Clinical Case Report

Biotinidase deficiency: An atypical presentation

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ABSTRACT

Biotinidase deficiency is a rare metabolic disorder which can cause dermatological manifestations and lead to severe neurological sequelae if untreated. Holocarboxylase synthetase deficiency also has similar manifestations and needs to be differentiated. We present a neonate who had atypical early onset symptoms and was diagnosed to have biotinidase deficiency.

Natl Med J India 2013;26:29–30

INTRODUCTION

Multiple carboxylase deficiency (MCD) is a rare inborn error of biotin metabolism. The two major disorders of biotin utilization are holocarboxylase synthetase (HCS) and biotinidase deficiency (BTD), both of which result in MCD. HCS has an early onset and is also known as neonatal MCD. It is a disorder of defective biotinylation. BTD which has a later presentation is known as late onset or infantile MCD, resulting in a defect in biotin recycling.[1] Both conditions can cause profound neurological sequelae and, at times, can be fatal. However, patients respond well to therapeutic doses of biotin. BTD is an important cause of preventable neurological impairment. The clinical manifestations include neurological, dermatological, immunological and ophthalmological abnormalities. The diagnosis can be confirmed by biotinidase enzyme assay and mutation analysis. We report a case of BTD which was unusual in presentation in the neonatal period. We also highlight the usefulness of diagnosis in the index case and the prenatal diagnosis of a subsequent pregnancy.

THE CASE

A 28-day-old neonate was referred for metabolic evaluation of persistent metabolic acidosis. Detailed history revealed that the child was born to second-degree consanguineous parents and that the antenatal period for the mother was uneventful. Delivery was at term by lower segment caesarean section because of breech presentation. A healthy girl, weighing 3.5 kg was delivered with an Apgar score of 7 and 8 at 1 and 5 minutes, respectively. At 6 hours of life, the baby had seizures which were managed with anti-epileptics. On day 10 of life, the mother noted icthyosiform changes below the ear which gradually spread and involved the entire body. The seizures increased in frequency and by then were not responsive to the commonly used anticonvulsants.

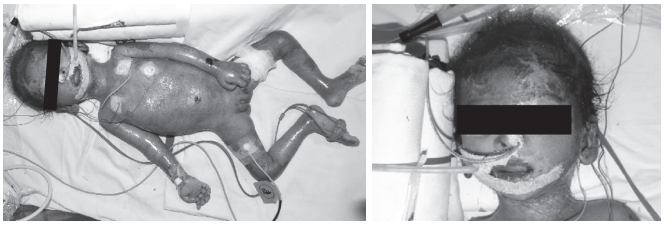

FIG 1. The child with icthyosis and alopecia

At the time of evaluation the child was dull, lethargic and hypotonic, responding only to pain with sluggish deep tendon reflexes. Ichthyotic changes were predominant with ectropion and eclabion. The child also had patchy alopecia with sparse hair, oedematous fingers and toes (Fig. 1). Preliminary investigations showed elevated lactate and pyruvate levels and persistent metabolic acidosis. Sepsis screen, blood sugar, haemogram, serum calcium, creatinine, sodium and potassium were normal. Neurosonogram showed ventriculomegaly and cystic changes in the periventricular area. Skin biopsy showed congenital non-bullous icthyosiform erythroderma. Tandem mass spectrometry showed elevated C5 OH carnitine. Urinary organic acid profile was consistent with MCD. The two possibilities in this child were HCS deficiency or BTD. In view of the early onset of symptoms, holocarboxylase enzyme deficiency was considered and mutation analysis for holocarboxylase was done. However, this was negative. A biotinidase enzyme assay was planned but the baby succumbed before further investigations could be done.

An available blood sample from the child and a parental sample were analysed for BTD. The child's sample could not be amplified; however, there was a heterozygous mutation in both the parents c.928G>A (p.Gly310Arg). In addition, the mother was a carrier for c.968A>G (p.His323Arg). Hence, the possibility of homozygote of the parental mutation c.928G>A (p.Gly310Arg) in the index case was considered. The parents were counselled about prenatal diagnosis in a subsequent pregnancy. A year later the parents reported to us with an early pregnancy and prenatal diagnosis was done using chorionic villus cells. Unfortunately, this foetus was also a homozygote for the mutation c.928G>A (p.Gly310Arg) and the parents opted to terminate the pregnancy.

DISCUSSION

MCD are inborn errors in the metabolism of biotin in which there is defective activity of the four carboxylases (pyruvate carboxylase, propionyl-coenzyme A [CoA] carboxylase, β-methyl crotonyl CoA carboxylase and acetyl-CoA carboxylase).[2] Each of the four carboxylases in humans require biotin as a cofactor. The carboxylases are first synthesized as inactive apoenzymes. After synthesis, biotin is added to the inactive proteins through two partial reactions, each of which is catalysed by the enzyme HCS. Ultimately, each of these active, biotin-containing enzymes is degraded. The biotin-containing products of degradation are

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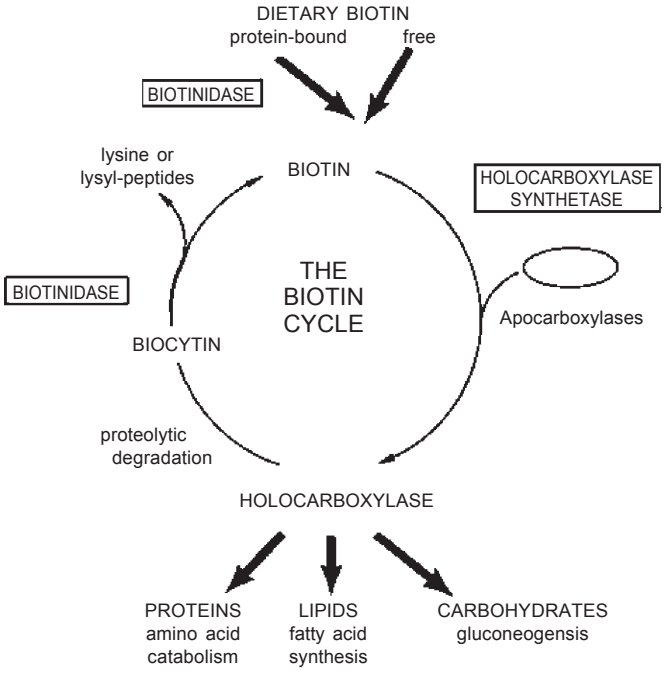

FIG 2. Pathways involved in the biotin cycle[1]

TABLE I. Comparison between biotinidase and holocarboxylase synthetase (HCS) deficiency[3,5–7]

Feature	Biotinidase deficiency	Holocarboxylase deficiency
Aetiology	Inability to liberate and recycle biotin which is lost in urine as biocytin	Decreased affinity of HCS for biotin impairing the formation of holocarboxylases
Age at onset	Late or juvenile, usually after 3 months	Early or neonatal
Skin lesions	Alopecia totalis, bright red scaly total body eruption	Patchy alopecia, acro-dermatitis enteropathica, icthyosis-like lesions
Metabolic disorder	Metabolic acidosis	Metabolic acidosis
Urinary organic	↑3-OH isovaleric acid and 3-OH propionic acid	↑↑3-OH isovaleric acid, 3-OH propionic acid and 3-methyl crotonylglycine
TMS	↑C5 OH carnitine	↑C5 OH carnitine
Renal loss of biotin	Absent	Present
Enzyme testing	Plasma biotinidase	Lymphocyte carboxylase activity
Confirmation	Mutation analysis	Mutation analysis

TMS tandem mass spectrometry

acted on by biotinidase to liberate biotin, which is recycled and enters the free-biotin pool (Fig. 2). Two distinct disorders have been described. In one, the defect is in the enzyme holocarboxylase synthetase which catalyses the molecular activation of the apocarboxylase proteins. In the other, the defect is in biotinidase which catalyses the reutilization of biotin and may be involved in its digestion and intestinal absorption. Recently, defects in biotin transporters have also been described. BTD results in inability to recycle endogenous biotin and to release dietary protein-bound biotin. Thus, the brain may not be able to recycle biotin adequately. This may lead to dependence on the biotin that crosses the blood–brain barrier, resulting in decreased pyruvate carboxylase activity in the brain and accumulation of lactate.[1] The neurological symptoms may be secondary to accumulation of lactic acid in the brain. BTD or the late onset or infantile form of MCD has an autosomal recessive mode of inheritance and was first described by Wolf and colleagues in 1985.[3] The reported incidence in various neonatal screening programmes worldwide is 1:61 067 live-births. BTD can be profound (<10% enzyme level) or partial (10%–30% enzyme level).[4] Children with untreated profound BTD usually have one or more of the following features—seizures, hypotonia, eczematous skin rash and alopecia, as was seen in our patient. Other features include conjunctivitis, candidiasis and ataxia. Older children and adolescents may exhibit limb weakness, paresis, scotomata, developmental delay, sensorineural hearing loss and vision problems such as optic atrophy. BTD must be differentiated from HCS deficiency (Table I) which generally has an earlier presentation. Most of the clinical features given in Table I under BTD were applicable to our patient, except for the very early onset of symptoms—seizures by 6 hours and dermatosis by 10 days of life. Presentation as early as one month has been reported with myoclonic seizures but without alopecia and dermatitis. Both BTD and HCS deficiency respond clinically and biochemically to oral biotin therapy. Whereas 10 mg/day or less is sufficient to treat profound BTD, the optimal biotin dose for patients with HCS deficiency must be assessed individually.[4] The prognosis of both disorders is good, if biotin therapy is introduced early and continued throughout life. However, delayed initiation of therapy in BTD can result in irreversible neurological damage, and in HCS deficiency a few patients have responded only partially even to massive biotin doses of up to 100 mg/day. Once therapy is instituted, cutaneous symptoms resolve quickly, as do seizures and ataxia. Some of the symptoms such as hearing loss and optic atrophy are less likely to be reversible. Partial BTD can probably be treated with lower doses of biotin (1–5 mg/day) and/or only during times of metabolic stress.[3,5–7] With the advent of newborn screening, many infants are being identified and treated much before the symptoms manifest. This helps to reduce the neurological impairment.

This case represents the diagnostic dilemma the clinician faces while evaluating rather unusual presentations of rare metabolic diseases.

Contributions. SJ and BS managed the case and prepared the manuscript, SS did the prenatal diagnosis and YS the mutation analysis.

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