J Inherit Metab Dis (2016) 39:171–172
DOI 10.1007/s10545-015-9906-9

EDITORIAL

3-Methylcrotonyl-CoA carboxylase deficiency: to screen or not to screen?

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Received: 18 November 2015 / Revised: 27 November 2015 / Accepted: 27 November 2015 / Published online: 11 December 2015

In this issue of the Journal a paper from Israel describes the biochemical, molecular, and clinical data of all the patients with 3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD) diagnosed as a result of 50 months of extended newborn screening—16 newborns, 20 affected mothers, and four other family members. Based on this report of mainly asymptomatic subjects, the Israeli Ministry of Health has decided to exclude 3-MCCD from routine newborn screening.

This is not the first paper to present these sorts of data. In the last 5 years six papers have reported on some follow-up of over 200 newborns with 3-MCCD detected by newborn screening. Overwhelmingly these subjects have either remained asymptomatic, or, in the few with symptoms reported, there was no clear relationship between symptoms and residual enzyme activities and some symptoms were probably not related at all to 3-MCCD. Not all were asymptomatic. Grünert et al (2012) report on 53 screen-detected children aged 2–12 years 13 of whom reportedly had symptoms. Again, not all symptoms (e.g., in a child with trisomy 21) were related to 3-MCCD, but five patients had had one or more metabolic decompensations, with hypoglycaemia and ketonaemia. This series was somewhat selective—samples were referred to a central expert laboratory for enzymatic and molecular analysis. There is also another report of metabolic decompensation in a screen-detected child.

This presents a dilemma that is becoming familiar in the expanded newborn screening of today: cases of disordered biochemistry with unclear clinical significance are being detected too often for comfort. For some disorders such as short-chain acyl-CoA dehydrogenase deficiency it is now apparent, although not universally accepted, that the disorder is benign and should not be included in screening. For 3-MCCD it is a little different, as there is a clear phenotype, metabolic decompensation with hypoglycaemia, ketonaemia and severe metabolic acidosis, that is found in a few cases. Making such a diagnosis can be beneficial, as clear instructions can be given so as to avoid or greatly shorten any decompensation during intercurrent illness. However, it can also be harmful; it is apparent that following diagnosis most children are medicalized to some extent, and even asymptomatic children are likely to be treated with a low protein or low-leucine diet, and certainly with carnitine. A diet is very intrusive. A Delphi-based consensus protocol (Arnold et al 2008) showed that a hand-picked group of clinicians did not recommend a diet for asymptomatic children or mothers, but in the real world it seems that probably half or more are receiving such treatment (Lam et al 2013).

We do not know what proportion of 3MCCD subjects will ever become sick—something perhaps like 4–5 %—but we should consider carefully the question: if 3-MCCD was considered today for new inclusion in a

Communicated by: Mike Bennett

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newborn screening program would it be recommended? With next-generation sequencing on the screening horizon this is a very serious question which may be repeated time and again for more and more conditions. To paraphrase a quotation attributed to Aldous Huxley—soon we will have scarcely a healthy baby left.

Compliance with Ethics Guidelines

Conflict of interest None.

This article does not contain any studies with human or animal subjects performed by the author.

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