A Case of Acquired Methymalonic Aciduria Secondary to a Subclinical Maternal Pernicious Anaemia

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Abstract

Inherited methymalonic acidurias are a group of autosomal recessive disorders caused by mutations in the genes encoding methylmalonyl-CoA mutase and proteins involved in cobalamin (Vitamin B12) metabolism. Methylmalonic aciduria can also arise as a result of severe cobalamin deficiency. We report the case of a male infant presenting at 5 months of age with a cobalamin sensitive methylmalonic aciduria, pancytopaenia, developmental delay, failure to thrive, hepatosplenomegaly and hypotonia. MRI brain imaging showed reduced white matter quantity and maturity. The cause was investigated and discovered to be a maternal subclinical pernicious anaemia. A rapid clinical improvement was made upon initiation of B12 supplementation. At follow up aged 18 months weight was above the 91st centile and height between the 75th and 90th. Although no delay in fine motor or social skills was noted at 18 month assessment, gross motor and language delay persisted and may reflect central nervous system damage due to the initial B12 deficiency.

Methylmalonic aciduria is relatively frequently detected in patients with lack of dietary B12. If careful assessment of the diet does not provide the answer, it is important to perform laboratory investigations even if no clinical signs or symptoms of pernicious anaemia can be detected. Cobalamin deficiency is common due to dietary restriction or malabsorption. As severe maternal cobalamin deficiency during pregnancy and breastfeeding can lead to devastating effects on the child, universal screening of cobalamin level in pregnancy should be considered.

Keywords: Anaemia; Methylmalonic aciduria; Cobalamin; Mutation

Abbreviations:

Cbl: Cobalamin; TDS: Three Times Daily; MMA: Methylmalonic Aciduria; LSCS: Lower Segment Caesarean Section

Introduction

Methylmalonic acid serves as a metabolic intermediary in the formation of succinyl-CoA via the action of methylmalonyl-CoA mutase. This reaction requires Cobalamin (Cbl) as a cofactor. Without it, methylmalonyl-CoA mutase cannot function and the levels of methylmalonic acid in blood and urine are greatly increased. The dietary lack of Cbl has been termed ‘acquired methylmalonic aciduria’ [1]. This is in contrast to ‘classical’ methylmalonic aciduria, which is an inborn error of metabolism due to defects in either Cbl metabolism or methylmalonylmutase activity [2,3].

Cbl also plays an important role in the synthesis of methionine from homocysteine through its action as a cofactor of methionine synthase [4], and, therefore, hyperhomocysteinaemia often also occurs. Here, we present the case of an infant with methylmalonic aciduria secondary to a congenital Cbl deficiency due to maternal subclinical pernicious anaemia.

Case Report

This male infant of Russian non-consanguineous parents was born at 41 weeks gestation via an emergency section, with a birth weight of 3.8 kg. He presented aged nine weeks with hepatosplenomegaly, pallor, a reduced interest in food, and a reduced level of consciousness. He had been otherwise asymptomatic until this point. He is the firstborn child and his mother has suffered three previous miscarriages. His full blood count showed he was anaemic with haemoglobin of 5.5 g/dL (reference range 2.4-8.8 g/L), platelets of 0.5x109/L (reference range 2.5-6.4). At this point he received a single unit of packed red blood cells and was discharged. He was readmitted one month later with pneumonia and was noted at this point to have hypogammaglobulinaemia, IgG 0.9 g/dL (reference range 2.4-8.8 g/L), IgA 0.07 g/L (reference range 0.1-0.5 g/L), IgM 0.24 g/L (reference range 0.2-1.0 g/L) Further Immunology investigations did not suggest a serious primary immunodeficiency.

The patient was started on intravenous immunoglobulin therapy given once every three weeks. He was followed up for this as an outpatient by the Immunology department at Great Ormond Street Hospital.

He was readmitted aged five months with anaemia, developmental delay, and hypotonia. An MRI brain scan at 5 months of age showed a reduced cerebral volume for age, a lack of white matter bulk and a delay in the maturation of myelin. Growth was proceeding along the...
25th centile for both head circumference and weight. At this point metabolic testing was carried out which noted a high ammonia (153 μmol/L; reference range <40), borderline high lactate of 2.8 mmol/L (0.7-2.1) and strongly raised urinary methylmalonate (3290 μmol/mol creatinine; reference range 0-30) and methylcitrate (107 μmol/mol creatinine; reference range 0-25).

At the time of diagnosis urinary methylmalonate had risen to 4280 μmol/mol creatinine and methylcitrate 179 μmol/mol creatinine.

He was started on oral vitamin B12 120 ml 3 hourly, L-carnitine 250 mg TDS and hydroxycobalamin1mg IM daily. After two days of this treatment there was a marked biochemical improvement, with ammonia normalisation at 34 μmol/L (reference range <40), and urinary methylmalonic acid falling to 19 μmol/mmol creatinine (Cbl levels became >1000 ng/L; reference range 293-1210).

Prior to this admission the child had been exclusively breastfed and the parents were advised to start formula feeds. A month after starting Cbl supplementation and formula feeds full blood count showed normal haemoglobin and platelet counts but a persistently low neutrophil count (0.65x10^9/L) (reference range 2.5-6.4).

In search of a cause for the infant’s initially elevated urinary methylmalonate, cobalamin studies were done on both parents. As there was a continued clinical improvement the infant was discharged from hospital after a week’s treatment with Cbl. It was discovered at this point that his mother had low Cbl level without any dietary clues such as exclusion of B12 sources from the diet. Further investigations revealed increased plasma homocysteine level and urine methylmalonic acid. Intrinsic factor antibody levels were raised suggesting an underlying diagnosis of pernicious anaemia.

Interestingly the maternal full blood count was normal, with a haemoglobin of 12.4 g/DL (reference range 12-16 g/DL), mean corpuscular volume of 93fl (reference range 80-100fl), platelets 230x10^9/L (reference range 150-400x10^9/L), white cell count 6.9x10^9/L (reference range 4-11x10^9/L), neutrophils 3.58x10^9 (reference range 2-7.0x10^9/L). It was postulated that there was, therefore, an inadequate supply of Cbl provided during the course of the pregnancy and breastfeeding, resulting in the acquired methylmalonic aciduria.

The patient was followed up at routine outpatient appointments where it was noted that by nine months of age he was on the 75th centile for weight and between the 75th and 50th for height. He was fed with normal diet and the Cbl were stopped. By 17 months he was just above the 91st centile for weight and between the 75th and 50th for height. He was noted to be age appropriate for development in his personal and social interactions, and his eye and hand coordination. He was noted to have a slight delay in his use of language and gross motor development.

Immune system support was continued in the form of an intravenous immunoglobulin infusion three times weekly from the age of 5 months until he was 18 months of age. It was then noted that his IgA had normalised, and the only remaining immunoglobulin abnormality was low IgM levels at 0.21 g/L (reference range 0.5-2.2 g/L). It was felt that there was no further need to continue IVIg infusions and the child has remained well 9 months after stopping the infusions and has no infections requiring antibiotics. He remains healthy at 2 years and two months of age. His IgG is slightly below the normal limit at 3.22 g/L (reference range 3.7-15.8 g/L) and his IgM levels are persistently low at 0.26 g/L (reference range 0.5-2.2 g/L). Given the absence of any infection it was felt that this was not an indication to continue supplementation. He will continue to be monitored.

**Discussion**

Methylmalonic acid elevation can result from: 1) Cbl deficiency, 2) inborn errors of metabolism, or 3) renal impairment [5]. The elevated urinary methylmalonic acid coupled with haematological abnormalities the clinical and biochemical improvement made once supplementation with Cbl began makes it very likely that Cbl deficiency was the underlying cause in this case. Although it is rare to see levels of methylmalonic acid:creatinine ratios as high as 4890 µmol/l in cases where the elevation is secondary to Cbl deficiency it is important, therefore, to consider all of the possible differential diagnoses for a raised methylmalonic acid, as the degree of rise seen does not necessarily point towards any specific diagnosis [6].

Cbl deficiency of any cause is common, with a prevalence of between 50-200 people/100,000 in the UK [7]. Pregnancy is known to be associated with an increased consumption of Cbl [8], the majority of which is utilised by the placenta. Pregnancy is therefore also associated with an increased risk of Cbl deficiency [9] independent of any haemodilution.

Under normal circumstances infants will receive a store of about 20-25 µg of Cbl from their mother during gestation. This will be sufficient to last 6-8 months [10] even with a Cbl deficient diet [11]. If, for any reason, there is a reduction in maternal stores of Cbl during the course of the pregnancy then it will not be possible to pass a suitably large reserve on to the infant. Symptoms of deficiency usually appear between 4-6 months of age [12] and are most commonly secondary to exclusively breast feeding mothers with vegan or vegetarian diets or pernicious anaemia [13]. This is in contrast to those with ‘classical’ methylmalonic aciduria, who will typically present within hours to weeks of birth [3]. In mothers with reduced Cbl levels, particularly those who, themselves, remain asymptomatic, exclusively breastfeeding an infant for the first months of life can lead to the development of deficiency [14].

The typical presentation of an infant with Cbl deficiency includes failure to thrive, feeding difficulties, hypotonia, lethargy, tremors, hyperirritability, and coma [13]. With prompt treatment with supplementation of Cbl there will be a rapid improvement, and, indeed, the majority of infants with Cbl deficiency do make this recovery. However, the longer the infant is left deficient, the greater the likelihood that they will develop irreversible residual neurological damage. The majority with Cbl deficiency that are treated within 3-6 months will show a full recovery, with no further neurological sequelae [15].

The damage caused by infantile deficiency of Cbl occurs typically in the first 6 months of life, and, as such, may affect the maturation of oligodendrocytes and myelination of the brain [16]. Indeed, this can result in permanent neurological impairment.

It is possible that hypogammaglobulinaemia can occur secondary to Cbl deficiency, and, this child was more profoundly hypogammaglobulinaemic than in most children affected by transient hypogammaglobulinaemia of infancy. This apparent phenomenon has been reported before in both infants [17] and adults [18]. However, the exact mechanism remains unclear.

The key to managing infants with a high methylmalonic aciduria is a high degree of suspicion of possible Cbl deficiency, early recognition.
of the symptoms, and an appropriate intervention at the earliest possible opportunity. The risk of permanent neurological damage is greatest in those where the maternal deficiency is unknown and where there is a significant diagnostic delay [14]. It has also previously been shown that pernicious anaemia may present non-classically, or may be asymptomatic. This puts all progeny of mothers with this disease but few or no symptoms [19], as shown in this case, at an increased risk of diagnostic delay. A high index of suspicion for low maternal Cbl levels should be maintained in children presenting with Cbl responsive methylmalonic aciduria even if the mother is asymptomatic.

Given the prevalence of Cbl deficiency in pregnancy and the irreversible damage that can result from Cbl deficiency, it may be time to consider the use of screening for B12 deficiency in pregnancy or the peripartum to prevent cases similar to that described here. Both methylmalonic acid and total homocysteine are more sensitive and specific tests, with methylmalonic acid more specific than total homocysteine, compared to total Cbl [20,21]. This is due, in part, to only 20% of total Cbl being bound to transcobalamin II and therefore available for metabolism. It is, therefore, a poor marker for the bioavailability of Cbl [22]. With this in mind, any nascent screening programme may consider using urinary methylmalonic acid levels as either a standalone screening test or alongside the other measures of Cbl deficiency described above.

Take Home Message

In infants presenting with methylmalonic aciduria a high degree of suspicion about low maternal cobalamin levels should be maintained, even if the mother is asymptomatic.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Author Contributions

SG collected the data and wrote the manuscript. HP, AJ, RL co-wrote and reviewed the manuscript; PG conceived the idea and reviewed the manuscript.

References