

Congenital Biotinidase Deficiency-Clinching the Diagnosis with Classic Imaging Features

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Abstract: Congenital biotinidase deficiency (CBD) is a rare inborn error of metabolism, resulting in biotin deficiency. The recognition of clinical, laboratory and magnetic resonance imaging findings can help us to arrive at a correct diagnosis at the earliest which can enable institution of appropriate early treatment and prevention of late complications. We present the typical MRI findings in a 3 ½ month old baby who presented with multiple episodes of seizures which finally turned out to be profound biotinidase deficiency.

Key Words: Congenital biotinidase deficiency, recurrent seizures, skin manifestations, bilateral symmetrical diffusion restriction, cerebral atrophy.

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I. Introduction

Congenital biotinidase deficiency (CBD) is a rare autosomal recessive congenital neuro- metabolic disorder,¹ which leads to profound deficiency of biotin which is an essential cofactor for many enzymes² Biotin deficiency can lead to neurological, cutaneous and visual problems.³ Making a diagnosis based on clinical manifestations alone is difficult. Brain imaging especially Magnetic Resonance Imaging (MRI) with advanced MR techniques like diffusion weighted imaging and MR spectroscopy (MRS) has typical features which can clinch the diagnosis. As MRI plays a key role in making the diagnosis at an early stage of the disease it should be considered in all patients who present with clinical features suggestive of metabolic disorders.

II. Case Report

A 3 ½ months old baby girl presented with complaints of recent onset of multiple episodes of seizures, lethargy, hypotonia, skin peeling and alopecia. The antenatal and birth history were unremarkable. The baby was born of a non-consanguineous marriage. Baby was immunized up to the age. The baby was developmentally normal till 3 months of age and attained social smile at 2 months. Head control has not yet been attained. The baby started to develop recurrent episodes of seizure for 15 days and regression of previously attained social smile. At presentation the child weighed 5.1kg. Head circumference measured about 40cm. In view of multiple episodes of seizures and lethargy, baby was admitted in neonatal intensive care ward and started on empirical antibiotic therapy. Routine blood investigations revealed markedly elevated lactate (11.6mmol/L), reduced bicarbonate (2.7mmol/L) and pH of 6.9. Further blood investigations showed elevated ammonia (200microgram/dl.) and urine ketones(3+). Blood culture and cerebrospinal fluid (CSF) culture were negative. In view of multiple episodes of seizures, skin manifestations, alopecia, severe metabolic acidosis and hyperammonemia, the diagnostic possibility of inborn errors of metabolism was suspected and referred to department of radiology for further evaluation with MRI of the brain.



Figure 1: Clinical photograph of the child showing severe alopecia and skin peeling.

MRI of the brain revealed prominent cortical sulci and fissures, mildly dilated ventricles— suggesting loss of brain volume. In addition there were confluent areas of T2/ fluid attenuated inversion recovery (FLAIR) sequence hyperintensities with T1 hypointensities involving bilateral fronto-parietal white matter, bilateral cerebellar white matter, and cerebellar vermis. There were also bilateral symmetrical areas of diffusion restriction seen in corona radiata, posterior limb of internal capsule, cerebellar white matter, cerebellar vermis, midbrain and left medial temporal gyri. In addition to the above findings, subdural hygroma noted along bilateral frontal convexities (more on the left side). No evidence of mass lesion / hemorrhage seen within brain parenchyma. MRS showed elevated lactate and glycine. Based on the above MRI findings, the diagnostic possibility of inborn errors of metabolism such as CBD, Maple syrup urine disease (MSD) and Leigh's syndrome (LS) were suggested.

With the combination of clinical and radiological findings, biotinidase deficiency was considered as most probable diagnosis and baby was started on oral biotin. Subsequently the diagnosis was confirmed with tandem mass spectroscopy which revealed profound biotinidase deficiency. The baby responded well to oral biotin with reduction of lactate and ammonia and rise in bicarbonate and pH levels.

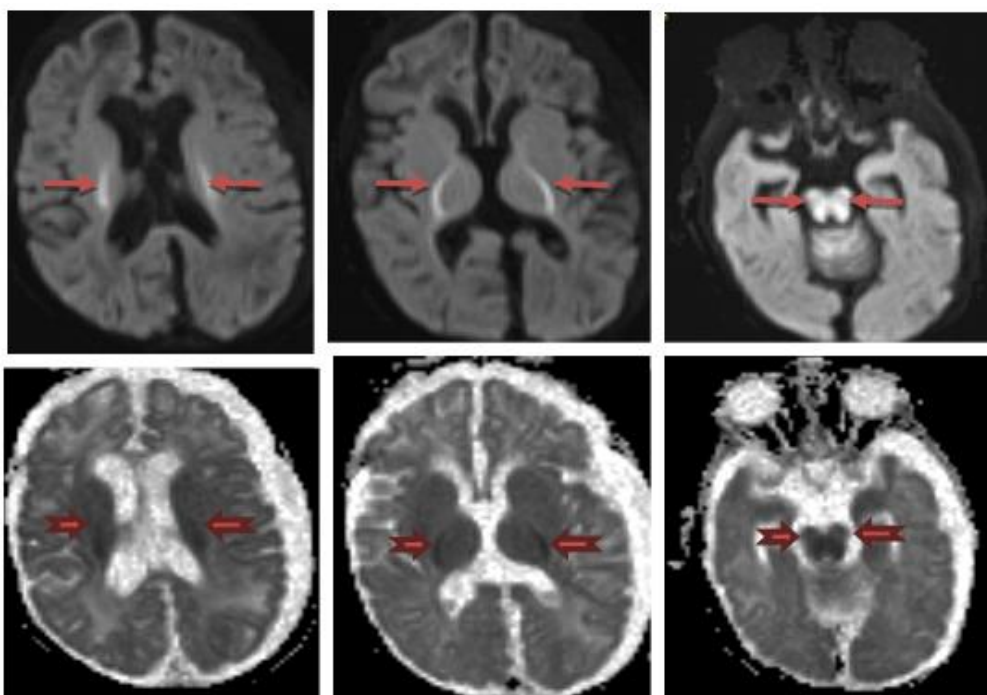


Figure 2: Diffusion weighted images (top row) and Apparent Diffusion Co-efficient (ADC) maps (bottom row) showing bilaterally symmetrical areas of diffusion restriction in the corona radiata, posterior limbs of internal capsule and midbrain which appear hyperintense in DWI (horizontal regular arrows in top row) and hypointense (horizontal notched arrows in bottom row) in ADC.

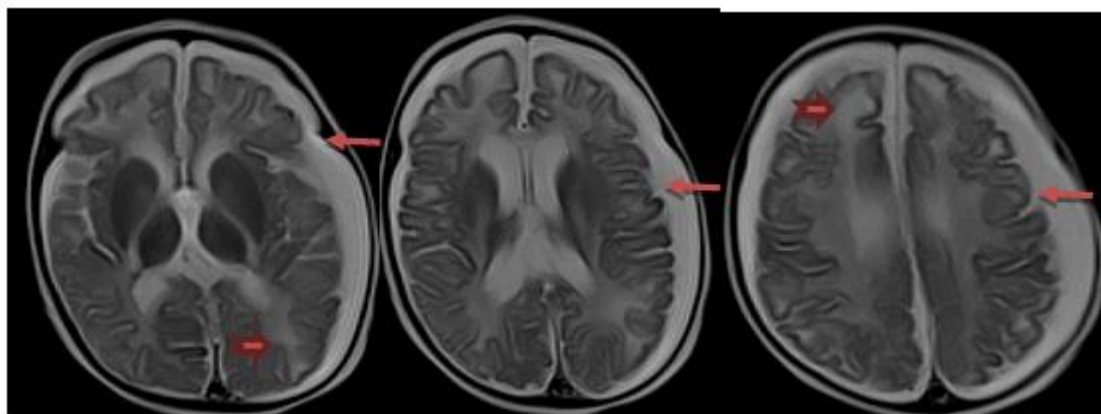


Figure 3: T2Weighted images showing bilateral prominent subdural hygroma (horizontal regular arrows) and abnormal hyperintense areas in the frontal and parieto-occipital white matter (Notched arrow)

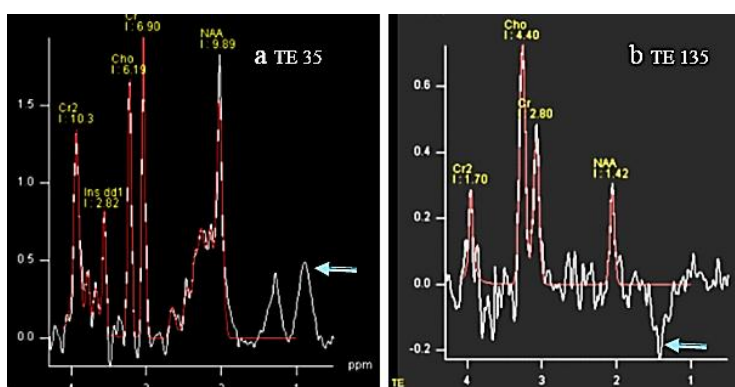


Figure 4: Magnetic resonance imaging H1 spectroscopy images (a, b) acquired with short time to echo (TE 35ms) and intermediate time to echo (TE 135ms). With short TE there is doublet peak at 1.3ppm (Horizontal arrow in a) and reversal of doublet in intermediate TE (horizontal arrow in b), consistent with lactate peak.

III. Discussion

CBD a neurocutaneous disorder, is a rare inborn error of metabolism with autosomal recessive inheritance in which the body is unable to breakdown the conjugated form of biotin (vitamin B7) and clinical biotin deficiency⁴. This condition manifests due to mutation in biotinidase (BTD) gene at chromosome 3q25. The estimated prevalence of profound biotinidase deficiency (<10% of normal level) is approximately 1:137000 newborns. The partial biotinidase deficiency (<30% of normal) is estimated at 1:60,000 newborns¹. The symptoms manifest in early to mid-infancy (mean age of onset – 3.5 months)⁵.

Biotinidase deficiency causes biotin deficiency through multiple mechanisms such as, prevention of release of biotin bound to protein in food particles thus preventing absorption of biotin from intestine, impaired recycle of biotin from carboxylases and histones. The biotin serves as a co-factor for many enzymes such as pyruvate carboxylase, acetyl co-A carboxylase, propionyl Co-A carboxylase, beta methylcrotonyl-coA carboxylase and hence the enzyme biotinidase plays a role in fatty acid synthesis, amino acid catabolism and gluconeogenesis. The substrates accumulated in case of biotinidase deficiency are 3-hydroxy isovaleric acid, 3-methyl crotonylglycine, methylcitrate and 3-hydroxy propionate⁶. When biotin is deficient, the activity of pyruvate carboxylase in CNS falls, leading to localized lactic acidosis. The alopecia and dermatitis in these patients are possibly due to depletion of fatty acids as a result of deficient acetyl-CoA carboxylase.

Clinically, the babies present with multiple episodes of seizures, lethargy, hypotonia, ataxia, developmental delays, coma, alopecia, skin rash (mucocutaneous candidiasis)². Hearing loss and decreased visual acuity are the late complications and are seen less frequently. Biochemically, there will be severe metabolic acidosis, ketosis, hyperammonemia, lactic acidosis and abnormal organic acids in urine. Ketosis and skin manifestations are the atypical features.

Radiologically, MRI will reveal, features of delayed myelination like abnormal T2/FLAIR hyperintensities with T1 hypointensities in bilateral fronto-parietal white matter, bilateral cerebellar white matter, and cerebellar vermis. There can be bilateral symmetrical areas of diffusion restriction involving corona radiata, posterior limb of internal capsule, cerebellar white matter, cerebellar vermis, anterior midbrain, medial

temporal gyri, hippocampi and parahippocampal gyrus¹. The changes of restricted diffusion will be seen more in the myelinated white matter fibers. MR spectroscopy will show elevated lactate and glycine and decreased N-Acetylaspartate and choline. Some studies have shown involvement of the corpus callosum as well, which was not seen in our study⁴.

There are few other conditions in which the MRI findings can closely mimic CBD, which should be considered in the differential diagnoses. They are 1. Maple syrup urine disease⁷ (MSUD) – here the onset of clinical signs and symptoms is relatively early, during first week of life with poor feeding, vomiting, dystonia and seizures. Skin manifestations will be absent. Biochemically – ketoacidosis and characteristic maple syrup odor in urine. In MRI, diffusion restriction is seen in deep cerebellar white matter, dorsal brain stem, cerebral peduncles, and posterior limb of internal capsule, basal ganglia and thalami. Basal ganglia and thalami are typically spared in CBD. 2. Leigh's syndrome (LS) – mitochondrial disorder which presents later, towards the end of first year with hypotonia, psychomotor deterioration, ataxia, ptosis and swallowing difficulties without any skin manifestations⁸. In MRI grey matter is more frequently involved, diffusion restriction can be less pronounced and seen only in acute phase in corpus striatum, sub thalamic nucleus, deep cerebellar nuclei, pons, medulla and periaqueductal grey matter. In MRS there will be large lactate peak and small NAA peak.

IV. Conclusion

When a baby presents in early infancy with multiple episodes of seizures, skin manifestations, elevated lactate, metabolic acidosis, ketosis and hyperammonemia with typical MRI findings of bilateral symmetrical areas of diffusion restriction and brain atrophy, the likely diagnosis of CBD has to be considered which will help to institute proper and timely treatment and thereby avoiding complications and long term sequelae of permanent neuronal damage. Since the structural changes are reversible, it is of paramount importance to make correct and prompt diagnosis of CBD.

Conflicts of interest: Nil

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