Biotinidase Deficiency, a Rare but Treatable Inborn Error of Metabolism

Amit Ranjan Rup, Arun Kumar Dash, Jyoti Ranjan Behera, Sibabratta Patanaik and Mukesh Kumar Jain

Department of Paediatrics, Klinga institute of Medical Sciences, Bhubaneswar, Odisha, India

Correspondence:
Jyoti Ranjan Behera
Department of Paediatrics,
Klinga Institute of Medical Sciences, Bhubaneswar, Odisha, India
Email: dr.jyoti2011@gmail.com

DOI: 10.3126/jnps.v41i2.32749

Submitted on: 2020-07-24

Accepted on: 2021-02-13

Acknowledgements: None

Funding: Nil

Conflict of Interest: None declared

Permission from IRB: Yes

To cite this article: Rup AR, Dash AK, Behera JR, Patanaik S, Jain MK. Biotinidase Deficiency, A Rare but Treatable Inborn Error of Metabolism. J Nepal Paediatr Soc. 2021;41(2):270-3.

ABSTRACT

Biotinidase deficiency (BTD) is a rare inherited metabolic disorder with predominant dermatogical and neurological manifestations, which if untreated leads to severe neurological sequelae. Early diagnosis and prompt treatment with biotin prevents further progression of neurological symptoms and resolution of cutaneous features. We report an interesting case of four and half year male child presenting with seizures, developmental delay with non resolving extensive skin lesions and alopecia, diagnosed as BTD and successfully treated.

Key words: Biotinidase deficiency; Icthyosis; Newborn Screening; Seizures

INTRODUCTION

Biotinidase deficiency (BTD) is one among few treatable Inborn Error of Metabolism (IEM) with prevalence of 1 in 60,000 live births worldwide.[1] Progressive neurological impairment and severe dermatological involvement are the usual manifestation, which responds dramatically to biotin therapy.[2]

CASE REPORT

A four and half year male child presented to our set up with history of cough and cold for seven days with low grade fever and difficulty in breathing for five days. On evaluation, child was lethargic with Glassgow coma scale (GCS) 5/15, with tachycardia and tachypnoea with normal blood pressure and saturation. Arterial blood gas revealed severe metabolic acidosis with normal blood sugar, positive ketone body. Mechanical ventilation was done in view of poor sensorium and sodium bicarbonate was given for correction of acidosis. He was the product of non consanguineous marriage, born at 36 weeks of gestation with uneventful perinatal period. At the age of eight months and 18 months, there were multiple episodes of convulsion requiring anti epileptic drugs. Neuroimaging at that time had slightly enlarged ventricular spaces with abnormal EEG. There was global developmental delay with history of sibling death at the age of six months due to refractory seizures. At the age of two and half years, erythematous scaly skin rashes appeared on abdomen which gradually progressed to involve the whole body. For these skin changes, varied diagnosis like acrodermatitis enteropathica, atopic dermatitis, staphylococcal scalded skin syndrome, drug allergy were made and treated with zinc, steroid, antibiotics etc. Despite all interventions, lesions progressed to develop crusting, peeling and icthyosis with intermittent flare ups. On examination, above described skin lesions were found predominantly over axilla, neck, abdomen and knees (figure 1, 2). Alopecia and seborrheic dermatitis were noted. There was no organomegaly and other system examinations were normal.

Laboratory investigation revealed increased serum lactate 8.8 mmol/L (Normal < 2 mmol/L) and ammonia 251 micromol/L (Normal 10 – 45 micromol/L) with normal serum electrolytes, liver function tests, complete blood counts and negative sepsis screen. On the background of available history, examination and relevant laboratory findings possibility of Multiple Carboxylase Deficiency (MCD), most likely BTD was considered and screening was sent for same. Child was started with high dose Biotin (10 mg/day). After two days, child recovered clinically with improved GCS (14 / 15), and with resolution of metabolic acidosis, the baby was extubated. Serum biotinidase level was 0.50 nmol/min/ml (Normal

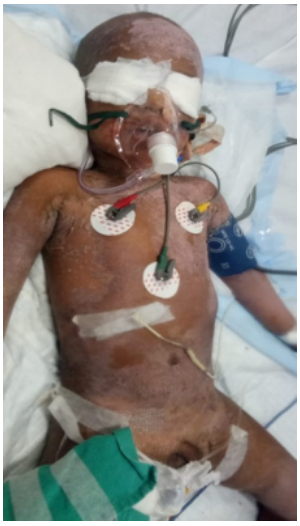

Figure 1. Skin lesions over axilla, neck and abdomen

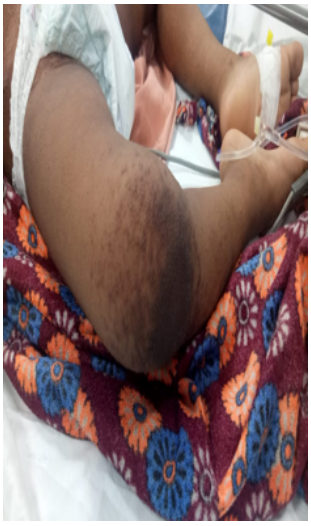

Figure 2. Skin lesions over knees

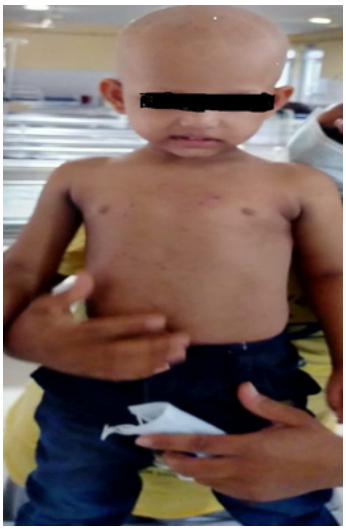

Figure 3. Post reatment- skin lesions completely disappeared and texture improved

4.1 - 14.5), which confirmed our diagnosis. Hearing assessment revealed profound sensorineural deafness (SNHL) which is a major clinical feature of BTD and hearing aid was advised. Within one week, skin lesions completely disappeared and texture improved (Figure 3). Child was discharged with biotin 10 mg for life long.

DISCUSSION

MCD is a rare disease, due to deficiency of either biotinidase or holocarboxylase synthase (HCS) enzyme, resulting in decrease or absent activity of the four carboxylases enzymes {pyruvate carboxylase, propionyl-coenzyme A (CoA) carboxylase, methyl crotonyl CoA carboxylase and acetyl-CoA carboxylase}.[3] Biotinidase enzyme releases biotin, making it available for reuse by cleaving dietary protein bound biocytin, which acts as coenzyme for four carboxylases that have roles in gluconeogenesis, branch-chain amino acids catabolism and fatty acid synthesis. BTD is an autosomal recessive disorder involving central nervous system (seizures, hypotonia, developmental delay, ataxia and profound sensory neural hearing loss), respiratory system (hyperventilation, laryngeal-stridor and apnea) with immunodeficiency and characteristic cutaneous lesions.[4] Neurological manifestations are attributed to accumulation of lactate in brain resulting from decreased pyruvate carboxylase activity.[5] Affected children typical have scaly, erythematous maculopapular eruption especially in moist and perioral areas. Chronically they progress to lichenification, crusting and are prone for candida. Seborrheic dermatitis with total alopecia is the typical feature. Recent evidence revealed that increase in serum odd chain fatty acid is the likely etiology behind cutaneous findings in BTD.[6] Enzymatic activity (Profound < 10%, partial 10 - 30%) determines the age of presentation and clinical spectrum. In case of partial activity, symptoms usually develop only in conditions of stress like infection, dehydration etc and hence results in delayed diagnosis as observed in our case. Biochemical profile of BTD includes ketotic metabolic acidosis, hypoglycaemia, mild elevated ammonia with marked hyperlactemia and diagnosis is confirmed by serum or leucocyte biotinidase level or genetic testing. Differential diagnosis include organic acidemias, HCS deficiency, acrodermatitis enteropathica, atopic dermatitis, essential fatty acids deficiency etc. Dramatic response to biotin and enzyme / genetic assay clinches the diagnosis. Life long oral biotin 10 mg/day (can be increased up to 40 mg/day if required) is the simple and effective treatment for this IEM. Skin lesions recover completely within weeks after initiation of biotin, but the CNS damages are irreversible with delayed diagnosis of BTD leading to profound intellectual disability, refractory seizures, coma and death.[7] Newborn screening (NBS) for BTD is an effective tool for early detection which is already adopted by various high prevalent counties like Israel.[8]

CONCLUSIONS

High index of suspicion for BTD is the key for a child with persistence of cutaneous manifestations and neurological features leading to prompt diagnosis and early biotin supplementation can lead to dramatic improvement in the cutaneous lesions.

.

REFERENCES

1. Biotinidase Deficiency. In: Kliegman RM, Shah SS, St Geme J, Berhman R (Eds). Nelson's Textbook of Paediatrics, 21st edition. Philadelphia: Saunders Elsevier; 2020:711
2. Wolf B. Biotinidase deficiency: "if you have to have an inherited metabolic disease, this is the one to have" Genet Med. 2012;14:565–75. DOI: 10.1038/gim.2011.6.

3. Canda E, Kalkan Uçar S, Çoker M. Biotinidase Deficiency: Prevalence, Impact and Management Strategies. Pediatric Health Med Ther. 2020 May 4;11:127-33. DOI: 10.2147/PHMT.S198656.
4. Behera B, Kumar A. Biotinidase Deficiency Presenting in Newborn Period: A Case Report. IJSR. 2018;9:680-82. DOI: 10.21275/ART20204101.
5. Jagadeesh S, Suresh B, Seshadri S, Suzuki Y. Biotinidase deficiency: an atypical presentation. Natl Med J India. 2013;26(1):29-30.
6. Navarro PC, Guerra A, Alvarez JG, Ortiz FJ. Cutaneous and neurologic manifestations of biotinidase deficiency. Int J Dermatol. 2000;39(5):363-5. DOI: 10.1046/j.1365-4362.2000.00841.x
7. Singh A, Lomash A, Pandey S, Kapoor S. Clinical, Biochemical and Outcome Profile of Biotinidase Deficient Patients from Tertiary Centre in Northern India. J Clin Diagn Res. 2015;9(12):8-10. DOI: 10.7860/JCDR/2015/12958.6941
8. Hayek W, Dumin Y, Tal G, Zehavi Y, Sakran W, Spiegel R. Biotinidase Deficiency: A Treatable Neurological Inborn Error of Metabolism. Isr Med Assoc J. 2019;21(3):219-21. PMID: 30905112.