

Depression in adult patients with biotin responsive basal ganglia disease

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Summary

Biotin responsive basal ganglia disease (BBGD), is a potentially treatable inherited metabolic disorder which clinically presents as sub-acute encephalopathy in children. Early diagnosis and treatment of this disorder results in good clinical recovery in childhood. However, there is no report in the literature on the long term outcome of these treated patients in adult life. We report two patients with BBGD who were metabolically stable on treatment and developed depression later in life. These cases highlight the association of depression with basal ganglia disorders and demonstrate that depression is the potential long term complication of BBGD.

Keywords: Basal ganglia disease, depression, biotin, thiamine

1. Introduction

Biotin responsive basal ganglia disease (BBGD) is an autosomal recessive neuro-metabolic disorder, also known as thiamine metabolism dysfunction syndrome-2 (THMD2) (MIM: 607483). It was first described by Ozand *et al.* in 1998 in ten Arab patients (1). Later causative mutation in *SLC19A3* gene was discovered with known founder mutation in Saudi Arabia [c.1264 A>G; p.T422A] (2). It is a pan-ethnic disorder which has been reported in European, Indian and Japanese patients (3,4). It presents as encephalopathy with extrapyramidal signs in children, often following a febrile illness. Brain magnetic resonance imaging (MRI) demonstrates bilateral symmetrical involvement of the basal ganglia. Administration of biotin and thiamine early in the course of disease, reverses the clinical sign and symptoms within days in this, otherwise potentially fatal disease (1,2). Nevertheless, like many other inherited metabolic disorders, there is no information

available on the course of BBGD in adult life. Herein, we report two siblings with BBGD who were described in the original report by Ozand *et al.* and they developed depression in adult life.

2. Case Report

2.1. Case 1

A 32-year-old lady, a known case of BBGD, was diagnosed at the age of 7 years when she presented with confusion, lethargy, dysarthria, dysphagia and severe spasticity of limbs. Her brain MRI demonstrated extensive bilateral T2 hyperintensity, with symmetrical involvement of the caudate nuclei and putamen. She showed remarkable response to biotin and thiamine therapy with resolution of symptoms except for persistent mild stuttering. Genetic testing later revealed homozygous mutation (c.1264A>G, p.T422A) in *SLC19A3* gene. She graduated from high school with average academic achievements. At 13 years of age in 1996, she developed mild episode of depression with no clear triggers. She continued to have recurrent episodes of mild depression till 2010 when her symptoms got worse with low mood, feeling of being isolated, poor sleep, poor appetite, fatigue and wishes of death without having any actual suicidal thoughts, intentions or plans. She lost 5 kilogram in weight

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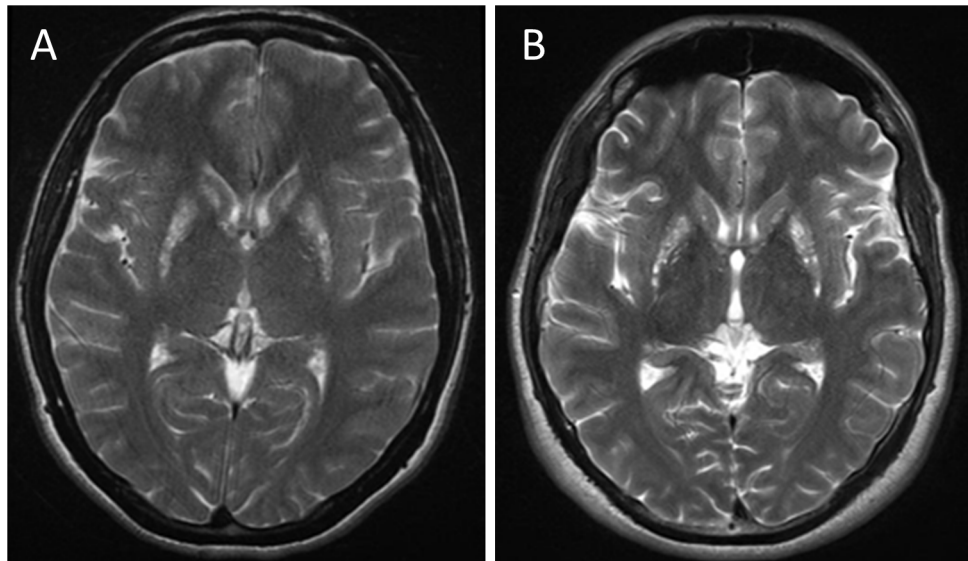


Figure 1. Magnetic resonance axial T2 weighted images showing necrosis of bilateral caudate and putamen in both patients.

during this episode, which lasted for a month. She was seen by a psychiatrist and a diagnosis of major depression was confirmed. She denied having any suicidal or homicidal ideation, manic symptoms, audiovisual hallucinations, or paranoid ideation. She was started on escitalopram but did not comply with the treatment due to the concerns about its side effects. She was later prescribed other antidepressant medications including paroxetine and paliperidone but she felt that her depression got worse with these medications and stopped treatment. Although she blames the death of her husband in 2014 in a motor vehicle accident for her depressive symptoms but is unable to explain the cause of depression starting from the younger age of 13. Her last depressive episode was two years ago. Currently, she feels better. She is sleeping and eating well. She has no symptoms suggesting generalized anxiety disorder, obsessive compulsive disorder, or post-traumatic stress disorder. She however, has social phobia. A recent brain MRI showed necrosis of bilateral caudate and putamen (Figure 1A) while magnetic resonance spectroscopy (MRS) was unremarkable.

2.2. Case 2

A 38-year-old gentleman, elder brother of patient 1, also a known case of BBGD, was diagnosed at the age of 12 when he presented with ptosis, dysarthria, dysphagia, and dystonic movement in the lower limbs. Based on the family history of affected younger sister with BBGD, he was started on biotin and thiamine. His brain MRI demonstrated similar changes as seen in his sister. Genetic testing confirmed the same homozygous mutation in *SLC19A3* gene. He also showed complete clinical recovery following treatment with biotin and thiamine except for mild dystonia in his left hand. At the age of 16, he developed seizures when he had

stopped taking biotin. This resolved after resuming the therapy. He received bachelor's degree in the management and was employed with good performance at work. He led an active life with regular participation in sports. However, in 2007 at the age of 29, he started having low mood, isolating himself with loss of interest. He had poor interrupted sleep, fatigue, decreased concentration and loss of appetite. He lost over 20 kg in weight in a few weeks. He denied having any thoughts of death, or suicidal ideation or psychomotor retardation. These symptoms persisted for about three weeks. He was seen by the psychiatrist and treated with venlafaxine and mirtazapine with significant improvement in his symptoms. He thought that the trigger for the first episode of depression was financial difficulties due to loss of money in the stock market. However, later he continued to have mild episodes of depression. Initially he had anxiety attacks as well, with symptoms of shaking and sweating. In addition, he had obsessive compulsive symptoms that included prominent fears of contaminations, for a brief period of 6 months in 2009. It responded well to the treatment with clomipramine. There were no complaints of any phobia, generalized anxiety disorder, or post-traumatic stress disorder symptoms. He remains compliant to the maintenance therapy with venlafaxine, trazodone and clomipramine. Currently he feels very well and denies having any depressive symptoms. He is working as an accountant and continues to actively participate in the sports. His recent brain MRI (Figure 1B) also showed necrosis of caudate and putamen while MRS study was unremarkable.

3. Discussion

Depression has been reported in a wide variety of inherited errors of metabolism (IEM) including

urea cycle disorders, porphyria, homocysteinuria, phenylketonuria, GM2 gangliosidosis, Niemann-Pick C disease and Fabry disease (5). With our report we are expanding the list of inborn errors of metabolism that can be associated with depression.

The two siblings in this report are the eldest patients with BBGD, seen in our hospital. They had good clinical recovery following initial presentation in childhood, yet they developed depression later in life, despite adequate metabolic control. The diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM IV) and they met the criteria for major depressive disorder. There was no recorded family history of depression.

The underlying pathophysiology of depression in IEM is still not fully understood. These patients may develop depression, secondary to the psychological and social issues related to their chronic medical illness. Nevertheless, depression may be a sequelae of the structural and functional changes in the brain secondary to their metabolic disease. Clinical and experimental data has shown basal ganglia involvement in controlling cognition and behavior in addition to movement control (6). Depression is well known in basal ganglia disorders like Parkinson's disease, Wilson's disease and Huntington's disease where it may precede the development of movement disorder (7). Basal ganglia are linked to the orbitofrontal and prefrontal cortices as well as limbic system *via* functional parallel circuits (6) and it has been postulated that disruption of cortico-basal ganglia connectivity due to neuronal degeneration or altered myelination may contribute to the development of depression in these patients (5,6). Moreover, dopamine or serotonin depletion, which affects the cortico-basal ganglia functional circuits, also contributes to the etiology of depression (5,6). It is interesting to note that in spite of good clinical recovery with successful treatment of BBGD, the recent brain MRI study of both patients after over 25 years of diagnosis, continues to show changes in the basal ganglia. This affirms the previous reports (1,8). In addition, Husain *et al.* have reported diminished volume of putamen in brain MRI of patients with major depression (9). Long standing basal ganglia pathology as seen in the brain MRI of both patients, therefore suggests that it may have a significant role in the development of major depression in these cases.

Despite having a chronic metabolic disorder, both patients led an active life with academic achievements prior to developing depression. The female patient first showed symptoms at the age of 13. Although she cites the death of her husband, for her symptoms, this does not explain the origin of depression since adolescence

and its periodic recurrence. Similarly her brother, the second patient, tends to blame external factors like loss of income for depression. This however, does not explain why his depression started at an early age and was episodic in nature. He had required maintenance therapy with psychotropic medications for the past 8 years. Early age of onset with no triggers and recurrent pattern suggest that depression in both patients is endogenous in origin. Hence, we postulate that depression in BBGD is likely to be organic in nature secondary to basal ganglion pathology rather than a reflection of chronic disease. Further research is required to better understand the long term neuropsychological outcome of this disease in adult life.

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