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Case Report

Biotin-thiamine responsive basal ganglia disease in the era of COVID-19 outbreak diagnosis not to be missed: A case report

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Abstract

Background: Biotin-thiamine-responsive basal ganglia disease (BTRBGD) is a rare treatable autosomal recessive neurometabolic disorder characterized by progressive encephalopathy that eventually leads to severe disability and death if not treated with biotin and thiamine. BTRBGD is caused by mutations in the *SLC19A3* gene on chromosome 2q36.6, encoding human thiamine transporter 2 (hTHTR2). Episodes of BTRBGD are often triggered by febrile illness.

Case report: The patient was 2 years 10 months old male child presented with fever and progressive acute encephalopathy associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus infection. MRI revealed bilateral symmetrical high signal involving both basal ganglia and medial thalami which is swollen with central necrosis, initially diagnosed as acute necrotizing encephalomyelitis with increased severity. Genetic analysis revealed BTRBGD.

Conclusion: BTRBGD requires high index of suspicion in any patient presenting with acute encephalopathy, characteristic MRI findings (that are difficult to differentiate from necrotizing encephalopathy), regardless of the existence of a proven viral infection.

Keywords: Biotin-thiamine responsive basal ganglia disease; SARS-CoV-2; Encephalopathy; Neurometabolic; COVID-19

1. Introduction

Biotin-thiamine-responsive basal ganglia disease (BTRBGD) is a curable, uncommon, and fatal inherited neurometabolic disease that is characterized by progressive brain damage. Without treatment, this condition can lead to severe neurological impairment and death. Mutations in the *SLC19A3* gene, found on chromosome 2q36.6, trigger the presence of BTRBGD by encoding for the human thiamine (vitamin B1) transporter 2. (hTHTR2) [1].

BTRBGD usually begins in children between the ages of 3 and 10, but can appear at any age, and is characterized by recurrent episodes of encephalopathy during which the patient may have disturbed consciousness, convulsions, ataxia, dystonia, and cranial nerve palsies. There is a possibility of hemi- or quadri-paralysis, these manifestations are most commonly triggered by fever [2]. In the first three months of life, lethal Leigh-like syndrome develops with poor feeding, vomiting, acute encephalopathy, and severe metabolic acidosis [3]. Late onset Wernicke-encephalopathy like presentation may

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occur in the form of ptosis, ophthalmoplegia, ataxia and status epilepticus [4].

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus has the potential to invade the central nervous system and cause a spectrum of neurological manifestations in coronavirus disease 2019 (COVID-19) patients through few basic mechanisms:1) Blood circulation pathway.2) Direct infection injury of the brain through the cribriform plate.3) Neuronal pathway 4) Immune-mediated and hypoxic injury of the brain cells [5]. Infection with CoV-2 in the central nervous system results in the production of numerous cytokines, which may impair the immune system, furthermore children with severe illness are at risk of developing specific neurological complications, encephalopathy, seizures, and they are detected in around 1% of cases [6,7].

2. Case report

Two years 10 months old male child, full-term, through a normal vaginal delivery, was born to healthy Kuwaiti consanguineous parents with appropriate growth parameters and developmental milestones, no significant antenatal history. He presented with three days history of fever, symptoms of upper respiratory tract infection, vomiting, three times sudden loss of posture, falling down, with no loss of consciousness, no abnormal movement, those attacks were lasting for 1–2 min. No history of trauma or drug intake. History of contact with relatives positive COVID 19 infections. Patient has strong family history of epilepsy- three aunts, two of them receiving antiepileptic drugs and one first cousin with attention deficit hyperactivity disease (Fig. 1).

On examination at the time of admission, he had stable vital signs, normal blood pressure, weight on 25th percentile, height on 50th percentile, head circumference on 25th percentile. He was conscious, alert, irritable, no signs of meningitis, pupils bilateral equal, rounded, and reactive. Deep tendon reflexes were elicited, symmetric with bilateral flexor plantar reflex, normal muscle tone and power. Other system examinations were unremarkable. Chest X-ray, electrocardiogram (ECG) unremarkable. He has positive reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2.

Lab investigations- complete blood count (CBC), inflammatory markers, D-dimer, biochemical investigations, lactic acid, ammonia, blood gases all were within normal range.

Within the first days after admission the subtle neurological symptoms progressed to frequent attacks of sudden falling down, associated with shivering, tremor, sweating and increased muscle tone in all extremities, prolonged episodes of irritability and screaming, the duration of those episodes last from for few minutes.

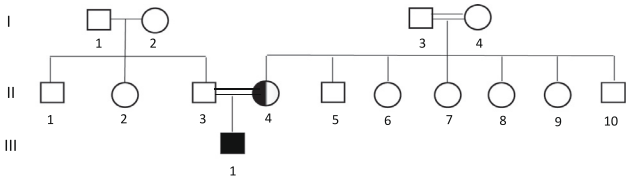

Fig. 1. Extended family pedigree of the index case: Black filled symbol is the diseased patient (index case); divided black symbol is heterozygous asymptomatic carriers; open symbols are unaffected individuals. Family members number 6, 7 and 8 in the second generation had epilepsy.

On 5th day, on examination: irritable, continuously crying, Glasgow coma scale (GCS) 11/15 (eyes opening 3, verbal response 4, motor response 4), severe spasticity in all extremities (flexed upper limbs, flexed elbow, bent wrist, pronated forearm, clenched fist), increased muscle tone, hyperreflexia, Babinski sign positive bilaterally, dysarthria, dysphagia, spontaneous clonus of ankles, ophthalmoplegia, truncal dystonia. Pupils equal, reactive. Normal vital signs, normotensive. Other physical examination unremarkable.

Repeated lab investigations CBC, inflammatory markers, D-dimer, venous blood gases, all within normal range. From biochemical investigations only creatine kinase (CK) 623 IU/L was elevated. Cardiac markers were within normal range. Blood virology study was negative for other common neurotropic viruses.

MRI brain was performed, and it showed: bilateral symmetric abnormal signal within the caudate and lentiform nuclei as well as scattered cortical area of abnormal signal; oedema around basal ganglia and cortical areas. Picture consistent with necrotizing encephalitis vs BTRBGD (Fig. 2).

Metabolic work up including acylcarnitine profile, plasma amino Acid chromatography and urine organic acids analysis showed no significant abnormalities. Cerebrospinal fluid (CSF) analysis was not done as lumbar puncture refused by parents. Serum autoimmune - antibodies test (anti-N-methyl D-aspartate receptor [NMDAR], anti-amphiphysin, anti-CV2, anti- paraneoplastic antigen Ma2 [PNMA2], anti-Ri, anti-Yo, anti-Hu- antibodies) were negative.

The child initially diagnosed as acute necrotizing encephalomyelitis and started pulse steroid therapy (methylprednisolone 30 mg/kg), intravenous immunoglobulin (1 gm/kg/day for two days), also trihexyphenidyl (1 mg/day), baclofen (0.5 mg/kg/day), acyclovir and cefotaxime were given.

On 7th day there was increased spasticity, irritability, and dystonia with deterioration of conscious level, so thiamin (100 mg/twice daily) and biotin (10 mg/kg/day) were given and genetic test for BTRBGD were sent, patient was started on physiotherapy, occupational therapy.

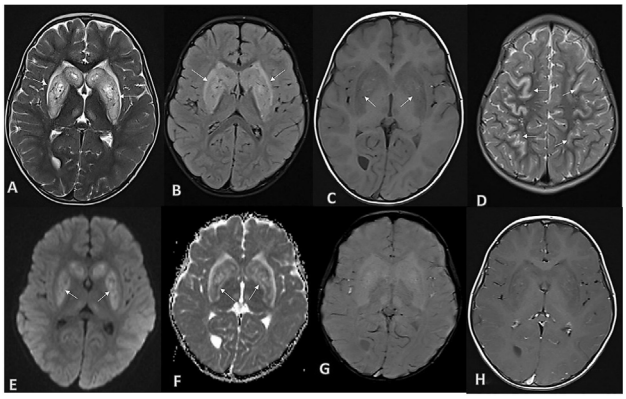

Fig. 2. MRI revealed bilateral symmetrical high T2 (arrows in A) & coronal fluid-attenuated inversion recovery (FLAIR) (B) signal involving both basal ganglia (caudate and lentiform nuclei) which is swollen with central necrosis and involving bilateral medial thalami with T1 low peripheral and high central signal (C). Also, bilateral high frontoparietal cortical high T2 signal (arrows in D) with partial high signal in diffusion-weighted imaging (DWI) (E) and low signal in apparent diffusion coefficient (ADC) (F). No blooming foci on susceptibility weighted imaging (SWI) sequence (G) and no enhancement after IV contrast (H). It was confirmed by genetic as Biotin-thiamine-responsive basal ganglia disease with gene (*SLC19A3*) mutation.

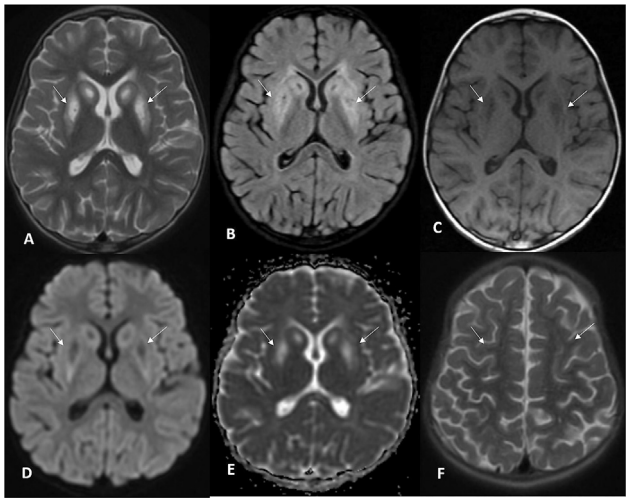

Fig. 3. Follow up MRI after treatment revealed regression of the previous abnormal high T2 (arrows in A) &FLAIR (B) signal involving both basal ganglia and medial thalami with resolution of the high central signal at T1 (C). Normalization of the diffusion restriction with low signal on DWI (D) and high signal on ADC (E). Also, resolution of the previous bilateral high frontoparietal cortical high T2 signal (arrows in F).

Genetic Test: Full Exome sequencing done by PCR and direct sequencing testing for most common mutations in *SLC19A3* gene confirmed- homozygous mutation {c.1264 A > G,p.Thr422Ala} which is associated with autosomal recessive BTRBGD.

2.1. Follow up

Within 15 days after initiation of treatment, the child showed gradual clinical improvement of extrapyramidal and pyramidal signs. Irritability, inability to swallow and talk disappeared in first few days. MRI brain on 15th day after starting treatment as compared to previous study, there was relative minimal regression of oedema either around the basal ganglia or within the affected cortical areas (Fig. 3).

On 21st day after starting the treatment child was able to say many monosyllable words, to walk without support, still he had mild ataxic gait, muscle rigidity, brisk deep tendon reflexes (DTR).

On 30th day, he had markedly improved muscle tone and normal DTR.

On 55th day he had normal physical and neurological status with only mild reduced sensation on fingers.

The family was educated regarding the importance of lifelong compliance with medical treatment with Thiamine and Biotin.

3. Discussion

Although BTRBGD often manifests as acute encephalopathy triggered by fever, the underlying processes remain unknown. Kohrogi et al. [8] reported that several neurological disorders including BTRBGD are frequently triggered by febrile illnesses. Fever is considered an exaggerated immune response leading to ATP consumption, energy depletion and oxidative stress which can induce neurological regression in mitochondrial disorders with deficient ATP stores [9]. *SLC19A3* is found in the basement membrane of the brain and is expressed by perivascular pericytes of cerebral arteries and the choroid plexus, where it transports thiamine across the blood–brain barrier. *SLC19A3* mutations are linked with decreased thiamine levels in the cerebrospinal fluid but not in the blood, implying poor transport to the central nervous system. In affected individuals, *SLC19A3* expression is significantly decreased in mutant neuronal cells in the cortex, basal ganglia, and cerebellum. Encephalopathy episodes are most likely produced by mutant neuronal cells' significantly decreased capacity to increase *SLC19A3* expression, which is required to adapt to stress conditions. It is unknown how *SLC19A3* deficiency results in brain lesions and neurological symptoms, or how extrinsic stimuli (e.g., fever, infection) may induce encephalopathy episodes [10,11].

The differential diagnosis of BTRBGD is often difficult especially regarding post-viral acute necrotizing encephalitis and other neurometabolic disorders (e.g., mitochondrial diseases, glutaric aciduria type I, methyl-malonic acidemia, 3-methyl-glutaconic aciduria) with similar MRI brain findings and triggering factors [12], furthermore early molecular identification is extremely significant because early treatment with high doses

of biotin and thiamine can stop further basal ganglia damage and put an end to the development of neurological symptoms [13].

SARS-CoV-2 is a novel neuropathogen associated with a broad spectrum of neurologic symptoms, including headaches, seizures, anosmia, dizziness, encephalopathy, and stroke. Although the exact mechanism of these manifestations is not completely understood, it is most likely a multifactorial process including neuro-invasion, sepsis, hypoxia, and immune mediated inflammation [14]. Complications of the nervous system are uncommon in children with COVID 19 and almost all documented patients of SARS-CoV-2-encephalitis, convulsions, and encephalopathy survived. The rare fatal cases documented are due to necrotizing encephalitis, which always mimics some neurometabolic conditions with basal ganglia involvement like BTRBGD [15,16].

4. Conclusions

Our case is an example of a classical childhood onset BTRBGD with most common homozygous mutations in *SLC19A3* gene. The disease is 1st time presented during COVID-19 infection. SARS-CoV-2 is a new neuropathogen. How it may cause acute and chronic neurologic disorders needs to be clarified in future research. BTRBGD requires high index of suspicion in any patient presenting with acute encephalopathy, characteristic MRI findings (that are difficult to differentiate from necrotizing encephalitis), regardless of the existence of a proven viral infection, moreover early treatment with high doses of biotin and thiamin is required in suspected cases even before genetic confirmation to prevent neurological deterioration.

In addition to the established ways through which the SARS-CoV-2 virus may induce neurological damage, we propose a novel mechanism in which the virus acts as a trigger for an underlying hereditary neurometabolic illness such as BTRBGD.

Ethical approval

Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors appreciate the cooperation of the patient's parents.

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