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Mitochondrial Diseases

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Mitochondrial diseases (MDs) are a clinically heterogeneous and often multisystemic group of metabolic disorders that are caused by a large variety of defects in mitochondrial energy metabolism that results in diminished adenosine triphosphate production.

Clinical symptoms and signs of MDs can be variable, but most commonly affect the brain and muscles, in which demands on oxidative energy metabolism are highest. Since 1988, when the first MD case was reported in Taiwan, physicians gradually have had a clearer picture of the disease. There are two types of MDs in clinical classification: syndromic MDs and non-syndromic MDs. Specific mitochondrial syndromes are easy to diagnose because each of them has its own clinical phenotypes. However, it is not easy to diagnose non-syndromic MDs during the early stage of disease course due to various clinical features.

Basic laboratory tests for MDs include blood lactate, oral glucose lactate stimulation test, metabolic assays of tandem mass and organic acids, and carnitine level. In addition, neuroimaging studies consisting of brain magnetic resonance imaging and magnetic resonance spectroscopy, specific histochemical staining and electron microscopic examination of muscle biopsy, respiratory chain enzyme analysis, genetic analysis of mitochondrial or nuclear DNA, are helpful for diagnosing MDs. Even though there are many diagnostic tools, none of them is sensitive enough to make a confirmative diagnosis without being used in combination with other tools.

With a high level of clinical alertness based on greater familiarity with notorious variability in clinical presentations and an organized diagnostic approach by gathering evidences from laboratory, pathological, neuroradiological, and genetic parameters, most MDs can be confirmed early in their course and be managed across all specialties.
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Key words: Mitochondrial diseases, Clinical manifestations, Diagnostic tools, Taiwan

INTRODUCTION

In 1962, Luft et al. initially introduced the concept of mitochondrial myopathies in terms of a patient presenting with non-thyroid origin hypermetabolism[1]. Furthermore, Engel and Cunningham used a modification of the Gomori trichrome stain that revealed abnormal accumulation of mitochondria as ragged red fibers (RRFs)[2]. Since then, there has been great interest in the diagnosis of mitochondrial diseases (MDs). MDs constitute a complex, heterogeneous and often multisystemic group of metabolic disorders that result from mutations in mitochondrial or nucleus-encoded oxidative phosphorylation subunit genes, which cause a large variety of defects in mitochondrial energy metabolism. This results in the

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diminishing of adenosine triphosphate (ATP) production, and ultimately clinical disorders. Recently, it has been estimated that the incidence or prevalence of mitochondrial respiratory chain disorders in adults or children is higher than we expected. The disorders can occur with a probable frequency in preschool children (age <6 years) of about 1 in 11,000[3]. The minimum birth prevalence for respiratory chain disorders with onset at any age was estimated at 1 in 7634[4].

In Taiwan, the first report of clinical MD was published in 1988[5], and the first mitochondrial DNA (mtDNA) mutation was identified in 1992[6]. Since then, more than 90 articles relevant to clinical MDs have been published in Taiwan[7-96] (Fig. 1). The wide variety of symptoms and clinical features complicates the diagnosis of MDs and the presentations may result in patients visiting numerous other subspecialists and receiving various diagnoses. Several recent studies[97,98,99] showed clinical features in patients with MDs support the maxim "any tissue and any signs at any age"[100]. In general, the clinical spectrum

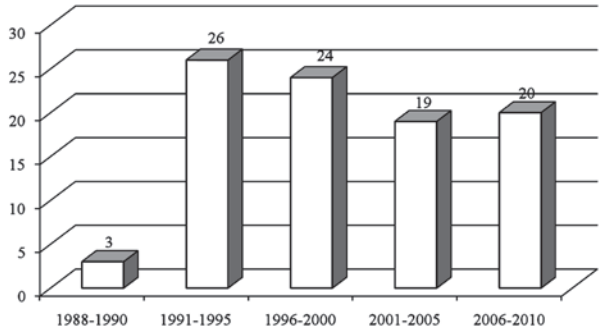

Fig. 1 Published papers of clinical mitochondrial diseases in Taiwan (1988-2010).

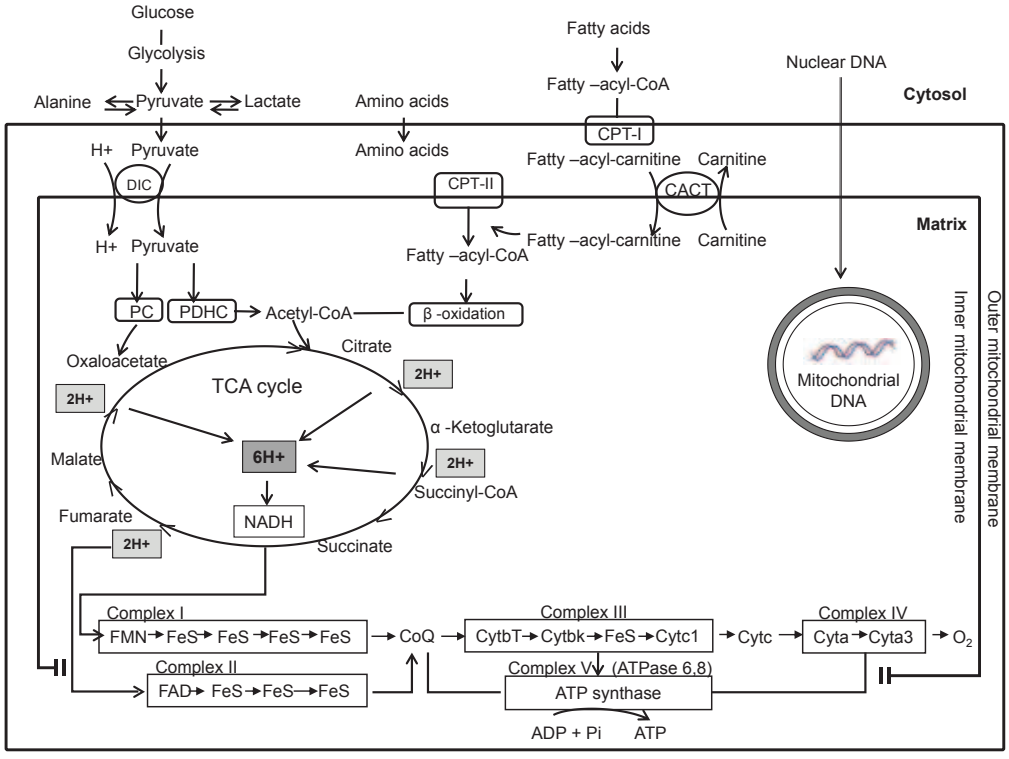

Fig. 2 Metabolic pathways in mitochondria.
ADP: adenosine diphosphate; ATP: adenosine triphosphate; CACT: carnitine–acylcarnitine translocase; CoQ: coenzyme Q; CPT: carnitine palmitoyltransferase; Cyta: cytochrome a; Cytb: cytochrome b; Cytc: cytochrome c; DIC: dicarboxylate carrier; FAD: flavin adenine dinucleotide; FeS: Iron sulfur protein; FMN: flavin mononucleotide; NADH: reduced nicotinamide adenine dinucleotide; PC: pyruvate carboxylase; PDHC: pyruvate dehydrogenase complex; TCA: tricarboxylic acid.

not only occurs in the neuromuscular system; indeed, a number of non-neuromuscular organs present symptoms and signs, such as the heart, eyes, ears, kidneys, endocrine glands, liver, bone marrow, and gastrointestinal tract.

For this review, I focus on the clinical MDs, including variable phenotypes, classifications, specific mitochondrial syndromes, differential diagnoses, diagnostic tools, and the recent advances in the treatment of MDs. Basic biochemical reactions and genetic characteristics of the mitochondrion are described briefly as well.

Mitochondrion and biochemical reactions

The mitochondrion, an extranuclear organelle, is 0.5-1 μm in size. It consists of outer and inner membranes, an intermembranous space, and an inner matrix compartment. The matrix contains various enzymes, ribosomes, transfer RNAs (tRNAs), and mtDNA molecules. Each cell contains many mitochondria which are responsible for cellular ATP production by oxidative phosphorylation. Energy production of mitochondria comes from the metabolism of glucose and fatty acids through a series of reactions.

Pyruvate, the end-product of aerobic glycolysis, is derived partly from blood-home glucose but mainly from endogenous glycogen. Once formed in the cell cytosol, pyruvate may be reduced to lactate, transaminated to alanine, or transported into the mitochondria where it undergoes oxidative decarboxylation to acetyl-CoA catalyzed by the pyruvate dehydrogenase complex (PDHC) (Fig. 2). Long-chain fatty acid, after being activated to fatty acyl-CoA in the cytosol, must be transferred across the inner mitochondrial membrane to be oxidized to acetyl-CoA. Acetyl-CoA then enters the citric acid cycle (Krebs cycle), which releases 8 hydrogen molecules and produces carbon dioxide and water through oxidative phosphorylation. This process liberates energy along the respiratory chain, which receives energy-rich hydrogen atoms from nicotinamide adenine dinucleotide (NADH) or flavin-adenine dinucleotide (FADH), produced mainly in the Krebs cycle and from fatty acid oxidation. Electrons from the hydrogen are passed between respiratory complexes in the chain. Complexes I, III and IV extrude protons from the mitochondrial matrix. Complex IV consumes oxygen to form water. Complex V couples ATP synthesis to proton reentry, which is powered by the electrochemical gradient[101]. Ultimately, the energy is stored as ATP.

In addition, mitochondria are deeply integrated in cell biology with important roles in urea, porphyrin and steroid hormone synthesis, apoptosis, calcium homeostasis and free radical production[101]. The term "mitochondrial diseases" indicates a class of disorders characterized by an impairment of the mitochondrial respiratory chain, which is where most of cellular ATP is generated.

Mitochondrial genetics

The human mitochondrial genome is a 16,569-bp double-stranded DNA circle that contains 37 genes, of which 13 genes encode subunits of the respiratory chain, 22 tRNAs and two ribosomal RNA genes (12S and 16S) translate mtDNA. Each cell contains many mitochondria with 2-10 mtDNA molecules. The mitochondrial genome contains no introns. The only non-coding region of mtDNA is the displacement loop (D-loop). The total mtDNA accounts for about 0.5% of the DNA in a nucleated somatic cell. The 13 mitochondrial proteins form the four enzyme components of the respiratory chain complexes required for oxidative phosphorylation: seven of them are subunits of complex I (NADH-ubiquinone oxidoreductase), one of complex III (ubiquinol- cytochrome *c* oxidoreductase), three of complex IV (cytochrome *c* oxidase), and two of complex V (H1-translocating ATP synthase). All of the subunits of complex II (succinate-ubiquinone oxidoreductase), the remaining subunits of the other mitochondrial respiratory chain complexes as well as the factors involved in mtDNA replication, transcription and translation are encoded by nuclear DNA (nDNA).

Mitochondrial genetics differ from Mendelian genetics in some fundamental aspects. First of all, mtDNA is maternally inherited because mitochondria derive solely from the oocyte. A normal cell has only a single mtDNA genotype and is therefore

homoplasmic. On the other hand, if the genomes represent a mixture of a wild-type and a mutated-type, the cell genotype is heteroplasmic. The clinical pictures of MDs are determined by the proportion of normal-to-mutated genomes in the mitochondria. Once the proportion exceeds a theoretical threshold, the biological behavior of the cell will change. This minimum critical amount is different from tissue to tissue and different tissues may be affected in various combinations and to different degrees. In addition, mitotic segregation of the mitochondria will influence the biological behavior that refers to the stochastic redistribution of wild-type and mutated genomes during mitochondrial and cell divisions. Thus, the concepts of threshold effect and mitotic segregation have provided theoretical explanations for the variable phenotype expressions of the MDs.

The mitochondrial metabolic pathway is under the control of both nuclear and mitochondrial genomes, which are strictly coordinated to ensure the correct functioning of the mitochondrial machinery. Recent studies have demonstrated that about 10-15% of MDs are caused by mutations in mtDNA[101].Nuclear gene mutations play an important role in development of MDs in terms of altering mitochondrial structural components and the integrity, stability and replication of mtDNA. The nuclear genes encoding mitochondrial proteins not only encode proteins regulating oxidative phosphorylation but also encode proteins involved in reactive oxygen species (ROS) formation, apoptosis. Therefore, the spectrum of mitochondrial genetic diseases caused by inherited mutations in nuclear genes is very broad.

Classification of mitochondrial diseases

MDs may present with various neurologic and extra-neurologic features. Lack of a clinically pathognomonic hallmark frequently makes laboratory investigations necessary to confirm the diagnosis. In some cases, diagnostic investigations provide definitively abnormal results. However, in many cases the results can be intermediate or ambiguous. The confirmation or exclusion of MDs is therefore a major challenge for clinicians. In 2002, Bernier et al.[102] proposed modifications to the Walker criteria[103] to improve their sensitivity and enable them to be used for pediatric patients as well as adults. The diagnosis of mitochondrial disorder was established on the basis of assigning major or minor criteria for clinical, pathological, enzymatic, functional, molecular, and metabolic parameters. Mitochondrial encephalomyopathies were categorized as definite, probable or possible. A definite diagnosis is defined as fulfillment of either of two major criteria or one major criterion plus two minor criteria. A probable diagnosis is defined as either one major criterion and one minor criterion or at least three minor criteria. A possible diagnosis is defined as either a single major criterion or two minor criteria, one of which must be clinical.

Patients who presented with characteristic clinical phenotypes reported in the literature were categorized as having specific mitochondrial syndromes[104-116], including Leigh syndrome (LS), Alpers' disease, lethal infantile mitochondrial disease(LIMM), Pearson's syndrome (PS), Kearns-Sayre syndrome (KSS), mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neuropathy, ataxia, and retinitis pigmentosa (NARP), mitochondrial neuro-gastrointestinal encephalomyopathy (MNGIE), chronic progressive external ophthalmoplegia (CPEO), and Leber's hereditary optic neuropathy (LHON). The patients who fulfilled the diagnostic criteria for MDs, but not specific syndromes, were classified as having non-categorized or non-syndromic MDs. Recently published[97,98,99] studies show that pediatric patients with non-syndromic MDs are not uncommon, and the clinical manifestations are nonspecific[95,117].

Specific mitochondrial syndromes

Some patients display a cluster of symptoms and signs (Table 1) that fall into a discrete clinical syndromes. The main defined phenotypes are described as follows:

LS (Leigh syndrome), or subacute necrotizing encephalomyelopathy, is an early-onset progressive neurodegenerative disorder exhibiting considerably variable clinical signs, symptoms, onset time and

Table 1. Clinical presentations of mitochondrial diseases.

Central nervous system	Extra-central nervous system
Seizures	Ophthalmologic system
Developmental delay	Ptosis
Altered level of consciousness	Retinitis pigmentosa
Floppiness	External ophthalmoplegia
Spasticity	Visual loss
Mental retardation	Nystagmus
Sucking difficulty	Exotropia
Involuntary movement	Blurred vision
Headache	Visual field defect
Apnea	Strabismus
External ocular motility limitation	Corneal clouding
Tremor	Optic nerve atrophy
Apneustic respiration	Cardiovascular system
Dystonia	Pericardial effusion
Stroke	Hypertrophic cardiomyopathy
Sudden infant death syndrome	Arrhythmia
Hypoventilation	Mitral valve prolapse
	Hypertension
	Dilated cardiomyopathy
	Gastrointestinal system
	Constipation
	Vomiting
	Intestinal obstruction
	Abdominal pain
	Diarrhea
	Hepatic system
	Liver function impairment
	Hepatomegaly
	Liver cirrhosis
	Urologic system
	Fanconi syndrome
	Renal tubular dysfunction
	Proteinuria
	Endocrinologic system
	Hypoparathyroidism
	Amenorrhea
	Short stature and/or failure to thrive
	Hearing system
	Peripheral nervous system
	Hematologic system
	Pancreas
	Psychic

course. It is caused by mitochondrial subunit gene mutations of the ND1-6, ATPase 6, tRNA, or COX III, or caused by nuclear gene mutations of the PDHC, NDUFS1-4, NDUFS7-8, NDUFV1-2, SDH, or CoQ. Characteristic neuropathologic features consist of spongiform necrosis, myelin degeneration, vascular proliferation, and gliosis in one or more areas of the CNS, including thalamus, basal ganglia, brainstem, and spinal cord[104]. Defects in mitochondrial energy production are generally present and are involved in the etiology of this degenerative CNS disease. Symptoms of LS usually emerge in the first few years of life and are heterogeneous depending on which areas of the CNS are involved, including hypotonia, psychomotor regression, ataxia, ocular movement abnormalities, seizures, dystonia, swallowing, and respiratory disturbances[92,118].

Alpers' disease, so called Alpers' Huttenlocher disease, is a cerebrohepatopathy characterized by clinical triad of psychomotor deterioration, seizures and liver dysfunction[106]. The onset age of patients ranges from the first year of life to the fifth year. The mtDNA polymerase gamma gene mutations acount for most of the cases. Other symptoms may include fasting hypoglycemia, failure to thrive, cortical blindness, gastrointestinal dysmotility, cardiomyopathy and deafness, etc.

Infantile mitochondrial myopathy (IMM) is mainly caused by cytochrome *c* oxidase deficiency. There are two forms, one is fatal form and other is benign form[108,109]. The onset age of patients ranges from neonate period to early infancy. Clininal manifestations include generalized weakness or hypotonia, respiratory distress, lactic acidosis, cardiomyopathy, renal tubular dysfunction, or Fanconi syndrome, etc.

PS (Pearson's syndrome), first described in 1979, is a disorder in early infancy presenting with a unique combination of refractory sideroblastic anemia, vacuolization of marrow precursors and exocrine pancreatic dysfunction[107]. Large-scale deletions in the mitochondria are responsible for this syndrome[81, 119,120]. Over recent years it has become clear that PS should be regarded as an early-onset, multi-system mitochondrial cytopathies resulting from severe

deficiency in mitochondrial energy supply in different organs. Patients with the syndrome usually die during infancy, with survivors later developing the features of KSS and/or Leigh-type neuropathology[121].

KSS (Kearns-Sayre syndrome) is the result of deletions in mtDNA from mother's ovum. Age of onset is before 20 years old. Clinical manifestations include the triad of chronic progressive external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction abnormalities[105]. Other symptoms may include failure to thrive, hearing loss, ataxia, endocrinopathies, renal tubular dysfunction, and elevated level of protein in the cerebrospinal fluid, etc. Some cases with KSS are evolved from Pearson's syndrome.

MELAS (Mitochondrial myopathy, Encephalopathy, Lactic acidosis, and Stroke-like episodes) is caused by mitochondrial gene mutations of the tRNA (tRNA-Leu-UUR) in the majority of cases. The onset age of patients ranges from early childhood to adolescence. Clinical features comprise headache, cortical blindness, focal weakness or stroke-like episodes, focal seizures or generalized seizures, exercise intolerance, lactic acidosis, vomiting, psychomotor retardation, failure to thrive, hearing impairment, ptosis, diabetes mellitus, cardiomyopathy, cardiac conduction abnormalities, such as Wolff-Parkinson-White syndrome, constipation, diarrhea, abdomen pain, peripheral neuropathy and psychiatric disorders, etc[113].

MERRF (Myoclonic Epilepsy with Ragged Red Fibers) is characterized by progressive myoclonic seizures, muscle weakness, exercise intolerance, ataxia, psychomotor retardation, short stature, hearing loss and poor night vision, etc[110,111]. The onset age of patients ranges from childhood to adult. Muscle biopsy reveals ragged red fibers. The most common gene mutations are related to tRNA-Lys.

MNGIE (Mitochondrial Neurogastrointestinal Encephalomyopathy) is caused by mutations in the thymidine phosphorylase (TP) gene. The onset age of patients ranges from late childhood or adolescence. Clinical symptoms include severe gastrointestinal dysmotility, vomiting, abdomen pain, cachexia, ptosis, peripheral neuropathy, seizures, and hearing loss, etc[114].

LHON (Leber's Hereditary Optic Neuropathy) is caused by mitochondrial gene mutations of the ND1, ND4 and ND6 subunit genes, which result in degeneration of retinal ganglion cells and their axons. The onset age of patients ranges from childhood to adult. Clinical manifestations include visual loss, tremor, and cardiac arrhythmia, etc[115].

NARP Syndrome (Neuropathy, Ataxia, and Retinitis pigmentosa) usually presents in young adult. It causes by mitochondrial subunit ATPase 6 gene mutations. Clinical presentation includes the triad of retinopathy, muscle weakness, and ataxia. Other symptoms may include nystagmus, seizures and hearing loss, etc[116]. Furthermore, Leigh syndrome may occur in some patients' relatives with NARP syndrome.

CPEO (Chronic Progressive External Ophthalmoplegia) is caused by mutations or deletions of mtDNA or nDNA. Clinical symptom includes slow progressive ophthalmoplegia[112]. Other symptoms may include exercise intolerance, cataract, hearing loss, peripheral neuropathy, depression and hypogonadism, etc.

Diagnostic evaluation of mitochondrial diseases

The major challenge to properly diagnosing MDs is the absence of a definitive biomarker in all patients. Therefore the diagnostic evaluation is necessarily broad, based on evidence gathered from clinical information, biochemical laboratory findings, tissue-biopsy evidence, and neuroradiologic features, as well as genetic analysis.

For basic laboratory investigation, blood lactate is used as a biochemical marker for the screening of MDs. The differential diagnosis of lactic acidosis includes physiological anaerobic exercise, systemic diseases that increase blood lactate levels, cerebral diseases that increase CSF lactate levels, metabolic diseases, poor collection technique, or poor sample handling[122]. However, blood lactate level is not always elevated in patients with MDs[97]. A glucose challenge test followed by successive blood lactate examinations is a better screening method than a single blood lactate test[3,12]. Depending on the associated effect

of the biochemical defect on the oxidation-reduction potential, lactate acidosis may be proportionate or disproportionate to the elevation of pyruvate. If the oxidation-reduction potential is unaffected by the biochemical defect, the lactate and pyruvate elevations will be proportional and the lactate/pyruvate ratio will be normal. In contrast, if the oxidation-reduction potential is disturbed by a primary defect involving the respiratory chain, the lactate values will be disproportionately elevated and the lactate/pyruvate ratio will be increased (>25).

Lactic acidosis can be caused not only by intramitochondrial (primary) disorders but also extramitochondrial (secondary) disorders. The latter include defects of metabolic pathways on glycogen, gluconeogenesis, or organic acids etc. Thus, a metabolic survey, including assays of plasma ketone body (3-OH butyrate/acetoacetate) ratio, plasma amino acid quantitation, tandem mass spectrometry (MS/MS), plasma acylcarnitine profile, and urinary organic acids, is helpful for differential diagnosis of MDs.

In the past few years, the clinical diagnosis of MDs has been greatly improved by advances in neuroimaging technology. Brain magnetic resonance imaging

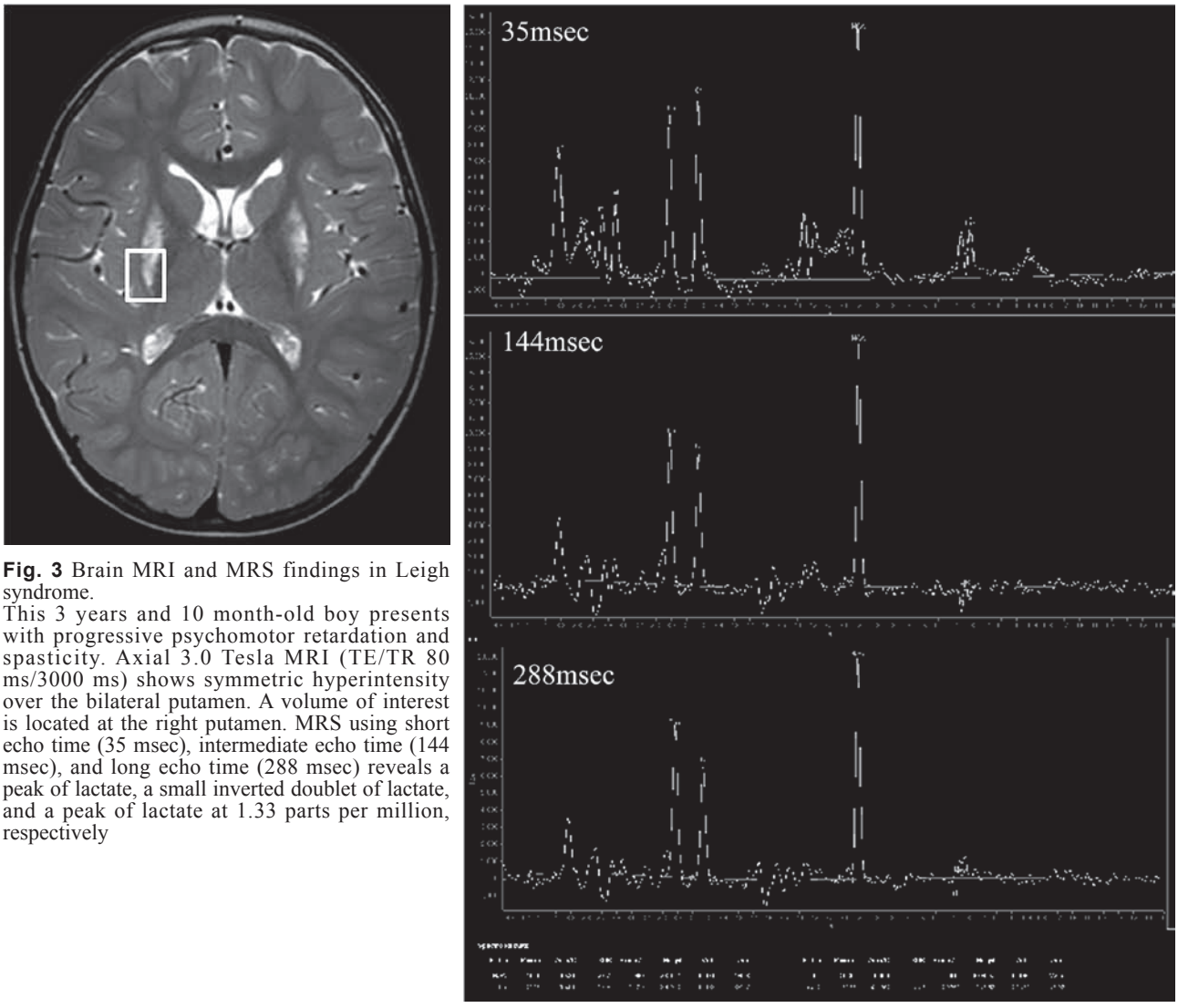

Fig. 3 Brain MRI and MRS findings in Leigh syndrome.
This 3 years and 10 month-old boy presents with progressive psychomotor retardation and spasticity. Axial 3.0 Tesla MRI (TE/TR 80 ms/3000 ms) shows symmetric hyperintensity over the bilateral putamen. A volume of interest is located at the right putamen. MRS using short echo time (35 msec), intermediate echo time (144 msec), and long echo time (288 msec) reveals a peak of lactate, a small inverted doublet of lactate, and a peak of lactate at 1.33 parts per million, respectively

(MRI) is sensitive to these diseases, especially in clinically phenotypic mitochondrial syndromes, including LS (Fig. 3), MELAS, MNGIE, and KSS. In infants and children with non-syndromic MDs, brain MRI can produce variable findings, from normal results to signal changes over the basal ganglia or brainstem[96], which remind physicians to be aware of a mitochondriopathy. MR spectroscopy (MRS) for detecting the concentration of a number of biochemical metabolites *in vivo* is reported to be a useful tool in helping differential diagnosis and monitoring of MDs as well[123].

A muscle biopsy by using light microscopic and electron microscopic examinations is an auxiliary diagnostic parameter of MDs. Morphological examinations include the modified Gomori trichrome staining for RRFs, adenosine triphosphatase staining for the assessment of myofibrillar integrity, muscle-type fiber predominance and distribution, and cytochrome *c* oxidase and succinate dehydrogenase staining for oxidative enzymes. RRFs showing on the modified Gomori trichrome stain are noted in a minority of patients, especially in children younger than 3 years[97]. Nevertheless, electron microscopic examination of muscle cells may reveal abnormal mitochondrial configurations and/or subsarcolemmal abnormal mitochondrial accumulation in those patients (Fig. 4). In addition to morphological examinations, mitochondrial respiratory chain complex enzyme analysis of biopsied muscle or skin fibroblasts will be helpful to confirm respiratory chain complex defects.

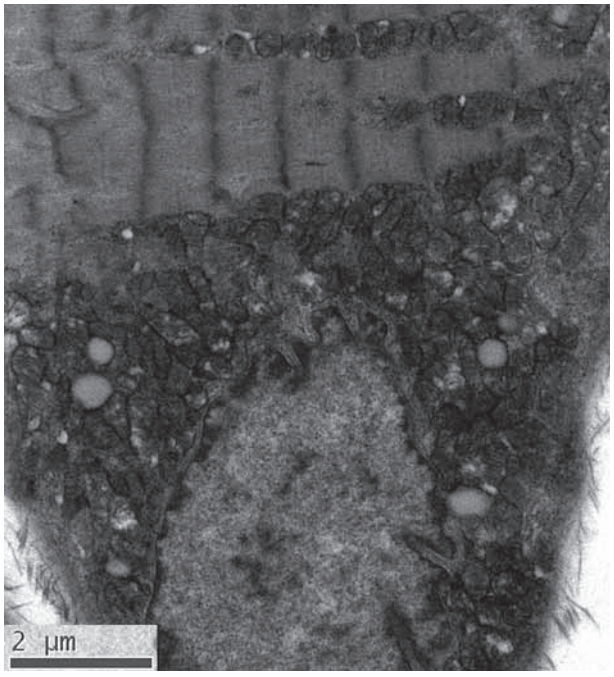

Fig. 4 Electron microscopic finding of muscle biopsy in mitochondrial disease.
Muscle cell reveals subsarcolemmal abnormal mitochondrial accumulation (original magnification 10,000 x2).

Regarding genetic analysis, mitochondrial diseases of nDNA origin include defects in oxidative phosphorylation related proteins, or defects in nuclear encoded mitochondrial proteins for mtDNA integrity. Mitochondrial DNA origin includes point mutations, deletions, or depletion. In author‘s previous study, mtDNA gene mutations or deletions are found in a minority of pediatric patients[95], suggesting that most pediatric patients probably have a Mendelian recessive inheritance[97,101].

Treatment

The prognosis for MDs is related to patients' age at disease onset and the level of damage to cardiac function[97]. There have been few controlled therapeutic trials for MDs, and effective management of MDs is seldom possible[124]. Many physicians use "mitochondrial cocktails" of unproven efficiency, containing vitamins and other antioxidants. Importantly, primary or secondary quinone deficiency can show the clinical efficacy of oral coenzyme Q10 supplement[125]. Pyruvate dehydrogenase-deficient patients may benefit from thiamine administration and/or ketogenic diet[126,127]. Dichloacetate can lower the lactate level in MDs and may be useful for short-term treatment of episodes of severe lactic acidosis[128].

Summary

With a high level of clinical alertness and an organized diagnostic approach, most MDs can be accurately diagnosed early in their course. Greater familiarity with the variable clinical manifestations of MDs will facilitate the proper diagnosis and management cohort of diseases that present across all specialties. It is essential for physicians in this field

to continue to conduct research for new and effective treatments for patients.

REFERENCES

1. Luft R, Ikkos D, Palmieri G, Ernster L, Afzelius B. A case of severe hypermetabolism of nonthyroid origin with a defect in the maintenance of mitochondrial respiratory control: A correlated clinical, biochemical and morphological study. J Clin Invest 1962; 41: 1776-1804.
2. Engel WK, Cunningham GG. Rapid examination of muscle tissue: an improved trichome stain method for fresh-frozen biopsy sections. Neurology 1963; 13: 919-23.
3. Darin N, Oldfors A, Moslemi AR, Holme E, Tulinius M. The incidence of mitochondrial encephalomyopathies in childhood: clinical features and morphological, biochemical, and DNA abnormalities. Ann Neurol 2001; 49: 377-83.
4. Skladal D, Halliday J, Thorburn DR. Minimum birth prevalence of mitochondrial respiratory chain disorders in children. Brain 2003; 136: 1905-12.
5. Chi CS, Kao KP, Hsu NY, Lin E, Chen YC, Fu MC. Kearns-Sayre syndrome with proterinuria, glucosuria, copperuria and prolapse of the mitral valve: report of a case. J Formosan Med Assoc 1988; 87: 95-100.
6. Lee CC, Ko YM, Chen SS. Chronic progressive external ophthalmoplegia with NADH-CoQ reductase deficiency: report of a case. Chin Med J (Taipei) 1992; 50: 77-82.
7. Chen CH, Chi CS. Hypodensity in the basal ganglion demonstrated on CT brain scan studies in children. Chin Med J (Taipei) 1989; 44: 203-8.
8. Tsai ML, Hung KL, Chen TY. Subacute necrotizing encephalomyelopathy (Leigh's disease): report of a case. J Formos Med Assoc 1990; 89: 799-802.
9. Mak SC, Chi CS, Chen CH. Mitochondiral encephalomyopathy presenting with clinical Leigh's disease: report of a case. Chin Med J (Taipei) 1991; 47: 54-8.
10. Lii YP, Chi CS, Mak SC, Chen CH. Myoclonic epilepsy with raggered-red fibers: report of one case. Acta Paediatr Sin 1991; 32: 251-6.
11. Shih KD, Yen TC, Pang CY, Wei YH. Mitochondiral DNA mutation in a Chinese family with myoclonic epilepsy and ragged-red fiber disease. Biochem Biophys Res Commun 1991; 174: 1109-16.
12. Chi CS, Mak SC, Shian WJ, Chen CH. Oral glucose lactate stimulation test in mitochondrial disease. Pediatr Neurol 1992; 8: 445-9.
13. Chen CM, Huang CC, Lee CC, Wai YY, Hsi MS, Chen SS. Hypothalamic amenorrhea in a case of mitochondrial encephalomyopathy. J Formos Med Assoc 1992; 91: 1195-9.
14. Shian WJ, Chi CS, Mak SC. Intramyelin splitting in the spongiform lesions of Leigh syndrome. Acta Paed Sin 1993; 34: 308-13.
15. Mak SC, Chi CS, Chen CH, Shian WJ. Clinical manifestation of mitochondrial diseases in children. Acta Paed Sin 1993; 34: 247-56.
16. Yen TC, Wei YH. Comparison of mitochondrial DNA polymorphism between Chinese subjects and patients with mitochondrial myopathy. Chin Med J (Taipei) 1993; 51: 1-6.
17. Fang W, Huang CC, Lee CC, Cheng SY, Pang CY, Wei YH. Ophthalmologic manifestations in MELAS syndrome. Arch Neurol 1993; 50: 977-80.
18. Chen RS, Huang CC, Lee CC, Wai YY, His MS, Pang CY, et al. Overlapping syndrome of MERRF and MELAS: molecular and neuroradiological studies. Acta Neurol Scand 1993; 87: 494-8.
19. Wu TS, Lee CC, Lin JT, Hsu HH, Lin ST, Jong YJ, et al. Leigh disease (subacute necrotizing encephalomyelopathy): report of one case. J Formosan Med Assoc 1993; 34: 301-7.
20. Chi CS, Mak SC, Shian WJ. Leigh syndrome with progressive ventriculomegaly. Pediatr Neurol 1994; 10: 244-6.
21. Lee ML, Chaou WT, Yang AD, Jong YJ, Tsai JL, Pang CY, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis and strokelike episodes (MELAS): report of a sporadic case and review of the literature. J Formosan Med Assoc 1994; 35: 148-56.
22. Huang CC, Chen RS, Chen CM, Wang HS, Lee CC, Pang CY, et al. MELAS syndrome with mitochondrial tRNA(Leu(UUR)) gene mutation in a Chinese family. J Neurol Neurosurg Psychiatry 1994; 57: 586-9.
23. Kao KP, Tsai CP. Mitochondrial disease with encephalopathy or limb girdle myopathy: a report of five cases. Chin Med J (Taipei) 1994; 53: 173-8.
24. Kao KP. Mitochondrial disease with chronic progressive external ophthalmoplegia: clinical analysis of 19 cases. Chin Med J (Taipei) 1994; 53: 95-100.
25. Liou CW, Huang CC, Chee EC, Jong YJ, Tsai JL, Pang CY, et al. MELAS syndrome: correlation between clinical features and molecular genetic analysis. Acta Neurol Scand 1994; 90: 354-9.
26. Fang W, Huang CC, Chu NS, Lee CC, Chen RS, Pang CY, et al. Myoclonic epilepsy with ragged-red fibers (MERRF) syndrome: report of a Chinese family with mitochondrial DNA point mutation in tRNA(Lys) gene. Muscle Nerve 1994; 17: 52-7.
27. Huang WY, Chi CS, Mak SC, Wu HM, Yang MT. Leigh syndrome presenting with dystonia: report of one case. Acta Paed Sin 1995; 36: 378-81.
28. Chiang LM, Jong YJ, Huang SC, Tsai JL, Pang CY, Lee HC, et al. Heteroplasmic mitochondrial DNA mutation in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. J Formos Med Assoc 1995; 94: 42-7.
29. Chen CM, Huang CC. Gonadal dysfunction in mitochondrial encephalomyopathies. Eur Neurol 1995; 35: 281-6.
30. Hsu CC, Chuang YH, Tsai JL, Jong HJ, Shen YY, Huang HL, et al. CPEO and carnitine deficiency overlapping in MELAS syndrome. Acta Neurol Scand 1995; 92: 252-5.

31. Yang CY, Lam HC, Lee HC, Wei YH, Lu CC, Han TM, et al. MELAS syndrome associated with diabetes and hyperthyroidism: a case report from Taiwan. Clin Endocrinol (Oxf) 1995; 43: 235-9.
32. Huang CC, Chu NS, Shih KD, Pang CY, Wei YH. Distribution and clinical expression of the tRNA(Lys) mutation in mitochondrial DNA in MERRF syndrome. J Formos Med Assoc 1995; 94: 159-63.
33. Huang CC, Wai YY, Chu NS, Liou CW, Pang CY, Shih KD, et al. Mitochondrial encephalomyopathies: CT and MRI findings and correlations with clinical features. Eur Neurol 1995; 35: 199-205.
34. Shian WJ, Chi CS, Mak SC. Neuroimage in infants and children with mitochondrial disorders. Acta Paed Sin 1996; 37: 96-102.
35. Mak SC, Chi CS, Liu CY, Pang CY, Wei YH. Leigh syndrome associated with mitochondrial DNA 8993 T -> G mutation and ragged-red fibers. Pediatr Neurol 1996; 15: 72-5.
36. Lee WT, Wang PJ, Young C, Wang TR, Shen YZ. Cytochrome c oxidase deficiency in fibroblasts of a patient with mitochondrial encephalomyopathy. J Formos Med Assoc 1996; 95: 709-11.
37. Huang MY, Jong YJ, Tsai JL, Liu GC, Chiang CH, Pang CY, et al. Mitochondrial NADH-coenzyme Q reductase deficiency in Leigh's disease. J Formos Med Assoc 1996; 95: 325-8.
38. Hou JH, Wei YH. The unusual structures of the hot-regions flanking large-scale deletions in human mitochondrial DNA. Biochem J 1996; 318: 1065-70.
39. James AM, Wei YH, Pang CY, Murphy MP. Altered mitochondrial function in fibroblasts containing MELAS or MERRF mitochondrial mutations. Biochem J 1996; 318: 401-7.
40. Li JY, Kong KW, Chang MH, Cheung SC, Lee HC, Pang CY, et al. MELAS syndrome associated with a tandem duplication in the D-loop of mitochondrial DNA. Acta Neurol Scand 1996; 93: 450-5.
41. Chen RS, Huang CC, Chu NS, Chu CC, Shih KD, Pang CY, et al. Tissue distribution of mutant mitochondrial DNA in a patient with MERRF syndrome. Muscle Nerve 1996; 19: 519-21.
42. Huang CC, Chen RS, Chu NS, Pang CY, Wei YH. Random mitotic segregation of mitochondrial DNA in MELAS syndrome. Acta Neurol Scand 1996; 93: 198-202.
43. Yen MY, Lee HC, Liu JH, Wei YH. Compensatory elevation of complex II activity in Leber's hereditary optic neuropathy. Br J Ophthalmol 1996; 80: 78-81.
44. Chen RS, Hiang CC, Chu NS. Coenzyme Q10 treatment in mitochondrial encephalomyopathies: Short-term double-blind, crossover study. Eur Neurol 1997; 37: 212-8.
45. Chu CC, Huang CC, Fang W, Chu NS, Pang CY, Wei YH. Peripheral neuropathy in mitochondrial encephalomyopathies. Eur Neurol 1997; 37: 110-5.
46. Liu AM, Mak SC, Tsai CR, Chi CS. Childhood MELAS syndrome presenting with seizure and cortical blindness: a case report. Chin Med J (Taipei) 1998; 61: 730-5.
47. Mak SC, Chi CS, Tsai CR. Mitochondrial DNA 8993 T > C mutation presenting as juvenile Leigh syndrome with respiratory failure. J Child Neurol 1998; 13: 349-51.
48. Yang CC, Hwang CC, Pang CY, Wei YH. Mitochondrial myopathy with predominant respiratory dysfunction in a patient with A3243G mutation in the mitochondrial tRNA (Leu(UUR)) gene. J Formos Med Assoc 1998; 97: 715-9.
49. Chen JN, Ho KY, Juan KH. Sensorineural hearing loss in MELAS syndrome: case report. Kaohsiung J Med Sci 1998; 14: 519-23.
50. 麥淑珍、遲景上：從粒線體DNA看粒線體疾病。中兒醫誌1998; 39(增刊B): 24-8.
51. Pang CY, Huang CC, Yen MY, Wang EK, Kao KP, Chen SS, et al. Molecular epidemiologic study of mitochondrial DNA mutations in patients with mitochondrial diseases in Taiwan. J Formos Med Assoc 1999; 98: 326-34.
52. Lin YC, Lee WT, Wang PJ, Shen YZ. Vocal cord paralysis and hypoventilation in a patient with suspected Leigh disease. Pediatr Neurol 1999; 20: 223-5.
53. Huang CC, Chu CC, Pang CY, Wei YH. Tissue mosaicism in the skeletal muscle and sural nerve biopsies in the MELAS syndrome. Acta Neurol Scand 1999; 99: 125-9.
54. Wang LC, Lee WT, Tsai WY, Tsau YK, Shen YZ. Mitochondrial cytopathy combined with Fanconi's syndrome. Pediatr Neurol 2000; 22: 403-6.
55. Liou CW, Huang CC, Tsai JL, Liu JY, Pang CY, Lee HC, et al. Absence of maternal A3243G mtDNA mutation and reversible hyperglycemia in a patient with MELAS syndrome. Acta Neurol Scand 2000; 101: 65-9.
56. Thajeb P, Lee HC, Pang CY, Jeng CM, Huang SF, Wei YH. Phenotypic heterogeneity in a Chinese family with mitochondrial disease and A3243G mutation of mitochondrial DNA. Chin Med J (Taipei) 2000; 63: 71-6.
57. Liou CW, Huang CC, Lin TK, Tsai JL, Wei YH. Correlation of pancreatic beta-cell dysfunction with coenzyme Q(10) in a patient with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome and diabetes mellitus. Eur Neurol 2000; 43: 54-5.
58. Hsieh RH, Li JY, Pang CY, Wei YH. A novel mutation in the mitochondrial 16S rRNA gene in a patient with MELAS syndrome, diabetes mellitus, hyperthyroidism and cardiomyopathy. J Biomed Sci 2001; 8: 328-35.
59. Lien LM, Lee HC, Wang KL, Chiu JC, Chiu HC, Wei YH. Involvement of nervous system in maternally inherited diabetes and deafness (MIDD) with the A3243G mutation of mitochondrial DNA. Acta Neurol Scand 2001; 103: 159-65.
60. Lu CY, Tso DJ, Yang T, Jong YJ, Wei YH. Detection of DNA mutations associated with mitochondrial diseases by Agilent 2100 bioanalyzer. Clin Chim Acta 2002; 318: 97-105.
61. Huang CC, Kuo HC, Chu CC, Lao LY. Rapid visual recovery after coenzyme q10 treatment of leber hereditary optic neuropathy. J Neuroophthalmol 2002;

22: 66.
62. Huang CC, Kuo HC, Chu CC, Liou CW, Ma YS, Wei YH. Clinical phenotype, prognosis and mitochondrial DNA mutation load in mitochondrial encephalomyopathies. J Biomed Sci 2002; 9: 527-33.
63. Yen MY, Chen CS, Wang AG, Wei YH. Increase of mitochondrial DNA in blood cells of patients with Leber's hereditary optic neuropathy with 11778 mutation. Br J Ophthalmol 2002; 86: 1027-30.
64. Yen MY, Wang AG, Chang WL, Hsu WM, Liu JH, Wei YH. Leber's hereditary optic neuropathy-the spectrum of mitochondrial DNA mutations in Chinese patients. Jpn J Ophthalmol 2002; 46: 45-51.
65. Liao SL, Huang SF, Lin JL, Lai SH, Chou YH, Kuo CY. Syndrome of mitochondrial myopathy of the heart and skeletal muscle, congenital cataract and lactic acidosis. Acta Paediatr Taiwan 2003; 44: 360-4.
66. Chang CW, Chang CH, Peng ML. Leber's hereditary optic neuropathy: a case report. Kaohsiung J Med Sci 2003; 19: 516-21.
67. Su WY, Kao LY, Chen ST. Alternate-sided homonymous hemianopia as the solitary presentation of mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes syndrome. Chang Gung Med J 2003; 26: 199-203.
68. Yen MY, Chen YJ, Lin CH, Wang AG, Wei YH. Genetic analysis in Leber's hereditary optic neuropathy using the comparative genomic hybridization technique. Clin Experiment Ophthalmol 2003; 31: 435-8.
69. Hung HL, Kao LY, Huang CC. Clinical features of Leber's hereditary optic neuropathy with the 11778 mitochondrial DNA mutation in Taiwanese patients. Chang Gung Med J 2003; 26: 41-7.
70. Chang TM, Chi CS, Tsai CR, Lee HF, Li MC. Paralytic ileus in MELAS with phenotypic features of MNGIE. Pediatr Neurol 2004; 31: 374-7.
71. 遲景上：乳酸性酸血症及粒線體疾病，編輯：李明亮：代謝性疾病-台灣經驗，一版。台北：合記圖書出版社，2004: 133-48。
72. Chou YJ, Ou CY, Hsu TY, Liou CW, Lee CF, Tso DJ, et al. Prenatal diagnosis of a fetus harboring an intermediate load of the A3243G mtDNA mutation in a maternal carrier diagnosed with MELAS syndrome. Prenat Diagn 2004; 24: 367-70.
73. Liou CW, Lin TK, Huang FM, Chen TL, Lee CF, Chuang YC, et al. Association of the mitochondrial DNA 16189 T to C variant with lacunar cerebral infarction: evidence from a hospital-based case-control study. Ann N Y Acad Sci 2004; 1011: 317-24.
74. Chung SH, Chen SC, Chen WJ, Lee CC. Symmetric basal ganglia calcification in a 9-year-old child with MELAS. Neurology 2005; 65: E19.
75. Chang MC, Hung SC, Chen WY, Chen TL, Lee CF, Lee HC, et al. Accumulation of mitochondrial DNA with 4977-bp deletion in knee cartilage-an association with idiopathic osteoarthritis. Osteoarthritis Cartilage 2005; 13: 1004-11.
76. Liu CS, Cheng WL, Chen YY, Ma YS, Pang CY, Wei YH. High prevalence of the COII/tRNA(Lys) intergenic 9-bp deletion in mitochondrial DNA of Taiwanese patients with MELAS or MERRF syndrome. Ann N Y Acad Sci 2005; 1042: 82-7.
77. Lee HF, Lee HJ, Chi CS, Tsai CR, Chang P. Corneal clouding: An infrequent ophthalmic manifestation of mitochondrial disease. Pediatr Neurol 2006; 34: 464-6.
78. Yen MY, Wang AG, Wei YH. Leber's hereditary optic neuropathy: a multifactorial disease. Prog Retin Eye Res 2006; 25: 381-96.
79. Thajeb P, Ma YS, Tzen CY, Chuang CK, Wu TY, Chen SC, et al. Oculopharyngeal somatic myopathy in a patient with a novel large-scale 3,399 bp deletion and a homoplasmic T5814C transition of the mitochondrial DNA. Clin Neurol Neurosurg 2006; 108: 407-10.
80. Tseng FY. Sensorineural hearing loss, diabetes, and mitochondrial DNA mutation in Taiwan. Laryngoscope 2006; 116: 506.
81. Lee HF, Lee HJ, Chi CS, Tsai CR, Chang TK, Wang CJ. The neurological evolution of Pearson syndrome: case report and literature review. Eur J Paediatr Neurol 2007; 11: 208-14.
82. Hung PC, Wang HS. A previously undescribed leukodystrophy in Leigh syndrome associated with T9176C mutation of the mitochondrial ATPase 6 gene. Dev Med Child Neurol 2007; 49: 65-7.
83. Hung PC, Wang HS. Diffuse leukoencephalopathy: unusual sonographic finding in an infant with mitochondrial disease. J Clin Ultrasound 2007; 35: 277-80.
84. Li JY, Hsieh RH, Peng NJ, Lai PH, Lee CF, Lo YK, et al. A follow-up study in a Taiwanese family with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes syndrome. J Formos Med Assoc 2007; 106: 528-36.
85. Chen JC, Tsai TC, Liu CS, Lu CT. Acute hearing loss in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Acta Neurol Taiwan 2007; 16: 168-72.
86. Wu CC, Chiu YH, Chen PJ, Hsu CJ. Prevalence and clinical features of the mitochondrial m.1555A>G mutation in Taiwanese patients with idiopathic sensorineural hearing loss and association of haplogroup F with low penetrance in three families. Ear Hear 2007; 28: 332-42.
87. Wang SB, Weng WC, Lee NC, Hwu WL, Fan PC, Lee WT. Mutation of mitochondrial DNA G13513A presenting with Leigh syndrome, Wolff-Parkinson-White syndrome and cardiomyopathy. Pediatr Neonatol 2008; 49: 145-9.
88. Chou HF, Liang WC, Zhang Q, Goto Y, Jong YJ. Clinical and genetic features in a MELAS child with a 3271T>C mutation. Pediatr Neurol 2008; 38: 143-6.
89. Chen ST, Fan PC, Hwu WL, Wu MH. Fibrous dysplasia in a child with mitochondrial A8344G mutation. J Child Neurol 2008; 23: 1447-50.
90. Wang W, Seak CJ, Liao SC, Chiu TF, Chen JC. Cardiac tamponade: a new complication in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes. Am J Emerg Med 2008; 26: 382. e1-2.

91. Liu CS, Cheng WL, Kuo SJ, Li JY, Soong BW, Wei YH. Depletion of mitochondrial DNA in leukocytes of patients with poly-Q diseases. J Neurol Sci 2008; 264: 18-21.
92. Lee HF, Tsai CR, Chi CS, Lee HJ, Chen CC. Leigh syndrome: clinical and neuroimaging follow-up. Pediatr Neurol 2009; 40: 88-93.
93. Huang CC, Hsu CH. Mitochondrial disease and mitochondrial DNA depletion syndromes. Acta Neurol Taiwan 2009; 18: 287-95.
94. Hsu YC, Yang FC, Perng CL, Tso AC, Wong LJ, Hsu CH. Adult-onset of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (melas) syndrome presenting as acute meningoencephalitis: a case report. J Emerg Med 2009 Dec 23. [Epub ahead of print]
95. Chi CS, Lee HF, Tsai CR, Lee HJ, Chen LH. Clinical manifestations in children with mitochondrial diseases. Pediatr Neurol 2010; 43: 183-9.
96. Chi CS, Lee HF, Tsai CR, Chen CCC, Tung JN. Cranial magnetic resonance imaging findings in children with nonsyndromic mitochondrial diseases. doi: 10.1016/j. pediatrneurol. 2010.09.009
97. Scaglia F, Towbin JA, Craigen WJ, Belmont JW, Smith EO, Neish SR, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. Pediatrics 2004; 114: 925-31.
98. García-Cazorla A, De Lonlay P, Nassogne MC, Rustin P, Touati G, Saudubray JM. Long-term follow-up of neonatal mitochondrial cytopathies: a study of 57 patients. Pediatrics 2005; 116: 1170-7.
99. Debray FG, Lambert M, Chevalier I, Robitaille Y, Decarie JC, Shoubridge EA, et al. Long-term outcome and clinical spectrum of 73 pediatric patients with mitochondrial diseases. Pediatrics 2007; 119: 722-33.
100. Munnich A, Rötig A, Chretien D, Cormier V, Bourgeron T, Bonnefont JP, et al. Clinical presentation of mitochondrial disorders in childhood. J Inherit Metab Dis 1996; 19: 521-7.
101. Debray FG, Lambert M, Mitchell GA. Disorders of mitochondrial function. Curr Opin Pediatr 2008; 20: 471-82.
102. Bernier FP, Boneh A, Dennett X, Chow CW, Cleary MA, Thorburn DR. Diagnostic criteria for respiratory chain disorders in adults and children. Neurology 2002; 59: 1406-11.
103. Walker UA, Collins S, Byrne E. Respiratory chain encephalomyopathies: A diagnostic classification. Eur Neurol 1996; 36: 260-7.
104. Leigh D. Subacute necrotizing encephalomyelopathy in an infant. J Neurol Neurosurg Psychiatry 1951; 14: 216-21.
105. Kearns TP, Sayre GP. Retinitis pigmentosa, external ophthalmoplegia, and complete heart block: unusual syndrome with histologic study in one of two cases. AMA Arch Ophthalmol 1958; 60: 280-9.
106. Sandbank U, Lerman P. Progressive cerebral poliodystrophy – Alpers' disease. Disorganized giant neuronal mitochondria on electron microscopy. J Neurol Neurosurg Psychiatry 1972; 35: 749-55.
107. Pearson HA, Lobel JS, Kocoshis SA, Naiman JL, Windmiller J, Lammi AT, et al. A new syndrome of refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. J Pediatr 1979; 95: 976-84.
108. DiMauro S, Mendell JR, Sahenk Z, Bachman D, Scarpa A, Scofield RM, et al. Fatal infantile mitochondrial myopathy and renal dysfunction due to cytochrome –c-oxidase deficiency. Neurology 1980; 30: 795-804.
109. DiMauro S, Nicholson JF, Hays AP, Eastwood AB, Koenigsberger R, De Vivo DC. Benign infantile mitochondrial myopathy due to reversible cytochrome c oxidase deficiency. Ann Neurol 1981; 10: 90.
110. Fukuhara N, Tokiguchi S, Shirakawa, Tsubaki T. Myoclonus epilepsy associated with ragged-red fibers (mitochondrial abnormalities): disease entity or a syndrome? Light- and electron-microscopic studies of two cases and review of the literature. J Neurol Sci 1980; 47: 117-33.
111. Shoffner JM, Lott MT, Lezza AM, Seibel P, Ballinger SW, Wallace DC. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA(Lys) mutation. Cell 1990; 61: 931-7.
112. Mitsumoto H, Aprille JR, Wray SH, Nemni R, Bradley WG. Chronic progressive external ophthalmoplegia (CPEO): clinical, morphologic, and biochemistry studies. Neurology 1983; 33: 452-61.
113. Pavlakis SG, Phillips PC, DiMauro S, De Vivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann Neurol 1984; 16: 481-8.
114. Bardosi A, Creutzfeldt W, DiMauro S, Felgenhauer K, Friede RL, Goebel HH, et al. Myo-, neuro-, gastrointestinal encephalopathy (MNGIE syndrome) due to partial deficiency of cytochrome-c-oxidase. A new mitochondrial multisystem disorder. Acta Neuropathol 1987; 74: 248-58.
115. Vilkki J, SavontausML, Nikoskelainen EK. Genetic heterogeneity in Leber hereditary optic neuroretinopathy revealed by mitochondrial DNA polymorphism. Am J Hum Genet 1989; 45: 206-11.
116. Mäkelä-Bengs P, Suomalainen A, Majander A, Rapola J, Kalimo H, Nuutila A, et al. Correlation between the clinical symptoms and the proportion of mitochondrial DNA carrying the 8993 point mutation in the NARP syndrome. Pediatr Res 1995; 37: 634-9.
117. Kim JT, Lee YJ, Lee YM, Kang HC, Lee JS, Kim HD. Clinical characteristics of patients with non-specific and non-categorized mitochondrial diseases. Acta Paediatrica 2009; 98: 1825-9.
118. Rahman S, Blok RB, Dahl HH, Danks DM, Kirby DM, Chow CW, et al. Leigh syndrome: clinical features and biochemical and DNA abnormalities. Ann Neurol 1996; 39: 343-51.
119. Rötig A, Cormier V, Blanche S, Bonnefont JP, Ledeist F, Romero N, et al. Pearson's Marrow-Pancreas syndrome: A multisystem mitochondrial disorder in infancy. J Clin

Invest 1990; 86: 1601-8.
120. Van den Ouweland JMW, De Klerk JBC, Van de Corput MP, Dirks RW, Raap AK, Scholte HR, et al. Characterization of a novel mitochondrial DNA deletion in a patient with a variant of the Pearson marrow-pancreas syndrome. Eur J Hum Genet 2000; 8: 195-203.
121. Santorelli FM, Barmada MA, Pons R, Zhang LL, DiMauro S. Leigh-type neuropathology in Pearson syndrome associated with impaired ATP production and a novel mtDNA deletion. Neurology 1996; 47: 1320-3.
122. Haas RH, Parikh S, Falk MJ, Saneto RP, Wolf NI, Darin N, et al. Mitochondrial disease: a practical approach for primary care physicians. Pediatrics 2007; 120: 1326-33.
123. Dinopoulos A, Cecil KM, Schapiro MB, Papadimitriou A, Hadjigeorgiou GM, Wong B, et al. Brain MRI and proton MRS findings in infants and children with respiratory chain defects. Neuropediatrics 2005; 36: 290-301.
124. Chinnery P, Majamaa K, Turnbull D, Thorburn D. Treatment for mitochondrial disorders. Cochrane Database Syst Rev 2006; CD004426.
125. Rötig A, Mollet J, Rio M, Munnich A. Infantile and pediatric quinone deficiency diseases. Mitochondrion 2007; 7(Suppl): S112-21.
126. Naito E, Ito M, Yokota I, Saijo T, Matsuda J, Kuroda Y. Thiamine-responsive lactic acidaemia: role of pyruvate dehydrogenase complex. Eur J Pediatr 1998; 157: 648-52.
127. Wexler ID, Hemalatha SG, McConnell J, Buist NR, Dahl HH, Berry SA, et al. Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets. Studies in patients with identical mutations. Neurology 1997; 49: 1655-61.
128. Stacpoole PW, Kerr DS, Barnes C, Bunch ST, Carney PR, Fennell EM, et al. Controlled clinical trial of dichloroacetate for treatment of congenital lactic acidosis in children. Pediatrics 2006; 117: 1519-31.

粒線體疾病

遲景上

粒線體疾病為源於各種不同程度的粒線體能量代謝異常，造成腺苷三磷酸製造減少所產生的疾患，其臨床症狀非常廣泛且常為多器官系統疾病。

粒線體疾病臨床症狀相當多樣化，最常被影響的器官為腦部及肌肉系統，因為這些器官的能量需求最高。國內在 1988 年提出第一例粒線體個案報告後，臨床醫師逐漸瞭解此病。粒線體疾病在臨床上可分為兩大類：一類為症候群粒線體疾病，這類症候群粒線體疾病中各自有特定的臨床症狀，因此易於做臨床診斷；另一類為非症候群粒線體疾病，這類患者的症狀非常廣泛，臨床醫師不易早期診斷。

粒線體疾病的實驗室檢驗項目，包括乳酸、口服葡萄糖乳酸刺激試驗、有機酸分析、胺基酸分析及肉鹼蛋白檢測。另外，可利用腦部核磁共振攝影、腦部核磁共振氫頻譜、肌肉切片之特殊染色及電子顯微鏡檢查、呼吸鏈酵素檢驗、粒線體或細胞核基因分析等協助臨床診斷。雖然診斷工具種類很多，但沒有單一診斷工具具高度敏感性足以診斷粒線體疾病。

熟悉粒線體疾病多樣化的臨床表現可使臨床醫師對此疾病提高警覺性，藉助實驗室數據、病理發現、神經影像學表現及基因分析之結果綜合判斷，大部分粒線體疾病能在疾病早期確診，使病患得到各專科醫師的適當的照顧。

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關鍵詞：粒線體疾病、臨床表現、診斷工具、台灣

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Effect of Second Generation Antipsychotics on the Metabolic Syndrome Parameters in Patients with Schizophrenia

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Purpose: Metabolic syndrome is a focus of attention in the application of second generation antipsychotics, which has been regarded as a risk factor of Type 2 Diabetes and cardiovascular diseases and may raise the incidence of coronary heart disease and stroke by a factor of three. This study aims to explore the effect of second generation antipsychotics on the occurrence of the metabolic syndrome of Taiwanese patients.

Method: A total of 41 schizophrenic patients without personal and family history of diabetes were recruited and they were treated with the second generation antipsychotics. An examination including biochemical status, blood, waistline and body weight was given to them and a judgment of metabolic syndrome was executed according to the diagnosis principles of NCEP ATP III modified criteria for Asians before and one year after the treatment. The statistic method applied including means comparison and analysis of variance.

Result: There were 6 metabolic syndrome patients found (14.6%) before treatment and the prevalence increased to 26.8% (11 of 41 patients) after one-year of treatment. No new diabetes patients were observed after taking the antipsychotics. Triglyceride values increased by an average of 37 mg/dl and presented a significant variance for all of the patients after taking the second generation antipsychotics. With regards to the individual drug, Clozapine and Olanzapine caused a significant variance in triglyceride values. Body weight of all patients increased in an average of 5.3 kg and exhibited a significant variance after taking the antipsychotics. With respect to individual drug, patients displayed a remarkable variance in body weight after taking Olanzapine. No significant variances exhibited for other items of drugs being examined.

Conclusion: This study demonstrated that part of second generation antipsychotics could exert remarkable influences on body weight and triglyceride value. And patients after taking the antipsychotics presented a higher prevalence rate of metabolic syndrome than general Taiwanese and American adults.

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Key words: Metabolic, Antipsychotics, Schizophrenia

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Life span of schizophrenia patients is characteristically shorter than the normal individuals due to the high prevalent rate of diabetes.[1] Both chronic disease may be associated with the occurrence of metabolic syndrome.

The second generation of antipsychotics is superior over the first generation ones in terms of the effect and extra-pyramidal side effects and has been the first choice for treating schizophrenia. However it doesn't reduce the onset of metabolic syndrome,[2] (Table 1) and thus constitutes a great concern in application of these second generation of antipsychotics to the patients.[2] In addition, it has also been regarded as a risk factor for inducing Type 2 Diabetes and cardiovascular diseases as well as increasing the risk for coronary heart disease and stroke by a factor of three.[3]

Metabolic syndrome referred to the occurrence dyslipidemia, hypertension, hyperglycemia and abdominal obesity.[4] At present, National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) is used for diagnosis principles. In addition, waist circumference standard is set at 90 cm and 80 cm for male and female respectively according to body type of Asians.[5] Schizophrenia can lead to a higher possibility of metabolic syndrome, of which incidence is about 24-43% in male and 27-52% in female respectively.[6,7,8] Metabolic syndrome can not only shorten the longevity of schizophrenia patients, but also cause poor drug compliance,[9] thus treatment efficacy will be affected. Since domestic studies about metabolic syndrome were scanty, furthermore, body type, lifestyle and relevant diagnosis principles of metabolic syndrome of Taiwanese are different from those of western people, a study emphasizing a specific population of Taiwanese patients should be desirable. The results obtained through this special arrangement of subjects being investigated should serve as good reference and guide for the domestic physicians to comply. The specific aim for this study is therefore to investigate the effects of treating patients of Taiwanese schizophrenia with the second generation antipsychotics in the acquisition of metabolic syndromes.

METHOD

We conducted a study aiming at schizophrenia inpatients in a teaching hospital in central Taiwan from January 2005 to December 2007. The inclusive criteria were schizophrenia patients between the ages of 20-50 who hadn't taken any antipsychotics two months prior to hospitalization and met diagnosis principles of DSM IV. Exclusive criteria involve schizophrenia patients who also suffered from mental retardation and personal or family diabetes, had taken blood pressure drugs or had taken other antipsychotics during the treatment with second generation antipsychotics mentioned above. (Table 2)

An examination on biochemical status, blood, waistline and body weight was provided to the patients

Table 1. Second Generation Antipsychotics and Metabolic Effect

Antipsychotics	Weight gain	Risk for diabetes	Dyslipidemia
Clozapine	+++	+	+
Olanzapine	+++	+	+
Zotepine	++(+)	(+)	(+)
Risperidone	++	+/-	+/-
Quetiapine	++	+/-	+/-
Aripriprazole	+/-	-	-
Ziprasidone	+/-	-	-
Amisulpride	-	-	-

Table 2. Demographic Characteristics of Subjects

Age	38.2 ± 9.3
Sex (M/F)	24/17
Ethnicity	Taiwaneses
No. of Hypertensives	0
No. of Diabetics	0
No. of Smokers	12

and a judgment on metabolic syndrome was executed according to the diagnosis principles of NCEP ATP III modified criteria for Asians before and one year after the treatment with second generation antipsychotics. The judgment principles included fasting blood-glucose ≧100mg/dl; triglyceride ≧150 mg/dl; HDL-C less than 40 mg/dl and 50 mg/dl for male and female individually; blood pressure ≧130/85mmHg or taking blood pressure drug; waist circumference more than 90 cm and 80 cm for male and female respectively. Dosage of the second generation of antipsychotics taken by all patients was adjusted based on their symptom by the attending psychiatrist in charge and met treatment dosage recommendation of Bureau of National Health Insurance, Taiwan.

A total of 41 patients including 24 males and 17 females took part in the study. Among them, 16 patients took Risperidone, 9 patients took Olanzapine, 6 patients took Quetiapine, 5 patients took Clozapine and 5 patients took Zotepine. Statistic methods applied include means comparison and analysis of variance and data collected was analyzed by SPSS10.0.

RESULTS

Among the 41 patients, there were 6 patients (14.6%) and 11 patients (26.8%) suffering from metabolic syndrome before and after taking the antipsychotics respectively; the new 5 patients with metabolic syndrome included 1 patient taking Risperidone, 2

Table 3. Effect of Five Antipsychotics on Triglyceride values

				Paired Samples Test		
Antipsychotic	N	Baseline Mean	After One Year Mean	Paired Difference Mean	t	P(2-tailed)
Risperidone	16	112.8 ± 25.8	115.9 ± 26.2	18.2 ± 21.8	-0.88	.231
Olanzapine	9	108.6 ± 28.1	170.2 ± 26.6	61.6 ± 25.2	-2.82	.013
Quetiapine	6	113.8 ± 30.5	142.2 ± 36.8	28.4 ± 18.5	-1.42	.156
Clozapine	5	109.3 ± 21.6	165.8 ± 20.8	56.5 ± 15.7	-2.70	.034
Zotepine	5	114.4 ± 34.0	157.9 ± 20.5	43.5 ± 34.4	-2.18	.089
Total	41	111.8 ± 23.8	148.8 ± 22.1	37.0 ± 16.9	-3.26	.006

Table 4. Effect of Five Antipsychotics on Body Weight

				Paired Samples Test		
Antipsychotic	N	Baseline Mean	After One Year Mean	Paired Difference Mean	t	P(2-tailed)
Risperidone	16	60.2 ± 11.8	63.0 ± 11.3	2.8 ± 7.2	-0.67	.318
Olanzapine	9	61.4 ± 10.9	69.2 ± 10.1	7.8 ± 7.0	-2.60	.039
Quetiapine	6	57.4 ± 12.1	62.8 ± 13.8	5.4 ± 8.6	-1.65	.128
Clozapine	5	61.6 ± 12.7	68.9 ± 11.8	7.2 ± 9.1	-2.37	.064
Zotepine	5	64.4 ± 13.0	71.1 ± 10.5	6.7 ± 7.6	-2.21	.080
Total	41	60.7 ± 8.7	66.0 ± 7.7	5.3 ± 5.7	-2.79	.016

patients taking Olanzapine, 1 patient taking Clozapine and 1 patient taking Zotepine. No significant variances exhibited in different antipsychotics for the new patients with metabolic syndrome. No new diabetes patients appeared after taking the antipsychotics.

Triglyceride values increased by an average of 37 mg/dl and presented a significant variance ($p<0.01$) for all of the patients after taking the second generation antipsychotics; regarding individual drugs, Clozapine ($p<0.05$) and Olanzapine ($p<0.05$) caused significant variances in triglyceride values and the remained three drugs didn't create any significant variance in triglyceride contents. (Table 3)

Body weight of all patients increased by an average of 5.3 kg and exhibited a significant variance ($p<0.05$) after taking the antipsychotics; with respect to individual drugs, patients displayed a remarkable variance ($p<0.05$) on body weight after taking Olanzapine and patients taking other four kinds of antipsychotics didn't show any remarkable significance on body weight. (Table 4)

Other examinations involving fasting blood glucose, HDL-C, blood pressure and waist circumference didn't show any significant variance regardless for all patients or individual drug.

DISCUSSION

A study reported that among the second generation antipsychotics, Clozapine, Olanzapine, Risperidone and Quetiapine had caused the onset of 27, 39, 4 and 3 new diabetes patients respectively.[10] Most of them were diagnosed with high blood glucose within 6 weeks of treatment and it was believed that body weight increases induced the symptom, which was probably caused by histamine antagonism.[11] Clozapine and Olanzapine are closely correlated with body weight;[12,13] a meta-analysis article indicated both of the drugs could lead to body weight increasing in an average of over 4 kg during 6-12 weeks of treatment.[14,15]

At present, some studies also mentioned Clozapine and Olanzapine were most likely to induce metabolic syndrome.[16] However, our findings indicated although Clozapine and Olanzapine didn't significantly cause more patients with metabolic syndrome than other drugs, they did result in remarkable increase of triglyceride values. Another study suggested Olanzapine could have patients to be at 5 times more risk of getting hyperlipidemia, albeit Risperidone didn't show such effect.[17] Furthermore, this study also found Olanzapine could increase body weight remarkably, and the reasoning behind this observation might be related to the change of insulin secretion, peripheral insulin resistance and change of glucose uptake.[18] Not all diabetes have relations with body weight increases because some patients suffering from diabetes without body weight increase. Therefore, it can be speculated that antipsychotics exerts a direct influence that leads to such diabetes.[19] Some study mentioned it might be concerned with genes.[20,21,22]

Body weight increase is the reason most likely causing metabolic syndrome and diabetes.[10] However, it has been found that behavior treatment can reduce body weight.[23] Along the same view, another 12-week body weight control study discovered diet control can reduce body weight by 3.94 kg and sport can reduce body weight by 1.48 kg;[24] some drugs such as Amantadine that can treat extrapyramidal symptoms and Parkinson's disease can improve Olanzapine caused body weight.[25] Similarly, Metformin also can improve body weight gain,[26] and reduce risk of diabetes.[27] Currently, it is believed that metabolic syndrome should be followed closely once it appears and it exhibits a favorable prognosis.[28]

This study found 26.8% of patients suffered from metabolic syndrome after taking the second generation of antipsychotics, which is higher than the average prevalence rate (19.7%) of Taiwan provided by Bureau of Health Promotion, Department of Health (2006), and the American adults (10-22%). Our data also report lower prevalence rate of schizophrenia patients than that of other countries.[6,7,8] It is probably because patients who had personal or family diabetes history or had taken blood pressure drugs before the treatment were excluded from the study and the included patients were supplied with limited diets, required to obey regular life habits and do morning exercises. However,

our study underscores necessity of conducting a large-scale research due to small sample size used.

REFERENCES

1. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry 2000; 177: 212-7.
2. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004; 27: 596-601.
3. Wilson PW, D_Agostino RB, Parise H, Sullivan L, Meigs JB.Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005; 112: 3066-72.
4. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-97.
5. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care 2004; 27: 1182-6.
6. Suvisaari JM, Saarni SI, Perälä J, Suvisaari JV, Härkänen T, Lönnqvist J, et al. Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey. J Clin Psychiatry 2007; 68(7): 1045-55.
7. De Hert MA, van Winkel R, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. Schizophr Res 2006; 83(1): 87-93.
8. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005; 80(1): 19-32.
9. Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res 2004; 66: 51-7.
10. Cohen D. Atypical antipsychotics and new onset diabetes mellitus. An overview of the literature. Pharmacopsychiatry 2004; 37: 1-11.
11. Melkersson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000; 61: 742-9.
12. Eder U, Mangweth B, Ebenbichler C, Weiss E, Hofer A, Hummer M, et al. Association of olanzapine-induced weight gain with an increase in body fat. Am J Psychiatry 2001; 158(10): 1719-22.
13. Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000; 157(6): 975-81.
14. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante Mc, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156(11): 1686-96.
15. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005; 19(Suppl. 1): 1-93.
16. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry 2007; 68(Suppl 4): 8-13.
17. Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, et al. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 2002; 59(11): 1021-6.
18. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353(12): 1209-23.
19. McIntyre RS, Mancini DA, Basile VS. Mechanisms of antipsychotic- induced weight gain. J Clin Psychiatry 2001; 62(Suppl.23): 23-9.
20. Ellingrod VL, Perry PJ, Ringold JC, Lund BC, Bever-Stille K, Fleming F, et al. Weight gain associated with the -759C／T polymorphism of the 5HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet 2005; 134B(1): 76-8.
21. Tsai SJ, Hong CJ, Yu YW, Lin CH. -759C／T genetic variation of 5HT(2C) receptor and clozapine-induced weight gain. Lancet 2002; 360: 1790.
22. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet 2002; 359: 2086-7.
23. Brar JS, Ganguli R, Pandina G, Turkoz I, Berry S, Mahmoud R, et al. Effects of behavioral therapy on weight loss in overweight and obese patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry 2005; 66(2): 205-12.
24. Kwon JS, Choi JS, Bahk WM, Kim CY, Kim CH, Shin YC, et al. Weight management program for treatment-emergent weight gain in olanzapine-treated patients with schizophrenia or schizoaffective disorder: a 12-week randomized controlled clinical trial. J Clin Psychiatry 2006; 67(4): 547-53.
25. Graham KA, Gu H, Lieberman JA, Harp JB, Perkins DO. Double-blind, placebocontrolled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. Am J Psychiatry 2005; 162(9): 1744-6.
26. Baptista T, Hernandez L, Prieto LA, Boyero EC, Mendoza S. Metformin in obesity associated with antipsychotic drug administration: a pilot study. J Clin Psychiatry 2001; 62(8): 653-5.

27. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346(6): 393-403.

28. Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM et al. Physical health monitoring of patients with schizophrenia. Am J Psychiatry 2004; 161(8): 1334-49.

第二代抗精神病藥物對精神分裂症病患代謝症候群影響研究

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目的： 代謝症候群是第二代抗精神病藥物在治療使用上的一個關注焦點，它已被建立為第二型糖尿病及心血管疾病之危險因子，且增加冠狀動脈心臟病及中風三倍的危險性。本研究希望能進一步了解第二代抗精神病藥物對國人代謝症候群之影響。

方法： 41 位無個人及家族糖尿病史之精神分裂症患者，使用第二代抗精神病藥物治療，在使用前及使用一年後給予生化、血壓、腰圍檢查，並依 NCEP（National Cholesterol Education Program）標準判定是否有代謝症候群。統計方法為平均數差異檢定及變異數分析。

結果： 41 位個案用藥前有代謝症候群者 6 位（14.6%），用藥後有代謝症候群者 11 位（26.8%）。用藥後無新增糖尿病患者。全數病患在使用第二代抗精神病藥物前後三酸甘油酯平均增加 37 mg/dl 呈現顯著差異，以個別藥物而言，用藥前後三酸甘油酯呈現顯著差異的是 Clozapine 及 Olanzapine。全數病患在使用第二代抗精神病藥物前後體重平均增加 5.3kg 呈現顯著差異，以個別藥物而言，用藥前後體重呈現顯著差異為 Olanzapine。其它各項檢查未呈現顯著差異。

結論： 研究結果顯示在第二代抗精神病藥物用藥後，部份藥物對體重及三酸甘油酯有顯著影響。用藥後出現代謝症候群者，比一般國人及美國成年人盛行率為高。

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關鍵詞：Metabolic, Antipsychotics, Schizophrenia

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Study on the Influence of Second Generation Antipsychotics on QTc Interval Prolongation in Patients with Schizophrenia

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Purpose: QTc interval prolongation is a focus of attention in application of antipsychotics as it may induce polymorphoric ventricular tachycardia, or *torsade de pointes*, and cause fatal risk. This study aims to investigate the influence of second generation antipsychotics on QTc interval prolongation for Taiwanese patients with schizophrenia.

Method: A total of 64 schizophrenic patients without heart disease and stroke history were recruited and treated with second generation antipsychotics. An electrocardiogram examination was provided to them before and half year after the treatment respectively. The data were statistically evaluated using comparison of means and analysis of variances.

Result: Average QTc of all of the patients after medication was 420ms, no more than 500ms. QTc of the patients prolonged in an average of 10.8ms and presented significant variances after they took the second generation antipsychotics. In terms of individual drugs, Quetiapine (13.3ms) and Clozapine (23.8ms) caused significant variances in QTc; but the remaining three drugs didn't pose any notable variance. In comparison, Clozapine posed a remarkably greater effect on QTc than Risperidone and the remaining drugs didn't create any significant variance.

Conclusion: Findings of this study indicated QTc intervals of all of the patients after medication were no more than 500ms; however some drugs still created significant influences on QTc. Clinically, physicians should be cautious in prescribing for schizophrenia patients with heart disease or using drugs that may affect QTc together with antipsychotics.

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Key words: QTc prolongation, Antipsychotics, Schizophrenia

It has been indicated that some non-cardiac drugs can prolong cardiac repolarization, induce *torsade de pointes* and cause sudden cardiac death. [1,2] QTc interval prolongation has also been the main reason for some drugs being withdrawn from the market or marked with warnings over the last decade. [1]

Antipsychotics are significantly effective and necessary for both acute and chronic schizophrenia treatment. At present, researchers have found schizophrenia can raise cardiovascular mortality; [3,4,5]

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however, some antipsychotics also can prolong QTc interval, induce polymorphoric ventricular tachycardia and further cause ventricular fibrillation that may lead to death. [6,7] Such phenomenon has brought misgivings to both physicians who may prescribe the drugs for schizophrenia patients. Thus, QTc interval prolongation has currently been an important focus of attention in the application of antipsychotics.

First generation antipsychotics are dopamine inhibitors that are likely to cause extra-pyramidal side effects and typically effective for positive symptoms (e.g. hallucination or delusion), but poorly effective for negative symptoms (e.g. social withdrawal or avolition). In addition, the cognitive function of the patients can also be affected. For these reasons, these drugs have seldomly been used in the past. Developed in the 1990s, the second generation of antipsychotics is classified as being serotonin-dopamine antagonists (Table 1), which are effective for both positive and negative symptoms and have fewer side effects.

Recently, some reports have suggested that most of the second generation antipsychotics wouldn't create notable effects on QTc interval when they were used according to the dosages recommended.[8,9,10,11] However, a similar type of study, to our knowledge, has never been carried out in Taiwan. Thus, the purpose of our investigation here is to study the influence of second generation antipsychotics on QTc interval prolongation for patients in Taiwan. This information can be a useful reference for the treatment of schizophrenia in Taiwan.

METHOD

We conducted a study aiming at schizophrenia inpatients in a teaching hospital located in central Taiwan from January 2004 to December 2007. The inclusive criteria were schizophrenic patients between the ages of 20-50 who hadn't taken any antipsychotic one week prior to hospitalization and met diagnosis principles of DSM IV. The exclusive criteria included patients with heart disease or stroke history or had taken other antipsychotics during the treatment with the second generation antipsychotics. (Table 2)

An electrocardiogram examination was provided to the patients before and half year after the treatment with second generation antipsychotics respectively. All patients took the second generation antipsychotics in conformity to the treatment dosages recommended by the Bureau of National Health Insurance, Taiwan.

A total 64 patients including 37 males and 27 females took part in the study. Among them, 22 patients took Risperidone, 15 patients took Olanzapine, 10 patients took Quetiapine, 10 patients took Clozapine and 7 patients took Zotepine. Statistic methods applied

Table 1. Types of Second Generation Antipsychotics

Type and Generic Name	Trade Name	Year of FDA Approval
First Generation Antipsychotics		
Chlorpromazine	Wintermin	1954
Trifluoperazine	Stelazine	1958
Thioridazine	Melleril	1959
Haloperidol	Haldol	1970
Second Generation Antipsychotics		
Clozapine	Clozaril	1990
Risperidone	Risperdal	1993
Olanzapine	Zyprexa	1996
Quetiapine	Seroquel	1997
Zotepine	Lodopin	

Table 2. Demographic Characteristics of Subjects

Age	37.2 ± 6.7
Sex (M/F)	37/27
Ethnicity	Taiwaneses
No. of Hypertensives	8
No. of Diabetics	0
No. of Smokers	18

composed of means comparison and analysis of variance and data collected was analyzed by SPSS10.0.

RESULTS

Average QTc of the 64 patients was 409.2ms (SD 26.7ms) and 420.0ms (SD 28.1ms) respectively before and after they took the second-generation antipsychotics, with both values were smaller than 500ms. For all of the patients, the average QTc interval prolonged by 10.8 ms after they took second generation antipsychotics and Paired T-test indicated significant variances after the treatment ($T=-3.62$, $p<0.01$).

In terms of individual drugs, QTc increased in an average of 1.1ms, 12.0ms, 13.3ms, 23.8ms and 16.6ms for Risperidone, Olanzapine, Quetiapine, Clozapine and Zotepine respectively; Quetiapine ($t=-2.28$, $p<0.05$) and Clozapine($t=-4.79$, $p<0.01$) exhibited remarkable variances in QTc interval after the treatment and the remaining three drugs didn't cause any significant variance. (Table 3) In comparison, Clozapine posed a remarkably greater effect on QTc than Risperidone ($t=-2.86$, $p<0.05$) and the remaining drugs didn't present any significant variance in this way.

DISCUSSION

In 2000, a study involving 495 patients discovered the traditional antipsychotic Thioridazine could prolong QTc and this might have a bearing with some patients' death. Therefore, it has been recommended that electrocardiogram examination must be made weekly if the drug is used for a patient. On the other hand, some study has mentioned Haloperidol also may prolong QTc if its daily dosage exceeds the recommendation of 20mg, even it is relatively safer.[12]

It is generally believed that QTc interval prolongation refers to as QTc interval more than 440 ms and 460 ms for male and female respectively.[13] QTc over 500ms can increase the risk of *torsade de pointes* notably, hence it is suggested using it cautiously and replacing it with another antipsychotic.[14] Findings of this study indicated that QTc intervals of all of the patients were no more than 500 ms after they took the second generation antipsychotics; however, some drugs still created significant influences on QTc. Clinical physicians should be cautious in prescribing for patients with heart disease and long QTc or using drugs that may affect QTc including tricyclic antidepressants such as Quinine and Atropine together with antipsychotics.[6,15]

Currently, researchers have discovered many factors can cause QTc interval prolongation, including age,[16] gender,[15] gene,[17,18] and tumor necrosis factor;[19] also it is positively correlated with dosage according to the preliminary study.[20] This study was limited by insufficient samples and non-random

Table 3. Effect of Five Antipsychotics on QTc Interval

				Paired Samples Test		
Antipsychotic	N	Baseline Mean	After 6 months Mean	Paired Difference Mean	t	P(2-tailed)
Risperidone	22	416.9 ± 35.0	418.0 ± 29.9	1.1 ± 22.6	-0.24	.816
Olanzapine	15	410.2 ± 25.5	422.2 ± 26.6	12.0 ± 25.2	-2.28	.049
Quetiapine	10	397.8 ± 33.4	411.1 ± 36.8	13.3 ± 18.5	-1.85	.086
Clozapine	10	408.3 ± 21.6	432.1 ± 20.8	23.8 ± 15.7	-4.79	.001
Zotepine	7	400.4 ± 34.0	417.0 ± 20.5	16.6 ± 34.4	-1.28	.249
Total	64	409.2 ± 30.7	420.0 ± 28.1	10.8 ± 23.9	-3.62	.001

selection and so on, so it is necessary to carry out further investigations for determining the influence of second generation antipsychotics on QTc prolongation.

REFERENCES

1. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004; 350: 1013-22.
2. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart 2003; 89: 1363-72.
3. Joukamaa M, Heliövaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Mental disorders and cause-specific mortality. British Journal of Psychiatry 2001;179:498-502.
4. Osborn DPJ, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. Archives of General Psychiatry 2007;64:242-9.
5. Saha S, Chant D, McGrath J. A systematic reviewof mortality in schizophrenia. Is the differential mortality gap worsening over time. Archives of General Psychiatry 2007; 64(10): 1123-31.
6. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000; 355: 1048-52.
7. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. American Journal of Psychiatry 2001; 158(11): 1774-82.
8. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley CJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997; 17: 407-18.
9. Kang UG, Kwon JS, Ahn YM, Chung SJ, Ha JH, Koo YJ, et al. Electrocardiographic abnormalities in patients treated with clozapine. J Clin Psychiatry 2000; 61: 441-6.
10. Czekalla J, Beasley CM, Jr, Dellva MA, Berg PH, Grundy S. Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis. J Clin Psychiatry 2001; 62: 191-8.
11. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. Arch Gen Psychiatry 1997; 54: 549-57.
12. Kriwisky M, Perry GY, Tarchitsky D, Gutman Y, Kishon Y. Haloperidol-induced torsades de pointes. Chest 1990; 98: 482-4.
13. Childers R. Risk assessment: the 12-lead electrocardiogram. In: Malik M, editor. Risk of arrhythmia and sudden death. London: BMJ Books, 2001: 65-97.
14. European Agency for the evaluation of Medicinal Products. Human Medicines Evaluation Unit. The Committee for Proprietary Medicinal Products (CPMP). Points to consider: The assessment of the potential for QT interval prolongation by noncardiovascular medicinal products. March 1997 (CPMP/986/96).
15. Mackin P. Hum. Cardiac side effects of psychiatric drugs. Psychopharmacol Clin Exp 2008; 23: 3-14.
16. Mackin P, Young AH. QTc interval measurement and metabolic parameters in psychiatric patients taking typical or atypical antipsychotic drugs: a preliminary study. J Clin Psychiatry 2005; 66: 1386-91.
17. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell 2001; 104: 569-80.
18. Priori SG, Barhanin J, Hauer RNW, Haverkamp W, Jongsma HJ, Kleber AG, et al. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management. Circulation 1999; 99: 518-28.
19. Pollmächer T, Schuld A, Kraus T, Haack M, Hinze-Selch D. Zur klinischen Relevanz der Wirkung von Clozapin auf die Freisetzung von Zytokinen und löslichen Zytokinrezeptoren. Fortschritte der Neurologie-Psychiatrie 2001; 69(SH2): S65-74.
20. Drici MD, Wang WX, Liu XK, Woosley RL, Flockhart DA. Prolongation of QT interval in isolated feline hearts by antipsychotic drugs. J Clin Psychopharmacol 1998; 18: 477-81.

第二代抗精神病藥物對國人心電導延長影響研究

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目的： 心電導延長（QTc interval prolongation）是抗精神病藥物在治療使用上的一個關注焦點，它可能導致多形性心室心搏過速（polymorphoric ventricular tachycardia, or *torsade de pointes*），而出現致命的危險性。本研究希望能進一步了解第二代抗精神病藥物對國人心電導延長之影響。

方法： 64 位無心臟及中風病史之精神分裂症患者，使用第二代抗精神病藥物治療，在使用前及使用半年後給予心電圖檢查。統計方法為平均數差異檢定及變異數分析。

結果： 全體個案用藥後 QTc 平均為 420 毫秒，均小於 500 毫秒。全數病患在使用第二代抗精神病藥物前後 QTc 平均延長 10.8 毫秒，並呈現顯著差異。以個別藥物而言，用藥前後 QTc 呈現顯著差異的是 Quetiapine 13.3 毫秒及 Clozapine 23.8 毫秒，其餘三者未呈現顯著差異。在不同藥物相互比較方面，Clozapine 對 QTc 之影響顯著高於 Risperidone，其餘未呈現顯著差異。

結論： 研究結果顯示在第二代抗精神病藥物用藥後，雖 QTc 皆未達 500 毫秒，但部份藥物對 QTc 有顯著影響。臨床醫師在開立處方時，如遇有心臟疾病患者或併用其他可能影響 QTc 藥物時，仍應審慎為之。

（童綜合醫誌 2010; 4: 70-74）

關鍵詞： QTc prolongation, Antipsychotics, Schizophrenia

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Pregnancy Complicating Primary Mediastinal Large B-cell lymphoma: A Case Report and Literature Review

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Pregnancy complicating malignancy occurs 1 in 1000 deliveries. Lymphoma associated pregnancy has become increasing during the past few years and is the fourth most commonly occurred malignancy in pregnancy. Most of the cases reported are Hodgkin's lymphoma. Primary mediastinal large B-cell lymphoma is a rare disease of the subtype of non-Hodgkin's lymphoma. The optimal treatment remains non prospective and mainly dependent upon a personal experience due to its rarity. The issue becomes more complicated as its management involved an ethical issue with the characteristics of the non-Hodgkin's lymphoma being more advanced and wide spread as its counterpart during pregnancy.

We report a case of primary mediastinal large B-cell lymphoma associated with pregnancy that result in fetal demise at 29 gestational ages. Severe congested heart failure imposed by the chemotherapy was noted during the treatment period.
(Tungs' Med J 2010; 4: 75-78)

Key words: Mediastinal large B-cell lymphoma, pregnancy, chemotherapy

INTRODUCTION

Malignant lymphoma in pregnancy has become increasing with majority of it being Hodgkin's lymphoma. While most of the Hodgkin's lymphomas are well response to chemotherapy, the Non-Hodgkin's lymphoma usually presented with more advanced stage and disseminated disease due to its delay diagnosis. The primary mediastinal large B-cell lymphoma is a rare variant of the diffuse large B-cells and always presenting with chest symptoms. The proper treatment of this disease remain a clinically challenge for the physicians especially when it is found in pregnancy.

Case history

A 31-year-old woman, gravid 3 Para 0 presented with cough, progressive dsypnea and painless left neck and armpits swelling for 1 month was admitted for incisional biopsy. She has undergone a CT-guided biopsy over her anterior mediastinum 2 months before admission with the diagnosis of lymphoma.

The serum tumor markers assay were all within normal limits and blood chemistries including the lactate dehyhydrogenase (LDH) and CBC/DC were also within normal range.

Definitive pathology revealed a high grade diffuse large B cell lymphoma with the immunohistochemical staining showed a positive CD 20 and CD 10 with negative CD 30 originated from thymus with the diagnosis of primary mediastinal large B-cells lymphoma (PMLBCL) and was staged as clinically 2b (no symptoms of night sweat, weight loss etc). The imaging

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studies disclosed a large anterior and superior mediastinal mass encapsulating the thoracic vessels including the superior vena cava. The visceral organs including the spleen, liver as well as the periaortic lymph nodes were normal at that time.

She was referring to the Obstetrician department at 19 weeks gestational age and a growth-restricted fetus with grossly normal structures was noted under sonography. She developed shortness of breath with redness and swelling of upper face after admission. It was possible resulting from tumor compression of superior vena cava vessels. Under the impression of superior vena cava syndrome, high dose of prednisolone was given for symptoms relieving. Chemotherapy with M-CHOP was schedule for her malignant lymphoma after thorough discussion.

Painless dilatation of cervical os was noted at 29 gestational age and a demised fetus was delivered in the emergency room after completion of her fourth course of CHOP.

The patient developed severe dyspnea with severe congested heart failure shortly after completion of the tenth course of chemotherapy. Her heart function deteriorated to 10% of ejection fraction shown by cardiosonography. The condition resolved to almost normal after six months treated by a cardiologist. The follow up with serial imaging studies including chest and abdominal computed tomography and a post chemotherapy FDG-PET indicated small residual disease.

Her menstrual cycle resume to normal within 6 months after chemotherapy. She is now followed up regularly at the Obstetrics/Gynecology and hematologic department.

DISCUSSION

Malignant lymphoma is a rare occurrence in pregnancy and account for 1 over 6000 deliveries and ranked the fourth most frequent cause of malignancy in pregnancy after breast, cervical and ovarian cancer[1,2,3]. It can be classified into Hodgkin's and non-Hodgkin's diseases. The non-Hodgkin's disease presented more advanced and having a worse prognosis as compare to Hodgkin's diseases during pregnancy.

Aviles et al.[2] presented 16 cases of non-Hodgkin's lymphomas in pregnancy with 8 women in remission after follow up for 4 to 9 years after delivery,15 babies are alive and with normal follow up of 3 to 11 years.

Spitzer et al.[3] report a successful treatment of a 28 weeks gestational baby with radiotherapy planned from gestational age of 30 weeks and completion of chemotherapy after delivery resulting in a healthy baby and no evidence of tumor recurrence in the mother.

Pohlman et al.[4] reported 96 pregnant women with non-Hodgkin's lymphoma in whom only 39 out of 90 were alive and disease free for a median of 21 months after delivery, 4 were alive with disease, and 47 died with a median of 6 months (range < 1 to 36 months) after delivery. Women who were diagnosed to have disease during the third trimester had a better outcome than that found in first and second trimesters.

The primary mediastinal large B-cell lymphoma is one of the 14 malignant lymphomas probably arising from a putative thymic medullar B-cell and occurring more often in young females. It is characterized by a locally invasive anterior mediastinal mass, often producing cough, chest pain, dyspnea, and superior vena cava syndrome. Features associated with poor prognosis are poor performance status, pericardial effusion, bulky disease, high serum LDH at diagnosis, a compromised dose-intensity of anthracycline and cyclophosphamide in pregnancy[4,5,6]. The optimal treatment is therefore based primarily in the experience of non pregnant cohort with a general principle of treatment options depends primarily in stages of diseases, gestational age, maternal overall performance status as well as the ethical issues conflicting the caregivers, patients and the family as weu.

The overall prognosis of NHL is worse than the HL due to its delay diagnosis and wide dissemination at the time of diagnosis[6,7]. The general acceptable options would be a therapeutic abortion if diagnosed during the first trimester follow with combination chemotherapy or a single agent chemotherapy (preferably vincristine).

Definitive full dose chemotherapy with CHOP (cyclophospamide, anthracycline, vincristine, prednisolone) or CHOP-R[5,6,7](Rituximab) is suggest in

the second and third trimester without increasing risk of fetal outcome. Delivery should be initiated either vaginally or abdominally (depend on obstetrical indication) 3 to 4 weeks after the last course of chemotherapy to avoid the toxicity that are not excreted by the fetal renal system.

The demise of the fetus in this case report probably attributable to mothers' underlying abortional history which remained to be elucidated.

Low ejection fraction and severe congested heart failure resulting from an anthracycline chemotherapy regimens as report in this case series is possible avoidable. The clinician should pay more attention to patient's cardiac functions before or during each cycle of chemotherapy given. The alternative regimens with CEPP (cyclophosphamide, etoposide, prednisone, procarbazine); CEOP (cyclophosphamide, etoposide, vincristine, prednisone) could be considered in case of severe cardiac dysfunction.

As suggested by the International Workshop Criteria (IWC)[8] for the assessing response to treatment in non-Hodgkin's lymphoma, an FDG-PET is more useful in the FDG-avid lymphoma. While in the case of an variably avid FDG such as the case of primary mediastinal large B-cell lymphoma, an conventional CT scan rather than routine use of the PET in the follow up of treatment result is enough.

As far as the fertility and diseases status are concerned, an ethical issue invariably will encounter once the patient try to conceive again in the near future. Thus, it is better to follow up for 2 years as most of the recurrence will occurs during this period and careful obstetrical care including the elucidation of her habitual abortional history should be carried out before a successful pregnancy could be attained.

REFERENCES

1. Dina Steiner-Salz, Joachim Yahalom, Arnon Samuelov. Non-Hodgkin's lymphoma associated with pregnancy A report of six cases, with a reviews of the literature. Cancer 1985; 56: 2087-91.
2. Aviles A,Diaz-Maqueo JC,Torras V,Garcia EL,Guzman R. Non-Hodgkin's lymphomas and pregnancy: presentation of 16 cases Gynecol Oncol 1990; 37(3): 335-57.
3. Spitzer M, Citron M, IIardi CF, Saxe B. Non-Hodgkin's lymphoma during pregnancy. Gynecol Oncolo 1991;43(3):309-12.
4. Pohlman B,Macklis RM.Lymphoma and pregnancy. Semin Oncol 2000; 27(6): 657-66.
5. Lishner M, Zemlickis D,Sutcliffe SB,Koren G.Non-Hodgkin's lymphoma and pregnancy.Leul Lymphoma 1994; 14(5-6): 411-3.
6. Pereg D,koren G,Lishner M Haematologica. The treatment of Hodgkin"s and non-Hodgkin's lymphoma in pregnancy.2007; 92(9): 1230-7.
7. Hodby K, Fields PA. Management of lymphoma in pregnancy. Obstetric Medicine 2(2): 46.
8. Anne-Sophie Michallet, Bertrand Coiffier .Recent developments in the treatment of aggressive non-Hodgkin lymphoma. Hematolgie. 2009; 23(1): 11-23.
9. Ward FT,Weiss RB.Lymphoma and pregnancy.Semin Oncol .1989; 16(5): 397-409.
10. Martelli M Ferreri AJ, Johnson P. Primary meditational large B-cell lymphoma

妊娠合併原發性縱膈腔大 B 細胞淋巴瘤：一病例報告及文獻回顧

劉錦成

妊娠期間合併惡性腫瘤的機率約為每一千個活產中有一位，而其中血液淋巴瘤於過去幾年間有逐漸增加之趨勢。血液淋巴瘤為懷孕期間第四常見之癌症，而其中大部分為何杰金氏淋巴瘤。原發性胸膈腔大 B 細胞淋巴瘤是一非常罕見之非何杰金氏淋巴瘤。其治療方式大部份來自個人治療經驗。非何杰金氏淋巴瘤合併妊娠於臨床上通常較何杰金氏淋巴瘤更加晚期及廣泛性擴散，因此除了臨床上問題外還合併醫療倫理之難題。

我們報告了一例妊娠 29 週合併原發性胸膈腔大 B 細胞淋巴瘤，發生胎死腹中並因化療而造成之嚴重心臟鬱血性心衰竭。

（童綜合醫誌 2010; 4: 75-78）

關鍵詞：縱膈腔大 B 細胞淋巴瘤、妊娠、化學治療

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Acute Myocardial Infarction Induced by Neostigmine After a Laryngoscopic Microsurgery: A Case Report

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Perioperative myocardial ischemia is always the anesthesiologist's major concern. We report herein a case who suffered from acute myocardial infarction after undergoing laryngoscopic microsurgery.

A 65-year-old female was scheduled as an outpatient surgery and the anesthesiologist's first visit was at the nurse station of the operation room on the operation day. All other systemic diseases were denied by the patient except hypertension. The operation only took 5 minutes, and we kept the patient anesthetized for 30 minutes to allow recovery from muscle relaxant. Neostigmine (0.5 mg) and atropine (0.2 mg) were given intravenously because patient was awaked and weak. Unfortunately, large amount of pink frothy sputum appeared in the endotracheal tube 5 minutes later. We explained the patient's condition to her daughter. Through our conversation, we noted that this patient had coronary artery disease and increased frequency of chest pain was noted in recent one week. Coronary angiography was performed 3 hours later and 50-60% stenosis of left anterior descending artery was revealed.

The time of occurring of myocardial infarction was compatible with the time of intravenous administering of neostigmine. Neostigmine had been reported to cause coronary vasospasm. This patient would have unstable angina before operation. Unstable angina is a major risk of perioperative cardiovascular complications. This procedure should have to be postponed if we had been awared of this patient's recent condition earlier. Thus, we suggest that using neostigmine in such patients should be more cautious.
(Tungs' Med J 2010; 4: 79-82)

Key words: myocardial infarction, neostigmine, pulmonary edema, laryngoscopic microsurgery

INTRODUCTION

Perioperative myocardial ischemia is always the anesthesiologist's major concern. The rising proportion of aging population in Taiwan is accompanied by a high prevalence of cardiovascular disease. In noncardiac surgery, the incidence of perioperative myocardial infarction in the patient with ischemic heart disease is 5.6%[1]. The rate of mortality after perioperative myocardial infarction is 17%[2]. Cardiac complications usually happened during major (emergent, vascular, orthopaedic, thoracic, and intra-abdominal operations)[3] or long operations[4].

We report herein a case who suffered from acute myocardial infarction after undergoing laryngoscopic microsurgery, which was usually considered a minor

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and short procedure. This episode of acute myocardial infarction may be associated with the usage of Neostigmine.

CASE REPORT

A 65-year-old female was scheduled for laryngoscopic microsurgery due to hoarseness for 2 years. The patient was 153 cm in height and weighed 69 kg. This patient was scheduled as an outpatient surgery and the anesthesiologist's first visit was at the nurse station of the operation room on the operation day. The conversation between patient and anesthesiologist was fluent. Reviewing the chart revealed that asthma was diagnosed half year ago. She has a history of hypertension for 10 years. Otherwise, all other systemic diseases were denied by the patient. The electrocardiograph showed normal sinus rhythm. Laboratory data were all within the normal limits.

Anesthesia was initiated with intravenous injection of lidocaine 60 mg, fentanyl 100 μg, propofol 100 mg, and rocuronium 30 mg. The size of endotracheal tube was 6.0 and the intubating procedure was uneventful. Then anesthesia was maintained by 2.5% sevoflurane in 100% oxygen. The operation only took 5 minutes, and we kept the patient anesthetized for 30 minutes to allow recovery from muscle relaxant. Anticholinesterase was not considered to give to this patient first because of asthma. But the patient was still weak and breathed shallowly when she awaked. To avoid inducing asthma attack, the dose of neostigmine was administered intravenously as low as 0.5 mg and combined with 0.2 mg atropine. Unfortunately, 5 minutes later, large amount of pink frothy sputum appeared in the endotracheal tube and oxygen saturation measured by pulse oximeter dropped from 100% to 85%. Blood pressure elevated to 165/100 mmHg and heart rate increased to 125 /minute. Intravenous morphine 10 mg and furosemide 20 mg were administered. We explained the patient's condition to her daughter who was waiting outside of the operation room, and she admitted that her mother had coronary artery disease and she ever received percutaneous transarterial coronary angioplasty in other hospital 2 years ago. But increased frequency of chest pain was noted in recent one week. Under the impression of cardiogenic pulmonary edema, precordial cardial echography was performed in the operation room and it revealed akinesis of interventricular septum, anterior and apical wall. Before sending to cardiac intensive care unit, blood pressure decreased to 100/70 mmHg. Coronary angiography was performed 3 hours later and it revealed long segmental 50-60% stenosis of left anterior descending artery. Intra-aortic balloon pump was also inserted at that time. After the medical treatment, patient recovered well and discharged 8 days later without other major sequelae.

DISCUSSION

The incidence of postoperative pulmonary edema is uncertain. There have been reported an incidence of 0.2% in female patients undergoing hysteroscopic surgery[5]. Pulmonary edema could be resulted in many situations. Even fentanyl and nicardipine, which have often been used intraoperatively, had also been reported as an etiology of pulmonary edema[6,7].

At the moment of the occurring of pulmonary edema in an outpatient who denied cardiac disease firstly, our first impression was not cardiogenic pulmonary edema because surgical procedures involving the upper airway have a higher risk of negative-pressure pulmonary edema[8]. After the angina history told by the family, our first impression that the patient may have cardiogenic pulmonary edema.

During emergence from anesthesia, we gave neostigmine (0.5 mg) and atropine (0.2 mg) to reverse the action of neuromuscular blocking agent. This was not an appropriate decision because neostigmine had been reported to cause coronary vasospasm[9]. Neostigmine, even as low as 5–10 μg/kg IV, could evoked significant anticholinesterase actions. An atropine-neostigmine mixture in small incremental doses was also not appropriate because the dose of atropine was insufficient to block the cardiac muscarinic effects. Low dose of atropine even increases the release of acetylcholine and may enhance the cardiac effect of neostigmine[10].

The time of occurring of myocardial infarction was also compatible with the time of intravenous administering of neostigmine. Because pulmonary edema did not occurred until 5 minutes after administering neostigmine and the anticholinesterase effect of intravenous neostigmine is evident within 2 minutes and reach peak effect in 7~10 minutes[11]. Although coronary vasospasm had rarely been recognized in anesthetic practice with neostigmine using, we should use neostigmine more carefully in patients with coronary artery disease.

Receiving percutaneous transluminal coronary angioplasty (PTCA) prior to surgery is benefit to patients with coronary artery disease. But if the interval between PTCA and operation is within 30 days, this increases the incidence of adverse cardiac outcomes[12]. This means that if we discovered the patient's coronary artery diasease before operation and advised her to receive PTCA, this patient would not be appropriate to accept operation in a few days until 30 days later.

Though endoscopic procedures are usually considered as low risk surgeries[13]. This patient would have unstable angina before operation. Unstable angina is a major risk of perioperative cardiovascular complications[13]. This procedure should be postponed if we had been awared of this patient's recent condition. Using neostigmine in patients with coronary artery disease should also be more cautious.

REFERENCE

1. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW. Myocardial infarction after noncardiac surgery. Anesthesiology 1998; 88: 572-8.
2. Sprung Juraj, Abdelmalak Basem, Gottlieb Alexandru. Perioperative Myocardial Infarction (PMI): A Never-ending Story. Anesthesiology 2001; 94: 541.
3. Lucreziotti S, Foroni C, Fiorentini C. Perioperative myocardial infarction in noncardiac surgery: the diagnostic and prognostic role of cardiac troponins. J Intern Med 2002; 252: 11-20.
4. Fleisher, Lee A. Preoperative Assessment of the Patient with Cardiac Disease. *ASA Refresher Courses in Anesthesiology* 2005; 33: 79-88.
5. Baggish MS, Sze EH. Endometrial ablation: a series of 568 patients treated over an 11 year period. Am J Obstet Gynecol 1996; 174: 908-13.
6. Soto J, Sacristan JA, Alsar MJ. Pulmonary oedema due to fentanyl? (Letter) Anaesthesia 1992; 47: 913-4.
7. Bal Laurence, Thierry Stéphane, Brocas Elsa, Adam Marie, Van de Louw Andry, Tenaillon Alain. Pulmonary Edema Induced by Calcium-Channel Blockade for Tocolysis. Anesth Analg 2004; 99: 910-1.
8. Westreich Richard, Sampson Ian, Shaari, Christopher M, Lawson William, Negative-Pressure Pulmonary Edema After Routine Septorhinoplasty: Discussion of Pathophysiology, Treatment, and Prevention. Archives of Facial Plastic Surgery 2006; 8: 8-15.
9. Kido K, Mizuta K, Mizuta F, Yasuda M, Igari T, Takahashi M. Coronary vasospasm during the reversal of neuromuscular block using neostigmine. Acta Anaesthesiol Scand 2005; 49: 1395-6.
10. Evers AS, Maze M. Anesthetic Pharmacology: Physiologic Principles and Clinical Practice. New York: Churchill Livingstone, 2004: 614.
11. Donati F, McCarroll SM, Antzaka C, McCready D, Bevan DR. Dose–response curves for edrophonium, neostigmine, and pyridostigmine after pancuronium and d-tubocurarine. Anesthesiology 1987; 66: 471-6.
12. Posner Karen L, Van Norman Gail A, Chan Victor. Adverse Cardiac Outcomes After Noncardiac Surgery in Patients with Prior Percutaneous Transluminal Coronary Angioplasty. Anesth Analg 1999; 89: 553-60.
13. Eagle Kim A, Berger Peter B, Calkins Hugh, Chaitman Bernard R, Ewy Gordon A, Fleischmann Kirsten E, et al. Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery-Executive Summary: A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Anesth Analg 2002; 94: 1052-64.

喉鏡顯微手術後發生 Neostigmine 誘發的急性心肌梗塞：個案報告

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手術期間的心肌缺血一直以來是麻醉醫師最關心的事情之一，我們報告一位進行喉鏡顯微手術之後發生急性心肌梗塞的個案。

一位 65 歲女性被安排做門診手術，麻醉醫師的第一次訪視是在手術當日的開刀房護理站，除了高血壓，病患本人否認任何的系統性疾患。手術時間只花了五分鐘，接下來的 30 分鐘病患繼續維持在麻醉狀態，以等待肌肉鬆弛劑藥效降低，病患甦醒後仍很虛弱，所以從靜脈給予 neostigmine 0.5 毫克與 atropine 0.2 毫克，很不幸的，5 分鐘後氣管內管內出現了大量粉紅色泡沫狀痰，我們向病患女兒解釋病患狀況後，病患女兒才提到病患有冠狀動脈疾病病史，並且最近一週胸痛頻率有增加情形，三個小時後我們為病患做了冠狀動脈攝影 , 顯示左前降支有 50-60% 的狹窄。

發生心肌梗塞的時間與靜脈給予 neostigmine 的時間相當符合，neostigmine 曾經報告引起冠狀動脈血管痙攣，這位病患在術前可能已有不穩定性心絞痛，由於不穩定性心絞痛是手術期間發生心血管併發症的主要危險因子，如果我們在術前即得知病患最近的病情，這個手術就應該延後，使用 neostigmine 在這類的病患也須特別小心。

（童綜合醫誌 2010; 4: 79-82）

關鍵詞：心肌梗塞、neostigmine、肺水腫、喉鏡顯微手術

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Aneurysm of the Left Atrium: Detection by Using Multidetector-Row Computed Tomography Imaging

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Left atrial aneurysms are quite rare and usually develop from the left atrial appendage. Life-threatening complications including intracardiac thrombus, embolism and arrhythmia may occur in these patients, which is why surgical intervention has been recommended by various authors. Application of multidetector-row computed tomography (MDCT) in cardiac imaging has become popular in recent years. It can be used in the evaluation of coronary artery, myocardial viability, myocardial perfusion, cardiac wall motion and heart valves. In the field of cardiac surgery follow-up and complex congenital heart disease, MDCT also plays an important role. Two patients are presented here with left atrial aneurysms involving the right lower portion of the left atrial walls which were diagnosed with multidetector-row computed tomography and post-processing imaging. Virtual endocardioscopy was performed to help interventional cardiologists in assessing the possibility of percutaneous closure of the left atrial aneurysm. 3D volume rendered images further clarifying the spatial relationship between an aneurysm and adjacent structures, thereby facilitating surgical planning.
(Tungs' Med J 2010; 4: 83-88)

Key words: Aneurysm, left Atrium, multidetector- row computed tomography, MDCT

INTRODUCTION

Aneurysms of the left atrium are rare abnormalities. The patient age at presentation varies widely. They can be congenital or acquired. Because of the risk of life-threatening complications, aneurysm resection and mitral valvuloplasty are recommended even in asymptomatic cases. We present two cases of left atrial aneurysms, including their clinical presentation and multidetector-row computed tomography imaging. 3D volume rendered images were performed to clarify the spatial relationship between the aneurysm and adjacent structures, such as mitral valve and pulmonary veins, thereby facilitating treatment planning.

CASE REPORTS

Case 1.

A 27-year-old female with an endocardial cushion defect had undergone previous repairs at 6 and 17 years of age. She had led an uneventful life after the second operation until a three-hour loss of consciousness while she was watching television. Frequent episodes of cardiac arrhythmia were noted at the emergency department. Her condition stabilized after anti-arrhythmic agents and pacemaker placement. Tracing her medical history, occasional palpitation and progressive abdominal distention were noted.

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Initially chest roentgenogram showed cardiomegaly with an obvious double-contoured the right heart border (Figure 1A). Subsequent abdominal ultrasound showed hepatomegaly.

Case 2.

A 13-year-old boy with aortic stenosis received aortic valve replacement at 7 years old. He was admitted because of progressive exertional dyspnea. Cardiomegaly and an obvious double-contoured the right heart border were noted on a chest roentgenogram (Figure 2A).

Both patients had multidetector-row computed tomography (MDCT) scans, along with 3D post-processing reconstruction. MDCT images identified left atrial aneurysms in both patients. Both aneurysms arose from right inferior portion of left atrium and without involvement of mitral valve. The right lower

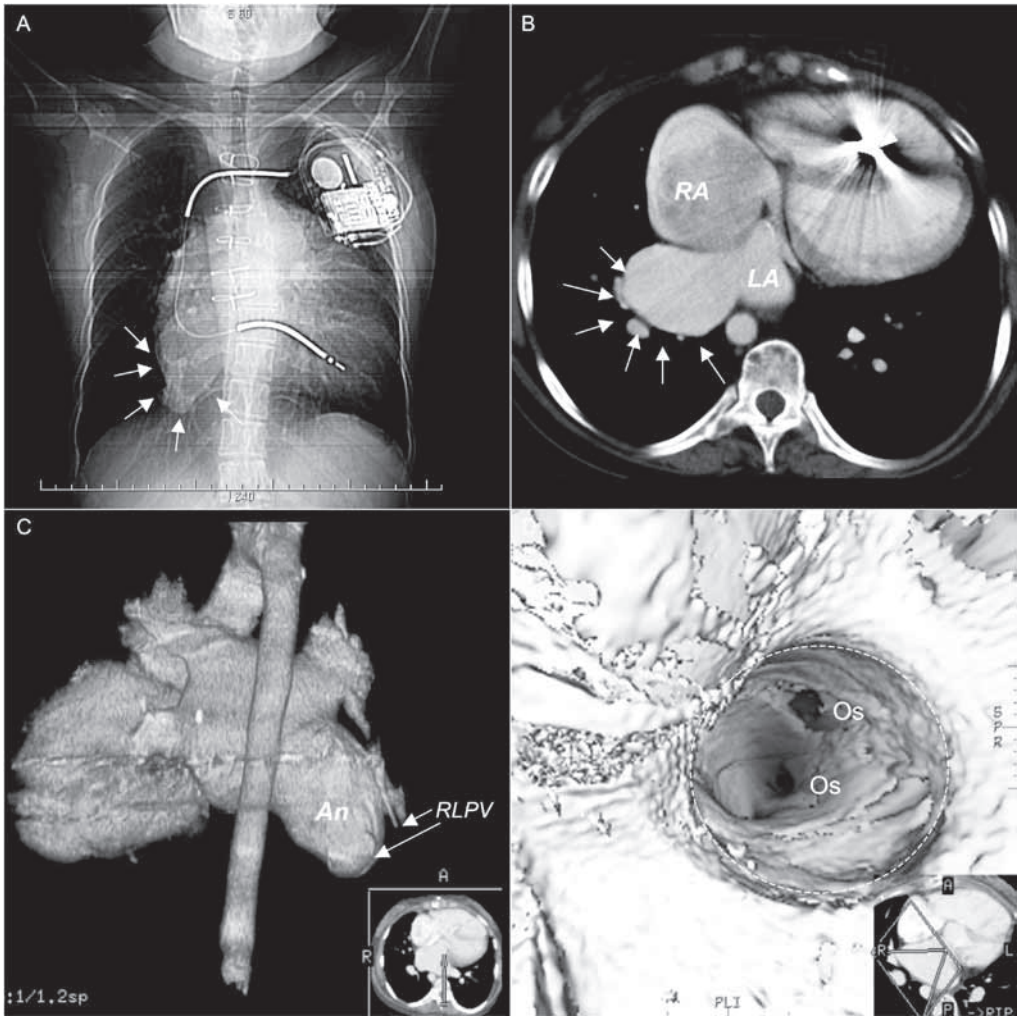

Fig. 1 A 27 year old female with an endocardial cushion defect that had undergone previous repair on two occasions. (A) Chest roentgenology showing cardiomegaly with an obvious double contour of the right heart border (arrows). (B) An axial contrast enhanced CT scan showing a focal aneurysmal dilatation (arrows) of the right lower portion of the LA. Severe artifact caused by a pacemaker wire is marked with an arrowhead. (C) A 3D image (posterior view) showing a LA aneurysm (*An*). The relationship of this aneurysm to the right lower pulmonary vein (*RLPV*) is clearly shown. (D) A virtual endocardioscopic image clearly showing the large opening of this aneurysmal sac (white dashed circle) and ostia (Os) of the right lower pulmonary veins.

pulmonary veins entered the aneurysm were revealed in both patients (Figure 1B and 2B). 3D volume rendering and virtual endocardioscopy images were reconstructed to better demonstrate the relationship between the aneurysms and pulmonary veins (Figure 1C, 1D, 2C and 2D). Both patients were given prophylactic anti-coagulant medications only. A follow-up CT scan five months later in first case showed that the aneurysm had not changed in size and no any intracardiac thrombus was seen.

DISCUSSION

Left atrial aneurysms (LAA) are quite rare and are potentially life threatening due to their complications which include intracardiac thrombus, embolism, arrhythmias and heart failure. [1, 2, 3] Most LAA cases are congenital[1,4] but it can be acquired.[5] Congenital

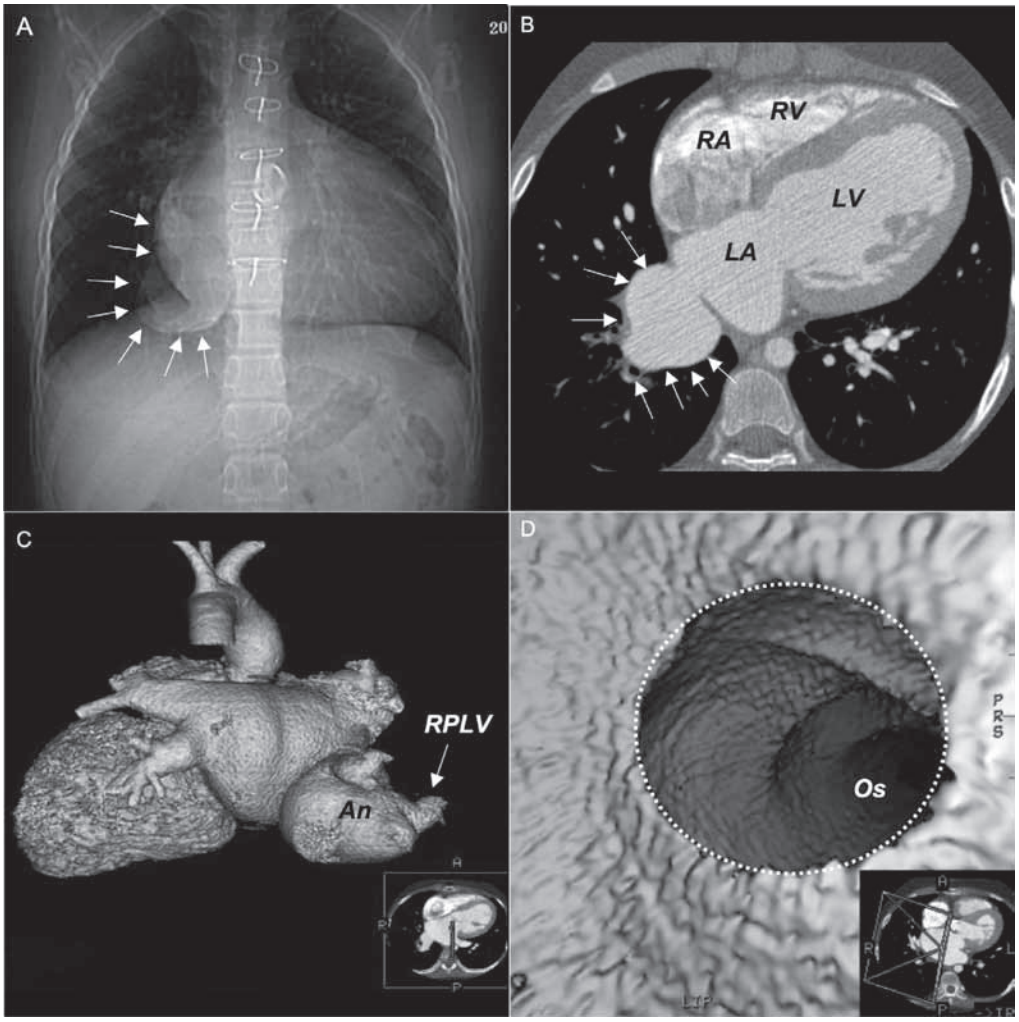

Fig. 2 A 13 year old boy with aortic stenosis who had previously undergone aortic valve replacement. (A) Chest roentgenology showing mild cardiomegaly with an obvious double contour of the right heart border (arrows). (B) An axial cut contrast enhanced CT scan showing focal aneurysmal dilatation (arrows) of the right lower part of the left atrium (LA). (C) A 3D volume rendering image (posterior view) showing a LA aneurysm (*An*) and its relationship to the right lower pulmonary vein (*RLPV*). (D) A 3D virtual endocardioscopic image clearly shows the large opening of the aneurysmal sac (white dashed circle) and ostium (Os) of the RLPV. LV = left ventricle; RA=right atrium; RV = right ventricle

type LAA could result from congenital virus infection of atrial wall or an absence of myoblasts in the atrial wall.[6] Acquired type LAA is thought to result from valvular disease or predisposing infection that weakens the myocardium. LAA most commonly arises from the left atrial appendage (68%), but can also arise from the atrial wall (32%), [4] as our patients. Turbulent flow can develop within the aneurysmal sac and lead to thrombus formation. Furthermore, the aneurysm can create an ectopic focus that can lead to an atrial arrhythmia. [1] Surgical resection of the aneurysm is therefore recommended in order to eliminate a potential source of emboli and arrhythmias. [1]

In our cases, both patients had undergone cardiac surgeries during their childhood and cardiopulmonary bypass was setup during operation. In cardiopulmonary bypass procedure, encircling of the caval veins was necessary. Because the LAA in both cases was at the right inferior portion of the left atrium near the inferior vena caval orifice, it is tempting to speculate that the LAA aneursym observed in our cases may result from the iatrogenic injury to the left atrial wall during cardiopulmonary bypass procedure. Thus far, LAA resulted from a complication of surgery has not been reported elsewhere in the literature.

It is important to assess how the neck of the aneurysm relates anatomically to the mitral valve and pulmonary veins since the aneurysm may extend into the mitral valve [5] or involve the pulmonary veins, as our two cases have demonstrated. If the aneurysm involves the mitral valve, a partial annuloplasty may be required to re-establish mitral competence. If the aneurysm involves the pulmonary veins, percutaneous closure by an interventional cardiologist is contra-indicated as it may compromise pulmonary venous return.

Most LAA diagnoses are incidental and unexpected. Physical examination is often unremarkable, and chest radiography may be normal or sometimes, a bulging right heart border. Transthoracic echocardiography may fail to fully delineate the extent of the aneurysm. Transesophageal echocardiography (TEE) is an excellent diagnostic tool for LAA, [2] but it is invasive and operator dependent. TEE was performed on the first patient but failed to diagnose the LAA. Cardiac angiography is also useful for diagnosing aneurysm, but may fail to fully define the anatomy of the pulmonary vein ostia, and does not allow 3D visualization.

Fortunately, multidectector-row computed tomography (MDCT) provides a unique approach to evaluation of the cardiac patient, which allows the physician to visualize coronary anatomy, the cardiac morphology and function. Combined with stress and rest myocardial perfusion imaging with coronary CT angiography in a single study can provide diagnostic accuracy comparable to single-photon-emission computed tomography (SPECT) [7]. These capabilities of multiplanar reconstruction and post-processing imaging provide excellent tool for complex congential heart disease and post-cardiac surgery evaluation. In our two presented cases, MDCT clearly demonstrated the neck of aneurysms and the relationship between aneurysm, mitral valve and right inferior pulmonary veins and provided almost all the information required for interventional planning.

To the best of our knowledge, no previous reports have discussed the use of MDCT with 3D virtual endocardioscopy[9] for the diagnosis of left atrial aneurysm and demonstrated the aneurysmal orifice and adjacent important structure. By helping to clarify the spatial relationships between an aneurysm and adjacent structures, 3D volume rendering and virtual endocardioscopic imaging can be of great assistance to the cardiac surgeon or interventional cardiologists when planning the management of a left atrial aneurysm.[10]

REFERENCES

1. Thadani U, Whitaker W, Watson DA. Congenital intrapericardial aneurysms of the left atrium. Thorax 1975; 30: 102-9.
2. Sigfusson G, Park SC, Ettedgui JA, Newman B, Siewers RD, Neches WH Intrapericardial left atrial aneurysm: noninvasive diagnosis. Pediatr Cardiol.1997; 18: 240-3.
3. Wang T, Anagnostopoulos CE, Resnekov L. Aneurysm of the body of the left atrium presenting with chest pain. Chest. 1975; 67(2): 226-8.
4. Gold JP, Afifi HY, Ko W, Horner N, Hahn R. Congenital giant aneurysms of the left atrial appendage. J Card Surg 1996; 11: 147-50.
5. Morales JM, Patel SG, Jackson JH, Duff JA, Simpson JW. Left atrial aneurysm. Ann Thorac Surg 2001; 71: 719-22.

6. Mansour E, Aldousany A, Arce1 O, Subramanian S, Ashraf MH. Recurrent congenital left atrial aneurysm in a newborn. Pediatr Cardiol. 1998; 19(2): 165-7.
7. Blankstein R, Shturman LD, Rogers IS, Rocha-Filho JA, Okada DR, Sarwar A, et al. Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography. J Am Coll Cardiol 2009; 54: 1072-84.
8. Robert CG, Alan HM, Leslie Ciancibello. Multi-section CT evaluation of the reoperative cardiac surgery patient. Radiographics 2003; 23: S3-17.
9. Chen HW, Chen SJ, Chiu IS. Computed tomographic virtual cardioscopy in a case of left atrial myxoma. Heart. 2004; 90(2): e8.
10. Lacomis JM, Wigginton W, Fuhrman C, Schwartzman D, Armfield DR, Pealer KM. Multi-detector row CT of the left atrium and pulmonary veins before radio-frequency catheter ablation for atrial fibrillation. Radiographics 2003; 23 (Special Issue): S35-48.

左心房動脈瘤多切面電腦斷層影像及其臨床意義

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左心房動脈瘤是一個罕見的疾病，大多是由左心耳處形成。患有左心房動脈瘤的病患臨床上可能會發生血栓、栓子或是心律不整等併發症。這也是為何許多文獻建議這類疾病需要進行積極治療的原因。近幾年來，多切面電腦斷層在心臟影像方面有了長足的進步。可以應用於評估冠狀動脈、心臟瓣膜、缺血性心臟病之後的心肌存活或是心臟壁運動的種種變化，甚至複雜的小兒先天心臟異常以及心臟手術的術後追蹤等等…。多切面電腦斷層都扮演著愈來愈重要的角色。這篇文章裡報告了兩個左心房動脈瘤病例的多切面電腦斷層的原始橫切面影像以及經由工作站重組之後的立體影像。這兩個病例的左心房動脈瘤皆位於左心房的右下方，與過去文獻所報告的案例不同。重組的心臟立體影像可以由心臟內部及心臟外部觀察左心房動脈瘤與左心房及鄰近大血管的關係，幫忙外科醫師或介入性心臟科醫師做治療上更精確的評估。
（童綜合醫誌 2010; 4: 83-88）

關鍵詞：動脈瘤、左心房、多切面電腦斷層

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小兒突發性耳聾

陳建志[1,2]　湯耀貿[3]　陳登郎[4*]

突發性耳聾好發於 40~60 歲，不足 15 歲者約佔所有突發性耳聾患者的 5%。小兒突發性耳聾可能病因為內耳發育畸形、內耳淋巴水腫、外淋巴瘻管、腮腺炎耳聾、積液性中耳炎、偏頭痛、大前庭導水管症候群或原因不明。一 10 歲小女孩，在罹患病毒性腮腺炎半年後，突發左側聽力障礙及耳鳴。症狀持續了 5 日，自地方診所轉診至本院，囑臥床休息，並靜脈注射類固醇及血漿容積擴張劑治療。患耳 250~4,000Hz 處之平均聽力閾值在住院後 1 日時為 61dBHL，住院後 5 日時為 30dBHL，出院後 2 日時為 15dBHL，出院後 3 週時為 2dBHL，聽力共恢復了 59dBHL。所有血液學檢查均為正常，梅毒血清測試、人類免疫缺乏病毒 IgM&IgG 抗體及其他病毒 IgM 抗體檢查均為陰性，而複響測試、語音辨識度檢查、聽性腦幹電波反應檢查、顳骨電腦斷層及腦部磁振造影均無異常發現。經過 2 年的追蹤，情況依然穩定。因此，本個案之突發性耳聾目前實為原因不明，根據病史，仍有可能是腮腺炎病毒感染所致，尚需長期的追蹤，以排除內耳淋巴水腫或偏頭痛的可能。

（童綜合醫誌 2010; 4: 89-92）

關鍵詞：突發性耳聾、小兒、病毒性腮腺炎耳聾、內耳淋巴水腫、偏頭痛

前　言

突發性耳聾（sudden deafness）定義爲 3 天內之純音聽力圖上連續 3 個頻率之平均聽力閾值喪失 30dBHL 以上，通常爲單側發病，雙側較爲罕見，好發於 40~60 歲的成年人（35.10%），平均年齡是 43.20 歲 [1]，大部分患者會有耳鳴或眩暈，病因目前尚不明，可能與腦部病變 [2]、病毒 [3]、血管性病變 [4] 或自體免疫 [5] 有關。不足 15 歲者約佔所有患者的 5% [6]，由於他們對於聽力的表達能力不一，或長輩未曾察覺，往往失去了早期診斷及治療的契機，其實，這種急症的診斷並不困難，只要簡單的理學檢查及音叉測試就可避免誤診。

病　例

一 10 歲小女孩，曾於 2007 年 3 月得過急性病毒性腮腺炎（acute viral parotitis, mumps），並無其他過去病史。半年後，因突發左側耳鳴及聽力障礙 5 天，無眩暈、頭痛或其他神經學之病症，在地方診所的聽力圖顯示左側 500Hz、1,000Hz、2,000Hz 及 4,000Hz 處之聽力閾值分別爲 70、60、50 及 45dB hearing level (dBHL)，遂轉診至本院。理學檢查顯示兩側耳膜正常，256Hz 之音叉測試顯示兩耳 Rinne 測試均爲陽性，Weber 測試偏向右側，臆斷爲突發性之左側感覺神經性聽障，隨即收治住院。住院期間囑咐臥床休息，根據體重 20kg，不僅每日靜脈注射血漿容積擴張劑 Dextran 40（Low molecular Dextran-Dextrose injection）500 ml，並給予副腎皮質素 methylprednisolone sodium succinate（Solu-Medrol）一前 3 日爲每日 2 次各 20mg，後 2 日爲每日 1 次 20mg。血液學檢查包括一般血球、電解質、腎功能、肝功能、飯前血糖值及抗核酸抗體指數（anti-nuclear antibody）均爲正常值，梅毒血清測試（rapid plasma reagin）爲陰性，

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人類免疫缺乏病毒（human immunodeficiency virus）IgM&IgG 抗體測試（EIA 法）爲陰性，其它病毒 IgM 抗體測試亦均爲陰性，包括德國麻疹病毒（rubella）、麻疹病毒（measles）、腮腺炎病毒（mumps）及巨大細胞病毒（cytomegalovirus）、第 1 型及第 2 型人類簡單疱疹病毒（herpes simplex virus）等。

住院後 1 日，左側 250Hz 、500Hz 、1,000Hz 、2,000Hz 及 4,000Hz 處之平均聽力閾值爲 61dBHL，右側爲 0dBHL（圖 1A）。3 日時左側平均聽力閾值已進步爲 40dBHL，5 日時更進步爲 30dBHL。爾後順利出院，攜帶 2 日之口服副腎皮質素，每日 2 次各 5mg 之 prednisolone。出院後 2 日之門診時聽力檢查顯示左側平均聽力閾值爲 15dBHL，兩耳複響測試 (short increment sensitivity index）均爲 0%，兩耳語音辨識度檢查（speech discrimination score）均爲 100%。3 週後，左側平均聽力閾值爲 2dB（圖 1B），聽性腦幹電波反應檢查（auditory brainstem response）顯示無波峰間潛值之延遲，高解析度顳骨電腦斷層及腦部磁振造影均無異常發現。經過 2 年的追蹤，情況依然穩定。

討　論

小兒突發性耳聾不見得都是病毒感染，以女孩爲多，年齡從 4~15 歲不等，平均 10 歲，可能病因如下 [6]：(1) 內耳淋巴水腫（endolymphatic hydrops）：會合併眩暈，特別容易誤診爲突發性耳聾，以複響之有無、電生理檢查（耳蝸電圖 electrocochleogram 或變頻耳聲傳射檢查 distortion-product otoacoustic emission（及 isosorbide 脫水法可診斷 [4]；(2) 外淋巴瘻管（perilymph fistula）：可由瘻管測試（fistula test）陽性臆斷，但確定診斷需仰賴手術，病患會有手術或外傷病史，往往會合併眩暈 [4]；(3) 腮腺炎耳聾（mumps deafness）：在公共衛生不發達的時代，是小兒突發性耳聾一種重要的原因，但現在仍可見到，診斷以血清學診斷爲主，而且，發病後的聽力喪失多無恢復 [7,8]；(4) 積液性中耳炎（serous otitis media）：聽力損失可以達到 40dBHL [9]，健側 Rinne 測試會呈現陽性，患側則會呈現陰性，Weber 測試結果會偏向患側，純音聽力檢查會呈現氣骨導閾值差（air-bone gap），鼓室圖檢查會呈現 B 型；(5) 偏頭痛（migraine）：通常會伴隨反覆發作的眩暈或頭痛，造成小兒的聽力喪失的機會並不大 [10]；(6) 大前庭導水管症候群（large vestibular aqueduct syndrome）：通常是雙側性，其診斷乃根據高解析度顳骨電腦斷層之軸向面顯示前庭導水管在後顱窩的外側孔開口距離大於 2mm，在磁振造影下可見患側之內淋巴囊腫大 [11]。

本個案無頭痛、眩暈或其他神經學病症，可排除內耳淋巴水腫、外淋巴瘻管及偏頭痛。固然半年前曾得過腮腺炎，但腮腺炎病毒 IgM 抗體測試爲陰性，可排除腮腺炎病毒急性感染內耳所致之腮腺炎耳聾，由於突發性耳聾患者可證實是腮腺炎病毒感染所致的機會爲 6.9%，其他陰性患者也無法完全排除是否爲 Mumps 感染所致 [12]，因此，縱然本個案之腮腺炎病毒 IgM 抗體測試爲陰性，仍無法完全排除該病毒感染的可能性。純音聽力檢查顯示無氣骨導閾值差（圖 1A），鼓室圖檢查爲 A 型，

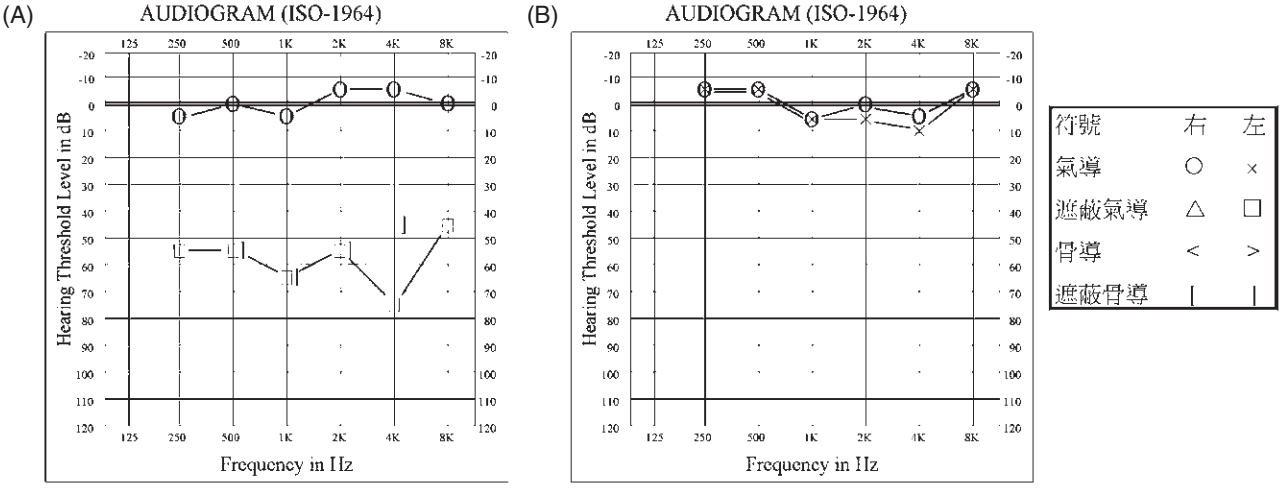

圖 1　(A) 住院後 1 日（發病後 6 日）之純音聽力檢查，無氣骨導閾值差。(B) 出院後 3 週（發病後 1 個月）之純音聽力檢查。

可排除積液性中耳炎。複響測試及聽性腦幹電波反應檢查無異常發現，可排除內耳耳蝸或耳蝸後（retrocochlear lesion）病變[13,14]，高解析度顳骨電腦斷層及腦部磁振造影均無異常發現，可排除小腦橋腦腳（cerebello-pontine angle）病變、大前庭導水管或內耳發育畸形等腦部器質性病變[15]，本個案之突發性耳聾目前實爲原因不明。由於早期的內耳淋巴水腫不會有眩暈，電生理檢查也會是正常，早期的偏頭痛發作也不見得會有典型的頭痛或其他神經學病症，因此，本個案尚需長期的追蹤，以排除內耳淋巴水腫或偏頭痛的可能。

小兒突發性耳聾與成人患者一樣，愈晚治療、聽力損失愈嚴重或愈高頻範圍，預後會愈差[1,6]，治療預後常常採用 250Hz 、500Hz 、1,000Hz 、2,000Hz 及 4,000Hz 等 5 個頻率之平均純音聽力閾值來評估[1]，若改善超過 30dBHL 者爲顯著回復，11~30dBHL 者爲輕微回復，10dBHL 以內者爲無變化。不僅需臥床休息，尚需根據中樞血管性或末梢性病變，給予血漿容積擴張劑 Dextran 或副腎皮質素[1]，惟劑量需根據體重來調整，由於無法分辨本個案是中樞血管性、中樞神經性或末梢性之病變，只好同時給予血漿容積擴張劑及副腎皮質素，最後，平均純音聽力閾值回復了 59dBHL，屬於顯著回復者。

結　論

小兒正值學習的階段，突發性耳聾將會嚴重影響到日後的學習，在急診或門診遇到這類病患時當提高警覺，當早期給予治療，以免造成日後的遺憾。本個案之突發性耳聾目前實爲原因不明，根據病史，仍有可能是腮腺炎病毒感染所致，往後尚需長期的追蹤，以排除內耳淋巴水腫或偏頭痛的可能。

參考文獻

1. 古偉杰、張慧珊、蘇茂昌、楊義良：突發性耳聾預後因素之臨床分析。中山醫誌 2004; 15: 205-12。
2. 朱世輝、李善敬：以眩暈及兩側突發性耳聾爲主要表徵的隱球菌性腦膜炎 - 病例報告。中耳醫誌 1992; 27: 40-4。
3. 鄭元凱、許權振、林凱南：病毒血清抗體力價反轉與突發性耳聾預後之關係。中耳醫誌 1996; 31: 492-6。
4. 楊怡和、蕭宏榮：內淋巴水腫與血管源起之突發性耳聾的鑑別診斷。中耳醫誌 1996; 31: 481-5。
5. 吳鳳旗、賴仁淙：雙側突發性耳聾－ Vogt-Koyanagi － Harada 症候群－病例報告。中耳醫誌 1997; 32: 496-500。
6. 朱裕民、楊怡和：小兒的突發性耳聾。中耳醫誌 1997; 32: 641-6。
7. 楊怡和、蘇右任：急性聽力喪失的惡化。中耳醫誌 1995; 30: 569-73。
8. Salvinelli F, Firrisi L, Greco F, Trivelli M, D'Ascanio L: Preserved otoacoustic emissions in postparotitis profound unilateral hearing loss: a case report. Ann Otol Rhinol Laryngol 2004; 113: 887-90.
9. 林鴻清：中耳炎對聽語的影響。台耳醫誌 2004; 39: 47-8。
10. 沈炳宏、賴仁淙：與偏頭痛有關的反覆性眩暈。中耳醫誌 2002; 37: 103-7。
11. 林君郁、歐俊巖、林政佑、吳俊良：幼兒大前庭導水管症候群併急性聽力惡化之緊急處置。台耳醫誌 2003; 38: 208-15。
12. Okamoto M, Shitara T, Nakayama M, Takamiya H, Nishiyama K, Ono Y, Sano H: Sudden deafness accompanied by asymptomatic mumps. Acta Otolaryngol Suppl 1994; 514: 45-8.
13. Hall JW, Antonelli PJ: assessment of peripheral and central auditory function. In Bailey BJ: Head & Neck Surgery-Otolaryngology, 3th edition, Philadelphia; Lippincott Williams & Wilkins, 2001: 1659-72.
14. 劉君毅、許權振、林凱南：突發性聽力喪失的聽力學與聽性腦幹反應。中耳醫誌 1994; 29: 1-11。
15. Wareing MJ, Lalwani AK, Jackler RK: development of the ear. In Bailey BJ: Head & Neck Surgery-Otolaryngology, 3th edition, Philadelphia; Lippincott Williams & Wilkins, 2001: 1609-19.

Sudden Deafness in a Child

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Sudden deafness (SD) usually affects people between 40 and 60 years old. Only 5% SD is younger than 15 years old. The possible etiologies are labyrinthine maldevelopment, endolymphatic hydrops, perilymph fistula, endolymphatic hydrops, mumps deafness, serous otitis media, migraine, large vestibular aqueduct syndrome or other unknown cause. Half year after a 10-year-old girl had suffered mumps, she presented with acute left hearing loss and tinnitus for five days. Transferred from a private clinic, she was treated with bed-rest, intravenous corticosteroids, and blood volume expander. One day after hospitalization, the average of hearing thresholds over 250~4,000Hz was 61dBHL in the affected ear; 5 days after hospitalization, 30dBHL; 2 days after being discharged, 15dBHL; and 3 weeks after being discharged, 2dBHL. Finally, her hearing was rescued 59dBHL. Blood examinations were within normal range. Rapid plasma regain of syphilis, anti-HIV (human immunodeficiency virus) IgM&IgG (EIA) and other virus IgM tests were all negative. Short increment sensitivity index, speech discrimination score, auditory brainstem response, high-resolution computed tomography of temporal bone, and magnetic resonance imaging of brain showed negative finding. In the following two years, it was uneventful. Therefore, the etiology of her SD is still unknown. According to clinical history, her SD may be attributable to mumps infection. Due to possible endolymphatic hydrops or migraine, she should be followed in the future.
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Key words: sudden deafness, pediatric, mumps deafness, endolymphatic hydrops, migraine

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顏明賢

童綜合醫學雜誌投稿相關規則

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 台中縣梧棲鎮中棲路一段 699 號童綜合醫學雜誌編審委員會。

壹、投稿前注意事項

1. 投稿時，需附原稿三份（一份原稿和兩份複印稿，但圖片應用三份原圖）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。
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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、簡題（running title）、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，英文摘要不超過 250 字，中文摘要不超過 500 字，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、請附三份原稿（一份原稿和兩份複印稿，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

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。

童綜合醫學雜誌

綜　論

原　著

病例報告