Tungs' Medical Journal

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**Mitochondrial Diseases**

Ching-Shiang Chi

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.

(Tungs’ Med J 2010; 4: 49-62)

**Key words: Mitochondrial diseases, Clinical manifestations, Diagnostic tools, Taiwan**

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**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
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\cite{3}. The minimum birth prevalence for respiratory chain disorders with onset at any age was estimated at 1 in 7634\cite{4}.

In Taiwan, the first report of clinical MD was published in 1988\cite{5}, and the first mitochondrial DNA (mtDNA) mutation was identified in 1992\cite{6}. Since then, more than 90 articles relevant to clinical MDs have been published in Taiwan\cite{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\cite{97,98,99} showed clinical features in patients with MDs support the maxim “any tissue and any signs at any age”\cite{100}. In general, the clinical spectrum

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**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
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 account 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. Clinical 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

<table>
<thead>
<tr>
<th>Table 1. Clinical presentations of mitochondrial diseases.</th>
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<tbody>
<tr>
<td><strong>Central nervous system</strong></td>
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<tr>
<td>Seizures</td>
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<td>Developmental delay</td>
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<tr>
<td>Altered level of consciousness</td>
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<td>Floppiness</td>
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<td>Spasticity</td>
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<td>Mental retardation</td>
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<td>Sucking difficulty</td>
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<td>Involuntary movement</td>
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<td>Headache</td>
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<td>Apnea</td>
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<td>External ocular motility limitation</td>
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<td>Tremor</td>
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<tr>
<td>Apneustic respiration</td>
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<tr>
<td>Dystonia</td>
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<tr>
<td>Stroke</td>
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<td>Sudden infant death syndrome</td>
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<td>Hypoventilation</td>
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<td>Hepatic system</td>
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<td>Liver cirrhosis</td>
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<td>Urologic system</td>
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<td>Fanconi syndrome</td>
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<td>Renal tubular dysfunction</td>
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<td>Proteinuria</td>
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<td>Amenorrhea</td>
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<td>Short stature and/or failure to thrive</td>
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<td>Hearing system</td>
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<td>Peripheral nervous system</td>
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<td>Hematologic system</td>
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<td>Pancreas</td>
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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.](image)
of patients, especially in children younger than 3 years\cite{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.

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\cite{95}, suggesting that most pediatric patients probably have a Mendelian recessive inheritance\cite{97,101}.

**Treatment**

The prognosis for MDs is related to patients’ age at disease onset and the level of damage to cardiac function\cite{97}. There have been few controlled therapeutic trials for MDs, and effective management of MDs is seldom possible\cite{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\cite{125}. Pyruvate dehydrogenase-deficient patients may benefit from thiamine administration and/or ketogenic diet\cite{126,127}. Dichloacetate can lower the lactate level in MDs and may be useful for short-term treatment of episodes of severe lactic acidosis\cite{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.

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粒線體疾病

過去上

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、腦部核磁共振氧譜、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有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。

（童綜合醫誌 2010; 4: 49-62）

關鍵詞：粒線體疾病，臨床表現，診斷工具，台灣
Effect of Second Generation Antipsychotics on the Metabolic Syndrome Parameters in Patients with Schizophrenia

Shang-Chien Huang1,2, Hsiang-Ping Huang3,4*, Li-Min Lee5, Li-Ya Chang6, Ming-Tzu Hung6

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 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.

(Tungs’ Med J 2010; 4: 63-69)

Key words: Metabolic, Antipsychotics, Schizophrenia
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 syndrome.

### 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>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Weight gain</th>
<th>Risk for diabetes</th>
<th>Dyslipidemia</th>
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<tr>
<td>Clozapine</td>
<td>+++</td>
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</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Zotepine</td>
<td>++(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Demographic Characteristics of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>No. of Hypertensives</td>
</tr>
<tr>
<td>No. of Diabetics</td>
</tr>
<tr>
<td>No. of Smokers</td>
</tr>
</tbody>
</table>
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 $\geq 100$ mg/dl; triglyceride $\geq 150$ mg/dl; HDL-C less than 40 mg/dl and 50 mg/dl for male and female individually; blood pressure $\geq 130/85$ mmHg 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**

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

**Table 4. Effect of Five Antipsychotics on Body Weight**

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>N</th>
<th>Baseline Mean</th>
<th>After One Year Mean</th>
<th>Paired Difference Mean</th>
<th>t</th>
<th>P(2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>16</td>
<td>60.2 ± 11.8</td>
<td>63.0 ± 11.3</td>
<td>2.8 ± 7.2</td>
<td>-0.67</td>
<td>.318</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>9</td>
<td>61.4 ± 10.9</td>
<td>69.2 ± 10.1</td>
<td>7.8 ± 7.0</td>
<td>-2.60</td>
<td>.039</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6</td>
<td>57.4 ± 12.1</td>
<td>62.8 ± 13.8</td>
<td>5.4 ± 8.6</td>
<td>-1.65</td>
<td>.128</td>
</tr>
<tr>
<td>Clozapine</td>
<td>5</td>
<td>61.6 ± 12.7</td>
<td>68.9 ± 11.8</td>
<td>7.2 ± 9.1</td>
<td>-2.37</td>
<td>.064</td>
</tr>
<tr>
<td>Zotepine</td>
<td>5</td>
<td>64.4 ± 13.0</td>
<td>71.1 ± 10.5</td>
<td>6.7 ± 7.6</td>
<td>-2.21</td>
<td>.080</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>41</td>
<td>60.7 ± 8.7</td>
<td>66.0 ± 7.7</td>
<td>5.3 ± 5.7</td>
<td>-2.79</td>
<td>.016</td>
</tr>
</tbody>
</table>
patients taking Olanzapine, 1 patient taking Clozapine and 1 patient taking Zotepine. No significant variations 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. 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. Clozapine and Olanzapine are closely correlated with body weight, 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.

At present, some studies also mentioned Clozapine and Olanzapine were most likely to induce metabolic syndrome. 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. 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. 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. Some study mentioned it might be concerned with genes.

Body weight increase is the reason most likely causing metabolic syndrome and diabetes. However, it has been found that behavior treatment can reduce body weight. 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; some drugs such as Amantadine that can treat extrapyramidal symptoms and Parkinson’s disease can improve Olanzapine caused body weight. Similarly, Metformin also can improve body weight gain, and reduce risk of diabetes. Currently, it is believed that metabolic syndrome should be followed closely once it appears and it exhibits a favorable prognosis.

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. 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


目的：代谢症候群是第二代抗精神病药物在治療使用上的一个關注焦點，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药物對國人代谢症候群之影響。

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药物治療，當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）標準判定是否有代谢症候群。統計方法為平均數差異檢定及雙變數分析。

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。全數患者在使用第二代抗精神病药物前後三酸甘油酯平均增加 37 mg/dl 呈現顯著差異，以個別药物而言，用藥前後三酸甘油酯呈現顯著差異的是 Clozapine 及 Olanzapine。全數患者在使用第二代抗精神病药物前後體重平均增加 5.3 kg 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药物用藥後，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。

（國綜合醫誌 2010; 4: 63-69）

關鍵詞：Metabolic, Antipsychotics, Schizophrenia
Study on the Influence of Second Generation Antipsychotics on QTc Interval Prolongation in Patients with Schizophrenia

Hsiang-Hsiung Huang¹, Hsiang-Ping Huang², Shang-Chien Huang³*

Purpose: QTc interval prolongation is a focus of attention in application of antipsychotics as it may induce polymorphic 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.

(Tungs’ Med J 2010; 4: 70-74)

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]
however, some antipsychotics also can prolong QTc interval, induce polymorphic ventricular tachy-
cardia 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 schizo-
phrenia 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

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

Table 2. Demographic Characteristics of Subjects

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37.2 ± 6.7</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>37/27</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Taiwanesees</td>
</tr>
<tr>
<td>No. of Hypertensives</td>
<td>8</td>
</tr>
<tr>
<td>No. of Diabetics</td>
<td>0</td>
</tr>
<tr>
<td>No. of Smokers</td>
<td>18</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Antipsychotic</th>
<th>N</th>
<th>Baseline Mean</th>
<th>After 6 months Mean</th>
<th>Paired Difference Mean</th>
<th>t</th>
<th>P(2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>22</td>
<td>416.9 ± 35.0</td>
<td>418.0 ± 29.9</td>
<td>1.1 ± 22.6</td>
<td>-0.24</td>
<td>.816</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>15</td>
<td>410.2 ± 25.5</td>
<td>422.2 ± 26.6</td>
<td>12.0 ± 25.2</td>
<td>-2.28</td>
<td>.049</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>10</td>
<td>397.8 ± 33.4</td>
<td>411.1 ± 36.8</td>
<td>13.3 ± 18.5</td>
<td>-1.85</td>
<td>.086</td>
</tr>
<tr>
<td>Clozapine</td>
<td>10</td>
<td>408.3 ± 21.6</td>
<td>432.1 ± 20.8</td>
<td>23.8 ± 15.7</td>
<td>-4.79</td>
<td>.001</td>
</tr>
<tr>
<td>Zotepine</td>
<td>7</td>
<td>400.4 ± 34.0</td>
<td>417.0 ± 20.5</td>
<td>16.6 ± 34.4</td>
<td>-1.28</td>
<td>.249</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>409.2 ± 30.7</td>
<td>420.0 ± 28.1</td>
<td>10.8 ± 23.9</td>
<td>-3.62</td>
<td>.001</td>
</tr>
</tbody>
</table>
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

第二代抗精神病藥物對國人心電導延長影響研究

黃湘雄1 黃湘萍2 黃尚堅3*

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 (polymorphic ventricular tachycardia, or torsade de pointes)，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，於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

KimSeng Law¹,²*

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 dehydorderase (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 (cyclophosphamide, 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 regimen 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

妊娠合併原發性縱隔腔大 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 細胞淋巴瘤是一個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常較何杰金氏淋巴瘤更加棘手及廣泛性擴散，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血流不全。

（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 aware of this patient’s recent condition earlier. Thus, we suggest that using neostigmine in such patients should be more cautious.

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
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 disease 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 aware of this patient’s recent condition. Using neostigmine in patients with coronary artery disease should also be more cautious.

REFERENCE


喉鏡顯微手術後發生 Neostigmine 誘發的急性心肌梗塞：
個案報告

王亮傑  馬振來  張錦新  黃國生  陳耀舜

手術期間的心肌缺血一直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病。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，
所以從靜脈给予 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情狀況後，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。

病發心肌梗塞的時間與靜脈給予 neostigmine 的時間相符，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
Aneurysm of the Left Atrium: Detection by Using Multidetector-Row Computed Tomography Imaging

Cheng-Chun Lee¹*, Chee-Chiang Chen¹

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.
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](image)

**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.\textsuperscript{[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\%),\textsuperscript{[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.\textsuperscript{[1]} Surgical resection of the aneurysm is therefore recommended in order to eliminate a potential source of emboli and arrhythmias.\textsuperscript{[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 aneurysm 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 \textsuperscript{[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,\textsuperscript{[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, multidetector-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)\textsuperscript{[7]}. These capabilities of multiplanar reconstruction and post-processing imaging provide excellent tool for complex congenital 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\textsuperscript{[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.\textsuperscript{[10]}

**REFERENCES**


左心房動脈瘤多切面電腦斷層影像及其臨床意義

李政君*  陳志強

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。這也是為什麼許多名醫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、心臓瓣膜、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臓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臓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
小兒突發性耳聾

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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、外淋巴囊管、腮腺炎耳聾、積液性中耳炎、偏頭痛、大前庭水管症候群或原因不明。－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，置床休息，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 日為 61dBHL，住院後 5 日為 30dBHL，出院後 2 日為 15dBHL，出院後 3 週為 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、純音腦幹電波反應檢查、顱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）定義為 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，通常為單側發病，雙側者較為罕見，好發於 40~60 歲的成年人（35.10%），平均年齡是 43.20 歲。大部份患者會有耳鳴或眩暈，病因目前尚不明，可能與腦部病變、病毒、血管性病變或自體免疫有關。不足 15 歲的約佔所有患者的 5%。由於他們對於聽力的表達能力不易，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 日，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 处之聽力閾值分別為 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 測試均為陽性，Weber 測試偏向右側，譜圖為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 日為每日 2 次各 20mg，後 2 日為每日 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）均為正常值，梅毒血清測試（rapid plasma reagin）為陰性，
人類免疫缺乏病毒 (human immunodeficiency virus) IgM及IgG 抗體測試 (EIA法) 為陰性，其它病毒 IgM 抗體測試亦均為陰性，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 處之平均聽力閾值為 61dBHL，右側為 0dBHL (圖 1A)。3 日時左側平均聽力閾值已進步為 40dBHL，5 日時更進步為 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為 15dBHL，兩耳複響測試 (short increment sensitivity index) 均為 0%，兩耳語音辨識度檢查 (speech discrimination score) 均為 100%。3 週後，左側平均聽力閾值為 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，高解析度顱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，以女孩為多，年齡從 4~15 歲不等，平均 10 歲，可能病因如下 [6]：(1) 内耳淋巴水腫 (endolymphatic hydrops)：會合併眩暈，特別容易誤診為突發性耳聾，以複響之有無、電生理檢查 (耳蝸電圖 electrocochleogram 或變頻耳聲傳射 distortion-product otoacoustic emission 及 isosorbide 脫水法可診斷 [4])；(2) 外淋巴囊管 (perilymph fistula)：可由囊管測試 (fistula test) 陽性聰聽，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 [6]；(3) 腺腺炎耳聾 (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，診斷以血清學診斷為主，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顱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、外淋巴囊管及偏頭痛。固然半月前曾得過腮腺炎，但腮腺炎病毒 IgM 抗體測試為陰性，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為 6.9%，其他陰性患者也無法完全排除是否為 Mumps 感染所致 [12]，因此，縱然本個案之腮腺炎病毒 IgM 抗體測試為陰性，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)，鼓室圖檢查為 A 型，

(A) AUDIOGRAM (ISO-1964) (B) AUDIOGRAM (ISO-1964)

![圖 1](A) 住院後 1 日 (發病後 2 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，可排除內耳聽或耳聾後 (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
性病変[15]，本個案之突發性耳聾目前實為原因不明。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[16]，治療預後
常常採用 250Hz、500Hz、1,000Hz、2,000Hz 及 4,000Hz
等 5 個頻率之純音聽力閾值來評估[1]，若改善超過
30dBHL 者為顯著回復，11~30dBHL 者為輕微回復，
10dBHL 以內者為無變化。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
突發性耳聾目前實為原因不明，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。

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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 61dBL in the affected ear; 5 days after hospitalization, 30dBL; 2 days after being discharged, 15dBL; and 3 weeks after being discharged, 2dBL. Finally, her hearing was rescued 59dBL. 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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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為參考文獻，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。
335:1-7.

二、本文內引用時，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
2. Yang KTA, Chen HD: A semi-automated method for edge detection in the evaluation of left ventricular

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 ]。

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, Isselbacher K,
Petersdorf RG eds. Harrison’s Principles of Internal Medicine, 8th ed. New York: Mcgraw-Hill,
1977:364-75。

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