# Two eminently treatable genetic metabolic myopathies

### **Woon-Chee Yee**

Department of Clinical Research, Singapore General Hospital, Singapore

Treatment of the genetic metabolic myopathies remains generally unsatisfactory with the exception of a select few. Multiple Acyl Co-A Dehydrogenase Deficiency (Glutaric Aciduria type II), in particular, has been shown to respond well to riboflavin supplementation. Recently, studies have also confirmed the effectiveness of recombinant enzyme replacement therapy for Acid Maltase Deficiency (Pompe's Disease). Accurate and early diagnosis of these diseases is vital to prevent serious complications and impaired recovery following delayed treatment.

**Key words:** Acid maltase deficiency, enzyme replacement therapy, glutaric aciduria Type II, human recombinant α-glucosidase, multiple Co-A dehydrogenase deficiency, Pompe disease, riboflavin

### Introduction

The genetically inherited metabolic myopathies encompass a large group of diseases associated with diverse inborn errors of metabolism, in particular muscle energy production, and including disorders of glycogen, lipid and mitochondrial metabolism. Despite major advances in understanding their molecular mechanisms and the identification of causative genes, treatment of these diseases remains inadequate or lacking. Nevertheless, a very small number of these diseases are amenable to treatment that may substantially reverse disease manifestations. Timely and accurate diagnosis of these diseases is, therefore, vitally important. However, owing to their relative rarity and wide range of presentations, these treatable diseases are often missed or diagnosed late. This review will focus on two specific metabolic myopathies for which appropriate therapy can significantly ameliorate or effectively cure the disease.

# Multiple Acyl CoA Dehydrogenase Deficiency (Glutaric Aciduria II)

To the neurologist or neuromuscular specialist,

multiple acyl co-A dehydrogenase deficiency (MADD) will likely be encountered in its late onset form presenting as a lipid storage myopathy. The pediatrician may encounter the distinct manifestations of severe neonatal MADD with hypoglycemic encephalopathy, hypotonia, organomegaly and sweaty feet odor, as well as the above myopathic form in childhood or adolescence. While no data on incidence is available, the disorder is probably not exceptionally rare.

### Molecular and metabolic pathophysiology

MADD is an autosomal recessive disorder that results from a defect of electron transfer from the primary flavoprotein dehydrogenases to coenzyme Q10 in the mitochondrial electron transport chain.<sup>[1-3]</sup> The disorder is linked to mutations in one of three genes coding for electron transfer flavoprotein (i.e. ETF  $\alpha$  and  $\beta$  subunits) and its electron acceptor, ETFubiquinone oxidoreductase (ETF-QO), which together are responsible for this electron transfer process.<sup>[3-7]</sup> The genes are respectively denoted as ETF-A, ETF-B and ETF-DH. The generalized defect of dehydrogenase function that results leads to impairment of fatty acid, amino acid and choline metabolism, although the biochemical and histological manifestations are largely related to disordered fatty acid β-oxidation associated with four chain-length specific dehydrogenases. MADD is the same disorder as Glutaric Aciduria II (GAII) and Ethylmalonic-Adipic Aciduria, which were terms used to denote cases identified by the characteristic urinary organic acid metabolites associated with the disorder.<sup>[1,8,9]</sup>

### Clinical features

Three clinical phenotypes have been characterized for MADD.<sup>[3,10-13]</sup> Two forms of the disease present in the neonatal period and share several common features, i.e. hypoglycemic encephalopathy associated with hypotonia, metabolic acidosis, organomegaly and sweaty feet odor. The more severe Type I is distinguished from Type II by additional features of congenital anomalies and early, inevitable death. Patients with the relatively

#03-03, Block C, Singhealth Research Facilities, 9 Hospital Drive, Singapore 169612. E-mail: yee.woon.chee@sgh.com.sg

milder or late onset form (Type III) typically present with a lipid storage myopathy associated with slowly progressive proximal weakness, reduced effort tolerance and muscle pain. The course in these patients may be punctuated by acute episodes of exacerbation with increased weakness, lethargy, vomiting, hypoglycemia and metabolic acidosis, often associated with physical stress. There may be hepatomegaly. However, the disease course and age of presentation in Type III can vary considerably, with onset ranging from early childhood to adult life, and the identification of asymptomatic as well as severe cases with respiratory failure.

Recently, another phenotype variation was identified as associated with MADD. Patients from five families, originally diagnosed to have an isolated myopathic form of coenzyme Q10 deficiency based on biochemical analysis of muscle respiratory chain complexes and coenzyme Q10, were found by tandem mass spectrometry (see below) to have MADD.<sup>[14]</sup> Their clinical presentation was, in fact, consistent with the Type III form of MADD. All these patients were found to have autosomal recessive mutations in *ETF-DH*.

### Differential diagnosis

While the infantile forms are distinctive, the differential diagnosis will include other diseases with Reye's syndrome-like presentation in infancy. In Type III MADD, especially in juveniles and adults, the apparent presentation as an acquired myopathy may entail a very broad differential diagnosis. Misdiagnosis as polymyositis has been reported.<sup>[15]</sup> The association of the myopathy with acute exacerbations, especially if triggered by physical stress and accompanied by vomiting and metabolic changes, should raise suspicion of MADD, although such exacerbations may also be seen in other mitochondrial disorders.

# Diagnostic tests

In patients presenting primarily as a myopathy, the muscle biopsy will likely provide the first suggestion of a possible diagnosis of MADD. Confirmation of the diagnosis, however, will require relatively complicated tests that are performed by special laboratories, namely urinary organic acid analysis by gas chromatography/ mass spectrometry or acylcarnitine profiling by tandem mass spectrometry. Molecular gene testing of the genes linked to the disease can also confirm the disease as well as identify the specific gene involved.

# Muscle biopsy

The muscle biopsy in MADD shows typical features of a lipid storage myopathy, with multiple small vacuolar changes in muscle fibers that are revealed on lipid stains to be associated with increased droplet accumulations of lipid. Mild changes of mitochondrial dysfunction,

### Urinary organic acids

MADD/GAII is characterized by elevated amounts of glutarate, ethylmalonate, isovalerate,  $\alpha$ -methylbutyrate, isobutyrate, aliphatic dicarboxylic acids and their derivatives.<sup>[16]</sup> MADD/Ethylmalonic-adipic aciduria is associated with elevated amounts of ethylmalonate, adipate and hexanoylglycine.<sup>[17]</sup> The identification of these patterns by gas chromatography/mass spectrometry is diagnostic of MADD. However, unlike the neonatal forms which show marked elevation of urinary organic acids, in the milder Type III form, the organic aciduria may only be evident during the episodes of exacerbation.

### Acylcarnitine profiling by tandem mass spectrometry

If tandem mass spectrometry (MS/MS) screening of serum or dried blood spot samples is available, the identification of increased concentrations of short, medium and long chain acylcarnitines (C4-C12) is characteristic of MADD.<sup>[18]</sup> This test has proven useful in identifying MADD cases in countries where MS/MS has been adopted for neonatal screening using dried blood spots.

### Molecular gene testing

All three MADD clinical phenotypes have been associated with each of the three genes linked to MADD. This suggests that mutational analysis of all three genes, i.e. *ETF-A*, *ETF-B* and *ETF-DH*, may be required to identify the specific genetic mutations in the individual patient. However, in view of the relatively frequent reports of late onset cases with *ETF-DH* mutations,<sup>[14]</sup> it may be appropriate to start with mutational analysis of *ETF-DH* in late onset Type III MADD.

# Free carnitine and free fatty acid levels

Free carnitine levels in the blood may be decreased in MADD, although this also occurs in other diseases with secondary carnitine deficiency and in primary carnitine deficiency. In the Type III form, carnitine levels may only be reduced during episodes of exacerbation. Likewise, free fatty acid levels in plasma may be elevated in MADD. Though not confirmatory for the diagnosis of MADD, both tests, if available, may help support the diagnosis.

### Treatment

MADD has consistently been reported to respond dramatically to oral riboflavin supplementation, with rapid remission of symptoms and signs.<sup>[4,5,13,14,19,20]</sup> Full recovery towards normality is seen in milder cases, and although recovery was said to be partial in severe neonatal cases, early therapy may possibly improve results. In this sense, MADD is an eminently treatable disease. The optimal riboflavin dose is unknown and may likely vary with disease severity, although doses up to 150 mg daily have been employed. Interestingly, among the patients with coenzyme Q10 deficient myopathy associated with *ETF-DH* gene mutations, although all showed improvement with coenzyme Q10 supplementation, two responded well to riboflavin alone without coenzyme Q10. However, in one patient, the combination of riboflavin and coenzyme Q10 was better than riboflavin alone. Hence, at least for those cases of MADD associated with *ETF-DH* mutations, it has been suggested that long-term therapy should include coenzyme Q10 in addition to riboflavin.<sup>[14]</sup>

General recommendations for the management of MADD include dietary management with low lipid, low protein, high carbohydrate intake, and the avoidance of physical stress. Because of the finding of low carnitine levels, supplementation with carnitine has also been suggested.<sup>[10]</sup> However, the efficacy of carnitine is unclear, as aggravation of MADD symptoms has also been reported following addition of carnitine.<sup>[21]</sup>

# Acid Maltase Deficiency (Glycogen Storage Disease Type II, Pompe's Disease)

Acid maltase deficiency (AMD), also known as glycogen storage disease Type II and Pompe's disease,<sup>[22,23]</sup> was first linked to an inherited deficiency of a lysosomal enzyme in 1963.<sup>[24]</sup> However, although attempts to treat the disease with enzyme replacement began not long after, they were unsuccessful until very recently. With the approval by US and European drug administrations in 2006 of a recombinant enzyme as therapy for AMD, the possibility to effectively treat this disease has now emerged.

### Molecular and metabolic pathophysiology

AMD is caused by deficiency of the lysosomal enzyme acid  $\alpha$ -glucosidase (GAA) as a result of autosomal recessive mutations in the GAA gene located on Chromosome 17.<sup>[25,26]</sup> About 150 mutations have been associated with the disease, although common mutations have been reported in some communities, e.g. the IVS1-13T>G splice site mutation in 70% of adult Caucasian patients<sup>[27]</sup> and the Asp645Glu mutation in most Pompe infants in Taiwan.<sup>[28]</sup> GAA acts to break down glycogen to glucose within lysosomes. Loss of functional GAA leads to the accumulation of glycogen within the lysosomes and in sarcoplasm with rupture of the lysosomal membrane. Glycogen accumulates in all tissues, most prominently in skeletal and cardiac muscle, where it likely impairs contractile function and reduces muscle mass via impaired regenerative capacity and increased apoptosis.

### Clinical features

The incidence of AMD shows ethnic and geographical variation. In the Western world, the combined estimated frequency of AMD is 1:40,000.<sup>[29,30]</sup> Pompe's disease of infants appears relatively more common in Taiwan and Southern China and among African-Americans, while later onset AMD appears relatively more common in the Netherlands.

The clinical phenotype of AMD exists as a continuous spectrum from severe, rapidly progressive early onset forms to more slowly progressive, less severe late onset forms.<sup>[22,31]</sup> Disease severity seems to correlate with the level of residual GAA activity. In clinical practice and for teaching purposes, it remains useful to categorize AMD according to clinical subtype.

# Infantile acid maltase deficiency (classic Pompe's disease)

The term Pompe's disease was originally applied to the severe infantile form, although there is a trend to use it for the entire spectrum of AMD. Symptoms typically present within two months after birth, initially as poor motor development and failure to thrive.<sup>[32]</sup> These infants develop feeding difficulties, profound muscle weakness and floppiness, and respiratory difficulties often complicated by pneumonia. Almost all patients develop cardiomyopathy with gross cardiomegaly. Other prominent findings include hepatomegaly, macroglossia and markedly elevated creatine kinase (CK) levels. Life expectancy is, on average, less than a year, with only a quarter of patients surviving beyond one year.

### Juvenile and adult onset acid maltase deficiency

The juvenile form of AMD, with onset from early childhood to adolescence, presents with progressive proximal muscle weakness in a limb girdle pattern, manifested as delayed milestones, or difficulty with walking, climbing stairs or getting up from sitting or lying.<sup>[31,33]</sup> Spinal deformities may develop owing to truncal weakness. Calf hypertrophy and scapular winging has also been reported. Development of respiratory weakness may occur, with orthopnoea and dyspnoea on exertion. AMD starting in adult life is also associated with proximal weakness, sometimes with striking selective involvement.<sup>[34,35]</sup> Respiratory weakness appears even more common in the adult form than the infantile form in the early stages, being the presenting symptom in about a third, and affecting all patients eventually. A late complication in juvenile and adult AMD is the development of cerebral aneurysm, especially basilar aneurysm, which may rupture. Unlike infantile AMD, cardiomyopathy is uncommon or absent, and the creatine kinase, though elevated, is not as high. The disease progresses more slowly, with severity correlating best with disease duration.

# Differential diagnosis

AMD should be suspected in the infant with a myopathy associated with organomegaly, especially cardiomegaly, weak muscles with firm consistency and ventilatory failure. It is in the differential diagnosis of the floppy baby with raised CK, and in infantile diseases with organomegaly. In young children and juveniles, AMD may be mistaken for muscular dystrophy, including Duchenne, Becker or a limb girdle muscular dystrophy, especially when there is associated calf hypertrophy, skeletal deformities and selective muscle involvement. In adults, AMD may be mistakenly diagnosed as polymyositis or limb girdle muscular dystrophy. AMD should always be in the differential diagnosis of myopathy associated with ventilatory failure, especially in juveniles and adults.

# Diagnostic tests

As with MADD, the muscle biopsy often provides the first clear indication of the disease although in infantile Pompe's disease, evidence of cardiomegaly plus the characteristic Electrocardiogram (ECG), may also offer strong supporting evidence. The specific test required to confirm the disease is measurement of GAA activity. As a rapid diagnosis of AMD is important in infants with AMD for whom enzyme replacement therapy is planned, an international working group has recently published a consensus guide on laboratory diagnosis of Pompe's disease, which the reader may find helpful.<sup>[36]</sup>

# Muscle biopsy

The typical finding of muscle biopsy in AMD is a vacuolar myopathy associated with glycogen storage, as demonstrated by Periodic Acid Schiff staining, and increased lysosomal activity, as suggested by increased acid phosphatase staining, which distinguishes it from other glycogen storage disorders. The histological picture in infantile AMD is highly characteristic, with marked widespread vacuolation and heavy glycogen accumulation. These changes are milder in the juvenile and adult forms of AMD, and may even be absent owing to 'sampling error'. This histological picture may possibly overlap with that of a disorder earlier reported as "lysosomal glycogen storage disease with normal acid maltase" and now identified as Danon's disease, although glycogen accumulation is not always seen in this rare autophagic vacuolar myopathy.

# Measurement of *a*-glucosidase activity

GAA activity may be assayed in lymphocytes, mixed leucocytes, fibroblasts or muscle tissue, as well as using dried blood spots, for diagnostic purposes. Although the most reliable measurement of residual GAA activity is in cultured fibroblasts, the ability to measure GAA activity in blood has simplified and expedited the test as no biopsy or tissue culture is required. The use of acarbose to eliminate interference by isoenzymes in blood has made this possible.<sup>[37]</sup> Dried blood spots are especially convenient, and also suitable for shipping and for neonatal screening.<sup>[38]</sup> In infantile forms, the diagnosis is confidently verified by the complete absence of GAA activity. In juvenile and adult forms, GAA activity may range between absent to about 40% of normal. Where GAA activity is partially present, correlation with clinical and laboratory findings is necessary.

# Molecular gene diagnosis

Molecular analysis of the *GAA* gene is usually not required for diagnosis if a reliable test to measure GAA activity is available. However, mutational analysis may be useful in mild cases in whom GAA activity may be near normal. *GAA* mutational analysis will be necessary if prenatal diagnosis is considered.

# Ancillary tests

Several ancillary tests are appropriate in AMD, to support the diagnosis or characterize disease severity or complications. These may include ECG, chest X-ray and echocardiography, Electromyography (EMG) and nerve conduction studies, CK levels and pulmonary function tests. Myotonic discharges (without clinical myotonia) in association with features of an irritable myopathy are typically associated with all forms of AMD. While these EMG findings are useful when AMD is suspected, they may also give rise to misdiagnoses of inflammatory myopathy or myotonic dystrophy in the unaware examiner. The ECG in the infantile form shows typical features of shortened PR intervals associated with large QRS complexes.

# Treatment

# Supportive therapy

Despite the emergence of specific enzyme replacement therapy, general supportive therapy of AMD remains highly relevant, especially with regards to complications of feeding difficulty, general weakness, and respiratory failure and pulmonary infections. Respiratory support, in particular, with noninvasive techniques such as nocturnal Bipap, will significantly improve quality of life and extend survival in juveniles and adults with respiratory failure.

# Dietary therapy

Dietary modifications tried in AMD, in an attempt to decrease glycogen deposition and increase utilization of alternate metabolic pathways, have included high protein intake with or without low caloric/ carbohydrate intake, and branched chain amino acid or L-alanine supplementation. In general, only single cases or small numbers of patients were studied, who were often older cases, in whom the disease progression is slower. No studies involved the infantile form and none were controlled. Some studies reported benefit<sup>[39-42]</sup> while others reported little or no benefit.<sup>[43-47]</sup> The exceptional study is that of Slonim et al.,<sup>[48]</sup> an uncontrolled prospective study of a highprotein, low-carbohydrate diet with exercise therapy in adult onset AMD cases. Comparing pre-therapy with post-therapy measurements, muscle function deterioration was reported to be significantly slowed by the therapy. However, eight of the original 34 cases could not adhere to the therapy regimen. It is, therefore, reasonable to conclude that dietary therapy is, at best, palliative, requires strict compliance and reported only in adult AMD cases.

#### Enzyme replacement therapy

Early trials of enzyme replacement using fungal or human derived enzyme were uniformly unsuccessful.<sup>[13,49]</sup> The breakthrough came in stages, first with identification of the mannose-6-phosphate receptor on cell surfaces enabling efficient endocytosis of mannose-6-phosphate labeled enzyme<sup>[50]</sup> and subsequently the development of recombinant DNA technologies to synthesize commercial quantities of human recombinant  $\alpha$ -glucosidase.<sup>[51]</sup> Early pilot studies of recombinant GAA infusion in a few infantile patients were highly encouraging,<sup>[52,53]</sup> followed by a Phase 1/II open label trial in 18 infantile AMD patients using a historical cohort as controls.<sup>[32,54]</sup> The results were dramatic and convincing, with 100% survival compared to 2% survival in the historical cohort at 52 weeks. The need for invasive ventilation was reduced by 92% and cardiac and motor function was significantly improved. The beneficial effect of recombinant GAA was substantiated by an open label trial of two adolescents and an adult, reviewed at three years and five years.<sup>[55,56]</sup> However, these studies also revealed that when treatment was initiated later, improvement was more limited and variable, especially with regards to ventilatory and motor function. This suggests that early diagnosis and treatment may be critical for better outcome. Serious or life-threatening reactions to recombinant GAA, specifically anaphylactic reactions, occurred in a few, warranting precautionary measures. However, the major factor prohibiting more general use of recombinant GAA is its high cost, especially in developing countries or where medical care is not subsidized, posing serious dilemmas for patients and their physicians. Nevertheless, the advent of enzyme replacement therapy has drastically changed the landscape for therapy of AMD. Firm confirmation of its promise to halt or reverse the disease process in AMD awaits longer term follow-up studies of all forms

### of AMD patients under treatment.

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