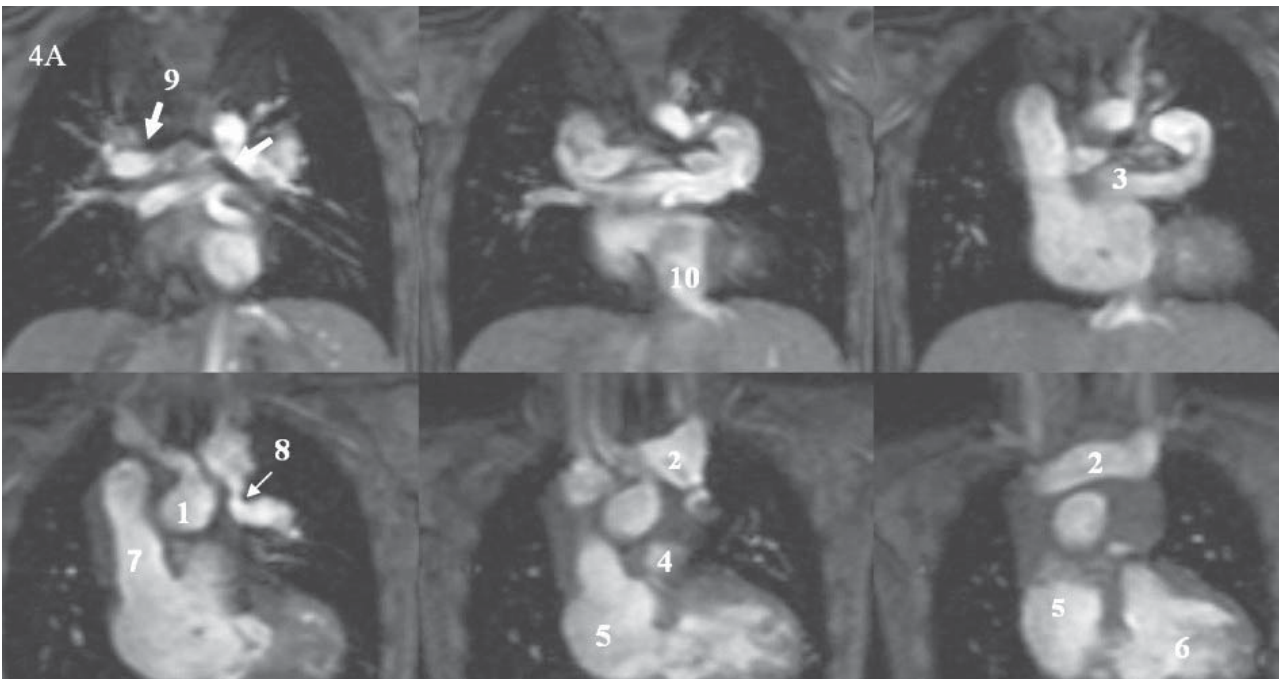


Figure 4A: Sequential segmental demonstration approach step IV is applied on a gradient echo MRI on the coronal view: 1 = Ascending aorta, 2 = Innominate vein, 3 = Vertical vein, 4 = MPA, 5 = Right atrium, 6 = Right ventricle, 7 = Right superior vena cava, 8 = Stenosis of the connection between the vertical vein and innominate vein, 9 = Bilateral right sided tracheal line (see arrow), 10 = Inferior vena cava.

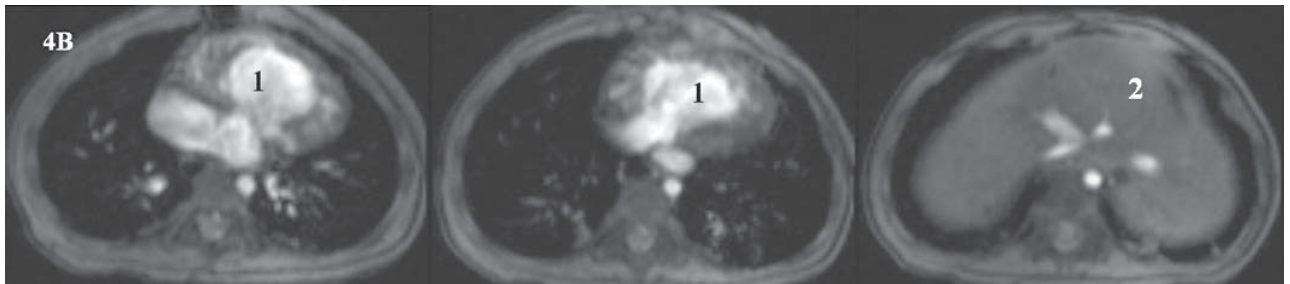


Figure 4B: Situs ambiguus with asplenia demonstrated on gradient CINE MRI images.
1= Single ventricle, 2= Liver at the mid abdomen.

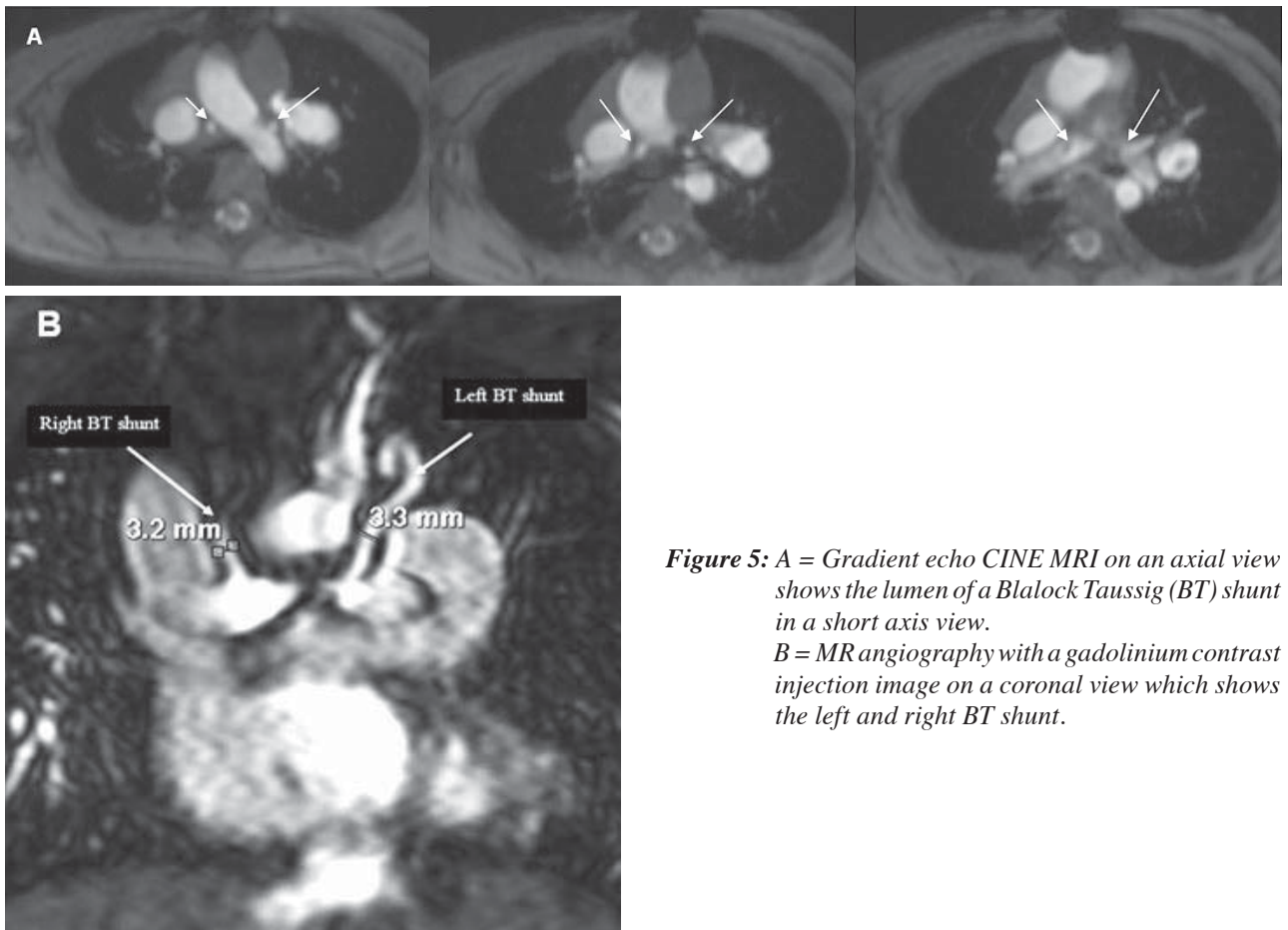


Figure 5: A = Gradient echo CINE MRI on an axial view shows the lumen of a Blalock Taussig (BT) shunt in a short axis view.
B = MR angiography with a gadolinium contrast injection image on a coronal view which shows the left and right BT shunt.

Conclusion

The application of a sequential segmental analysis approach towards imaging is a very good method to analyze cardiac anatomy in a complex congenital heart disease case. This article has demonstrated this, by showing that the inside of the snowman sign hides a complicated story that is much more than a TAPVR. We have shown that the use of an MRI in synchronization with a sequential segmental analysis approach method is a successful approach to

explore this condition. The MRI is a promising tool, given its high resolution, well tissue characterization, high reproducibility, no limited window scan, widening field of view and its many different pulse sequence techniques. This tool is well suited to be used in synchronization to a sequential segmental analysis method for cardiovascular anatomical evaluation in complex congenital heart disease.

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Jejunal Tubulovillous Adenomas



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Jejunal tubulovillous adenomas are a rare entity among the benign small bowel tumors. Usually they are found at the duodenum, ileum and jejunum respectively. They are for the most part asymptomatic. We present a case of jejunal tubulovillous adenomas with abdominal pain. The investigations include a plain film x-ray and computed tomography (CT) of the whole abdomen. These revealed a tumor located at the jejunum. The patient underwent an exploratory laparotomy and a segmental small bowel resection was performed. The procedure was uneventful. The pathological finding showed a tubulovillous adenomas. No malignant change was observed.

Case Report

A 74-year-old man presented with a history of abdominal pain associated with vomiting on and off for six days. Three years before, a colonoscopic examination had been performed and a benign polyp was removed. He had recently experienced weight loss of 5 pounds (lbs). The physical examination revealed a mildly distended abdomen, no mass was palpable. The rectal examination showed an empty ampulla. The laboratory investigations' results were within normal ranges. The plain abdomen supine position (Figure 1) shows moderate dilated small bowel with multi air and fluid levels, with no gas in the colon detected. The findings are consistent with mechanical small bowel obstruction.



Figure 1: The plain abdomen supine position shows moderate dilated small bowel with multi air and fluid levels, with no gas in the colon detected.

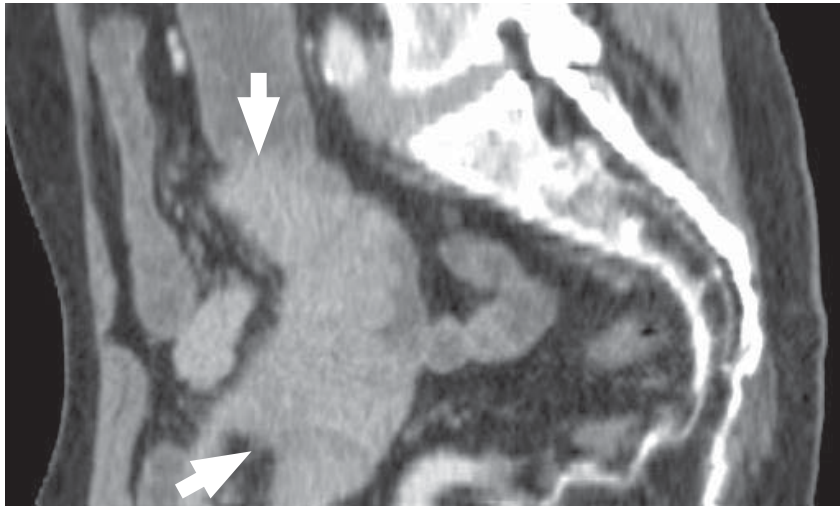


Figure 2: The CT of the whole abdomen with contrast enhancement, sagittal section shows an intestinal mass at wall of jejunum (see arrows) with proximal jejunal dilatation. There is no evidence of regional node enlargement.

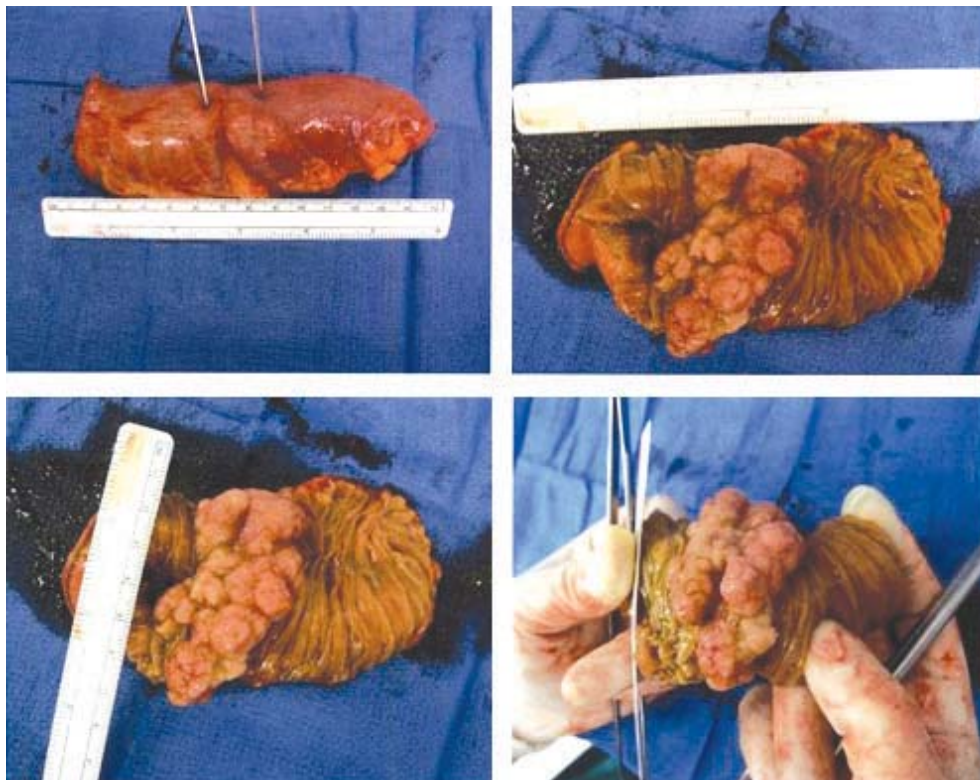


Figure 3: Shows small bowel obstruction at proximal jejunal due to tumor mass 7 cm in length.

The CT of the whole abdomen with contrast enhancement, sagittal section (Figure 2) shows an intestinal mass at the wall of the jejunum (see arrow) with proximal jejunal dilatation. There is no evidence of regional node enlargement. Jejunal tumors include adenoma, with or without malignant change, gastrointestinal stomach tumor (GIST), hemangioma or lymphoma.

The patient underwent an exploratory laparotomy. The operative findings (Figure 3A-D) showed an exophytic mass arising from mid jejunal wall, measuring 7 cm in length. The jejunal serosa is normal. There was no evidence of regional nodes enlargement. A segmental jejunal resection was performed. The specimen showed a tubulovillous adenoma measuring 7x3 cm. The microscopic examination (Figure 4A-B) revealed a benign tubulovillous adenoma with focal high grade dysplasia; no malignancy was detected.

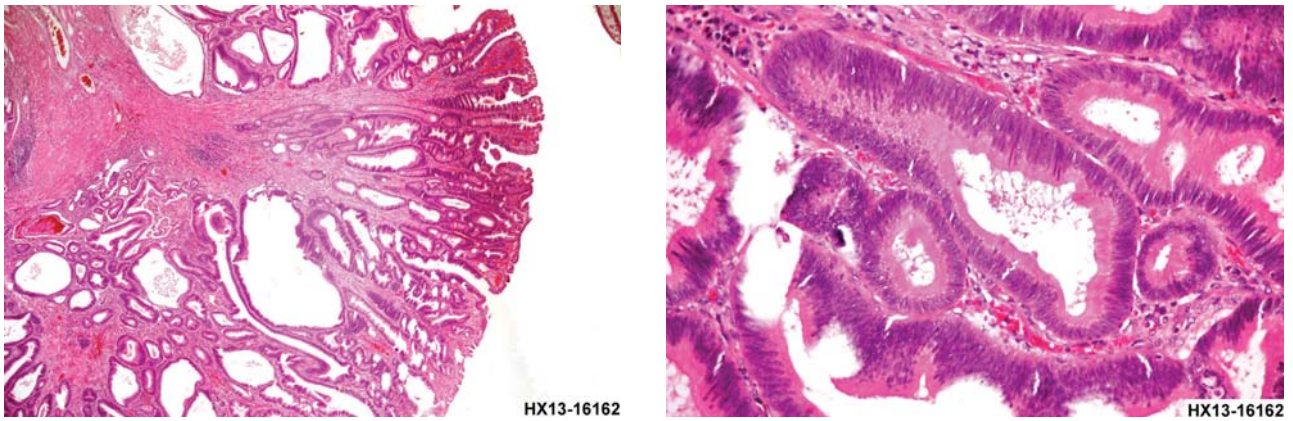


Figure 4A-B: Microscopic examination shows segments of the jejunum. It reveals a tubulovillous adenoma with focal high-grade dysplasia (villous component, about 40%). There is no evidence of invasive carcinoma. Both resected margins are free of the tumor.

Discussion

There are three types of small bowel adenomas: true adenomas, tubulovillous adenomas and Brunner gland adenomas. True and tubulovillous adenomas are thought to behave like colorectal adenomas which are found at a precancerous stage. The early stage is asymptomatic. When the tumor is more than 5cm enlarged, it is very likely to present malignant change² but the Brunner gland adenomas are benign tumors in length. This is found only at the duodenum. The symptoms are similar to peptic ulcer disease, with no malignant change. The treatment of choice is segmental small bowel resection. If true or tubulovillous adenomas with malignant changes occur, an extensive bowel and regional node resection are recommended. Furthermore, biomarkers by molecular proliferating (MP)³, should be identified using a combination of techniques including next generation sequencing (NGS),

fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), immunohistochemistry (IHC) and polymerase chain reaction (PCR). The deoxyribonucleic acid (DNA) coding sequence can be referred to once the biomarkers have been identified. This will contribute to detecting progressive cancer or to alter the choice of anti-cancer therapy and/or target treatment more effectively. It potentially improves overall progression-free survival (PFS) rates and improves quality of life⁴ over an unidentified MP.

Conclusion

This presentation is a rare case of jejunal tubulovillous adenomas with abdominal pain. The investigations revealed a small bowel obstruction: a jejunum tumor. The patient underwent a segmental jejunal resection and recovered fully. The procedure was uneventful.

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Acute Fulminant Hepatitis due to Herpes Simplex Type 1 Infection



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Cases of fulminant hepatitis caused by herpes virus infection is quite rare.¹ Most reported cases are pregnant woman and immune suppressed patients such as renal transplantation patients and patients on prolonged steroid therapy.²⁻⁶ Most cases of herpes infection leading to fulminant hepatitis, are post mortem diagnosis.¹ Early diagnosis and treatment can save the patient's life and avoid the need for liver transplantation.

Here we report on an immunocompetent patient who developed fulminant hepatic failure caused by herpes simplex type I infection. Although the patient came to our hospital presenting an infection after seven days of illness, early diagnosis and treatment saved his life and prevented fatal liver failure. We demonstrated the use of real-time polymerase chain reaction (PCR) as a useful tool in therapeutic monitoring of herpes simplex virus (HSV) type I clearance. By using the PCR threshold cycle (Ct), we could show that the HSV infection clearance was quite slow from the serum results. Further studies should be investigated to identify the optimal dose and duration of the administration of acyclovir therapy in this setting.

Case Report

A 47-year-old man presented with a previous history of good physical health. He had been living with diabetes mellitus (DM) type 2 for years without obvious DM complications. His HbA1C tested one month prior to admission was 5.7 mg/dl. He is an occasional alcohol drinker. He presented with symptoms of mild sore throat and fever. He sought treatment in a private clinic and was treated for acute pharyngitis with amoxicillin/clavulanic acid. Three days later, he was admitted to another hospital due to persistent fever accompanied with increased malaise and anorexia. Further investigations indicated a possible case of Epstein Barr viral (EBV) infection. Four days later, he was transferred to Bangkok Hospital for further evaluation and proper management.

A physical examination was undertaken on arrival at Bangkok Hospital at 15:00 on August 29, 2013. The patient presented as febrile (body temperature 38.5°C), no dyspnea but looked weak and was somnolent, yet conscious.

His heart rate was 86/min at rest, with a respiratory rate of 20/min and his blood pressure was 145/80 mmHg. He was not pale and showed no icteric sclera. The pharynx was not infected and there was no exudate on either tonsil. Chest and abdominal examinations were unremarkable. There was no stigma of chronic liver disease observed. No skin blister lesions were found. From the physical findings, no active focal infection was detected.

Investigations and results

The significant abnormal liver function test (LFT) revealed a high elevation of transaminases (ALT 2561 U/L, AST 3209 U/L), total bilirubin 1.2mg/dl, direct bilirubin 0.9 mg/dl, total protein 6.38g/dl, albumin 3.71g/dl and prolonged prothrombin time (PT) 14.2 seconds (sec) (the normal range is 10.5-13.4sec). Complete blood count (CBC) revealed Haemoglobin (Hb) 16.6g/dl, leucopenia with total white blood cell count (WBC) 2,510 cells/mm² (polymorphonuclear cell (PMN) 62.9%, lymphocyte 16.5%) and a platelet count that dropped to 92,000 cells/mm³. These results indicated that the patient was suffering from acute fulminant hepatitis with impending liver failure. Therefore a working diagnosis for etiologic agents causing fulminant hepatitis was investigated.

The patient was treated with empirical antibiotics while investigations took place, and the liver transplantation team was informed to prepare a liver transplantation if required. The patient was suspected to be suffering from EBV infection with complicated and progressive liver failure. The hematologist performed a bone marrow biopsy, and the result ruled out infections associated with hemophagocytosis syndrome and other hematologic diseases. On admission day 2, he became more confused, accompanied with blurred consciousness and a persistent high intermittent fever of 39-40°C. We transferred him to the intensive care unit for closer observation so the patient could receive 24 hours care. The follow-up blood chemical tests and LFT of the patient (Table 1) showed a marked increase in transaminase and progressive jaundice. He also developed acute pancreatitis. Computer tomography of the abdomen revealed no significant abnormality of the liver gall bladder and the common

bile duct apart from a mild swelling of the pancreas and spleen. At around 48 hours after admission, we received a positive identification of the PCR-Herpes Simplex virus (HSV) type I while all other viral studies were negative (Table 2).

We started acyclovir therapy on August 31, 2013 at 9.00 am (around 48 hours after admission). We observed that his clinical outcome slowly improved. Fever presented up to 12 days after the medication was administered, while the transaminase and bilirubin levels gradually improved. The patient responded slowly and clinical intermittent fever and HSV type I was still detected in blood samples, so we applied our in-house laboratory real-time PCR to monitor his treatment.

Monitoring the Herpes virus during therapy

The quantitative real-time PCR for Herpes virus is not commercially available for monitoring the viral load as in the case of other viruses. We developed a real-time PCR based on SYBR Green I chemistry for comparative quantification of the Herpes Simplex virus. The key conceptual innovation to the quantification in real-time PCR is the threshold cycle (Ct), that is, the cycle at which the fluorescence signal from the PCR reaction exceeds the baseline fluorescence. The Ct is dependent on the amount target present at the beginning of the reaction; the fewer cycles it takes to reach a detectable fluorescence the greater the initial copy number. With most real-time PCR machines it takes about 10¹⁰ copies of PCR product to produce a significant signal. The equation $N_n = N_0 (1+E)^n$ predicts that if there are 1,000,000 copies at the beginning of the PCR reaction, the instrument will detect a signal around cycle 14.

Table 1: Results of blood chemistry and transaminase.

Test Item	29/08/2013	31/08/2013	1/09/2013	2/09/2013	3/09/2013	4/09/2013
CBC						
Total WBC (cell/mm ³)	2,510	2,930	1,650	1,840	10,900	10,080
Hb (g/dl)	16.6	15.5	12.2	12.0	11.7	11.5
PMN (%)	62.9	57	50	41.9	81.9	77.6
Lymphocyte (%)	15.5	30	30	33.7	12.9	15.3
Platelet (/mm ³)	92,000	55,000	111,000	149,000	145,000	154,000
LTF						
Bilirubin Total (mg/dl)	1.2	4.0	5.3	4.7	4.1	4.4
Bilirubin Direct (mg/dl)	0.9	3.6	4.1	3.6	3.3	3.5
ALT (U/L)	2,561	6,696	2,933	1,699	669	511
AST (U/L)	3,209	11,309	6,969	3,559	1,067	731
PTT (sec) (22.5-31.6)	34.0	57.3	61.5	54.2	52.2	51.1
PT (sec) (10.5-13.4)	14.2	26.5	20.4	20.2	18.9	17.4
P-Amylase (U/L) (8-53)	-	103	299	336	200	237
Lipase (U/L) (0-190)	-	164	1,232	1,368	759	469

Table 2: Initial results of viral and other etiologic tests that may be a cause of fulminant hepatitis.

Viral and other etiologic tests	Result
HAVIg M	Negative
Hepatitis BcIgM	Negative
Dengue Virus IgG/IgM	Negative
Dengue PCR	Negative
EBV PCR	Negative
IgM	Negative
CMV PCR	Negative
IgM	Negative
Hepatitis E	Negative
HCV	Negative
PCR HSV type I	Detected
HSV IgM	Negative
Malaria parasites	Negative
Leptospirosis IgM	Negative
Rickettsia Ab	Negative
Melioidosis titer	Negative
Blood culture	No growth
Urine culture	No growth
ANF, ANA (AntiNuclear factor)	Negative
Ceruloplasmin (g/L) (normal 0.200-0.600)	Normal

If the starting copy number is 100,000 the first signal will appear around cycle 17. A serial tenfold dilution of standard levels shows that the Ct value differs by 3.3 for each dilution.^{7,8} We can assume on this basis that if the virus responds to the therapy regimen, the Ct of consecutive samples should rate higher than previous samples, which means in should be that the viral load is decreasing or responding to therapy.

Clinical Specimens and DNA extraction

A total of seven consecutive whole-blood specimens were collected during the clinical course and therapy intervention from September 4, 2013 to October 12, 2013. The nucleic acid was extracted from 0.2ml of plasma by using MagnaPure Compact Nucleic Acid Isolation Kit I according to the manufacturer's instructions. DNA was eluted in the final volume of 50 μ l of elution buffer and was stored at -30°C until used.

Comparative Quantification of HSV DNA with Real-time PCR

The PCR primers HSV3 (5'-gcg ceg tca gcg agg ata ac-3') is a common forward primer for Herpes Simplex virus type 1 and 2 (HSV1, HSV2), primer HS1 (5'-ggg gta ctt aca gga gcc ctt-3') is a specific reverse primer for HSV1, primer HS2 (5'-gcc ctc ttg gta ggc ctt c-3') is a reverse primer specific for HSV2. Five μ l of extracted DNA from each sample was mixed with 0.4 μ M of forward primer and

0.8 μ M of reverse primer in a 20 μ l reaction volume using a SensiFAST SYBR No-ROX Kit (Bioline Reagents Ltd. United Kingdom). The samples were amplified in a Light-Cycler Nano Real-time PCR system (Roche Diagnostic, USA). The real-time PCR condition consisted of a two steps cycling of 95°C for 10 seconds and 60°C for 30 second for 45 cycles followed by melting analysis from 65°C to 95°C. For each consecutive sample the previous DNA sample was repeated in the same run to check the stability of the DNA sample and for comparison with later samples.

Results

HSV1 was detected from each sample according to the date of serum sample and the Ct of the first serum collection on September 4, 2013 was 16.20 and the Ct values increase in consecutive serum samples (Table 3 and Figure 1). With the last serum sample taken on October 12, 2013 the Ct value was 37.66 which is not a signal from a specific PCR product because the melting temperature (Tm) of the PCR product is 85.76°C. The HSV1 specific PCR product has a Tm around 87.7-88.0°C (Table 3, Figure 2). The PCR products were verified by agarose gel electrophoresis to check for a PCR product size of 152 bp. (data not shown). The real-time PCR assay using specific primers for HSV2 were negative for all samples tested. The results showed that the Ct increased in the consecutive samples which meant that the amount of HSV1 virus was decreasing probably from therapeutic intervention and the virus was cleared from circulation as a PCR result on October 12, 2013. From this study, the qualitative real-time PCR can be used to monitor the virus in circulation by using a comparative PCR between consecutive samples. According to the result of the PCR HSV-threshold cycle (Ct), we continued therapy with Acyclovir intravenously for 2 weeks and followed by oral Valacyclovir up to 6 weeks until the negative test result of October 12, 2013. The patient returned for a follow-up on December 15, 2013, with almost a full physical recovery. The liver transaminases returned to nearly normal levels as follows: ALT 49 U/L, AST 35 U/L, Total bilirubin 1.3 mg/dl and direct bilirubin 1.0mg/dl.

Table 3: The Ct value from consecutive samples show that the viral load from the first serum collected is high, as the Ct value is dependent on the amount of target present at the beginning of the reaction. The signal from the HSV on 12/10/2013 is a signal from the primer dimer. The Tm of HSV1 PCR product in °C from consecutive samples is as follows: HSV on 4/9/2013 to HSV on 28/9/2013 and a Tm of primer dimer HSV on 12/10/2013.

Sample	Ct	Tm
HSV 4/9/2013	16.207	87.93
HSV 6/9/2013	17.754	87.88
HSV 9/9/2013	21.562	87.92
HSV 14/9/2013	24.351	87.96
HSV 20/9/2013	28.006	87.94
HSV 28/9/2013	34.583	88.00
HSV 12/10/2013	37.663	85.76

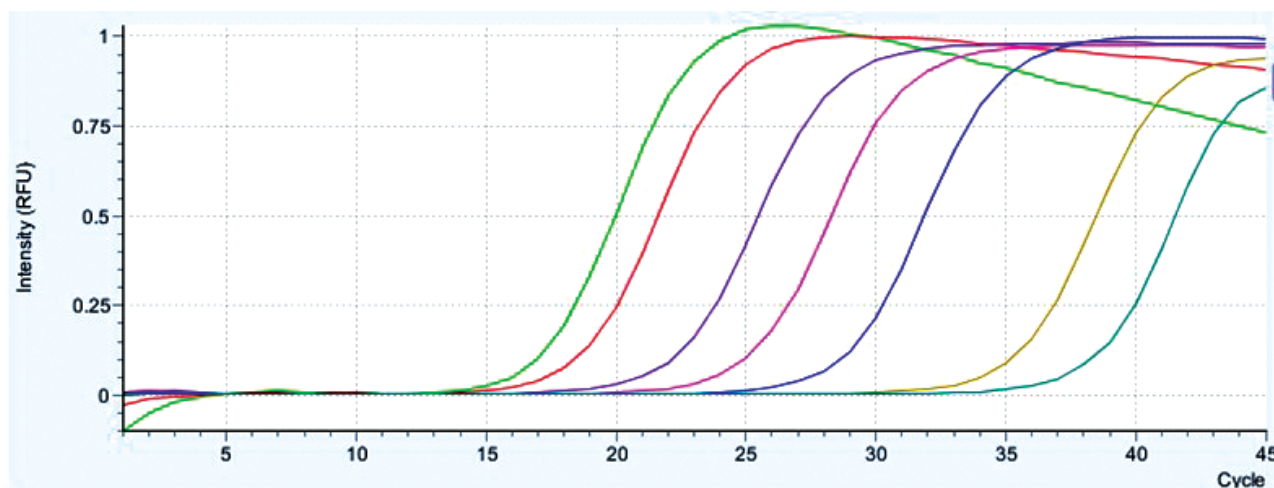


Figure 1: The amplification plot of real-time SYBR Green I PCR assay for Herpes Simplex type 1 from consecutive serum samples from a fulminant hepatitis patient. (The light green is the sample from 4/09/2013, the red from 6/09/2013, the purple from 9/09/2013, the pink from 14/09/2013, the blue from 20/09/2013, the yellow from 28/09/2013 and the green from 12/10/2013).

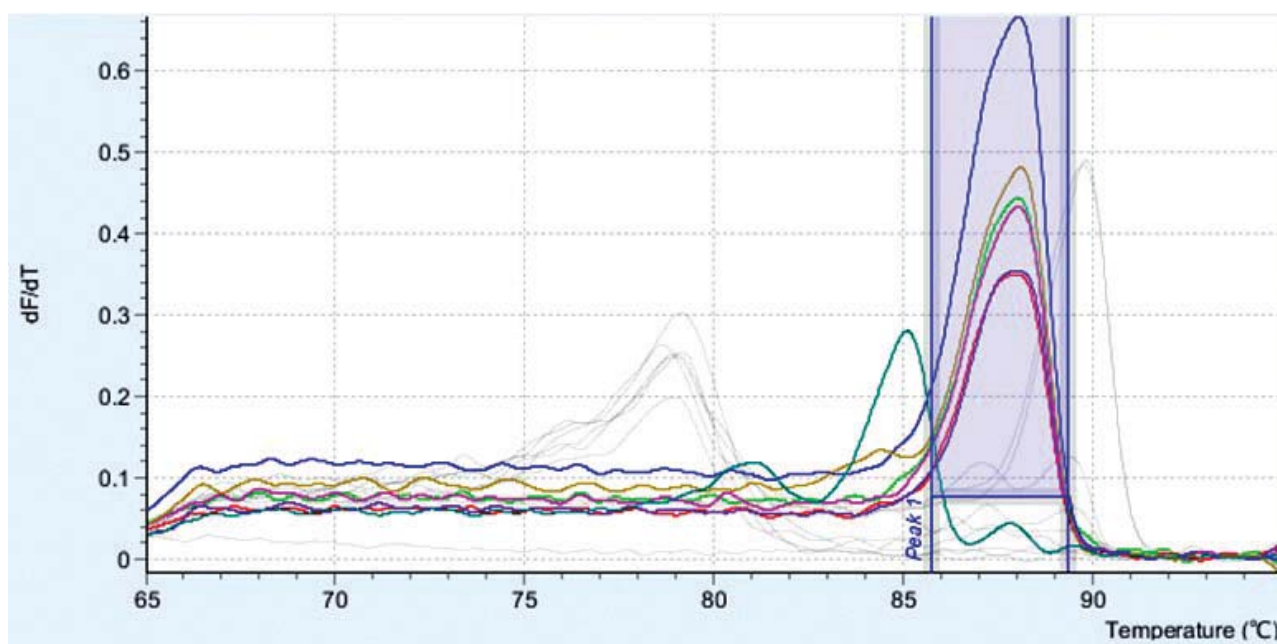


Figure 2: The melting curve profiles of HSV1 real-time PCR. The HSV1 PCR products have a T_m around 87.8-88.0 but the primer dimer product has a T_m of around 85.7 which is clearly separate from the HSV1 PCR product.

Discussion

Herpes Simplex virus (HSV) typically causes mucocutaneous vesicular oral (herpes labialis) or genital lesions (herpes genitalis); visceral involvement may occur in some clinical settings. HSV hepatitis is rare and accounts for only 1% of all acute liver failure (ALF) cases and only 2% of all viral causes of ALF.¹ HSV hepatitis is one of several clinical manifestations of HSV sepsis or disseminated disease leading more frequently to encephalitis, pneumonia and esophagitis², which mostly affects immunocompro-

mised patients such as organ transplant patients³⁻⁴, pediatric patients⁵ and patients in the third trimester of pregnancy⁶, but there have been reported cases of up to 25% in immunocompetent patients as well.⁹ Both HSV-1 and HSV-2 have been implicated as etiologic agents. Compromised cellular immunity is a major risk factor for HSV sepsis, either as a primary infection or as a reactivation of occult chronic HSV infection. HSV hepatitis after liver transplantation and heart transplantation has been reported. HSV reactivates after transplantation in approximately 60% of recipients not given antiviral prophylaxis.

Reactivation of HSV usually occurs during the first 1-2 weeks after transplantation.¹⁰ HSV infection of neonates is uncommon. The three major forms of neonatal HSV infection are disseminated disease (25%), central nervous system disease (30%) and skin, eye, and mouth disease (45%). Death from disseminated disease is usually caused by severe coagulopathy; and extensive hepatic and pulmonary involvement.¹¹ Around 2% of women acquire HSV during pregnancy. Changes in the immune system during pregnancy make pregnant patients more susceptible to acute HSV hepatitis, with a 40% risk for HSV-related ALF and death. Humoral and cell-mediated immunity are most depressed in the third trimester, as demonstrated by a decreased T-cell count and altered B-/T-cell ratios. In immunocompetent hosts, however, only primary infections have been associated with hepatitis. Severe HSV hepatitis in immunocompetent patients is a very rare condition, but it may lead to fulminant deterioration of liver function and can be rapidly fatal. HSV hepatitis is often left undiagnosed due to the absence of specific signs or symptoms, which include flu-like illness, fever and abdominal discomfort. Mucocutaneous lesions are only present in up to 50% of cases.¹²

Typically, anicteric hepatitis is seen in patients with HSV hepatitis. Anicteric hepatitis refers to a liver profile showing a significant increase in transaminases (100-1000 fold) with a relatively normal or low bilirubin. There may be a marked elevation of AST greater than ALT.¹³ Mild, asymptomatic liver enzyme elevations may be seen in 14% of immunocompetent patients with acute genital HSV infection. Severe HSV hepatitis is usually marked by significant elevations in transaminases, hyper-bilirubinaemia and coagulopathy. Disseminated intravascular coagulopathy (DIC) is frequently reported, and encephalopathy is a late sign of the disease.

A total of 137 cases (132 from literature, 5 institutional) of HSV hepatitis were reported. The main features at clinical presentation were fever (98%), coagulopathy (84%), and encephalopathy (80%). Most cases (58%) were first diagnosed at autopsy and the diagnosis was suspected clinically prior to tissue confirmation in only 23%. The course of the disease is often rapid and frequently fatal. The mortality rate can be as high as 75-90%, mainly because of delayed diagnosis and treatment with antiviral therapy.⁹

The diagnosis of HSV hepatitis should be considered in any patient with acute hepatitis, particularly with fever, leukopenia, and a negative hepatitis serology for hepatitis A, B, C, D, E, EBV and CMV especially when DIC is present and liver failure is suspected. Viral serology and cultures are extremely sensitive and can be used as a screening tool but are very poorly specific. Rapid viral culture is available for HSV which shortens the time for isolation to 4 days. Detection of HSV DNA by PCR appeared to be more discriminating than serological testing

for diagnosing or excluding HSV as a cause of ALF. All HSV hepatitis cases had high DNA levels, supporting the use of HSV PCR as a screening test for indeterminate ALF to formulate a rapid management plan versus other inaccurate and invasive tests, such as serology and liver biopsy.¹⁴

Although not always possible due to coagulopathy, the gold standard for diagnosis of HSV hepatitis is liver biopsy. Histology shows extensive areas of hepatocyte necrosis with adjacent congestion but minimal inflammatory infiltrates (Figure 3).¹³ Cowdry type A inclusions, nuclei with large eosinophilic ground glass-like inclusions surrounded by a clear halo, are pathognomonic for HSV hepatitis. Immunohistochemical staining can be done to confirm the diagnosis, and the presence of viral antigens can be demonstrated by immunoperoxidase staining and by identifying monoclonal antibodies against HSV antigens (Figure 4).¹³

HSV associated fulminant hepatic failure carries a high mortality risk, early intervention with acyclovir has been shown to be life-saving.¹⁵ Norvell JP, et al reported⁹ in HSV hepatitis cases, 49 (36.6%) of 134 patients received acyclovir treatment. Patients who received treatment were less likely to die or require liver transplantation (51% vs. 88.1%, $p < 0.001$) compared to untreated patients. In treated patients, the mean time from overt symptoms to treatment with acyclovir was 4.2 ± 1.8 days. There was a delay in the initiation of treatment (mean 4.7 vs. 3.5 days, $p = 0.03$) in patients who died or required liver transplantation as compared to patients who survived. Variables on presentation associated with death or need for LT compared to spontaneous survival: male gender, age > 40 year, immunocompromised state, ALT $> 5,000$ U/L, platelet count $< 75 \times 10^3$ /L, coagulopathy, encephalopathy, and absence of antiviral therapy.⁹ Therefore, it is a generally accepted consensus to begin antiviral therapy pre-emptively with acyclovir in cases of acute liver failure of unknown origin.

Acyclovir is classified as a category B drug in pregnancy with no fetal risk demonstrated in animal or human studies. High-dose intravenous acyclovir (at least 10 mg/kg every eight hours) is effective and appears to be safe in pregnancy. The safety of acyclovir in pregnancy has been reported in multiple studies where the rates of birth defects (2.6%) were not different from the expected rate (3.2%) in the general population.¹⁶ The current treatment recommendation for fulminant HSV hepatitis in pregnancy is intravenous acyclovir, with the addition of foscarnet for acyclovir-resistant cases.¹⁷ Therapeutic plasma exchange (TPE) has been reported to treat post-partum HSV-related ALF patients. TPE may have a therapeutic role in acute inflammatory disorders by reducing viral load, attenuating systemic inflammation and liver cell injury. However, further investigation is needed to clarify this potential role.¹⁸

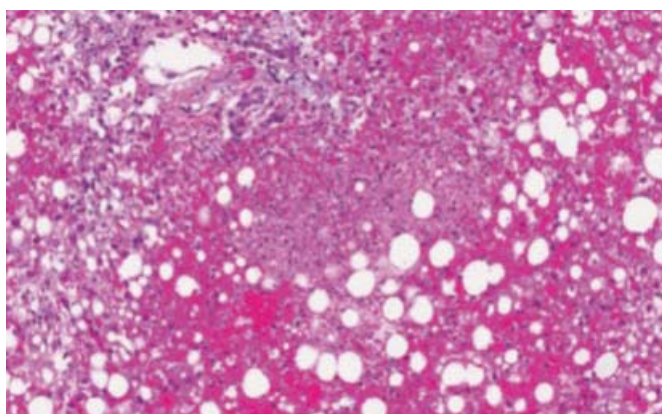


Figure 3: Liver pathology of HSV hepatitis: Zones of hepatocyte necrosis surrounded by hemorrhage without significant inflammation [100x magnification; Hematoxylin-Phloxine-Saffron (HPS) stain].¹³

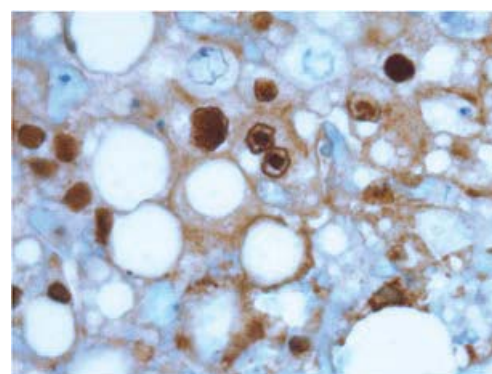
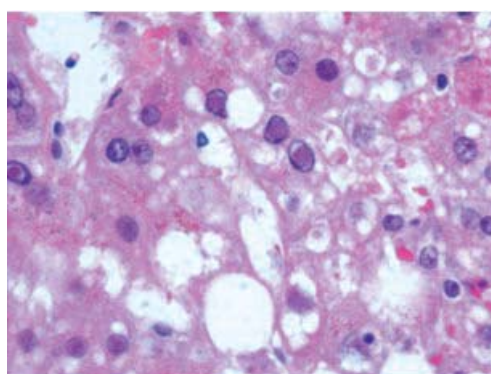


Figure 4A-B: HSV inclusions in infected hepatocyte.¹³
(A) Viral inclusions are readily visible in infection hepatocytes. (600x magnification; Hematoxylin-Phloxine-Saffron (HPS) stain).
(B) Immunohistochemistry for HSV virus highlights viral inclusions (600x magnification).

High urgency liver transplants should also be considered early in the course of the disease as it has been shown to improve outcomes. So far, 148 HSV-related ALF cases have been published, of which 9 underwent liver transplantation (LT). The reported post-transplant survival is poor, with over 60% dying in the first year.⁹ Dosing and duration of antiviral therapy after LT are not established. Quantitative HSV DNA testing is useful in predicting morbidity and mortality after LT and in determining the optimal type and length of antiviral regimen to use post-transplant. Because of the risk of recurrence, life-long prophylaxis with acyclovir is recommended.¹⁹

Moldovan B, et al.²⁰ based on the Scientific Registry of Transplant Recipients registry (USA), reported a better recovery in children than in adults. During the study period (1985-2009), 30 patients were listed for HSV hepatitis: 7 recovered spontaneously and 5 died, prior to transplantation. The remaining 10 children and 8 adults were transplanted. The chance of recovery was significantly

higher in children than in adults (7/19 vs. 0/11, $p = 0.02$). In children, survival was similar between HSV patients and the matched controls (5-year survival: 69% vs. 64%, $p = 0.89$). Conversely, survival was poor in adult HSV (5-year survival: 38% vs. 65%, $p = 0.006$), with 62% of them dying within the first 12 months.²⁰

Conclusion

HSV hepatitis represents a broad spectrum of disease from mild aminotransferase elevation to fulminant liver failure and death. HSV hepatitis should be considered in patients with fulminant liver failure of unknown cause. Acyclovir given in the early stages of fulminant hepatic failure may prevent mortality and avoid the need for liver transplantation. At an advanced stage, liver transplantation should also be considered. HSV DNA testing is useful in predicting morbidity and mortality after LT and in determining the optimal type and length of antiviral regimen to use post-transplant.

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Tenosynovitis of Extensor Carpi Ulnaris with Formation of Rice Bodies



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Formation of rice bodies in joints commonly occur in tuberculosis, rheumatic diseases and osteoarthritis. Sometimes rice bodies are found in synovial structures like tendon sheaths and periarticular bursa. Its occurrence always denotes the chronic state of the underlying disease. There are several hypotheses put forth to facilitate its etiology but there is no proof regarding its origin.^{1,2} Here we report a case where there was formation of rice bodies in the tenosynovium of extensor carpi ulnaris which healed completely after thorough surgical debridement.

Case Report

A 45-year-old woman farmer presented to us with complaints of pain and swelling over the ulnar side of the extensor aspect of right wrist for 2 years (Figure 1-2). Swelling was initially small and later gradually progressed to attain the size at presentation. Earlier, the swelling was associated with mild pain only during work. Later as the swelling progressed there was an increase in pain and numbness over the ring and little finger. There were no complaints of polyarthralgia or any symptoms of inflammatory back pain. The resultant restriction of activity caused the patient to seek treatment.

Clinical evaluation was suggestive of a lobulated swelling measuring about 4x2 cms which was cystic in consistency. Its margins were diffuse and extended proximally and distally. Fluctuation and translumination were positive which gave an exact picture of a dorsal ganglion except for its large size. Plain radiographs of the wrist merely showed a soft tissue swelling. Routine laboratory investigations and inflammatory markers such as erythrocyte sedimentation rate (ESR) and C - reactive protein (CRP) were within normal limits. Patient had a negative Mantoux test, rheumatoid arthritis (RA) factor and anti-cyclic citrullinated peptide (anti-CCP) immunoglobulin G (IgG).

Based on the findings, surgical excision was planned. A vertical incision over the entire length of the swelling was made. After superficial dissection, the lobulated ganglionic mass was found to arise from the tenosynovium of extensor carpi ulnaris. On opening the sac, numerous rice bodies were seen along with fibrous material and straw colored fluid (Figure 3). Complete debridement of the inflamed tenosynovium was done with removal of all rice bodies (Figure 4). Specimen was sent for histopathology and culture.

Histopathology revealed presence of bulbous fronds of hyperplastic synovial tissue with underlying intense chronic inflammatory cells like lymphocytes, plasma cells, multinucleated plasma cells and histiocytes in the fibrocollagenous stroma suggestive of chronic inflammation (Figure 5). Culture revealed no growth of any organism.



Figure 1: Dorsoulnar ganglion measuring 4x2 cms.



Figure 2: Lobulated swelling clearly seen from the lateral aspect.

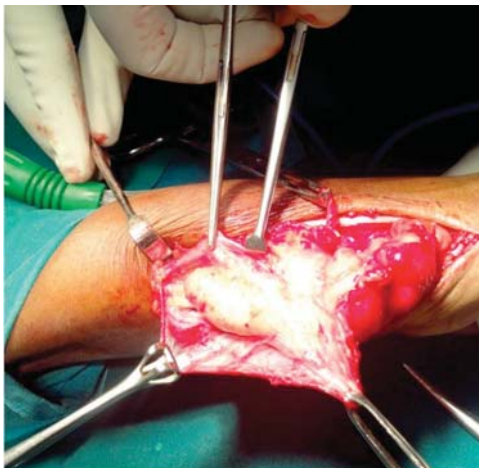


Figure 3: Rice bodies seen along with fibrinous material and straw colored fluid.

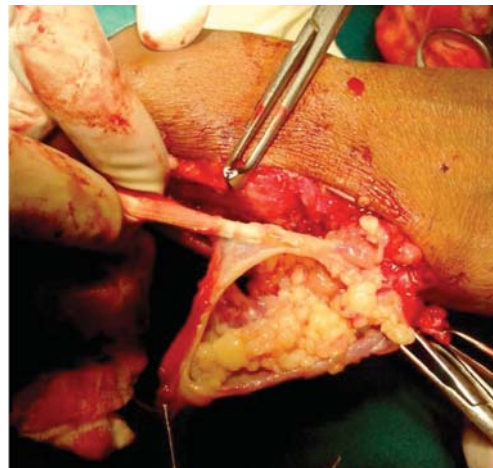


Figure 4: Extensor carpi ulnaris clearly seen during debridement.

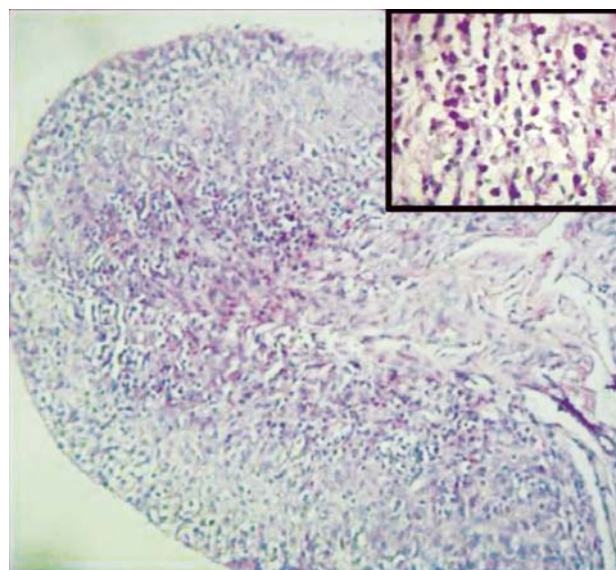


Figure 5: Histopathological slide showing hyperplastic synovial tissue with underlying intense chronic inflammatory cells (Magnified image shows multinucleated plasma cells).

The patient did not fit into the criteria for diagnosis of rheumatoid arthritis or peripheral spondyloarthropathies as it was an isolated issue of the extensor carpi ulnaris alone. Keeping the chronicity of this condition in mind an intensive therapy including anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs) were started. Six month follow up was uneventful with complete recovery of the condition.

Discussion

Most authors attribute the formation of rice bodies to a chronic response to synovial inflammation.¹⁻³ Literature states that rice bodies can occur either from the joints or any other synovial structures like periarticular bursa or tenosynovium.^{4,5} The condition is frequently associated with tuberculosis, rheumatoid arthritis, seronegative rheumatoid arthritis and sometimes osteoarthritis.^{6,7} Although extensor and flexor aspects of the wrist are the most common sites for tenosynovial inflammation, the site of occurrence varies. Reports reveal uncommon sites like biceps, semimembranosus and tibialis anterior tendons.^{5,8} Rice bodies can also be associated with calcific material.⁹

In our case, tenosynovium of extensor carpi ulnaris was inflamed and gave a picture of an unusually large dorsal ganglion. Symptoms of numbness could be attributed to

compression of the cutaneous branches of the ulnar nerve. Restriction of motion could be due to the unusually large size of the swelling. Thorough surgical debridement was the mainstay of treatment and care was taken not to leave behind any inflamed material.¹⁰ Similar to various reports in the literature, there was no recurrence following extensive surgical debridement.^{2-5,7,9,11}

An unusually large ganglion is a response to tenosynovial inflammation but whether such persistent untreated conditions lead to rice body formation needs to be researched. Formation of villous folds, presence of focal lymphoid nodules, fibrinous exudates and plasma cell infiltration are all signs of chronic inflammation.¹¹ The strong association between chronic synovial inflammation and formation of rice bodies cannot be ruled out. Its mere presence denotes the chronicity of the condition and the need for extensive debridement to prevent any recurrence. Such conditions are completely manageable and the patient can return to their best functional status.

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Plantar Fasciitis Heel Pain: Part 1 a Practical Management



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Plantar fasciitis is a common foot problem that occurs in 10% of the population.^{1,2} The most involved age group is 40-50 years old. Chronic inflammation and foot pain can be a result of calcification and is correlated with heel spur.^{3,4} Actually, symptoms of foot and heel pain can occur due to many different etiologies. Clinical history and physical examination are major keys to unlock the differential causes of heel pain. A knowledge of functional biomechanics of plantar fascia will help both physicians and patients to understand for prevention and rehabilitation techniques.

The treatment options are various and may not be limited to only one best treatment; a combination of therapies can be used. Furthermore, physicians should adjust the proper treatments of choice in accordance with the different circumstances of each person and treating hospital. Nowadays, physicians will use multi modal therapies, combining treatments of choice for a better and faster recovery.

Our review focuses on the practical management of degenerative plantar fasciitis. Mostly successful treatments are conservative, such as load absorbing insoles, stretching exercises and heat modalities.

Etiology and biomechanics

Plantar fascia is the strong elastic tissue that gives primary static and dynamic stability during walking, running and jumping⁵ (Figure 1). It has a functional structure of medial arch support for absorption of ground loading activity.⁶⁻⁸ Due to daily activities over a lifetime, the plantar fascia tends to degenerate by overuse, patients being overweight and middle age extending over longer periods. Actually, etiologies cannot be concluded, but it can show in the associated multifactorial factors such as poor quality footwear, arthritic diseases and structural deformity.⁹

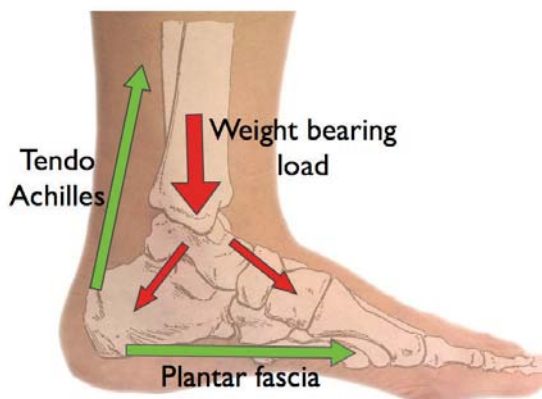


Figure 1: Weight bearing load.

Abnormal arch, low arch, flat feet and high arch have not been shown to be the true cause of plantar fasciitis although abnormal arch can be a cause of fatigue and cuff muscle myalgia.^{8,10} Abnormal arch can also be a cause of limited sport activities due to limited load absorption. Adequate loading supports such as orthotics, insoles and modified sport shoes are recommended for this group of patients.

Heel spur has not been a proven cause heel pain; chronic heel pain and inflammation may however, induce the calcific formation at plantar fascia origin.^{3,11,12} Moreover, a large heel spur can be a cause of abnormal overload and lateral plantar nerve entrapment. Since this condition can be a secondary cause of heel pain later on, then surgical options may be beneficial.

Clinical symptoms

The classic symptoms of plantar fasciitis are pain and tenderness at the medial heel area with the first steps in the morning or after long periods of rest. The clinical signs will improve after warming up with a few more steps and taking a warm bath. Physical examinations found the maximum tender point to be at the medial calcaneal origin of plantar fascia^{1,13-17} (Figure 2,3). Radiography may show a calcific formation at the calcaneus call heel spur (Figure 4).

However, even if radiography shows evidence of chronic inflammation, it is not a pathognomonic sign nor does it indicate the surgical removal of calcification. Before using radiography, the author suggests discussion with patients and explaining the natural history of the condition and treatment plan.^{18,19} Usually, this author would not recommend taking routine radiography because patients get increasingly nervous about calcific spur formations.

Sever's disease is a calcaneal apophysitis (an inflammation of the apophysis of the heel) in adolescents that in radiography appears slightly sclerotic or as a fragment of calcaneal apophysis (Figure 5). For differential diagnosis,^{2,4,7,20-23} the locations of maximum pain in the initial examination are the guide to pathological problems: pain in the posterior part leads one to consider Achilles tendinitis and retrocalcaneal bursitis, medial pain suggests tarsal tunnel syndrome and lateral pain may indicate Peroneal tendinitis^{17,24-26} (Figure 3). For medial calcaneal heel pain, differential diagnoses include heel pad syndrome, calcaneal stress fracture and tarsal tunnel syndrome. Tarsal tunnel syndrome can induce pain referred to the medial calcaneal area and then a positive Tinel's sign can indicate medial plantar nerve entrapment (Figure 6). MRI investigation can be helpful in cases where conservative evaluations have failed. MRI findings of plantar fasciitis can be thickened fascia, peritendinous edema and partial tears.^{16,21}



Figure 2: Differential diagnosis landmarks.



Figure 3: Differential diagnosis pathology.



Figure 4: Heel spur in radiography.



Figure 5: Sever's disease in radiography.

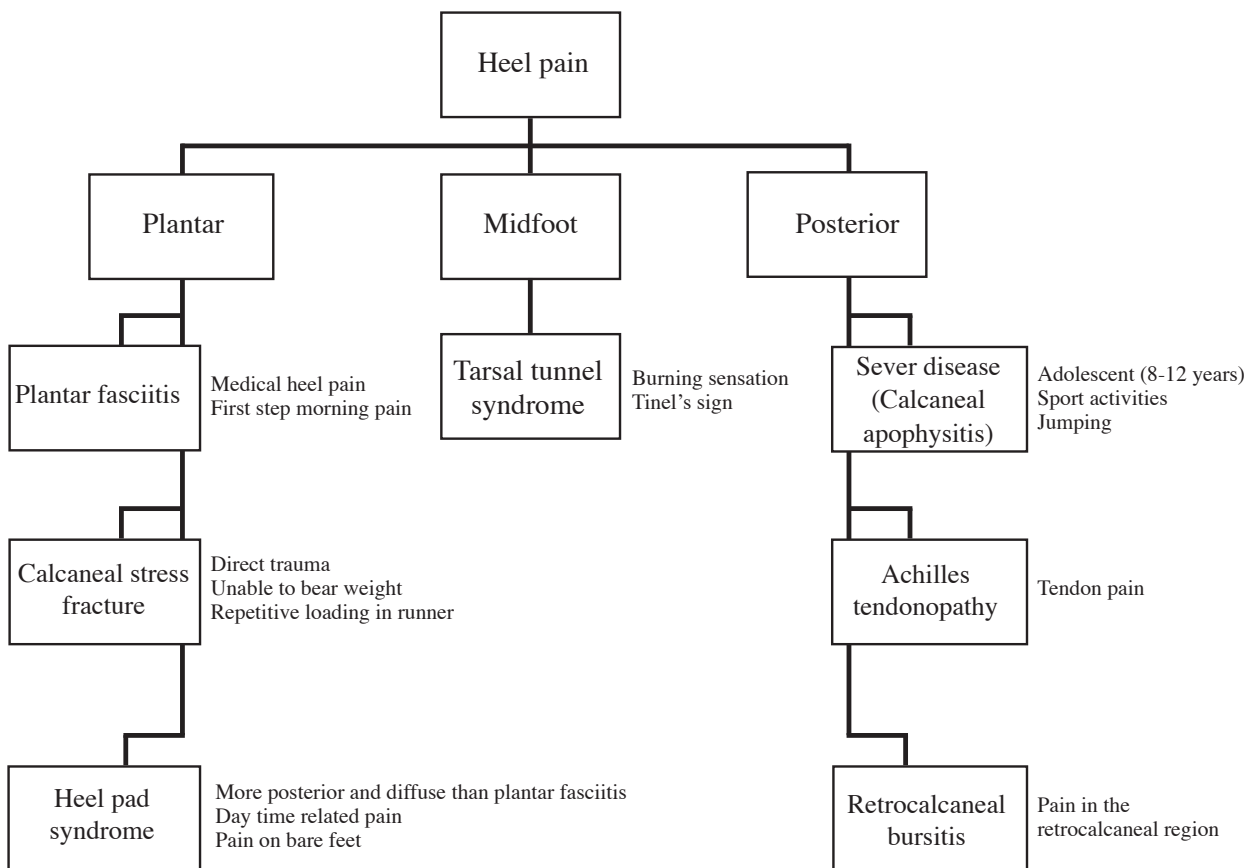


Figure 6: Heel pain diagnosis guideline.

Treatment Guidelines

Usually, the major treatments of heel pain with high success rates in good compliance patients are nonoperative.^{7,14,20-23,27} These included the following: a short term use period of NSAIDs can be prescribed for active symptoms of inflammation and pain;²⁸ steroid injections should be limited to cases of chronic and failure of first line treatment. First line treatment should be combined in multiple nonoperative treatments.²⁹ With the important landmark injection, physicians should be trained and address the needle directed properly to avoid complication of heel fat pad atrophy and plantar fascia ruptures.²⁹ The American College of Foot and Ankle Surgeons has issued good practice guidelines which be can adapted to be used in each hospital facility.²³

The first line of treatment includes insoles, foot taping, foot padding and oral nonsteroidal anti-inflammatory drugs (NSAIDs)^{1,28,30-32} (Figure 7, 8). Cold and heat therapy should be applied at the appropriate time. Cold therapy (including ice or gel packs) is appropriate for the acute period of inflammation, usually in the first 24 hours, because

the inflammatory process needs to be reduced. Usually, heat therapy is of more importance because of increasing tissue elasticity and increasing blood circulation for the healing process. Heat therapy includes soaking in warm water 10 to 15 minutes morning and evening, and heat treatment with paraffin but deep heat ultrasound shock waves may be used as a second line. However, the first line warm bath is of practical use. Reducing pressure loading is of importance to avoid repetitive mechanical trauma. Pressure reducing supports include heel cushions, heel cups, insoles, and running shoes. Patients should avoid using flat shoes, walking barefoot, and impact sport or load inducing activities.³³ For the latter, regular Achilles and plantar fascia stretching is significant in long-term recovery and needs to take place after pain and inflammation have been well controlled. For the first line treatment, the author aims to educate patients for long-term success and self-help. Initially, continued treatments should be taken within 1 to 3 months with good patients' compliance. The author advises use of insoles in all shoes (including house slippers), warm bath, short period of NSAIDs (less than 2 weeks) and then stretching exercises (after pain improvement).

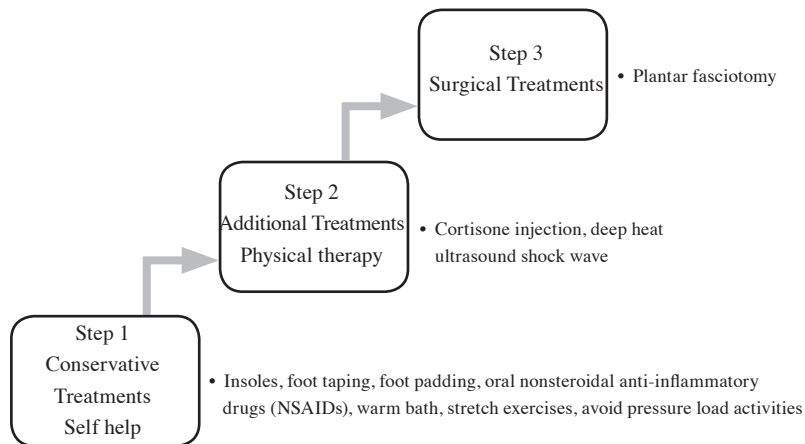


Figure 7: Plantar fasciitis treatment guideline



Figure 8: Insole absorbs weight bearing load.



Figure 9: Insole composite properties.

Nowadays, insoles are widely accepted for reducing pain in plantar fasciitis.^{31,34} The author has developed a specially formulated composite insole, Smile feet™ (Images and information from: <http://www.smile-feet.com/>) (Figure 9) for reducing foot pain and fatigue. Our preliminary research shows its effectiveness in reducing pressure and pain.

The second line of treatment includes continuation of the first line of treatment, cortisone injection,^{21,29,35} extracorporeal shock wave and night splints.^{14,36-40} These treatments should be started if first line treatments show no response in one month or little response within three months. Usually, second line treatments will show improvement within 2 months but patients need to understand that treatment should continue until resolution of all symptoms. However, unresponsive patients need to seek reevaluation of cause, diagnosis, associated conditions and their own compliance.

If 6 months have passed and all previous treatments have failed, surgery should be considered as the third line of treatment. However, since almost all plantar fasciitis patients have success with conservative treatment, surgery is the last consideration. Surgical techniques depend on surgeons' experience and may include endoscopic plantar fasciotomy, in-step fasciotomy, or minimally invasive surgical techniques.^{21,41,42}

Summary

Plantar fasciitis is a common condition of heel pain. Clinical symptoms show pain in the morning with the first steps taken and tenderness at the medial heel area of plantar fascia origin. Multi modality treatments are the key to success and include use of insoles, warm baths, short period of oral nonsteroidal anti-inflammatory drugs (NSAIDs) and then stretching exercises. After three months, patients less responsive to treatment should be given cortisone injections and deep heat ultrasound shock wave. The last treatment option for unresponsive cases is plantar fasciotomy surgery.^{41,42}

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A New Approach to Medicine: the Anti-Aging Framework



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Cell degeneration depends on many factors including complex genetics that influence aging. All factors leading to aging are partially controllable, and aging is fundamentally a result of controllable abnormal defects. Doctor Denham Harman postulated a “**free radical theory of aging**” more than 50 years ago. With a study of mice exposed to radiation, Dr Harman observed destructive molecules as free radicals that changed the cell function irretrievably. Malnutrition and exposure to toxins increases the risk of cell oxidation.² Previous studies supported the theory that the free radical is a primary cause of common diseases such as brain disease and kidney diseases.

Persistent inflammation occurs frequently with aging and is a primary contributor to the deterioration that our body undergoes as we grow old.³ Inflammation can be triggered by both internal and external causes, making it difficult to prevent. For instance, excess belly fat releases inflammation-causing molecules called cytokines.⁴ Continuous low-level inflammatory assaults inflict damage on everything from brain cells and arterial walls, to cell regulatory genes.⁵ Heart attack, stroke, heart valve failure, cancer, and Alzheimer’s have all been linked to chronic inflammation that occurs in most of us as we age.

Glycation is the result of excessive glucose in the body reacting with the body’s protein forming toxic substances and nonfunctioning units.⁶ Glycation can sometimes result in two strands of protein being joined together, called cross-linking.⁷ This is a process which can damage the body’s organs.⁸ Methylation is the process of replacing a hydrogen atom with a methyl group. Human beings depend on methylation to detoxify poisons, to repair DNA and to supply anti-aging hormones. Hormone decline is one factor in the aging process and aging is caused by hormone imbalances. All male and female hormones affect the mental and physical well being of humans. An abnormal hormone concentration is a serious contributory factor of illness.

Overcoming the effects of aging

Preventing free radical damage⁹ is the most important factor to fight aging. People need to take a series of measures in order to reduce free radicals. These include consuming chemical-free foods, avoiding exposure to ultraviolet radiation and toxins, in order to prevent radical damage.^{11,12} People can counteract the effects of these damaging factors by supplementing their daily diet with^{13,14} vitamins, carotinoids, selenium, zinc, manganese, coenzyme Q10, and lipoic acid. All of these substances are essential to attack free radicals.¹⁵⁻¹⁷ Most people obtain phytochemicals from fruits and vegetables in their diet but this is not deemed sufficient for optimal antioxidant protection.^{18,19}

C-reactive protein and fibrinogen are important blood markers.²⁰ A slight elevation of these markers can double the risk of heart disease. Supplementary nutrition such as omega-3 fatty acids and curcumin play an active role in the reduction of inflammation.^{22,23} Homocysteine destroys the vascular endothelial lining which is the cause of cholesterol deposits on the vascular wall.²⁴⁻²⁷ Consumption of folic acid, vitamin B6 and B12 counteract the negative effects of homocysteine.^{28,29} The prevention of glycation with carnosine is one of the most effective anti-aging measures to be taken.³⁰⁻³⁵ An anti-aging lifestyle requires adequate diet, exercise, sleep and stress reduction.

The anti-aging lifestyle

The prevention of anti-aging incorporate essential components; diet, exercise, sleep and stress reduction. The diet should emphasize the quality of lean protein complex carbohydrates and healthful fats rather than the quantity.

Recommendations for anti-aging diet are:

- Eliminating sugar and refined carbohydrates.
- Increased more unsaturated fats (olive oil and nuts) and essential fatty acids (omega 3 acid salmon and other fatty fish).
- Increased consumption of quality protein. At least one third of calories consumption should be from fish, egg white, lean cuts of organically raised beef and poultry, low-fat organic dairy products, beans.
- Take fresh vegetables and the widest possible variety of brightly colored fruits and vegetables in red, yellow and green foods; these are health promoting phytochemicals.

The role of anti-aging (regenerative medicine) is based on an accurate diagnosis and treatment of disease. The goal of regenerative medicine is to achieve good health and sustained wellness throughout the whole human life span. Each step of anti-aging medicine uses scientific and medically tested technologies including detection, prevention, treatment and attempts at the reversal of existing dysfunction and diseases on a treatment basis. Regenerative medicine is based on a combination of traditional and alternative approaches.

The four domains of regenerative medicine are:

1. Improved health and reversal of disease
2. Prevention of a disease before it occurs.
3. An holistic approach, considering each aspect of the patient's health.
4. A combination of traditional and alternative treatments based on an open minded approach albeit founded on a scientific basis.

Anti-Aging focuses on preventing damage and rejuvenating the entire body to achieve total wellness and longevity. Anti-aging medicine addresses fundamental preventive measures like proper diet and exercise, and the importance of living a healthy lifestyle. At the same time, advanced technology is utilized to thoroughly investigate each organ system through a range of specialized tests to create a tailor-made health program for each individual.

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The Significance of Vitamin D3



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In 1921, scientists discovered that sunlight helped strengthen bones and prevented Rickets in childhood and Osteomalacia in adulthood.¹ Moreover, sunlight supported our bodies in creating vitamin D. Scientists also found that fish liver oil contains vitamin D. The United State (U.S) has been supplementing vitamin D in milk and various foods since 1930, which has reduced the incidence of Rickets and Osteomalacia.²

Sources of vitamin D

1. Mushroom, spinach, broccoli and other green vegetables contain vitamin D2 which is created by ultraviolet rays (UV) from sunlight. Vitamin D2 will then transform into vitamin D3 in our bodies, but this is not sufficient for our body's needs.
2. Vitamin D3 can be created by ultraviolet B (UVB) from sunlight in skin within one day. Skin can produce vitamin D3 up to 20,000 international units (IU) after getting sufficient sunlight over a period of time.
3. Vitamin D3 can be found in sea fish such as salmon, mackerel, sardine etc. although these sources alone do not have sufficient levels of vitamin D3. For example; 5 ounces (oz) of salmon, 7 oz of halibut, 30 oz of cod, 7 oz of tuna may contain as much as vitamin D3 400 IU. Although fish liver oil has a lot of vitamin D, it has excessive vitamin A. An egg yolk has only 25 IU vitamin D but contains cholesterol of up to 275 milligrams (mg). Daily intake of cholesterol should not exceed 300 mg. 3.5 oz of cow liver contains 46 IU vitamin D3.
4. Vitamin D3 can be obtained from fortified milk cereal, bread and vitamin supplements. A cup of milk has approximately 100 IU vitamin D.

Vitamin D added to yoghurt, orange, juice, cereal and some kinds of bread is a low dose of vitamin D.³ A regular multivitamin pill has 400 IU vitamin D3. For most people who do not have vitamin D deficiency one pill per day will suffice.

Note: Vitamin D originating from sunlight is kept in the body for a month but vitamin D sourced from food and supplements will remain in the body for two weeks.

The transformation of vitamin D in the body

There are two types of vitamin D. The first type, vitamin D3 comes from plants. Vitamin D3 is derived from skin synthesis, sea food, beef and pork, and nutritional supplements. Vitamin D2 will change into vitamin D3 in the body to merge with existing vitamin D3 levels and then passes through the liver and is processed to become inactive vitamin D3, 25-hydroxyvitamin D or 25(OH)D. Most inactive vitamin D3 will pass through the kidneys

in order to change into active vitamin D3 1,25-dihydroxyvitamin D [1,25(OH)₂D]. Before the body is able to use active vitamin D₃, it passes through the blood vessels to go to four important organs namely intestine, kidney, bones and the parathyroid gland. These four organs are responsible for controlling the levels of calcium and phosphorus in our blood. Both inactive vitamin D₃, 25(OH)D and active vitamin D₃, 1,25(OH)₂D will circulate in blood vessels and they play a role in controlling the function of organs. Inactive vitamin D₃, 25(OH)D which the liver produces can be transformed into active vitamin D₃, 1,25(OH)₂D in many organs.⁴

The quality of Vitamin D

Many cells in our body use vitamin D in order to control the cell system to work properly and effectively as follows:

1. Increase the strength of bones, to control the absorption of calcium in the intestine, to maintain normal levels of calcium in the blood, to help prevent vertebral compression fractures and hunchback as we age, bones are harder to break in the elderly, and to prevent decayed teeth.
2. Increase muscle strength, to allow us to sit down and get up from a chair easily without stumbling and falling.
3. Increase the flexibility of our blood vessels, to help improve the expansion and shrinking of blood vessels, to control blood pressure.
4. Control the growth of blood vessels and to prevent them from increasing too much.
5. Improve the work of the cardiac muscle.
6. To help our lungs to work better, to help asthmatics to breathe properly.
7. Help control diabetes by producing insulin to decrease blood sugar levels.
8. Help to improve immunity to protect against infections
9. Prevent dementia and multiple sclerosis.
10. Control the dividing of cells, both in terms of size and amount of cells produced, and to help prevent large intestine cancer up to 28%.
11. Control the cell life cycle.
12. Help to control the parathyroid hormone to remain normal. In cases of a deficiency in vitamin D, parathyroid hormone levels will be high, which aggravates mental instability, insomnia and paresthesia muscle cramps and palpitations. Vitamin D helps to increase calcium levels, which has an impact on parathyroid hormone reduction. Symptoms will then disappear. But when vitamin D levels are normal and there is a high level of calcium in the blood, there are other issues that will be discussed below.

The cause of Vitamin D deficiency^{3,4}

Vitamin D deficiency is found in people who get too little sunlight. For example, people who live above or below latitude 35 (except Eskimos who do not lack of vitamin D because they regularly consume fatty fish).

Generally in winter, people will experience a lack of vitamin D if they do not have enough sunlight. Sun block and lotion with sun protect factor (SPF) 30 that protect against UVB rays up to 99%, leads to an inability of the skin to produce vitamin D. People with black skin lack vitamin D because the black melanin pigment protects against UVB. People who wear clothes that cover the whole body do not get enough exposure to UVB. UVB cannot penetrate the skin of people who are older than 50 years, so they lack vitamin D as well. Moreover, vitamin D deficiency is found in people who are vegetarian, are pregnant without enough exposure to sunlight and lack food and vitamin D supplements. Infants who only drink their mother's milk lack vitamin D because mother's milk has low levels of vitamin D. People who have a problem with their liver and kidney will lack vitamin D because the liver cannot produce the inactive vitamin D₃, 25(OH)D and the kidney cannot produce active vitamin D₃, 1,25(OH)₂D. Vitamin D that we ingest that the intestine cannot digest is found to cause malabsorption syndrome, an effect of gastric surgery and a disorder of vitamin D metabolism. People who use steroid anticonvulsive drugs and statins can also be vitamin D deficient.

The control of calcium levels and the change of phosphate levels in the blood when there is a lack of Vitamin D

The organs that control calcium levels and the change of phosphate levels are the intestine, parathyroid gland, bones and kidneys. When inactive vitamin D levels, 25(OH)D in the blood is low, active vitamin D, 1,25(OH)₂D will be low as well. This process decreases the ability of the intestine to absorb calcium and phosphate from food. As a result, calcium and phosphate levels in the blood are low. Calcium is essential for neuromuscular function and cardiac function. The body cannot let calcium levels drop, so the parathyroid glands release more parathyroid hormone, which results in the reduction of calcium and phosphate levels in bones. Calcium and phosphate from bones are taken into the blood and circulated in order to maintain normal calcium levels in the blood and to ensure the heart and nervous system work normally. This process, however, has an impact on osteopenia, osteomalacia and osteoporosis. This is one of the important factors which contribute to bone fractures. When the blood flows to the kidneys, calcium and phosphate is distilled via urine but the kidney retains calcium in the blood vessels while the phosphate is flushed out by urine. Consequently, the blood has normal levels of calcium but very low levels of phosphate. This symptom is found in people who lack vitamin D.^{5,6}

How to detect vitamin D levels in our blood

If we detect inactive vitamin D₃ (25 (OH) D) with a testing serum, inactive D₃ can exist for 15 days (half-life 15 days) and active vitamin D₃ (1,25(OH)₂D) can exist for 15 hours (half life 15 hours). So, we do not use this

method to determine the level of vitamin D3. The readings are as follows:

Vitamin D3 lower than 20	< 20 ng/ml	High loss
Vitamin D3 lower than 30	< 30 ng/ml	Loss
Vitamin D3 level 30	≥ 30 ng/ml	Normal
Vitamin D3 higher level	> 150 ng/ml	Toxic level

Note: nanogram per one milliliter (ng/ml)

The result of taking a lot of vitamin D3 can lead to headaches, vomiting, nausea and mental disorders. These are the symptoms of abnormally high calcium levels in the blood.

X-ray to detect Bone Mineral Density (BMD)

Testing for BMD used to be part of a diagnosis paired with blood tests for inactive vitamin D, 25(OH)D. If a low BMD shows osteopenia, we will find that vitamin D3 in the blood is low (loss). If BMD shows osteomalacia or osteoporosis, we will find that inactive vitamin D3 in the blood is very low (high loss).

Flushing out vitamin D

By the process of hydroxylation action inactive vitamin D3, 25(OH)D and active vitamin D3, 1,25(OH)2D will disintegrate and go through the liver in order to travel via the bile duct and then the intestine to leave the body via excrement. When the liver does not function, there is no change of vitamin D in the liver and the vitamin D3 will then be disintegrated via urine directly by the kidneys.⁷

Dose of vitamin D per day³

Recommended Daily Allowances

Age	Male	Female	Pregnancy	Breast feeder
0-12 months	400 IU	400 IU		
1-13 years	600 IU	600 IU		
14-18 years	600 IU	600 IU	600 IU	600 IU
19-50 years	600 IU	600 IU	600 IU	600 IU
51-70 years	600 IU	600 IU		
>70 years	800 IU	800 IU		

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Important note

Normally, we use vitamin D3 to prevent many diseases. The dose recommended is given above in the table. If we increase our intake of vitamin D3 to more than 1,000 IU daily to cure many diseases including vitamin D deficiency diseases, we should consult a doctor. This is because vitamin D can be toxic if we consume more than 40,000 IU per day.

Importantly, we should also check calcium and phosphate levels in the serum annually. Toxic levels of vitamin D (> more than 150 mg/ml) will be found when calcium and phosphate levels are higher than normal. This may cause metastatic calcification, kidney destruction and mental disorders.

High levels of calcium in the blood can come from other diseases, for example, a tumor of the parathyroid gland, cancer, chronic infections such as Tuberculosis (TB), Fungus, Sarcoidosis and Wegener's Granulomatosis, etc.

According to The American Blood Pressure Control Medical Association, daily levels of calcium in food and medication must not exceed 1,230 mg. According to The Diabetes Association, calcium consumption is limited to 1,000-1,500 mg per day.

People who have low vitamin D3 levels should take calcium and vitamin D3 in order to prevent bone hungry syndrome which causes many symptoms of low calcium in the blood because the bone leaches calcium from the blood rapidly. This process results in carpedal spasm, convulsion and other symptoms of hyperparathyroidism.



Rescue Treatment for Migraine Headache in Emergency Department Part 1: Diagnosis, General Management, and Role of Dopamine Antagonists and NSAIDs



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Migraine is a common recurrent neurological disorder with a high impact and is debilitating. Approximately 14.7% of the global population has migraine (an estimated 6% in men and up to 18% in women).¹ A recent report ranked migraine headache as the third most common disease in the world (behind dental caries and tension type headache).² On the basis of migraine attack disability alone, migraine was ranked seventh highest among specific causes of disability globally (responsible for 2.9% of all years of life lost to disability).^{1,2} Recent data from US public health surveillance studies showed that headache was the fifth leading cause of emergency department (ED) visits in the United States, estimated to account for over 4 million visits annually (1.2% of outpatient visits). The burden of headache was highest in females aged 18-44, where the 3-month prevalence of migraine or severe headache was 26.1% and head pain was the third leading cause of ED visits.³ Most migraineurs who visit ED for treatment generally have severe and/or prolonged symptoms concomitant with nausea/vomiting, and usual acute medications are not effective. Over half of the patients use simple analgesics to treat their headache attack but often to no effect.⁴ Migraine-specific medications (triptans or ergotamine) have been used only in a few patients.⁵ The goal of ED therapy is to deliver medicines with rapid, complete relief of pain and associated migraine symptoms, restore functional ability, with minimum adverse effects and without recurrence of headache after ED discharge.⁶ Intravenous medications that are used specifically for rescue treatment in migraine included dopamine antagonists, NSAIDs, opioids, magnesium, valproate, and corticosteroids. This paper consists of 2 parts; part 1 reviews the role of dopamine antagonists, NSAIDs, and opioids that are available in Thailand for migraine treatment in ED.

Diagnosis of migraine in the emergency setting

A detailed history and physical examination can help confirm the diagnosis and rule out life-threatening causes of secondary headaches such as subarachnoid hemorrhage, arterial dissection, meningitis, temporal arteritis, cerebrospinal fluid outflow obstruction, and elevated or low intracranial pressure. The clinical characteristics of secondary cause of headache can be memorized from the mnemonic “SNOOP4”:

- Systemic symptoms (fever, weight loss) or Systemic disease (malignancy)
- Neurologic symptoms or signs
- Onset sudden (acute or thunderclap headache)
- Onset after age 50 years
- Previous headache history (new or different)
- Progressive
- Precipitation by Valsalva (cough, bend)
- Postural

If one or more of the SNOOP4 features are present, the diagnostic tests including neuroimaging (computed tomography or magnetic resonance imaging), lumbar puncture, and blood tests may be considered.⁷

Migraine is diagnosed by clinical criteria provided by the International Classification of Headache Disorders 3rd Edition beta (ICHD-III beta; Table 1).⁸ Migraine headache is characterized by unilateral location, pulsating quality, moderate to severe intensity, aggravated by routine physical activity, and accompanied by photophobia (sensitivity to light) and phonophobia (sensitivity to sound) or nausea and/or vomiting.

The accurate diagnosis of headache can be troublesome at the ED due to the severity of the migraine attack, the associated symptoms especially nausea and/or vomiting that might require emergency treatment, and also because of the complicated ICHD-III beta criteria. A brief self-administered migraine screener (ID-Migraine), consisting of questions on disability, nausea, and photophobia, is a valid and reliable screening instrument for migraine headaches in the primary care setting. The test outcome is positive when the answer is “yes” for at least two out of the three questions.⁹ (Table 2)

The study role of ID-Migraine in emergency departments showed that the ID-Migraine exhibited a high sensitivity of 0.94 and high specificity of 0.83 with high positive predictive value (PPV) of 0.99 in primary headache.¹⁰ A negative ID Migraine score, less than 2 positive responses, reduces the post test probability of migraine from 59% to 23%.¹¹

Management for acute migraine in the emergency room

Intravenous fluid

The patient should be assessed for volume depletion because nausea occurs in more than 90% and vomiting occurs in approximately 70% of migraineurs. In those who experienced nausea or vomiting, 30.5-42.2% indicated that it interfered with their ability to take their oral migraine medication.^{12,13} Intravenous fluid replacement is useful for rehydration and in avoiding postural hypotension associated with dopamine antagonist treatment and provides some degree of renal protection if non-steroidal anti-inflammatory drugs (NSAIDs) are used.^{14,15} A quiet, darkened and comfortable area in ED can provide additional benefits to these patients.

Dopamine antagonists (Neuroleptics)

Dopamine plays an important role in migraine pathogenesis probably by acting on central pain control pathways and on cranial blood vessels.¹⁶ Recent genetic studies show evidence of genetic polymorphism of the dopaminergic and dopamine transporter genes.^{17,18} The dopamine

metabolite is increased in cerebrospinal fluid (CSF) during the migraine attack and the levels correlate with the severity of pain.¹⁹ Dopamine antagonists are very useful in rescue treatment of migraine and appear to be equivalent to the migraine specific medications (sumatriptan and dihydroergotamine) in migraine pain relief.²⁰ There are 2 major subclasses of neuroleptics, the phenothiazines group (e.g., prochlorperazine, chlorpromazine, promethazine, and methotrimeprazine) and the butyrophenones group (droperidol and haloperidol). Metoclopramide is in its own third class. The phenothiazines, chlorpromazine and prochlorperazine, were commonly used in ED. Thirteen trials showed that phenothiazines were markedly more effective than placebo for headache relief (OR 15.02; 95% CI, 7.57-29.82) and clinical success (OR 8.92; 95% CI, 4.08-19.51). The phenothiazines were more effective than metoclopramide (OR 2.25; 95% CI, 1.29-3.92) for clinical success, but not different for headache relief. The clinical success rate of phenothiazines was 78% (95% CI, 74-82).²¹

Neuroleptics act on the postsynaptic dopamine D2 receptor in the hypothalamus, limbic system, periaqueductal grey, and basal ganglia. Neuroleptics also have anticholinergic, antiadrenergic, anti-serotonergic and antihistaminergic effects. The most common side effects of neuroleptics are sedation and drowsiness due to blockage of muscarinic cholinergic and histamine receptors. Extrapyramidal side effects dystonia and akathisia are commonly seen in parenteral form and more often with prochlorperazine. Dystonia and akathisia can be prevented by premedication with anticholinergic agents (e.g., benztropine, diphenhydramine, or trihexyphenidyl). Due to α -adrenergic antagonist effects, postural hypotension can occur but is infrequently reported in phenothiazine. Neuroleptic malignant syndrome, which is characterized by fever, rigidity, confusion, and autonomic function instability, is a rare side effect. Droperidol and haloperidol can cause QT interval prolongation that increases risk of fatal ventricular arrhythmias and cardiac arrest.²¹

- Chlorpromazine

Several randomized controlled trials and head-to-head trials supported the efficacy of chlorpromazine in acute migraine.²⁰ Pool clinical analysis showed the success rate of acute migraine treatment is 81% for chlorpromazine (95% CI, 75-86%).²³ In a randomized controlled trial in an emergency room setting, chlorpromazine at dose 0.1 mg/kg intravenous (IV) showed a significantly reduced pain score compared with placebo in 128 migraineurs. Pain free at 1 hour for migraine with aura (66.7% in chlorpromazine group vs. 6.7% in placebo; $p < 0.01$) and migraine without aura (63.2% vs. 10%; $p < 0.01$).²⁴ In comparison trials, pain reduction (VAS) was greater for chlorpromazine 0.1mg/kg IV (up to 3 doses) than meperidine 0.4 mg/kg IV plus diphenhydramine 25mg (VAS -70.6 vs. -44.5; $p < 0.05$).²⁵ Chlorpromazine 12.5 mg IV (could be repeated up to 37.5mg) was compared

Table 1: The International Classification of Headache Disorders, 3rd edition (beta version) for migraine without aura and migraine with aura.

Migraine without aura	Migraine with aura
<p>Diagnostic criteria:</p> <p>A. At least five attacks¹ fulfilling criteria B-D</p> <p>B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)^{2,3}</p> <p>C. Headache has at least two of the following four characteristics:</p> <ol style="list-style-type: none"> 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) <p>D. During headache at least one of the following:</p> <ol style="list-style-type: none"> 1. nausea and/or vomiting 2. photophobia and phonophobia <p>E. Not accounted for by another ICHD-3 diagnosis</p> <p>Note:</p> <ol style="list-style-type: none"> 1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 Migraine without aura but have had fewer than five attacks, should be coded 1.5.1 'Probable migraine without aura'. 2. When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of waking. 3. In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than 2 hours in children has not been substantiated). 	<p>Diagnostic criteria:</p> <p>A. At least two attacks fulfilling criteria B and C</p> <p>B. One or more of the following fully reversible aura symptoms:</p> <ol style="list-style-type: none"> 1. visual 2. Sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal <p>C. At least two of the following four characteristics:</p> <ol style="list-style-type: none"> 1. at least one aura symptom spreads gradually over ≥ 5 minutes, and/or two or more symptoms occur in succession 2. each individual aura symptom lasts 5-60 minutes¹ 3. at least one aura symptom is unilateral² 4. the aura is accompanied, or followed within 60 minutes, by headache <p>D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.</p> <p>Note:</p> <ol style="list-style-type: none"> 1. When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3x60 minutes. Motor symptoms may last up to 72 hours. 2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

Table 2: The ID-Migraine.

- During the last 3 months, did you have the following with your headaches:

You felt nauseated or sick to your stomach

Yes No

Light bothered you (a lot more than when you don't have headaches)

Yes No

Your headaches limited your ability to work, study or do what you needed to do for at least one day.

Yes No

with lidocaine 50mg IV (could be repeated up to 150 mg) and with dihydroergotamine (DHE) 1 mg IV (could be repeated once). Pain reduction (11 PPS) was greater with chlorpromazine than with lidocaine or DHE (chlorpromazine -79.5% vs. lidocaine -50% vs. DHE -36.7%; $p < 0.05$).²⁶ Chlorpromazine 12.5 mg IV (could be repeated up to 37.5mg) was compared with sumatriptan SQ 6mg. At 2 hours, there was no difference in pain reduction (VAS) (chlorpromazine -54.3 mm vs. sumatriptan -63.3 mm).²⁷

- Metoclopramide

Metoclopramide is widely available, inexpensive, and commonly used for the treatment of nausea, vomiting, and gastroparesis. In addition to dopamine antagonists, metoclopramide also has serotonin antagonist effect. Common side effects include fluid retention (caution in congestive heart failure and liver disease), lower seizure threshold, mild sedation and extrapyramidal side effects. Meta-analysis from 13 randomized controlled trials for parenteral metoclopramide in acute migraine showed metoclopramide is an effective treatment for migraine headache in adults and should be considered as a primary agent in the treatment of acute migraine in emergency departments.²⁸ Metoclopramide 10mg IV showed superior to placebo in three studies for all outcomes related to pain and nausea. Pooled data from three studies showed that metoclopramide more often leads to significant reduction in headache pain (OR 2.84; 95% CI, 1.05-7.68).²⁸ Metoclopramide was more effective than placebo in reducing nausea in four studies.^{29,31,32}

Three studies compared metoclopramide with other neuroleptics (chlorpromazine and prochlorperazine).^{30,33,34} These studies suggested that metoclopramide was less effective in relieving pain and nausea than phenothiazine. Pooled results from all three studies showed that patients who received metoclopramide were more likely to require rescue drugs (OR 2.0; 95% CI, 1.04-4.17).²⁸ In comparison to non-emetics, metoclopramide 10mg IV was similar in pain reduction to metoclopramide plus ibuprofen 600 mg PO (VAS -75 vs. -50) but VAS reduction was larger than ibuprofen alone or placebo. Patients in the metoclopramide group were significantly less likely to require rescue drugs.³¹ Metoclopramide 10mg IV was compared with magnesium 2g IV and with placebo. Pain reduction was similar in three groups but in metoclopramide and magnesium groups the requirement of rescue medications was less than in placebo (38% and 44% vs. 65% in placebo; $p = 0.04$).³⁴ Metoclopramide 20mg IV plus diphenhydramine 25mg IV (dose up to 4 times) was found to be superior to sumatriptan 6mg SQ as a percentage of pain free response at 2 hours (59% vs. 35%; $p = 0.04$) but not for 1 hour ($p = 0.22$) and 24 hours ($p = 0.23$).³⁶

In a dose-finding randomized double-blind clinical trial of 356 patients, intravenous metoclopramide 10mg had similar efficacy as metoclopramide 20 or 40mg in

pain reduction (11PPS) at 1 hour (-4.7 vs. -4.9 vs. -5.3; $p = 0.19$). Sustained pain free rate was low in all doses (16% vs. 20% vs. 21%). The most common adverse event was drowsiness (69% at 1 hour), which impaired function in 17%. Akathisia developed in 9% and dizziness in 8% with similar rates across doses.³⁷

- Haloperidol

Haloperidol is a butyrophenone derivative acting mainly by blocking D2 dopamine receptor with some antagonist with D1 dopamine, 5-HT2 serotonin, H1 histamine, and α_2 adrenergic receptors in the brain. Haloperidol 5 mg in 500 mL normal saline (NSS) IV was compared with placebo NSS 500 mL IV. Pain reduction (VAS) was greater with haloperidol (from 7.7 to 2.3; $p < 0.0001$) compared to placebo (from 7.2 to 6.3; $p < 0.01$). Eighty percent who received haloperidol felt marked relief from pain, whereas only 15% responded to placebo ($p < 0.0001$). The common side effects were motor agitation (akathisia) in 53% and drowsiness in 53%. Sixteen percent of the patients considered the side effects intolerable and were unwilling to be treated with haloperidol in the future.³⁸ Due to black box warnings for prolonged QTc, together with high incidence of sedation and akathisia, haloperidol should be reserved for use only when other rescue medications failed to relieve headache. Electrocardiogram (ECG) should be done before and after treatment. Pretreatment with IV fluid and an anticholinergic (benztropine, trihexyphenidyl, diphenhydramine or benzodiazepine) are recommended.²⁰

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit both cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2), the neurogenic inflammatory cascade and thereby prostaglandin synthesis, and platelet aggregation associated with the release of vasoactive agents that are involved in initiation and prolongation of migraine.³⁹

- Ketorolac

Ketorolac is a NSAID with strong analgesic activity. Ketorolac attenuates moderate to severe pain especially in patients with migraine headache and is usually as effective as an opioid. The analgesic effect of ketorolac tends to be slower in onset than that of morphine or meperidine but persists longer.⁴⁰ Most adverse events involve the gastrointestinal tract (GI), ranging from mild upset to ulceration and hemorrhage. Overall, parenteral ketorolac is associated with only a slightly increased risk of GI or operative site bleeding compared to opioids (OR 1.30 and 1.02, respectively). The risk of bleeding is strongly linked to increased age, high dosage and treatment for more than 5 days.⁴¹ All NSAIDs have the potential to cause nephropathies, but these occur more frequently in patients with hypovolemia or patients with hemodynamic compromise.⁴²

The total daily dosage of parenteral ketorolac should not exceed 60mg in patients aged ≥ 65 years or those with renal impairment or body weight < 50 kg. Ketorolac is contraindicated in patients with congestive heart failure, hepatic impairment, hypertension or conditions that may lead to a reduction in blood volume and in those who are hypersensitive to NSAIDs. Ketorolac should not be co-administered with other NSAIDs, probenecid, pentoxifylline or lithium and should be administered cautiously to patients on anticoagulation therapy (including low dose heparin).⁴⁰ High quality evidence from randomized controlled trial studies (RCTs) shows ketorolac efficacy; it is used in up to 16% of ED visits for migraine.⁴³ The US FDA approved parenteral ketorolac for abortive treatment of migraine. A recent systematic review which included 8 RCTs (321 patients) examined the effectiveness of ketorolac in acute migraine and suggested ketorolac is associated with pain reduction in adult migraine attack patients.⁴⁴ Ketorolac (30-60mg IM) had similar efficacy to meperidine (50-100 mg IM) in pain score reduction at 60 minutes (weight mean difference (WMD) 0.44; 95% CI, -0.4 to 1.38, $p = 0.35$). Due to risk of abuse and addiction associated with meperidine, ketorolac is a preferred agent in ED. Furthermore, patients with acute migraine who were treated with narcotic agents showed an increased likelihood to return to the ED within 7 days.⁴⁵

A single study demonstrated that ketorolac IV 30mg was significantly more effective than nasal sumatriptan 20 mg (WMD = -4.07; 95% CI, -6.02 to -2.12).⁴⁶ Ketorolac has not been compared with other more effective routes of sumatriptan (subcutaneous and oral). However, most patients have often used triptans as an abortive agent before ED arrival. Two studies compared IV ketorolac with IV phenothiazines (prochlorperazine and chlorpromazine). The pool analysis found no statistical difference in pain relief (WMD 0.82; 95% CI, -1.33 to 2.98). Heterogeneity was high, trends may suggest phenothiazines are more effective.^{47,48}

- Parecoxib

Parecoxib is a cyclooxygenase-2 (COX-2) specific inhibitor widely used for acute pain in ED. In animal models, parecoxib show significantly attenuated plasma protein extravasation (PPE) in rat dura mater and reduced expression of c-fos within the ipsilateral trigeminal nucleus caudalis (TNC) that are involved in neurogenic inflammation correlated with migraine pathophysiology.⁴⁹ Only one open-label pilot study investigated the efficacy of intravenous parecoxib, oral fast-dissolving tablet of rizatriptan, and subcutaneous injection of sumatriptan in patients with acute migraine. Using the visual analog scale for pain intensity at baseline before and then after the drug intake at intervals of 20, 30, 60, and 120 minutes, rizatriptan 10mg was more efficacious than parecoxib 40mg and sumatriptan 6mg, and parecoxib was more effective than sumatriptan at 20 and 30 minutes after drug administration.⁵⁰

Opioids

Opioids have long been used to treat various types of pain include headache. Parenteral opioids are very frequently used in the ED setting, for example for more than 50% of all migraine visits to EDs in US and in Canada.^{51,52} Opioids can modulate nociceptive input to the spinal trigeminal nucleus (nucleus caudalis) but they have no effect on neurovascular inflammation in migraine pathophysiology.⁵³ A large US population-based study demonstrated that opioid use is common for the acute treatment of migraine. Approximately 30% of the population reported use of opioids for migraine, 15.9% were currently using opioids. Around 16% of current opioid users were dependent. Opioid use for migraine is associated with more severe headache-related disability, symptomology, comorbidities (depression, anxiety, and cardiovascular disease), and greater health-care resource utilization for headache.⁵⁴ The major concern about the use of opioids in acute migraine attack regards the possible association with an increased risk of medication overuse headache (MOH) and chronic migraine (CM). Overuse of short-acting opioids may be associated with worsening of migraine, increasing the risk of CM and MOH. Clinical-based and population-based longitudinal studies support an association between CM and opioids use.⁵⁵ In the American Migraine Prevalence and Prevention (AMPP) study, the risk of CM is higher for opioids use (with an OR = 1.48). Critical level of exposure is around 8 days per month, and the effect is more evident in men (OR = 2.76) than in women (OR = 1.28).⁵⁶

In addition, opioid-induced hyperalgesia (OIH) can occur with even brief durations of narcotic treatment. Of patients who were exposed to opioids, their pain thresholds declined, and their pain sensitivity, pain location, and pain intensity increased to any stimulus. The phenomenon of OIH can be temporarily overcome with increased doses of opioids, but the basic pathophysiology is different from tolerance.⁵⁷ Pathophysiology of OIH involves cholecystokinin up-regulation in the rostral ventromedial medulla (RVM), peripheral expression of calcitonin-gene related peptide (CGRP) in primary afferent neurons is up-regulated, there is an increase in dynorphin, pro-inflammatory peptides, activation of NMDA glutamate receptors, and activation of glia cell via the toll-like receptor 4 (TLR4), resulting in inflammation and release of neuroexcitatory substances.⁵⁸ Opioids are pro-nociceptive, prevent reversal of migraine central sensitization, and interfere with triptan effectiveness.⁵⁹ Adverse effects of opioids include sedation, respiratory depression, bradycardia and hypotension, seizure, in addition to long term dependence.

- Meperidine

Meperidine is the opioid most frequently used and most studied for headache treatment in ED.⁶⁰ In a meta-analysis of meperidine of 19 RCT trials with a total 254

patients, meperidine had less efficacy than DHE (OR 0.3; 95% CI, 0.09-0.97) and trended toward less efficacy than antiemetics (OR 0.6; 95% CI, 0.19-1.1) but with a similar efficacy to ketorolac (OR 1.75; 95% CI, 0.84-3.61). Meperidine caused more sedation (OR=3.52; 95% CI, 0.87-14.19) and dizziness (OR=8.67; 95% CI, 2.66-28.23) than DHE, less pyramidal side effects than antiemetics, and similar rates of gastrointestinal adverse effects (OR=1.27; 95% CI, 0.31-5.15) and sedation (OR=1.70; 95% CI, 0.23-12.72) to ketorolac.⁶¹

A review of 75 studies of rescue therapy for acute migraine found opioids (meperidine, tramadol, and nalbuphine) were superior to placebo in relieving migraine pain, although meperidine combined with promethazine was not. Meperidine 75mg was superior to ketorolac 30 mg IM but was similar to ketorolac 60mg IM even when combined with an antihistamine. Meperidine 75mg IM or 1.5mg/kg IV was similar in pain relief to DHE 0.5mg IV but inferior to DHE 1mg IV.⁶²

- Tramadol

Tramadol hydrogen chloride is an atypical opioid that has relatively weak mu opioid receptor binding properties and also inhibits serotonin and norepinephrine re-uptake. Tramadol is better tolerated than other opioids because of its low impact on the respiratory, cardiac, and gastrointestinal systems at therapeutic doses.⁶³ Tramadol 100mg IV was compared with placebo (NSS) IV. Pain reduction (VAS) at 1 hour was greater in the tramadol group (70.6% vs. 35.3%, $p=0.04$) but the percent pain free at 1 hour was not different in both groups (29.4% vs. 11.8%, $p=0.40$). Side effects were not observed at 1 hour.⁶⁴ In the prospective, randomized, double-blind study, tramadol 100 mg IM was compared with diclofenac sodium 75mg IM; headache relief was the same in both groups (80%).⁶⁵

Conclusion

Migraine is a common disabling disorder. Migraine attacks with moderate to severe pain and other debilitating associated symptoms such as nausea, vomiting, photophobia, and phonophobia that lead to emergency room visits. Detailed history taking, physical examination, and

appropriate diagnostic tools should rule out secondary headache. The mnemonic “**SNOOP4**” is a useful for recognizing secondary causes of headache. ID-migraine, the short 3 item questionnaire, is recommended as a screening diagnosis tool for migraine. Intravenous fluid can be useful in patients with nausea and vomiting, and to prevent postural hypotension in patients who will be administered a dopamine antagonist.

Dopamine antagonists (chlorpromazine and metoclopramide) are very effective in rescue migraine treatment. Effective doses of chlorpromazine in migraine ranged from 0.1mg/kg to 37.5mg administered intravenously or via intramuscular injection. The efficacy of chlorpromazine in pain relief was up to 80%. Metoclopramide 10mg IV had an average pain relief of 70%. The most common adverse effects of dopamine antagonists were drowsiness, postural hypotension, and akathisia. Dopamine antagonists are recommended as the first line treatment for migraine attack in ED.

Ketorolac, the parenteral NSAID, should be considered a second line rescue treatment in ED. The recommended ketorolac dose is 30mg IV or 60mg IM. Average percentages of pain relief of ketorolac are 60% for ketorolac 30mg IV and 37% for ketorolac 60mg IM. Ketorolac and meperidine had similar pain scores at 60 minutes and ketorolac was not different from phenothiazines in pain relief at 60 minutes. Adverse effects were risk of GI bleeding and nephropathies that increased with age, high dosages, and prolonged use for more than 5 days.

Meperidine is most frequently used in ED. Efficacy of meperidine 75mg IM is similar to ketorolac 60mg IM and DHE 0.5mg IV but less efficacious than antiemetics and DHE 1mg IV. Average percentage of pain relief of meperidine is 58%. Tramadol 100mg IM had similar efficacy to diclofenac 75mg IM. Side effects of opioids included sedation, dizziness, GI discomfort, nausea and vomiting, and akathisia (less than neuroleptics). Opioids are not recommended for rescue migraine treatment due to a high rate of headache recurrence, increased risk of medication overuse, chronic migraine transformation, opioid-induced hyperalgesia, central sensitization, nausea and dizziness, and raised concerns for overuse and abuse.

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Os Trigonum Syndrome or Posterior Ankle Impingement (PAI)

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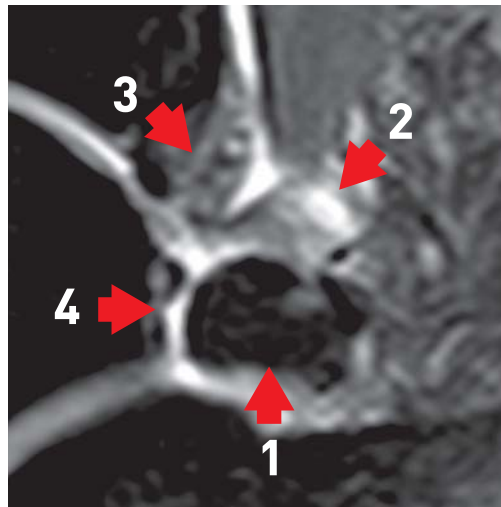
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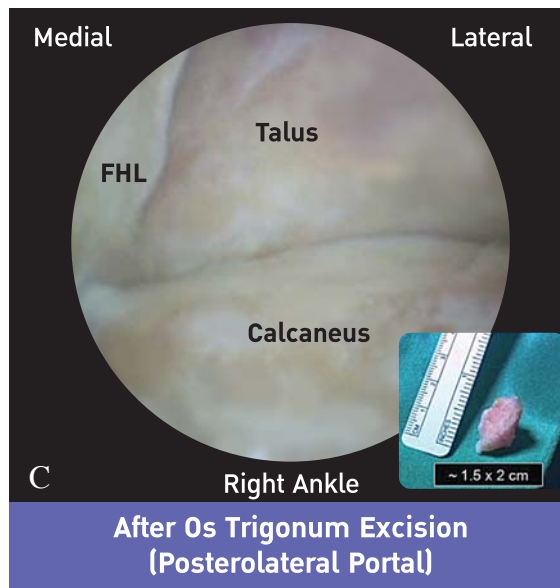
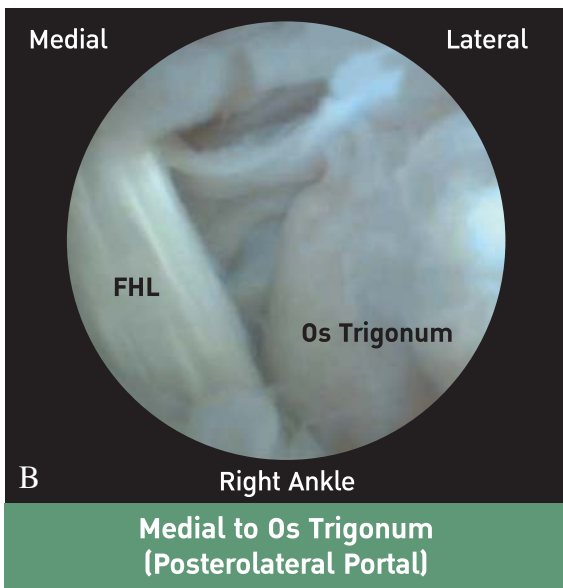
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- 1 = Os trigonum
- 2 = Surrounding soft tissue edema
- 3 = Bone marrow edema of posterior tibia
- 4 = Synchondrosis edema



Os trigonum is a normal variant of an accessory bone found posterior to the talus. The os trigonum is present in around 5-15% of normal feet. Usually it is asymptomatic, until there is a minor to blunt injury on the anterior aspect of the foot. The injury becomes painful on the hyperplantarflexion test. The pain is located at posterolateral aspect of the ankle associated with swelling known as the 'os trigonum syndrome'^{1,2} or posterior ankle impingement (PAI).

A 26-year-old man presented with painful posterolateral aspect of the right ankle joint after sustaining a blunt injury on the anterior aspect of the right foot. Physical examination revealed tenderness on the posterolateral aspect of the right ankle. The hyperplantarflexion test was positive.

An MRI was performed for the right ankle, using the PDFS technique (Figure A). This showed the size of os trigonum to be 9x13mm (arrow 1), and with surrounding soft tissue edema (arrow 2), bone marrow edema at the posterior tibia (arrow 3) and synchondrosis edema at the posterior of the talus (arrow 4).

Os trigonum syndrome or PAI was diagnosed preoperatively. An operative arthroscopy showed os trigonum impingement at the posterior border of the tibia on the plantarflexion position. An os trigonum excision was then performed (Figure B-C).

Discussion

Os trigonum syndrome or posterior ankle impingement (PAI) results from sustained blunt foot trauma associated with pain and tenderness at the posterolateral aspect of the ankle joint. The MRI shows the lesion with bone marrow edema and surrounding soft tissue edema. Arthroscopy shows os trigonum impingement at the posterior border of the tibia on the plantarflexion position. This condition commonly occurs with ballet dancers. This is because the os trigonum affects the posterior tibia in the hyperextension position. This condition can also affect soccer players and other athletes.^{3,4}

A different diagnosis is posterior tibia tendon dysfunction which is the most common complaint. It occurs after trauma, when the tendon becomes inflamed or torn and this may cause instability, resulting in flat foot.⁵ Pain develops along the medial aspect of the foot and ankle. In contrast PAI pain develops on the posterolateral aspect.

Conclusion

Os trigonum syndrome or PAI is a condition with painful posterolateral aspect of the foot and/or hyperplantarflexion test after a blunt injury. The diagnosis is confirmed by an MRI scan. A conservative approach is the treatment of choice. The excision of os trigonum is indicated only when the patient does not improve with conservative treatment.

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The Benchmark between the NCQA Diabetes Recognition Program (DRP) and the JCI Condition-Specific Certification for DM Type 2 at the Bangkok Hospital Medical Center



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Diabetes mellitus (DM) has become a major public health problem around the world. According to statistics from the World Health Organization (WHO) Diabetes Fact Sheet, this disease currently affects 347 million people worldwide. Due to the increasing burden of diabetes patients, an excellent diabetes care center is needed to provide international standard quality care. To address this need, the Bangkok Hospital Medical Center (BMC)'s Diabetes Center applied for the Joint Commission International (JCI) Condition-Specific Certification (DCSC) Program for a DM Type 2 Pathway. The certification was awarded to the BMC in November 2011. Soon after, we achieved all the target performance indicators recommended by JCI, and we gradually added further performance indicators at our diabetes clinic. We are ready for re-certification this coming November 2014.

In an attempt to assess and identify performance measures based on management guidelines, we found that most of JCI measurements assess the care process being delivered. To better understand how to improve quality care for type 2 DM patients, we can draw on the tangible measure of the treatment's outcomes. In other words, in addition to good standard processes of care we also focus on good treatment outcomes. These two must go hand in hand to achieve the maximum benefit for our patients. There are several disease-specific and specialty-specific professional organizations that have developed diabetes management guidelines. In consideration of the significant improvements we have seen in recent years, we examined best practices to identify the best tool to achieve even better clinical outcomes. After surveying many organizations already using diabetes performance measurements, we were impressed with the National Committee for Quality Assurance (NCQA) and its approach to address the clinical outcome even further. This paper is an introduction to NCQA and aims to compare JCI and NCQA standards in terms of measuring diabetes clinics' performance and the clinical outcome. The purpose of using the NCQA standard as a benchmark for our expert care provision for Type 2 DM patients, we have assessed relevant clinical results and this process will continue for the next 6 months. We aim to report on the results in the next edition of the Bangkok Medical Journal.

The National Committee for Quality Assurance (NCQA)

The NCQA is a private, not-for-profit organization dedicated to improving health care quality. Since it was founded in 1990, the NCQA has been a leading institution in driving improvement throughout the health care system, helping to raise the issue of health care quality to the top of the national agenda. The NCQA accredits and certifies a wide range of health care organizations. It also recognizes clinicians and practices in key areas of performance.

**The Benchmark between the NCQA Diabetes Recognition Program (DRP) and
the JCI Condition-Specific Certification for DM Type 2 at the Bangkok Hospital Medical Center**

The NCQA is the first DM accreditation organization to use performance measures to assess the impact of programs on care for people with DM.

The standards are organized into seven categories:

- Evidence-Based Programs
- Patient Services
- Practitioner Services
- Care Coordination
- Measurement and Quality Improvement
- Program Operations
- Performance Measurement

*For more information, please visit: <http://www.ncqa.org>

The NCQA Diabetes Recognition Program (DRP)

The DRP assesses the effectiveness of DM management by measuring the clinical outcome as well as the intervention process. The requisite quality indicators are shown below.

Outcome Measures:

- HbA1c Control > 9.0%*
- HbA1c Control < 8.0%
- HbA1c Control < 7.0%
- Blood Pressure Control ≥ 140/90 mm Hg*
- Blood Pressure Control < 130/80 mm Hg
- LDL Control ≥ 130 mg/dl*
- LDL Control < 100 mg/dl

Process Measures:

- Eye Examination
- Foot Examination
- Nephropathy Assessment
- Smoking Status and Cessation Advice or Treatment

Joint Commission International (JCI)

JCI stands apart as a leading advocate for patient safety and quality improvement in the global community. It was created in 1994 by The Joint Commission, and the JCI has a presence in more than 90 countries today. JCI works with health care organizations, governments, and international advocates to promote rigorous standards of care and provide solutions for achieving peak performance. JCI experts help organizations help in three ways: accreditation, education, and advisory services.

*For more information, please visit: www.jointcommission-international.org

JCI standards for Clinical Care Program Certification (CCPC)

To receive certification for any JCI DCSC program, the health care organization must meet the following 5 standards:

1. International Patient Safety
2. Program Leadership and Management (PLM)

3. Delivering or Facilitating Clinical Care (DFC)
4. Clinical Information Management (CIM)
5. Performance Measurement and Improvement (PMI)

Joint Commission International Condition-Specific Certification (JCI DCSC) Type 2 DM

There are several recommendations for DM management, such as an intensive therapy for poorly controlled diabetics, therapy for hyperlipidemia, use of angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) therapy for albuminuria and self-management education and ensuring the clinical documentation is kept complete. The table below presents our current performance measurements for the JCI DM DCSC program.

Comparison of the NCQA and JCI DM DCSC

Overall, the NCQA and JCI accreditation processes are quite similar in format and general requirements. After the application is submitted, a detailed documents review takes place, and several days of surveyors conducting on-site visits are compulsory. Both organizations arrange for levels of accreditation ranging from rejected to full accreditation. They also have specific disease management certification programs. In terms of the DM management program, these two organisations are somewhat different in the choice of diabetes performance indicators. DRP gives more values to the clinical outcome indicators, while most of JCI standard measures focus on the process of providing essential treatments and care. NCQA accreditation is a comprehensive quality scorecard. Therefore, the DRP used a standardized data set for measuring plan performance and clinical outcomes. In the scoring process for accreditation, NCQA assigns a greater weight to clinical outcome measurements.

DRP Scoring of Measures

The table below list the indicators required by DRP, the grey row indicates the clinical indicators and the white row indicates the process indicators.

Scored Measures	Threshold (% of patients in sample)	Weight
-HbA1c Control >9.0 %*	≤ 15	12.0
-HbA1c Control <8.0 %	60	8.0
-HbA1c Control <7.0%	40	5.0
-BP Control >140/90 mm Hg*	≤ 35	15.0
-BP Control <130/80 mm Hg	25	10.0
-LDL Control >130 mg/dl*	≤ 37	10.0
-LDL Control <100 mg/dl	36	10.0
-Eye Examination	60	10.0
-Foot Examination	80	5.0
-Nephropathy Assessment	80	5.0
-Smoking Status and Cessation Advice or Treatment	80	10.0
Total Points		100.0

**Points to Achieve Recognition = 75.0

Table : Performance Measurement for JCI DM DCSC.

Performance Measures	Type of indicator	Rational
Intensive therapy for poorly controlled diabetics	Process indicator	Patient HbA1c ≥ 9 should receive intensive therapy as needed to achieve treatment goals
Therapy for hyperlipidemia	Process indicator	Patient LDL > 100 should receive a statin as a first choice as needed to achieve treatment goals
Use of ACEI or ARB therapy for albuminuria	Process indicator	Patient MAU > 30 should receive ACEI or ARB therapy twice as needed to achieve treatment goals
Self-Management Education	Process indicator	Patient should receive diabetes self-management education as needed to achieve treatment goals
Completeness of medical record (DM Pathway)	Process indicator	Medical records complete as needed to achieve treatment goals
DM Patient Perception	Outcome indicator	Evaluating the quality of care processes and identifying areas that may need more intense investigation or inquiry

Conclusion

The BMC diabetes clinic pursues a consistent drive to improve quality and clinical outcomes. We found that the DRP standard is a helpful clinical outcome measurement tool to assess the efficiency of our DM management program. Only health care organizations located in the United States are eligible to apply for DRP, which is unfortunate. Nevertheless we plan to use the standard set by the DRP performance measurement as a benchmark this year. In addition to the quality indicators required by JCI Type 2 DM DCSC, the clinical results of the patient who consents to participate in the DM pathway are also being recorded at present. Currently, we are verifying the percentage of patients in each level of HbA1C and LDL cholesterol and the percentage of patients with selected blood pressure levels. We are eager to deliver excellent service to our patients; we expect our patients will enjoy

greater benefits as a result of the clinic benchmarking selected clinical performance measures appropriate for an international health care organization.

By comparing the performance levels with DRP scoring measures, we expect that our endocrinologists will achieve better clinical outcomes for the patients. The clinician will quickly see tangible improvements by increasing the level of attention paid to treatment and monitoring. We hope that these selected clinical outcome indicators will mirror the effectiveness of our DM management pathway and most importantly will deliver higher quality care to our DM patients.

In the future, more work is planned to assess the possibility of using Type 2 DM clinical outcomes selected by NCQA as a Key Performance Indicator (KPI) to measure the proficiency of all endocrinologists who treat Type 2 DM patients at the Bangkok Medical Center.

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What have we learned from the past 7 years and the millions of dollars spent on the genome-wide association studies?



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The advance in genomic technology has allowed us to genotype millions of single nucleotide polymorphisms (SNPs) across the human genome at the same time. This high-throughput technology, genome-wide association studies (GWAS), enables us to search for genes contributing to many diseases from age-related macular degeneration, type 2 diabetes, coronary heart disease, cancer to common traits such as obesity, height, eye color. To date, there are over 1,779 studies and 12,126 SNPs reported to be associated with more than 300 diseases.¹

Quite a few of GWASs have been conducted in the Thai population. Searching from HuGE Navigator (an integrated, searchable knowledge base of genetic associations and human genome epidemiology: <http://hugenavigator.net/>) with a search term “**Thai**” showed 7 articles. Disease phenotypes studied in the Thai population using the GWAS approach so far are: severity in β 0-thalassemia/Hb E², susceptibility to tuberculosis³, chronic hepatitis B^{4,5}, systemic lupus erythematosus (SLE)⁶, thyrotoxic hypokalemic periodic paralysis⁷ and nevirapine-induced rash in HIV infected patients.⁸ The results from these GWAS have been used for personalized medicine ranging from disease risk prediction, treatment selection and medication dosing guide.⁹

The origin of GWAS design came from an attempt to map genomic loci to a disease. Sequencing the whole 3 billion nucleotides in the genome was prohibitively expensive. To study the whole genome, geneticists employed a concept of tagging SNP, using a SNP as a proxy marker for nearby genetic variants. Through correlation between untyped genetic variants and genotyped SNPs, several tagged genetic variants can be represented with a single SNP on a GWAS panel. The SNPs on the GWAS panel are then used to test for association with diseases. Genome-wide significant association signals imply that the genomic location of these variants play a role in disease-causing mechanisms. For example, in a genome-wide association study, rs11591147 was found to have genome-wide significantly associated with hypercholesterolemia.¹⁰ As the rs11591147 is located within *PCSK9* gene, the function of *PCSK9* will be implicated in hypercholesterolemia. Functional implication of these SNPs is quite straightforward if the identified SNPs are functional variants, e.g. non-synonymous mutation, stop codon mutation. However, as more than 80% of the signals from GWAS fall into inter-genic or non-coding regions, establishing the causal relationship between these variants and disease mechanisms is still challenging.

The major success of GWAS is in identification of several new common disease loci. GWAS assume that most complex diseases can be explained by a few common genetic variants. This assumption is known as the common disease/common variant hypothesis

(CDCV). CDCV has been proven in several studies of common complex genetic diseases. For example, the region on chromosome 9p21.3 near genes has been associated with coronary artery disease in European descent population the studies of three common SNPs (rs1333049, rs10757274, and rs2383207)¹¹, all have MAF close to 50%.¹²

Although correlations between common variants and some less common variants allow us to identify the variants with MAF < 5% from the GWAS platform, many rare variants that are not tagged by common variants may have been missed. As a result, we are left with an incomplete characterization of the underlying genetic mechanisms of the studied diseases. Correlation between genetic markers (linkage disequilibrium: LD) can also cause a problem in identification of causal loci in a region with high LD among genetic variants.

GWAS also allow us to estimate genetic risks from the associated genetic variants. Using the same CAD associated variants mentioned above as an example, 9p21.3 risk loci and CAD was estimated to contribute to an OR of 1.25 (95% CI, 1.21-1.29).¹¹ However, for most diseases, the identified variants had small effects on the diseases and explained a small proportion of the estimated heritability. Heritability of height, the proportion of variance in height explained by genetic factors, has been estimated to be as high as 80-90%. But, the results from GWAS revealed genetic loci that explained only 5% of the variation in height in the human population.¹³ For risk prediction, the small effects associated with the disease limit the use of genetic markers found from GWAS on disease risk classification, especially for disease with well-established risk factors such as coronary artery disease.¹⁴

One limitation of GWAS is the ability to characterize structural variation, such as insertion/deletion polymor-

phisms, duplication, and rearrangement. Although copy number variations (CNV) have been widely studied using GWAS array, the ability to detect CNV vary greatly among different methods for CNV prediction. How well GWAS SNPs correlate with structural variations in that area determines whether GWAS will be able to detect the association between the structural variants and diseases.

Despite the discovery of many novel genes in these complex diseases, researchers worldwide are frustrated that they have not uncovered the complete biological mechanisms of these diseases. The main criticism for GWAS is a small proportion of the phenotypes that can be explained by the genetic variants found on the GWAS panel. Hence, when next-generation sequencing (NGS) came into the picture, many groups of scientists were ready to switch from GWAS to NGS.¹⁵

NGS technology fills in several gaps that GWAS. Unlike GWAS which genotypes only limited number of variants included on the genotyping platform, NGS enables rapid sequencing of the whole human genome at a much lower cost compared to traditional sequencing methods. All variants in the genome detected including structural variants, small/large insertion/deletion. NGS have been used for several clinical applications such as diagnoses of difficult to diagnose genetic diseases, choosing the appropriate chemotherapy for cancer patients, or investigating novel genetic causes of complex diseases. Although the cost for sequencing may get cheaper, the later steps after sequencing are still a big challenge. The downstream processes to interpret the genome require experts in several fields e.g. bioinformatics, computational biology, statistical genetics, and biostatistics. Hence, it might cost a thousand dollars to sequence the genome, but 100,000 dollars to understand the meaning of.¹⁶

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AO Davos Courses



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President Elect AO Foundation,
Davos, Switzerland.

AO's vision is excellence in the surgical management of trauma and disorders of the musculoskeletal system. The mission is to foster and expand the network of health care professionals in education, research, development, and clinical investigation to achieve more effective patient care worldwide.

AO offer events, symposia, and courses worldwide featuring lectures, hands on practical exercises and interactive discussion groups for surgeons and Operating Room Personnel at every stage of their career helping them to acquire the specific and up-to-date knowledge progressively to fit their needs and clinical practice.

Davos is a leading congress destination, and is located in a mountain setting accessible at any time of the year, in Grisons, Switzerland. This small town with its impressive mountain scenery setting is also the home base of the AO Center and the AO Research Institute. Over two weeks each December, AO Davos courses welcome more than a thousand clinical professionals from all over the world.

53 years of AO Davos Courses

In 1960, the first AO course was held in Davos, Switzerland and was attended by 69 orthopedic surgeons. The course was held to train surgeons in the application of the innovative orthopedic surgical tool kits and pioneering implants. The lectures took place in local cinemas while the practical exercise on bones was partially performed in basements.



*AO Laboratory for
Experimental Surgery Forschungsinstitut Obere Strasse*





Now the AO Davos Course is held at the newly expanded Congress Center Davos and has become the single largest educational event in various surgical trauma fields. The course currently offers a range of principles in operative fracture management up to master's courses on very complex treatment selections. The courses are enhanced by the most modern learning methods and tools. This includes knowledge sharing through discussion groups, online references, online broadcasted lectures and iPhone apps to give surgeons information quickly on hand. In addition, to date more than 350,000 surgeons and 150,000 operating room personnel have been trained worldwide by the AO Foundation.

Overview of the 2013 AO Davos Courses



*Professor Jaime Quintero
President of the AO Foundation*

From November 30 to December 13, 2013, AO offered 18 orthopedic trauma, spine, veterinarian and cranio-maxillofacial and neurotrauma courses, to more than 1,700 participants with nearly 500 expert faculty members representing 78 countries. This is a foremost educational global event. This year the course extended professional learning, and contributed to educational activities for the individual Continuing Professional Development (CPD) program. One of the highlights of the CPD program is an opportunity for 70 courses participants to meet 30 faculty members including nine past presidents to discuss the role of coaching and mentoring in the professional development of AO surgeons.



Group of AO Foundation past and present Presidents



AO Trauma highlights

AO Trauma offered 12 course modules from basic to master level for fracture management:

- Basic Principles of Fracture Management for Swiss Residents
- Management of Fractures of the Hand and Wrist
- Fragility Fractures and Orthogeriatrics
- Basic Principles of Fracture Management
- Advanced Principles of Fracture Management
- Advanced Principles of Fracture Management for Swiss Residents
- Acetabular and Pelvic Fracture Management

AO Trauma Masters Course:

- Current Concepts
- Lower Extremity
- Upper Extremity
- Complications and Complex Fractures



AO Trauma faculty

It was another extraordinary achievement year for AO Trauma. More than 1,200 participants and 350 international faculty members attended twelve courses and 70 CPD activities. Especially at the masters' level courses, there was an increase in anatomical specimen laboratories offered, and coaching for faculty members.

AO Spine highlights

Year 2013 is the 10th anniversary of the founding of AO Spine. Since 2003, AO Spine's global community has grown to more than 3,000 members representing some of the world's top talent in spine care management. This year, AO Spine gave the participants a rich and excellent mix of master level educational courses and highly popular CPD activities. Of special significance was AO Spine's introduction to a new modular course format, which allows participants to structure their own learning plan. This was extremely well received by participants, faculty and chairpersons alike. Based on the AO Spine Curriculum and the AO Spine Principles, each of the master modules comprises five case discussions, followed by solutions and evaluations. Overall, it was another highly successful AO Spine Davos Course.

AO CMF highlights

AO CMF Principles in Craniomaxillofacial Fracture Management Course began with a review of the basic principles of operative fracture care, and an emphasis on how the treatment of fractures is influenced by the biology of bone-healing. The scientific rationale for rigid and stable fixation was discussed based on pioneering scientific work done by the AO Foundation. The evolution of internal fixation, hardware, biomechanics of the facial skeleton, variations on internal fixation and principles of plating technology, and the re-establishment of the premorbid functional occlusal relationship was presented.



As in previous years, the AO CMF principles course included many exciting highlights such as a symposium on Biomaterials in CMF surgery (which was webcasted) and led by subject experts in this field. All CMF-related CPD activities were highly appreciated by both faculty and participants: in particular the hands-on session on Bimaxillary Orthognathic Surgery, led by Mark Engelstad (US) and Manuel Chamorro (ES), was attended by 80 participants (well over the capacity of 60 available places). The first AO CMF Advanced Symposium discussed challenges and pitfalls in facial trauma. The course was enhanced by three keynote lectures based on the experience of outstanding specialists in the rapidly expanding field of biomaterials. The course ended with breakout-sessions to allow participants to explore focused topics in greater depth.

AO Neuro highlights

AO Neuro is an initiative of the AO Foundation to expand its activities into the area of cranial neurosurgery. Paul Manson, a past president of the AO Foundation, described AO Neuro as an organization of cranial neurosurgeons who wish, through AO education, to improve the outcomes of cranial neurosurgery patients throughout the world.

One of the goals of AO Neuro is to create a number of educational activities that have an impact on cranial neurotrauma, skull base surgery and cerebrovascular surgery and to create greater visibility for AO Neuro. Therefore, the first AO Neuro Trauma Course was held during the AO Davos Courses 2013 under the banner of the AO Neuro initiative, and attracted 28 participants from 14 countries.



The objective of the courses is to teach the theoretical basis and practical principles for managing neurotrauma, addressing complications, and performing up-to-date reconstructive surgery. A live Webinar on 'Neurocranial Reconstruction: Standards, Controversies and Trends' and a live Webcast on 'How to classify a neurotrauma patient: Methods and solutions' were presented. Both were highly successful with online participants from around the world.



AO VET highlights

This year, AO VET delivered a Special Focus Course in Small Animal Fracture Management and an Advanced Course in Equine Fracture Management. The participants were presented with the most up-to-date information in the science of articular injuries, and advanced management of fracture fixation in veterinary medicine through presentations, discussions, and hands-on laboratory sessions. A significant feature of this course was the interaction between participants and the faculty. One session from each course was broadcast online to members around the world. At the booth, a new AO VET image film was

launched and was very well received by all viewers. The iPad App Veterinary Insights was introduced to the faculty and to participants, and this app is now available for free-download from Apple. AO VET and Medical Insights are collaborating positively to bring the most relevant and comprehensive evidence to the veterinary world.

In Summary: Due to the enormous enthusiasm of all expert faculty members, AO staff and partnerships, AO Davos Courses successfully furthered AO knowledge with a high level of educational and technical input, and a high standard of teaching provided to all participants. The AO Davos Courses team will build on their hard work and efforts to prepare a great welcome to other clinicians to join the AO Davos Courses 2014. As the inauguration of the AO Center, Martin Allgower said:

“AO remains at the forefront of surgery and science. Looking ahead, we have no monopoly on brilliant new ideas. We therefore must remain open and attractive for the younger generation.”

A Brief History of Development of the Cyclotron and PET Center at Wattanosoth Cancer Hospital

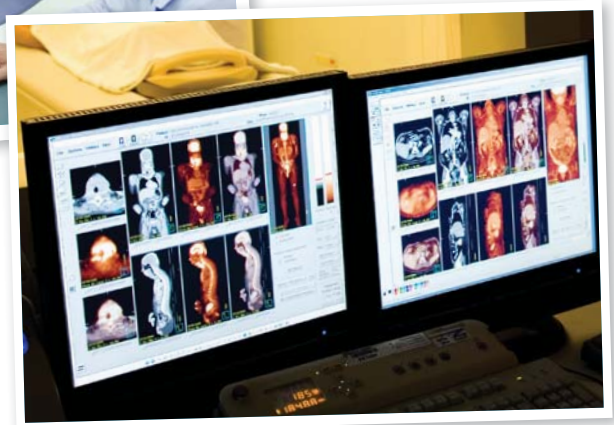


Ananya Ruangma, PhD
Specialist

Located on the basement floor of the Wattanosoth Building, you will find many highly specialized technical medical equipment. For this is where the Department of Oncology Imaging and Nuclear Medicine, and the Department of Radiation Therapy are located. Both of these departments are part of Wattanosoth Cancer Hospital. Her Royal Highness Princess Maha Chakri Sirindhorn bestowed the name of “Wattanosoth” to the hospital in 2006. The meaning of Wattanosoth is “**hospital for advanced medicine**”.

Wattanosoth Cancer Hospital is entirely devoted to provide cancer patients with the most effective range of traditional and innovative cancer treatment available. It is Thailand’s first private hospital devoted entirely to the treatment of cancer. The hospital is committed to improving the quality of life of cancer patients and survivors and to share research with fellow scientists, professionals, students and the community at large.

The building was a school, the Archeewa-Chalermart, before it became Wattanosoth Cancer Hospital. Bangkok Hospital built a new building on the site inaugurated as the Wattanosoth Cancer Hospital here after the school closed. The plan to build a cancer hospital was initially conceived back in 2003. Dr. Prasert Prasarttong-Osoth asked Dr. ChirochanaSuchato and Dr. Pongsak Viddayakorn to help with the project. In order to provide complete cancer care, the hospital had to invest in highly specialized medical technological equipment. Dr. Prasert Prasarttong-Osoth foresaw the great benefit of acquiring a Positron Emission Tomography/ Computed Tomography (or PET/CT) at that time. A diagnostic tool at the molecular level such as PET/CT is vital to provide a comprehensive treatment of cancer.



Bangkok Hospital set up a project management team which consisted of several specialists in the medical field. The process for procurement of medical equipment ran parallel to the design of the new building in 2004. The goal was to have services available for patients in late 2005.

The most expensive and complicated medical equipment that Bangkok Hospital invested in at the time were the PET/CT, Cyclotron and Novalis. These now sit on the basement floor of Wattanosoth Building. Novalis is a premium BrainLab technology for radiosurgery and stereotactic body radiation therapy (SBRT). The installation of the Novalis was completed in late 2005. The Novalis was first used in the treatment of patients in October 2005.

PET/CT is nuclear imaging technology. It requires the administration of a PET radiopharmaceutical. The most commonly used PET radiopharmaceutical is the F-18 FDG (Fludeoxyglucose) which is a cyclotron-produced isotope with a half-life of 110 minutes. At that time, there were no medical cyclotrons available in Thailand. So in order to provide PET examinations for patients, a cyclotron and hot lab was needed to produce PET radiopharmaceuticals.

The sourcing process began in mid-2004, and the winning company was instructed to provide a cyclotron, synthesis modules, and quality control equipment tools and design the facility according to internationally recognized standards. Bangkok Hospital agreed to purchase cyclotron and radiopharmaceutical equipment from Supreme Products Ltd. The agreement also included responsibility for overseeing the production of PET radiopharmaceuticals, and the management of radiophar-

maceuticals production and after sale services.

After having selected the company for the cyclotron and hot lab project, the contract was signed in January 2005. The contract included the placement of on-site specialist for 6 months to facilitate knowledge transfer after the completion of installation and commissioning. Supreme Product Ltd sourced a cyclotron from the Advanced Cyclotron System Inc (ACSI), Vancouver, Canada (previously EBCO). It is a TR-19 PET cyclotron which can provide a protons beam of up to an energy emission of 19 MeV. The synthesis module for the FDG production was also sourced from ACSI. Hot cells were sourced from TEMA Synergy, Italy.

There were 2 phases for the installation of the cyclotron and hot lab. The first phase included the production of FDG. The second phase was for the production of other PET radiopharmaceuticals such as C-11 acetate which was planned to take place for about a year after the first phase was completed. Most of the equipment for the cyclotron and hot lab arrived at the hospital on April 20th, 2005. The construction of the hospital was still underway at that time. The Cyclotron was shipped from Vancouver, Canada. Hot cells and radiation production equipment were shipped from TEMA Synergy, Italy. Since the hospital was keen to commence services using the PET/CT before the end of 2005, the hot cells needed



Figure 1: The installation site for cyclotron.



Figure 2: The TR-19 PET cyclotron.



Figure 3: Installation of hot cells in the hot lab.



Figure 4: Equipment in the quality control room.

to be shipped by air freight. This was extremely costly. Supreme Product Ltd also needed to provide equipment for quality control tests of the radiopharmaceuticals. Most of the equipment for the quality control (QC) such as the High Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), and Thin layer chromatography were ordered from local suppliers in Thailand.

The installation of the cyclotron and hot lab took around three to four months. Figure 1-2 and 3 show the cyclotron and hot lab being installed. Figure 4 shows the quality control equipment in the QC room. The entire cyclotron and hot lab system was installed and commissioned in November 2005. The first volunteer PET/CT patient was scanned on November 24th 2005.

Establishing a PET and Cyclotron Center is a very complicated project. It needs a lot of effort, dedication, excellent planning, with specialist advice from highly qualified personnel. Many experts in the field of nuclear medicine in Thailand such as Associate Professor Dr. Anchali Krisanachinda, Associate Professor Dr. Rujaporn Chanachai were consulted at the time. A specialist, Professor John Wilson, spent a month here helping to set up the cyclotron, the hot lab and the production of

radiopharmaceuticals. Professor John Wilson is a PET radiopharmaceutical expert and facility manager at the Edmonton PET Center at the Oncologic Imaging Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, Alberta, Canada.

To start with, Wattanosoth Hospital outsourced Supreme Product Ltd to manage the production of PET radiopharmaceuticals. Since this was the very first PET and Cyclotron Center in Thailand, not many people had the technical capability to handle this delicate equipment. All of the people who worked on this project were very new to the technology at that time. During the first couple of months, there were a lot of problems related to the failure of FDG production and to the delay of FDG production. The causes of the problems included: lack of experienced production staff and cyclotron engineers, an uncontrolled facility environment dealing with variations of temperature, humidity, the temperature of chilled water, and the electricity etc. The equipment downtime was very high since the engineers did not have enough knowledge and experience to handle cyclotron and hot lab equipment. The stock management was also an important issue because most of the materials and supplies needed to be imported from outside Thailand.

In the end, Wattanosoth Hospital took over full management of PET radiopharmaceutical production by mid- 2006. A lot of changes have taken place since the hospital took over the management of PET radiopharmaceutical process. The hospital has hired engineers, chemists, and a pharmacist to form a PET radiopharmaceutical production team and arranged the necessary training for them for both on-site training and abroad. Monthly meetings with hospital mechanics and engineers were arranged to solve any problems related to facility environment such as room temperature, humidity, electricity, and chilled water system etc. Another FDG synthesis module was purchased as a back-up system in 2006. To improve the quality of the radiopharmaceutical production, a standard for radiopharmaceutical production needed to be applied. In 2007, the hot lab was renovated to make it meet international clean room standards and to meet the international standard for a PET radiopharmaceutical production facility. A system to monitor room temperature, humidity, and pressure was installed. The production team has implemented many continuous quality improvement projects to improve production processes and to cut costs.

In June 2009, the module for the C-11 acetate was installed. There were many problems during the development of C-11 acetate. The most severe problem was the leakage of radioactive gas when the production failed. Expert advice from many facilities was consulted. A system to contain radioactive gas was applied. The service for C-11 acetate PET was made available in August 2009.

The project for C-11 PIB (Pittsburgh Compound B) PET for the diagnosis of Alzheimer's disease was initiated in 2010. The synthesis module for C-11 PIB production was purchased from iPhase Company in Melbourne, Australia. The installation of the module was finished in May 2011. The first volunteer patient for C-11 PIB PET scan was on May 24th, 2011. Production of C-11 radiopharmaceutical is more complicated than the production of FDG because it is a gas phase production. A lot of caution concerning the potential contamination of cold C-12 in the product needs to be taken. There were many problems to solve, and a lot of experienced technical personnel had to be involved. The C-11 PIB PET scan is the only one of its kind available in Southeast Asia. With such a very short half-life of C-11 (20 minutes), the C-11 PIB has to be produced on-site, close to PET scanner room. There were many problems related to the production, namely the contamination of C-12 in the system which resulted in low specific activity of the product, the management of supplies of material and chemicals for the production, and the leakage of C-11 radioactive gas, etc. It took the team almost a year to gain enough experience in the C-11 PIB production process to make the production stable.

In 2012, there was demand for an FDOPA-PET for the diagnosis of Parkinson's Disease. Wattanosoth Hospital decided to invest in FDOPA production in November 2012. The synthesis module for FDOPA was purchased from Trasis, Belgium. The facility preparation, including the gas leakage system and an additional hot cell installation were completed in June 2013. The synthesis module was installed in July 2013. Due to problems with the supply of necessary chemicals, and many problems related to production, the project was delayed for several months. Finally, the FDOPA PET was opened for patient service in January 8th, 2014.

The PET/CT project was also quite a difficult task for the team. The PET/CT at Wattanosoth Cancer Hospital is the first PET/CT in Thailand. It was a very new and very sophisticated technology at that time. Not many people in the medical field were familiar with the technology. Many members of the general public had never heard of PET/CT. A medical team for PET/CT was put together for the PET/CT project at Wattanosoth Hospital during the installation of the PET/CT in mid-2005. The team had to plan for training and education for team members as well as raising awareness of all related medical staff, marketing staff and the general public. Morning briefings were scheduled every day between the management team, support team and medical team to keep everyone informed about the ongoing process and any problems to resolve.

The PET/CT was installed in the basement of Wattanosoth Building while the building was still under construction. The plan was to launch each service simultaneously to complete cancer care management for our patients. PET/CT was one of the services that was planned to open for service together with other departments at Wattanosoth Cancer Hospital. While the building was still under construction, the team was working at the Bangkok Hospital building. In September, some areas in Wattanosoth Building were open for staff to work. Many documents and related medical equipment needed to be prepared to prepare for the opening of the PET/CT service. The facility also had to be prepared according to a radiation safety program. Staff members were also trained in risk assessment and in the safe use of radioactive substances.

In terms of PET/CT installation and commissioning, a medical physicist had to check and calibrate the system working with engineers from abroad. An expert medical physicist, Assistant Professor Dr. Napapong Pongnapang from Mahidol University, was invited to assist with the acceptance test for the PET/CT. The acceptance test for PET/CT was assessed according to NEMA standard and it took about a week to finish. The team worked very hard to make the PET service available as quickly as possible and the first volunteer PET/CT patient was on November 24th, 2005.

Dr. Samart Rajchadara has worked very hard to educate medical staff and members of the general public about PET/CT. It took many years to source physicians familiar with PET/CT who knew how to use PET/CT properly. The marketing team has arranged several seminars in hospitals and public arenas for Dr. Samart to talk about PET/CT and to present the clinical uses of PET/CT.

With a great contribution from the team who has put in an enormous effort to make the PET service available for the first time in Thailand, we are very proud to have been able to work around the difficulties and problems until the PET service was successfully established for the use of patients. We have faced many problems during the learning and development phases of this project. The team includes physicians, physicists, technicians, nurses, engineers, chemists, and management staff. They are working to continuously improve the quality of services and the quality of processes to keep up with international standards. We have been able to develop the necessary skills and acquire important knowledge about PET/CT and cyclotron-produced radiopharmaceuticals and we are willing to share our valuable knowledge with a wide group of professionals in medical circles.

Acknowledgements

The author would like to acknowledge service engineers from Supreme Product Ltd, particularly Mr. Songkhun Siri, for their hard work and dedication during the first phase of the PET and Cyclotron installation and commissioning project. The author thanks Ms. Pornphan Nawarungruang, Ms. Mayuret Panyawong, the PET center and Cyclotron facility team at Wattanosoth Cancer Center including all the doctors, nurses, physicists, technicians, chemists, engineers and pharmacists. The engineers from the medical engineering team from N-Health have also provided tremendous support. Over the past six years, they have put in a lot of effort to continue improving the quality of the services we provide. Finally, the author is very grateful for the support from the executive of the Bangkok Hospital Medical Center and Wattanosoth Cancer Center.



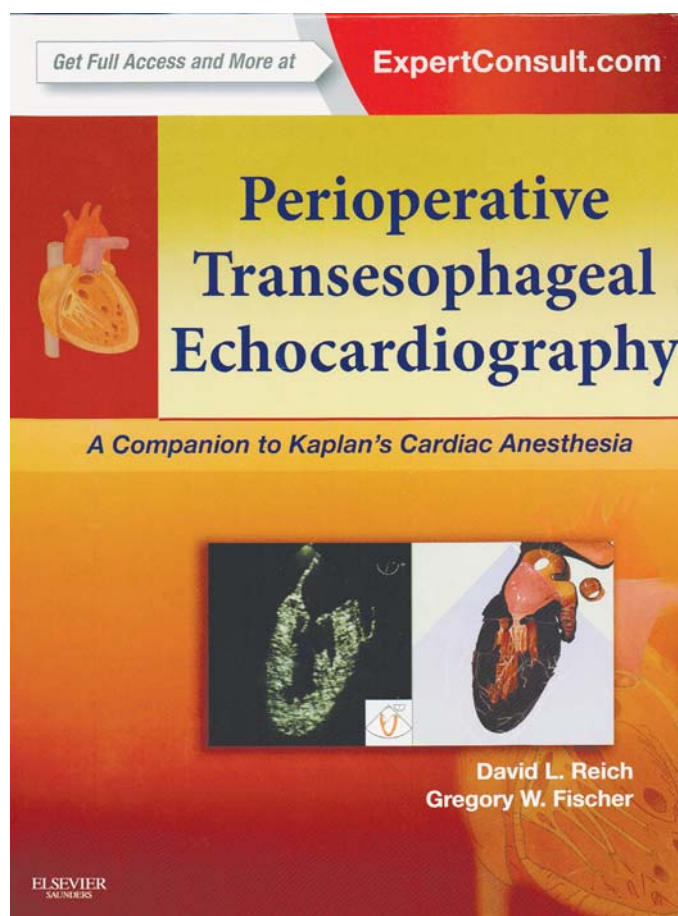
Perioperative Transesophageal Echocardiography

A Companion to Kaplan's Cardiac Anaesthesia.

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Perioperative Transesophageal Echocardiography (TEE) is used in the diagnosis of cardiac diseases. It was first introduced to diagnose cardiac valvular myocardium and pericardial diseases. But it has multiple applications beyond diagnosis. Cardiologists are increasingly working closely with experienced echocardiographers in complex patient cases, and many cardiologists handle all their cases with the use of TEE. TEE is used during the operation and post-operatively in the ICU for monitoring the patient. It may be needed in cases of perioperative cardiac aortic surgery and during the postoperative period. The great benefit of TEE is that it can immediately detect any critical problem as it occurs. TEE can be applied to non-cardiac interventions also, such as liver transplantation and neurosurgical operations to detect the risk or presence of venous air embolisms. This enhances patient safety and successful treatment outcomes. TEE is undeniably an indispensable tool in the perioperative care of cardiac surgical patients. Recently, the use of TEE has been introduced to strengthen the anaesthesiology practice and teaching programmes. This guide covers the following major areas of interest:

- Basic principles of normal cardiac anatomy and physiology
- Cardiovascular pathology in TEE
- Monitoring the quality of perioperative echocardiograms

The guide encourages the reader to look beyond the use of TEE as a diagnostic tool, and to view the cardiac patient more holistically, with a more thorough understanding of the patient's history and the planned clinical outcomes of the surgery. Thus the guide offers several chapters with contributions from cardiologists. It builds on existing texts to bring us the latest findings on three dimensional TEE, speckle tracking, and flow visualisation. We highly recommend all anaesthesiologists, cardiologists, cardiac surgeons and all physicians who work with cardiac, aortic and post-operative ICU patients to read this guide. Finally, the sub-speciality of cardiac anaesthesia has assumed an important role at the heart of the anaesthesiology profession. We encourage all anaesthesiologists to pursue the certification to achieve Testamur Status as a precursor to acquiring full certification offered by several international associations. This guide is a resource for the current and next generation of anaesthesiologists keen to further their career.