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

To the Editor: Megaloblastic anaemic in childhood is usually caused by dietary folate deficiency or, rarely, congenital disorders of vitamin B_{12} or folate metabolism. Thiamine-responsive megaloblastic anaemia (TRMA) is a rare autosomal-recessive disorder caused by inactivating mutations of a thiamine transporter gene.[1]

We report on a 2-year-old girl referred after 2 episodes of diabetic ketoacidosis. She was clinically pale and had sensorineural deafness. Control of her diabetes required 18 units of insulin daily.

Her haemoglobin concentration was 5.4 g/dl, the mean cell volume 101 fl, and the corrected reticulocyte count 1.4%. There were oval macrocytes on the blood smear. Red cell folate and serum vitamin B_{12} levels were normal. Her bone marrow aspirate was hypercellular with predominantly erythroid hyperplasia and trilineage megaloblastic dysplasia. An iron stain showed numerous ringed sideroblasts (20%).

A provisional diagnosis of TRMA was made and we administered an intramuscular dose of 100 mg of thiamine, followed by 50 mg daily by mouth. There was a rapid reticulocytosis (10.2%) and the haemoglobin concentration increased to 9.8 g/dl after 14 days. Her daily insulin requirements fell to 4 units. Unfortunately attempts to demonstrate apoptosis of fibroblasts in a thiamine-free medium proved unsuccessful.

Three years after diagnosis the patient receives 100 mg of oral thiamine daily, maintains a haemoglobin concentration of 12.2 g/dl and requires only 3 - 5 units of insulin daily. She has a hearing aid and attends a school for deaf children.

TRMA is the result of mutations of the SLC19A2 gene (chromosome 1), which codes for a high-affinity thiamine transporter.[2,3] Rapid transport of thiamine by this facilitated transport system appears to be essential only for haematopoietic, pancreatic islet and auditory nerve cell function. Cumulative cell loss via apoptosis explains why the clinical manifestations are not apparent in early infancy.[4] Passive uptake by a separate low-affinity, high-capacity system appears adequate to protect other tissues from intracellular thiamine depletion. Hence TRMA patients receiving adequate dietary thiamine seldom manifest the classic signs of beriberi (peripheral neuropathy and cardiomyopathy). Thiamine in pharmacological doses compensates by increasing passive uptake via the low-affinity system in the affected tissues.

Our patient ran a typical course with a rapid improvement in the anaemia and a partial response with regard to insulin requirements on thiamine supplementation, but characteristically the sensorineural deafness has persisted.[1]

We suggest that megaloblastic anaemia with normal vitamin B_{12} and folate levels should prompt a therapeutic trial of thiamine, particularly in a deaf and/or diabetic child.

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Sulpiride and breastfeeding

To the Editor: I have been informed by a number of women that in order to promote the production/flow of breastmilk their obstetrician-gynaecologist has prescribed sulpiride. The dosage used is on average 50 mg 3 times a day. The practice of prescribing sulpiride appears to have become widespread and I am concerned about the liberal use of a psychotropic agent that has the potential to affect the newborn infant's neurobiological system.

According to the Maudsley Guidelines all psychotropics pass into the breastmilk so no decision is risk-free. The *Psychotropic Drug Directory*[1] states the following: 'Breast milk is more acidic than plasma so basic compounds may be retained and concentrations accumulate. Drug binding to milk protein is less than to plasma proteins and the higher lipid content of the 'hind' milk makes it likely to have a higher drug concentration than the first half. Milk levels are usually around 1% of maternal plasma levels, but there have been few formal studies. Furthermore drugs should be avoided if the infant is premature (or has renal, hepatic, cardiac or neurological impairment).'

As sulpiride at low dose acts as a dopaminergic agent it is likely to have an influence on dopamine release and therefore receptor synthesis in the newborn. This effect in turn may have an impact on early neurodevelopment as well as behaviour. Dopamine as a key neurotransmitter is implicated in a number