Megaloblastic anaemia, diabetes and deafness in a 2-year-old child

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To cite this article: Alan Davidson FCPaed, Patricia S Hartley FC Paed, Peter Berman MMed (ChemPath) & Margaret H G Shuttleworth MMed (Haem) (2005) Megaloblastic anaemia, diabetes and deafness in a 2-year-old child, Journal of Endocrinology, Metabolism and Diabetes of South Africa, 10:2, 62-63, DOI: 10.1080/22201009.2005.10872119

To link to this article: http://dx.doi.org/10.1080/22201009.2005.10872119

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First described by Rogers, thiamine-responsive megaloblastic anaemia (TRMA) is a rare autosomal-recessive disorder characterised by megaloblastic anaemia, insulin-dependent diabetes mellitus and sensorineural deafness.1

The diagnosis is supported by a megaloblastic bone marrow, particularly the presence of ringed sideroblasts.2 Paranuclear iron-laden mitochondria are seen in normoblasts on electron microscopy.2 The diagnosis can be confirmed by demonstrating apoptosis in skin fibroblasts cultured in thiamine-depleted medium. Where available, DNA sequencing is definitive.3

There is rapid reticulocytosis after thiamine administration. We recommend a trial of therapy for megaloblastic anaemia not responding to folate and vitamin B₁₂, especially in a deaf and/or diabetic child.

Case report

A 2-year-old girl was seen at a regional hospital at the age of 1 year with severe macrocytic anaemia and diabetic ketoacidosis (DKA). She was transfused and commenced on folate and was discharged off insulin without further monitoring of her blood glucose. At follow-up she was found to have a chronic macrocytic anaemia with a high serum lactate dehydrogenase. A presumptive diagnosis of a congenital haemolytic disorder was made, and she was maintained on folate.

After another episode of DKA, she was referred to our service. There was no history of neonatal jaundice, and no family history of anaemia or consanguinity. Her motor milestones were normal but she had never acquired meaningful speech, being able only to babble.

She was well nourished, pale without jaundice and there were no dysmorphic features. She was profoundly deaf. Audiological assessment confirmed severe bilateral sensorineural hearing loss. Control of her diabetes required 18 units of insulin daily.

Her haemoglobin concentration was 5.4 g/dl with a mean cell volume of 101 fl, and a reticulocyte count of 68 x 10⁷/μl (1.4% corrected). The white cell count and differential count were normal, as was the platelet count. The smear revealed oval macrocytes and poikilocytosis. Red cell folate (2.114 ng/ml), serum vitamin B₁₂ (615 pg/ml) and ferritin (184 ng/ml) levels were normal. Investigations for
intracellular thiamine depletion. Hence TRMA patients appear adequate to protect other tissues from uptake by a separate low-affinity, high-capacity system transport of thiamine by this facilitated transport system transport of thiamine across cell membranes. The rapid First identified in 1999,6 the product of this gene is a high- mutations of the SLC19A2 gene located on chromosome 1. This autosomal-recessive disorder is the result of elucidated.

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The patient was given a hearing aid, and discharged to the regional hospital on lifelong thiamine supplementation.

Three years after diagnosis the patient maintains a haemoglobin concentration of 12.2 g/dl with a mean cell volume of 92 fl and requires 3 - 5 units of insulin daily. She has been referred to a school for deaf children.

Discussion

Rogers et al1 first reported TRMA in 1969. They described an 11-year-old girl with megaloblastic anaemia, diabetes and deafness. The molecular biology has recently been elucidated.

This autosomal-recessive disorder is the result of mutations of the SLC19A2 gene located on chromosome 1. First identified in 1999, the product of this gene is a high-affinity thiamine transporter7 that mediates facilitated transport of thiamine across cell membranes. The rapid transport of thiamine by this facilitated transport system appears to be essential only for haematopoietic, pancreatic islet and auditory nerve cell function. Passive uptake by a separate low-affinity, high-capacity system appears adequate to protect other tissues from intracellular thiamine depletion. Hence TRMA patients with adequate dietary thiamine seldom manifest the classic signs of severe thiamine deficiency typical of beriberi, including peripheral neuropathy, cardiomyopathy and central nervous system involvement.

A consequence of intracellular thiamine depletion is a decrease in activity of thiamine-dependent transketolase, thereby critically reducing the synthesis of ribose via the non-oxidative arm of the pentose phosphate pathway.7 Lack of ribose for nucleic acid synthesis leads to cell-cycle arrest and triggers apoptosis. It has been suggested that cumulative cell loss in sensitive tissues explains why the clinical manifestations are not apparent in early infancy.8 The gradual decline in glucose tolerance seen in our patient is consistent with this hypothesis.

Thiamine supplementation in pharmacological doses can compensate to a degree by increasing passive uptake via the low-affinity system. The ability of pluripotent haematopoietic stem cells to repopulate the bone marrow after the death of thiamine-deficient red cell precursors explains the recovery of the red cell indices. Ongoing macrocytosis demonstrates that their thiamine-replete successors remain sensitive to the high-affinity transport defect.7 Low-turnover pancreatic beta cells and auditory nerve cells presumably require thiamine primarily to maintain their adenosine triphosphate (ATP) levels by oxidative phosphorylation, rather than for nucleic acid synthesis. Beta cells seem to be of intermediate sensitivity to intracellular thiamine depletion, demonstrating a degree of recovery with supplementation, whereas auditory nerve cells are exquisitely sensitive, presumably because of their higher energy requirements. Here ongoing apoptosis results in irreversible deafness.

Our patient ran a typical course with rapid improvement in the anaemia and a partial response with regard to insulin requirements. The sensorineural hearing loss has not improved, and this is consistent with the experience of others.1 We suggest that the typical clinical presentation together with megaloblastosis in the face of normal vitamin B12 and folate levels should prompt a therapeutic trial of thiamine. Fibroblast culture or DNA sequencing would be definitive.