A Japanese patient with neonatal biotin-responsive basal ganglia disease

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INTRODUCTION

Biotin-responsive basal ganglia disease (BBGD) is an autosomal recessive disorder that causes catastrophic subacute metabolic encephalopathy. BBGD includes a wide variety of neurological phenotypes, including early-infantile Leigh-like encephalopathy, classic recurrent subacute encephalopathy, and adult-onset Wernicke-like encephalopathy. Patients with the most severe phenotype present with poor feeding, vomiting, and acute encephalopathy with severe lactic acidosis. BBGD is now recognized as thiamine metabolism dysfunction syndrome and is thought to cause this disease. In most cases, early-infantile severe encephalopathies in BBGD are caused by nonsense or frameshift variants. Therefore, loss of ThTR2 function is essential, especially with onset in the neonatal or early infancy period.

DATA REPORT

Biotin-responsive basal ganglia disease (BBGD) with SLC19A3 mutation was first reported in 1998, and over 30 mutations have been reported. We report a neonatal BBGD case with sudden-onset feeding difficulty and impaired consciousness. Encephalopathy resolved after the initiation of biotin and thiamine treatment. Genetic testing revealed a novel heterozygous mutation [c.384_387del, p.Tyr128fs];[c.265 A > C, p.Ser89Arg] in SLC19A3. Early treatment for BBGD is essential, especially with onset in the neonatal or early infancy period.

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heterozygous SLC19A3 mutation, NM_025243.4: [c.384_387del,p.-Tyr128fs];[c.265A>C,p.(Ser89Arg)], was identified in the patient. A novel truncating mutation [c.384_387del,p.Tyr128fs] inherited from the mother appears to be pathogenic. A variant [c.265A>C,p.(Ser89Arg)] inherited from the father is likely pathogenic because it has already been reported in four cases; it is predicted to be deleterious/damaging by 4 of 5 variant prediction programs (Supplementary Table 1). We classified the variants according to the ACMG_AMP classification guideline. [c.384_387del,p.Tyr128fs] is thought to be pathogenic in PVS1 (the variant is thought to cause early truncation resulting in loss of function), PM2 (extremely low frequency), and PP4 (not been reported, but the phenotype of the compound mutations with other clinical BBGD cases is very specific). [c.265A>C,p. Ser89Arg] is likely pathogenic in PM2 (extremely low frequency; allele frequency = 0.00024 in the Japanese population; GnomAD exomes homozygous allele account = 0), PM3 (the other allele is thought to cause early truncation resulting in loss of function, and the phenotype is thought to be a recessive disorder), PP3 (multiple lines of computational evidence of a deleterious effect of the variant are provided in Supplementary Table 1), and PP4 (reported in four cases with LS or BBGD, clinically specific phenotypes for the gene). Sanger sequencing for the parents and patient confirmed the mutations identified (Supplementary Fig. 1). We did not find any SNPs that account for the developmental delay, only the SLC19A3 aberration. The patient’s follow-up brain MRI showed high-intensity signals in the bilateral thalamus, liquefaction of the dorsal putamen, and atrophy in the cortex, subcortical white matter, and white matter as sequela of neonatal encephalopathy.

Table 1. Related demography and outcome by mutations of neonatal encephalopathy patients.

| Reference          | Mutations        | Age at onset | Consanguinity | treatment          | Outcome            |
|--------------------|------------------|--------------|---------------|--------------------|--------------------|
| This case          | c.384_387del,p.(Tyr128fs) | 28 days      | No            | Biotin and thiamine | Bedridden          |
|                    | /c.265A>C,p.(Ser89Arg) |    |               |                    |                    |
| Yamada et al.14    | c.958G>C,p.(Glu320Gln) | 1M           | Yes           | NP                 | Bedridden          |
|                    | /c.958G>C,p.(Glu320Gln) |    |               |                    |                    |
| Perez-Duenas et al.15 | c.68G>T,p.(Gly23Val) | 1M           | ND            | Biotin and thiamine | Gait               |
|                    | /c.68G>T,p.(Gly23Val) |    |               |                    |                    |
| Gerards et al.16   | c.20C>A,p.Ser7Ter  | 1M           | No            | NP                 | Death              |
|                    | /c.20C>A,p.Ser7Ter |    |               |                    |                    |
| Haack et al.17     | c.982del,p.(Ala328Leufs*) | Neonatal    | Yes           | NP                 | Death              |
|                    | /c.982del,p.(Ala328Leufs*) |    |               |                    |                    |
| Haack et al.17     | c.982del,p.(Ala328Leufs*) | 18 days     | Yes           | Biotin and thiamine | Normal             |
|                    | /c.982del,p.(Ala328Leufs*) |    |               |                    |                    |
| Kamasak et al.18   | c.623_624insA,p.(Ser179fs) | 30 days    | No            | Thiamine           | Responds to mother |
|                    | /c.623_624insA,p.(Ser179fs) |    |               |                    |                    |
| Kamasak et al.18   | c.620delinsAA,p.(Ala178fs) | 30 days    | No            | Biotin and thiamine | ND                 |
|                    | /c.620delinsAA,p.(Ala178fs) |    |               |                    |                    |
| Kamasak et al.18   | c.894T>G,p.(Tyr298*) | 23 days     | No            | Biotin and thiamine | Death              |
| Kılıç et al.19     | p.His200Serfs*,c.(597InsThr) | 20 days    | Yes           | Biotin and thiamine | Death              |
|                    | /p.His200Serfs*,c.(597InsThr) |    |               |                    |                    |
| Kılıç et al.19     | c.894T>G,p.(Tyr298*) | 21 days     | Yes           | Biotin and thiamine | Quadriplegia        |
|                    | /c.894T>G,p.(Tyr298*) |    |               |                    |                    |

ND not described, NP not performed.

Fig. 1 The patient’s magnetic resonance images. a, b Acute-phase brain MRI showed high-intensity signals in the bilateral thalamus, putamen and globus pallidus. c, d Follow-up brain MRI showed high-intensity signals in the bilateral thalamus, liquefaction of the dorsal putamen, and atrophy in the cortex, subcortical white matter, and white matter as sequela of neonatal encephalopathy.
by cells. Thiamine malabsorption due to loss of thiamine transporter type 2 causes BBGD. Thiamine pyrophosphate (TPP), which accounts for 80% of thiamine in the entire body, is produced from thiamine and binds to the pyruvate dehydrogenase complex as a coenzyme. If TPP is not synthesized or if it is undersynthesized, acetyl-CoA from pyruvate in the TCA cycle is not produced, leading to energy depletion in cells.

Biotin is a coenzyme for carboxylases, including pyruvate carboxylase in the TCA cycle, and helps to produce oxaloacetic acid as a coenzyme. If TPP is not synthesized or if it is produced from thiamine and binds to the pyruvate dehydrogenase complex as a coenzyme, the patient achieved independent gait (Table 1). Furthermore, before biotin and thiamine are initiated, neuronal damage may be too severe to gain favorable intellectual or motor development. As we performed target sequencing, we cannot deny the possibility that variants outside of the targeted genes influenced his development. Nevertheless, vitamin combination therapy may prevent a second attack or encephalopathy, as in our patient. Treatment before the onset of encephalopathy is required to attain better neurological outcomes. Moreover, elucidation of biomarkers for BBGD may provide a screening method and improve outcomes.

HGV DATABASE

The relevant data from this Data Report are hosted at the Human Genome Variation Database at https://doi.org/10.6084/m9.figsphere.hgv.3225, https://doi.org/10.6084/m9.figsphere.hgv.3228.

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AUTHOR CONTRIBUTIONS

Y.S. and M.N. treated the patient. A.M., M.K., K.M., and Y.O. contributed to genetic analysis, designed the experiment and analyzed data. T.Y. supervised the writing. M.K. and H.O. are responsible for writing and the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41439-022-00210-z. Correspondence and requests for materials should be addressed to Hitoshi Osaka.

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