A case report of biotin–thiamine-responsive basal ganglia disease in a Saudi child
Is extended genetic family study recommended?
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Abstract
Background: Biotin–thiamine-responsive basal ganglia disease (BTRBGD) is a neurometabolic autosomal recessive (AR) disorder characterized by subacute encephalopathy with confusion, convulsions, dysarthria, and dystonia. The disease is completely reversible if treated early with biotin and thiamine, and can be fatal if left untreated.

Methods: An index case of BTRBGD and his family underwent thorough clinical and radiological assessment along with genetic molecular testing.

Results: Two-and-half years old Saudi male child whose parents are consanguineous fulfilled the clinical and magnetic resonance imaging (MRI) criteria of BTRBGD. He was proved by molecular genetic testing to have homozygous mutation of c.1264A>G (p. Thr422Ala) in the SLC19A3 gene of BTRBGD. Extended clinical, radiological, and genetic family study revealed 2 affected members: a neglected symptomatic cousin with subtle neurological affection and an asymptomatic brother carrying the disease mutation in homozygous status. Heterozygous pattern was detected in his parents, his grandma and grandpa, his aunt and her husband, 2 siblings, and 1 cousin while 1 sibling and 2 cousins were negative to this mutation.

Conclusion: BTRBGD requires high index of suspicion in any child presenting with unexplained subacute encephalopathy, abnormal movement, and characteristic MRI findings. Extended family study is crucial to diagnose asymptomatic diseased cases and those with subtle neurological symptoms.

Abbreviations: AR = autosomal recessive, BTRBGD = biotin–thiamine-responsive basal ganglia disease, MRI = magnetic resonance imaging.

Keywords: biotin, biotin–thiamine-responsive basal ganglia disease, encephalopathy, neurometabolic, SLC19A3, thiamine

1. Introduction

Biotin–thiamine-responsive basal ganglia disease (BTRBGD) (OMIM: 607483) is inherited in autosomal recessive manner.
misdiagnosed as a mitochondrial disease due to similarities in clinical, biochemical, and MRI findings. [8]

Although of this devastating picture, the good thing is that early administration of high doses of biotin and thiamine can ameliorate the symptoms of BTRBGD within few days, with no recurrence unless treatment is discontinued but delayed treatment usually leaves residual paraparesis, mild mental retardation, or dystonia. [9]

Recently, this disease became under focus in our country; Saudi Arabia; as most of the reported cases are Saudi. [1,2,8]

We herein present our experience with BTRBGD from a single center from Saudi Arabia. Our report is the 1st to use the strategy of extended genetic family screening which proved ultimate success in diagnosing asymptomatic and subtle cases where treatment was provided before disease become overt as it is well known that once disease became overt, no one can guarantee its long-term sequels.

2. Case report

A 2.5-year-old male Saudi child presented with sudden onset of ataxia and left-sided dystonic posturing of all limbs of 1 day duration which was preceded by a history of runny nose and cough for several days but no history of fever, vomiting, abnormal movement, or skin rash. There was no history of any drug intake or herbal medications. The patient was fully alert but with hypertonia and hyperreflexia of all his limbs especially on the left side. He was able to walk with support with ataxic gait. Other systemic examination was unremarkable. The parents were consanguineous and other siblings were apparently healthy. MRI brain of the patient showed basal ganglia changes consistent with BTRBGD (Fig. 1A). Molecular genetic analysis and screening of the family for SLC19A3 mutation was carried on. The 5 coding exons and the exon–intron boundaries of SLC19A3 gene were amplified by polymerase chain reaction and analyzed by direct sequencing which revealed at position c.1264 in exon 5 of the SLC19A3 gene the nucleotide exchange (c.1264A>G), resulting in a substitution of the evolutionarily highly conserved threonine to alanine at position 422 of the protein sequence (p. Thr422Ala) in homozygous state in the patient, one of his cousins, and an asymptomatic brother (Fig. 2). Heterozygous pattern was detected in his parents, his grandma and grandpa, his aunt and her husband, 2 siblings, and 1 cousin while 1 aunt, 1 uncle, 1 sibling, and 2 cousins were negative to this mutation.

Figure 1. (A) Abnormal signal intensity due to necrosis of the caudate and putamen, diffuse brain involvement with cortical and subcortical white matter, and the infratentorial regions; (B) partial improvement at 2 months of treatment; (C) complete resolution at 6 months of treatment.

Figure 2. Pedigree of the extended family of the index case.
dose of thiamine (10 mg/kg per d) and further decreased it overtime[12] but that was likely not enough to sustain clinical improvement, it may only have contributed to longer life span.

We believed that thiamine is the most crucial that is why we used high dose of 600 mg/d at initiation of treatment and during periods of stress as a dose of 300 mg/d was not sufficient to induce remission in our patients. Biotin was used at a dose of 2 mg/kg per day all through to benefit from its synergistic effect. Thiamine was decreased to 300 mg/d after improvement and continued to maintain remission. We plan to keep patients on the lowest maintenance doses which can keep remission.

Due to the relatively high number of BTRBGD patients in Saudi Arabia, a Saudi multicenter center study is underplanning to study the special peculiarities of the Saudi patients, their demographics, disease characteristics, disease severity, and different treatment, and maintenance regimens.

The outcome of our report with early diagnosis and treatment of asymptomatic patients had led us to suggest adding another arm to the Saudi multicenter study using extended molecular testing of families of index cases for proper characterization of our country genetic mutations along with identifying homozygous cases who are asymptomatic or having subtle symptoms aiming for prevention of overt disease rather than waiting it until it became symptomatic.

4. Conclusions

BTRBGD is a relatively missed disease which needs to be put in the differential diagnosis of any patient presenting with encephalopathy, convulsions, and deteriorating neurological functions especially in countries with relatively high number of cases like Saudi Arabia.

The disease is reversible if treatment started promptly. Biotin and high doses of thiamine are the mainstay of treatment.

We recommend a national program to screen high-risk tribes so that presymptomatic treatment could be started to prevent much of the morbidity and mortality. This approach if adopted will also serve to increase the awareness among vulnerable population for premarital testing and well in the long way limits the prevalence of the condition.

References


