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Review Article

Stress Hyperglycemia

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Abstract

Morbidity and mortality in Intensive Care Units (ICU) occurring beyond the first few days of critical illness are attributable to the increased susceptibility to infectious complications. As is the case in insulin resistance in type II DM, increase of hepatic glucose output and decrease of peripheral glucose utilization in critically ill patients resulting in high blood glucose are the core mechanisms of stress hyperglycemia. After 2001,Van den Berghe G considered that persisted hyperglycemia leads to the disturbance of cellular energy metabolism and subsequent organ failure. Maintaining glucose concentration (140 mg/dL - 200 mg/dL) using insulin infusion aggressively is a new strategy of current ICU practice. The most complicated factor is exogenous nutritional inputs exacerbating the original problem: glucose control or targeting nutrition goal. It is still a subject of debate of how long hypocaloric feeding can be tolerated in acutely ill patients. Blood sugar control with insulin infusion seems to be simple and straightforward. The molecular mechanisms of stress hyperglycemia and clinical benefits of IIT need to be further studied.

Key words: stress hyperglycemia, insulin resistance, intensive insulin therapy

Introduction

Hyperglycemia associated with insulin resistance is common in critically ill patients, even in those who have previously not had diabetes. Hyperglycemia was first identified by Thomas Willis during episodes of stress in the 17th century. Later on, Allison and associates, Carey et al., described the terms "stress diabetes or diabetes of injury" as the decrease of insulin secretion that occurs during the early phase of injury. Persistence of glucose intolerance and hyperglycemia when a patient enters the "flow" phase suggests that certain target tissues of an injured patient are relatively insensitive to the effects of circulating insulin[1].

Although the prevalence of stress hyperglycemia is about 14% to 42% which is based on the variability of studied subjects, the Leuven group demonstrated that 97.5% of the 1548 enrolled patients in the surgical ICU had stress hyperglycemia defined as having blood sugar > 110 mg/dL[2]. Since the Leuven study in 2001 illustrated that aggressive correction of hyperglycemia using insulin can reduce morbidity and mortality in critically ill patients, it has been widely accepted into the clinical practice[3-4]. More importantly, it inspired a renewed and widespread interest in the risk of hyperglycemia in critically ill patients. Ongoing studies still remains. The mechanisms behind these observations have been thoroughly studied. Recent reports suggest that tight glycemic control with insulin may modulate the balance between pro-inflammatory and anti-inflammatory mediators and improve the outcome of critically ill patients. However, several specific questions are still unresolved. How long before an asymptomatic patient with hyperglycemia suffers irreversible organ damage? What are the clinical implications of transient elevated blood sugar in the critically ill patients? What is an acceptable target blood glucose level in stress situations? When should the combined enteral-parenteral therapy be initiated? Can pre-existing nutrition status

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be a deciding factor of nutrition support? The aim of this article is to review the pathophysiology of stress hyperglycemia in the critically ill patient as well as to outline a treatment strategy for the management of this disorder.

History of Glucose and Glucose Homeostasis

Grain products are rich sources of complex carbohydrates, essential components of human growth. In ancient times, the hunter-gatherer mode of survival did not allow for grain consumption, and it was only when agriculture was adopted that grain became a staple of the human diet. As a result, the development of cultivation and animal husbandry has been a major survival advantage on the evolution of mankind. But it took the human race thousands of years of trial and error to discover which kinds of foods that are essential for survival. In the early 18th century, nutrition science was started, allowing humans to greatly increase their harvest in cultivation.

In 1747, Andreas Marggraf isolated glucose for the first time from raisins. It was later named by the French chemist Jean Baptiste Andre Dumas in 1838. Traditionally, scientists believed that all the nutrients essential for survival should be derived from plants. In 1816, William Prout analyzed the components of blood and urine and found that there was a strong correlation between the components of food and the composition of blood, which was in turn similar to that of human tissue. They believed the glucose found in human blood originated from starch during the course of alimentary digestion. It was in 1853 when Claude Bernard demonstrated that the liver possesses the power to produce sugar.

Diabetes mellitus as high blood sugar and sweet urine was first described by Thomas Willis in 1674. Later on, German doctors Joseph von Meringand and Oskar Minkowski removed the pancreas from a dog, which developed diabetes in 1889. The Nobel Prize for medicine was awarded to Dr. Banting for his pivotal contribution to extract insulin from pancreas in 1921.Glucose homeostasis is strictly regulated by hormones such as insulin, glucagon, catacholamines. Persisted higher blood glucose level outside the normal range and failure to respond adequately to circulating insulin (insulin resistance) may eventually cause permanent organ damage. Insulin resistance was first described by Prof. Wilhelm Falta and published in Vienna in 1931; it was later confirmed by Sir Harold Percival Himsworth in 1936.

Insulin not only lowers blood sugar, but also increases uptake of circulating lipids in fat cells, increasing glycogen synthesis in liver cells, and enhanceing amino acid uptake by muscle cells.

Molecular mechanism of Stress Hyperglycemia

Glucose is a water soluable molecule that is transported across the cell membrane by transporter proteins, a type of specialized transmembrane proteins, on the cell surface. Sodium Glucose Co-transporter was first mentioned by Robert K. Crane in 1960 as the mechanism for intestinal glucose absorption, which uses energy to go against an uphill glucose gradient. The other pathways of cellular glucose uptake is mediated by glucose transporters. Three of five transporter isoforms, GLUT 1, GLUT 2, and GLUT 4 are most important for glucose uptake. GLUT 1 is commonly found in many different types of tissues and is responsible for basal glucose uptake. GLUT 2 mediates uptake and release of glucose by hepatocytes and regulation of glucose-stimulated insulin secretion in the pancreas. GLUT 4 is involved in glucose transport in tissues where uptake is mediated by insulin, which includes skeletal muscle, cardiac muscle, and adipose tissue[5].

Since GLUT 4 is mediated by insulin, insulin resistance in skeletal muscle, cardiac muscle, and adipose tissue during critical illness results in less GLUT 4 being translocated from intracellular compartments to the plasma membrane, which decreases the amount of glucose entering into the cell.

Elevated levels of non-esterified fatty acid (NEEA) in the blood stream and increase of intramyocellular lipid metabolites such as fatty acyl CoAs and diacylglycerol, which are seen in chronic insulin resistant states such as diabetes and obesity, have been found in many studies to contribute to diminished insulin sensitivity[6]**.** Horton, Tracy J. et al. demonstrated that prolonged fasting (72 hours) resulted in a significant decrease in carbohydrate oxidation and an increase in fat oxidation in a healthy person. This was associated with higher circulating free fatty acids[7].

What is the molecular mechanism responsible for NEEA reducing insulin-stimulated glucose transport/phosphorylation activity? Recent evidence show that impairment of IRS-1-PI3-kinase-AKT activation sequences by intracellular lipid metabolites, as shown in Figure (1), is an essential step for insulin-induced

defect of GLUT4 translocation. It is still unclear whether accumulation TG in muscle (spillover-storage of lipid outside the adipose tissue) associated with decrease of mitochondrial biogenesis in the muscle cell is a cause or an effect of insulin resistance[8-9].

On the contrary, insulin binding with hepatic insulin receptors also results in a cascaded signaling reaction through insulin receptor protein 2 (IRS-2), which is not involved in GLUT 2 activity. GLUT 2 ensures the liver is freely permeable to glucose uptake into hepatocytes so that it is in equilibrium with the level of extracellular glucose. Hepatic insulin resistance, also caused by IRS-2 signaling impairment, which normally down-regulates glycogen synthesis and gluconeogensis, leads to increase of hepatic glucose output in spite of hyperinsulinemia[10].

Just like well known insulin resistance in the cases of type II DM, increase of hepatic glucose output and decrease of peripheral glucose utilization despite insulin action leading to hyperglycemia is also found in critical illness. This is a necessary endogenous response to a stressful situation such as injury or infection, mobilizing glucose to enable increased cellular metabolic requirements. Increased hepatic glucose output may therefore be more important than peripheral insulin resistance in the genesis of stress hyperglycemia. Recent human data suggest that hepatic insulin resistance (PEPCK suppression) remains refractory to intensive insulin therapy[11].

Increased lipolysis and proteolysis and providing substrates for gluconeogenesis in the liver is caused by neuroendocrine responses such as elevation of glucagon and cortisol levels during critical illness. Catecholamines also enhance hepatic glycogenolysis and inhibit glycogenesis for increasing hepatic glucose output. The capacity of hepatic glucose output is also governed by liver blood flow, substrate concentration and the ability of the liver to extract the gluconeogenetic precursors at the same time, which are all modulated by synergistic interactions between the accompanying hormonal response[12].

TNF-α and interleukin (IL)-1 can stimulate the hypothalamic–pituitary axis directly, releasing the adrenocorticotrophic hormone, whereas IL-1 and IL-2 can stimulate the adrenal cortex to enhance glucocorticoid synthesis. Glucocorticoid indirectly increases the substrate supply for gluconeogenesis. It has been proved recently that infusion of TNF-α may, transiently, directly increase serine phosphorylation of IRS-1 that impaired insulin signaling[13]. Clinical observations show that type II diabetes mellitus and critical illness have a synergistic effect of impairing peripheral glucose utilization. Cynthia M Cely et al. observed that patients with an abnormal baseline glucose control, classified by HbA1c to be greater than 6.4%, and preexisting diabetes had significantly higher hyperglycemia levels than patients with a normal baseline glucose control[14]. Schricker et al. who compared whole-body glucose and leucine turnover two days after major colorectal surgery in seven patients with and seven patients without type II diabetes demonstrated that the patients of type II

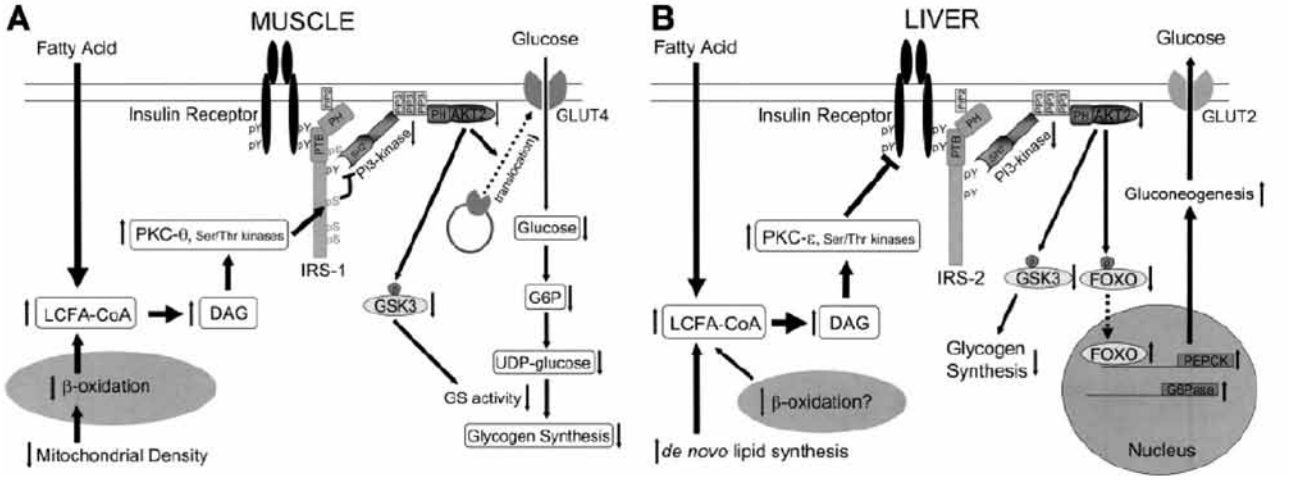

Fig. 1 The molecular mechanism of fat-induced insulin resistance in skeletal muscle (A) and liver (B).

Table 1. Complications of Hyperglycemia

Increased infectious complications
• Decreased phagocytosis
• Glycosylation of immune globulins
Altered collagen synthesis—poor wound healing
Fluid and electrolyte abnormalities
Aggravate symptoms of gastroparesis
Attenuates promotility action of erythromycin
Increased serum osmolality
Hypertriglyceridemia—decreased lipoprotein lipase activity
Accelerated catabolic state
Delays nutritional repletion by preventing optimal nutrient utilization

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diabetes had higher endogenous glucose release and oxidized more protein[15].

Consequences of Short-Term Hyperglycemia and Glucose Toxicity

Hyperglycemia in critical illness is commonly considered to be an adaptive response, supplying adequate glucose to injured tissue. Evidence is accumulating that persisted elevation of blood sugar results in a number of undesirable physiologic consequences that have relevance to acutely ill populations (see Table (1): complications of hyperglycemia). Recent observations showed that immunologic disturbance caused by acute hyperglycemia is strongly related to major infection and mortality[16]. Even short-term hyperglycemia increases circulating cytokine concentrations such as IL-6, TNF-, and IL-18 within two hours as shown by hyperglycemic clamp study in non-diabetics patients. Short term increases in these stress mediators are more pronounced in subjects with impaired glucose tolerance and septic patients[17-18].

Immunoglobulin G can be glycosylated, which impairs complement fixation[19]. Matthias Turina et al., in an in-vitro study using venous blood samples of twenty healthy volunteers, observed the impairment of monocyte HLA-DR expression, an index of the monocyte's capability to present antigen, after exposure to high glucose (400 mg/dL) and insulin (100 U/mL) for 24 hours[20].

Cendoroglo et al. proved that incubation of PMN cells from healthy subjects in media with high glucose concentrations inhibited phagocytosis and respiratory burst after 30 minutes of incubation[21]. Short term hyperglycemia leads to increased glucose uptake by endothelial cells that triggered the abnormal intracellular signaling transduction and then eventually organ dysfunction[22]. Worsening of beta-cell function by prolonged exposure high glucose (glucotoxicity) diminishes insulin secretion in response to glucose. Direct cellular glucose toxicity may be caused by increased generation of reactive oxygen species (ROS) and/or deficient scavenging systems ROS produced concomitantly by activated glycolysis and oxidative phosphorylation. When more glucose enters the cell and more pyruvate is being used for oxidative phosphorylation more superoxide will be generated[23].

Clinical observations have shown that hyperglycemia is significantly associated with an increased relative risk of death[24], increased the risk of critical illness polyneuopathy[25], and increased mortality in the patients of neurologic injury or stroke[26].

Exogenous glucose administration in critical illness

Zdenek Rusavy et al. described that septic patients had an elevated rate of glucose oxidation and a reduced amount of peripheral glucose storage in comparison with volunteers by hyperinsulinemic euglycemic clamp study[27]. Using isotope study, Sheridan RL et al. demonstrated that the fraction of exogenous glucose oxidation in burn children is 59% +/- 5%. They also demonstrated that total glucose oxidation was increased from 3.2 to 3.8 mg/kg/min while the glucose intake increased from 5 to 8 mg/kg/min. As glucose intake is increased, a greater portion of infused glucose enters non-oxidative pathways, which is unlikely to improve energy balance the patient[28].

Hepatic glucose uptake during exogenous glucose administration (TPN) is a main regulation center for glucose homeostasis. Nearly 75% of the glucose taken up by the liver was released as lactate and delivered to peripheral tissues (reverse Cori cycle). In acute glucose loading, glycogen synthesis was initiated by overexpression of glucokinase. Staehr P et al. suggested that in the presence of elevated glucose, the increase of dose-dependent "Net Hepatic Glucose Uptake" is mediated in part by the insulin-induced suppression of FFA release[29]. In the liver, increase

of hepatic glucose uptake when the oxidative limit for glucose is reached, hepatic lipogenesis occurs regardless of the overall energy state[30]. However, in critically ill patients, high carbohydrate intake did not suppress endogenous hepatic glucose production and gluconeogenesis but can stimulate whole body de novo lipogenesis (liver, adipose tissue) [31]. Supra-physiologic insulin dosage can partially overcome the effect of insulin resistance by increasing the rate of peripheral glucose uptake, which includes glucose oxidation and storage[32].

Clinical benefits of intensive insulin therapy

We know that hyperglycemia may serve as a surrogate marker for more severe illnesses and blood glucose control has always been an important topic in patient care. Patients with extreme high blood glucose, such as Diabetic ketoacidosis (DKA), or hyperosmolar hyperglycemic nonketotic coma (HHNK) must immediately be hospitalized for insulin infusion treatment for achieving the targeted blood sugar < 200 mg/dL. Since 2001, based on the work done by Van den Berghe et al. tight blood sugar control with intensive insulin administration (IIT) has become a new feature of current practice in lieu of the traditional concept of tolerating glucose levels as high as 11.1 mmol/L (200 mg/dL) [33]. The IIT requires frequent monitoring of blood glucose and an intravenous infusion of insulin in saline even if the patient has mild hyperglycemia (>110 mg/dL ,with a goal of 80-110 mg/dL) in ICU. Studies have shown decreases in blood stream infections as well as reduced antibiotic use, renal replacement therapy, mechanical ventilation, and ICU stay in patients who had tight glycemic control[34-35].A systematic review and meta-analysis was published by Pittas in 2005 which included 38 relevant studies from 1965 to 2005 that showed insulin therapy may decrease mortality in certain group of critical ill patients. Targeting euglycemia appears to be the main determinant of the benefit of insulin therapy[36].

The divergent results of IIT were also demonstrated in many randomized controlled trials studies after 2001. The GLUCONTROL study[37], which recruited subjects in a mixed population of critically ill patients, was suspended by the steering committee and the data safety monitoring board because of significantly increased mortality rate in those patients who experienced hypoglycemia in the tight glycemic control group. Ilse Vanhorebeek et al. argued that hypoglycemia did not cause early deaths: only minor immediate and transient morbidity was seen in a minority of patients, and no late neurologic sequelae occurred among hospital survivors[38]. Wiener RS et al. proposed that tight blood glucose control was not associated with significant difference in mortality when stratified by glucose goal based on a meta-analysis which included twenty-nine randomized controlled trials totaling 8432 patients[39]. So far, there are still many challenges to the original Leuven study, which makes it unsuitable for wider applicability.

Recent NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study involving 42 hospitals in Australia, New Zealand, Canada, and the United States from December 2004 through November 2008 has demonstrated that, compared with conventional therapy (maintaining the glucose concentration at <180 mg/dL), IIT was associated with an increased mortality 90 days after randomization[40]. NICE-SUGAR devised a new standard of glycemic control in the ICU: do not treat hyperglycemia unless the glucose level increases higher than 180 mg/dL; when you do treat hyperglycemia, aim for a target blood glucose concentration between 144 and 180 mg/dL[41]. Corey Scurlock et al. contended that NICE-SUGAR due to its methodological differences cannot be read as a direct comparison to the original Leuven study[42].

Many factors have been mentioned that the conflicting results were possibly influenced by the staff-to-patient ratio, the degree of experience of nurses, varying nutrition goals of calorie administration, different types of nutrition support, the categories of studied subjects such as postsurgical, MICU, cardiovascular, differing algorithm of blood glucose control, various source of blood sample (arterial line, venous, capillary), a variety of bedside glucose meters, rate of glycemic change, and insulin infusion rate[43-47].

Mechanism of IIT

It is still unclear whether the clinical benefit by IIT is correlated with tight glucose control or insulin action. Clinical observations done by Leuven group confirmed that the largest benefit of IIT was gained by prevention of the excessive hyperglycaemia rather than by the insulin dose administered[48-49]..Ilse Vanhorebeek et al. demonstrated that tight blood

Table 2. The beneficial effects of exogenous insulin

insulin promotes muscle protein synthesis1 and inhibits lipolysis
suppresses nuclear factor κ–β expression and free radical generation
enhances endothelial nitric oxide generation
reduces thromboxane A, reducing platelet aggregation
increasing fibrinolysis
suppresses TNF production in a dose dependent manner21
formation of prostaglandin E2 and I2 precursors

glucose control prevented the glucose toxicity in the liver that maintains the mitochondrial ultrastructure through electron microscopy in biopsy samples[50].

It has been reported that intracellular glucose overload induces overproduction of superoxide by the mitochondrial respiratory chain in the liver, and eventually leads to mitochondrial dysfunction ("cytopathic hypoxia") which impairs the cellular energy metabolism of hepatocytes that cause organ damage[51]. But mitochondrial respiratory chain enzyme activities remained normal in skeletal muscle, regardless of the glucose and insulin levels. The tissue-specific effects on the morphologic change between liver and muscle may be explained by insulin-dependent glucose uptake, which may be relatively well protected in view of the development of insulin resistance[52].

Conversely, many researches reported that insulin mediated vascular dilatation and an acute reduction in plasma concentrations of ICAM-1, MCP-1 and pro-inflammatory transcription factor, early growth response factor 1, and plasminogen activator inhibitor-1 (PAI-1) can minimize endothelial dysfunction-a key role of organ failure[53-54]. In short, insulin exerts independent protective effects on the endothelium. S. Fujita et al. has demonstrated that supraphysiological hyperinsulinaemia can overcome the insufficiency of age-related muscle protein synthesis in healthy older individuals[55].

Anabolic effect of insulin may contribute muscle protein synthesis[56], direct anti-apoptotic properties of insulin provides myocardial protection in critically ill children[57], as well as dyslipdemia partially reversed (HDL and LDL cholesterol) by insulin therapy[58] all support the mechanisms of direct insulin effect during critical illness.

It is not surprising that exogenous administration of insulin and tight glucose control are both responsible for the beneficial effects in critically ill patients[59]. The following list of beneficial effects of exogenous insulin is shown on the table (2). Although several mechanisms involving glycemic and lipid control and interrelated functions between insulin, endothelial function and inflammation remains to be explored, it is really impressive that the current practice of a simple measurement of blood glucose level while maintaining normoglycemia with insulin is all that is needed for successful treatment[60].

Tight glucose control in nutrition perspective

Early nutrition support (ENS) and maintaining energy balance using early parenteral supplement is commonly interpreted as aggressive nutrition support during critical illness. ENS is defined by the Canadian Clinical Practice Guidelines for Nutrition Support as within the first 24–48 h following admission to an ICU in all critically ill patients. A previous concern was that combined enteral parenteral therapy dealt more harm than benefit[61]. Conversely, given that a cumulative energy deficit is strongly correlated with poor outcome[62], the latest ESPEN guidelines for critically ill patients advocate that parenteral nutrition be initiated whenever enteral nutrition is insufficient to meet caloric needs[63]. The controversy between these concepts is based around the application of tight glucose control during nutrition therapy.

Overfeeding in critical ill cases are commonly associated with high infectious complications and metabolic disturbances including hepatic steatosis, hypertriglyceridemia, hypercapnia, and the refeeding syndrome. Overfeeding is prohibited in the current practice of nutrition support especially in critically ill patients[63-64].

Karen C. McCowen et al. demonstrated that hypocaloric nutrition support strategy with limiting protein and lower rate of glucose administration in obese patients did not reduce iatrogenic hyperglycemia. Based on feeding weight, caloric intake averaged over the duration of the study was 14 kcal/kg in the hypocaloric vs. 18 kcal/kg in controls[65].

We know that hypermetabolism, persisted somatic protein wasting, is undoubtedly a result of prolonged hypocaloric feeding. However, the strategies of permissive hyponutrition go against the current ESPEN guideline[63]. So far, it is commonly believed that both prolonged hypocaloric feeding and hypercaloric feeding may be detrimental in ICU patients[66]. But it is still a subject of debate on how

long hypocaloric feeding can be tolerated in acutely ill patients[67-68].

Glucose and fatty acids are the major oxidative fuels in mammals. Traditionally, based on the concept of energy balance, both were considered as interchangeable. Randle and his colleagues in 1960 described a glucose–fatty acid cycle that interlinks carbohydrate and fat metabolism. In brief, elevation of glucose concentration can inhibit NEEA utilization even in the presence of high concentrations of fatty acids and vice versa. In normal physiology, the competition of substrates utilization in muscle is strongly coordinated in accordance with meal compositions. It makes perfect physiological sense: the muscle adapts to their use of metabolic fuels in a dynamic manner.

Glucose restriction and insulin therapy is considered a standard treatment for hyperglycemia in extremely low birth weight (ELBW) infants[69]. V R Kairamkonda et al. proposed that initial glucose infusion rate was 9 mg/kg/min and maximal reduction of glucose infusion was up to 6 mg/kg/min if uncontrolled hyperglycemia persisted. Glucose infusion did not beyond 12 mg/kg/min, which appears to be the maximal glucose oxidative capacity in the neonate[70]. Escalating glucose intake should not go beyond its maximal oxidation capacity for energy supply and avoiding lipogenesis in the liver. (RQ > 1)

Can we use lipid emulsion for replacing high glucose load in the critical illness preventing from stress-induced hyperglycemia? It may not be the answer. It has been reported that only 10% of IV fat emulsion are oxidized[71]. The oxidation rate of exogenous fat emulsion using isotopes demonstrated by Jorgen Nordenstrom, M.D. in the trauma patients was 22.1% ± 2.8 in TPN lipid system, which was 47 ± 2% of the non-protein calories as fat. The rest of the non-oxidized fat emulsion is degraded by lipoprotein lipase to free fatty acid, which enters into adipose and liver cells for storage. The remnants of plasma lipid particle are also trapped by the liver by endocytosis. Futile fatty acid–TG cycle is more activated in the critical illness[72]. High lipid load has many side effects such as hyperlipidemia, hepatic steatosis, cholestasis, allergic reactions, and pulmonary dysfunction. It should be used with caution in septic patients[73]. The optimal rate of daily lipid emulsion intake in critical illness ranges from 0.7 g/kg up to 1.5 g/kg over 12–24 h as suggested by ESPEN guideline. At the same time, CHO infusion should not be exceed 5mg/kg/min and basal requirement of glucose is estimated to be roughly 2 g/kg/day for an adult[74].

Fatty acid is not just as a fuel for human cells. A large variety of exogenous fatty acid incorporation into cell membranes influence the inflammatory and immune response, modulating gene expression, membrane fluidity and exposure of receptors on the cell surface[75]. Appropriate modulation of inflammatory response by lipid emulsions in critical illness can improve a patient's survival rate.

It is therefore advisable that in clinical practice, fat emulsions should not be considered as interchangeable with glucose and their metabolic effects should be taken into consideration[76]. Each source of non-protein calorie (fat, glucose) seems to have unique characteristics, and are not to be mutually replaced.

Target glucose level and barriers to ICU glucose control

Blood glucose concentrations of 160-200mg/dL (11 mmol/L) were recommended to maximize cellular glucose uptake in non-insulin dependent tissues while avoiding hyperosmolarity[77]. In the conventional insulin treatment, insulin infusion was started when blood glucose exceeded 200mg/dL (11 mmol/L) and blood glucose levels were targeted to be between 150-160mg/dL (8-9 mmol/L). Two Leuven studies[78-80] reported an improved vital outcome when insulin therapy was titrated to achieve a range of 80–110 mg/dL, as opposed to 180–200 mg/dL. Many arguments question the validity of the conclusions made by the Leuven study based on an unusual ICU practice and the presence of study bias (single center, most of cardiac surgical patients) [81].

NICE-SUGAR and the GLUCONTROL trials, were designed to compare the effects of insulin therapy titrated to 80–110 mg/dL vs.140–180 mg/dL. The risk-to-benefit ratio seems more advantageous when using the higher glucose target. Although a further confirmation of these findings is desirable, most clinicians felt comfortable using this intermediate range as a target for intensive insulin therapy[82]. In 2011, the guideline of the American College of Physicians suggested that IIT can be implemented in ICU patients with target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) [82].

Blood sugar control with insulin infusion seems to be simple and straightforward. But frequent monitoring of blood sugar and adjustment of insulin dose need more nursing time and ready-to-use equipment.

Every hour, the nursing caregiver must locate a glucose meter, perform a fingerstick, document the results, and make the necessary insulin drip adjustments. It is tedious and time-consuming. In addition, clinical patients variability such as fluctuating severity of illness, changes in nutritional delivery, off-unit visits to diagnostic imaging all influence competence of protocol performing. Many insulin infusion protocols have been developed, but there is no one protocol that fits for all[84]. Obviously, it is difficult to compare the performance of a protocol without actually incorporating it into patient use. Applying multiple protocols to the same patient is likewise impractical. In real-life clinical practice, since there exists a diverse set of ICU patients, a single insulin infusion protocol will produce unpredictable responses in each individual patient. The ideal insulin infusion protocol should achieve glycemic control in a reasonable time frame with minimal hypoglycemia, low operator error rate, and require minimal nursing time.

The most complicated factor is exogenous nutritional inputs exacerbating the original problem: glucose control or targeting nutrition goal. Table (3) lists some barriers for glucose control in the Intensive Care Unit that goes beyond blood glucose level or the dosage of insulin.

Sliding scale insulin (SSI) therapy was first used in 1939 to guide diabetes patients to check blood glucose level before every meal and give insulin based on the measurement, which predicts the amount of elevated blood glucose caused by feeding. Clinicians rely on SSI to manage hyperglycemia rather than adjusting the patient's regimen. SSI is a reactive rather than proactive protocol for blood glucose control. While many studies reported that SSI is an inappropriate approach to blood glucose control in diabetic patients, SSI is entrenched in current medical practice because of minimal workload of medical team. In addition, subcutaneous administration of insulin is not appropriate for critical illness due to altered blood flow in surface skin. Intravenous methods of insulin administration provide a continuous and titratable method of glucose control in critically ill patients[85].

SPRINT protocol (Specialized Relative Insulin Nutrition Tables), designed by Chase, modulates both nutrition and insulin to provide tight glycemic control together with easy clinical implementation. It based on hourly or 2-hourly blood glucose measurements, total insulin prescribed limited up to 6 U/hour, a goal rate of enteral feeding: 25 kcal/kg per day and 2.7 to 9 kcal/kg per day from carbohydrates. Chase showed that SPRINT, a process that is fully implemented by the nursing staff**,** significantly decreases hospital mortality rate especially in subjects who stayed in the ICU for increasingly longer periods (ICU length of stay > 3 days) [86].

Table 3. Barriers to Glucose Control in the Intensive Care Unit

Labor-intensive glucose control protocols
Two much decision making
Failure to begin insulin therapy
Inadequate communication among health care professionals
Algorithms should be designed by adapting to individual patient responses to insulin
Address monitoring and treatment of low potassium concentrations
Complex calculations.
Lack of Consensus Glucose Control Guidelines
Fear of hypoglycemia
Glucometer

Sometimes severe hyperglycemia occurs regardless of escalating insulin infusion dose, which causes further insulin resistance, B-cell dysfunction, and impaired glucose disposal. It is usually imperative to temporarily stop all calorie provision until glucose control is established. Table (4) summarizes some strategies for improving glycemic control and maximizing the benefits and minimizing the risks[87].

New technology of subcutaneously sampled, continuously measured glucose concentrations for glucose monitoring correlate well with intermittently measured arterial glucose concentrations, which helps to avoid hypoglycemic episodes[88]. In addition, it enables us to collect more data regarding blood glucose levels during IIT and more accurate calculations of insulin dosage.

Alternative strategies for glucose control other than insulin infusion

It is not surprising that the magnitude of the surgical trauma strongly determines the degree of postoperative insulin resistance. The minimally invasive techniques such as laparoscopic cholecystectomy and laparoscopic segmental colectomy attenuated the metabolic responses compared with conventional open surgery[89-90]. Alexandre Ouattara et al. showed that poor intraoperative glycemic control despite

Table 4. Strategies for Improving Glucose Control in the Intensive Care Unit

Do not overfeed.
Provide carbohydrates preoperatively; minimize nil per os duration preprocedure.
Ensure continuous enteral feeding while patient receives insulin infusion.
Provide a mixed fuel source for parenteral nutrition.
Administer hypocaloric feedings for obese patients.
Provide hypocaloric initial feedings for patients who are at increased risk of hyperglycemia or in the acute phase of illness.
Add longer-acting insulin once stable.
• Care must be taken for patients who are in renal failure or who have poor glycogen stores, as in severe liver disease.
If hyperglycemia is sustained despite increasing insulin levels, stop parenteral nutrition for 24 hours while glucose is controlled;this may be due to glucose desensitization.

Adapted from and used with permission: Parrish CR, Krenitsky J, McCray S. University of Virginia Health System Nutrition Support Traineeship

the use of intensive insulin therapy during cardiac surgery was significantly more frequent in patients with severe postoperative morbidity (37% *vs.* 10%; $P < 0.001$)[91]. In elective surgery, provision of carbohydrate beverage 2-3 h prior surgery can trigger the so-called Staub–Traugott effect and increase insulin sensitivity at the time of surgery and postoperatively.

Conclusion

Stress Hyperglycemia is a landmark of the severity of illness. When higher blood glucose levels arise, more deaths are observed. Tight glycemic control is a breakthrough concept of ICU practices. Although IIT with various protocols has been implemented in ICUs worldwide, there is still a high percentage of uncontrolled-hyperglycemic subjects that have been reported.

Continuous monitoring of blood sugar would provide early warning for doctors as well as a mechanism for gauging precise dosages of insulin while also enabling us to collect more information during IIT. Employing this simple clinical practice will allow us to approach the patient's problem along different avenues, different strategies that would not have been available otherwise. In this ever-changing field, the search for a better answer is unremitting, and as such the study of tight glucose control with insulin in critically ill patients should never be at an end.

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應激性高血糖血症

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摘要

如第二型糖尿病患者，在胰島素阻抗狀態下，肝細胞葡萄糖輸出增加及周邊組織葡萄糖利用率下降，導致了危重病患的高血糖血症。這是應激性高血糖血症的核心機制。2001 年之後，Van den Berghe G 認為高血糖可以導致細胞能量代謝異常及後續器官衰竭，所以在病患進住重症加護病房幾天以後，發生併發症及死亡，可歸因於高血糖及感染性併發症的增加。所以積極使用胰島素，維持血糖濃度（140 mg/dL - 200 mg/dL），是當前 ICU 照護的新策略。更複雜的事，是外源性營養素的投入，加劇了最初的問題：嚴格血糖控制或是否營養攝取達到預定目標。這是兩難的議題，因為長期低熱量餵養會導致病患營養不良。但急重病患可以容忍多長時間低熱量餵養，仍在辯論中。利用胰島素輸注控制血糖，看起來多麼簡單，但應激性高血糖血症的分子機制與臨床效益，仍需要進一步的探討。

關鍵詞：高血糖血症、胰島素阻抗、積極胰島素治療

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Original Article

Brain Magnetic Resonance Imaging Findings in Children with Syndromic Mitochondrial Diseases

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Abstract

Purpose: To describe the brain magnetic resonance imaging (MRI) findings in children with syndromic mitochondrial diseases (MDs).
Methods: From 1988 to July 2008, brain MRI of 30 patients diagnosed as syndromic MDs were reviewed. Definite diagnosis of syndromic MDs was made based on the modified diagnostic criteria of mitochondrial diseases.
Results: Among the 30 recruited patients, 14 had Leigh syndrome, five exhibited mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome, three manifested mitochondrial cardiomyopathy, two had Kearns-Sayre syndrome, one exhibited fatal infantile mitochondrial myopathy, one manifested myoclonic epilepsy with ragged red fibers, one had Leber hereditary optic neuropathy, one exhibited deafness dystonia syndrome, one manifested chronic progressive external ophthalmoplegia, and one had Pearson syndrome.
One patient with mitochondrial cardiomyopathy did not perform brain MRI and five cases (two mitochondrial cardiomyopathies, one fatal infantile mitochondrial myopathy, one chronic progressive external ophthalmoplegia, and one Pearson syndrome) had initially normal brain MRI findings. Initial brain MRI abnormalities were found in 24 out of 29 patients (83%). The most common signal changes on the initial brain MRI were abnormal signal intensity over the basal ganglia, gray matter, and brainstem in 17 (71%), 10 (42%), and 9 (38%) patients, respectively. 14 out of 15 cases (14/15; 93%) were found to have evolutionary changes on the follow-up brain MRI.
Conclusions: Brain MRI is a useful tool helping to make the diagnosis of syndromic MDs in children, especially abnormal signal intensity over the basal ganglia. Follow-up brain MRI is important for assessing clinical evolution of the disease.

Key words: syndromic mitochondrial diseases, MRI, children

Introduction

Mitochondrial diseases (MDs) are a clinically heterogeneous and often multisystemic group of disorders, caused by a large variety of defects in mitochondrial energy metabolism resulting in diminished adenosine triphosphate production. Although mitochondrial dysfunction manifests over a wide range of clinical expressions, it most often affects the muscles and brain, where the dependence on oxidative energy metabolism is greatest. Classification of MDs remains complex and it is challenging to make a diagnosis even with the recent advances of molecular genetics. The diagnosis is often based on multidisciplinary approach by means of clinical, biochemical, and neuroradiologic findings, as well as genetic analysis.

In the last decade, the clinical diagnosis of MDs

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has been greatly improved by the development of brain magnetic resonance imaging (MRI) which is sensitive to demonstrate of these diseases, especially in clinically phenotypic MDs including Leigh syndrome (LS), mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), and Kearns-Sayre syndrome (KSS), etc.[1-4]

The aim of this study is to investigate brain MRI findings in children with syndromic MDs focusing on neuro-radiological features at the initial onset and during the follow-ups.

Methods

From 1988 to July 2008, medical records and neuro-imagings of syndromic MDs 30 patients (15 males and 15 females) were reviewed. The median age at the initial clinical presentation was 17.5 months, ranged from 1 month to 15 years of age. Patients were examined by serial neurologic examinations and metabolic evaluations, including assays of blood amino acids and urinary organic acids, and an oral glucose lactate stimulation test (OGLST). [5] Mitochondrial DNA common point mutations (mt DNA 3243, 8344, 8993, and 9176) and deletions were screened. A skeletal muscle biopsy for light microscopic and electron microscopic examinations was performed. Morphologic examination of skeletal muscle tissue included histochemical stains in terms of modified Gomori trichrome staining for ragged red fibers, adenosine triphosphatase staining for myofibrillar integrity, muscle-type fiber predominance and distribution, and cytochrome *c* oxidase and succinate dehydrogenase staining for oxidative enzymes.

Our diagnostic criteria for syndromic MDs were revised on the basis of the modified mitochondrial diseases criteria proposed by Bernier et al.[6] The major criteria include (1) clinically complete respiratory chain encephalomyopathy, including Leigh syndrome (LS), Alpers disease, fatal infantile mitochondrial myopathy (FIMM), deafness dystonia syndrome (DDs), Pearson syndrome (PS), Kearns-Sayre syndrome (KSS), mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial cardiomyopathy (MCM), neuropathy, ataxia, and retinitis pigmentosa (NARP), mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE), and Leber hereditary optic neuropathy (LHON), and (2) molecular identification of a mt DNA mutation of undisputed pathogenecity. The minor criteria include (1) histologically abnormal mitochondrial configurations and/or abnormal subsarcolemmal mitochondrial accumulation of muscle cells, and (2) an abnormal metabolic indicator of OGLST. Definite diagnosis of syndromic MDs was made in all patients, i.e., two major criteria or the major criterion (1) plus two minor criteria.

MR studies were performed on a 1.5 Tesla (Siemens sonata unit), sometimes at different institutions, and 3.0 Tesla MR in one. Standard MRI was performed, including T1 weighted image (T1WI) (TE/TR 11ms/550ms), T2 weighted image (T2WI) (TE/TR 93ms/4000ms) and fluid attenuated inversion recovery (FLAIR) (TE/TR 110ms/10000ms). MRI was conducted within one week from the first hospital visit and it was followed base on clinical features. The radiological studies were interpreted by a board-certified neuroradiologist and two pediatric neurologists.

Results

Among the 30 recruited patients, 14 were LS, five were MELAS syndrome, three were MCM, two were KSS, one was FIMM, one was MERRF, one was LHON, one was DDs, one was CPEO, and one was PS.

We excluded one case with MCM who did not receive brain MRI. Five out of 29 cases' (5/29; 17%) brain MRI findings results were normal: two were MCM, one was FIMM, one was CPEO, and one was PS. 24 out of 29 children (24/29; 83%) had abnormal findings on brain MRI. As shown in table 1, these findings were quite diverse from nonspecific findings, such as cortical atrophy, generalized atrophy or ventriculomegaly to prominent abnormal signal intensity over the basal ganglia, brainstem, gray matter, white matter or cerebellar hemisphere (Figures 1 and 2). The frequency of signal changes were basal ganglia, gray matter, and brainstem in 17 (71%), 10 (42%), and 9 (38%) patients, respectively.

We observed that two distinct MRI features could be found in patients with MELAS syndrome (Figure 2). One was abnormal signal intensity over the basal ganglia and alternating focal abnormal signal intensity of cortex, especially over the occipital lobes, the other one was progressive focal cortical atrophy.

Follow-up brain MRIs were performed on 15 cases, including seven LS, four MELAS syndrome, one LHON, one DDs, one PS, and one CPEO, depending on clinical evolution. Among them, 14 (14/15; 93%) cases showed evolutionary changes according to disease stages except for one case with CPEO. Two

Table 1. Initial brain magnetic resonance imaging (MRI) results in patients with syndromic mitochondrial diseases.

MRI	LS	MELAS	KSS	MERRF	LHON	DDs	PS	MCM	FIMM	CPEO	Total n (%)
Total, n	14	5	2	1	1	1	1	2	1	1	29 (100)
Normal, n	0	0	0	0	0	0	1	2	1	1	5 (17)
Abnormal, n	14	5	2	1	1	1	0	0	0	0	24 (83)
Nonspecific findings											
Cortical atrophy	1	1	0	0	0	0	0	0	0	0	2 (8)
Ventriculomegaly	8	0	0	0	0	1	0	0	0	0	9 (38)
Generalized atrophy	6	1	0	1	0	1	0	0	0	0	9 (38)
Parenchymal lesions											
Cerebellum	1	0	1	0	0	0	0	0	0	0	2 (8)
Brainstem	7	0	2	0	0	0	0	0	0	0	9 (38)
Basal ganglia	12	3	0	0	1	1	0	0	0	0	17 (71)
Gray matter	5	5	0	0	0	0	0	0	0	0	10 (42)
White matter	2	3	1	0	0	0	0	0	0	0	6 (25)

DDs: deafness dystonia syndrome; KSS: Kearns-Sayre syndrome; LHON: Leber hereditary optic neuropathy; LS: Leigh syndrome; MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome; MERRF: myoclonic epilepsy with ragged red fibers; n: numbers; PS: Pearson syndrome.

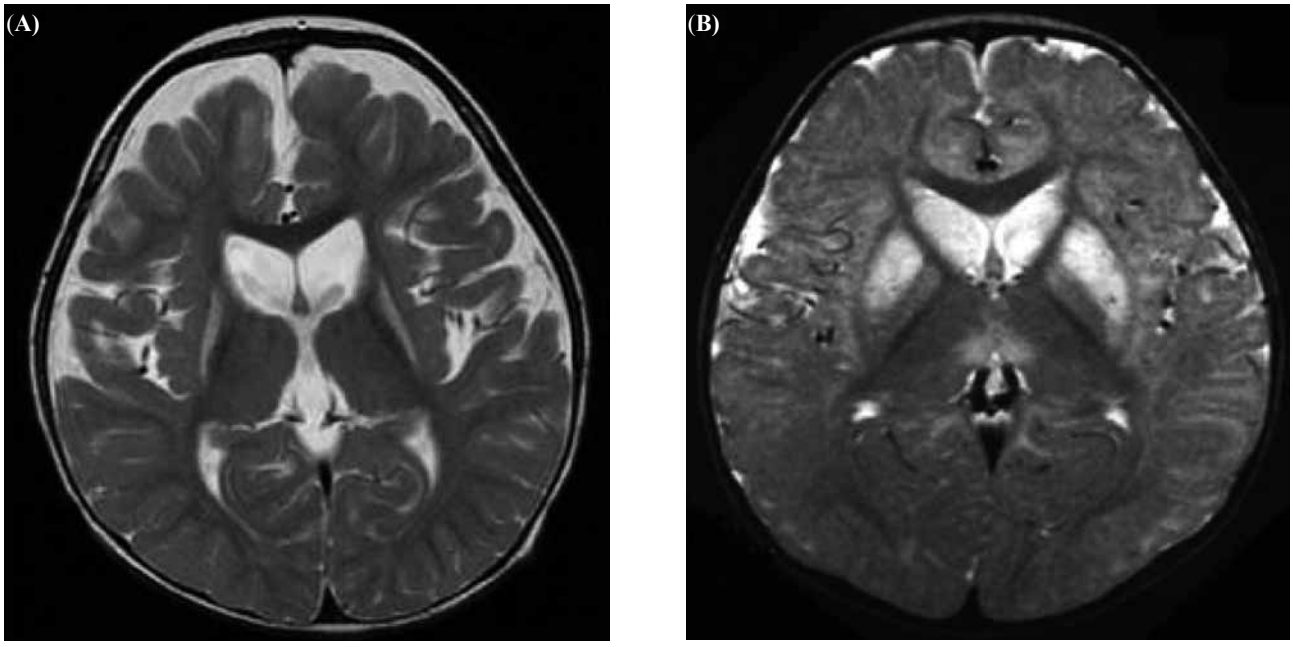

Fig. 1 Basal ganglion involvement of brain magnetic resonance imaging (MRI) in syndromic mitochondrial diseases. **A.** A 4-month-old male infant with deafness dystonia syndrome. Axial 1.5T MRI (TE/TR 93ms/4000ms) showed symmetric involvement of the bilateral putamen. **B.** An 8-month-old female infant with Leigh syndrome. Axial 1.5T MRI (TE/TR 93ms/4000ms) showed symmetric high signal intensity in bilateral putamen, heads of bilateral caudate nucleus, and periaqueductal area.

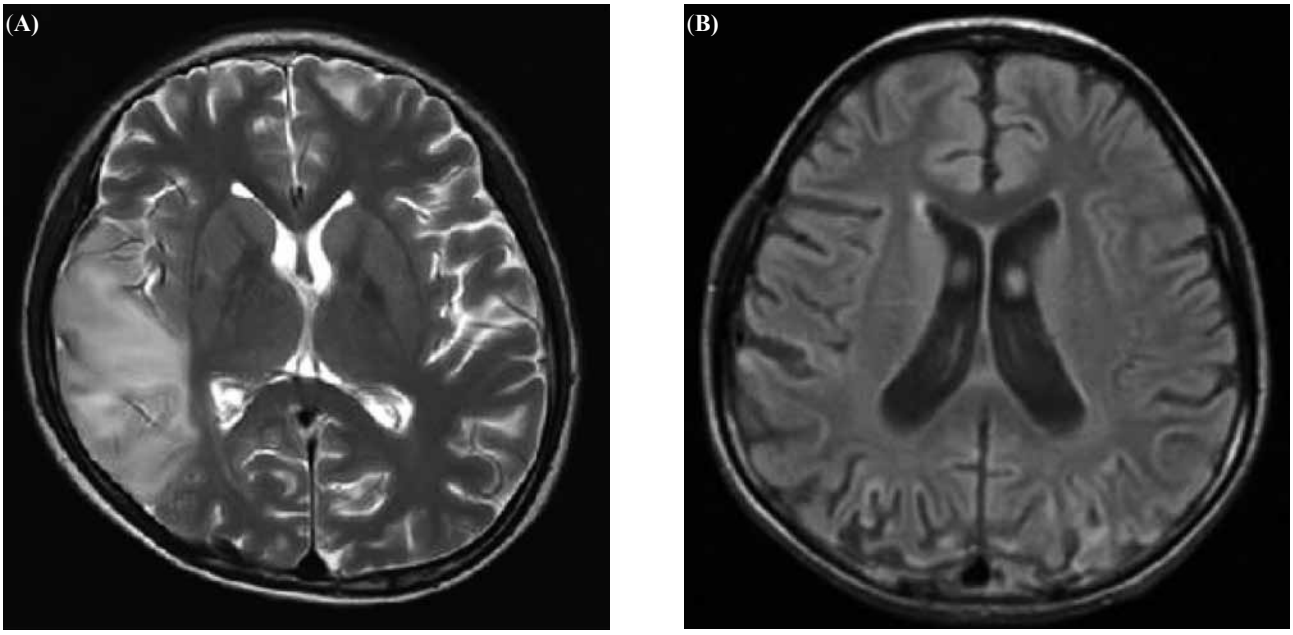

Fig. 2 Brain magnetic resonance imaging (MRI) in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome. **A.** A 13-year-old girl (mt DNA A3243G) presented with diarrhea, constipation and poor appetite in the early childhood. Severe headache, vomiting, and alternating hemiconvulsion developed in her teenage. Axial 3.0 T MRI (TE/TR 80ms/3000ms) showed high signal intensity in bilateral internal capsules and right temporal and occipital areas. **B.** An 11-year-old boy (mt DNA A3243G) presented with altered level of consciousness, seizures, failure to thrive and short stature. Axial 1.5T MRI ((TE/TR 110ms/10000ms) at age of 13years showed focal cortical atrophy in bilateral occipital areas.

patients, one DDs and one PS, with initially normal brain MRI features showed prominent signal changes over the basal ganglia, brainstem, gray matter, and/or cerebellum on the follow-up brain MRI. Progressive brain atrophy involving all brain structures or alternating focal lesion sites was commonly seen on the follow-up brain MRI scan.

Discussion

In our case series, the findings of brain MRI in children with syndromic MDs were variable, i.e. nonspecific changes to specific lesion site abnormalities. The order of lesion sites was 71% basal ganglia, 42% gray matter, 38% brainstem, 38% ventriculomegaly, 38% generalized atrophy, 25% white matter, 8% cerebellum, and 8% cortical atrophy.

The most common abnormality is located in the basal ganglia. There might be a subjective limitation since the majority of patients with abnormal brain MRI findings were LS (14/24; 58%). The typical MRI features of LS were characterized by abnormal signal intensity over the brainstem, cerebellar and/or basal ganglia. Symmetric or asymmetric lesions in variable shapes over the caudate nucleus, thalami and putamen were found in different subgroups of syndromic MDs (Figure 1). Dorsal aspects of the pons and medulla, periaqueductal region, red nucleus, cerebellum, and cerebral peduncles were also frequently affected. Our findings were consistent with the previous literature report[7]: basal ganglia and/or brainstem are particularly vulnerable structures that are highly dependent on glucose consumption, which should be considered as a strong feature leading to the diagnosis of MDs.

Regarding gray matter involvements, 42% of our patients had abnormal findings, including five LS cases, and five MELAS syndrome cases. The MRI figures might be focal or multifocal abnormal signal changes over the cortex, which usually accompanied by other lesion sites over the basal ganglia, brainstem, or cerebellum.

Abnormal signal intensity over the white matter suggestive of MDs included pure "symmetric and

diffused" or "asymmetric scattered focal" lesions, cyst lesions, both cerebral and cerebellar lesions with or without the combination of bilateral basal ganglia lesions.[8-11] Our case series revealed a diffuse leukodystrophic pattern in three syndromic MDs cases: two were LS and one was KSS. Isolated or predominant cerebellar volume loss, atrophy or hypoplasia, had been reported as a neuroradiologic presentation of pediatric mitochondrial encephalomyopathies.[12] Three cases in our study, one LS, one KSS, and one PS, had cerebellar involvement combined with other abnormalities, including basal ganglia, brainstem, gray matter, and/or white matter during the initial and/or follow-up brain MRI features.

Nonspecific findings, including 38% ventriculomegaly, 38% generalized brain atrophy, and 8% cortical atrophy, were also not uncommon in our study. Those findings were rarely mentioned in the literature. Our observation revealed one case with MERRF had "pure" nonspecific brain MRI findings. In such cases, clinical features of multisystemic involvements, episodic or progressive deterioration of neurological symptoms following a minor infection could be a useful feature leading to the working diagnosis.

Our study showed 17% of our patients had normal brain MRI results in the initial scan. Even in the course of disease evolution, one CPEO patient still had normal brain MRI features. This suggested that syndromic MDs should be included in the differential diagnoses, especially in patients who have normal brain MRI appearances but there are unexplained encephalopathies or encephalomyopathies clinically.

Regarding follow-up brain MRI scan, 93% of the clinically deteriorated patients showed evolutionary changes in our study. Follow-up brain MRI played an important role in monitoring disease progression and raising suspicion of MDs in patients who had an initial normal brain MRI, which affected our decision making for specific workups such as muscle biopsy and mitochondrial gene analysis. The evolutionary changes were shown not only on the brain MRI but also in the clinical disease process. Overlap syndromes among syndromic MDs were also found in two cases: one was MELAS with phenotypic MNGIE[13] and the other one was PS evolving into LS.[14]

In conclusion, brain MRI findings in children with syndromic MDs may also be ranging from nonspecific findings to specific patterns just like its clinical presentations. However, the combination of clinical presentations and brain MRI findings can help us to establish the diagnosis more accurately.

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兒童症候群粒線體疾病腦部核磁造影之表現

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摘要

目的：描述兒童症候群粒線體疾病之腦部核磁造影表現。
方法：自1988年至2008年7月，我們回顧30位診斷為症候群粒線體疾病病童之腦部核磁造影影像，症候群粒線體疾病的確定診斷則是以修正之粒線體疾病診斷準則為依據。
結果：30位病人中，14位為Leigh症候群，5位為粒線體腦症合併乳酸血症及類中風發作，3位為粒線體心肌病變，2位為Kearns-Sayre症候群，1位為致死性嬰兒粒線體肌病變，1位為肌跳躍癲癇合併紅色襤褸肌細胞，1位為遺傳性Leber氏視神經病變，1位為失聰張力失調症，1位為慢性進行性眼外肌麻痺症及1位Pearson症候群。
其中1位粒線體心肌病變病人沒有做腦部核磁造影，5位病人（2位粒線體心肌病變、1位致死性嬰兒粒線體肌病變、1位慢性進行性眼外肌麻痺症及1位Pearson症候群）初始腦部核磁造影是正常的。24位病人（24/29；83%）出現異常腦部核磁造影影像。腦部核磁造影中最常出現異常訊號的病灶為基底核（17/24；71%），其次為大腦灰質（10/24；42%）及腦幹（9/24；38%）。15位追蹤腦部核磁造影的病童中有14位（14/15；93%）出現影像上演化性改變。
結論：腦部核磁造影在診斷兒童症候群粒線體疾病為一有用的輔助工具，尤其當異常訊號出現在基底核時。除此之外，依疾病的臨床變化追蹤腦部核磁造影也是很重要的。

關鍵詞：症候群粒線體疾病、腦部核磁造影、兒童

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Original Article

以感應耦合電漿質譜分析儀研究頭髮內各元素與聽力閾值的相關性

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摘要

背景及目的：聽力障礙是一種複雜的疾病，與環境及遺傳因素有關。患聽力障礙可能會影響病人的生活品質及心理健康。文獻指出，暴露於鉛、汞、鎘和砷等元素污染的工作環境與聽力障礙有關，但少有研究在不侷限於特定工作場域下，探討生活環境中潛在的元素與聽力的相關性。在此研究計畫中，我們分析39種元素和聽力之間的相關性。

方法：本研究的樣本來自海線地區某區域教學醫院耳鼻喉科就診的聽力障礙病患（n=19）及同一醫院中接受健康檢查無聽力障礙之自願受試者（n=10）。此研究排除因遺傳、外力傷害或感染等因素造成聽力障礙及已接受過治療的病人。我們採集這些人的頭髮，利用感應耦合電漿質譜分析儀（inductively coupled plasma-mass spectrometry, ICP-MS）檢測39種元素含量，以雙耳聽力檢查報告紀錄的聽力閾值測度聽力，另以問卷調查可能的干擾因子。

結果：以混合回歸模式分析聽力閾值與其它變項的相關性，結果顯示校正干擾因子後，與聽力閾值呈正相關的元素包括鉍、鎳、錫、釩、鈉和碘；與聽力閾值呈負相關的元素包括鋁、鎘、鋯、硼和鈾。

結論：在此橫斷研究法中我們找出與聽力具相關性的元素，但無法釐清各種元素進入人體的途徑，因此，針對海線地區探討各元素如何進入並積存於人體，是未來進一步研究這些元素對聽力的作用及致病機轉前應努力的方向。

關鍵詞：聽力障礙、重金屬、微量元素、聽力閾值、相關分析

前　言

聽力障礙是一種複雜的疾病，與環境及遺傳因素有關 [1-3]。患聽力障礙可能影響病人的生活品質及心理健康，與人溝通困難將導致聽力障礙病人的社會孤立、喪失獨立生活能力、沮喪、焦慮，最後造成對社會不滿 [4]。研究指出，與聽力障礙發生有關的危險因子包括噪音 [5]、化學物質 [6]、賀爾蒙 [7]、酒精 [8] 以及吸煙 [9-10] 等等。

由於工業發展造成環境污染日益嚴重，使人體遭受化學物質的危害機率大增，甚至造成體內重金屬含量增加，並造成急性或慢性疾病。先前研究指出，鉛（Lead, Pb）、汞（Mercury, Hg）、鎘（Cadmium, Cd）、砷（Arsenic, As）等元素皆會影響聽覺功能 [11-14]，重金屬的危害大部分爲藉著影響中樞或週邊神經系統，進而造成聽力損傷。另一方面，有少數研究探討人體中的必須或微量元素與聽力障礙發生的相關性，鍺化合物對各種器官具有毒性，包括中樞神經系統，在 2009 年 Lin 等人針對鍺化合物對聽覺系統的影響進行研究，在老鼠身上發現鍺化合物會抑制電位控制型鈉離子通道（voltage-gated sodium channel）作用，進而影響聽覺系統的正常功能 [15]；Rizzetti 等人則在 2009 年的研究中提出鉻可能

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造成視力與聽力損失 [16]。

相較於過去的研究都針對暴露於高濃度之特定元素下對聽力的影響進行探討，本研究選擇 39 種生活環境中的潛在元素，分析它們在人體的濃度與聽力的相關性。

材料與方法

本研究分別自海線地區某教學醫院之聽力障礙病患（聽障組）與同一醫院內接受健康檢查的民眾（體檢組）取樣，分析聽力與元素濃度的相關性。聽障組招募條件爲 2008 年 10 月至 2009 年 6 月間初次進入耳鼻喉科門診的患者，且經專科醫師判定其聽力障礙（平均聽力閾值大於 25 分貝或耳鳴等）非由疾病、外力或遺傳引起，並排除有耳部手術或中耳、耳道問題之病患；體檢組則由同一時期於同一醫院接受健康檢查的民眾中招募無任何聽力障礙的民眾，最後符合條件且同意參與試驗的民眾，在聽障組有 19 位，在體檢組有 10 位。所有人都進行問卷訪視、頭髮樣本採集及收集雙耳聽力資料。資料收集方面，以問卷調查年齡、性別、吸煙與否、飲酒與否及飲用水來源，由聽力檢查報告取得不同頻率下的聽力閾值，聽力閾值爲受試者在特定頻率下可察覺到聲響的最小數值，單位爲分貝（dB），本研究以此值代表聽覺能力，其值越大聽力越差，每位受試者分別於 250Hz 、500Hz 、1000Hz 、2000Hz 、4000Hz 與 8000Hz 等頻率下測雙耳聽力閾值。

體內元素累積濃度資料由頭髮檢體分析結果取得。一般檢測體內重金屬含量，主要以血液、尿液以及頭髮爲主要檢體，毒性重金屬元素在頭髮中的累積，常會比在血液或尿液中的累積高出數百倍，以血汞爲例，其濃度約略爲髮汞的 1/150 至 1/200，而尿液檢測則容易被其中的氯鹽所干擾，造成誤判。因此，如欲檢驗人體暴露於重金屬污染的程度，頭髮被認爲是較好的標的組織。本研究中採集所有受試者的頭髮，藉由測定頭髮檢體內的 39 種元素濃度，來代表個案的暴露程度。頭髮樣本重金屬檢測是採集受試者靠近頭皮 3-5 公分、重量約 0.25 克的頭髮，以小夾鏈袋裝好並送至國外進行感應耦合電漿質譜儀（Inductively Coupled Plasma-Mass Spectrometry, ICP-MS）分析。感應耦合電漿質譜儀主要包括樣品導入系統、感應耦合電漿離子源和質譜儀三大部分，感應耦合電漿包含一組約 1500 瓦產生氬氣電漿的焰炬（Torch），在 5000~10000K 的高溫電漿中分解、游離注入的分析物，成爲帶一價或二價正電荷的原子態離子或化合物離子，作爲質譜儀的離子源 [17]，因此可用來分析頭髮中的元素濃度。本研究利用感應耦合電漿質譜儀分析 39 種元素（鋁、銻、砷、鋇、鈹、鉍、鎘、鉛、汞、鉑、鉈、釷、鈾、鎳、銀、錫、鈦、鈣、鎂、鈉、鉀、銅、鋅、錳、鉻、釩、鉬、硼、碘、鋰、磷、硒、鍶、硫、鈷、鐵、鍺、鋯、鈀、鋯）在頭髮中的濃度。資料統計與分析方面，針對資料型態分別應用 Spearman rank 檢定、Mann-Whitney 檢定、Fisher's exact 檢定、t 檢定等方法，分析聽障組與體檢組的聽力閾值，以及各組的人口學變項、生活習慣因子及各元素濃度，並以混合回歸模式（mixed regression model）校正干擾因子下分析各元素濃度和聽力閾值的相關性。所有檢定都設 0.05 爲顯著水準。

結　果

表 1 爲聽障組與體檢組在不同頻率下的聽力閾值分析結果，以配對 t 檢定分析各頻率下左右耳之聽力閾值差異，只有在 4000Hz 下呈現顯著差異（P=0.026）；聽障組的左耳與右耳聽力閾值皆隨著頻率增加而上升，其他研究 [12] 亦觀察過相同結果。本研究中兩組之聽力檢測環境及設備不同，依據臨床經驗，體檢中心的聽力檢測值平均較耳鼻喉科門診之聽力檢測值高 5dB，使得少數頻率下體檢組的聽力閾值平均顯得比聽障組的高；因此，需要在控制頻率及組別下分析聽力閾值與其他變數的相關性。

表 2 列出各元素濃度之平均值及全距，但是，由於九成以上受試者體內之鈹（Be）、鉑（Pt）、鉈（Tl）和釷（Th）四種元素低於儀器可檢測之濃度，所以，只有 35 種元素的濃度檢測值用於後續的分析之中。

本研究的受試者特徵分布分析結果列於表 3，整體平均年齡爲 45.6 歲，聽障組平均年齡顯著地高於體檢組，聽障組女性比例較體檢組高，但未達統計上顯著差異。其他生活型態的分布在兩組間皆未呈顯著差異，其中素食者、吸煙與喝酒的人數相當少，故在混合回歸模式中這三個因子不被考慮作爲解釋變項。

各元素濃度與不同頻率下雙耳聽力閾值具顯著相關性者，其 Spearman 相關係數估計結果列於表 4。表中數據顯示與低頻的聽力閾值具相關性者多爲重金屬元素，而與高頻的聽力閾值具相關性者多屬微量元素；除了鋯 (Zr) 其他元素與聽力閾值的相關性多呈正相關。由於許多元素及各頻率下的聽力閾值都分別與性別、是否飲用地下水等因子具相關性（參考表 1、表 2 標記之檢定結果），且以複回歸模式分析發現，控制組別情況下，鎳、銅、鋯、鉻、鉀、錫、鋅、鎘、銀同時與年齡具線性相關（本文未列出此結果），因此，考慮控制組別、頻率及這些干擾因子下，分析各元素與聽力閾值的相關性。

本研究中每名受試者的雙耳都在 6 種頻率下測試一次聽力閾值，我們以混合回歸模式處理每名受試者 12 次聽力閾值之間的相依性，在控制頻率、組別間聽力閾值之差異及干擾因子（年齡、性別、是否飲用地下水）

表 1 聽障組與體檢組之各頻率下聽力閾值分析結果

頻率	聽障組		體檢組	
	右耳	左耳	右耳	左耳
250 Hz	16.1 ± 14.3*c	20.3 ± 16.9*abc	18.5 ± 5.80	13.5 ± 8.18
500 Hz	17.1 ± 14.1	20.0 ± 12.8*abc	16.5 ± 6.26	15.0 ± 8.82
1000 Hz	21.3 ± 13.0	25.5 ± 13.6*a	16.5 ± 6.26	16.0 ± 7.38
2000 Hz	25.3 ± 20.8	32.6 ± 21.4*a	13.5 ± 6.69*a	13.0 ± 9.19
4000 Hz**	31.1 ± 24.4	40.0 ± 23.5	14.0 ± 6.58*a	16.0 ± 11.0
8000Hz	37.1 ± 24.9	46.3 ± 23.0	16.0 ± 6.15*a	16.5 ± 11.1
平均聽力閾值				
(250Hz＋500 Hz＋1000 Hz＋2000 Hz＋4000Hz＋8000Hz)/6	24.6 ± 14.6	30.8 ± 14.4	15.8 ± 4.8	15.0 ± 7.5

*固定組別、頻率、左右耳下，分別檢定聽力閾值與 a年齡 b性別 c是否飲用地下水之相關性的P值小於0.05；聽力閾值與年齡之相關性使用Spearman rank檢定，與性別、是否飲用地下水的相關性檢定使用Mann-Whitney檢定。
**以配對t檢定分析固定頻率下左右耳測得之聽力閾值具顯著差異。

表 2 聽障組與體檢組之各元素濃度分析結果

元素	聽障組		體檢組		P值[a]
	平均值 ± 標準差	全距	平均值 ± 標準差	全距	
鋁(Al)(μg/g)	5.15 ± 4.56	1.6-20	2.19 ± 0.64	1.3-3.2	0.005*
銻(Sb)(μg/100g)	3.37 ± 4.04	1.1-18	2.81 ± 3.18[b]	1-9.2	0.080
砷(As)(μg/10g)	1.25 ± 1.18[d]	0.13-5.5	0.93 ± 0.59	0.51-2.5	0.713
鋇(Ba)(μg/g)	3.24 ± 10.86	0.11-48	0.57 ± 0.48[b]	0.09-1.7	0.291
鉍(Bi)(μg/100g)	2.56 ± 3.04	0.5-14	0.87 ± 0.81	0.2-2.8	0.008*
鎘(Cd)(μg/100g)	9.61 ± 7.59	0.9-32	6.53 ± 3.99	2-14	0.271
鉛(Pb)(μg/g)	1.78 ± 4.94	0.14-22	1.53 ± 3.00[b]	0.21-10	0.872
汞(Hg)(μg/g)	2.70 ± 1.70	0.77-7.4	3.84 ± 2.21	0.47-7.9	0.108
鈾(U)(μg/100g)	1.02 ± 0.87	0.1-2.7	0.66 ± 0.76[c]	0.1-2.5	0.153
鎳(Ni)(μg/10g)	3.81 ± 6.41	0.4-28	2.41 ± 2.59[b]	0.7-9.5	0.927
銀(Ag)(μg/10g)	0.25 ± 0.22	0.06-0.9	0.20 ± 0.25	0.1-0.9	0.515
錫(Sn)(μg/10g)	2.15 ± 4.66[d]	0.3-21	0.88 ± 0.48	0.3-1.9	0.629
鈦(Ti)(μg/10g)	5.48 ± 1.90	2.9-10	4.93 ± 3.26	2.8-14	0.047*
鈣(Ca)(μg/mg)	1.39 ± 1.34	0.393-5.78	0.91 ± 0.52	0.403-2.17	0.435
鎂(Mg)(μg/10mg)	1.31 ± 1.42	0.22-6.5	0.91 ± 0.72	0.3-2.8	0.409
鈉(Na)(μg/10mg)	2.10 ± 1.80	0.23-5.9	1.27 ± 0.85	0.2-3.1	0.323
鉀(K)(μg/10mg)	1.09 ± 1.04	0.04-3.5	1.29 ± 1.43	0.05-4.5	0.836
銅(Cu)(μg/100mg)	1.62 ± 0.73	0.97-3.8	1.99 ± 1.16	0.79-4.6	0.520
鋅(Zn)(μg/10mg)	1.98 ± 0.93	1-5.2	2.02 ± 0.68	1.2-3.7	0.629
錳(Mn)(μg/10g)	3.78 ± 3.88[c]	0.6-16	2.28 ± 2.12[c]	0.7-8	0.408
鉻(Cr)(μg/10g)	4.86 ± 1.98	2.7-10	3.41 ± 0.35[c]	2.8-3.9	0.026*
釩(V)(μg/100g)	4.92 ± 4.81	1.2-23	2.32 ± 0.57	1.5-3.2	0.051
鉬(Mo)(μg/100g)	8.95 ± 19.70[d]	1.3-88	2.75 ± 0.55	1.9-3.7	0.103

（續下頁）

表 2 （續）

元素	聽障組		體檢組		P值[a]
	平均值 ± 標準差	全距	平均值 ± 標準差	全距	
硼(B)(μg/g)	1.38 ± 1.09[d]	0.18-4.2	1.11 ± 0.74	0.14-2.5	0.801
碘(I)(μg/g)	0.66 ± 0.68	0.16-3.2	0.49 ± 0.46	0.12-1.5	0.224
鋰(Li)(μg/100g)	1.13 ± 0.86	0.4-3.8	1.21 ± 0.45	0.5-1.8	0.240
磷(P)(μg/10mg)	1.97 ± 0.55	1.49-3.97	1.93 ± 0.17	1.65-2.22	0.383
硒(Se)(μg/g)	0.99 ± 0.22[d]	0.38-1.4	0.90 ± 0.12	0.74-1.1	0.059
鍶(Sr)(μg/g)	5.61 ± 6.01[c]	0.75-27	3.90 ± 3.83	1.3-14	0.323
硫(S)(μg/0.1mg)	4.58 ± 0.26	4.31-5.25	4.41 ± 0.25	4.16-4.98	0.043*
鈷(Co)(μg/100g)	1.81 ± 2.83	0.3-11	1.30 ± 2.51	0.2-8.4	0.102
鐵(Fe)(μg/g)	13.21 ± 13.32[d]	4.3-58	9.15 ± 2.72	6.4-14	0.963
鍺(Ge)(μg/100g)	3.40 ± 0.40	2.7-4.4	2.68 ± 0.47	2-3.5	0.001*
銣(Rb)(μg/100g)	9.37 ± 8.67	0.7-30	9.68 ± 9.92	0.6-30	0.945
鋯(Zr)(μg/100g)	3.90 ± 1.32	1.5-5.9	3.60 ± 2.51[cd]	1.7-10	0.242

[a]以Mann-Whitney檢定P值小於0.05者（標*號）表該元素濃度在聽障組與體檢組間呈顯著差異。
[b]以Spearman rank檢定顯示該組之元素濃度與年齡具顯著相關。
[c]以Mann-Whitney檢定在是否飲用地下水兩組間，元素濃度存在顯著差異。
[d]以Mann-Whitney檢定在男女間元素濃度呈顯著差異。

表 3 研究對象之人口學變項與生活型態之分析結果

變　數	聽障組	體檢組	總計	P值[†]
個案數	19	10	29	
年齡（歲，平均值 ± 標準差）	50.0 ± 13.1	37.3 ± 9.7	45.6 ± 13.4	0.012*
性別				
男(%)	4(21.1)	6(60.0)	10(34.5)	0.051
女(%)	15(78.9)	4(40.0)	19(65.5)	
素食者				
是(%)	1(5.3)	0(0)	1(3.4)	1.000
否(%)	18(94.7)	10(100)	28(96.6)	
吸煙與否				
有(%)	2(10.5)	1 (10.0)	3(10.3)	1.000
無(%)	17(89.5)	9(90.0)	26(89.7)	
喝酒與否				
有(%)	2(10.5)	1(10.0)	3(10.3)	1.000
無(%)	17(89.5)	9(90.0)	26(89.7)	
喝地下水與否				
有(%)	6(31.6)	3(30.0)	9(31.0)	1.000
無(%)	13(68.4)	7(70.0)	20(69.0)	

*表P值<0.05有差異。
†年齡變項使用兩樣本t檢定，其他變項使用Fishe's exact test。

對聽力閾值的影響後，分析元素與聽力閾值間的線性相關。

分析過程中發現，本研究的資料無法同時評估年齡、性別及飲用水對聽力閾值的影響，因此，在分別校正年齡及校正性別與飲用水下，估計混合回歸模式，分析結果列於表 5。模式 1 爲校正年齡下的估計結果，當中鎳、鉀雖然未達顯著相關，其 P 值已接近 0.05，且一旦將其移除，則模式中錫、鋯、硼之影響皆變得不顯著，考慮鉀、錫、鋯皆直接與聽力閾值具顯著相關性（表 4），故選擇保留鎳、鉀於模式中。模式 2 結果顯示校正多種元素後，年齡對聽力閾值之相關性將變得不顯著。模式 3 爲校正性別、飲用水下的估計結果。整體來看，控制音頻、組別及其他干擾因子下，與聽力閾值具負相關的元素有鋁、鎘、鋯、銣、硼；與聽力閾值具正相關的元素爲鉍、鎳、錫、釩、鈉、碘。

討論與結論

先前已有眾多研究針對體內重金屬與聽力障礙發生的相關性進行探討，研究對象大部分暴露在特定污染源下，例如鉛蓄電池或鋼鐵工廠的工人，體內重金屬含量較一般人爲高。而本研究則是以一般民眾爲主要的研究對象，來源爲醫院的門診病人與健康檢查者，對其進行頭髮採集並檢測元素含量。檢測的種類除了常見的 17 種重金屬與毒性元素外，還包括鮮少研究的 22 種必須或微量元素，全面性的探討各元素和聽力的相關性。

人自出生後內耳的聽覺細胞即開始慢慢退化，一般會從高頻率的聽力慢慢影響到次高頻區，最後甚至連低頻區域也受到影響。本研究的聽障組研究對象的平均年齡爲 50 歲，聽力閾值會隨著頻率的升高而上升（表 1），代表其聽力自高頻往低頻逐漸退化，但此現象不顯現於體檢組（平均年齡爲 37.3 歲），除了年齡因素外，也可

表 4 不同頻率下左右耳聽力閾值與頭髮中各元素濃度之 Spearman 相關係數估計結果

	250Hz		500Hz		1000Hz		2000Hz		4000Hz		8000Hz	
	L†	R	L	R	L	R	L	R	L	R	L	R
鋁(Al)	0.328	-0.088	0.304	-0.051	0.227	-0.059	0.204	-0.040	0.125	-0.027	0.175	0.077
鉍(Bi)	0.162	-0.013	0.180	0.187	0.213	0.224	0.099	0.231	0.121	0.100	0.196	0.212
鎳(Ni)	0.136	-0.110	0.215	-0.087	0.370 *	0.009	0.331	0.044	0.239	0.161	0.223	0.186
錫(Sn)	0.005	0.137	0.131	0.457 *	0.172	0.447 *	0.254	0.295	0.065	0.224	-0.011	0.079
鎘(Cd)	0.083	-0.265	0.110	-0.070	0.133	-0.004	0.090	-0.007	-0.113	-0.205	0.099	-0.026
鋯(Zr)	0.021	-0.460 *	-0.117	-0.420 *	-0.248	-0.360 *	-0.168	-0.281	-0.274	-0.284	-0.155	-0.195
鉀(K)	-0.015	0.145	-0.030	0.209	0.079	0.349	0.372 *	0.448 *	0.246	0.378 *	0.004	0.199
銣(Rb)	-0.022	0.100	-0.042	0.181	0.070	0.339	0.377 *	0.460 *	0.250	0.381 *	0.027	0.218
釩(V)	-0.046	-0.114	0.012	0.178	0.149	0.395 *	0.386 *	0.447 *	0.272	0.437 *	0.235	0.318
鈉(Na)	0.077	-0.102	0.069	-0.093	0.150	0.074	0.433 *	0.275	0.395 *	0.392 *	0.213	0.245
硼(B)	-0.121	-0.027	-0.042	0.175	-0.021	0.168	0.096	0.274	0.045	0.176	0.074	0.284
碘(I)	0.023	-0.174	0.104	-0.131	-0.161	-0.236	-0.034	0.005	-0.138	-0.193	0.047	-0.042
銻(Ti)	0.081	-0.122	0.249	0.102	0.194	-0.003	0.414 *	0.066	0.265	0.197	0.256	0.131
鉛(Pb)	0.022	0.111	0.153	0.384 *	0.140	0.285	0.275	0.280	0.077	0.306	0.063	0.235
銅(Cu)	0.413 *	0.089	0.354	0.088	0.149	-0.139	-0.087	-0.267	-0.213	-0.270	-0.134	-0.281
錳(Mn)	0.075	-0.138	0.133	0.036	0.237	0.114	0.333	0.168	0.278	0.373 *	0.308	0.401
鉻(Cr)	-0.059	-0.165	-0.077	0.182	0.068	0.470 *	0.319	0.552 *	0.153	0.388 *	0.214	0.358
鋰(Li)	-0.395 *	-0.074	-0.259	-0.149	-0.050	-0.101	0.167	0.116	0.214	0.084	0.100	-0.069
鈷(Co)	-0.191	-0.395 *	-0.236	-0.082	0.061	0.033	0.031	0.085	0.191	0.181	0.185	0.297
鍺(Ge)	-0.024	-0.425 *	0.031	-0.162	0.225	0.078	0.263	0.184	0.221	0.066	0.244	0.049

*表P值小於0.05。 † L表左耳，R表右耳。

表 5 控制頻率、組別下聽力閾值與其他變項的混合回歸模式分析結果

	模式1			模式2			模式3		
	β	SE	P值	β	SE	P值	β	SE	P值
250Hz vs. 8000Hz	-15.52	2.55	<.0001	-15.52	2.55	<.0001	-15.52	2.55	<.0001
500Hz vs. 8000Hz	-15.34	2.55	<.0001	-15.34	2.55	<.0001	-15.34	2.55	<.0001
1000Hz vs. 8000Hz	-11.98	2.55	<.0001	-11.98	2.55	<.0001	-11.98	2.55	<.0001
2000Hz vs. 8000Hz	-9.40	2.55	0.0003	-9.40	2.55	0.0003	-9.40	2.55	0.0003
4000Hz vs. 8000Hz	-4.48	2.55	0.0802	-4.48	2.55	0.0802	-4.48	2.55	0.0802
組別（聽障組 vs. 體檢組）	7.00	2.90	0.0161	5.09	2.49	0.0419	5.01	2.90	0.0854
年齡(歲)	0.28	0.13	0.0304	0.18	0.11	0.1123	–	–	–
性別（男 vs. 女）	–	–	–	–	–	–	-8.81	2.81	0.0019
是否飲用地下水（是 vs. 否）	–	–	–	–	–	–	9.50	2.51	0.0002
鋁(Al)	-2.08	0.58	0.0004	-1.57	0.52	0.0028	-1.73	0.52	0.0011
鉍(Bi)	1.19	0.50	0.0173	1.89	0.48	0.0001	1.39	0.46	0.0026
鎳(Ni)	0.43	0.24	0.0752	0.65	0.21	0.0024	–	–	–
錫(Sn)	1.48	0.56	0.0084	1.85	0.49	0.0002	2.03	0.53	0.0002
鎘(Cd)	-	-	-	-0.68	0.26	0.0092	–	–	–
鋯(Zr)	-2.07	0.78	0.0088	-3.17	0.75	<.0001	-2.50	0.72	0.0005
鉀(K)	-3.07	1.64	0.0625	-4.40	1.46	0.0027	17.31	6.41	0.0073
銣(Rb)	–	–	–	–	–	–	-2.97	0.86	0.0006
釩(V)	–	–	–	–	–	–	0.81	0.37	0.0282
鈉(Na)	5.33	1.22	<.0001	6.97	1.14	<.0001	6.26	1.11	<.0001
硼(B)	-2.94	1.48	0.0474	-3.65	1.28	0.0045	–	–	–
碘(I)	–	–	–	4.65	1.82	0.0111	–	–	–

能是取樣條件（體檢組符合無聽力障礙的聽力閾值標準爲原測值減 5 後小於 25dB）的限制所致。年齡對聽力閾值的影響在校正多種元素後未達統計上顯著差異（表 5，模式 2），代表這些元素整體對聽力的影響可能更勝於老化所造成的聽力減退。另外，分析經驗發現，控制鈉對聽力閾值的影響之下，元素鉀與聽力閾值之相關性方向會因是否同時控制銣而異。然而，本研究中未能釐清各元素進入人體的途徑及順序，不適於對各元素間的關係建立假設，故並未進一步討論這些元素之交互作用與聽力閾值的相關性。

鋯大量存在於土壤、植物及食物中，是一種無毒的元素。氧化鋯除了具有精密陶瓷應有的高強度、硬度、耐高溫、耐酸鹼腐蝕及高化學穩定性等條件外，還具備較一般陶瓷高的堅韌性，使得氧化鋯被運用在各個工業，像是軸封軸承、切削元件、模具和汽車零件等，甚至可用於人體，像是人工髖關節當中 [18]。鋯存在於軟組織和骨骼，可通過胎盤與血腦障壁，對聽力的影響目前還沒有被提及。在本研究中，則發現鋯的濃度越高，聽覺能力越好，代表其似乎存在某種保護作用，由於該元素在人體中含量較低，眞正的生理功能究竟是直接作用於細胞，或是對影響聽覺的元素進行擷抗，有待進一步的研究。

鋁對聽力影響的報告相當有限，一般洗腎患者血液中鋁濃度會有過高的現象。 2007 年 Chu 等人針對血液透析病人的聽力進行分析，發現其高頻的聽力會受到影響 [19]。人體與動物模式發現過量的鋁會對中樞神經產生毒性，但少量的累積並不會馬上產生症狀。我們的研究對象其頭髮中鋁含量大多介於 1.3-5.9 μg 之間，分析結

果發現控制干擾因子下鋁元素濃度與聽力閾值呈負相關（表 5）。雖然鋁是人體的非必須元素，但檢測發現人體中皆有少量的鋁元素存在，其對動物體的其他生理作用有待釐清。

有機錫化合物毒性較無機錫化合物高，主要用途爲聚氯乙烯的熱穩定劑、殺菌劑、木材防腐劑和催化劑，人體一但接觸或發生錫中毒，會刺激皮膚或影響中樞神經系統，其引起聽力障礙的研究侷限在動物小鼠上，包括三甲基錫（trimethyltin, TMT）[20-24] 和三乙基錫（triethyltin, TET）[25-26]，可能透過影響中樞神經系統或改變聽覺系統功能來影響聽力。

鉍爲毒性低的非必須元素，但攝取過多的無機鉍會導致腎毒性以及造成腦病變。鉍可由日常生活的物件中接觸到，來源包括化妝品、含鉍的藥物、陶瓷、玻璃的彩色顏料、牙科用接合劑、乾電池等。鉍中毒的症狀包括便秘、腸功能不規律、呼吸阻礙、抑鬱。高劑量的鉍累積於體內則會導致尿蛋白等腎臟毒性或顫抖、記憶流失、單發性痙攣、關節變形、癡呆的神經毒性症狀。

鈉是身體的必須元素，主要功能爲維持細胞外電解質平衡，頭髮中鈉含量可以代表體內的飲食及營養狀態。雖然目前還沒有研究指出鈉元素對聽力障礙的發生具有直接的關聯性，但國內曾有報導指出一名男子因嗜喝運動飲料，導致體內鈉離子濃度過高而誘發梅尼爾氏症的發生，進而引起眩暈、單耳或雙耳的耳鳴以及時好時壞的感覺神經性的聽力喪失。梅爾尼氏症的致病機制目前還不是十分清楚，心理壓力過大、自體免疫出現問題或上呼吸道感染造成細菌及病毒入侵內耳道也會引起，造成內淋巴回流受阻或吸收障礙，導致內耳迷路壓力增高而致病 [27-28]。

眾多研究指出，某些常見的重金屬元素如鉛、汞、鎘、砷被發現與聽覺損失有關 [11-14]，鉛的毒性主要是藉著影響中樞神經系統的整體效應而傷害聽覺神經與聽覺腦幹部位；汞化合物則是影響中樞神經系統與耳蝸；砷會影響週邊神經系統而傷害耳蝸毛細胞。這些研究皆以特定工作場所的工人爲研究對象，研究對象皆受到特定重金屬較高的暴露量，而我們的研究對象屬於非受到特定重金屬暴露的人員，因此，本研究並未發現類似的結論屬合理的結果。而其中鎘呈現與聽力閾值負相關的結果（表 5，模式 2），或許代表其他與鎘一同進入人體的成分對聽力具有保護作用。

1997 年 Farahat TM 等人 [29] 與 Forst LS 等人 [30] 針對重金屬鉛對聽力所進行的相關性研究指出，體內的鉛含量越高，其分別會對 1000-8000Hz 和 4000Hz 的聽力閾值造成影響；1987 年 Schwartz J 等人 [31] 則發現鉛與 500-4000Hz 的聽力閾值有關；另外，2002 年 ABREU 等人 [32] 的研究指出鎘影響 4000 與 6000Hz 的聽力閾值；1977 年 Bencko V 等人 [33] 則發現砷影響 250 及 8000Hz 的聽力閾值；本研究則發現重金屬鋁和錫會影響 250-1000Hz 的聽力閾值，綜觀以上的研究結果發現，重金屬對於聽力閾值的影響不會侷限在特定的頻率上。

在此橫斷研究法中我們找出與聽力具相關性的元素，但不能以此研究結果推論各元素對聽力具保護或傷害作用，因本研究無法釐清各種元素進入人體的途徑，因此，針對海線地區探討各元素如何進入並積存於人體，是未來進一步研究這些元素對聽力的作用及致病機轉前應努力的方向。

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The Association of Elements with Hearing Threshold – A Study Using Inductively Coupled Plasma-Mass Spectrometry on Hair Sample

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Abstract

Background and Purpose: Hearing impairment is a complex condition, which may be associated with both environmental and hereditary factors. Individuals with hearing impairment may be affected in their life quality as well as psychological well-being. Previous literatures showed that exposure in work environment polluted by elements such as lead, mercury, cadmium and arsenic were associated with hearing loss. However, very few studies have looked into the association of elements inherent in the living environment and hearing. In this research, we analyzed the association between these 39 elements and hearing impairment.

Material and Methods: This investigation collected samples from patients who visited the Department of Otolaryngology in a coastline regional teaching hospital. Those patients presented with hearing impairment (n=19). Normal volunteers, without hearing impairment, were enrolled from the health examination center within the same hospital. This study excluded patients with hearing impairment associated with genetic, trauma-induced or infectious etiologies, or patients who had been managed. We collected the hair samples from these individuals, using inductively coupled plasma-mass spectrometry (ICP-MS) we have detected the levels of 39 elements, bilateral hearing levels were measured by pure tone audiometry, and questionnaires were used to exclude other possible confounding factors.

Results: Applying the mixed regression model to analyze the relationship between hearing threshold and other variables, the results after correcting for interference factors, showed positive correlation for hearing threshold and elements including bismuth, nickel, tin, vanadium, sodium and iodine, and negative correlation for elements including aluminum, cadmium, zirconium, boron and rubidium.

Conclusion: In this cross-sectional study, we have uncovered the elements associated with hearing, but we were unable to verify the pathways each element took in entering the human body. Future endeavors may focus on investigating how each element enters and accumulates in the human body for residents whom reside in the coastline region, and to gain a better understanding in its pathogenesis.

Key words: hearing impairment, heavy metals, trace element, hearing threshold, association analysis

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Original Article

Incidence and Characteristics of Pulmonary Embolism in Taiwanese Patients: Impact of Active Malignancy from a 5-year Single Center Experience

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Abstract

Introduction: Cancer patients have increased risk of venous thromboembolism (VTE) and experience more adverse outcome in the treatment of VTE. Pulmonary embolism (PE) particularly could be fatal and contributes significantly to the morbidity and mortality. However, the characteristics and impact of cancer in PE patients are scarcely reported from Oriental societies.
Aims: To assess the incidence and clinical characteristics of patients with PE in Taiwan and investigate the impact of active malignancy.
Methods: Patients with confirmed diagnosis of PE were retrieved from the hospitalization database of Taipei Veterans General Hospital between January 2004 and December 2008. Clinical characteristics and treatment outcome of cancer and non-cancer patients were recorded via medical chart review and compared using statistical analysis as appropriate.
Results: Totally 161 patients with PE were identified and 51 (31.7%) of them had a diagnosis of active cancer. Estimated incidence of PE was 9.8/100,000 per patient-year. Median age was 73.2 years (range 23-94). Ninety-one (56.5%) patients were presented with PE over bilateral pulmonary arteries and concurrent deep vein thrombosis was detected in 28.0% of patients. Lung cancer was the most common subtype (35.3%) in PE patients with cancer, followed by prostate (11.8%), ovarian (9.8%), and hepatocellular (9.8%) histologies. Recurrent VTE rate was higher in cancer group (23.5% vs 9.1%, *P*=0.013) and major bleeding was more often encountered in cancer patients as well (23.5% vs 4.5%, *P*<0.001). By logistic regression analysis, hazard ratio of cancer patients for VTE recurrence and major bleeding was 3.30 (95% confidence interval [CI], 1.24-8.77, *P*=0.017) and 6.47 (95% CI, 1.9-22.0, *P*=0.003) respectively. Furthermore, 100-day survival after PE was also inferior in cancer patients. (68.4% vs 89.8%, *P*=0.001)
Conclusion: In contrast to Western countries, incidence of PE is lower in Taiwanese patients. However, cancer remains a major factor influencing the outcome of PE.

Key words: incidence, pulmonary embolism, cancer, bleeding, recurrence

Introduction

Venous thromboembolism (VTE) refers to the presence of deep vein thrombosis (DVT) or pulmonary embolism (PE) and is the third most common cause of cardiovascular mortality after coronary heart disease and stroke in the United States. The cost of care related to VTE in the United States has been estimated at 1.5 billion dollars per year[1]. The incidence of VTE exceeds 1 per 1000, ranging from 71–117 cases per 100,000 persons; over 200,000 new cases occur in the United States annually[2-5]. Approximately one-third of patients with symptomatic VTE manifest PE, whereas two-thirds manifest DVT alone[6]. Although DVT and PE encompass one

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disease entity, important differences exist. PE is a potentially lethal disease and is difficult to diagnose initially. The annual incidence of PE has been reported to range between 23 and 69 cases per 100,000 population[2,5]. As many as 300,000 people in the United States died from acute PE each year and the diagnosis is often not made until autopsy[7-8]. Of those who have acute PE, one-quarter of patients present as sudden death, and 30% develop VTE recurrence and venous stasis syndrome within 10 and 20 years, respectively[9]. The mortality rates vary widely depending on the severity of the disease; even so, the average fatality rate within 2 weeks of diagnosis is approximately 11%[9]. Even the patients survive acute PE episode, chronic pulmonary hypertension may persist and debilitate the cardiopulmonary function.

Many risk factors have been identified with increasing incidence of VTE, and cancer is considered one of the major factors. Since Trousseau, the association of thromboembolic complications and cancer is well established. Probably because of the procoagulant activity generated by tumor cells, macrophages, platelets and vascular endothelial cells, the sum of these cellular effects contributes to clot formation in cancer patients. The risk of thromboembolism is influenced by the type of cancer, the stage of the disease and the co-morbidity. Not only could cancer increase the risk of VTE by 2 to 7-fold[10-12], but it could also complicate the outcome of VTE. Cancer has been associated with more extensive clot burden and symptomatic events[13]. Also, cancer patients with established VTE are more likely to develop recurrent thromboembolic complications and major bleeding than VTE patients without malignancy[10].

Many previous studies have implied that the prevalence of VTE varies, significantly among different ethnic groups even though the real cause remains largely undetermined. African-American patients have a significantly higher rate of incident VTE, particularly when encountering a provoking risk factor whereas Asians/Pacific Islanders have a 70% lower prevalence of VTE for both idiopathic VTE and provoked VTE[14]. Recent large scale Taiwanese population-based cohort study also shows a markedly lower incidence in Taiwanese population than in Caucasians[15].

Here we conducted this study in a single tertiary referral hospital in Taiwan to investigate the clinical characteristics of PE in Taiwanese population. Also, we elucidated the predictive factors affecting the outcome of PE patients.

Methods

Patients

Patients with confirmed diagnosis of PE or cancers were identified by integrated search with ICD codes (415.1) and keyword "pulmonary embolism" from the hospitalization database in Taipei Veterans General Hospital, which is a tertiary medical center, between January 2004 and December 2008. Clinical characteristics and treatment outcome were collected by systemic chart review. Lab data and reports were retrieved by inpatient database search.

Definitions of PE, major bleeding, and VTE recurrence

Patients selected from the inpatient database were reviewed and included to the study by meeting the criteria for PE. The widely accepted criteria encompasses the radiographic evidence of PE in contrast-enhanced computed tomography which could be observed in most of the patients (144/161, 89.4%) and/or clinical suspicion with high probability of ventilation-perfusion scan[16]. The definition of major bleeding has been described previously. The patient was considered experiencing major bleeding episode as long as one of the four criteria occurred, including drop in hemoglobin level of at least 2 g/dL, need for transfusion of 2 or more units of red cells, any retroperitoneal or intracranial hemorrhage or permanent discontinuation of treatment[10]. Recurrence is defined as readmission for VTE including DVT and another episode of acute PE. Progressive PE, which was refractory to the treatment, was also deemed as recurrence. Concomitant cancer was defined as active disease that required treatment or was still symptomatic. Patients who carried diagnoses with cancer but were asymptomatic or had been cured would not be enrolled in this study.

Comorbid diseases

For each patient, the comorbidities for VTE were retrieved from both the inpatient and outpatient databases before and during the index VTE hospitalization. Prior history of VTE was defined as being hospitalized because of VTE before the index VTE event. Chronic lung disease included emphysema, chronic bronchitis, bronchiectasis, and other obstructive

pulmonary diseases. For neurologic diseases, we recorded only serious illness, including stroke or other central and peripheral nervous diseases associated with extremity paresis or paralysis which led to prolonged immobility. Hormone therapy included the use of estrogen and/or progesterone in hormone replacement therapy and oral contraceptives.

Statistical analysis

Demographic and clinical characteristics of study patients were compared by X^2 or Fisher exact test as appropriate. The cumulative incidences of recurrent thromboembolic events and major bleeding in patients with and without cancer were estimated according to Kaplan-Meier method. The hazard ratios and 95% confidence interval reported in univariate and multivariate analysis for predictive factors of major bleeding or recurrence of VTE were estimated by the binary logistic regression model. All analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 161 patients with PE were identified and 51 (31.7%) of them had a diagnosis of active cancer. Estimated incidence of PE was 9.8/100,000 per patient-year. Median age was 73.2 years (range, 23-94) and man to female ratio was 1.64 to 1. Ninety-one (56.5%) patients were presented with PE over bilateral pulmonary arteries and concurrent DVT was detected in 28.0% of patients. When comparing the initial clinical characteristics between cancer and non-cancer patients, cancer patients tended to be younger. Otherwise, there was no significant difference in gender, usage of diagnostic tool, PE locations, or incidence of concomitant DVT (Table 1). However, the initial laboratory data showed that cancer patients had lower hemoglobin (P=0.067) and platelet counts (P=0.027), but higher lactate dehydrogenase (LDH) level (P=0.048). The level of d-dimer was not different between cancer and non-cancer groups.

Among all 51 PE patients with cancer, lung cancer was the most common subtype (35.3%), followed by

Table 1. Clinical characteristics of 161 patients with pulmonary embolism from January 2004 to December 2008.

	Cancer (n=51)	Non-cancer (n=110)	P*
Age, median (range)	68.2 (32-90)	74.9 (23-94)	0.061
Male, no. (%)	32 (62.7%)	68 (61.8%)	0.91
PE location, no. (%)			0.323
Right PA	12 (23.5%)	36 (32.7%)	
Left PA	8 (15.7%)	8 (7.3%)	
Bilateral PA	29 (56.9%)	62 (56.4%)	
Others$^+$	2 (3.9%)	4 (3.6%)	
Concomitant DVT, no. (%)	16 (31.4%)	29 (26.4%)	0.510
Hemogram			
WBC>10^9/L, no(%)	20 (39.2%)	50 (45.5.%)	0.458
Hb<10 g/dL, no(%)	9 (18.4%)	9 (8.3%)	0.067
PLT<100x10^9/L, no(%)	6 (12.2%)	3 (2.8%)	0.027
Biochemistry			
Albumin <3.5 g/dL, no(%)	27 (61.4%)	42 (47.7%)	0.139
Creatinine>1.5mg/dL, no(%)	8 (16.3%)	17 (15.7%)	0.926
LDH>250 U/L, no(%)	24 (70.6%)	42 (50.6%)	0.048
D-dimer			0.796
Median (range)	2.65 (0-65.9)	2.67 (0-208.00)	0.319

*By Mann-Whitney U test, X^2 test, or Fisher exact test as appropriate +Pulmonary vein or unknown PA: pulmonary artery
WBC: white blood cell, Hb: hemoglobin, PLT: platelets, LDH: lactate dehydrogenase

Table 2. Prevalence of PE according to cancer types from 2004-2008

	PE case No	Total case No	Prevalence (‰)
All cancers	55	22059	2.5
Lung	20 (36.4%)	3415	5.9
Adenocarcinoma	14 (25.5%)		
Squamous cell carcinoma	2 (3.6%)		
Poor-differentiated	1 (1.8%)		
Small cell carcinoma	3 (5.5%)		
Breast	2 (3.6%)	1733	1.2
Head and neck	1 (1.8%)	2018	0.5
Gastrointestinal	15 (27.3%)	7003	2.1
Esophageal cancer	2 (3.6%)	467	4.3
Gastric cancer	2 (3.6%)	1021	2.0
HCC	5 (9.1%)	2375	2.1
Pancreatic cancer	3 (5.5%)	274	10.9
Colon cancer	2 (3.6%)	2536	0.8
Cholangiocarcinoma	1 (1.8%)		
Genitourinary	8 (14.5%)	2765	2.9
Prostate cancer	6 (10.9%)	1470	4.1
RCC	2 (3.6%)	654	3.1
Ovary	5 (9.1%)	508	9.8
Sarcoma	2 (3.6%)	449	4.5
Non-Hodgkin lymphoma	2 (3.6%)	1335	1.5

HCC: hepatocellular carcinoma; RCC: renal cell carcinoma

prostate (11.8%), ovarian (9.8%), and hepatocellular (9.8%) histologies(Table 1). As shown in Table 3, 43 patients (84.3%) had locally advanced or metastatic diseases when PE was diagnosed. Sixteen (31.4%) patients were found to have cancer when PE was confirmed. Clinical characteristics between patients who developed PE at diagnosis or during the course of cancer therapy were similar, but median age of the latter group was significantly higher (54.4 vs 71.7, P=0.01).

As shown in Table 4, most of the patients, regardless of their cancer status, received low molecular weight heparin or unfractionated heparin as first-line treatment (70.5% vs. 67.3%). Recurrent VTE rate was higher in cancer group (23.5% vs 9.1%, P=0.013) and cancer patients developed major bleeding events more frequently than non-cancer patient after the first PE episode (23.5% vs 4.5%, P<0.001). Gastrointestinal tract was the most common site of bleeding. Furthermore, the 30-day survival after PE was also low in cancer patients (68.4% vs 89.8%, P<0.001) (Figure 1).

We employed univariate and multivariate analysis to identify factors that would contribute to the recurrence and bleeding events in the subsequent treatment course. The results turned out that initial white blood cell counts (HR 0.15, 95% CI 0.04-0.56, P=0.005), active cancer (HR 3.3, 95% CI 1.24-8.77, P=0.017), and the presence of concomitant DVT (HR 3.0, 95% CI 1.10-8.17, P=0.032) were the independent predictive factors for the recurrence of VTE (Table 5). Active bleeding, on the other hand, was predicted only by the status of active cancer (HR 6.47, 95% CI 1.90-22.00, P=0.003) (Table 6).

Table 3. Characteristics of PE in cancer patients

	All (n=51)	PE at diagnosis (n=15)	PE during treatment (n=36)	P*
Age at PE diagnosis, years Median (range)	68.2 (32-90)	54.4(47-80)	71.7 (32-90)	0.010
Sex				0.370
Male, no. (%)	32 (62.7%)	8 (53.3%)	24 (66.7%)	
Stage of cancer at PE, no. (%)				0.072
0	1 (2.0%)	0	1 (2.8%)+	
I	2 (3.9%)	2 (13.3%)	0	
II	5 (9.8%)	2 (13.3%)	3 (8.3%)	
III	8 (15.7%)	4 (26.7%)	4 (11.1%)	
IV	35 (68.6%)	7 (46.7%)	28 (77.8%)	
Cancer status, no. (%)				
Fresh	15 (29.4%)	15 (100%)	-	
Fresh under treatment	14 (27.5%)	-	14 (38.9%)	
Fresh completed treatment	1 (2.0%)	-	1 (2.8%)	
Relapse	6 (11.8%)	-	6 (16.7%)	
Relapse under treatment	15 (29.4%)	-	15 (41.7%)	
Preexisting cured cancer, no. (%)	9 (16.4%)	1 (6.7%)	8 (22.2%)	0.180
Time from cancer to PE, months Median (range)	3.8 (0-122.7)	0.3 (0-0.9)	10.7 (1.2-122.7)	

*Comparison between "PE at diagnosis" and "PE during treatment" groups using Fisher exact test, χ^2 test, or Mann-Whitney U test as appropriate +During adjuvant therapy PE indicates pulmonary embolism

Table 4. Initial treatment and outcome

	Cancer (n=51)	Non-cancer (n=110)	*P**
Initial Treatment, no(%)			0.227
LMWH/UFH	36 (70.5%)	74 (67.3%)	
Warfarin	2 (3.9%)	11 (10.0%)	
Thrombolysis	2 (3.9%)	11 (10.0%)	
OP	0 (0%)	2 (1.8%)	
Others	2 (3.9%)	1 (0.9%)	
No treatment	9 (17.6%)	11 (10.0%)	
VTE recurrence, no(%)	12 (23.5%)	10 (9.1%)	0.013
PE	6	6	
DVT	8	5	
Both	2	1	
Major bleeding, patient no.(%)	12 (23.5%)	5 (4.5%)	<0.001
GI	8	3	
GU	1	1	
Hemoptysis	1	1	
Soft tissue/Mucocutaneous	1	1	
ICH	1	0	

*By X^2 test +Urokinase or recombinant tissue plasminogen activator
LMWH: low molecular weight heparin, UFH: unfractionated heparin, GI: gastrointestinal tract, GU: genitourinary tract, ICH: intracerebral hemorrhage

Discussion

This is the first study investigating the epidemiology and the impact of cancer on pulmonary embolism directly among Asian population in the real world. Even though there's already a previous study employing Taiwanese National Health Insurance claims databases, but the healthcare claims data inherently contain potential disease misclassification bias. This hospital-based research validates the previous studies and truly reflects that Asian population has much lower incidence for pulmonary embolism. The crude incidence is 9.8/100,000 per patient-year, whereas the incidence in western countries range from 23~69/100,000 per patient-year[2, 5, 17].

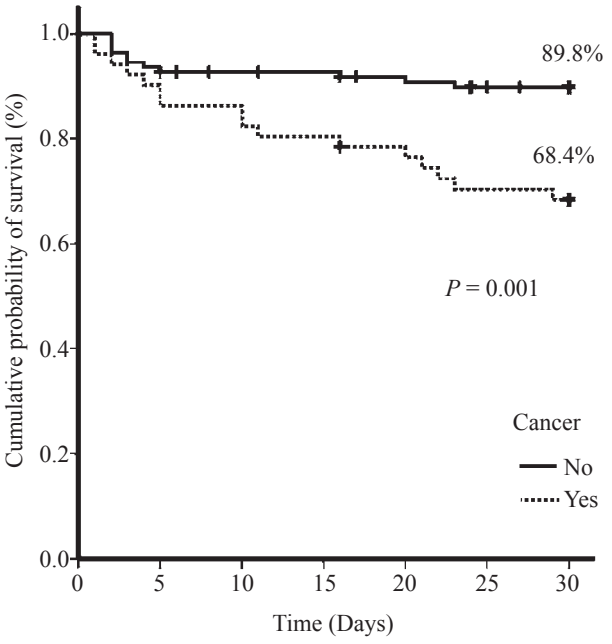

Fig. 1 Post-PE 30-day survival

Even though this discrepancy has been recognized in many studies. The explanation has not reached universal consensus. Different hypotheses have been postulated. Some researchers claim that lower incidence of VTE in Asian population may be partly attributed to a lower incidence of primary hypercoagulable disease predisposing to VTE. Previous studies have shown a lower incidence of FV Leiden mutation in Asian populations than in Caucasians[18-20]. In addition, Steffen et al. reported that abundant vegetables, fish and light on meat consumption was associated with lower risk of incident VTE[21]. Different dietary habits between Eastern and Western countries may possibly contribute to the difference in VTE incidence.

The clinical characteristics of PE did not disclose demographic difference between cancer group and non-cancer group. But the baseline laboratory data reveals that cancer patients have lower hemoglobin, platelet counts and higher LDH level when PE was diagnosed. It makes sense because patients are likely

Table 5. Recurrence: Univariate and multivariate analysis

	Univariate			Multivariate		
	OR	CI	P*	OR	CI	P*
Age > 60 vs. <= 60 years	0.52	0.20-1.36	0.184			
Sex F vs. M	0.57	0.21-1.55	0.274			
DVT Yes vs. No	2.48	0.98-6.23	0.054	3.00	1.10-8.17	0.032
Cancer Yes vs. No	3.08	1.23-7.70	0.016	3.30	1.24-8.77	0.017
WBC > $10x10^9$/L vs. <= 10×10^9/L	0.18	0.05-0.62	0.007	0.15	0.04-0.56	0.005
Hb < 10 vs. >= 10 g/dl	1.54	0.40-5.90	0.531			
PLT > 30×10^9/L vs. <= $30x10^9$/L	1.99	0.69-5.72	0.203			
Creatinine > 1.5 vs. <= 1.5 mg/dl	0.99	0.27-3.68	0.986			
Albumin < 3.5 vs. >= 3.5 g/dl	0.57	0.19-1.71	0.317			
LDH abnormal vs. normal	0.89	0.28-2.83	0.843			

*By binary logistic regression test, P < 0.1 in univariate analysis were enrolled into multivariate analysis
OR: odds ratio, CI: confidence interval

Table 6. Active bleeding: Univariate and multivariate analysis

	Univariate			Multivariate		
	OR	CI	P*	OR	CI	P*
Age > 60 vs. <= 60 years	1.08	0.33-3.53	0.894			
Sex F vs. M	2.13	0.66-6.86	0.205			
DVT Yes vs. No	1.47	0.51-4.24	0.478			
Cancer Yes vs. No	6.46	2.14-19.53	0.001	6.47	1.90-22.00	0.003
WBC > 10×10^9/L vs. <= $10x10^9$/L	0.70	0.25-2.00	0.507			
Hb < 10 vs. >= 10 g/dl	1.79	0.46-6.94	0.402			
PLT > 30×10^9/L vs. <= $30x10^9$/L	2.53	0.48-13.32	0.272			
Creatinine > 1.5 vs. <= 1.5 mg/dl	2.50	0.80-7.86	0.117			
Albumin < 3.5 vs. >= 3.5 g/dl	2.80	0.84-9.29	0.093	2.36	0.68-8.20	0.178
LDH abnormal vs. normal	1.27	0.39-4.14	0.693			

*By binary logistic regression test, P < 0.1 in univariate analysis were enrolled into multivariate analysis
OR: odds ratio, CI: confidence interval

to receive chemotherapy which could affect bone marrow function and also nutrition status in cancer patients is usually inferior to non-cancer patients malignancy also could increase serum LDH.

Among all the cancer patients in our study, lung cancer was the most common subtype (35.3%), followed by prostate (11.8%), ovarian (9.8%), and hepatocellular (9.8%) histologies. This finding is mostly compatible with previous observation. Blom et. al demonstrated that gastrointestinal cancer, lung cancer, and hematological cancer are associated with a very high risk for venous thrombosis[21]. In another prospective observational study[22] , the highest rates of VTE occurred in patients with upper gastrointestinal cancers (including gastric, pancreatic, and hepatobiliary) and lung cancer.

Our study demonstrates that patients with cancer have a higher risk for recurrent thromboembolic events and bleeding during anticoagulation than patients without cancer. The risk for recurrent VTE in cancer patients was increased around 2.5 times(23.5% vs. 9.1%) in our study. Based on previous investigation, venous thromboembolism has a recurrence rate of 5 to 10 percent per year[23-25], and about 30% of patients develop VTE recurrence within the next ten years eventually. Though the pathogenesis of recurrences is multifactorial, initial disease severity, male gender, cancer, and a history of VTE predicted an increased risk of recurrent thrombotic events[24,26].

The recurrence rate we reported here is lower and the relationship between gender and recurrence was not observed. However, cancer was identified as the major risk factor for future recurrence. In addition, concomitant DVT and white blood cell counts less than 10,000/cumm were recognized as two independent factors predicting future recurrence. It's not hard to understand why concomitant DVT is associated with higher future recurrence rate, possibly due to greater clot burden and disease severity. Jimenez et al. reported that the risk of early death among patients with acute symptomatic PE is four times higher in those who present with concomitant DVT, which implied that concomitant DVT is, indirectly, related to greater disease severity.

As for the association between lower white counts and greater recurrence likelihood, we couldn't find any prior study to support this finding. Some researches have reported that elevated WBC, particularly neutrophils, is strongly associated with increased risk of VTE, but still, the pathophysiology has remained largely unknown[27]. Future investigation is required prove the cause-effect relationship.

It's well-established cancer patients who developed VTE are twice likely to encounter major bleeding events under anticoagulation therapy[10]. Likewise, the risk for major bleeding event in cancer patients was increased around 5 times (23.5% vs. 4.5%) in our study and the this increased risk is associated with

cancer status alone, without any other predictive factors including gender, age and concomitant DVT. Interestingly, the increased risk for bleeding in cancer patients was not due to more frequent anticoagulant intensities outside the therapeutic range[10]. In fact, at the time of bleeding, only a smaller proportion of patients with cancer had supratherapeutic levels of anticoagulation. It proves that there must be other intrinsic factors in cancer patients that make them bleed easier than patients who don't have cancer.

In summary, the incidence of PE is lower in Taiwanese population in contrast to that of Western countries and this study reveals the significant impact of cancer on the outcome of pulmonary embolism. Concomitant malignancy is identified as a major prognostic factor for post-PE 30-day survival, VTE recurrent and major bleeding events.

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台灣肺栓塞病人的發生率及特性：惡性腫瘤的影響單一醫學中心五年經驗

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摘要

介紹：癌症病人有較高風險產生靜脈血栓且在治療過程易發生較多不良反應。肺栓塞尤其是具致命性且明顯造成發病及死亡。然而在東方人，癌症在肺栓塞病人上的特性及影響鮮少被報告。
目的：本研究目的在於評估台灣肺栓塞病人的臨床特性及發生率，並研究惡性腫瘤之影響。
方法：收集在2004年一月到2008年十二月於台北榮總住院資料庫中確診是肺栓塞的病人，對於非癌症病人及癌症病人的臨床特性及治療結果經由病例複閱及適當統計分析比較後加以記錄。
結果：共161位肺栓塞病患確診，其中51為有惡性腫瘤（Active cancer）。預估肺栓塞發病率為9.8/100000人年，年齡中位數為73.2歲（23-94歲），91位病患（56.5%）為兩側肺動脈栓塞且28%的病人有併發深層靜脈血栓。肺栓塞病患確診有腫瘤最常見為肺部腫瘤（35.3%），其次為前列腺腫瘤（11.8%）、卵巢腫瘤、（9.8%）及肝細胞腫瘤（9.8%）。腫瘤病患有較高靜脈血栓復發率（23.5% vs 10.9% p 0.036）及大出血機率（37.3% vs 9.1% p 0.001）。經由迴歸分析（logistic regression analysis），腫瘤病患靜脈血栓復發危險比率（hazard ratio）為2.51（95% confidence interval [CI], 1.04-6.07, P=0.041），大出血機率5.94（95% CI, 2.51-14.1, P<0.001）。此外在肺栓塞後百日存活率在癌症病人較低（57.9% vs 86.6%, P<0.001）。
結論：與西方國家相比較，台灣人有較低肺栓塞發生率。然而癌症還是一個影響肺栓塞育後的重要因子。

關鍵詞：發生率、肺栓塞、惡性腫瘤、出血、復發

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Case Report

Non-traumatic Brain Injury Vs. Traumatic Brain Injury

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Abstract

Physical violence against children, whether intentionally or accidentally, causes injury to both their bodies as well as emotions and may even lead to permanent damage or death. Hence it is important to health-care professionals to be alert and report to the appropriate authorities in time once inconsistencies in the history or physical examination are noted. Only by doing so, we can help the law enforcement authorities to take action against those violators and reduce the incidence of future abuses.

Key words: Child abuse, Traumatic, Non-traumatic, brain injury, shaken baby syndrome (SBS).

Case Report

A 4-year-old boy was brought to the ER by his family for altered level of consciousness. Physical examination revealed swelling and tenderness over the right parietal scalp, and tenderness in the right hip. Initial brain CT scan was conducted at a regional hospital, which revealed SDH and SAH in the right parietal and frontal lobes. Other radiographs (skeletal survey for non accidental injury (NAI)) revealed no abnormalities. He was then admitted to ICU under neurosurgery care. His general condition and consciousness improved gradually with conservative treatments. He was transferred to the general ward from ICU on the 3rd day of hospitalization. A repeat brain CT scan was performed on the 6th day, which had detected partial absorption of blood clots. He was discharged on the 12th day of hospitalization. His general condition was much improved on discharge from the hospital, although he still suffered from left leg weakness, unsteady gait, and intermittent headache and dizziness.

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Introduction

Head injury is the leading causes of traumatic death in children and child abuse fatality[1]. Head injury due to accident is rarely seen in children under 5 years of age unless they were overtly involved in an accident. The majority of brain injuries in this age-group are due to child abuse. The diagnosis of physical abuse in the past is by excluding other possible causes[1]. The advent of computed tomography (CT) in mid-1970s has helped diagnosis and magnetic resonance imaging (MRI) in mid-1980s further enhanced the diagnostic capabilities[5]. Emergency physicians should be more vigilant and proactive in recognizing clinical findings and radiological signs that support the diagnosis of child abuse so as to prevent mortality or morbidity as sequelae of abusive injury to the children[1].

Non-traumatic Brain Injury

The problem of child abuse was first described in 1962 by Kempe et al. in their landmark article entitled "the battered child syndrome"[4]. Non-traumatic Brain Injury, commonly known as shaken baby syndrome (SBS), was first describe in 1972 by John Caffey, a pediatric radiologist, who coined the term "infantile whiplash shaking syndrome" to describe the constellation

of clinical findings in infants with intracranial and intraocular hemorrhage in the absence of external trauma to the head[16]. One year earlier, Guth Kelch had postulated that whiplash forces caused subdural hematomas by tearing cortical bridging veins[6]. Injuries in Shaken baby syndrome are the result of violent trauma and likely to induce death of the child or may result in severe neurologic consequences[1]. In contrast, injuries sustained to the head by common accident do not result in constellation of intracranial and intraocular hemorrhage[1]. Such violent behaviors often result from carers who have unrealistic expectations of their children, or from parents who are experiencing stress as a result of environmental, social, biological or financial problems[1].

Shaken baby syndrome should be suspected in all children younger than one year of age who present with drowsiness, coma, seizures or apnea[2]. Signs of shaken baby syndrome may vary from mild and nonspecific to severe and immediately identifiable clinically as head trauma[1]. The signs may be subtle that seeking medical advice seems unnecessary to the carers. A sublethal case may present with a history of poor feeding, vomiting, lethargy, and/or irritability for days or even weeks. These nonspecific signs may be mistaken for viral illness, feeding dysfunction, or colic by physicians[7]. In milder cases, signs may resolve without the true cause being discovered. In the most severe cases, which usually result in death or severe neurologic consequences, the child usually loss consciousness instantly and suffers from rapidly escalating, life-threatening central nervous system dysfunction.

When a young infant is violently shaken, he or she may lapse into unconsciousness, which is mistaken by the carer as sleeping and hopes that the baby will later recover. Hence the carer does not seek medical help immediately and thus misses the opportunity for early treatment[7]. It is only when the brain-injured infant started to vomit, having altered level of consciousness, not be able to suck or swallow, and be unable to track with eye movements, smile or vocalized then the carer bring him/her to seek medical attention. Occasionally, the comatose state may be unrecognized not only by caretaker, but also by medical professionals who assume that the infant is sleeping, lethargic, or suffering from a minor acute ailment or possible infection. Sometimes, severe brain injuries may cause respiratory difficulty and progress to apnea or bradycardia that require cardiopulmonary resuscitation immediately on arrival to ER.

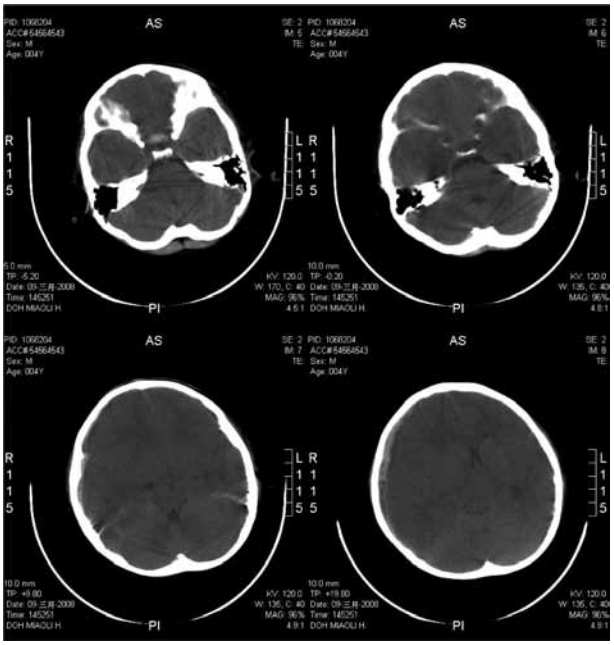

Fig. 1 Initial brain CT without contrast showed SDH at right parietal lobe, SAH at right parieto-frontal lobe.

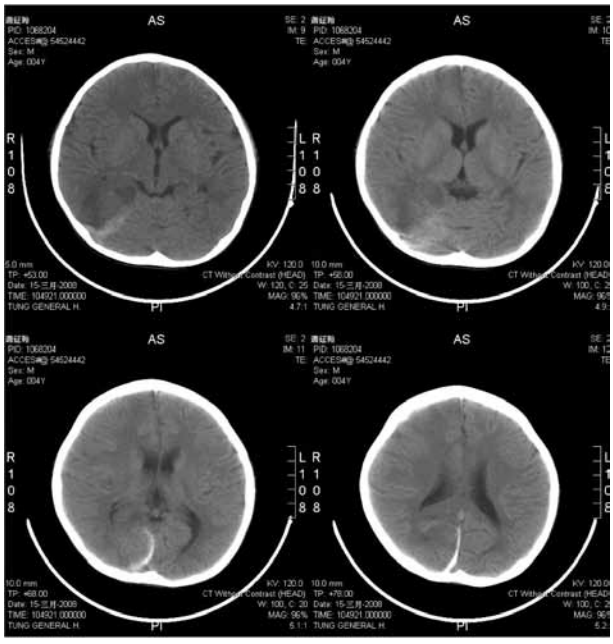

Fig. 2 Follow up brain CT without contrast taken 6 days later revealed partial absorption of blood clot. Hypodensity change at right temporal-occipital lobe signifies contusion injury of brain

Unilateral or bilateral retinal hemorrhages are present in 75% to 90% of cases. Emergency physician should consult pediatric ophthalmologist, pediatric neurologist, pediatric neurosurgeon, or other experienced physician who is familiar with such hemorrhages, with suitable equipment, otherwise the diagnosis may be missed. The severity may vary, but generally speaking, more severe retinal hemorrhages are associated with more severe brain injury[8].

Pathologically, subdural hemorrhage may be most prominent in the inter-hemispheric fissure and minimal over the convexities of the hemispheres[9]. Cerebral edema with subarachnoid hemorrhage may be the only finding or may have co-existing subdural hemorrhage and subarachnoid hemorrhage. Visible cerebral contusions are unusual, but diffuse axonal injury is common[10]. Isolated or concomitant hypoxic-ischemic damage may result in mild to severe cerebral edema initially and cerebral infarction later. Chronic extra-axial fluid collections, cerebral atrophy, and cystic encephalomalacia are common late sequelae[11].

Evidence of other injuries, such as bruises, rib fractures, long-bone fractures, and abdominal injuries, should be meticulously searched for and documented. A skeletal survey of the hands, feet, long bones, skull, spine, and ribs should be obtained as soon as the infant's medical condition permits[1]. Repeated physical examinations may reveal additional signs of trauma.

Mortality rates range from 15 to 38 percent[1]. Sixty percents of infants who present with coma on initial examination died or had profound mental retardation, spastic quadriplegia, or severe motor dysfunction. Other infants initially present with seizures, irritability, or lethargy but had no lacerations or infarctions of brain tissue did not have profoundly elevated intracranial pressure, subtle neurologic sequelae, or persistent seizures[11]. Long term neurologic sequelae such as cortical blindness, spasticity, seizure disorders, microcephaly, chronic subdural fluid collections, enlarging ventricles, cerebral atrophy, encephalomalacia or porencephalic cysts, learning difficulty, and motor or behavior problems, are observed in those who survived from severe brain-injury[12].

Traumatic Brain Injury

Unlike non-traumatic cause, history and mode of injuries are evident and consistent in those cases induced by trauma. Obvious external injuries are usually observed. In addition, physical findings are consistent with the history. It can occur in any age. Retinal hemorrhage is nearly absent unless the baby has sustained direct trauma to the eyeballs. The type of intracranial hemorrhage is usually extradural. Bony injuries are usually found at diaphysis rather than metaphysic. Multiple skeletal injuries are rare.

Radiology and Clinical Findings

CT without intravenous contrast is generally the investigation of choice for demonstrating

Table 1.

	Non-traumatic	Traumatic
Causes	Child abuse	Traffic accidental
History	Vague, inconsistent	Clear, consistent
Evidence	(-)	(+)
History & Injuries	Incompatible	Compatible
Mechanism	Angular, rotational force	Translational force
Force	Trivial	Large
Age	< 3, upto 5 years	Any age
External visible injury	Often absent	Obvious
Intracranial Hemorrhage	SDH, SAH	Usually EDH
Retinal hemorrhage	Present, usually bilateral	Absent
Skeletal	+, may be subtle	Evident
Fracture sites	Metaphysis	Diaphysis
Ribs fracture	Multiple, posterior	Isolated

subarachnoid hemorrhage, mass effect, and large extra-axial hemorrhages[12]. CT should be repeated after a time interval or if the neurologic picture changes rapidly[11]. Any surgically treatable injuries can be detected by CT.

MRI is considered complementary to CT and should be obtained 2 to 3 days later if possible[1]. It substantially improves the ability to detect and define intra-parenchymal lesions of brain[12], and/or small extra-axial hemorrhages in infants with equivocal CT Findings[3].

Skeletal survey should be repeated after 2 weeks to better delineate new fracture that may not be apparent initially[13]. Extra-cranial abnormalities are detected in 30-70% of abused children with head injuries[17,18]. Skull fractures that are multiple, bilateral, diastatic, or cross suture lines are more likely to be non-accidental[19]. Single or multiple fractures of the midshaft or metaphysic of long bones or rib fractures may be associated findings.

Differential Diagnosis

The SBS is so unique that no other medical condition fully mimics all the features of shaking-impact syndrome[3]. However, emergency physicians should also pay attention to other causes which may be mistaken with child abuse so as to prevent misaccusation to the families.

Accidental Injury is the single most common diagnosis mimicking non-accidental injuries. Small epidural hemorrhages and traumatic subarachnoid hemorrhages can be mistaken for subdural hematomas[20]. However, the history is clear and consistent, the symptoms reflect the forces described and no unexplained skeletal injuries are present.

Coagulopathies, such as hemophilia and hypoprothrombinemia caused by vitamin K-deficiency may be associated with intracranial hemorrhage without apparent cause or injury in infants[21,22]. These disorders are suggested by the clinical history and physical findings and can be proved by laboratory tests. In contrast, mild to moderate changes in coagulation studies are common with brain trauma[14].

Osteogenesis imperfecta is a rare inherited disorder of connective tissue that results from an abnormal quantity or quality of type I collagen. Although similar in skeletal survey, other suggestive findings such as blue sclerae, hearing impairment, dentinogenesis imperfecta, bowing and angulation of healed fractures, and progressive scoliosis exclude the possibility of child abuse. In addition, subdural hemorrhage is a rare complication of this disease[23].

Glutaric aciduria type I is a metabolic disorder caused by defect of glutaryl-coenzyme A dehydrogenase. Although some signs and symptoms are similar to SBS, skeletal injuries and retinal hemorrhages are absent in this disease[24].

Meningitis[15] sometimes present with similar signs and symptoms. But centrifuged CSF that is xanthochromic should raise the suspicion of cerebral trauma that is at least several hours old and not the result of a traumatic spinal tap.

Respiratory tract infection may mimic SBS by presenting with lethargy and poor feeding, but chest roentgenograms may appear normal or show unexplained rib fractures in SBS[1].

Munchausen's syndrome[4] is a variant of child abuse, in which parents concoct fictitious illness in their children for their own purposes.

Summary

The differential diagnosis of head trauma is predominant that of accidental versus inflicted injury. Prompt and accurate investigation and diagnosis is essential to save the life of the victim and to decide whether to report immediately to the appropriate authorities. The diagnostic team comprising of specialists in pediatric radiology, pediatric neurology, pediatric neurosurgeon, ophthalmologist and a pediatrician who specializes in child abuse should be formed in a general hospital or medical center. Shaken baby syndrome should be suspected in all children the age of one presenting with drowsiness, coma, seizures or apnea. A combination of subdural hematomas together with retinal hemorrhages whom has minimal or no trauma and in the absence of coagulopathy is almost pathognomonic. Physical signs of violence are often absent or subtle and the syndrome may easily be mistaken for a serious infection or seizures disorder[2].

The differentiating points are summarized in the table below.

Conclusions

The future safety of a child with the shaking baby syndrome relies on the physician's ability to recognize

its characteristic features. Effective prevention strategies must be guided by improved understanding of the pathophysiology and causes of this common disorder. It is advisable for the pediatrician to ask about caretaker stress, discipline practices, substance abuse, and response to the crying infant. A system involves regular home visits should be established to prevent intra-familial physical abuse. However, it is more difficult to prevent extra-familial abuse.

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非創傷性與創傷性腦部傷害

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摘要

兒童的身體虐待，不管是故意或意外，會造成身體及精神上的損傷，甚至可導致永久的傷害成死亡。因此醫療人員有責任提高警覺，一旦從病史或理學檢查發現到異常，應立即向主管機關報告。只有如此，我們才能幫助執法單位，採取行動對付施暴者，以減低未來的兒虐發生率。

關鍵詞：虐待兒童、非創傷性、創傷性、腦部傷害、搖晃嬰兒症候群

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Case Report

A Case Report of MELAS with MR Spectroscopy Examination

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Abstract

MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes) syndrome is a mitochondrial disorder characterized by myopathy, encephalopathy, lactic acidosis and stroke-like episodes.

We reported a case of 14-year-old boy with no prior medical history presenting with recurrent seizures and blurring of vision. He was suspected to be a case of MELAS. In mitochondrial disease, MRI findings are non-specific or change over time, thus greatly lowering its diagnostic sensitivity. In our case, Magnetic resonance spectroscopy (MRS) was deployed in addition to traditional method of diagnostic investigations such as biochemical studies, mitochondrial DNA analysis and MRI to aid the diagnosis.

Key words: MRS, MELAS syndrome, mt DNA point mutation, seizures.

Introduction

Mitochondrial diseases constitute a complex and heterogeneous group of metabolic disorders caused by heritable abnormalities of the respiratory electron transport cascade [1–3]. Although mitochondrial dysfunction manifests over a wide range of clinical expression, it most often affects muscle and brain, where dependence on oxidative energy metabolism is highest. MELAS syndrome is a mitochondrial disorder characterized by myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). It is also characterized by seizures, migraine-like headaches, lactic acidosis, episodic vomiting, short stature and recurrent cerebral stroke-like episodes causing hemiparesis, hemianopia, or cortical blindness [1]. MELAS is associated with at least four different mutations. The first mutation, found in about 80% of cases, is an A®G transition at point 3243 in the tRNA $^{Leu(UUR)}$ gene. The second mutation, found in about 10% of cases, is a T®C transition at point 3271, also in the tRNA $^{Leu(UUR)}$ gene [2]. The third mutation occurs in the same tRNA gene at position 3291[3]. And the last one in the gene specifying subunit III of cytochrome c oxidase [4].

Magnetic resonance imaging (MRI) and spectroscopy (MRS) are important tools in the diagnosis of children suspected of having a mitochondrial disorder, and may be used to monitor therapy. MRI may be especially useful in children where nonspecific neurologic symptoms are common, mtDNA defects may be absent, and biochemical and morphologic findings can be marginal. There is a spectrum of abnormalities seen that will vary based on the metabolic brain defect, stage of the disease, and age of the patient.

A relatively new neuroimaging technique, proton MRS has evolved from which important metabolic information can be derived utilizing the same acquisition parameters needed for MRI[16]. MRS is a noninvasive nonquantitative method used to assess CSF lactate levels and tissue metabolism in vivo[15]. MRS measurement of cerebral spinal fluid (CSF) and brain lactate has been shown to be helpful in the diagnosis and monitoring of mitochondrial disease [20], but its practical application to the diagnostic evaluation of a population that is considered to be at risk for mitochondrial dysfunction has not been established. MRS frequently reveals abnormalities in an at risk cohort,

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which identifies MRS as an important and practical tool in the diagnostic evaluation of mitochondrial disorders.

Case Report

A 14-year-old boy is the second child of healthy, non-consanguineous parents. He was born at 38 weeks, weighed 2750 gm and had no perinatal insult. He was born via normal vaginal delivery. His previous psychomotor development was normal. School performance was fair. He suffered from repeated vomiting since in primary school. He was brought to the hospital with the chief complaint of recurrent seizures since March of 2009. First attack of seizures was associated with cyanosis vomiting, blurred vision and generalized tonic clonic pattern. Second and third attacks of seizures were left sided focal seizures.

Upon admission, physical and neurological examination revealed acute ill-looking appearance, clear consciousness and blood pressure of 110/60 mmHg. Body weight was 31 kg (below 5th percentile); height, 141 cm (below 5th percentile). There was no facial dysmorphism. His pupils were isocoric with normal light reflex; eye movement was full and free; no nystagmus was found. Eye fundus examination revealed no abnormality. The cranial nerves were intact. Both muscle tone and deep tendon reflexes were normal. The family history was noncontributory. No history of stroke-like episode, migraine, hearing loss, or diabetes mellitus was noted in his maternal family members. Laboratory data showed a normal hemogram. Liver and renal function tests, CSF examination were normal as well. Arterial blood gas analysis revealed pH 7.439, PaO_2 96.8 mmHg, and HCO_3 21.7 mmol/L. An oral glucose lactate stimulation test (OGLST) revealed persistent hyperlactatemia, with readings of 40 mg/dl, 30 mg/dl, 29 mg/dl, 24 mg/dl and 21 mg/dl at 0 minutes, 30 minutes, 60 minutes and 120 minutes respectively. The electroencephalogram showed a slow background for the boy's age. MRI of the brain revealed a hyperintense in right temporo-parietal occipital region on T2 weighted image (Figure 2a), and hypointense in the same area on T1 weighted (Figure 2b). MRS revealed increased level of Lactate/creatinine and decreased level of N-acetylaspartate/creatinine (Figure 1).

A mitochondrial DNA analysis revealed an A®G mutation at nucleotide position 3243. Mutation was not found in other members of his family. The patient is now being treated with oxcarbazepine (Trileptal), phenytoin (Dilantin), neuquinon, vitamin B6 and B1.

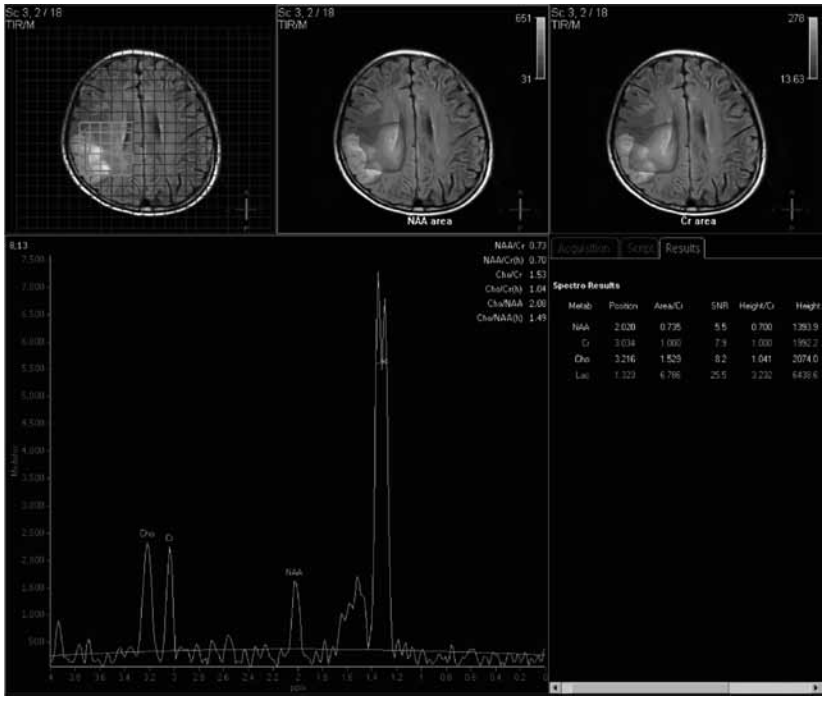

Fig. 1 Magnetic resonance spectroscopy demonstrates elevated lactate shown as a doublet at 1.3 ppm.

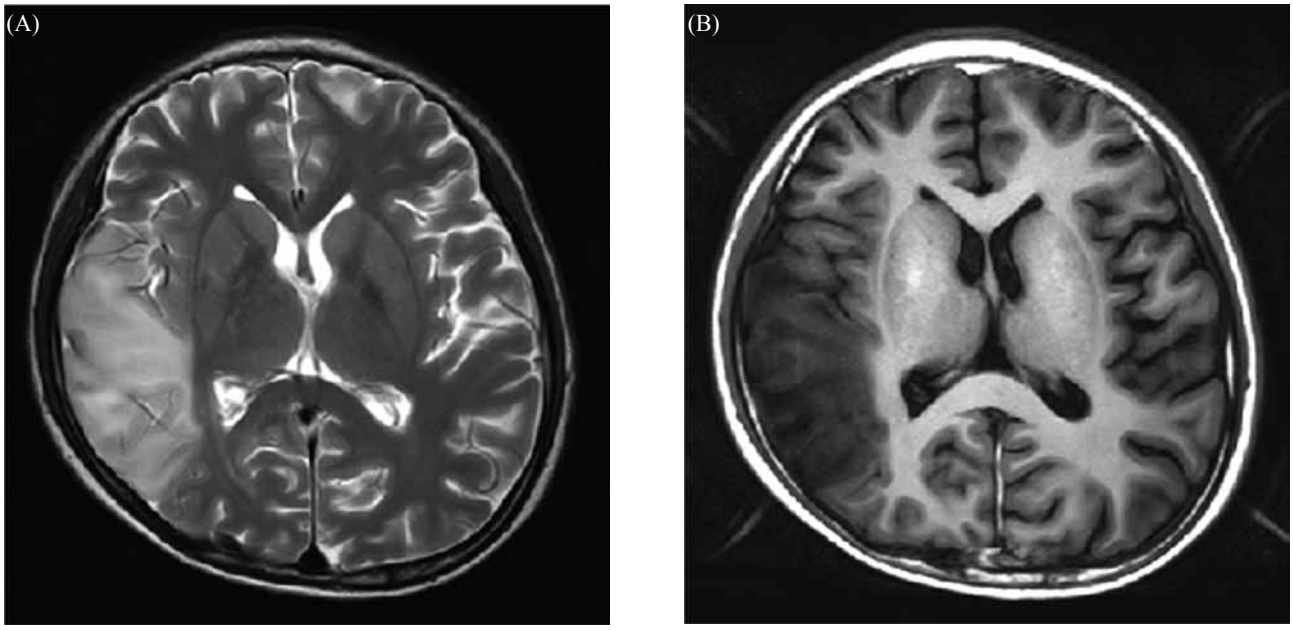

Fig. 2 (A) T_2-weighted magnetic resonance image (MRI) shows the hyperintense right temporo-parietal occipital region. (B) T_1-weighted magnetic resonance image (MRI) shows the hypointense right temporo-parietal occipital region

He is still being followed up at our out-patient department. Seizures were noted occasionally, but were well-controlled with trileptal.

Discussion

MELAS was first described by Pavlakis et al [1] in 1984 and has since been recognized as a unique mitochondrial disorder. Symptoms absent from MELAS which help to differentiate it from other forms of mitochondrial disorder include significant cerebellar dysfunction, interictal myoclonus, heart block, opthalmoplegia, and retinal pigmentary changes [1]. Although MELAS can often be differentiated from other mitochondrial disorders on clinical grounds, overlap syndrome can occur, making distinction among them difficult. With the advent of molecular genetic and biochemical studies, MELAS can be differentiated from other mitochondrial disorders.

The mitochondrial genome is exclusively inherited from the mother in a segregated manner. Clinical manifestation of involved family members varies depending on the proportion of mutant mitochondrial DNA they possess. In most mitochondrial diseases, a small amount of wild type mtDNA may have a protective effect. The proportion of mutant mtDNA needed to cause symptoms in MELAS is usually between 50% to 96%.

MELAS is a common mitochondrial disease seen in adults. Reports of childhood MELAS are rare. In reported cases, the age of onset and symptoms of childhood MELAS vary from early infancy to 16 years[7-10]. Patients with earlier onset of symptoms (<2 years old) involvement tends to be more diffuse, with failure to thrive and early onset of delayed development. Patients whose symptoms appeared later tend to have focal neurological deficit with migraine-like headaches, and the rate of cognitive regression reflects the rapidity of disease progression[7]. Common clinical features of childhood MELAS include episodic encephalopathy, vomiting, myoclonus, seizures, headaches, hearing loss, short stature, homonymous hemianopia, cortical blindness[9-11] and stroke-like episodes[11]. Some unusual manifestations such as slurred speech, aggressive behavior, chronic asthma[10], depression[10] and respiratory failure [12] have also been reported.

The clinical course of the patient described in this report is consistent with MELAS syndrome. MRS demonstrates elevated lactate shown as a doublet at 1.3 ppm. MRI revealed hyperintense right temporo-parietal occipital region on T2 weighted images[13,15].

These findings are consistent with the characteristics of MELAS as reported in the literature[11]. These lesions frequently tend to be in the parietal and occipital lobes, but often do not correspond to a defined vascular territory[1,13]. The nonvascular nature of the infarct suggests the ischemia may be cellular in origin, perhaps relating to the inability of the defective mitochondria to respond adequately to periods of high metabolic demand [13]. Initially these patients seem to improve despite the abnormalities seen in MRI scans. Their course is that of episodic exacerbation of stroke-like symptoms followed by partial recovery and eventual deterioration. Angiography has failed to reveal any significant vascular disease in these patients [21].

MELAS syndrome should be considered in the differential diagnosis of young patients presenting with seizures and stroke-like episode. If clinical and radiological findings are suggestive, serum pyruvate and lactate levels should be obtained, as well as skeletal muscle biopsy and mitochondrial DNA analysis to avoid missing any mitochondrial disease. As a very low percentages of mutant mtDNA in the blood may escape detection, it is necessary to screen the muscle for mutation in suspected cases[14]. Unfortunately in our case, we were unable to perform muscle biopsy because of the family's refusal to sign permission probably due to the custom. Analysis of any one tissue does not permit a reliable estimation of prognosis, but a concordant high percentage (>80%) of mutant mtDNA in both muscle and blood probably indicates a poor prognosis[14].

Lactate is not detected above the lipid background in normal infants, children, and adults. When metabolism shifts to anaerobic glycolysis in mitochondrial respiratory chain deficiencies, lactate levels become increased in brain tissue. Two studies showed the sensitivity of lactate peaks in mitochondrial disease to be 18-27%[16]. Lactate peaks vary depending on whether a patient is undergoing an exacerbation of their disease, as well as whether their lesions are acute, subacute or chronic. Absence of a lactate peak does not rule-out mitochondrial disease, as the specific tissues involved in mitochondrial disease vary, as does the location of brain involvement. MRS specificity for mitochondrial disease is further limited by the possibility of other conditions giving rise to lactate peaks. However, identification of a lactate peak in a suspicious case of mitochondrial disease indicates a more invasive diagnostic evaluation.

MRS measurements of N-acetyl-L-aspartate (NAA) appear to be one of the best surrogate biomarkers for neuronal integrity. A decrease in NAA levels when normalized to creatine may reflect mitochondrial disease. The ratio of each metabolite to creatine is used as a standard reporting value due to fairly uniform CNS creatine levels in most individuals. As with elevated lactate, decreased NAA is not specific for mitochondrial or even metabolic disease because other disorders may also present with NAA signal alterations. However, additional clinical and biochemical evaluation may often help to differentiate these disorders from primary mitochondrial disease.

Proton MRS represents a useful tool for the noninvasive investigation of neurometabolic disorders, in particular mitochondrial disease. Additional information is obtained over conventional MRI, as metabolic changes can be visualized even in areas of brain that appear structurally normal. In the correct context, MRS can greatly increase the sensitivity of the diagnostic evaluation for mitochondrial disease[16].

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質子核磁共振光譜學用於診斷粒腺體疾病：腦肌病症候群一病例報告

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摘要

腦肌病症候群（MELAS syndrome）是一種粒腺體疾病，其特徵為肌病變、腦病變、乳酸中毒、類中風事件。

我們報告一件案例是一位之前沒有任何病史的十四歲少年，他出現了反覆癲癇發作和視力模糊，他被懷疑是腦肌病症候群的患者。就粒腺體疾病而言，核磁共振造影（MRI）的發現是非特異性的，且隨著時間的推移而變動，因此大大的降低它的診斷敏感度。就我們的病例而言，除了傳統的診斷研究方法（例如生化研究、粒腺體DNA分析、及核磁共振造影）之外，核磁共振光譜（MRS）的推展應用也幫助了我們的診斷。

關鍵詞：核磁共振光譜、腦肌病症候群、粒腺體DNA點突變、痙攣

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童綜合醫學雜誌投稿相關規則

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本雜誌刊載與醫學有關之論述，包括原著論文、臨床病理討論、病例報告等論述及特別約稿之綜論（review article）、special article 、communication（包括 brief communication）、Editorial（編著的話）等。惠稿請送 43503 台中市梧棲區中棲路一段 699 號童綜合醫學雜誌編審委員會（E-mail: Tungs_Journal@ms.sltung.com.tw）。

壹、投稿前注意事項

1. 投稿時，需附原稿兩份（一份原稿和一份複印稿，但圖片應用兩份原圖）並以電腦打字（請以 MS WORD 文書處理格式，中文字型以標楷體，英文字型以 Time New Roman 12 號字大小，稿紙之左右緣爲 2.54 公分，上下緣爲 3.17 公分），請勿裝訂，同時須提供最後版本之電子檔一份，若圖片或照片有電子檔提供者，請以附檔 jpg 的形式提供。
2. 文件內容需清晰，內容與原稿一致，若複印稿與原稿有差異或遺漏，由作者自行負責。著作中若牽扯到版權所有之內容，作者需取得其使用權，法律責任由作者負責。
3. 投稿同時請附上著作權讓與同意書。所有作者必須實際參與並同意該論述。本院於接受稿件且印刷完成後，將致贈稿酬並贈送 20 份抽印本給通訊作者，如需額外抽印本請於校稿時言明，並酌收成本費用。第一作者若需抽印本可提出申請，依份數酌收成本費用。
4. 本刊對於原稿經徵得著者之同意得伸縮或修改之。如不合本刊宗旨者，得退還之。
5. 凡刊載於本雜誌之著作，若涉及「研究用人體檢體採集」及「人體試驗」等情事，應遵守該注意事項，以落實保障受檢人權益。詳文請參考須附上相關審議認可之文件。
6. 論文中如涉及使用脊椎動物進行科學應用計畫者，應檢附該計畫業經所屬機構動物實驗管理小組審議認可之文件，以落實實驗動物之人道管理。

貳、寫作原則

1. 原著論文按下列順序撰寫：摘要、前言、材料與方法、結果、討論與結論、誌謝、參考文獻、附表、圖片說明、圖片（含照片）。
2. 病例報告按下列順序撰寫：摘要、前言、病例、討論、參考文獻、附表、圖片說明、附圖、照片。
3. 病例報告，每篇以五頁以內爲限（即約 9,000 字），依題目、所屬機構、作者姓名（作者以 5 人爲限）、病例之病史經過及重要之診療資料、主要之臨床問題、討論或分析、結論、推薦讀物等順序繕寫。凡病患顏面部位之相片必須遮去眼睛部位，表示尊重隱私。診療資料或臨床經過之圖表，原則上均限六個月以內。
4. 綜說不必按原著論文格式撰寫，但必須列出參考文獻。
5. 其他類文章連圖表，以不超過四頁（每頁約 2,000 字）爲原則，但特約稿例外。學術文章，題目、姓名均須以中文書寫。
6. 其他細節，請參閱國際指導委員會（International Steering Committee）發表之生物醫學雜誌稿件統一規格（Uniform Requirements for Manuscripts Submitted to Biomedical Journals，見 The New England Journal of Medicine 336:309-315,1997）。

參、投稿須知

一、稿件須符合「生物醫學雜誌投稿之統一規定」[1]，請以電腦隔行 double space 書寫並編頁碼。

二、第一頁爲標題頁，須列出中文及英文之論文題目、中英文作者姓名、所屬機構及單位之中英文稱號（分屬不同單位，請以阿拉伯數字標出作者與單位）、聯絡人姓名、電話及中英文通訊錄。

三、第二、三頁爲中文及英文之摘要及關鍵詞（請提供 3 至 5 個關鍵詞或簡短片語），中英文摘要

須完全相同，摘要分段撰寫，依序爲背景及目的（Background and purpose）、方法（Methods）、結果（Results）及討論（Discussion）。

四、請附兩份原稿（一份原稿和一份複印稿，但圖片應使用原圖），包括附表、附圖及照片。圖表應專業製作，一張紙僅一個附圖或附表，依引用順序以阿拉伯數字標出排列。附表須有標題及說明。照片須 5 × 7 吋光面黑白，背面以鉛筆編號，附圖須有簡單說明（Legend），並另頁撰寫。光學或電子顯微鏡照片，請註明擴大倍率或比例。

註：[1] 根據「生物醫學雜誌投稿之統一規定」第五版，刊載於 Annals of Internal Medicine 1997;126(1): 36-47.

肆、參考文獻

未經發表之論文或摘要不得列爲參考文獻，但可於本文中說明並註明「未發表」（unpublished observations）。博碩士論文可引用。已被任何雜誌接受刊發但仍未發表之著作，請列出雜誌名稱及年份，並註明「in press」。

原著論文、臨床病理討論、病例報告等論述及特別約稿之綜論（review article）按下列格式撰寫：

一、雜誌名稱之簡稱須按照 Index Medicus 型式，作者人數小於 6 位時，詳列所有作者姓名，超過 6 位時，只須列出前 6 位，其它以「等」（et al）代替。

例：Bhasin S, Storer TW, Berman N, Callegari C, Clecenger B, Phillips J, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996; 335:1-7.

二、本文內引用時，若兩名以下作者請列出姓氏。兩名以上則列出第一名之姓氏，其他以「等」（et al）代替，並以阿拉伯數字方括弧表示於引用之後。

例：One of the first well documented reports of ECH poisoning with fatality in young children was reported by Miller et al. in 1970[2].

例：Boulet 等人 [3] 報告氣喘患者接受衛教後的知識改變量不受個人因素影響。

三、參考範例

A. 期刊：[作者姓名：題目。雜誌簡稱 年代；卷數（期數）：起迄頁數]

1. 許吟姿、楊光道、張恆鴻：結締組織疾病併發間質性肺病變患者 99mTc-DTPA 肺廓清率之臨床研究。內科學誌 1992;3:79-83.
2. Yang KTA, Chen HD: A semi-automated method for edge detection in the evaluation of left ventricular function using ECG-gated single-photon emission tomography. Eur J Nucl Med 1994;21:1206-11.

B. 單行本：[作者姓名：書名，版數（卷數）。發行地；出版公司，年代：引用部份頁數]。

1. 楊志良：生物統計學新論，一版。台北；巨流圖書公司，1984：33-8.
2. Plum F, Posner JB: Diagnosis of Stupor and Coma. 3rd ed. Philadelphia: Davis, 1980:132-3.

C. 多重作者之單行本：[有關文章作者姓名：書名，版數（卷數）。發行地；出版公司，年代：引用部份頁數]。

1. 蔣欣欣：護理與健康，編輯：顧乃平：護理專業導論，一版。台北；匯華出版公司，1991：83-121。
2. Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, lsselbacher K, Petersdprf RG eds. Harrison's Principles of Internal Medicine, 8th ed. New York: Mcgraw-Hill, 1977: 364-75.

伍、著作權

若著作人投稿於本刊經收錄後，同意授權本刊得再授權國家圖書館或其他資料庫業者，進行重製、透過網路提供服務、授權用户下載、列印、瀏覽等行爲。並得爲符合各資料庫之需求，酌作格式之修改。若爲摘譯、譯稿或改寫稿，需附原作者之正本同意書，並附原文影本一份；來稿如涉及版權，概由作者自負文責。

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