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Case Report

Biotinidase deficiency: a novel phenotype from a tertiary care centre

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ABSTRACT

Biotinidase deficiency (BD) (OMIM 609019) autosomal recessive inherited metabolic disorder where enzyme biotinidase, is defective and biotin is not recycled in body. One novel phenotype reported from our tertiary care centre, 3-month-old baby presented with bilateral corneal haziness, development delay and seizures. Evaluation showed metabolic acidosis, persistent lactate elevation and MRI showed acute infract. Metabolic evaluation showed profound BD, confirmed by molecular testing. Treatment and follow up with biotin showed clearing of corneal opacity, resolution of bleed and improvement in development and seizures. BD has got wide range of clinical manifestations- neurologic, dermatologic, ophthalmologic and immunological features. Acute infract and corneal opacity are not yet reported in OMIM literature and BD not considered in differential diagnosis of stroke in metabolic disorders. Being clinicians, it is our responsibility to add novel associations and clinical findings and thus broaden the phenotype.

Keywords: BD, Corneal opacity, Acute infract, Metabolic disorder

INTRODUCTION

Biotin is an essential vitamin needed as coenzyme for many carboxylation reactions in our body. It is usually obtained through food ingested and our body has mechanism to recycle. Biotinidase is the enzyme seen in serum, liver and kidney and main function is to cleave biotin from organic compounds (endogenous and dietary proteins). BD can be profound (<10%) or partial (10-30%) absence of enzyme. Partial deficiency has subtle or no symptoms but profound deficiencies usually have severe presentations. Hence BD has a wide range of clinical manifestations-ophthalmic, neurologic, dermatologic and immunological.[1]

Role of biotin in treatment of carboxylase deficiencies have been noted about 40 years back.[2] Most of the phenotype of varying BD have been described in literature. Association of corneal haziness and acute infract has not yet been described in profound deficiency cases.

CASE REPORT

Three-month-old male, 3rd child born out of consanguineous marriage admitted for the evaluation of abnormal body movements. Antenatal no issues noted and all scans were reported normal, post-natal baby CIAB, uneventful and detected bilateral corneal dystrophy and under follow up with topical medications. Baby had mild delay in development and hypotonia, abnormal body movements hence admitted for evaluation.

Three-generation family tree showed consanguinity and elder brother with mild developmental delay, seizures and poor scholastic performance, diagnosed ADHD and on medications.

No other significant family history, no genetic diseases running in family (Figure 1).

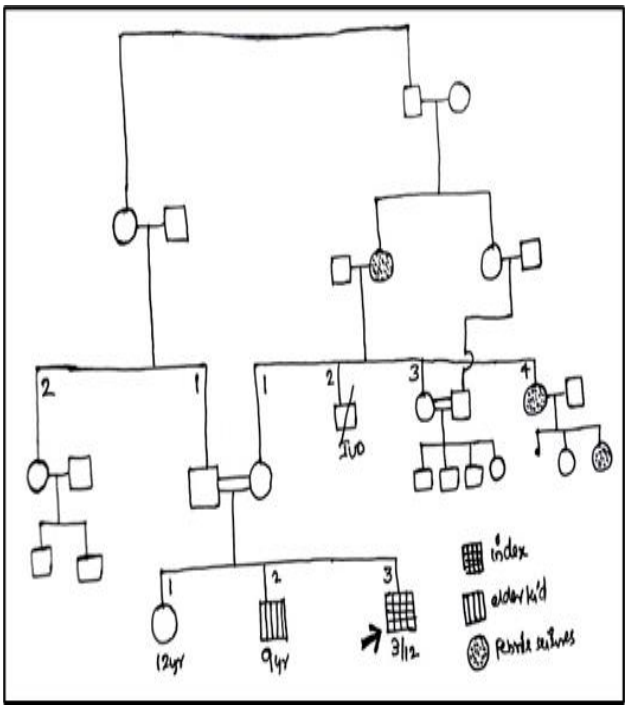

Figure 1: Extended family pedigree showing consanguinity and high risk for AR disorders.

On examination (Figure 2) baby had subtle facial dysmorphism, mild hypotonia, reflex normal, bilateral corneal opacity, scalp hair was mild hypopigmented and sparse, no dermatitis features seen. No feeding issues in past and no failure to thrive features. Counts, CRP, electrolytes were normal, VBG showed metabolic acidosis and lactate elevation, follow up VBG after correction of shock and sepsis also showed persistent lactate elevation. During the hospital stay he developed one episode of GTCS got controlled with medications-EEG showed epileptiform discharges and MRI brain showed acute infract with reduced ADC. ECHO evaluation showed 2 OS ASD and muscular VSD. With the above-mentioned associations suspected IEM and planned for work up. Detailed opthal examination done for baby and mother for cornea verticillata (Fabry's disease), optic atrophy (mitochondrial/IEM) and reported normal. Baby started on aspirin, vitamin cocktail, anti-epileptics and got stabilised with supportive medications.

Metabolic work up: Urine GCMS and blood TMS showed profound BD and sequencing confirmed the pathogenic variant in BTD gene. Baby was started on oral biotin 10 mg once daily, stopped other vitamin supplements and responded well. Follow up showed resolution of corneal haziness, no seizures and developmental delay/hypotonia improved (Figure 3). Elder sibling biotinidase enzyme levels done showed low values and in view of suspected partial BD, gene sequencing done and reports awaited.

Figure 2: Mild depressed nasal bridge, corneal opacity, high forehead, sparse hypopigmented hair, elder sibling with facial dysmorphism, high forehead, inattention, diastema, normal pigmented hair.

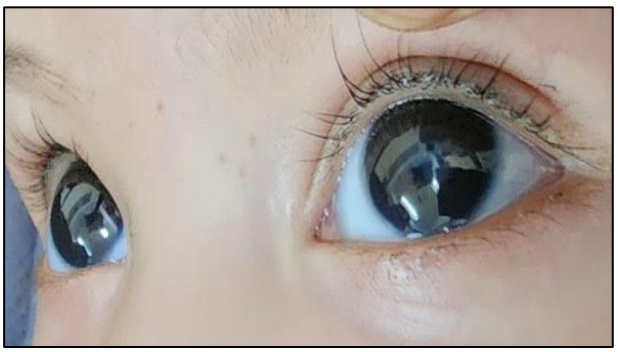

Figure 3: Clearing of corneal opacity after biotin supplementation.

DISCUSSION

Carbon based life forms in earth sustain by coupling environmental CO_2 in to sugar- a process called carboxylation. In human body mainly four carboxylase enzymes (acetyl-CoA carboxylase, methyl crotonyl-CoA carboxylase, propionyl-CoA carboxylase, and pyruvate carboxylase) take part in this biogenic pathway and here vitamin biotin act as a cofactor. Multiple carboxylase deficiency (MCD) is defined as rare autosomal recessive

metabolic disorder occurs due to lack of carboxylation reactions. MCD caused by either holocarboxylase synthetase enzyme (HLCSD, OMIM# 253270) deficiency or biotinidase enzyme deficiency (BTD, OMIM# 253260).[3] HLCSD usually present at neonatal period and older kids usually have BTD. Biotinidase is coded by BTD gene (3p25.1) contains 4 exons and span 23kb. Both conditions will respond to oral biotin supplementation and role of biotin have been known since 1971 in literature.[2] Clinical features of BD varies on whether a profound (<10%) or partial (10-30%) activity of the enzyme. Partial cases will have subtle or no clinical features but profound deficiency have a) neurological-hypotonia, developmental delay, seizures, optic atrophy and coma b) cutaneous- alopecia, seborrheic dermatitis, skin rashes and conjunctivitis c) other-immunological dysfunction, stridor, apnoea, lactic acidosis and organic aciduria.

Consanguineous relationship is defined as one between individuals who are second cousins or closer. As the degree of consanguinity increases the proportion of nuclear genes shared decreases but this still increases the birth prevalence of recessive disorders (Table 1).[4] A detailed 3-generation pedigree is always recommended in genetic cases and if any suspicion of a common ancestor or multigenerational consanguinity better to extended family tree. Our case showed a first cousin once removed consanguinity and 6.5% DNA shared, this also increases the chance of having an AR disorder (Figure 4).[4]

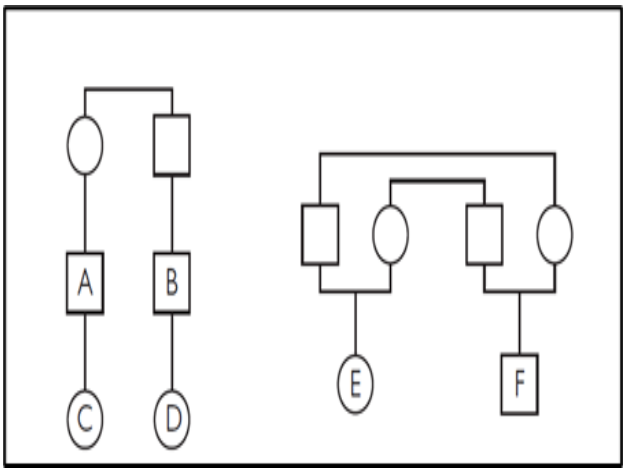

Figure 4: Diagram showing terminology of relationships. A and D and B and C are first cousins once removed. E and F are double first cousins.[4]

Table 1: Probability of homozygous in consanguinity.[4] Our case 6.25% DNA shared, increases AR diseases.

Relationship	Probability
Double first cousins (Fathers are sibs, CA mothers are sibs)	1/16
Uncle/aunt: niece/ nephew	1/16
First cousins once removed	1/16
Double second cousins	1/16

Due to multiple associations and clinical features "stroke in metabolic disorders" considered in approach. Our differentials included-homocystinuria, fabrys disease, MELAS, glutaric aciduria type I, organic acidaemias-propionic acidaemia. Absence of corneal verticillata in index case and mother (X linked, more severe in males) ruled out Fabry also DBS reported normal alpha-galactosidase values. Homocystinuria usually don't present these early months of life and blood homocysteine levels were normal. HCU opthal association is ectopia lentis and myopia, corneal opacity not usually described. GA type I have "progressive macrocephaly" clinical features starts as acute neurological crisis between 3-18 month.

MRI findings in metabolic diseases is usually nonspecific if done on early periods of life. GA I present as frontotemporal atrophy with widening of sylvian fissure (Bat-wing appearance) and BD delayed myelination and white matter edema is the common findings (Figure 5).[6] Our MRI (1.5T) without contrast showed multiple small acute infracts with diffusion restriction in bilateral parieto-occipital regions. Subtle T2/FLAIR hyperintensities involving bilateral cerebral as well as cerebellar white matter suggestive of mild demyelination with reduced ADC (Apparent diffusion coefficient), where in "stroke like episodes" of MELAS ADC is increased. This pattern of acute infracts in a non-vascular distribution, mainly affecting posterior head region; along with persistently elevated lactate made us suspect mitochondrial cytopathy also.

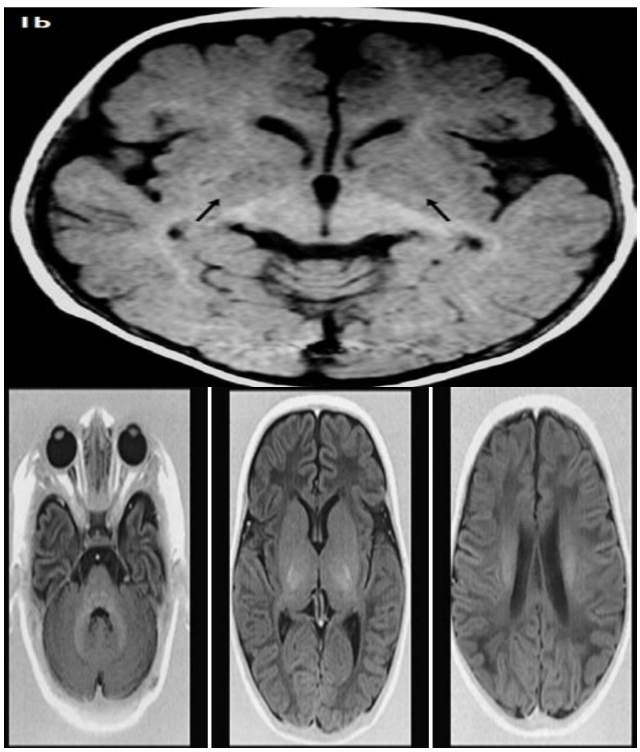

Figure 5: MRI of "batwing" frontotemporal atrophy with dilated opercula and widening of sylvian fissure seen in GAtype1.5 Delayed myelination seen in BD.[6]

Whole exome sequencing with mitochondrial coverage was ordered and a homozygous missense variant in exon 4 of BTD gene (3p25.1) detected which resulted in amino acid substitution of asparagine for serin at codon 139[c.416G>A] (p.Ser139Asn). This novel variant not listed in disease specific database till now and considered as variant of uncertain significance (VUS), but was reported in previous profound BD case.[7] Phenotype was confirmed using urine GCMS and blood TMS analysis and clinical response with biotin supplementation. Computational analysis/In silico predicts this variant produces a splice site change, leading to altered protein structure and function of the BTD enzyme.[8] Pre-test and post-test genetic counselling given to parents and extended family members. Recurrent risk and prenatal options explained. Biotinidase enzyme levels of elder sibling showed low values and gene sequencing done-result awaited.

CONCLUSION

AR metabolic disorders should be considered in doubtful cases where parental consanguinity present. Detailed extended family pedigree should be plotted in all relevant cases. Acute infract and corneal opacity till now not considered in BD also BD not included in "stroke in metabolic disorders" differentials. Addition of this novel associations will broaden the BD phenotype and raise clinical suspicion. This case report also shows the need for newborn screening panel (NBS) in periphery when a previous affected child and parental consanguinity present, for early detection and treatment.

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