Biotin-responsive basal ganglia disease revisited: Clinical, radiologic, and genetic findings
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Biotin-responsive basal ganglia disease revisited
Clinical, radiologic, and genetic findings

ABSTRACT
Objective: To investigate the clinical, genetic, and neuroradiologic data of biotin-responsive basal ganglia disease (BBGD) and clarify the disease spectrum.

Methods: We first investigated all patients attending our Division of Pediatric Neurology with a genetically proven diagnosis of BBGD between 2009 and 2011. All patients underwent a detailed medical history and clinical examination, extensive laboratory investigations including genetic tests, and brain MRI. Finally, we conducted a systematic review of the literature.

Results: We enrolled 10 patients meeting the diagnostic criteria for BBGD, and analyzed the data on 14 patients from 4 previous reports. The BBGD occurred predominantly in preschool/school-aged patients in the Saudi population, but it was also observed in other ethnic groups. The typical clinical picture consisted of recurrent subacute encephalopathy leading to coma, seizures, and extrapyramidal manifestations. The brain MRI typically showed symmetric and bilateral lesions in the caudate nucleus and putamen, infra- and supratentorial brain cortex, and in the brainstem. Vasogenic edema characterized the acute crises as demonstrated by diffusion-weighted imaging/apparent diffusion coefficient MRI. Atrophy and gliosis in the affected regions were observed in patients with chronic disease. Early treatment with a combination of biotin and thiamine resulted in clinical and neuroradiologic improvement. Death and neurologic sequelae including dystonia, mental retardation, and epilepsy were observed in those who were not treated or were treated late.

Conclusion: BBGD is an underdiagnosed pan-ethnic treatable condition. Clinicians caring for patients with unexplained encephalopathy and neuroimaging showing vasogenic edema in the bilateral putamen and caudate nuclei, infra- and supratentorial cortex, and brainstem should consider this disorder early in the hospital course because a therapeutic trial with biotin and thiamine can be lifesaving.

GLOSSARY
BBGD = biotin-responsive basal ganglia disease; hTHTR2 = human thiamine transporter 2; WE = Wernicke encephalopathy.

Biotin-responsive basal ganglia disease (BBGD; OMIM #607483) was first described by Ozand et al.1 in Saudi Arabia in 1998. Patients with BBGD typically presented in childhood with subacute episodes of encephalopathy, which were often triggered by febrile illness and characterized by confusion, dysarthria, dysphagia, and external ophthalmoplegia, and patients progressed to severe dystonia, quadriparesis, and coma. These symptoms disappeared within a few days after administration of high doses of biotin. The brain MRI showed bilateral lesions of the caudate nuclei and putamen.1 The disease is autosomal recessive and associated with mutations in the SLC19A3 gene.2 The SLC19A3 gene encodes human thiamine transporter 2 (hTHTR2),3 a second thiamine transporter. Because biotin is not a substrate for hTHTR2, the precise mechanism by which biotin is effective in improving this condition remains unknown.4
The literature on BBGD is poor (only 14 cases reported), and there are no systematic reviews of published cases. This report includes the detailed clinical and neuroradiologic data of 10 genetically proven cases of BBGD, and provides a systematic review of the literature up to April 2012. We aimed to identify the recent advances in the diagnostic, genetic, and management tools of this enigmatic disease, and to discuss the nosology of this disease.

METHODS We retrospectively studied patients attending the Pediatric Neurology Division, Riyadh Military Hospital in Riyadh, Kingdom of Saudi Arabia between 2009 and 2011 with a firm diagnosis of BBGD based on genetic analysis. The patients underwent a detailed family history and neurologic examination, as well as blood tests, CSF analysis, and neuroradiologic investigations. The neuroradiologic investigations included a brain MRI in all patients. Brain MRIs were reviewed independently by 2 certified neuroradiologists (Z.A., G.Z.) with adjudication. The MRI examinations were performed at a field strength of 1.5 T (Signa; GE Healthcare, Milwaukee, WI). Imaging sequences of the brain included T1- and T2-weighted sequences in multiple planes. Contrast-enhanced T1-weighted images were obtained in 1 patient. Diffusion-weighted imaging and apparent diffusion coefficient map images were also evaluated. MRI findings were represented by symmetric or asymmetric hypertensities on T2-weighted and fluid-attenuated inversion recovery images within the cortex, basal ganglia, and brainstem, and symmetric or asymmetric hypointensities on T1-weighted images within the cortex, basal ganglia, and brainstem. Increased diffusion-weighted imaging signal and increased apparent diffusion coefficient value were considered consistent with vasogenic edema. Single-voxel magnetic resonance spectroscopy data obtained during the acute phase of the disease in 4 patients were also analyzed. Molecular genetic analysis of the SLC19A3 gene was performed in the Center for Human Genetics (Bioscientia, Ingelheim, Germany). Laboratory investigations included blood for lactate, pyruvate, ammonia, biotinidase, creatine phosphokinase, tandem mass spectrometry, copper, ceruloplasmin, biotin level, and thiamine level; urine for organic acids; and CSF for cell counts, protein level, glucose level, lactate, and pyruvate. A PubMed/Ovid search was performed up to April 2012 using the keywords “biotin-responsive basal ganglia disease,” “biotin deficiency,” and “SLC19A3 mutations.” We analyzed the data for demographic and clinical features, genetic and neuroradiologic findings, and treatment efficacy.

Standard protocol approvals, registrations, and patient consents were obtained. The local hospital ethical review committee approved this study.

RESULTS Personal series. Ten patients were identified (5 females and 5 males), and the demographic, clinical, genetic, and neuroradiologic findings are shown in tables 1 and 2. All patients were Saudi. The age of presentation ranged from 3 to 12 years, with a mean age of 7 years. Eighty percent had positive consanguinity. We identified a trigger factor (febrile illness or mild trauma) in half of the patients. Nine patients (90%) had an acute-subacute onset consisting of ataxia, seizures, and encephalopathy. Rapid deterioration of these symptoms motivated their transfer to the intensive care unit. All patients exhibited parkinsonian signs (dystonia, cogwheel rigidity) and pyramidal tract signs (quadrriparesis, hypertreflexia). Cerebellar signs, supranuclear facial nerve palsy, or external ophthalmoplegia was present in 5 patients. One patient (patient 9) had a slowly progressive course with dystonia involving the face and 4 limbs, and mild psychomotor delay. Nine patients received a combination of biotin (2–3 mg/kg/d) and thiamine (100–300 mg/d). One patient (10%) died with severe encephalopathy, rhabdomyolysis, and cardiac arrest. He did not receive any treatment, as he was diagnosed retrospectively after the diagnosis of his sister. Two patients (20%) had severe neurologic sequelae: generalized dystonia and quadriplegia. Both these patients had frequent attacks of decompensation and were treated late. Seven patients (70%) had a good outcome with no or minimal sequelae, including mild dystonia or dysarthria not interfering with daily life or school activities. These 7 patients were diagnosed and treated earlier. All patients underwent MRI. During the acute crisis, brain MRI revealed bilateral and symmetric involvement of the putamen and caudate nuclei in all patients (figures 1 and 2). Seven patients (70%) showed symmetric involvement of the medial dorsal nucleus of the thalamus. Five patients (50%) showed involvement of the brainstem nuclei. Eight patients (80%) showed extensive involvement of the cortex. Seven patients (70%) showed alterations in the cerebellar cortex and vermis. One patient (10%) showed involvement of the periventricular regions of the third ventricle. None of our patients disclosed subcortical white matter involvement. Vasogenic edema was identified in the affected brain regions during the acute phase of the disease. None of the patients showed cytotoxic edema. Magnetic resonance spectroscopy was obtained in 4 patients disclosing decreased N-acetylaspartate and increased lactate peaks (see figure e-1 on the Neurology® Web site at www.neurology.org). Follow-up MRI showed evolving brain lesions consistent with remote injury (figure 3, table e-1). Laboratory investigations including blood, urine, and CSF tests were negative in all patients. Sequencing of SLC19A3 identified a pathogenic homozygous mutation c.1264A>G (p.Thr422Ala) in all 10 patients, and their parents were heterozygous for the mutation.

Review of the literature. We collated 14 cases that were reported in 4 publications. The demographic, clinical, genetic, and neuroradiologic findings are shown in table e-2. Of these 14 patients, 9 were female and 5 male. The mean age at presentation was 5.5 years (range 1–12 years). Seven patients were Saudi, 2 Portuguese, 2 Yemeni, 1 Indian, 1 Lebanese, and 1 Syrian. Eight patients presented with acute/subacute encephalopathy. The remaining patients presented with extrapyramidal manifestations. Seizures...
were observed in 10 patients. Brain MRI showed lesions in the caudate and putamen nuclei in all patients. Other involvement was reported in only 2 patients. At follow-up evaluation, 4 patients were found to be neurologically normal and 10 showed neurologic sequelae including mild mental retardation and/or dystonia.

**DISCUSSION** From this study of 10 patients with genetically proven BBGD, followed by a systematic review of the literature (table e-2), we obtained a detailed picture of the clinical presentation, genetics, and treatment of BBGD.

Although this disease is a pan-ethnic condition, it is most prevalent in Saudi Arabia, and usually occurs in preschool- and school-aged children. The typical clinical presentation of patients with BBGD is recurrent subacute episodes of encephalopathy, often triggered by febrile illness or mild trauma and characterized by confusion, seizures, dystonia, external ophthalmoplegia, and dysphagia.

### Table 1  Clinical and genetic findings in patients with BBGD

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age at onset, y</th>
<th>Origin</th>
<th>Consanguinity</th>
<th>Neurologic presentation</th>
<th>Seizures</th>
<th>Treatment</th>
<th>Outcome</th>
<th>SCL19A3 gene mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/8</td>
<td>Saudi</td>
<td>+</td>
<td>Subacute encephalopathy, ataxia</td>
<td>+</td>
<td>Biotin + thiamine</td>
<td>Mild dystonia, dysarthria</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>2</td>
<td>F/3½</td>
<td>Saudi</td>
<td>+</td>
<td>Subacute encephalopathy, ataxia, dystonia</td>
<td>–</td>
<td>Biotin + thiamine</td>
<td>Normal</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>3</td>
<td>M/4</td>
<td>Saudi</td>
<td>+</td>
<td>Subacute encephalopathy, ataxia, mutism</td>
<td>+</td>
<td>Biotin + thiamine</td>
<td>Normal</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>4</td>
<td>M/7½</td>
<td>Saudi</td>
<td>+</td>
<td>Subacute encephalopathy, ataxia, dystonia, dysphagia</td>
<td>+</td>
<td>Biotin + thiamine</td>
<td>Mild ataxia, dystonia, and dysarthria</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>5</td>
<td>M/3</td>
<td>Saudi</td>
<td>+</td>
<td>Subacute encephalopathy, ataxia, dystonia</td>
<td>–</td>
<td>Biotin + thiamine</td>
<td>Normal</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>6</td>
<td>F/6</td>
<td>Saudi</td>
<td>+</td>
<td>Subacute encephalopathy, ataxia, dystonia, dysphagia</td>
<td>+</td>
<td>Biotin + thiamine</td>
<td>Mild ataxia and dysarthria</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>7</td>
<td>M/11</td>
<td>Saudi</td>
<td>+</td>
<td>Subacute encephalopathy, dystonia</td>
<td>+</td>
<td>Biotin + thiamine</td>
<td>Normal</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>8</td>
<td>M/12</td>
<td>Saudi</td>
<td>–</td>
<td>Subacute encephalopathy, ataxia, dystonia, dysarthria</td>
<td>+</td>
<td>No treatment</td>
<td>Died</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>9</td>
<td>F/3</td>
<td>Saudi</td>
<td>–</td>
<td>Severe dystonia of the face and limbs</td>
<td>+</td>
<td>Biotin + thiamine</td>
<td>Dystonia</td>
<td>c.1264A&gt;G</td>
</tr>
<tr>
<td>10</td>
<td>F/12</td>
<td>Saudi</td>
<td>+</td>
<td>Acute encephalopathy, dystonia</td>
<td>+</td>
<td>Biotin + thiamine (started 1 mo after the onset of encephalopathy)</td>
<td>Quadriplegia</td>
<td>c.1264A&gt;G</td>
</tr>
</tbody>
</table>

Abbreviation: BBGD = biotin-responsive basal ganglia disease; = absent (negative), + = present (positive). *Patients 1 and 2 are siblings, as are 6 and 7, and 8 and 9.

### Table 2  MRI findings during the acute crisis (before treatment)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Brainstem</th>
<th>Cerebellum</th>
<th>Basal ganglia</th>
<th>Thalamus</th>
<th>Frontal lobe</th>
<th>Temporal lobe</th>
<th>Insula</th>
<th>Parietal lobe</th>
<th>Occipital lobe</th>
<th>Cortex</th>
<th>Vasogenic edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R, CN3, SN</td>
<td>CH, V</td>
<td>P, C</td>
<td>DM</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>V</td>
<td>P, C</td>
<td>DM</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>RN</td>
<td>CH</td>
<td>P, C</td>
<td>DM</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>R-SCN</td>
<td>CH, V</td>
<td>P, C</td>
<td>DM</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>P, C</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>No</td>
<td>P, C</td>
<td>DM</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>CH</td>
<td>P, C</td>
<td>DM</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>R-SCN, RN</td>
<td>CH, V</td>
<td>P, C</td>
<td>DM, PR 3rd V</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>R-SCN, DLF, RN</td>
<td>CH, DN</td>
<td>P, C</td>
<td>DM, PR 3rd V</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: C = caudate nucleus; CH = cerebellar hemispheres; CN3 = oculomotor nerve nucleus; DLF = dorsal longitudinal fasciculus; DM = dorsomedial nucleus of the thalamus; DN = dentate nucleus; NA = not available; P = putamen; PGM = periaqueductal gray matter; PR 3rd V = periaqueductal regions of the 3rd ventricle; R = raphe; RN = red nucleus; R-SCN = raphe, superior central nucleus; SN = substantia nigra; V = vermis.

*Asymmetric patterns.

*Patient 6 underwent contrast administration with no enhancement identified. Please note that none of the patients disclosed restricted diffusion.
eventually leading to coma and even death.1,5–7 Less frequently, patients with BBGD present with a chronic or slowly progressive condition characterized by dystonia, seizure disorders, and psychomotor delay. Seizures are mainly simple partial seizures or generalized and are easily controlled with 1 antiepileptic drug. Early administration of biotin and thiamine results in partial or complete improvement within days. Treatment given later in the disorder or the lack of treatment may result in death or neurologic sequelae including dystonia, quadriparesis, epilepsy, or mild mental retardation.

Ozand et al.1 demonstrated that the MRI pattern of patients with BBGD is bilateral necrosis in the central part of the caudate heads and part or all of the putamen; our study confirms this, and adds important additional diagnostic information of BBGD in a patient presenting with acute-subacute encephalopathy. During the acute crisis, other neuroimaging features, including vasogenic edema and infra- and supratentorial cortex and brain-stem involvement, are present and potentially reversible if treated in a timely manner. However, in not-treated or late-treated chronic patients, gliosis and atrophy are present, particularly in the caudate and putamen nuclei.

Our patient population with BBGD shares multiple neuroradiologic findings observed in Wernicke encephalopathy (WE),8–10 such as involvement of the medial dorsal nucleus in the thalami (same butterfly appearance), periventricular regions of the third ventricle, brainstem, central gray matter, basal ganglia, and cerebellum. However, based on the study at hand, the main MRI difference between BBGD and WE is that in BBGD mamillary bodies are spared and that BBGD leads to a more extensive infra- and supratentorial cortical involvement compared with that observed in WE.10 Magnetic resonance spectroscopy depicts lactate peaks and decreased N-acetylaspartate in injured areas, accounting for an early brain injury and neuronal loss; these findings are nonspecific.

BBGD maps to chromosome 2q36.3, and is due to mutations in SLC19A3.2 Several mutations have been described in the SLC19A3 in patients with BBGD, including the following mutations in decreasing order of frequency: c.1264A>G (p.Thr422Ala), c.68 G>T (p.G23V), c.74dupT, c.980-38dupA, and c.980-14 A>G.2,7 The SLC19A3 gene is one of the SLC19 (solute carrier family 19) gene family (comprising SLC19A1, SLC19A2, and SLC19A3) that is responsible for the uptake of water-soluble vitamins into cells.2,11 The SLC19A3 was cloned based on its homology with SLC19A1 and SLC19A2, and encodes hTHTR2, a second thiamine transporter.11,12 Three apparently unrelated disease phenotypes are associated
with mutations of \textit{SLC19A3}. In 2005, it was demonstrated that homozygous mutations in \textit{SLC19A3} are the cause of BBGD.\textsuperscript{2} Recently, compound heterozygous mutations (E320Q, K44E) in \textit{SLC19A3} have been associated with Wernicke-like encephalopathy, characterized by acute onset of epilepsy, ataxia, nystagmus, and ophthalmoplegia in the second decade of life. Thiamine treatment effectively alleviated symptoms.\textsuperscript{13} The third phenotype includes epileptic spasms in early infancy, severe psychomotor retardation, and characteristic brain MRI findings of progressive brain atrophy and bilateral thalami and basal ganglia lesions, and is caused by a homozygous mutation (\textit{c.958G>C} [p.E320Q]) in \textit{SLC19A3}.\textsuperscript{14}

Early diagnosis of BBGD is crucial because expeditious treatment may reverse all its manifestations.\textsuperscript{1,5–7} Treatment with a combination of biotin and thiamine results in improvement of the clinical symptoms and severe psychomotor retardation, and characteristic brain MRI findings of progressive brain atrophy and bilateral thalami and basal ganglia lesions, and is caused by a homozygous mutation (\textit{c.958G>C} [p.E320Q]) in \textit{SLC19A3}.\textsuperscript{14}

Early diagnosis of BBGD is crucial because expeditious treatment may reverse all its manifestations.\textsuperscript{1,5–7} Treatment with a combination of biotin and thiamine results in improvement of the clinical symptoms and severe psychomotor retardation, and characteristic brain MRI findings of progressive brain atrophy and bilateral thalami and basal ganglia lesions, and is caused by a homozygous mutation (\textit{c.958G>C} [p.E320Q]) in \textit{SLC19A3}.\textsuperscript{14}

Figure 2 Patient 10

Asymmetric cerebellar edema is noted on fluid-attenuated inversion recovery image (arrows, A). Involvement of the dorsal longitudinal fasciculus (arrows, B) and of the raphe superior central nucleus (arrowhead, B) is demonstrated. Periaqueductal signal intensity alteration resembling Wernicke encephalopathy is noted (arrows, C). Mild involvement of the substantia nigra is present (arrows, D). Bilateral involvement of the red nucleus is present in (E) (arrows). Basal ganglia (arrowheads, F) and periventricular region of the third ventricle (arrows, E) involvement is also identified. Diffuse bilateral cortical involvement is noted (asterisks, A–F).

Figure 3 Patient 1 follow-up MRI

Chronic changes consistent with atrophy and gliosis are identified in the basal ganglia (arrows, A–C) and cerebral cortex (arrowheads, A–C) on axial fluid-attenuated inversion recovery images.
prevention of damage to the brain, and may even prevent death. Patients require counseling regarding lifelong treatment. The mechanism of action of biotin remains unclear. The presence of serum biotin and thiamine deficiency and the efficacy of high doses of biotin in the previous reports suggest that high doses of biotin increase the expression of SLC19A3, thus restoring some function of the mutated receptor by increasing its expression.\textsuperscript{13–17}

The optimal dose of biotin in this disease, however, remains unknown. Ozand et al.\textsuperscript{1} reported high doses of biotin: 5 to 10 mg/kg/d. Our study and others used lower doses (2–3 mg/kg/d) in addition to thiamine (100–300 mg/d) with the same efficacy. Interestingly, a few patients did not improve with high doses of biotin\textsuperscript{7} but did improve only after the addition of thiamine, thus reinforcing the hypothesis that impaired thiamine transport has a critical role in BBGD, and that biotin and thiamine may act synergistically. We suggest using a combination of high doses of biotin and thiamine during the acute crisis of the disease and lower doses for long-term treatment.

BBGD is a novel entity, first reported by Ozand et al.\textsuperscript{1} In the original study, patients responded only to high doses of biotin and not to thiamine. Of note, thiamine only was used for 1 patient for 3 months’ duration without improvement. However, our recent understanding of the disease has advanced regarding the following issues: 1) the SLC19A3 gene mutation inhibits thiamine transport via hTHTR2; 2) biotin is not a substrate for hTHTR2; 3) patients in acute crisis share several neuroradiologic features of WE; 4) several patients improve only after adding thiamine to biotin, reinforcing the hypothesis that both biotin and thiamine are important lifesaving drugs in this disease. Based on these available data, it is inaccurate to append only the word “biotin” to BBGD. We therefore recommend that the medical community open the dialog to consider formally discontinuing this nosology (“BBGD”) and to adopt the use of the term “biotin-thiamine responsive basal ganglia disease associated with SLC19A3 gene mutations.”

CONCLUSION BBGD is an underdiagnosed pan-ethnic treatable condition. Clinicians caring for patients with unexplained encephalopathy and neuroimaging showing vasogenic edema in the bilateral putamen and caudate nuclei, infra- and supratentorial cortex, and brainstem should consider this disorder early in the hospital course because a therapeutic trial with biotin and thiamine can be lifesaving. The prognosis of the disease largely depends on the time from diagnosis to biotin and thiamine supplementation.

AUTHOR CONTRIBUTIONS Dr. Tabah and Dr. Al-Hashem, and Drs. Al-Adwani and Al-Zawahm, Al-Hashem, Dr. Al-Hashem, Dr. Biary, Dr. Al-Zawahm, and Dr. Khan revised the manuscript for intellectual content.

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