Medium Chain Acyl CoA Dehydrogenase Deficiency and Eating Disorders: An Underreported Coincidence

Kharis A. Burns¹,², Catherine Manolikos¹, Samantha Hodge¹ and Damon A. Bell¹,²,³

Abstract
Medium chain acyl-coA dehydrogenase deficiency (MCADD), the most common fatty acid oxidation disorder, has been regarded as a relatively benign condition with low risk of mortality in patients with a known diagnosis, if adequate caloric intake is met. However, inadequate energy provision, as occurs in eating disorders, significantly amplifies the risk of metabolic decompensation. This case series describes four patients with MCADD and a concomitant eating disorder and aims to raise awareness of the potentially under-recognised coexistence of these conditions. All patients were female with signs of disordered eating in adolescence and young adulthood though latency in diagnosis was apparent. Three of the patients had low body mass index (BMI) and the other was overweight. Metabolic decompensation and hospitalisation occurred in three of four patients secondary to extreme risk-taking behaviour with caloric restriction. The coexistence of MCADD and eating disorders is of significant concern, placing the patient at substantial risk of decompensation in an otherwise relatively stable metabolic condition. Awareness of disordered eating in this population is paramount, as early recognition of signs and symptoms of eating disorders in the MCADD population may facilitate prompt intervention and avoidance of morbidity and potential mortality.

Keywords
Medium Chain Acyl CoA Dehydrogenase Deficiency, MCADD, Eating disorders, Young adults, Inborn errors of metabolism.

Introduction
Medium chain acyl-coA dehydrogenase deficiency (MCADD) is the most common disorder of fatty acid oxidation with a varied prevalence depending on ethnicity [1,2]. In Western Australia the incidence has been reported at 1:12,000 live births though it is more common in individuals of European origin, with an incidence of as high as 1:4900 live births reported in German populations [3,4].

Traditionally, patients with MCADD have been considered at relatively low risk of metabolic instability during adulthood, particularly since newborn screening programs were introduced. The risk of decompensation is primarily mitigated by avoidance of fasting and early implementation of treatment plans when unwell [5]. Outcomes in patients with MCADD improved dramatically following the implementation of newborn screening, with a relative risk reduction in adverse events of 74% in the first two years in screened populations [6]. In patients with confirmed MCADD, mortality rates dramatically improved following confirmed diagnosis with one study reporting a reduction from 20% to 0% during six years (median) of follow up post primary diagnosis [7]. Regardless, patients with MCADD remain at risk of severe consequences including hyperammonaemia and related sequelae should they become unwell or unable to maintain adequate caloric intake.

The hallmark of metabolic instability in MCADD is hypoglycaemia with relative hypoketosis secondary to impaired fatty acid oxidation and thus inadequate ketogenesis [1,8]. It should be noted that ketosis may not be absent, rather inappropriate for the degree of hypoglycaemia. Hypoglycaemic

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seizures can result, leading rapidly to metabolic decompensation with risk of death [1].

The management of MCADD focuses primarily on preventative measures with avoidance of fasting to prevent catabolism and hypoglycaemia [2]. Lifelong dietary management is prescribed with recommendations for adequate carbohydrate intake. Restriction of fats below recommended daily intake is controversial, as evidence supporting toxicity secondary to the accumulation of medium chain fats is lacking [9]. Alcohol should also be avoided owing to the additional effects on suppression of hepatic glucose production, accumulation of toxic fatty acids and risks of vomiting with intoxication amplifying hypoglycaemia risk [10].

Eating disorders are common in the general population, particularly in women, with a lifetime prevalence of 8.4% (3.3-18.6) and 2.2% (0.8-6.5%) in women and men respectively, according to a recent global report [11]. These figures, however, likely underestimate the true magnitude of the problem with one report suggesting up to 17% of the population have disordered eating [12] and there is evidence of an increasing prevalence [11]. These disorders most commonly begin in adolescence, although can also arise in adulthood [13].

Eating disorders are associated with substantial physical and psychological morbidity, and the risk of mortality is also significant [14]. Higher rates of disordered eating are known to occur in chronic health conditions involving attention to diet, such as inflammatory bowel disease and diabetes [15]. Within the milieu of inborn errors of metabolism (IEM), where optimum management demands strict attention to diet and relevant modifications to avoid decompensation, it is perhaps unsurprising that disordered eating may arise. However, there is a lack of epidemiological information regarding the prevalence of disordered eating in patients with disorders such as MCADD. We present a case series of 4 female patients with concomitant diagnoses of disordered eating and MCADD, that occurred in young adulthood, highlighting the need for regular review and heightened awareness of the risk of these issues with access to multidisciplinary care if these are diagnosed.

Case Series

Case 1

This patient was first identified with weight loss aged 15, initially attributed to a primary gastrointestinal issue with a diagnosis of functional dyspepsia. On the initial review, in the adult IEM clinic, this 19-year-old female dancer weighed 54.4kg with height 1.69m (BMI 19.05kg/m^2) (Table 1). Thorough dietary review suggested adequate carbohydrate intake appropriate for exercise patterns. Six months later, the patient was admitted to hospital with hypoglycaemia, nausea, vomiting and abdominal pain, on a background of poor oral intake. This followed a weekend of competitive dancing. On presentation the patient was mildly hypoglycaemic (glucose 3.8mmol/L) with normal ammonia necessitating IV dextrose. On examination her weight had declined to 49.8kg (BMI 17.4kg/m^2). A diagnosis of eating disorder was entertained though denied initially by the patient. In time, the patient admitted to anxiety around food with restrictive eating patterns since early adolescence and a diagnosis of Avoidant Restrictive Food Intake Disorder (ARFID) was made. An intensive approach with the metabolic team and specialist eating disorder dietitian was adopted while awaiting review at a specialised eating disorders clinic. Although now well supported, with an improvement in body weight (56kg), the patient remains at high risk of decompensation.

Case 2

At her initial appointment in the adult IEM clinic, this 27-year-old female with multiple food intolerances and allergies (including anaphylaxis) presented with regular ‘unexplained’

Table 1. Characteristics of patients with MCADD and eating disorders.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis on New born screening</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Genetic Mutation</td>
<td>ACADM</td>
<td>unknown</td>
<td>ACADM</td>
<td>ACADM</td>
</tr>
<tr>
<td>Age of Eating Disorder Diagnosis (years)</td>
<td>19</td>
<td>23</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Age of first signs/symptoms of ED * (years)</td>
<td>15</td>
<td>21</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Nadir Weight (kg)</td>
<td>49.8</td>
<td>45.6</td>
<td>42</td>
<td>75.3</td>
</tr>
<tr>
<td>Nadir BMI (kg/m^2)</td>
<td>17.4</td>
<td>17.2</td>
<td>18.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Eating Disorder Diagnosis</td>
<td>ARFID</td>
<td>ARFID</td>
<td>ARFID</td>
<td>Bulimia</td>
</tr>
<tr>
<td>Need for hospitalisation</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Engagement with Eating Disorder Service</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ED – Eating Disorder
*Made in retrospect
ARFID – Avoidant Restrictive Food Intake Disorder
two years (Table 1). The patient was unhappy with this weight loss, the behaviour was concerning.

Background of diarrhoea and reduced oral intake occurred instability, and one presentation for a decompensation on the inflammatory bowel disease in adulthood causing metabolic which progressed to purging after eating. A new diagnosis of transitioning (Table 1). Despite a lack of significant weight gain and began restricting energy intake to 1200 calories per day with a goal of weight loss. Alcohol intake increased (5-6 standard drinks/day). She was subsequently diagnosed with attention deficit hyperactivity disorder with prescription of dexamphetamine, further suppressing her appetite. She required a hospital admission for nausea, vomiting and reduced oral intake although there was no biochemical evidence of decompensation. Currently the patient admits to avoidance of oral intake for up to 18 hours per day, combined with alcohol use at work (increased to 10 standard drinks/day), and inappropriate use of stimulant medications. Nadir BMI was 18.2kg/m² in the context of dexamphetamine use causing loss of appetite. Regular follow ups were often cancelled by the patient and attempts to intervene with the above behaviour, including education regarding significant risks and involvement of other clinicians, have been unsuccessful.

Case 4

This 19-year-old female transitioned to the adult service with known disordered eating and concomitant mental health issues, particularly depression. The history was significant for hospital admissions for decompensations in adolescence related to food restriction. The patient reported unhappiness with body image and desire to lose weight by skipping meals, which progressed to purging after eating. A new diagnosis of inflammatory bowel disease in adulthood causing metabolic instability, and one presentation for a decompensation on the background of diarrhoea and reduced oral intake occurred shortly after transition to adult services. Currently the patient admits to regular oral intake during the day however often fasts for prolonged periods overnight. On examination at the first adult IEM clinic appointment her weight was 81.1kg and height was 1.65m, (BMI 29.8kg/m²), though weight had increased to 85kg at most recent review, 18 months since transitioning (Table 1). Despite a lack of significant weight loss, the behaviour was concerning.

In retrospect, there were signs of disordered eating from mid-adolescence in all patients though notable latency before a formal diagnosis of pathology was made. In the last case, the absence of weight loss may have delayed a diagnosis, though the patient voluntarily disclosed this information. All patients avoided significant sequelae associated with metabolic instability, including significant hypoglycaemia, with early introduction of carbohydrates orally and intravenously in those who required hospital admission.

Discussion

MCADD is an autosomal recessively inherited condition due to genetic mutations in the ACADM gene on chromosome 1p31, which codes for the enzyme responsible for medium chain fatty acid catabolism. The most common associated genotype is a homozygous missense mutation of 985A>G in ACADM, which results in lysine being substituted for glutamic acid in the protein in position 304 (p.Lys304Glu); this is found in approximately 80% of patients [9,16,17,18]. This results in protein misfolding, loss of function, insufficient medium chain acyl-CoA dehydrogenase enzyme production and ultimately accumulation of medium chain acylcarnitines [9,18].

Most cases of MCADD are currently diagnosed through newborn screening programs, with the introduction of this disorder into screening panels in 2005 in Western Australia. Specifically, elevations in medium chain acylcarnitines (C6, C8,C10, C10:1) and an increased C8/C2 ratio suggest this diagnosis [4].

Patients with MCADD are at risk of several life-threatening issues should they develop metabolic decompensation. In previously undiagnosed patients, case series have quoted mortality rates as high as 50% in adults with acute presentations, compared to approximately 25% in the infantile population [10,19]. Phenotypic heterogeneity in MCADD is also apparent, with some patients more prone to metabolic decompensation than others. This may be the result of variability in residual enzyme activity between patients or differences in individual management and timing of initiation of treatment [20]. Thus, all patients with MCADD are at risk of metabolic decompensation and should receive specialist care accordingly.

Cardiac arrhythmias can arise due to medium chain acylcarnitine accumulation, with ventricular arrhythmia being the most common MCADD-associated arrhythmia reported. Supraventricular arrhythmia and ventricular fibrillation progressing to cardiac arrest has also been described [8]. MCADD can be associated with liver dysfunction with evidence of transaminitis and hepatomegaly, secondary to fatty infiltration, in severe life-threatening illness [8,10].

The management of MCADD and many other inborn errors of metabolism necessitates a prescriptive diet from the time of diagnosis. Accordingly, affected patients are required to consider their diet and think about nutrition and thus body
weight regularly. The development of obesity is a risk for patients with MCADD, presumably owing to the reiteration of recommendations to avoid fasting and increase carbohydrate intake, particularly when unwell [19]. Long term outcome studies have demonstrated that these patients are prone not only to excessive weight gain but also to type 2 diabetes [2,19]. These patients may be particularly vulnerable to disordered eating during adolescence, when the influence of peers and body image are paramount, combined with an increase in risk-taking behaviour that accompanies this stage of life. Despite these aspects of management, there are minimal reports of the prevalence and a low awareness of eating disorders in MCADD patients.

Interestingly, despite the risk-taking behaviour displayed by these patients, none developed severe sequelae of restricting carbohydrate intake, with the lowest glucose recorded at 3.8mmol/L. This is higher than the level of 3.0mmol/L, documented to be accepted as the threshold for hypoglycaemia in adults with inherited metabolic disease [21]. Low glucose levels may be observed in healthy patients with low BMI, in part due to lower glycogen stores. Fasting states and catecholamines are known potent stimulators of lipolysis and increase the circulating concentration of fatty acids and glycerol to act as oxidative substrates [22] thus restrictive oral intake needs to be regarded as dangerous in patients with fatty acid oxidation disorders.

The umbrella diagnosis of eating disorder encompasses a range of conditions including Anorexia Nervosa, Bulimia Nervosa, Binge Eating Disorder, Other Specified Feeding and Eating Disorders (OSFED), Avoidant/Restrictive Food Intake Disorder (ARFID), Unspecified Feeding of Eating Disorder (UFED), Rumination Disorder and Pica. Restrictive dieting, compulsive eating and skipping meals are all potential behaviours seen [12]. Most organ systems can be affected by eating disorders though cardiac issues, including arrhythmias and heart failure, may develop and are one of the leading causes of death [23,24,25]. Liver dysfunction with transaminitis can also manifest [26]. The primary pathophysiology is thought to be hepatocyte injury secondary to starvation, though fatty liver can also develop with refeeding [27].

Eating disorders are associated with significant health sequelae themselves, although there are some overlaps between the morbidity outcomes seen in patients with eating disorders and poorly controlled MCADD. Cardiac and hepatic pathology may be common to both diagnoses, albeit via different mechanisms. The potential cardiac stress, often multifactorial in nature, that could arise in patients with both MCADD and disordered eating is of significant concern. Furthermore, a state of starvation regardless of disordered eating, impacts psychologically leading to symptoms of depression and anxiety [26]. The resulting loss of concentration with these psychological states could theoretically exacerbate the risk taking behaviour and inability to follow or institute management plans [28]. The coexistence of these pathologies may amplify the risk of several sequelae placing the patient at significant risk of poor outcome.

Furthermore, patients with eating disorders are often secretive about their behaviour [29], and specific questioning is potentially needed to elicit the diagnosis. Delays in diagnosis are common with one study reporting a median delay of 10-15 years between the onset of symptoms and seeking help in anorexia and bulimia respectively [30]. It is recognised that patients with eating disorders undergo treatment with barriers attributed to personal and health care provider factors [31,32]. Patients may avoid seeking care due to reduced awareness of the severity of these disorders and/or perceived social stigma. A lack of recognition of signs by healthcare providers and lack of appropriate referral may also be implicated [31,32].

Recognition of the prevalence of concomitant eating disorders and explicit attempts to uncover an eating disorder may have led to earlier identification in the patients described in this case series. This approach, however, needs to be undertaken without judgement to ensure patient rapport is maintained. The management of eating disorders is intensive, often necessitating a multidisciplinary approach with regular and graded review [14,26]. Nutritional rehabilitation with management of medical comorbidities and psychological support with behavioural therapy are the principles of treatment [14,26]. However, behavioural interventions may not be effective long term, with vulnerability to relapse highlighting the need for ongoing review [26].

Various models of care exist for management of MCADD in adults. Within the paediatric domain, MCADD patients are typically reviewed more frequently with dietetic assessment and reiteration of education at each visit [33]. As patients reach adolescence and young adulthood however, dietetic input may be less frequent, and focus may shift to other issues including counselling surrounding risk taking behaviour such as alcohol intake, which is a recognised risk for decompensation in this age group [2].

MCADD may be considered a less severe metabolic disorder requiring less medical input compared to other fatty acid oxidation disorders from a patient perspective, but also potentially shared by clinicians. Furthermore, because patients mostly feel well and typically have no evidence of any disease, their risk of metabolic sequelae may be forgotten [2]. Mortality of up to 50% has been reported in undiagnosed patients presenting with an acute metabolic decompensation highlight the significance of this disorder [10]. Arguably, despite a known diagnosis, those patients who are non-adherent to recommended management strategies may face the same magnitude of risk if treatment is not instituted early.

These cases suggest that eating disorders should be considered in the routine assessment of MCADD patients especially during adolescence and young adulthood, which is a challenging period for the delivery of healthcare in general, owing to the gradual independence of the patient from their parents, who until this point had typically helped institute care. More regular review, perhaps with a specific focus on psychological aspects during the young adult years and transition from paediatrics to adult
care, may help facilitate detection of various issues and provide an opportunity for timely intervention.

It has been proposed that the frequency of clinic review for patients with MCADD aged 18 years and older should be biennially, in comparison to 4 visits per year in early childhood [33]. The experience with the patients presented in this case series challenges this notion, potentially transitioning via 6 monthly review during the young adult years perhaps until the age of 25 unless further instability persists. This interval is supported by some other groups, with specific advice to focus on repetition of educational goals in this age group [2]. However, a tailored approach to individual patient care should be practised. Although this case series has limited sample size, the proportion of patients with MCADD and evidence of disordered eating in our clinic was 40%. Accordingly, we suggest that clinicians need to be vigilant regarding the potential for disordered eating in MCADD as well as other metabolic disorders.

Conclusion

Disordered eating is likely more common than currently recognised in patients with metabolic disorders such as MCADD, which predisposes these patients to metabolic decompensation. Specialised dietetic input with the dual focus of detecting disordered eating as well as specific metabolic advice is required lifelong for MCADD patients, though is possibly most crucial during adolescence when patients are at most risk. Further investigations are required to determine the magnitude and optimise the care of disordered eating in patients with metabolic disorders.

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Declaration of Conflicting Interests

The authors wish to declare that there is no conflict of interest.

References


