Biotinidase deficiency

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INTRODUCTION

Biotinidase deficiency is a rare autosomal recessive disorder which was first described by Wolf and colleagues in 1983.¹ Biotin, a vitamin B complex is necessary to activate the carboxylase enzymes system which is essential for the metabolism of amino acids, carbohydrate, and fatty acids. Biotin is normally required in a very small quantity as most of it is recycled by biotinidase enzyme. With biotinidase deficiency there is depletion of body biotin stores which leads to severe metabolic consequences. Clinical manifestations include neurological, dermatological, immunological, and ophthalmological abnormalities. We report a case of profound biotinidase deficiency that was being treated for chronic skin manifestation and diagnosis was made when his condition deteriorated.

CASE REPORT

This 3-month-old male infant, second child of unrelated parents, was admitted with progressive breathlessness, seizures,

lethargy, and refusal of feed for two days. He was born at term with mother having no significant antenatal history. He had progressed well until eight weeks of age when he was treated as seborrhoeic dermatitis for a diffuse rash which developed after an upper respiratory tract infection. As this did not improve a tentative diagnosis of acrodermatitis enteropathica was made and zinc supplement was started with some improvement. At 10 weeks of age he had one episode of generalised seizures that was treated with phenobarbitone, which had to be increased as he had two more episodes of convulsions in the same week. Computed tomography scan of cranium at that time was reported normal. His elder sibling had died at five months of age due to pneumonia and skin lesions. On admission, he was drowsy with tachypnoea, responding to only painful stimuli. There were no dysmorphic features. He had conjunctivitis,

Figure 1 Severe seborrhoeic dermatitis with alopecia before treatment.

Figure 2 Seborrhoeic dermatitis.

Figure 3 Normal hair growth and disappearance of rash after treatment.

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alopecia, and skin showed an erythematous rash around neck, back, and perineal region (Figures 1 and 2). Neurological examination revealed a lethargic child with dull and expressionless face, normal tone but exaggerated deep tendon reflexes. Other systemic examination was normal. Investigations revealed a normal haemogram, liver functions, serum electrolytes, but blood gas analysis showed compensated metabolic acidosis. His cerebrospinal fluid was normal with sterile cultures and negative C-reactive protein. Skin scrapping showed *Candida*, which also grew thereafter in cultures. He was treated with empirical antibiotics, phenytoin, and bicarbonates along with other supportive care, but deteriorated neurologically into coma requiring ventilatory support. He was investigated further for a metabolic disorder in view of poor therapeutic response and elder sibling dying with similar complains. Plasma and urine aminoacidogram was normal. Tandem mass spectrometry (TMS) revealed increased C5 hydroxycarnitine levels, suggestive of holocarboxylase deficiency. The urine organic acid profile showed marked increase of 3-hydroxyisovalerate, 3-methylcrotonylglycine and methyl citrate suggesting the possibility of multiple carboxylase deficiency, most likely biotinidase deficiency. Specific enzyme assay showed deficient biotinidase activity of 0.2 nmol/min/mL (normal >5 nmol/min/mL). A diagnosis of biotinidase deficiency was made and he was started on oral biotin (10mg/day). He showed dramatic improvement within 24 hours with decrease in hyperventilation, normalisation of blood gas, and improved sensorium. By the end of a week there had been considerable improvement in skin lesions and all anticonvulsant treatment were stopped. He was discharged on biotin supplements and is presently doing well after four months (Figure 3).

DISCUSSION

Biotinidase deficiency is a rare metabolic disorder with reported incidence in various neonatal screening programmes worldwide of 1:60,000 live births, though profound disease where the enzyme levels is <10% is much rare (1:137,401 population).¹ Only few confirmed reports of biotinidase deficiency could be traced in Indian literature, of which one was detected on routine neonatal screening.²⁻⁴

Clinical presentation may vary depending upon the severity of the deficiency.⁵ The onset may be acute or insidious, with either a steady progression or a series of acute incidents interspersed with periods of apparent normality. The latter is usually seen in children with partial biotinidase deficiency (10–30% activity) which may present with milder symptoms, especially during stress e.g. infection. Some children, who were otherwise asymptomatic but had intractable seborrhoeic dermatitis, were found to be due to partial deficiency which resolved with biotin supplement.⁶ Profound deficiency may present as early as one week of age but usually manifests around three months of age, due to presence of sufficient free biotin derived from mother or from diet. The presentations are: (a) neurological manifestations (acute metabolic encephalopathy, neuro-developmental

delay, anti-epileptic drug resistant seizure disorder, and muscular hypotonia); (b) skin manifestations (eczematous skin rash, seborrhoeic dermatitis, alopecia); (c) respiratory problems (hyperventilation, laryngeal stridor and apnoea); and (d) immunodeficiency (from T-cell abnormalities). Candidiasis is common, which may be related to immunological dysfunction following accumulation of toxic metabolites or biotin deficiency itself. Older children may exhibit ataxia, limb weakness, spastic parasis,⁴ neurosensory hearing loss and impairment of the optic nerve and visual pathways. Symptomatic children often have different cortical lesions on magnetic resonance imaging, e.g. cerebral oedema, attenuated white matter signal, cerebral atrophy, and compensatory ventricular enlargement which may improve after biotin treatment.⁷ Conjunctivitis is common. Most cases with biotinidase deficiency exhibit metabolic ketolactic acidosis, mild hyperammonaemia, and organic aciduria. Biotinidase deficiency has to be differentiated from common neonatal conditions, e.g. sepsis, meningitis, or epilepsy. It may be confused with holocarboxylase deficiency previously called early onset or infantile multiple or combined carboxylase deficiency. Present case had a negative sepsis workup, absence of clinical or radiological signs for respiratory illness despite marked breathlessness, skin changes, severe metabolic acidosis, and death of elder sibling which led us to suspect biotinidase deficiency. A simplified newborn screening on dried blood spots is presently in use.^{8,9} Diagnosis of biotinidase deficiency is confirmed by measurement of enzyme activity in serum. There is also a need to screen asymptomatic siblings. Prenatal molecular diagnosis for mutations or enzyme activity in cultured amniotic cells is available, although seldom performed due to treatability of the disorder. Molecular genetic tests are also used for detection of carrier state.⁹

Treatment with biotin results in dramatic clinical and biochemical response and supplements are needed life-long biotin (up to 5–20 mg/day). Raw eggs must be avoided as it contains avidin that binds biotin. Though the overall prognosis is good with complete resolution of the metabolic, skin and hair abnormalities, some features like optic atrophy, hearing loss or developmental delay may not be reversible and should be followed with periodic evaluations, and relevant interventions.¹⁰

CONFLICTS OF INTEREST

None identified.

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