Biotinidase deficiency: presymptomatic treatment

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SUMMARY Biotinidase deficiency presents with clinical signs of biotin deficiency at the age of 3 months, or soon after. In an infant in whom the diagnosis was made on cord blood, vision and hearing were normal before presymptomatic treatment with biotin. Physical and mental development are good at 14 months.

Biotinidase deficiency is an autosomal recessive condition. Skin rashes, alopecia, seizures, hypotonia, developmental regression, and ataxia occur at the earliest at 3 weeks, but more usually soon after the age of 3 months.¹ All children previously reported have been recognised after symptoms characteristic of biotin deficiency developed. In the present patient the diagnosis was made on cord blood and the infant treated presymptomatically.

Case report

When our patient's mother was 16 weeks pregnant, the first child of her present marriage became acutely unwell at the age of 8 months with seizures, a rash, alopecia, developmental regression, hypotonia, severe lactic acidosis, and 3-methylcrotonylglycin and 3-hydroxyisovaleric aciduria. Biotin (10 mg daily) produced a dramatic clinical and biochemical recovery. Biotinidase deficiency was subsequently diagnosed.

The pregnancy with our patient was uncomplicated. His birthweight at term was 3.4 kg. Serum separated from cord blood was frozen and sent for biotinidase estimation. Since the infant remained symptom free, further measurements of biotinidase activity in venous samples were arranged at 2 weeks and 1 month of age. No biotinidase was found in the cord blood, the activity was 0.3 nmol/min per ml in the serum taken at 2 weeks, but none was recorded in the repeat specimen at 4 weeks. Other biochemical measurements are shown in the Table. Formal testing of vision at 9 weeks and electrocochleography at 10 weeks were normal. At almost 11 weeks, when the boy was still clinically well, but

Table *Biochemical determinations in an infant with biotinidase deficiency*

	Age (wks)					
	2	4	10*	10*	10*	B 11
Capillary pH†	7.43		7.41	7.34	7.28	7.4
Base deficit (mmol/l)†	1.5		4.2	7.1	8.9	3.0
Serum lactate ^a (mmol/l)†	2.00		1.6	1.75	2.75	3.6
Serum pyruvate ^b μmol/l)†	Nil		140	140	130	50
Serum amino acids	N			N		
Urinary amino acids	N		N			
Urinary organic acids	N	N	N			

^a Normal range up to 120 mmol/l; ^b Normal range up to 100 μmol/l. † Fasting samples; * Samples taken on three consecutive mornings; N = normal. B: biotin treatment started at the end of the 10th week.

the fasting serum lactate and pyruvate concentrations were marginally raised and the fasting capillary pH increasingly low on three consecutive mornings, oral biotin (10 mg daily) was begun. The fasting capillary pH rose and the fasting serum pyruvate fell immediately, but the lactate concentration remained raised initially. Subsequent physical and biochemical monitoring has been normal. At the age of 7 months, the patient's hair was a little sparse, but he has never had true alopecia. His skin is normal. He is an alert, responsive baby who has had no seizures. He sits unsupported, stands with two hands held, reaches accurately for objects and will hold and bang two objects together. His weight is on the 50th centile for his age. At 14 months, vision and hearing remain normal.

Discussion

Biotinidase is the enzyme responsible for the release of biotin from biocytin (ε-N-biotinyl-L-lysine). It permits the recycling of biotin for reutilisation in the activation of apocarboxylases to active holocarboxylases and is thus an essential link in the metabolism of pyruvate. In the absence of biotinidase biocytin gradually accumulates and the development of low serum and urinary biotin values leads to clinical signs of biotin deficiency. Although cases of biotin responsive, late onset, multiple carboxylase deficiency have been published since 1979,² the role of biotinidase was not recognised until 1983.³

The presenting features in symptomatic cases are now well established.¹⁻⁴ After reports of dramatic neurological and biochemical responses to biotin, it is disappointing that sensorineural deafness has been recognised in about half the known cases of biotinidase deficiency.^{5,6} Visual impairment is reported less often and may be due to optic atrophy¹ or severe myopia with possible retinal epithelial dysplasia.⁵ The cause of the auditory and visual impairments remains unclear. Treatment with exogenous biotin would not be expected to prevent the continued accumulation of biocytin, and it has been suggested that this and larger biotinyl peptides might be ototoxic.⁶ In the present patient, it was possible to confirm normal vision and hearing before biotin treatment, but monitoring will continue throughout childhood.

The infant in this report was not treated until the diagnosis had been confirmed on three samples taken at intervals of two weeks. Since it is presumed, however, that symptoms are only evident when a baby with biotinidase deficiency has used up all possible sources of endogenous biotin, treatment should perhaps ideally be given as soon as the diagnosis has been made. Although it seems that biotinidase does not cross the placenta, there is little justification for prenatal diagnosis, since good pro-

gress is being made in the present patient whose treatment was started just before the age of 11 weeks.

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Acute lymphoblastic leukaemia presenting with raised intracranial pressure

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SUMMARY A child presented with raised intracranial pressure for which no cause was established. Five months later a further cerebrospinal fluid examination showed lymphoblasts expressing the common acute lymphoblastic leukaemia phenotype. Bone marrow infiltration was not present. This case illustrates the difficulties that may be encountered in establishing the diagnosis of central nervous system leukaemia.

These patients frequently present with features of raised intracranial pressure and excessive weight gain—the 'hypothalamic syndrome'.¹ The diagnosis is usually made on clinical grounds and by the presence of lymphoblasts in the cerebrospinal fluid, although occasionally no cellular infiltrate is found.¹ We describe a child presenting with features typical of central nervous system leukaemia in whom the diagnosis was not initially established due to the absence of leukaemic cells in the cerebrospinal fluid or peripheral blood.

Case report

A 10 year old boy presented with a six week history

The central nervous system is a common site of relapse of childhood acute lymphoblastic leukaemia.