

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) in the Irish Paediatric Population

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Abstract

Aim

This study aims to investigate the disease frequency of Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) among the Irish population.

Methods

Children (<18 years) with MCADD were identified via the National Centre for Inherited Metabolic Disorders and the metabolic laboratory at Temple Street Children's University Hospital. Central Statistics Office population data was used to calculate epidemiological figures.

Results

From 1998 to 2016, 17 children (<18 years) were diagnosed with MCADD including two patients whose initial presentation was fatal. The mean age at initial presentation was 1.48 years (Range: 0.005 to 2.86). The incidence was 1:71650 with mortality at 15.38%. No child subsequently died post diagnosis. The common c.985A>G mutation accounted for 88% of alleles.

Conclusion

The incidence of MCADD in Ireland is lower than global estimates. The potential for under-ascertainment and late diagnosis of cases exists in Ireland and is of concern for a treatable condition with a significant mortality when undiagnosed. The authors welcome the introduction of MCADD to the National Newborn Bloodspot Screening Program.

Introduction

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) is the most common disorder of fatty acid oxidation and is associated with a significant risk of mortality at first clinical presentation.¹ It is caused by recessive mutations in the *ACADM* gene causing a deficiency of medium chain acyl-CoA dehydrogenase (MCAD), an enzyme required to metabolize medium chain fatty acids and necessary to the mitochondrial beta oxidation of fatty acids and the formation of ketone bodies.^{2,3,4,5} Genetic deficiency of the MCAD enzyme, known as MCADD, leads to improper metabolism of medium chain fatty acids, resulting in their accumulation in the blood along with decreased ketogenesis and gluconeogenesis.⁵ The metabolic crisis presents clinically as hypoketotic hypoglycemia and encephalopathy at times of decreased dietary glucose intake or increased metabolic expenditure.^{2,3,4} Without rapid treatment it can result in liver and brain damage, and subsequent death.⁵

Patients with MCADD typically present within the first two years of life (3-24 months) in an encephalopathic state with clinical features such as vomiting, lethargy, and seizures, which can progress to coma and/or death. This episode is usually prompted by fasting related to an intercurrent illness such as gastroenteritis.^{3,4} The diagnosis of MCADD is confirmed through the acylcarnitine profiling by tandem mass spectrometry of dried blood spots or plasma. In the Republic of Ireland, MCADD has just very recently (in December 2018) been incorporated into the National Newborn Bloodspot Screening Program and there is no published data characterizing the disease frequency in this population. Following the death of two children due to MCADD in Ireland, the current study aims to characterize the epidemiology and clinical features of MCADD in the Irish population in the pre-screening era to inform policy with regards to newborn screening and future studies.

Methods

Children under 18 years of age diagnosed with MCADD in the Republic of Ireland were identified via the National Centre for Inherited Metabolic Disorders (NCIMD) and the metabolic laboratory at Temple Street Children's University Hospital (TSCUH). Clinical and demographic data (i.e. age & sex) were gathered from the patients' clinical chart for those attending NCIMD. Clinical data obtained included cause of, and age at, initial metabolic decompensation, symptoms at presentation such as features of encephalopathy, and results of laboratory investigations including genetic testing for *ACADM* mutations. Population data was obtained from the Central Statistics Office (www.cso.ie) and used to calculate epidemiological figures. The study was conducted with the approval of the TSCUH Research and Ethics Committee.

	Mutation Analysis			
		Total	Frequency	Percentage
Allele	c.985A>G	22	0.88	88%
	c.583G>A	1	0.04	4%
	c.157C>T	1	0.04	4%
	c.799G>A	1	0.04	4%
Genotype	.985A>G/c.985A>G	8	0.5714	57.14%
	c.985A>G/unknown	3	0.2143	21.43%
	c.985A>G/c.583G>A	1	0.0714	7.14%
	c.985A>G/c.157C>T	1	0.0714	7.14%
	c.985G>A/c.799G>A	1	0.0714	7.14%

Table 1: Table showing allele and genotype data of patients diagnosed with MCADD in Ireland. The majority were homozygous for the common *ACADM* mutation (c.985A>G). Three were compound heterozygotes sharing the common c. 985A>G mutation. Three other patients had just one mutation detected (c.985A>G) on common mutation analysis, however, were diagnosed with MCADD due to characteristic biochemical features.

Results

Epidemiology

From 1/1/1998 to 30/8/2016, 17 children were diagnosed with MCADD in Ireland. Of these, four children were diagnosed via family screening and two patients were diagnosed post mortem. The average age at clinical presentation was 1.48 years (Range: 0.005 to 2.86). The childhood incidence of MCADD during this period was calculated to be 1:71650 children with a mortality rate of 15.38% in the first clinical presentation. No child died following a diagnosis of MCADD being made. The common c.985A>G mutation accounted for 88% of alleles with 57.14% of patients being homozygous for the common mutation (Table 1). The current prevalence of MCADD in the Irish paediatric population was calculated to be 1.23 per 100,000 children.

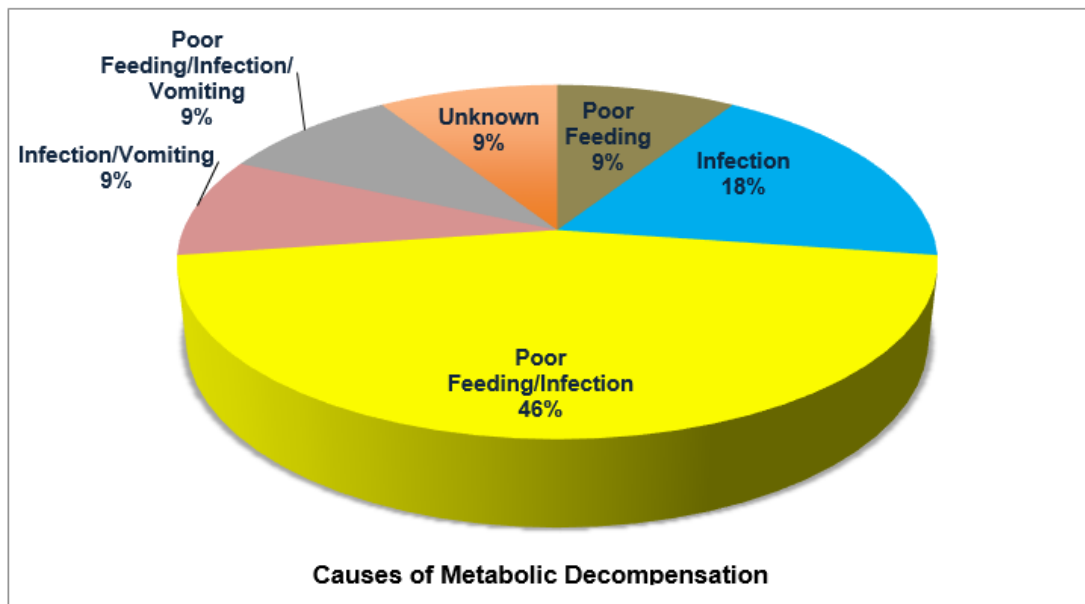


Figure 1: Chart showing most common causes and combinations which resulted in initial clinical decompensation and diagnoses in patients who survived.

Clinical Features of Survivors

Of the 15 children who attend NCIMD, the commonest cause of initial decompensation involved a combination of infection and poor feeding (Figure 1). All patients who were symptomatic at presentation had features of encephalopathy and 72.7% of patients were hypoglycemic (blood glucose levels < 2.6 mmol/l) at presentation with 63.6% having detectable ketones, however, the degree of ketosis was not able to be accurately determined in retrospect. All children who survived their initial clinical presentation (n=11) suffered no known long-term disability. The four children who were diagnosed through high risk screening due to a positive family history have not had any metabolic crises due to pre-emptive treatment during times of metabolic stress (e.g. intercurrent illness).

Discussion

While the incidence of MCADD in Ireland at 1 in 71650 is lower than European estimates, the current study's findings support a previously unpublished study where 1000 Irish newborn bloodspot screening cards were screened for the common mutation and an incidence was calculated at 1 in 66,000 births using the Hardy Weinberg equation (Personal communication, PD Mayne).

Within Europe, countries which have established newborn screening (NBS) for MCADD report higher incidences, ranging from 1:4,900-1:24,900 (Figure 2).³ Internationally, Tandem Mass Spectrometry is used for routine newborn screening for MCADD.³ In Ireland, until very recently, the diagnosis of MCADD relied on symptomatic presentation and screening of at-risk family members. Two known deaths (15.38%) have occurred during the study period in Ireland due to symptomatic presentation. However, it must be mentioned that one child would not have benefited from a NBS program due to death occurring in the first days of life, prior to the 72-120 hour period when NBS sampling is usually performed.^{1,3,4} The outcome of successful treatment following diagnosis within the Irish healthcare system highlights the treatable nature of the disease.^{3,4} The mainstay of treatment is avoidance of fasting and ensuring adequate glucose intake to prevent lipolysis during times of metabolic stress such as intercurrent illness.

In Ireland, the potential for under-ascertainment and late diagnosis of MCADD exists and is of concern for a treatable condition which has a significant risk of mortality when undiagnosed. The current study's findings will allow better understanding of national disease characteristics. The authors support and commend the very recent introduction of newborn blood spot screening for MCADD and it is anticipated that morbidity and mortality due to MCADD will decline in the decades to come.

Declaration of conflicts of interest:

The authors have no conflicts of interest to declare.

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