Biotin-Responsive Basal Ganglia Disease: Neuroimaging Features before and after Treatment

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ABSTRACT

BACKGROUND AND PURPOSE: Biotin-responsive basal ganglia disease is an autosomal recessive neurometabolic disorder presenting with subacute encephalopathy that can cause death if left untreated. The purpose of this study is to assess the neuroimaging and clinical features of the disease before and after treatment with biotin.

MATERIALS AND METHODS: We retrospectively reviewed the clinical, laboratory, and neuroimaging features of 15 genetically-proved Middle Eastern cases of biotin-responsive basal ganglia disease. Brain MR imaging was done at the onset of symptoms in all cases and within 2–8 weeks after biotin and thiamine therapy in 14 patients. The MR imaging datasets were analyzed according to lesion location, extent, and distribution.

RESULTS: Brain MR imaging showed bilateral lesions in the caudate nuclei with complete or partial involvement of the putamen and sparing of the globus pallidus in all cases. In 80%, discrete abnormal signals were observed in the mesencephalon, cerebral cortical-subcortical regions, and thalami. In 53%, when the disease was advanced, patchy deep white matter affection was found. The cerebellum was involved in 13.3%. The signal abnormality of the mesencephalon, cortex, and white matter disappeared after treatment whereas the caudate and putamen necrosis persisted in all patients, including those who became asymptomatic.

CONCLUSIONS: Biotin-responsive basal ganglia disease is a treatable underdiagnosed disease. It should be suspected in pediatric patients with unexplained encephalopathy whose brain MR imaging shows bilateral and symmetric lesions in the caudate heads and putamen, with or without involvement of mesencephalon, thalami, and cortical-subcortical regions, as the therapeutic trial of biotin and thiamine can be lifesaving.

ABBREVIATIONS: BBGD = biotin-responsive basal ganglia disease; MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF = myoclonic epilepsy associated with ragged red fibers; WE = Wernicke encephalopathy

Biotin-responsive basal ganglia disease (BBGD) was first described by Ozand et al in 10 patients of Arab ancestry in 1998.1 Subsequently, cases have been reported in patients of different ethnicities including those of Portuguese, Indian, Japanese, and German origin.2-6 BBGD is an autosomal recessive neurometabolic disorder. It is characterized by subacute encephalopathy with confusion, seizure, dysarthria, and dystonia following a history of febrile illness. If left untreated with biotin, the disease can progress to severe quadriaparesis and even death.7

Biotin is a water-soluble vitamin belonging to the B complex and acts as a co-enzyme for the 4 important carboxylases in humans.8 Biotin-dependent carboxylases catalyze the fixation of bicarbonate in organic acids and play crucial roles in the metabolism of fatty acids, amino acids, and glucose. The carboxylase activities decrease substantially when there is biotin deficiency.8 The etiology of biotin deficiency is believed to be caused by a genetic defect in the transporter system of biotin across the blood-brain barrier.1 In 2005, it was demonstrated that homozygous mutation in SLC19A3 is the genetic defect that causes BBGD.9 BBGD responds to the administration of high doses of biotin, which ensures some biotin transport into brain by nonspecific diffusion.10 It also increases the expression of the SLC19A3 gene, thus restoring some function of the mutated receptor.11,12 Recently, thiamine has been added to biotin in the treatment regi-
men of BBGD based on the hypothesis that the impairment of thiamine transport in the brain also has a critical role in this disorder. This combination of biotin and thiamine proved to prevent the recurrence of encephalopathy crisis.7,9

It is important to recognize this disease because its symptoms may be reversed and the progression of its clinical course can be prevented simply by the administration of biotin and thiamine.1,7

The purpose of this study is to assess the clinical and neuroimaging features of the disease on MR imaging before and after treatment with biotin and thiamine.

MATERIALS AND METHODS

We retrospectively reviewed the clinical, laboratory, and neuroimaging features of 15 genetically proved cases of biotin-responsive basal ganglia disease. The patients were 9 females and 6 males with an age range (at the time of symptom onset) of 2 to 11 years (mean: 6 years). MR imaging of the brain was done in all cases at the onset of symptoms. Follow-up MR imaging within 2–8 weeks after the administration of high doses of biotin (5–10 mg/kg/d) and thiamine (100–300 mg/d) was done in 14 patients.

All patients were of Arab (Middle East) ancestry, and 73% had consanguineous parents. Recessive genetic defect was detected in all cases. All cases were found to have the same homozygous mutation in exon 5 of the SLC19A3 gene and their parents were heterozygous for this mutation. The molecular genetic analysis of the SLC19A3 gene was performed in the Center for Human Genetics (Bioscientia, Ingelheim, Germany). The blood and CSF chemical tests for organic and inorganic toxic compounds, carboxylases, and biotinidase values were normal in all patients.

All patients presented with subacute or acute encephalopathy leading to seizures, extrapyramidal symptoms, quadriaparesis, or quadriplegia and coma.

The MR imaging was performed in all patients using the Signa LX 1.5T machine (GE Healthcare, Milwaukee, Wisconsin). Our brain MR imaging protocol included sagittal spin-echo T1WI (TR 535 milliseconds, TE 13 milliseconds), axial and coronal FSE T2WI (TR 3500 milliseconds, TE 182 milliseconds), axial FLAIR (TR 9000 milliseconds, TI 2500 milliseconds, TE 104 milliseconds), axial spin-echo T1WI (TR 535 milliseconds, TE 13 milliseconds), and axial DWI (b = 0–1000). Postgadolinium axial and coronal T1WI were performed in 9 cases.

Spectroscopy (1H-MR) was performed in 6 cases at the time of onset of symptoms and before starting the biotin therapy. After therapy MR spectroscopy was done in only 1 of these 6 cases. MR spectroscopy was performed through point-resolved proton spectroscopy sequences with TE of 35 and 144 msec. The voxels were positioned in axial T2WI on areas showing an abnormal signal at the basal ganglia and parieto-occipital cortical-subcortical regions of either the left or right side. Voxels were 2 × 2 × 2 cm in size. NAA was assigned at 2.02 parts per million, Cho at 3.2 ppm, Cr at 3.03 ppm, and lactate at 1.3 ppm. Metabolite ratios (NAA/Cr and Cho/Cr) were also measured. All data processing was performed by software provided by the scanner manufacturer.
Spinal cord MR imaging was done in 7 cases. The MR imaging spine protocol included sagittal T1WI (TR 397 milliseconds, TE 12 milliseconds) and T2WI (TR 3700 milliseconds, TE 103 milliseconds). Axial T2WI (TR 4220 milliseconds, TE 101 milliseconds) was performed at cervical and dorsal levels.

Image Analysis
MR examinations of the brain and spine and MR spectroscopy datasets were reviewed by 2 experienced radiologists in consensus with an emphasis on the involvement or sparing of the mesencephalon, cerebellum, caudate nuclei, globus pallidi, putamina, thalami, cortical-subcortical regions, and deep white matter before and after treatment as well as the presence of lactate doublet, NAA peak, and NAA/Cr ratio on MR spectroscopy.

The study was approved by the ethical committees of our institutions.

RESULTS
Our study enrolled 15 patients (their clinical and neuroimaging data are shown in the On-line Table). Eleven cases (73%) had positive consanguinity. On presentation, 13 patients (86.7%) had subacute onset in the form of encephalopathy, ataxia, and seizures, whereas only 2 patients (13.3%) presented by acute crisis with severe neurologic deficit, generalized dystonia, quadriplegia, and coma. Pre-existing trigger factor (febrile illness or trauma) was found in 7 cases (46.7%).

The brain MR imaging showed bilateral and symmetric lesions in the caudate heads in all of our patients with complete or partial involvement of the putamen (Figs 1–4). The globus pallidi were spared in all patients. In 12 cases (80%), discrete abnormal signal changes were observed in the mesencephalon (Fig 2), cortical-subcortical regions, and the medial dorsal nuclei of the thalami (Figs 1–3). In 8 cases (53%), when the disease was advanced, patchy deep white matter affection was found. The cerebellum along the cerebellar cortex and vermis was involved in only 2 patients (13.3%) (Figs 1 and 2). The affected brain regions showed variable swelling and vasogenic edema during the acute/subacute phase. No cytotoxic edema was found. No pattern of diffusion restriction on diffusion-weighted images or significant contrast enhancement was detected.

The MR imaging of patients under treatment showed evolution of the basal ganglia from swelling into atrophy and necrosis in all cases with resolution of the abnormal high signals of the cortex and subcortical regions. Resolution of the cerebellar abnormal signal was also observed in the 2 patients who showed cerebellar involvement. However, the abnormal signals of the caudate and putamen persisted in all patients (Figs 1–4).

Pretherapy 1H-MR spectroscopy showed consistent elevation of lactate within the affected regions and decrease in NAA peak and NAA/Cr ratio in all cases. Disappearance of the lactate peak after biotin/thiamine therapy was noted in the single obtained posttherapy MR spectroscopy (Fig 4).
BBGD is an autosomal recessive neurometabolic disorder. It was first described in 1998 in 10 patients from the Middle East. Re-analysis of the MR imaging findings in the original report by Ozand et al.1 The MR imaging findings consisted of bilateral necrosis in the basal ganglia, particularly at the central part of the caudate heads and part or all of the putamen with severe edema during the acute/subacute crisis in addition to white matter involvement at the gray–white matter junction. Subsequent reports confirmed these findings and added the involvement of the thalamus, cerebellum, and brainstem.2,5 Our results supported the findings of these previous reports regarding the MR imaging distribution of lesions in all cases. In addition, the globus pallidi were spared in all patients in agreement with most of previous reports.1,2,13

Alfadhel et al1 emphasized diffuse involvement of the cortical and subcortical white matter in the acute phase and atrophy and necrosis of the basal ganglia in the chronic phase in all cases. The thalamus and brain stem were involved in one-third of their patients. In the present study, we demonstrated discrete abnormalities in the thalami and brain stem.2,5 This finding is in absolute agreement with earlier reports.1-4,7,13

Follow-up of our patients under treatment confirmed the evolution of the basal ganglia from swelling into atrophy and necrosis with resolution of the abnormal high signals of the cerebral cortex and subcortical areas disappeared after treatment whereas the caudate and putamen necrosis persisted in the 14 cases that underwent follow-up. Despite the extensive abnormal findings observed on the brain MR imaging, 80% of our patients with biotin-responsive encephalopathy remained asymptomatic under treatment. This observation suggests that enough tissue may be preserved in the target areas of the disease, to permit neurologic function.1

Interestingly, in the report by Alfadhel et al,1 a patient demonstrated spinal cord involvement with increased T2 signal intensity particularly at the cervical region, which was not reported on earlier studies. They thought that the spinal cord involvement could be part of the disease and advised performing spinal MR imaging for all patients with BBGD. However, 7 of our patients were investigated by spinal MR imaging and none showed spinal cord involvement, which strongly argues against spinal cord involvement as a part of the disease. The absence of spinal cord lesions in...
considered nonspecific.\textsuperscript{13}

NAA could be explained by early brain injury and neuronal loss.\textsuperscript{13}
appeared in the single posttherapy MR spectroscopy. Decreased
lactate peaks and decreased NAA in all cases. The lactate doublet
of onset of symptoms and before initiation of therapy. It depicted
processes including mitochondrial diseases,\textsuperscript{14} these findings are
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in basal ganglia and in parieto-occipital cortical-subcortical le-
We found no appreciable differences between the MR spectrum
cept the 1 reported by Alfadhel et al.\textsuperscript{7}
our patients is consistent with all previously described cases, ex-
cept the 1 reported by Alfadhel et al.\textsuperscript{7}

Spectroscopy (\textsuperscript{1}H-MR) was performed in 6 of our cases at time
of onset of symptoms and before initiation of therapy. It depicted
lactate peaks and decreased NAA in all cases. The lactate doublet
could be interpreted as sign of ongoing apoptosis. It has disap-
ppeared in the single posttherapy MR spectroscopy. Decreased
NAA could be explained by early brain injury and neuronal loss.\textsuperscript{13}
We found no appreciable differences between the MR spectrum
in basal ganglia and in parieto-occipital cortical-subcortical le-
ions. As increased CNS lactate can be found in other pathologic
processes including mitochondrial diseases,\textsuperscript{14} these findings are
considered nonspecific.\textsuperscript{13}

In our study, because assessment of the response to therapy
was limited clinically to the reversibility of symptoms and radi-
ologically to the regression of the swelling and vasogenic edema
of the affected regions, none of our patients had follow-up MR spec-
troscopy except 1. Interestingly, in this patient (Fig 4), the lactate
peak has almost disappeared reflecting that MR spectroscopy
could provide additional information as a monitor of response to
therapy. The short half-time of lactate could be valuable as an
early indicator of response to treatment in the future.

Bilateral and symmetrical basal ganglia lesions are caused by
different systemic or metabolic conditions that share some find-
ings with BBGD. However, the dramatic response to biotin ther-
apy and persistence of caudate and putaminal signal abnormality
without neurologic sequelae are characteristic features of BBGD.
Wernicke encephalopathy (WE) is an example of these diseases. It
can involve the medial dorsal nucleus in thalami, periventricular regions of the
third ventricle, brain stem, central gray matter, basal ganglia, and cerebellum
similar to BBGD. However, the main MR imaging differences between the two are
that in BBGD, the mammillary bodies are spared when usually involved in WE and
the supra- and infratentorial cortical in-
volvement in BBGD is more extensive
compared with WE.\textsuperscript{15}

Mitochondrial disorders can also mimic BBGD because of similarity in
deep gray matter involvement. They in-
clude Leigh disease, MELAS (mitochon-
drial myopathy, encephalopathy, lactic
acidosis, and stroke-like episodes), and
MERRF (myoclonic epilepsy associated
with ragged red fibers). Like BBGD, Leigh
disease typically causes symmetric put-
aminal involvement, which may be asso-
 ciated with abnormalities of caudate nu-
clei, thalami, and brain stem; however, it
less frequently involves the cerebral cor-
tex and rarely involves the white matter.\textsuperscript{16}
In MELAS, the multiple cortical and sub-
cortical infarctlike lesions that cross vas-
cular boundaries are a distinctive fea-
ture.\textsuperscript{16} In MERRF, the imaging findings
are nonspecific. The cerebral and cerebellar white matter is re-
ported to show patchy T2 prolongation on MR imaging. Cerebral
and cerebellar atrophy are almost always present. Involvement
of the deep gray matter nuclei with degeneration and calcification of
dentate and globus pallidus are the most common manifesta-
tions.\textsuperscript{17} On the contrary, in BBGD the globus pallidus is usually
not affected.\textsuperscript{1,2,13,18} This also differentiates the disease from toxic
causes of encephalopathy such as carbon monoxide poisoning,
which has propensity to affect the globus pallidus.\textsuperscript{19}

Although the disease described responds to biotin, biotinidase
deficiency is absent. The brain imaging findings are also different
from those seen in biotinidase deficiency, in which the neurora-
diologic changes indicate diffuse low attenuation of the white
matter followed by progressive marked cerebral atrophy.\textsuperscript{20}

In contrast to the swelling of the caudate heads and putamen
in patients with BBGD, the main radiologic feature in juvenile
Huntington disease is caudate atrophy and increased proton at-
tenuation and T2 signal in the atrophic caudate nuclei and puta-
tamina.\textsuperscript{21} In patients with acute destructive lesions of the basal
ganglia, ie, the so-called benign form of infantile bilateral striatal
t necrosis, the basal ganglia lesions might return to normal\textsuperscript{22} while
they persist after treatment in BBGD.\textsuperscript{4}

Generally, BBGD should be thought of in any pediatric patient
with neurologic symptoms and bilateral and symmetrical affec-
tion of caudate nuclei and putamina in MR imaging. Biotin and
thiamine treatment is then suggested until either BBGD is ex-
cluded or 1 of the other differential diseases has been clearly
identified.\textsuperscript{23}
In our study, 12 cases (80%) had a good (favorable) outcome with no clinical sequelae, whereas 3 patients had an unfavorable outcome, 2 (13.3%) had dystonia and dysarthria, and 1 patient (6.7%) died from severe encephalopathy because of delayed diagnosis and treatment. These data suggested better outcome results when compared with Alfadhel et al. who had 4 of 18 (22%) patients who died, 6 (33.3%) patients who showed mild to moderate neurologic deficit, and 2 (11%) cases in which the patients had severe neurologic deficits.

The gap between the age of disease onset and the date of starting treatment by biotin and thiamine correlates directly with the neurologic outcome. Two of our 15 patients who had delayed diagnosis displayed neurologic deficits and another patient died for the same reason; the remaining patients who were diagnosed early and received immediate treatment achieved good outcomes and became asymptomatic.

It is important to check for the presence of BBGD in children with acute onset extrapyramidal symptoms as it can be managed without further neurologic deterioration. Because there is no known biochemical marker for the disease, the only way to confirm the diagnosis is the detection of a mutation in the SLC19A3 gene.

**CONCLUSIONS**

BBGD is a treatable underdiagnosed condition. Children with unexplained encephalopathy and bilateral signal alterations of the caudate nucleus and putamen in MR imaging should be suspected of having the disease and a therapeutic trial with biotin and thiamine seems to be mandatory as the prognosis depends on the time interval between the diagnosis and initiation of therapy.

**REFERENCES**

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