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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1. Thiamine-Responsive Megaloblastic Syndrome; TRMA. **http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id 249270** (last accessed 29 December 2004).
2. Stagg AR, Fleming JC, Baker MA, Sakamoto M, Cohen N, Neufeld EJ. Defective high-affinity thiamine transporter leads to cell death in thiamine-responsive megaloblastic anaemia syndrome fibroblasts. *J Clin Invest* 1999; **103:** 723-729.
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4. Diaz GA, Banikazemi M, Oishi K, Desnick RJ, Gelb BD. Mutations in a new gene encoding a thiamine transporter cause thiamine-responsive megaloblastic anaemia syndrome. *Nat Genet* 1999; **22:** 309-312.

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

of psychiatric and neurological disorders and one questions the practice of prescribing an agent such as sulpiride for breastfeeding mothers.

Research has shown that several processes affecting brain structure such as myelination of axon fibres, arborisation of neurons and synaptogenesis occur after birth, and medical practitioners are therefore duty bound to warn breastfeeding mothers of the potential risk to the newborn infants when prescribing a psychotropic agent.

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1. Bazire S. *Psychotropic Drug Directory. Salisbury*, UK: Fivepin Publishing, 2003/04: 209-216.
2. Stahl SM. *Essential Psychopharmacology*. 2nd ed. Cambridge: Cambridge University Press, 2002.

High expenses for doctors

To the Editor: I refer to the letter by Dr Ger[1] in a recent issue of the *Journal*. Numerous educational studies have shown that memory retention among health care professionals is poor, and that practical skills deteriorate within months of training.[1] Indeed, as Dr Ger states, 'Knowledge … is poor after one year rewrite or lose your licence to practice' has been the policy in many leading international medical institutions for many years, particularly in the USA.

Although annual recertification in basic and advanced life support skills may be optimal, the Resuscitation Council of Southern Africa has adopted the American Heart Association policy of recommending renewal in Advanced Cardiovascular Life Support (ACLS) and Paediatric Advanced Life Support (PALS) training every 2 years for health care professionals with a duty to respond to a cardiac or paediatric emergency.

ACLS and PALS courses offered by the Resuscitation Council of Southern Africa, recognised as being of the highest international standard and utilising simulators and equipment costing between $^1/_4$ and $^1/_2$ a million rands, are attended by doctors, nurses and paramedics from all over South Africa and worldwide, as they are being offered at a fraction of the price of similar overseas advanced life support courses.

We note that Dr Ger would like his SAMA membership fee to cover the cost of his 'CPD points, congresses, and revision courses, plus protection fees'. Indeed, the acquisition of CPD points and attendance at congresses and revision courses would very likely lead to a reduction in medical protection fees.

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1. Ger SS. High expenses for doctors (Letter). *S Afr Med J* 2005; **95:** 366.
2. Berden HJJM, Willems FF, Hendrick JM, Pijls NH, Knape JT. How frequently should basic cardiopulmonary resuscitation training be repeated to maintain adequate skills? *BMJ* 1993; **306:** 1576-1567.

HPCSA – a voice from the other side

To the Editor: With regard to the letter in your May issue,[1] our CPD Manager Barbara van Staden (who incidentally is a woman, not a 'him' as referred to in the letter) has not received any enquiries from C D Karabus regarding his CPD points or any other matter, not have I been requested for a response to his letter as stated in the Editor's note below the letter (all media enquiries are referred to my office).

We are disappointed that the *SAMJ* has resorted to such tactics.

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1. Karabus CD. HPCSA – the sound of silence. *S Afr Med J* 2005; **95:** 286.

Professor Karabus replies: After several abortive letters of request to the HPCSA I thought a letter of complaint to the *SAMJ* might be indicated and produce results. It has!

I am now told that Mrs B van Staden is the senior manager for CPD records and claims never to have received any letters from me. As my bona fides are called into question may I provide the following?

1. My 71 point 2002 CPD portfolio (posted to the HPCSA on 12 April 2003, full copy available) was not acknowledged.

2. My e mail dated 21 January 2004 to Mrs Y Meintjies at the HPCSA (having been told in error that she was involved with CPD), together with her very prompt response of 22 January saying that she had forwarded my request to the CPD department.

3. My letter dated 24 March 2004 attached to my CPD portfolio for 2003.

4. My final letter dated 21 May 2004 to the so called CPD manager requesting certification.

Copies of all the above have been sent to the Editor of the *Journal*.

To put it mildly I am not impressed with the HPCSA.

Erratum

In the article entitled 'The cost of treating serious firearm related injuries in South Africa' by D Allard and V C Burch, which appeared on pp. 591 594 of the August 2005 *SAMJ*, there were two errors in the second paragraph of the discussion. In the first sentence, 'US$2.9 million' should have read 'US$29 million', and in the third sentence '4% of the total' should have read '1% of the total'.