

Atypical Presentation of Biotinidase Deficiency in An Iraqi Child with A Biotinidase Deficiency Mutation, A Case Report

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Abstract

Background: This article reviewed the clinical features of a patient diagnosed with Biotinidase deficiency and his genetics test result.

Case presentation: The child presented with mild paroxysmal attacks of head dropping initially relieved by sleep then deteriorated gradually in form of ataxia, abnormal behavior, hallucination, loss of ability to walk, and finally lost consciousness. The child was diagnosed with biotinidase deficiency depending on abnormal brain imaging and genetic mutation of "c.175C>T; p; Arg59 Cys", a homozygous pathogenic variant.

Conclusion: As biotinidase deficiency has variable and atypical symptoms of presentation, children presented with paroxysmal attacks of discoordination, hallucination, and developmental regression with brain image finding similar to those of Leigh or thiamine deficiency should be tested for biotinidase deficiency, and a biotin trial should be given especially in areas lacking newborn screening programs for biotinidase deficiency.

Keywords: biotinidase deficiency, ataxia, head dropping, hallucination, genetic mutation.

Background

Biotin is an essential vitamin that acts as a coenzyme for carboxylases. The Biotinidase enzyme is responsible for the cleavage of biotin from biocytin or biotinyl Peptides, so the absence or deficiency of this enzyme impairs the free biotin formation and affects the biotin-dependent carboxylase functions ⁽¹⁾. Biotinidase deficiency, is also known as late-onset multiple carboxylase deficiency is inherited as an autosomal recessive metabolic disorder and has an estimated incidence of 1:60,000 newborns in Western countries, while the worldwide incidence of profound biotinidase deficiency has been estimated at 1:112,271.^{(2) (3) (4)}. Based on enzyme activity Biotinidase deficiency is classified as either partial or profound; partial when the activity is between 10–30%. While profound biotinidase deficiency when enzyme activity is less than 10% ^{(1) (3) (4)}. Biotinidase Deficiency is characterized by neurological, skin, and metabolic derangements. Neurological symptoms include myoclonic seizures, ataxia, optic atrophy, hearing impairment, hypotonia, and developmental delay. Skin manifestations include alopecia and rash, while metabolic derangement includes lactic and ketoacidosis, and elevated ammonia levels. Respiratory symptoms and fungal infection can be found. Fortunately, an appropriate dose of biotin therapy can reduce and sometimes completely reverse many of these symptoms, however, vision; hearing, and developmental problems may be irreversible. So newborn screening, early recognition, and early treatment result in better outcomes and can prevent neurological abnormalities. ^{(5) (6)}

Genetic mutations causing biotinidase deficiency:

The biotinidase enzyme which is encoded by the biotinidase deficiency (BTD) gene is located on chromosome 3p25. Many different mutations in the BTD genes have been reported. The vast majority of patients are either homozygous or compound heterozygous. ^{(1) (2) (6) (7)} Most of these mutations were found in USA children, also several unique mutations were found among Turkish, Saudi Arabian, Japanese, and Austrian children with Profound Biotinidase Deficiency ^{(7) (8) (9) (10)}.

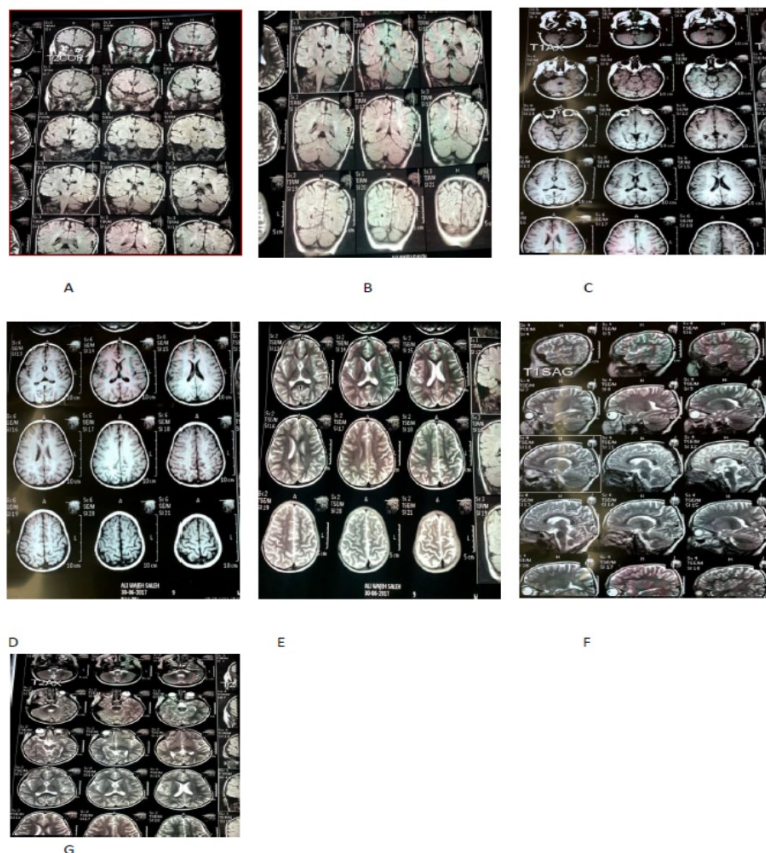
In the symptomatic children, the most common mutations were G98: d7i3, found in 35% of alleles ⁽¹²⁾, and R538C, found in about a third of the alleles. ⁽¹¹⁾ While partial Biotinidase deficiency is mainly caused by a single 1330G>C mutation that results in D444H on one allele. ⁽⁷⁾

Case presentation

A.W. is a 4-year-old boy who was enjoying good health with fair development until the age of 2 years and 3 months when he suddenly developed attacks of head dropping to either side and tripping easily while playing. These attacks lasted for about 10 minutes were not associated with fever, ocular manifestations, nausea, vomiting, headache, weakness or tremor, and were not preceded by a history of head trauma. These attacks used to occur once every one to two months in the beginning. The family attributed that to tiredness and the baby was sent to sleep, when he was awakened, he retained his normal status and became normal as the mother mentioned. A few months later the attacks became more frequent so the family sought medical help. Basic investigation, electroencephalogram, and brain imaging were done and reported normal, based on this data the initial diagnosis was migraine variant. Ibuprofen, depakin, and CoQ10 were prescribed without any improvement in contrary the attacks became more frequent in the next couple months so the family changed medications to propranolol tablets and tonics based on medical advice and no further attacks happened for the next few months apart from once or twice. After 1 year the attacks became more frequent, more prolonged, and more severe eventually child lost his ability to walk, He became disoriented, developed sensory and visual hallucinations by seeing foreign bodies moving in his arms, saw people in the room not present there, developed poor concentration and impaired memory, speech regression, and mild intellectual disability. One day in the morning, his mother found him cyanosed and unconscious, so he was urgently admitted to the respiratory intensive care unit. This was preceded by one week of lethargy, poor activity, and poor interaction with his surroundings. The family couldn't recall any triggering factors, no fever no seizure, no hearing impairment, or visual deterioration. Perinatal history was not eventful.

Family history: First-degree relative parents, his father has migraine, he had one older healthy sibling, no similar illness or sudden death in the family.

By examination at the time of admission in October 2021: The child was unconscious with Glasgow Coma Scale 5/15, he had no meningeal irritation, Cranial nerves examination was normal, his ophthalmological exam was normal as well as hearing assessment.



BRAIN MRI BEFORE TREATMENT(A-G) Shows: Bright signal intensity in mammillary bodies and periaqueductal grey matter noted at T2 and FLAIR images, subtle bright T2 signal in the medial thalamus, normal basal ganglia, normal white matter.

Upper limbs were normal in tone, power, and reflexes, Lower limbs tone was decrease, power was grade 2, reflexes were normal, Babinski was flexor bilaterally. The sensory and cerebella exam were not applicable.

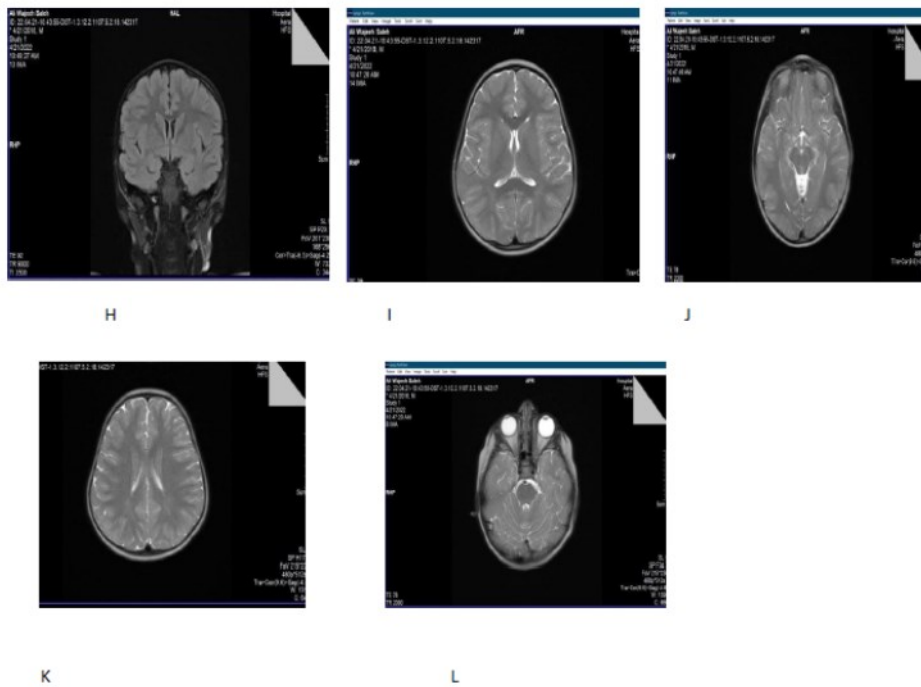
Blood investigation; complete blood count, renal and liver function test, blood gas analysis, and ammonia level all were normal. Biotinidase activity level was not performed because it is unavailable in Iraq.

Brain image showed bright signal intensity in mammillary bodies and periaqueductal grey matter noted at T2 and FLAIR images, subtle bright T2 signal in the medial thalamus, normal basal ganglia, normal white matter, normal brain volume and no signs of atrophy. The image suggests the diagnosis of thiamine deficiency, and mentioned mitochondrial disease as differential diagnosis.

Genetic test: single gene analysis detected a homozygous likely pathogenic variant in the biotinidase deficiency gene, which consistent with biotinidase deficiency disease. Gene variant c.175C>T; p; Arg59 Cys, Zygosity homo, Hereditary AR .MAF% <0.01, In silico prediction pathogenic, Classification likely pathogenic

He started thiamine 100 mg twice daily and biotin 5000 micrograms three times a day supplements until March 2022 when he was reexamined. His general condition quietly improved, he was playing and interacting normally, and his general and neurological examination was normal without residual deficit apart from slight coarse hair.

His newest brain image done in April 2022 (5 months later) was showing: a subtle hyper intense signal in the periaqueductal gray matter on the T2 sequence with normal plate and normal mammillary bodies.



BRAIN IMAGE AFTER TREATMENT (H-L) shows a subtle hyper intense signal in the periaqueductal gray matter on the T2 sequence with normal plate and normal mammillary bodies.

Discussion

As it is well known, in profound biotinidase deficiency the child may present with many neurological symptoms like hypotonia, resistant seizure, cerebellar symptoms, vision, hearing loss, developmental delay, and learning disabilities Other non-neurological symptoms like skin rash, and alopecia. While in partial biotinidase deficiency, affected children may have any of the previously mentioned symptoms but at a milder level depending on whether the children are under stressful conditions. This child was normal until the second year of life when he started to have paroxysmal attacks of discoordination relieved by sleep with a positive family history of migraine, he has no history of seizures no hearing or vision problems, no skin rash or hair loss, no attacks of acidotic breathing. Brain MRI showed lesions similar to those observed in Leigh syndrome and thiamine deficiency a finding similar to that mentioned by Shi C, Chang JM (13). So the imaging was not conclusive and his final diagnosis was reached by a Genetic test that showed mutation; c.175C>T; p; Arg59 Cys", homozygous pathogenic variant,

The serum biotin concentrations measurement is not available in Iraq and there is no facility to send the blood sample abroad for biochemical tests, in addition to that, the paroxysmal attacks of the child presentation at first make the biotinidase deficiency less likely with a wide list of differential diagnosis so genetic tests were considered early.

He was kept on a high dose of biotin 5000 micrograms three times a day and a thiamine tab of 100 mg twice daily. After the result of the genetic test revealed the biotinidase deficiency gene, thiamine was stopped and kept only on a high dose of biotin 5000 micrograms three times a day with a dramatic response in his general condition and brain image that became nearly normal after only 5 months of treatment. He had no head drooping or hallucination. He was playing and interacting normally, and his general and neurological examination was normal apart from slight coarse hair.

Conclusion

As biotinidase deficiency has variable and atypical symptoms of presentation, children presented with paroxysmal attacks of discoordination, hallucination, and developmental regression with MRI finding similar to those of Leigh or thiamine deficiency should be tested for biotinidase deficiency, and a biotin trial should be given especially in areas lacking newborn screening programs for biotinidase deficiency.

Ethics approval and consent to participate

The manuscript had the approval of the Ethics Committee of the Children Welfare Teaching Hospital/Medical City. Written informed consent was taken from the parents of the patient.

Consent for publication

Written informed consent was obtained from the parents of the patients.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Hula R. Shreef conceived and designed the study, Hula R. Shreef and Basma A.Ibrahim performed clinical assessments, and contributed to data acquisition, analysis and interpretation. All authors contributed to critical revision of the manuscript for intellectual content and final approval of the manuscript. All authors have read and approved the manuscript.

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