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증 례

CEP290 돌연변이로 인해 발생한 Joubert 증후군 말기 신부전 1례

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A Case of End-Stage Renal Disease with Joubert Syndrome due to *CEP290* Mutation

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Joubert syndrome (JS) is a rare genetic disorder that is characterized by ataxia, hypotonia, developmental delay, respiratory abnormalities such as apnea-hyperpnea, and abnormal eye movements. The pathognomonic diagnostic finding is the "molar tooth sign" (MTS) on brain magnetic resonance imaging (MRI), described as cerebellar vermis hypoplasia or dysplasia, thick and horizontally oriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa. JS is characterized by genetic heterogeneity: pathogenic variants in over 30 genes have been identified to date. The *CEP290* protein, which is on chromosome 12q21.3, is most frequently mutated in patients with JS, especially with renal involvement. Here, we report a case of JS in a 14-year-old male patient with end-stage renal disease. To the best of our knowledge, this is the first Korean report of a patient with JS due to *CEP290* mutation (c.6012-12T〉A) whose diagnosis was confirmed after repetitive MRI. We suggest consultation with an experienced neuro-radiologist and follow-up MRI studies to detect a "hidden" MTS if clinical findings suggest a diagnosis of JS. Furthermore, even in the absence of an MTS, whole exome sequencing should be considered.

Key words: Joubert syndrome, Molar tooth sign, Chronic renal failure, *CEP290* mutation

Introduction

Joubert syndrome (JS) is related to agenesis of the cerebellar vermis and was initially described in 1969 in four siblings of a French-Canadian family with hyperpnea, abnormal eye movements, ataxia, and cognitive deficits[1)]. The prevalence has been reported to be between 1 per 80,000 and 1 per 100,000 live births, but these numbers may underestimate the actual prevalence because of low awareness of this condition due to its rarity, ongoing identification of additional causative genes

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and private mutations, and reports of a broader range of phenotypic findings[2-5]. In addition to clinical findings, the so-called molar tooth sign (MTS), caused by unique hypoplasia or agenesis of the cerebellar vermis and brainstem malformation, is recognizable on brain magnetic resonance imaging (MRI) and is a mandatory criterion for diagnosis of JS[2,6-8]. JS can be clinically suspected as early as the first few months of life upon observance of hypotonia progressing to cerebellar ataxia, global developmental delay, intellectual disability of variable severity, abnormal ocular movements (mainly ocular motor apraxia and nystagmus), and breathing dysregulation (short alternating episodes of apnea and tachypnea or episodic tachypnea alone)[2-4]. The clinical phenomenology of JS is quite diverse because it can affect multiple organs, most commonly the eye (retinal defects that range in severity from Leber congenital amaurosis to slowly progressive retinopathies with partially preserved vision), kidney (nephronophthisis, cystic dysplastic kidneys), and liver (congenital liver fibrosis)[2-4].

The genetic bases of JS are extremely complex despite the tremendous acceleration in gene discovery enabled by next-generation sequencing techniques[2]. At least 30 causative genes have been identified to date[2,3,5,9]. These genes universally encode proteins localizing to the primary cilia, the cell organelles that function as environmental sensors and signaling pathways during development and homeostasis. Thus, JS is considered a ciliopathy[2-4]. The gene for the *CEP290* protein is on chromosome 12q21.3 and is mutated in about 50% of patients with JS. The *CEP290* protein is localized to the base (centrosome) and stalk of primary cilia and is most frequently associated with JS cases with renal involvement of nephronophthisis at 12q21.3 and the Meckel-Gruber syndrome-associated gene TMEM67 at 8q22.1[2-5,9].

We report a case of JS caused by *CEP290* mutation in a male patient with end-stage renal disease whose diagnosis was initially suspected by clinical features and by atypical MTS identified after repetitive MRI.

Case Report

The patient was a male baby and the only child of a healthy 32-year-old mother and a healthy 33-year-old father, neither of whom had a family history of neurological or hereditary disorder. The patient weighed 3,700 g (90th percentile) at birth at a gestational age of 40 weeks by Cesarean section delivery due to cephalopelvic disproportion. On the 12th day of life, he was treated for alternating episodes of tachypnea and apnea.

He first visited the outpatient clinic of our hospital at 8 months of age with developmental delay. Head control and rolling had not been achieved. A chromosome study, brain MRI, and metabolic work up were performed and revealed no specific findings. At 15 months of age, he was diagnosed with mitochondrial disease through various tests, including muscle biopsy at other tertiary hospital. At that time, he could not talk, follow with or turn his eyes toward objects or sound, hold up or control his head, sit upright independently, or hold his bottle.

The patient continued with rehabilitation treatment until he was 7 years 8 months old, when he returned to the hospital with his first afebrile seizure due to hyponatremia shortly after hemodialysis. At that time, electroencephalogram (EEG) test result was normal. He was only able to roll over at the time of his visit, and he had been in hemodialysis for two weeks ago due to an un-

known cause of end stage renal disease. He experienced another seizure, a generalized tonic-clonic (GTC) type, at 7 years 10 months of age immediately after dialysis. On physical examination at that time, he had facial dysmorphisms, including prominent forehead, right-dominant bilateral ptosis, high rounded eyebrows, broad and shallow nasal bridge, lower lip eversion with trapezoid-shaped open mouth, and tongue protrusion (Fig. 1). He also showed both corneal band keratopathy, corneal opacity and nystagmus in the ophthalmologic examination. The patient suffered intracranial hemorrhage at 9 years 4 months of age, with a systolic blood pressure of 190 mmHg during hemodialysis. At that time, MTS findings were suspected on brain computed tomography (CT), suggesting the possibility of JS, but genetic testing was not possible due to economic and other problems. Although brain CT or MRI has been performed previously, radiological readings at the age of nine diagnosed hypoplastic cerebellar vermis with MTS characteristics and he was clinically suspected as JS at that time based on his clinical features and MTS (Fig. 2).

Finally, at 13 years 10 months of age, he was finally confirmed with JS through whole exome sequencing (WES) revealed identification of a c. 6012-12T>A, homozygote mutation in *CEP290* (Fig. 3). The following method of WES was utilized for gene analysis. An Agilent SureSelectXT Human

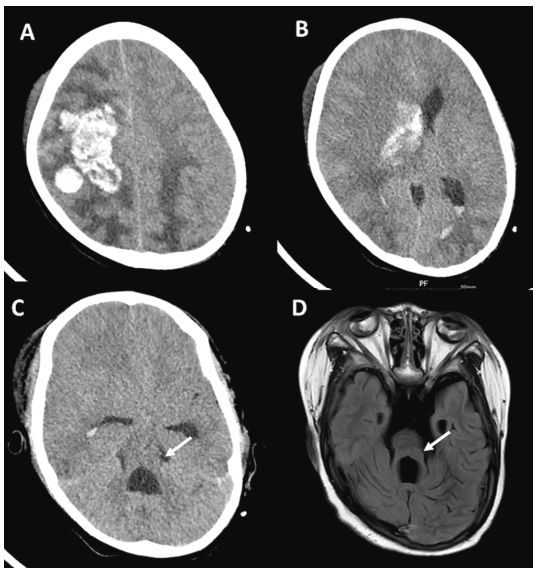

Fig. 2. At 9 years 4 months of age, the patient underwent brain computed tomography (CT) that showed intracranial hemorrhage, intraventricular hemorrhage, and midline shifting to the left side due to hypertension (A and B). The molar tooth sign (MTS) was observed on brain CT performed at 9 years 4 months of age (C) and on brain magnetic resonance imaging (MRI) at 12 years 2 months of age (D). Axial T2-weighted MRI shows an MTS appearance of the midbrain with thickened superior cerebellar peduncle (arrow) and vermian hypoplagia.

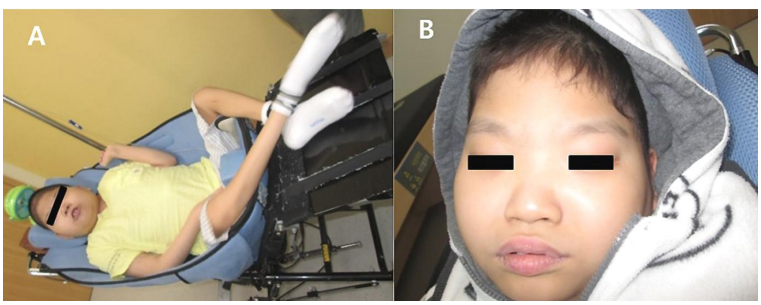

Fig. 1. A photograph of the patient at 14 years in which he sat in a wheelchair due to global developmental delay (A). His facial photograph shows facial dysmorphisms, including prominent forehead, right-dominant bilateral ptosis, high rounded eyebrows, broad and shallow nasal bridge, lower lip eversion with trapezoid-shaped open mouth, and tongue protrusion (B). Publication of gross photos was permitted by his parents through informed consent.

all Exon 50 Mb kit (Agilent, Santa Clara, CA, USA) was used to enrich the exon regions of the genome. Paired-end 100-bp sequencing was performed using Illumina HiSeq platform (Illumina, San Diego, CA, USA). The produced sequencing data were analysed using NextGENe software v2.4.0.1. (SoftGenetics, State College, PA, USA). Finally, the detected variants were classified as a pathogenic variant according to the American College of Medical Genetics and Genomics 2015 guidelines[10].

The patient started peritoneal dialysis at age 14 years 2 months, and he still uses a wheelchair for ambulation.

Discussion

Joubert syndrome (JS) is a rare, predominantly autosomal, recessive, ciliopathic condition that is clinically characterized by congenital cerebellar ataxia, hypotonia, global developmental delay, and specific mid-hindbrain malformation ("molar tooth sign" [MTS] on brain MRI because of its resemblance to the cross-section of a tooth on axial imaging)[2,3,6,11]. Its three key diagnostic criteria are (1) radiologic finding of MTS; brain MRI findings demonstrating the hallmark imaging features of MTS on axial imaging with these three components: a) midline cerebellar vermis hypoplasia (characterized by incomplete lobulation and enlarged fourth ventricle), b) deepened interpeduncular fossa (and dysgenesis of the isthmus [part of the brainstem between the pons and inferior colliculus], which is seen as elongation and thinning of the ponto-mesencephalic junction), and c) thick, elongated, and straight superior cerebellar peduncles; (2) hypotonia in infancy with later ataxia; and (3) developmental delays/intellectual disability of variable severity. Additionally, one or both of the following are not required but are supportive of diagnosis: a) irregular breathing pattern in infancy (episodic tachypnea and/or apnea) and b) abnormal eye movements (nystagmus, jerky eye movements, and oculomotor apraxia or difficulty with smooth visual pursuits)[2,15]. Although not a pathognomonic finding on MRI, a sagittal vermis cleft (incomplete fusion of the halves of the vermis) on axial or coronal MRI plane is often visualized in patients with JS[3,6]. Because the spectrum of neuroimaging findings in JS is wide, neuroimaging plays a key role in diagnosis[8]. In the presence of neurological features suggestive of JS, the diagnosis is easily confirmed upon demonstration of the MTS on

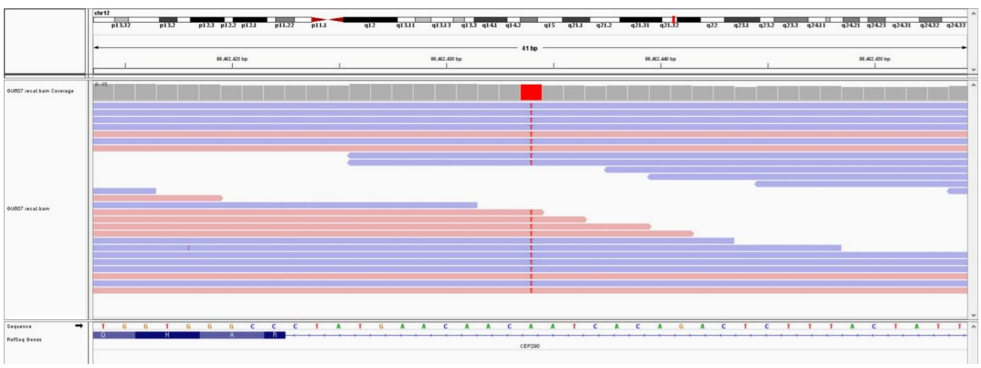

Fig. 3. Identification of a c.6012-12T>A, homozygote mutation in CEP290 (NM_025114.3). The BAM file displayed in The Integrative Genomics Viewer (IGV) shows c.6012-12T>A, homozygote is indisputable in the forward (red in IGV) and reverse (blue in IGV) strands.

brain MRI[2]. All patients with JS have some degree of vermis hypoplasia and the MTS, and both are mandatory features for diagnosis[8]. However, although a high-resolution MRI scan with 3 mm sections is recommended for visualizing the MTS, its shape varies considerably. Therefore, without examination of multiple MRI cuts for subtle MTS findings and vermis hypoplasia, even experienceed neuro-radiologists may miss this diagnostic hallmark, as in the present case[5]. According to the literature, 12% of JS cases were initially diagnosed with Dandy-Walker malformation; after posterior fossa decompression and re-expansion of the cerebellar hemispheres, these patients were diagnosed with JS[8]. This finding emphasizes the importance of follow-up MRI studies in patients with suspected Dandy-Walker malformation or JS to detect a "hidden" MTS[8]. The MRI finding of vermis hypoplasia in the absence of other typical clinical features does not lead to diagnosis of JS[3]. Neuroimaging does not predict the genetic cause and is considered of limited value in predicting cognitive function in JS, although it may predict the neurodevelopmental outcome[8]. A high degree of vermis hypoplasia correlates with a worse neurodevelopmental outcome[8].

The three aforementioned cardinal features are necessary for diagnosis of JS, and 29% of patients do not have extra-neurological organ involvement, although the syndrome does manifest several other variable features, as in our case[2,8]. The most prominent feature in the newborn period is an abnormal respiratory pattern characterized by episodic hyperpnea, consisting of alternating tachypnea and/or apnea[6,12]. This abnormal breathing pattern of distinctive, short, alternating episodes of apnea and hyperpnea or episodic hyperpnea alone is sometimes described as 'panting like a dog' and may intensify with stress. Some neonates demonstrate worrisome bouts of apnea requiring pharmacological intervention, like our patient[6,13]. This abnormal respiratory pattern progressively improves with age and usually disappears around sixth months of age; however, death occurring before the age of 6 years in JS is most often (35%) due to respiratory failure[13].

Ocular and oculomotor involvement is common in JS, and it manifests variable phenotypes among patients[5,13,14]. Abnormal eye movements are typically characterized by oculomotor apraxia, jerky eye movements and head thrusting (resulting from absence or defect in controlled, voluntary, and purposeful eye movements), as well as coloboma, nystagmus, strabismus, and ptosis of the eyelids [5,11,14]. In addition, the most severe manifestations are congenital blindness in the spectrum of Leber congenital amaurosis[2,5]. This retinal degeneration may develop with age and is slowly progressive with partially preserved vision[2,5,14]. Overall, retinal involvement is present in about 80% of patients with *CEP290* and *AHI1* mutations, and severe retinal degeneration that is early and aggressive is also seen in these patients[14].

Several studies report renal manifestations in 23-32% of patients with JS, most commonly in those with mutations in *CEP290*, TMEM67, and *AHI1*. Patients generally demonstrate one of two forms: nephronophthisis (NPHP) or cystic kidneys [15]. Subjects with renal manifestations show early onset hypertension, diagnosed shortly after birth or within the first years of life, before any measurable decrease in estimated glomerular filtration rate, and renal failure (37.5%) was the most common cause of death, especially in older individuals[5,13,15,16]. NPHP, the most typical form of JS, manifests as chronic tubulointerstitial nephropathy and may present in the first or second decade of life, often progressing to end-stage

renal disease within a decade[5,15,16].

Like other syndromic ciliopathies, JS is characterized by extreme genetic heterogeneity. Since the first gene for JS, *NPHP1*, was identified in 2004[17], bi-allelic pathogenic variants in over 30 genes encoding proteins of the primary cilium have been identified to date: *AHI1, ARL13B, ARMC9, CC2D2A, CEP104, CEP290, INPP5E, KIF7, NPHP1, OFD1, RPGRIP1L, TCTN1, TCTN2, MKS1, TMEM67 (MKS3), TMEM237, TMEM2167*, etc[3,5,8,9]. Although most mutations resulting in JS are inherited in an autosomal recessive manner, as are the majority of ciliopathies, Oral Facial Syndrome 1 (OFD1) demonstrates X-linked recessive inheritance[5]. Of note, because almost all these genes have also been implicated in other ciliopathy disorders, it typically is difficult to identify clear-cut genotype-phenotype correlations for many of these genes[5]. However, in a mouse model of JS due to *CEP290* mutation, gene therapy has demonstrated reduction of cystic kidney disease burden and rescued retinal degeneration[5,18,19].

In conclusion, we describe a male patient with end-stage renal disease, to the best of our knowledge, who was firstly confirmed to have JS with *CEP290* mutation (c.6012-12T>A) by a molecular test after repetitive brain CT and MRI in Korea. Although the classic symptoms of JS developed in sequence in this patient, it was not diagnosed clinically until the fifth brain CT due to the relatively atypical appearance of the MTS. Therefore, because the shape of the MTS varies considerably, MRI with multiple and thin sections should be performed when JS is clinically suspected so as to not miss this diagnostic hallmark. In addition, follow-up MRI studies should be performed to detect a possibly "hidden" MTS. Furthermore, if the possibility of JS is high, genetic molecular test should be considered even if there is no demonstration of the MTS.

요 약

쥬버트 증후군(JS, Joubert syndrome)은 대부분 상염색체 열성으로 유전되는 유전성 대사질환으로 임상증상은 신생아 시기부터 발현된다. 저자들은 신생아기부터 특징적인 임상 증상이 순차적으로 발현되어 임상적으로 JS를 의심하였으나 특징적인 뇌 MRI 소견인 molar tooth sign (MTS)이 늦게 나타난 후 전장엑솜분석(WES, whole exome sequencing)으로 확진 된, 말기 신부전을 동반한 JS 1례를 경험하였기에 보고하고자 한다. 14세 남자 환자는 출생 직후 반복적인 무호흡과 과호흡으로 치료받은 병력이 있으며, 생후 8개월때부터 전반적 발달 지연과 관련되어 처음 병원을 방문하여 기본적인 발달 지연에 관한 검사를 시행하였으나 특이 소견 없었고, 이후 15개월 때 근육생검을 포함한 여러 검사를 통해 사립체(mitochondrial) 질환으로 진단 되었었다. 이후 물리 치료만 하며 관찰 하던 중 안구진탕과 망막질환이 확인되었다. 생후 7세 8개월에는 처음 발작이 있었으며, 말기 신부전이 있어 8세부터 혈액투석을 시작한 후, 혈액 투석 직후 수차례 발작이 있었으나 전해질 불균형으로 인한 발작으로 진단하여 항뇌전증 약물 치료는 하지 않았다. 9세 4개월 때 고혈압으로 인한 뇌출혈로 치료 받았으며, 이때 시행한 뇌 CT상 MTS가 처음 의심되었다. 13세 10개월에 시행한 뇌 MRI 검사상 MTS가 명확히 확인되었고, 전장엑솜분석으로 JS의 *CEP290* mutation (c.6012-12T>A)이 확인되었다. 환자는 신생아기부터 발현된 특징적인 임상 소견과 말기 신부전 상태, 뇌 CT 또는 MRI소견, 그리고 전장엑솜분석 검사로 JS로 확진하였다. JS는 임상 양상이 다양할 뿐만 아니라 진단에 중요한 MTS 소견이 초기에 보이지 않더라도, 임상적으로 의심된다면 확진을 위해서 전장엑솜분석을 시행하는 것이 필요하다.

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