

## CASE REPORT

# DIAGNOSTIC DILEMMA OF BIOTINIDASE DEFICIENCY: CASE OF A CHILD FROM PAKISTAN

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Biotinidase deficiency is an autosomal recessive in born error of metabolism which is characterized by the lack of cleavage of biotin. This disease has been reported very rarely with the incidence found to be 1 per 60,089 and 1 per 112,271 of live births, respectively. This condition has profound effects on the neurological system, various neurocutaneous manifestations and metabolic derangements. We report a case of 3-year-old male child who presented in ER with severe respiratory distress for 1 day in a tertiary care set up. He had been referred from multiple peripheral centres. His associated complaints included severe rash, restlessness and progressive mental deterioration for 2 years. He was managed on symptomatically initially, later a diagnosis of Biotinidase deficiency was made, he responded well on supplemental biotin. Our intention to document this case was for sake of its uniqueness with very common symptoms, varied presentation and rarity of the disease which makes it a diagnostic dilemma.

**Keywords:** Biotin, Biotinidase deficiency; Metabolic disorder; Diagnostic dilemma

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## INTRODUCTION

Biotinidase deficiency is an autosomal recessive metabolic disorder which is characterized by the lack of cleavage of biotin a vitamin (water-soluble vitamin B<sub>7</sub> formerly known as vitamin H or coenzyme R) and important enzyme co factor in several carboxylation reactions. Usually parents of patients of this inborn error of metabolism are carriers and siblings of the affected patients have the altered gene.<sup>1</sup> This disease has been reported very rarely with the incidence found to be 1 per 60,089 and 1 per 112,271 of live births, respectively.<sup>1</sup> This condition has the profound effects on the neurological system, various neurocutaneous manifestations and metabolic derangements, which responds well to biotin enzyme supplements and also prevent severe consequences and disabilities due to the deficiency.<sup>1,2</sup> Frequently neonates present to the clinics demonstrate metabolic ketolactic acidosis, organic aciduria, and mild hyperammonemia, condition is asymptomatic until the child develops metabolic ketolactic acidosis organic aciduria.<sup>2</sup>

Biotinidase deficiency can be diagnosed in the newborn through the prenatal molecular analysis for mutation, it has been recommended that child with the positive family history must undergo the genetic analysis to diagnose the carrier state.<sup>3</sup>

Biotinidase deficiency most of the time presents at the age of 2-3 years but few cases though have been reported in the neonatal age group, therefore Biotinidase deficiency must be screened in new-borns with the suspected symptoms as well as those with the positive family history.<sup>4</sup>

## CASE REPORT

This is a case of 3 years old male child who presented in ER of a tertiary care setup being referred from multiple peripheral centres, he came with the complaint of Cough for 10 days Difficulty in breathing for 1 day, was in significant respiratory distress. His other associated complaints included severe rashes all over the body for past 2 years; also he reported increased restlessness and mental deterioration. Child has multiple visits in peripheral centres for rashes, He had given vitamin E for 1 year and his rashes were resolved but after stopping vitamin E rashes again reappeared.

On Inquiring Past Medical History, he had 2 episodes of febrile fits at 1 year 5 months of age, His Birth History was unremarkable normal vaginal delivery; Feeding History includes normal regular diet. He was developmentally normal, achieved milestones appropriate to age, but since last 2 years the child seems to be more restless and less responding. His parents were a contagious marriage had 2 Sisters & 1 Brother, vaccinations were up to date. Vitality he was stable except for marked tachypnea, height and weight of the child on 50<sup>th</sup> centile.

On detailed systemic examination: Cardiovascular system was unremarkable for any pathology showed normal heart sounds and perfusion. Neurological examination showed marked irritability and ataxia. His chest had bilateral crepts and conducting sounds plus wheezes, child was having marked respiratory distress. Abdomen was soft non-tender, without viceromegaly. Ear, nose and throat were grossly unremarkable except mucosal

ulcers, however alopecia and diffuse eczematous rash over the body more on neck, trunk and genital area was observed along with desquamation of fingers, palm and sole. On observing patient very closely it was also noted that the child was also showing slight hearing difficulties, he was limping, he had difficulty in seeing nearby objects, his behaviour was irritable and non-cooperative, not obeying commands too.

Initial impression was made as child suffering from Pneumonia/Reactive Airway Disease along Mucocutaneous candidiasis. His baseline workup was sent, which showed normal haemoglobin, haematocrit & platelet count, slightly raised total lymphocyte count. His electrolytes were giving a picture of metabolic acidosis (low serum bicarbonate levels=11.8), rest renal & liver function test were unremarkable and no growth on blood culture. Chest x ray also showed no active pulmonary pathology.

Differentials hitting on mind were Autoimmune Poly Endocrine Syndrome 1 (APECED), Hyper IgE (Job Syndrome), Wiskot Aldrich Syndrome, Vitamin B complex deficiency, Langerhan Histiocytosis, Autoimmune Deficiency–Disseminated Candidiasis? Considering diagnostic dilemma Dermatology, Infectious diseases & Metabolic Diseases experts were taken on board.

Dermatology team advised for Nail & Skin Scrapping, they advised topical hydrocortisone, Paraffin. Infectious disease team advised for fluconazole. Metabolic Team advised for urine test for reducing substance & organic acid, bera testing & referred child to eye clinic. Out of all the advised tests and examinations, urine test came out to be conclusive, result of chromatogram showed, marked excretion of 3-hydroxyisovaleric acid & adipic acid, moderate excretion of 3-methylcrotonylglycine, methylcitric acid and a tiny peak of 3-hydroxypropionic acid. This profile was suggestive of Biotinidase or Holocarboxylase deficiency.

So, after clinical correlates of supporting points like alopecia, metabolic acidosis, skin rash, respiratory difficulties, ataxia & some history of difficulty in visualizing nearby object and hearing difficulty a diagnosis of Biotinidase Deficiency was made. This patient was managed for his respiratory distress and given biotin supplements at a starting dose of 5 mg/day, he showed remarkable progress within 2 days.

## DISCUSSION

Clinical presentation of Biotinidase deficiency depends upon the severity of the condition, onset may be sudden with progressive disease or may have a fluctuating course of the disease, latter is most commonly seen among the children with the partial

Biotinidase deficiency (10–30%), along with the milder symptoms during stress e.g., infection, few asymptomatic children may present with seborrheic dermatitis.<sup>4,5</sup>

Profound deficiency may present as early as 1 week of life but it usually demonstrates symptoms around 3 months of age, due to presence of sufficient free biotin derived from mother or from dietary source. It may present as (a) neurological manifestations (acute metabolic encephalopathy, neuro-developmental delay, anti-epileptic drug resistant seizure disorder, and muscular hypotonia); (b) skin manifestations (eczematous skin rash, seborrheic dermatitis, alopecia); (c) respiratory problems (hyperventilation, laryngeal stridor and apnea) and (d) immunodeficiency (from T-cell abnormalities), it has been reported that children with Biotinidase deficiency suffer with candidiasis due to low T–cell count.

Older children may present with ataxia, limb weakness, spastic paresis<sup>6</sup>, hearing loss, impairment of optic nerve and visual pathways, symptomatic children usually have cortical lesion on MRI e.g. Cerebral oedema, cerebral atrophy, compensatory ventricular enlargement, which are gradually reversible after biotinidase therapy<sup>7</sup> few children also have conjunctivitis.

Disease is chiefly diagnosed via new-born metabolic screening (activity assay). Mutational assay identifies the mutation and confirmed by decrease enzyme activity in serum, prenatal molecular diagnosis for mutations or enzyme activity in cultured amniotic cells is available, but rarely performed due to available management of the disease.<sup>7,8</sup>

If Biotinidase deficiency is suspected in later age group recommended blood tests include the following: arterial blood gas (ABG), serum chemistries, ammonia. Other tests include EEG, BERA & ophthalmological Examination. Accurate and timely diagnosis of the Biotinidase deficiency is essential, if done so, treatment with life-long biotin (up to 5–20 mg/day) leads to dramatic reversal of the symptoms.<sup>8</sup>

Patient has to be counselled to avoid raw eggs because they contain ‘Avidin’, an egg-white protein that binds biotin and decreases the bioavailability of the vitamin. Annual vision and hearing evaluation should be conducted; child should be periodically evaluated by a metabolic specialist. Also, testing of asymptomatic siblings of a proband ensures that biotin therapy for unaffected siblings can be instituted in a timely manner as in preventive measure.

## CONCLUSION

Failure to recognize and treat patients with Biotinidase deficiency may cause permanent neurologic, ocular, and auditory damage and can

result in death. However, its clinical recovery of the child is good in terms of metabolic, skin and hair abnormalities but conditions such as optic atrophy, developmental delay may not be reversible. Periodic evaluation, relative interventions and biotin supplementation may help though.

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