Disorders of Vitamin B12 Metabolism Presenting Through Newborn Screening

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Abstract

Elevated propionyl C3 carnitine is the most common abnormality seen in tandem mass spectrometry newborn screening profiles, with an incidence of 0.15% seen in our South Australian newborn screening programme. The most common cause for this result in our population is vitamin B12 deficiency but differential diagnoses include the inherited disorders of propionic and methylmalonic acid metabolism and cobalamin deficiencies. An approach to confirmatory testing and subsequent management of infants with elevated propionic carnitine is presented.

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Detection of disorders of B12 metabolism in the newborn period by tandem mass spectrometry relies on finding elevated propionyl (C3) carnitine or methylmalonyl (C4DC) carnitine. Although sensitive, C3 carnitine is not specific for a single condition. It is a marker of vitamin B12 deficiency and propionic academia as well as the methylmalonic acidurias, caused by deficiencies of the methylmalonyl coenzyme A mutase apoenzyme (*mut*o, *mut*-), or its cofactor adenosylcobalamin, as well as the cobalamin abnormalities, *cblC*, *cblD*, and *cblF* deficiencies, all of which have associated homocystinuria.

Mass newborn urine screening for methylmalonic aciduria has been performed on 1,745,753 newborn samples collected at age 21 days in Quebec since 1975.[1] This programme has provided valuable information on the spectrum of methylmalonic aciduria: from severe, neonatal acidosis to benign asymptomatic organic aciduria. In this population, the incidence of symptomatic methylmalonic aciduria is 1 out of 83,131 births with persistent benign methylmalonic aciduria seen in a further 1 out of 49,900 births. Importantly for this latter group, low to moderate methylmalonic acid excreters without determined biochemical phenotypes had normal outcomes and, when reviewed at 1 year, the MMA excretion had resolved in half of these individuals.[1]

In the South Australian newborn screening programme, elevated C3 carnitine is the most common abnormality seen in the acyl carnitine profile. Repeat blood spot sampling has been performed in 280 infants out of 191,464 screened (0.15%), with a higher recall rate (0.6%) seen in the central Australian (Northern Territory) population. Nine babies with higher metabolite levels or ratios have been recalled for clinical review and further testing (rather than re-sampling) and 8 of these have been shown to be deficient in vitamin B12. All 8 babies tested have had elevated plasma methylmalonic acid but only mildly elevated urine methylmalonic acid was seen in only 2 infants, and in the others, it was normal. We have seen no cases of methylmalonic aciduria or propionic aciduria but 1 case of cobalamin D deficiency presented clinically in the early days of the programme.

The foundation of confirmatory testing is urine organic acid analysis, looking for methylmalonic acid, propionic acidemia metabolites and ketones. Urine and/or plasma amino acid analysis should be performed with particular attention paid to levels of methionine, glycine, homocystine. Plasma total homocysteine and Vitamin B12 estimation should be performed but B12 levels may not reliably predict deficiency. If available, stable isotope quantitation of plasma and urine MMA should be performed. Of great

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Table 1. Acute Management after Recall will Depend on Whether the Baby is Sick or Well.

If Baby is sick	**If Baby is well**
Contact metabolic specialist	Counsel parents
Admit to hospital	Take diagnostic samples
Check blood pH	Encourage breast feeding (low protein content)
Take diagnostic samples	Give vitamin B12 1 mg intramuscular injection if deficient or significant level of MMA
Stop all protein (short term)	Warn parents of possible decompensation with viral illness
Calorie supplement parents are concerned	Write action plans for if/when
(dialysis or haemofiltration may be required in propionic acidemia)	Provide copy of action plan to:· • Parents • Local hospital • Local medical service
Give B12 1 mg IMI	Arrange follow up
Counsel parents	
Cardiac and renal function testing	

assistance is the clinical response to treatment with vitamin B12. Specific enzyme assays on cultured skin fibroblasts are available in specialist laboratories in Basle, Switzerland (Dr Brian Fowler) and Montreal, Canada (Dr David Rosenblatt).

REFERENCES

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