

Joubert Syndrome Caused By Novel Mutation in ARMC9 with a Unique Ocular Finding: Case Report & Literature Review

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ABSTRACT

Joubert Syndrome is autosomal- recessive disorder affecting the development and maturation of cerebellar vermis and some parts of the brain stem. The diagnosis is usually based on clinical, imaging and genetic testing. JS has diagnostic clinical features and they are (developmental delay, ataxia and hypotonia). In our patient, patient has a global developmental delay and ataxia which meets 2 of the diagnostic clinical features as well as the Molar tooth appearance on MRI. Furthermore, the patient has a unique presentation with asymmetric static ptosis. Genetically, he has a homozygous variant in ARMC9 gene which has been recently described as a causative gene for JS. Asymmetrical ptosis seems to be a good clinical clue in cases of joubert syndrome secondary to mutations in ARMC9 gene

Key words: Joubert Syndrome, ARMC9 Gene, Ptosis.

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INTRODUCTION

Joubert Syndrome (JS) was first described in 1969 by Dr. Marie Joubert et al. The patients she described were siblings from a large consanguineous French-Canadian family. JS has unique clinical and MRI features. Joubert Syndrome is autosomal-recessive disorder affecting the development and maturation of cerebellar vermis and some parts of the brain stem. Brain imaging (CT or MRI) shows the characteristic “molar tooth sign”. Many case series were published highlighting the variable manifestations and genetics of this disorder.¹⁻⁴ In this report, we present a Saudi Arabian family with JS, having a novel mutation in ARMC9 gene and with a unique clinical presentation of unilateral static ptosis.

CASE REPORT

The patient was a 3 -year old boy, initially seen with developmental delay. There was a similarly affected sister aged 1 year. He was born through elective cesarean section due to premature rupture of membrane at 35 weeks gestation. No significant perinatal problems were reported. At the age of 3 months, the mother noticed asymmetry of the upper eye lids with ptosis on the right. Developmentally, he started to sit and rollover at age 18 months. He walked after the age of 2 years. Once he started walking, the mother noticed ataxic gait with frequent falls. At 3, he could use spoon and cup with difficulty due to coordination. He was described as hyperactive boy. His language

was delayed. At age 3, he was saying only single words but no sentences. He obeyed simple commands. His hearing was normal. He was noted to have ptosis on right eye more obvious upon waking up. Parents are second- degree cousins.

On examination at age 3, Head circumference was 52 cm on the 95th percentile. He was hyperactive. He had right eye fixed, non-fatigable ptosis [figure 1]. Extraocular movements were intact. No facial asymmetry. The tongue and uvula were midlines. Muscle tone, power and reflexes were normal. Plantars were down going bilaterally. He had dysmetria of bilateral upper limbs and ataxic, wide-based gait. The back exam was normal. General examination was otherwise normal.

CBC, renal, bone and hepatic profiles were unremarkable.

Brain imaging (MRI) showed characteristic molar tooth sign of Joubert syndrome (figure 2).

At age 5, his motor skills slowly improved but his ptosis was the same. It was not affecting vision and therefore no surgical repair was attempted.

Genetic testing:

Whole exome testing showed a novel homozygous variant of ARMC9 (ARMC9: NM_001291656:exon17:c.1559C>T:p.P520L). The affected sister was homozygous and both parents were heterozygous for the same mutation. The above variant scored PM2 (absent from >7,000 Saudi controls) and PP3 (predicted to be pathogenic by SIFT, PolyPhen and CADD).



Fig 1: Showing asymmetric ptosis worse on right side

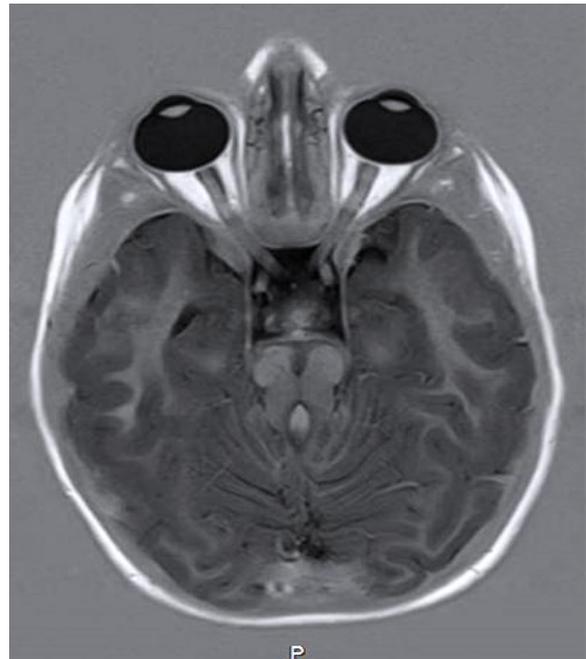


Fig 2: (MRI) of brain showing mild superior vermis/ cerebellum atrophy “molar tooth sign”.

Table 1: Clinical features of JS

Clinical features of Joubert Syndrome	
CNS manifestations	Ptosis, Ataxia, Epilepsy, Autism, Language and speech delay, Motor skills delay Congenital
Eye abnormalities	Oculomotor apraxia, Retinal dystrophy, Coloboma, Nystagmus, Strabismus
Renal manifestations	Renal cyst, Nephrolithiasis, Chronic renal disease
Hepatic manifestations	hepatic fibrosis
Respiratory manifestations	Sleep apnea, Hyperpnea
Facial dysmorphism	Low set ear, Broad nasal bridge, Rounded eyebrows
Skeletal abnormalities	Scoliosis

DISCUSSION

Joubert syndrome is a rare disorder worldwide. It's estimated incidence is 1:80.000 live births [9] The diagnosis is usually based on clinical and imaging criteria.^{2,5} The most common features in Joubert syndrome are developmental delay, ataxia and hypotonia.¹⁻⁹ Table 1 summarizes the clinical features of JS. However the genetic causes of JS continue to expand, with no clear genotype-phenotype correlation that may guide genetic testing. In our case, the patient has a global developmental delay and ataxia which meets 2 of the diagnostic clinical features as well as the Molar tooth appearance on MRI. Furthermore, the patient has a unique presentation with asymmetric static ptosis. (Fig 2) Genetically, he has a homozygous variant in ARMC9 gene which has been recently described as a causative gene for JS.^{10,11} The ptosis seems a consistent finding in most of the reported cases of ARMC9 associated JS.¹¹ This is an important clue for the clinician to pursue direct gene sequencing. It's notable also that our patient and the reported cases did not manifest so far renal disease.

CONCLUSION

Asymmetrical ptosis seems to be a good clinical clue in cases of Joubert syndrome secondary to mutations in ARMC9 gene. Based on our literature review this finding seems to be consistence in most reported cases so far.

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