CASE REPORT

Treatable Leigh-like encephalopathy presenting in adolescence

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SUMMARY

Wernicke's encephalopathy is a triad of ophthalmoplegia, ataxia and confusion seen in alcoholics with dietary vitamin B_1 (thiamine) deficiency. A rare genetic defect of thiamine transporter-2 may lead to similar clinical features, biotin-thiamine responsive basal ganglia disease (BTBGD). A 15-year-old girl developed rapid onset ptosis and ophthalmoplegia evolving into a subacute encephalopathy. Neuroimaging demonstrated symmetrical basal ganglia and mid-brain lesions reminiscent of Leigh's subacute necrotising encephalomyelopathy. Oral biotin and thiamine were started, and symptoms improved dramatically the next day. The therapeutic response suggested *SLC19A3*, encoding thiamine transporter-2, as a strong candidate gene and Sanger sequencing revealed a novel homozygous c.517A>G;p.Asn173Asp mutation, which segregated with disease within the family. BTBGD is a potentially treatable neurological disorder and should be considered in the differential diagnosis of Leigh syndrome and Wernicke's encephalopathy. Since delayed treatment results in permanent neurological dysfunction or death, prompt diagnosis and early initiation of biotin and thiamine therapy are essential.

BACKGROUND

Acute encephalopathy presenting in adolescence is a rare event. Causes include viral and other infectious encephalitides, immune-mediated encephalitis and metabolic disorders, in particular the mitochondrial disorders such as Kearns-Sayre and Leigh syndromes. The prognosis is frequently poor. We report a devastating clinical syndrome amenable to effective therapy by administering oral vitamin supplementation with biotin and thiamine. Recognition of this treatable cause of adolescent-onset encephalopathy is important, to prevent severe disability and death.

Biotin-responsive basal ganglia disease (MIM 607483) is an autosomal recessive disorder first reported in 10 Saudi children who presented with subacute encephalopathy and dystonia associated with bilateral symmetrical basal ganglia lesions, which responded within days to pharmacological doses of biotin.[1] The genetic cause of this disease was subsequently attributed to mutations in the *SLC19A3* gene,[2] encoding a ubiquitously expressed thiamine transporter (hTHTR2) mediating high-affinity thiamine uptake into tissues. Nutritional thiamine deficiency in alcoholics presents with a triad of ophthalmoplegia, ataxia and confusion known as Wernicke's encephalopathy, and so it is interesting that more recently *SLC19A3* mutations have also been linked to a Wernicke-like presentation.[3]

Since monotherapy with either biotin or thiamine has been used successfully to treat patients with *SLC19A3* mutations, and moreover improved outcomes have been observed with combination therapy,[4] the term biotin-thiamine responsive basal ganglia disease (BTBGD) has been recently suggested as a more appropriate description of the disorder.[4] Untreated BTBGD typically develops as an episodic encephalopathy, often triggered by febrile illness, presenting as confusion, dystonia, rigidity and seizures leading to coma and death. We describe adolescent-onset presentation with rapidly developing ptosis and external ophthalmoplegia associated with a novel homozygous *SLC19A3* mutation. Furthermore, our patient demonstrated almost complete symptom resolution following treatment, highlighting the importance of early diagnosis and prompt vitamin supplementation.

CASE PRESENTATION

A previously healthy 15-year-old girl presented with rapid onset ptosis, progressive ophthalmoplegia and fatigue. During a 2-week family holiday in Thailand she complained of lassitude and her parents reported an episode of unusual behaviour when she felt that everyone was staring at her. The fatigue continued until she returned to the UK when she began to nap during the day. About a week later she attended school and a classmate noticed that her eyelids were drooping. The episode seemed to have resolved by the time she returned home but her mother noticed droopy eyelids the following day and sought medical advice. The patient felt her eyes were increasingly 'heavy' during the day and were better in the morning or after an afternoon nap. The next day, following an episode of right visual blurring, she was referred for an ophthalmological assessment. Ocular myasthenia was suspected and an urgent neurological opinion was sought. Examination revealed bilateral partial ptosis, which appeared to worsen with repetitive blinking. However, there was no evidence of lid lag with prolonged upgaze and she demonstrated a full range of eye movements without diplopia. Stimulation single fibre electromyogram showed no evidence to support a diagnosis of myasthenia gravis. A brain MRI revealed fairly symmetrical, bilateral signal changes with swelling in the caudate nuclei and putamen, with further abnormalities in the periaqueductal region of the mid-brain (figure 1A).

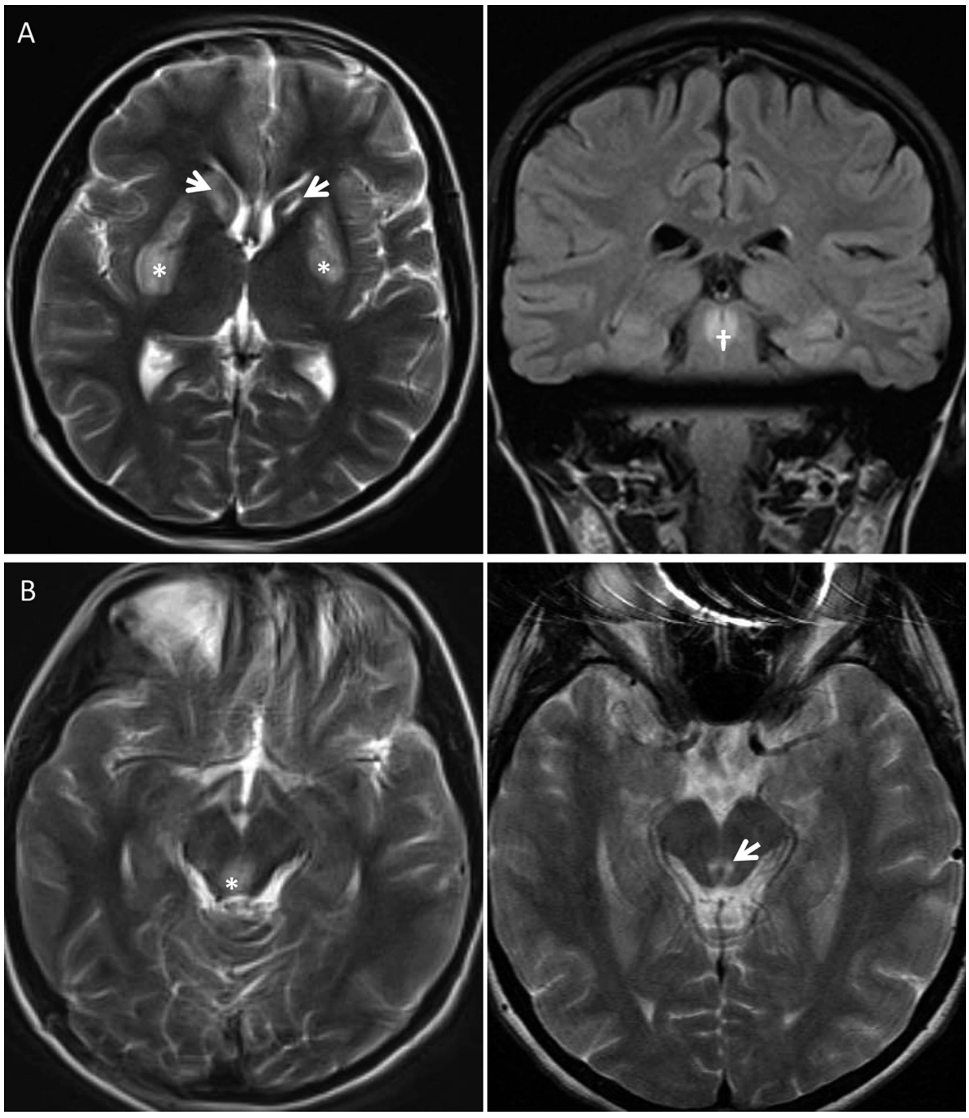

Figure 1 Initial axial (left) and coronal (right) T2-weighted images demonstrating signal abnormality and swelling of the caudate nuclei ↗, putamen* and periaqueductal region of the mid-brain† (A). Axial T2-weighted images before (left) and after (right) treatment showing the resolution of periaqueductal oedema* leaving some gliotic scarring in the mid-brain ↗ (B).

Over the next 3 weeks she reported difficulties in swallowing saliva, episodic vomiting, a sensation of incomplete bladder emptying and constipation. Her parents noticed that she was walking slowly and that she seemed to be exhausted after a few hours of being awake. Examination at the time revealed bilateral ptosis (figure 2A), but additionally a prominent divergent squint with bilateral impairment of upward and downward gaze was noted. She had mild dysarthria. Her weight was 35.7 kg (<0.4th centile), height 145.7 cm (0.4th centile), body mass index 16.8, head circumference 52.9 cm (50th centile) and blood pressure was 110/62. Her muscle strength was Medical Research Council grade 4/5 in all four limbs, with normal limb tone but brisk reflexes and downgoing plantar responses. Her gait appeared normal and she was able to complete a 6 min walk test without apparent fatigability.

The patient is from a non-consanguineous Indian family and was born at term by ventouse delivery. She achieved developmental milestones appropriately throughout childhood and is currently performing well in school. She was physically active until 8 years of age, but has avoided sports since then and feels she cannot run for long distances. Since 8 years of age she also reported intermittent early-morning vomiting, often precipitated by anxiety and she has always had a small appetite. A 13-year-old brother is well.

Investigations

An echocardiogram, performed to investigate a possible multisystem mitochondrial disorder, was normal. Blood investigations including full blood count, renal and liver function, lactate, amino acids, acylcarnitines, very long chain fatty acids, biotinidase, white blood cell ubiquinone, riboflavin, leucocyte lysosomal enzymes and acetylcholine receptor antibodies and urine organic acids were normal. Serology tests for *Rickettsia*, *Coxiella*, Q fever, enterovirus, arbovirus, hantavirus, herpes simplex virus, varicella zoster and cytomegalovirus were also negative. Cerebrospinal fluid analysis for protein, glucose, lactate, culture, oligoclonal bands and neurotransmitters were within normal limits. Skeletal muscle histology was unremarkable and respiratory chain enzyme activities were normal in muscle.

TREATMENT

The patient was started on a trial of thiamine, biotin and coenzyme Q_{10} immediately after the muscle biopsy. She took a single

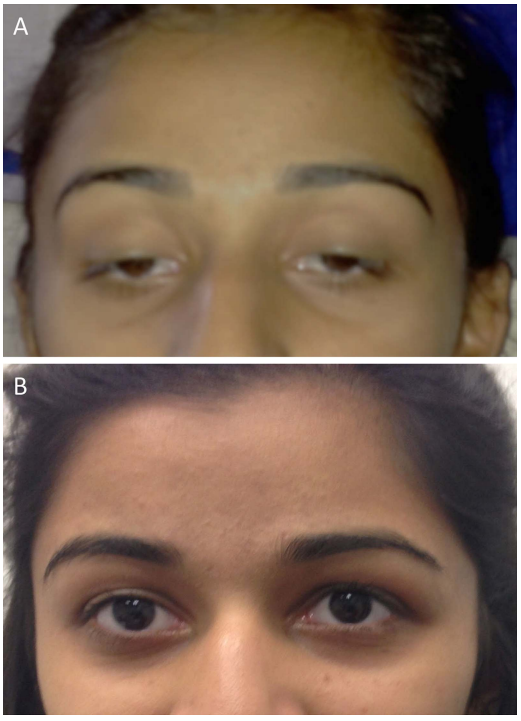

Figure 2 The patient presented with rapid onset bilateral ptosis and ophthamoplegia (A) which resolved after treatment with thiamine 100 mg and biotin 10 mg twice a day (B).

dose of thiamine 150 mg and biotin 10 mg at night and woke up the next day to find the ptosis and ophthalmoplegia had improved remarkably. She continued to take both vitamins (thiamine 100 mg twice a day and biotin 10 mg twice a day), and 5 months later she was markedly better except for brisk lower limb reflexes and very slight reduction in eye convergence (figure 2B). Repeat MRI performed 8 weeks after the start of therapy demonstrated improvement in the basal ganglia and brain stem lesions (figure 1B). After 6 months of therapy she reported facial twitching and the biotin dose was increased to 100 mg twice a day (5 mg/kg/day).

Genetic investigations

Large-scale rearrangements of mitochondrial DNA (mtDNA) associated with Kearns-Sayre syndrome and common mtDNA point mutations linked to Leigh syndrome (subacute necrotising encephalomyelopathy) were excluded in DNA extracted from blood lymphocytes. Following the dramatic response to vitamin supplementation, BTBGD was diagnosed clinically and sequence analysis of the candidate gene *SLC19A3* was undertaken. Sanger sequencing of *SLC19A3* revealed that the patient carried a novel homozygous c.517A>G;p.Asn173Asp mutation and parents were both heterozygous for this mutation (figure 3).

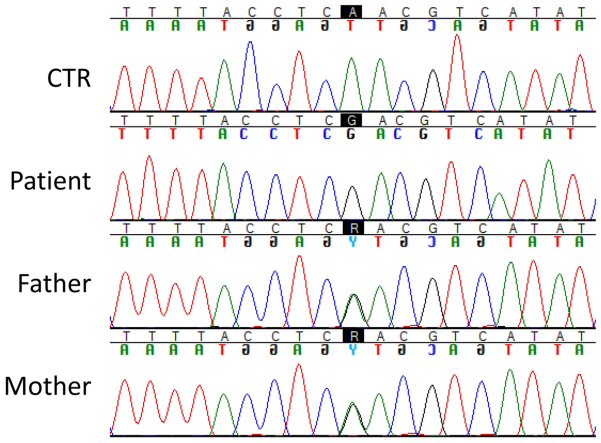

Figure 3 The patient carries a homozygous c.517A>G; Asn173Asp mutation in the *SLC19A3* gene. Both parents carry the same mutation in heterozygous state, demonstrating that it segregates with the disease within the family pedigree. The control at the top shows a homozygous wild-type sequence.

DISCUSSION

We report an adolescent-onset presentation of BTBGD characterised by rapid onset ptosis, ophthalmoplegia and fatigue with bilateral lesions in the caudate, putamen and periaqueductal region of the mid-brain on MRI, which improved dramatically following oral biotin and thiamine supplementation. BTBGD is caused by autosomal recessive mutations in the *SLC19A3* gene encoding thiamine transporter-2 (hTHTR2),[2] and accordingly we identified a novel homozygous *SLC19A3* mutation, c.517A>G;p.Asn173Asp, in our patient. Evidence for pathogenicity of this mutation is that it segregates with disease in the family and affects an amino acid residue that is highly conserved through evolution (figure 4).

To date five main clinical phenotypes have been linked to *SLC19A3* mutations. These likely represent a clinical continuum and are listed here in order of age at presentation: (1) neonatal lactic acidosis[5]; (2) Leigh syndrome[6 7]; (3) infantile spasms with progressive brain atrophy and bilateral thalamic and basal ganglia lesions[8]; (4) biotin responsive basal ganglia disease[1] and (5) late-onset Wernicke-like encephalopathy.[3] Reasons for this clinical heterogeneity are not yet understood and there is no clear genotype–phenotype correlation, since variable age of onset has been reported even for the same mutation within a family.[4]

The active form of thiamine (vitamin B_1) is thiamine pyrophosphate (TPP), an essential cofactor required for three key enzymes

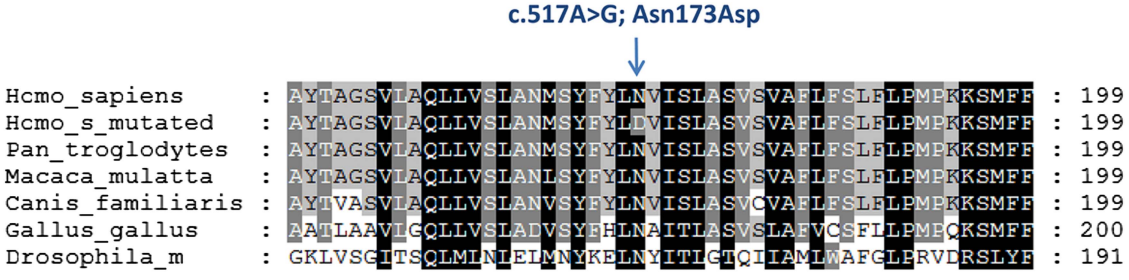

Figure 4 The asparagine at position 173 is very conserved through species, from human to fruit fly. The missense mutation substitutes an acidic uncharged asparagine for a negatively charged aspartic acid, which is predicted to affect the protein structure resulting in impaired function.

involved in cellular energy production: transketolase, α-ketoglutarate dehydrogenase and pyruvate dehydrogenase. Nutritional deficiency of thiamine may cause peripheral neuropathy (dry beri-beri), high output cardiac failure (wet beri-beri) or, most frequently in Western societies, an acute confusional state in alcoholics associated with ophthalmoplegia and ataxia (Wernicke's encephalopathy). It is interesting that dysfunction of hTHTR2 caused by *SLC19A3* mutations resembles Wernicke's encephalopathy, as in our patient, whereas mutations of *SLC19A2* encoding hTHTR1 present with Rogers syndrome of megaloblastic anaemia, diabetes mellitus and sensorineural deafness, which also improves with high doses of thiamine.[9 10] The differential clinical features associated with dysfunction of these two human thiamine transporters likely reflect their tissue distribution. In both disorders, high-dose thiamine appears to circumvent the transporter defect leading to measurable clinical improvement. It is not clear whether high-dose thiamine overcomes defective thiamine uptake through the dysfunctional transporter, or whether the alternative transporter is used instead.

A proportion of cases demonstrated significant improvement following biotin administration alone.[1] The reasons for the observed therapeutic response to biotin supplementation in this disorder of thiamine transport are currently unclear. It has been demonstrated that hTHTR2 does not transport biotin[11] but it is possible that biotin may increase *SLC19A3* expression, which may partially compensate.[6] Biotin is also essential for a number of enzymes involved in mitochondrial energy metabolism (including propionyl coenzyme A and pyruvate carboxylases and 3-methylcrotonyl coenzyme A carboxylase). It is possible that the higher level of biotin after administration in patients may increase the activity of these enzymes, resulting in an overall improvement of the energy production system, bypassing the thiamine-dependent enzyme reactions. Considering the positive treatment outcomes reported with both vitamins individually, it is prudent to treat BTBGD patients with a combination of high-dose thiamine and biotin. Furthermore it has been recently reported that patients initially responsive to biotin alone subsequently relapsed, but when thiamine was added further improvement was observed, with no further episodes of decompensation.[4]

The neuroimaging lesions in our patient and in other previously reported cases with *SLC19A3* mutations[6 7] are highly suggestive of Leigh syndrome[12]: bilateral symmetrical basal ganglia lesions typically involving the head of the caudate nucleus and putamen, as well as the globi pallidi, thalami, dentate nuclei, midbrain, pons and white matter. Indeed, Leigh syndrome was postulated to be a disorder of thiamine metabolism because of neuropathological similarities to Wernicke's encephalopathy.[12 13] Mutations in *SLC25A19* encoding the mitochondrial TPP transporter cause bilateral striatal necrosis, providing further evidence linking limited mitochondrial thiamine availability to a Leigh-like phenotype.[14] Furthermore *SLC19A3* mutations have recently been reported to cause a Leigh-like encephalopathy in the Alaskan Husky dog.[15] Mitochondrial disease in the Leigh syndrome spectrum frequently has a grave prognosis with no effective treatment, with the possible exception of inherited defects of coenzyme Q_{10} biosynthesis.[16] In the case reported here, investigative findings such as normal blood and CSF lactate, normal mitochondrial respiratory chain enzyme activities and normal mtDNA rearrangement screen made a typical mitochondrial disease less likely; however, the diagnosis of mitochondrial disease is challenging due to possible bigenomic inheritance and extreme clinical, biochemical and genetic heterogeneity.

In conclusion, BTBGD should be considered very early in the differential diagnosis of basal ganglia disease including Leigh syndrome, since the clinical outcome is critically dependent on the time duration from the onset of symptoms to initiation of treatment.[17] Early clinical suspicion and initiation of treatment is crucial to halt progression, avoid permanent neurological sequelae and, as demonstrated in our case, to enable reversal of acute neuropathological changes. If a therapeutic response is observed, the clinical diagnosis should be verified by sequence analysis of the *SLC19A3* gene, so that presymptomatic diagnosis and treatment can be offered to other family members.

Patient's perspective

Being a teenager, it is normal to feel more tired and lose your appetite a little; so when I went on a 2-week trip to Thailand, I found this kind of behaviour standard. However, while in Thailand, I noticed unusual behaviour such as suddenly becoming self-conscious in crowded places. However, when I returned to the UK, my appetite came back and I did not feel as self-conscious any more. A new term at school started a week later and I felt tired again, but I thought that this was because I had not recovered from the jet lag. Later that day, my friend pointed out that my eyelids had become lower; yet, when I checked in the mirror, they were perfectly fine. The next day, I noticed that my eyelids had gotten lower and they would not come back up again. I was scared because I thought I had an eye infection and I had a GCSE geography field trip the next day. I came home, and my mother took me straight to my local general practitioner. They referred me to the nearest accident and emergency department. I was worried and confused as to how they did not know what was wrong and worried that I could not attend my field trip, which could affect my grades. The next day, my optician suggested that I should go to Moorfields, the eye hospital, to see if they knew what to do to help me. They did not know either. A few weeks passed, and I remained in bed for most of it, as my eyelids would come up after a night's sleep or an afternoon nap. I felt like I was in a continuous cycle of not knowing what was happening, and I kept my feelings bottled up because I wanted my parents to know that I was not scared when in actual fact I was terrified. Terrified that my eyes may never look the same again. Terrified of the looks I would get from people when I stepped out of my house. Another week passed, and my mum got a call from Great Ormond Street. They said that they might be able to get me in so they could do some tests so they might be able to find out what was happening. I felt happy. I thought that I would be well. I stayed in hospital for a week and had numerous tests, including a muscle biopsy. The day after my muscle biopsy, the hospital gave me some vitamins to see if they could find out what was causing my eyelids to droop. They gave me biotin, thiamine, riboflavin and ubiquinone. I was nervous to take the tablets, worried about if they would make a difference. I did not take the full dosage of two of them because I was still feeling nauseous from the anaesthetic from my biopsy. They did make a difference because the next day my eyelids came up and I did not feel as tired any more. I felt relieved and happy that something had worked. I returned to school soon after, and I worked on catching up on the things that I had missed. Great Ormond Street had many possibilities about what I could have and some of them had long names, which was a tad scary. Seven months later, Great Ormond Street had found a diagnosis. I had biotin thiamine responsive basal ganglia disease, which explains why my eyelids had come up after I had some of the dosage of the full medication. I now feel better and more relieved that I now have a diagnosis and I know that the vitamins are making a difference.

Learning points

- Biotin–thiamine responsive basal ganglia disease is a treatable condition which is difficult to distinguish from classical Leigh syndrome or Leigh-like mitochondrial disease, for which no curative therapies exist.
- To avoid permanent neurological impairment, the diagnosis should be considered early in all cases with basal ganglia lesions.
- A trial of high-dose biotin and thiamine supplementation should be started with clinical monitoring of therapeutic response.
- If a therapeutic response is observed, analysis of the *SLC19A3* gene should be undertaken to confirm the diagnosis of biotin–thiamine responsive basal ganglia disease and patients should be counselled about the importance of lifelong therapy.

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Contributors SR was the overall study principal investigator who conceived the study. SR, EF and YW designed and oversaw the study, produced data, interpreted the results and drafted and synthesised the manuscript. CD, WKC and LJC also acquired and interpreted data and revised the manuscript.

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Patient consent Obtained.

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