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Case report

A case of Bardet-Biedl syndrome complicated with intracranial hypertension in a Japanese child

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Abstract

Bardet-Biedl syndrome (BBS) is a rare heterogeneous autosomal recessive disorder characterized by rod-cone dystrophy, postaxial polydactyly, truncal obesity, hypogonadism, learning disability, and renal anomaly that are caused by ciliary dysfunction. 16 genes have been associated with the BBS phenotype. Although recent pathophysiological studies using animal models have shown that ciliary dysfunction may induce hydrocephalus, there have been no reports of BBS with intracranial hypertension. We here describe a 9-year-old Japanese girl who was diagnosed as having BBS and later received renal transplantation due to chronic renal failure. She also exhibited intracranial hypertension, including papilledema and increased intrathecal pressure (260–300 mmH_2O), but her brain magnetic resonance imaging was normal. No genetic abnormalities were detected by DNA chip analysis or exome sequencing. Her papilledema improved following administration of acetazolamide. This is the first report of a case of BBS complicated with intracranial hypertension and its treatment.
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Keywords: Bardet-Biedl syndrome (BBS); Cilia; Ciliopathy; Intracranial hypertension

1. Introduction

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive, genetically heterogeneous ciliopathy syndrome characterized by renal abnormality, rod-cone dystrophy, and obesity that are caused by ciliary dysfunction [1]. Recent studies have implicated several candidate genes with the pathogenesis of this disease. Although cilia have long been considered only as sensory cellular antennae, they are now recognized to play an important role in the development of nervous systems and cerebrospinal fluid (CSF) secretion and flow [2]. Here, we report the first case of BBS complicated with intracranial hypertension.

2. Case report

A 9-year-old girl was admitted to our hospital because of proteinuria and renal dysfunction. She was the first child of non-consanguineous healthy parents. There was no remarkable family history. Her birth

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weight was 2662 g after 40 weeks of gestation. Apgar scores were 6 at 1 min and 9 at 5 min. She had polydactyly that was resected soon after birth and atrial septal defect which was surgically treated at the age of 1. Other past histories included exudative otitis media and hearing impairment, strabismus, hyperopia, astigmatism, and night blindness.

On admission, the patient's height, weight, head circumference, and body mass index were 132.0 cm, 40.0 kg, 51.5 cm, and 23.0 mg/m^2, respectively. Her heart rate was 63/min and blood pressure was 115/84 mmHg. She had obesity and borderline intellectual impairment (full IQ was 76, verbal IQ was 81, and performance IQ was 75 as determined by WISC-III) without any other abnormal neurological findings, such as impaired cranial nerves, pyramidal signs, involuntary movements, ataxia, or sensory disturbances. Laboratory data are shown in Table 1. Her urinary protein level was 0.5 g/day, and serum creatinine and cystatin C levels were slightly elevated (0.75 mg/dL and 1.09 mg/L, respectively). Renal biopsy showed obsolescence in 25 (83%) of 30 glomeruli, hyalinization in the remaining glomeruli, fibrosis in interstitial tissue without tubule involvement, and negative immunofluorescence staining for IgG, IgA, IgM, C3, and fibrin. On ophthalmologic examination, we noted intermittent exotropia, a best-corrected visual acuity of 1.2 OD and 0.9 OS, and normal intraocular pressure (19.7 mmHg in the right eye and 18.7 mmHg in the left eye). Rod-cone dystrophy was detected (Fig. 1), and ERG responses were severely reduced in both eyes. Goldmann perimetry revealed visual field constriction. Based on these findings, we diagnosed our patient as having BBS. She also exhibited papilledema with dilatation and tortuosity of retinal blood vessels. Brain MRI and magnetic resonance angiogram findings were normal (Fig. 2), but intracranial pressure was elevated at 260–300 mmH_2O, which indicated intracranial hypertension. Following treatment with acetazolamide, the girl's papilledema showed improvement. However, her kidney function worsened, and she eventually received a renal transplantation from her mother at the age of 11.

Table 1
Laboratory data.

Chemical analysis	
TP	7.5 g/dL
Alb	4.0 g/dL
BUN	16 mg/dL
Cr	0.75 mg/dL
UA	5.3 mg/dL
TC	145 mg/dL
TG	267 mg/dL
AST	39 IU/L
ALT	31 IU/L
ALP	573 IU/L
LDH	308 IU/L
CK	114 IU/L
Na	141 mEq/L
K	4.3 mEq/L
Cl	107 mEq/L
CRP	0.15 mg/dL
β_2MG	2.7 mg/L
Cystatin C	1.09 mg/L
HbA1c	5.1%
Blood analysis	
WBC	6.360/μL
Nut	51%
Mon	6%
Eos	2%
Bas	1%
Lym	40%
RBC	502×10^4/μL
Hb	14.1 g/dL
Ht	42.9%
Plt	17.7×10^4/μL
Urinalysis	
pH	6.0
RBC	1–4/HPF
WBC	10–19/HPF
U-Cr	53.25 mg/dL
U-TP	26 mg/dL
U-NAG	4.9 U/L
U-β_2MG	99 μg/L
CSF	
Pressure	260–300 mmH_2O
Cell	0.33/μL
TP	15 mg/dL
Glu	49 mg/dL
IgG	2.0 mg/dL
NSE	15 ng/mL
MBP	<31.2 pg/mL

CSF, cerebrospinal fluid; NSE, neuron-specific enolase; MBP, myelin basic protein.

For genetic analysis, a DNA chip study was performed at Asper Biotech Ltd. (Tartu, Estonia) after obtaining informed consent from the patient and parents. The DNA chip (version 5) analysis, which covered 131 pathological mutations in 13 genes known to cause BBS (BBS1-13), identified no pathological alterations. However, as these mutations covered approximately one-third of currently known causative mutations for BBS, we also performed exome sequencing of this patient. Briefly, genomic DNA was captured using the SureSelect Human All Exon v4 kit (Agilent Technologies) and sequenced using a high throughput sequencing platform (HiSeq2000, Illumina). Reads were aligned to the human genome reference sequence (hg19) with the Burrows-Wheeler Aligner program, and single-nucleotide variants and small insertions and/or deletions were identified using the Genome Analysis Toolkit (GATK). Our results showed no pathogenic point-mutations or small insertions/deletions in any of the coding sequences and exon/intron junctions among the BBS1-14 genes. We nevertheless cannot exclude deletions of whole exons or mutations in the promoter or other regulatory sequences in these genes.

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