

## Development of end-stage renal disease at a young age in two cases with Joubert syndrome

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Joubert syndrome (JS) is an autosomal recessive genetic disorder. To date, mutations in 20 genes of the genetically heterogeneous JS and JS-related disorders (JSRD) have been reported. Renal involvement occurs in 2-20% of JS cases. Identified renal abnormalities are cystic dysplasia and nephronophthisis.

Here we report the clinical course and management of renal failure in early childhood. We present two cases diagnosed with JS that developed end-stage renal disease at young ages. In the genetic studies, a c.5668G>T (p.G1890\*) homozygous stop mutation was identified in the CEP290 gene of one of the patients and a c.1303C>G (p.R435G) homozygous mutation in the INPP5E gene of the other.

It has been emphasized that it is important to evaluate patients in terms of renal disease when monitoring the progress of Joubert syndrome, a condition that predominantly causes mental and motor development retardation.

**Key words:** Joubert syndrome, Joubert syndrome-related disorders, nephronophthisis, chronic kidney disease.

Joubert syndrome (JS) is a rare clinical and autosomal recessive genetic disorder. Clinical characteristics of classic JS are frequently described as infantile hypotonia, stunted growth/mental retardation, abnormal breathing patterns in infancy and abnormal eye movements<sup>1</sup>. It is known that structural and/or functional defects of the primary cilia cause phenotypic features; therefore JS belongs to the "ciliopathies"<sup>2</sup>.

In JS-related disorders (JSRD), the heterogeneity of the genetics is also reflected in clinical practice. Diagnosis requires the evaluation of both clinical and neuroradiological findings. Although structural cerebral disorders are not progressive, renal, hepatic or retinal functions may deteriorate progressively<sup>3</sup>. Here we report the genetic findings and the clinical course of end-stage renal disease (ESRD) in early childhood in Joubert syndrome.

### Case Reports

#### Case 1

A female patient, 9 years of age, had been referred to our hospital at the age of 5 and had been diagnosed as having ESRD. Because she suffered from febrile seizures at the 6th month of life, phenobarbital treatment was started. The family history revealed that the parents were consanguineous and the patient had a cousin with similar symptoms.

The patient exhibited phenotypic characteristics of JS, with a prominent forehead, ptosis of the left eyelid, horizontal nystagmus in both eyes, and a short neck (Fig. 1a). There was no urinary or bowel control. The patient did not learn to walk and could only sit. On clinical examination, severe mental retardation, neuromotor apraxia, a lack of balance, frequent lower respiratory tract infections, involuntary movements of

the eye and advanced vision loss, as well as hyperpigmentation and retinal degeneration were found. Laboratory investigations showed anemia, uremia, hyperparathyroidism and acidosis. In the renal ultrasonography (USG), bilateral kidney dimensions were small, and multiple cortical cysts, the largest being 1.5 cm, were found in the parenchyma. The cranial magnetic resonance imaging (MRI) displayed vermis agenesis and the “molar tooth sign.” With the patient’s family history and phenotypic characteristics, the neurological findings and the cranial MRI results, the case was diagnosed as JS. The patient was treated with chronic hemodialysis (HD).

Candidate gene sequencing of the *CEP290* gene (NM\_025114) revealed a nonsense mutation c.5668G>T (p.G1890\*) in exon 41 in homozygous state in the index patient and heterozygous state in the parents. Because we found a homozygous nonsense mutation, we did not pursue further genetic investigations.

## Case 2

This female patient, now 4 years old, had been referred to our pediatric nephrology clinic with the diagnosis of anemia and acute kidney injury. Initially, diagnosis was made at the age of 15 months. This child also had a family history of consanguineous marriage. Her intrauterine USG examination revealed the presence of ventriculomegaly and renal cysts. The patient was found to have macrocephaly, ptosis, horizontal nystagmus, a cystic mass underneath the tongue, low-set ears, retro/micrognathia and postaxial polydactyly in the right hand (Fig. 1b-c-d). Both kidneys could be palpated during the abdominal examination. The patient had head-lag and could not sit, talk or visually follow an object. The optic fundus was normal in the examination. In the USG, the patient was found to have bilaterally large kidneys, with multiple cysts on both, and no corticomedullary junction (Fig. 2a). The infantile hypotonia, as well as the stunted growth/mental retardation, the irregular breathing pattern in the infantile stage, and the abnormal eye movements were compatible with JS. We could not perform a renal biopsy to show the characteristic triad of tubular basement membrane disruption, tubulointerstitial nephropathy and corticomedullary cysts. Therefore, our patient was diagnosed to

have infantile nephronophthisis with clinical features, early-onset arterial hypertension and bilaterally large kidneys and corticomedullary cysts in the USG. Her echocardiogram was normal; no situs inversus was observed. In the cranial MRI, a typical “molar tooth sign” was seen (Fig. 2b). The patient was diagnosed as JS with these clinical and radiological findings.

At the age of 15 months, the patient was diagnosed with chronic kidney disease (CKD), and 7 months later, she was taken into a chronic peritoneal dialysis (PD) program. The patient, currently 4 years old, continues to have PD.

In the genetic analysis carried out for the diagnosis of JS, we initially sequenced *CEP290* and *AH11* and could not find a mutation. Subsequently, we performed homozygosity mapping (data not shown), which led to *INPP5E* as the functional and positional candidate gene. Sequencing of the *INPP5E* gene (NM\_019892) showed a mutation c.1303C>G (p.R435G) in exon 6, homozygous in the index patient and heterozygous in the parents. This mutation is located in the inositol phosphate phosphatase domain of *INPP5E* and absolutely conserved during evolution (data not shown).

## Discussion

Joubert syndrome is a rare (1:100,000), autosomal recessive condition. Its known phenotypic and genotypic characteristics have been steadily expanded to include other clinical abnormalities that are seen in ciliopathies, and have been established as clinically very variable. It is a member of the class of diseases that are now classified as JS-related disorders (JSRD)<sup>4</sup>.

Since the molar tooth sign is not specific to classical JS, a differentiating diagnosis should be made for JSRD. The absence of cystic dysplastic kidney-hepatic fibrosis-coloboma in Case 1, together with the genetic mutation, differentiated it from Dekaban-Arima syndrome and “cerebellar vermis hypo/aplasia, oligophrenia (mental retardation), ataxia, ocular coloboma and hepatic fibrosis syndrome” (COACH). Further, the absence of severe sight loss and cystic dysplastic kidney led to a diagnosis differentiating it from Senior-Loken syndrome. While polydactyly in Varadi-Papp syndrome is preaxial, in our case it was postaxial. In Case 2, the absence of retinal dystrophy-hepatic fibrosis as well as the absence of Dekaban-

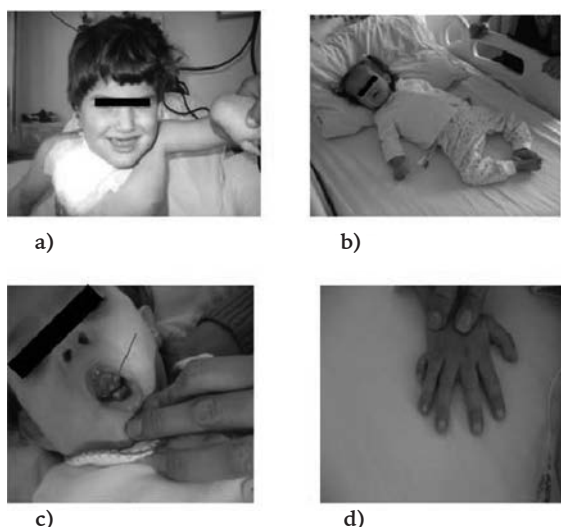


Fig. 1.

- (a) General appearance of 5.5-year-old Case 1  
 (b) General appearance of 4-year-old Case 2  
 (c) Sublingual cystic mass in 4-year-old Case 2  
 (d) Polydactyly in 4-year-old Case 2

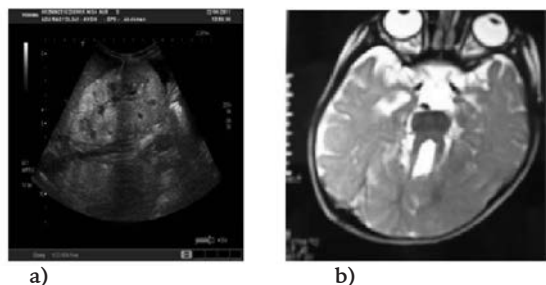


Fig. 2.

- (a) Appearance of corticomedullar cysts in renal USG of Case 2  
 (b) Molar tooth sign in cranial MR of Case 2

Arima and coloboma-hepatic fibrosis, together with the genetic mutation, differentiated the condition from COACH; the absence of retinal dystrophy-cystic dysplastic kidney-central polydactyly differentiated it from Senior-Loken and Varadi-Papp syndromes.

Renal abnormalities are rarely seen in JS, exhibiting a frequency of 2%-20%<sup>5</sup>. The following abnormalities have been identified: nephronophthisis, nephronophthisis-medullary cystic kidney disease (MCKD) and cystic dysplasia. Nephronophthisis is classified as the juvenile or infantile type. Typically, outside of the infantile type, the dimensions of the kidneys in the USG are small or normal. In addition, the corticomedullar line is absent and there are corticomedullary cysts. Juvenile

nephronophthisis is the most frequent genetic cause of initial renal failure in the first and second decades and leads to ESRD in adolescence<sup>5-7</sup>. Infantile nephronophthisis causes ESRD before the age of four years. To our knowledge, this report of the development of kidney failure in a 5-year-old (our first case) exhibiting juvenile nephronophthisis on the USG and in a 15-month-old (our second case) exhibiting infantile nephronophthisis on the USG is the first reference of its kind in the literature.

Saraiva et al.<sup>8</sup> found congenital retinal dystrophy in all JS cases with renal disorders. But although this concurrence is frequent, it does not necessarily have to be present. While our first case had retinal dystrophy, the examination of our 4-year-old second case proved normal. One caveat is that the retinal dystrophy may develop later, and regular ophthalmological examination is indicated in cases with JS. Isolated retinal dystrophy is dominantly inherited.

With the advances in molecular genetic studies, the genetic bases of JS and JSRD have been elucidated. According to the OMIM classification, to date there have been 20 genes linked to JS<sup>9</sup>. These are: *BTS1/INPP5E*, *JBTS2/TMEM216*, *JBTS3/AHI1*, *JBTS4/NPHP1*, *JBTS5/CEP290*, *JBTS6/TMEM67*, *JBTS7/RPGRIP1L*, *JBTS8/ARL13B*, *JBTS9/CC2D2A*, *JBTS10/OFD1*, *JBTS11/TTC21B*, *JBTS12/KIF7*, *JBTS13/TCTN1*, *JBTS14/TMEM237*, *JBTS15/CEP41*, *JBTS16/TMEM138*, *JBTS17/C5orf42*, *JBTS18/TCTN3*, *JBTS19/ZNF423*, *TCTN2*, and *JBTS20/TMEM231*.

The mutations of the *CEP290* gene<sup>10</sup> on chromosome 12q21.32 cause nephronophthisis-associated ciliopathies. The mutations of this gene are basically seen in 10% of JSRD cases and are associated with retinal dystrophy or congenital blindness and with renal disorders in some families [11]. In our first case a c.5668G>T (p.G1890\*) homozygous stop mutation was found within the *CEP290* gene. The same mutation was reported earlier by Valente et al.<sup>12</sup> in two adolescent siblings from Turkey with Joubert syndrome and nephronophthisis; however, no details about the severity of renal insufficiency were given. Sayer et al.<sup>13</sup> reported two families from Turkey, each with two affected children due to the p.G1890\* mutation, with onset of ESRD

between 11 and 13 years of age. Remarkably, one infant had reduced renal function at 2 months of age, confirming our observation that ESRD may develop much earlier. It may well be that the c.5668G>T mutation is a founder mutation in the Turkish population; however, further haplotyping of these cases would be required to prove this. Interestingly, two cases from the Emirates were reported to have the same homozygous mutation, but apparently one case had a normal kidney ultrasound while the other had nephronophthisis<sup>12</sup>.

*JTBS1/INNP5E* is located on chromosome 9q34.3 and has been found to be responsible for 2.7% of the mutations among JSRD cases<sup>14</sup>. In our second case, a c.1303C>G (p.R435G) mutation of the *INPP5E* gene was found to be homozygous. Remarkably, renal involvement seems to be rare in *INPP5E*-related ciliopathy, as indicated by a large recent study where there were 12 different mutations in 17 patients with JSRD (from 11 families), but none of the patients had kidney, liver or skeletal involvement<sup>14</sup>. But as ESRD can be life limiting, regular monitoring of renal function is essential, as the case reported here proves that *INPP5E* mutations may indeed cause renal failure.

In conclusion, although JSRD can be diagnosed on the basis of clinical and radiological findings, molecular genetic studies should also be done for differential diagnosis. During the follow-up of JSRD patients, detailed kidney evaluation should also be performed, and these patients should be closely monitored from infancy for signs of end-stage chronic disease.

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