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A Rare Case of Profound Biotinidase Deficiency

Neha Tyagi[1], Manojkumar Patil[2*], Shradha Salunkhe[3], Sampada tambolkar[4], Shailaja Mane[5]

[1]Postgraduate in department of Pediatric, Dr. D.Y. Patil Medical College, Hospital and Research Center & Dr. D.Y.Patil Vidyapeeth {Deemed to be University}, Pimpri, Pune, Maharashtra,

[2*]Professor & Head of the Paediatric Intensive Care Unit, Professor, Dr. D.Y. Patil Medical College, Hospital and Research Center & Dr. D.Y.Patil Vidyapeeth {Deemed to be University}, Pimpri, Pune, Maharashtra, India

[3]Professor, Dr. D.Y. Patil Medical College, Hospital and Research Center & Dr. D.Y.Patil Vidyapeeth {Deemed to be University}, Pimpri, Pune, Maharashtra, India

[4]Professor, Dr. D.Y. Patil Medical College, Hospital and Research Center & Dr. D.Y.Patil Vidyapeeth {Deemed to be University}, Pimpri, Pune, Maharashtra, India

[5]Professor & Head Of Department of Pediatrics, Dr. D.Y. Patil Medical College, Hospital and Research Center & Dr. D.Y.Patil Vidyapeeth {Deemed to be University}, Pimpri, Pune, Maharashtra, India

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ABSTRACT:

Inborn Errors of Metabolism (IEM) are genetic disorders with detectable biochemical anomalies which impair normal metabolism. These include conditions with defects in the metabolism of amino acids, carbohydrates, lipids, mucopolysaccharides, etc.

These disorders can become apparent immediately after birth or in a few days or weeks after birth. However, in India due to economic constraints, lack of awareness and education amongst parents in addition to scarcity of reliable investigations, many IEMs remain undiagnosed and untreated.

One such rare IEM we recently came across in our centre, which was a welcome challenge to diagnose, was biotinidase deficiency.

Biotinidase deficiency is a rare autosomal recessive metabolic disorder with an estimated incidence of 1:61067 population, though severe or profound disease is even more rare with an incidence of 1: 137401 population. [1]

Clinically patients of biotinidase deficiency can present with a variety of neurological and dermatological signs, such as seizures, hypotonia, feeding problems, developmental delay, hearing loss, optic atrophy ataxia, alopecia, and skin rash.

The objective of this case report is to analyse the clinical and laboratory profile, diagnostic challenges and outcome of a child presenting with a rare inborn error of metabolism presenting for the first time to the Paediatric intensive care unit (PICU) in a tertiary care teaching hospital, Dr. D Y Patil Medical College and Hospital, Pune.

1. Introduction

The enzyme biotinidase cleaves biotin, from biocytin and from dietary protein-bound sources, allowing recycling of biotin. [2] Biotin is the coenzyme for four carboxylases that have roles in gluconeogenesis, the catabolism of several branch-chain amino acids and fatty acid synthesis. [3]

Outcomes of new-born screening programs support that biotin treatment started after birth prevents patients with biotinidase deficiency from developing symptoms. However, presence of late-onset cases with different clinical findings indicates that there is still much to learn about BD. [4]

There might be irreversible neurological damage, growth retardation and development of autistic behaviour pattern if not diagnosed in time or if there is any delay in treatment. The therapy's aim is to increase biotin bioavailability by 5–20 mg, daily, lifelong biotin replacement.

Case

A 9-month-old female child presented with complaints of laboured breathing, reduced activity and reduced feeding. 15 days prior to this there was also history of up rolling of eyes associated with tightening of all 4 limbs, which was followed by postictal drowsiness lasting 4 hours?
There was past history of epilepsy at 7 months of age of similar semiology, 2 episodes each lasting a few seconds. The child was not evaluated for these episodes.

The child was born to a third degree consanguineously married couple. Antenatal period and delivery of the baby were uneventful. Workup for Metabolic disorders was not done in the neonatal period.

On taking further history and on examination, it was noted that the child had motor, social and language delays. Predominant being the gross motor delays, as even neck holding hadn't been achieved.

The child was immunised up to age as per the National Immunisation Schedule. She had been started on family pot diet complimentary to breast feeds.

On presentation, child was drowsy, febrile, tachycardic, tachypnoeic and having nasal flaring with mild subcostal retractions. On neurological examination, he was drowsy but responsive to pain, with axial and appendicular hypotonia. No organomegaly was palpated.
There were small bald patches on the occipital region of the head. In addition the child was also noted to have dry scaly skin associated with history of intermittent erythema and itching.
On anthropometric measurements the child was falling into the category of Severe Acute Malnutrition.

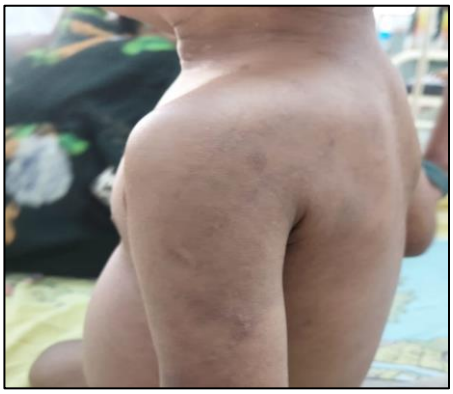

Image 1- Dry scaly skin (Dermatitis)

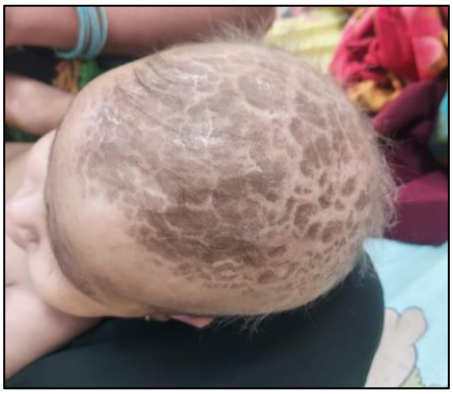

Image 2- Scaly scalp with bald patches (Alopecia)

She was initially treated as a case of lower respiratory tract infection with developmental delay with seizures under evaluation in a case of severe acute malnutrition. The child went into status epilepticus on day 2 of admission and required mechanical ventilation in view of deteriorating GCS.

Lumbar Puncture was done with suspicion of Encephalitis; however, the routine microscopy, culture and virology reports came out to be normal and negative respectively.
MRI brain plain was done to rule out structural causes of epilepsy and developmental delay.

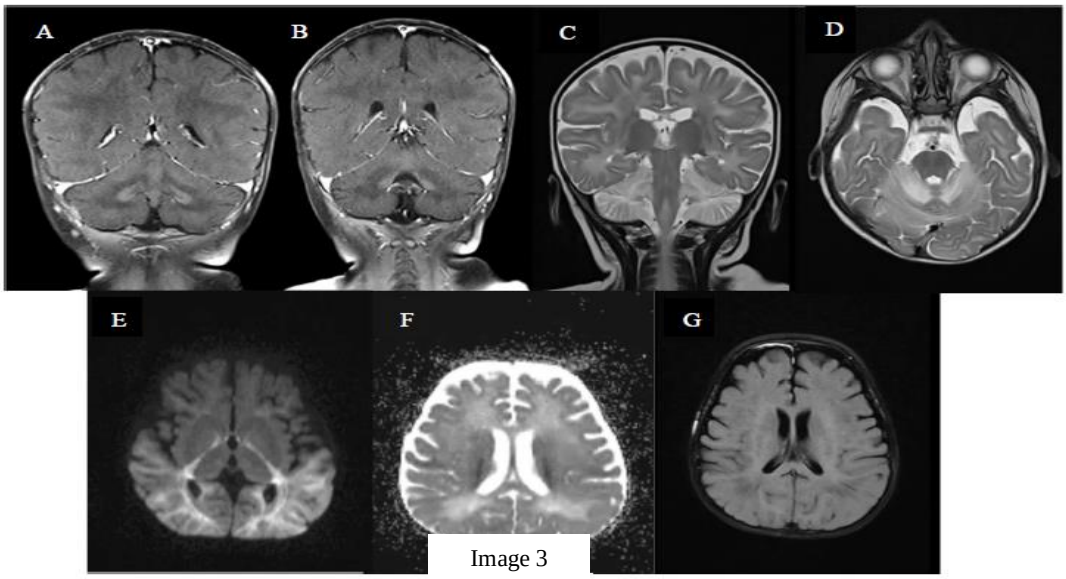

Image 3

IMAGE 1:

(A-D) MRI Brain Coronal Images
(D-E) MRI Brain Axial Images
[A, B] FLAIR showing hyperintensities.
[D] Thickened bilateral optic nerves with abnormal signal in the bilateral optic nerves, optic chiasma an optic tract showing diffusion restriction.
[E-G] Symmetrical areas of diffusion restriction with corresponding low ADC values in the bilateral internal capsule, temporo-occipital-parietal region, optic radiations, bilateral hippocampi, and para hippocampal gyri, cerebral peduncle and medulla (along the corticospinal tracts), bilateral central tegmental tracts, cerebellar white matter and middle cerebellar peduncles, rest of the medulla and cervico-medullary junction.

To our surprise there was diffusion restriction with low ADC values in bilateral regions of the cerebrum including internal capsule. After ruling out, infective and structural causes, our diagnosis with the presence of MRI changes was narrowed down to some metabolic disease.

Keeping in mind a high suspicion for inborn error of metabolism, Tandem Mass Spectrometry (TMS) and urine Gas Chromatograph Mass Spectrometry (GCMS) was sent.

After taking required samples the child was started on a metabolic cocktail as it is most commonly referred to as, containing L-Carnitine 100m/kg/day, Co-Enzyme Q 20 mg/kg/day, Biotin 20mg/kg/day, Vitamin B12 1mg/kg/day, Thiamine 10mg/kg/day, Riboflavin 100mg/day, Pyridoxine 50mg/day and Folinic Acid 20mg/day.

TMS showed increased levels of Methylmalonylcarnitine and Urine GCMS analysis showed increased excretion of 3-Hydroxyisovaleric acid. Further as confirmation biotinidase enzyme assay was performed which showed decreased levels of Biotinidase. So the child was diagnosed as a case of profound biotinidase deficiency, a multiple carboxylase deficiency. Rest of the metabolic cocktail was stopped and only Biotin was continued along with antiseizure medications and inotropes, which were also gradually tapered off as the child's general condition improved and was extubated after 3 more days.
Child started accepting breastfeeds, activity also improved and hence was discharged with advice to continue biotin and syrup Levetiracetam till further advice. On follow up visit after 15 days and again in 1 month, child was active, on breastfeeds and began neck holding, social smile was noted by mother, and had no complaints of seizures. Our diagnosis was further strengthened by the improvement seen after biotin supplementation.

2. Discussion

From a birds eye point of view, an infant presented with neurological signs and symptoms associated with a parental history of consanguinity. These were the only two clues we had to start off our differentials with. However as we moved forward with examination of the child, the presence of alopecia and eczema led us to be more suspicious of biotinidase deficiency.
It took us 4 days to narrow down to the diagnosis of a metabolic disease due to the vagueness of clinical features and the cost of diagnostic tests making it a differential thought of only after exclusion of all rest. However it was a difficult task to suspect biotinidase out of the large spectrum of IEMs, in addition to already having malnutrition to be attributed for the cutaneious findings.
Nevertheless, no improvement in the child's condition despite appropriate antibiotic therapy and antiseizure medications, we were forced to widen our horizons and think of a more integrated diagnosis, that could explain all the symptoms.
However to our credit, there are only two reports of biotinidase deficiency that could be traced in Indian literature, of which one was detected on routine neonatal screening. So suspecting biotinidase deficiency was last on our differentials list.
There may be profound and partial BTD deficiency due to different mutations in the *BTD* gene. Usually it is only in profound BTD deficiency, we see a severe pathogenic condition. A high frequency of new-borns are affected with the partial deficiency worldwide but usually remain asymptomatic. [5]

In symptomatic cases of profound deficiency, clinical manifestations predominantly involve the skin and central nervous system. Common presentations are usually alopecia, hypotonia, seizures with or without developmental delay, ataxia, optic nerve atrophy, sensorineural hearing loss and seborrheic dermatitis. There is commonly t-cell dysfunction, which may lead to immune deficiency resulting in opportunistic infections. [6] Respiratory complaints can be seen in the form of distress with hyperventilation and apnoea.
Mainstay of treatment is supplementation of biotin at a dose of 5-20 mg, per day, which has proven to dramatically improve clinical and biochemical outcomes. Some children might require higher doses of biotin 30-60 mg per day.

3. Conclusion

In any infant presenting with recurrent seizures that are difficult to curtail with a background of developmental delay, associated with history of persistent vomiting, alopecia and failure to thrive, we must suspect early biotinidase deficiency.
And as paediatricians it is this which we need to practice more often, a larger view point but an integrated and narrow diagnostic approach.
It is important on our parts as diagnosticians to recognise this condition as early as possible since it is a treatable condition and symptoms are well controlled by biotin supplementation, on the other hand no treatment can lead to a high rate of mortality.

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