



## EXCEPTIONAL CASE

## Joubert syndrome diagnosed renally late

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### ABSTRACT

Joubert syndrome is a genetically heterogeneous multisystem disorder typically diagnosed in childhood. Nephronophthisis is the most common renal pathology in Joubert syndrome, and renal failure usually occurs in childhood or in young adults. We report a 61-year-old female diagnosed with *AHI1*-related oculorenal Joubert syndrome, who presented initially with decline in renal function in her 50s. Our report describes exceptionally late presentation of renal disease in Joubert syndrome and highlights the importance of continued renal function monitoring in older adults with Joubert syndrome.

**Keywords:** *AHI1* mutation, CKD, Joubert syndrome, molar tooth sign, nephronophthisis, prognosis, retinal dystrophy

### BACKGROUND

Diagnosis of Joubert syndrome is usually made in childhood at a mean age of 33 months [1]. The major features of this rare congenital disorder are developmental delay, intellectual impairment and infantile hypotonia that may progress to ataxia; the ‘molar tooth sign’, a characteristic appearance of the brainstem in axial plane on magnetic resonance imaging (MRI), is highly specific to this condition. Other early features include irregular breathing patterns in infancy, nystagmus and oculomotor apraxia, and early-onset retinal dystrophy. Patients may have additional features involving the liver, kidneys and/or skeletal malformations. Kidney involvement typically leads to end-stage renal disease (ESRD) in childhood or in young adults.

We present a 61-year-old female who received a diagnosis of Joubert syndrome with oculorenal disease at the age of 57 years. Decline in renal function, due to nephronophthisis, was initially noted at the age of 51 years.

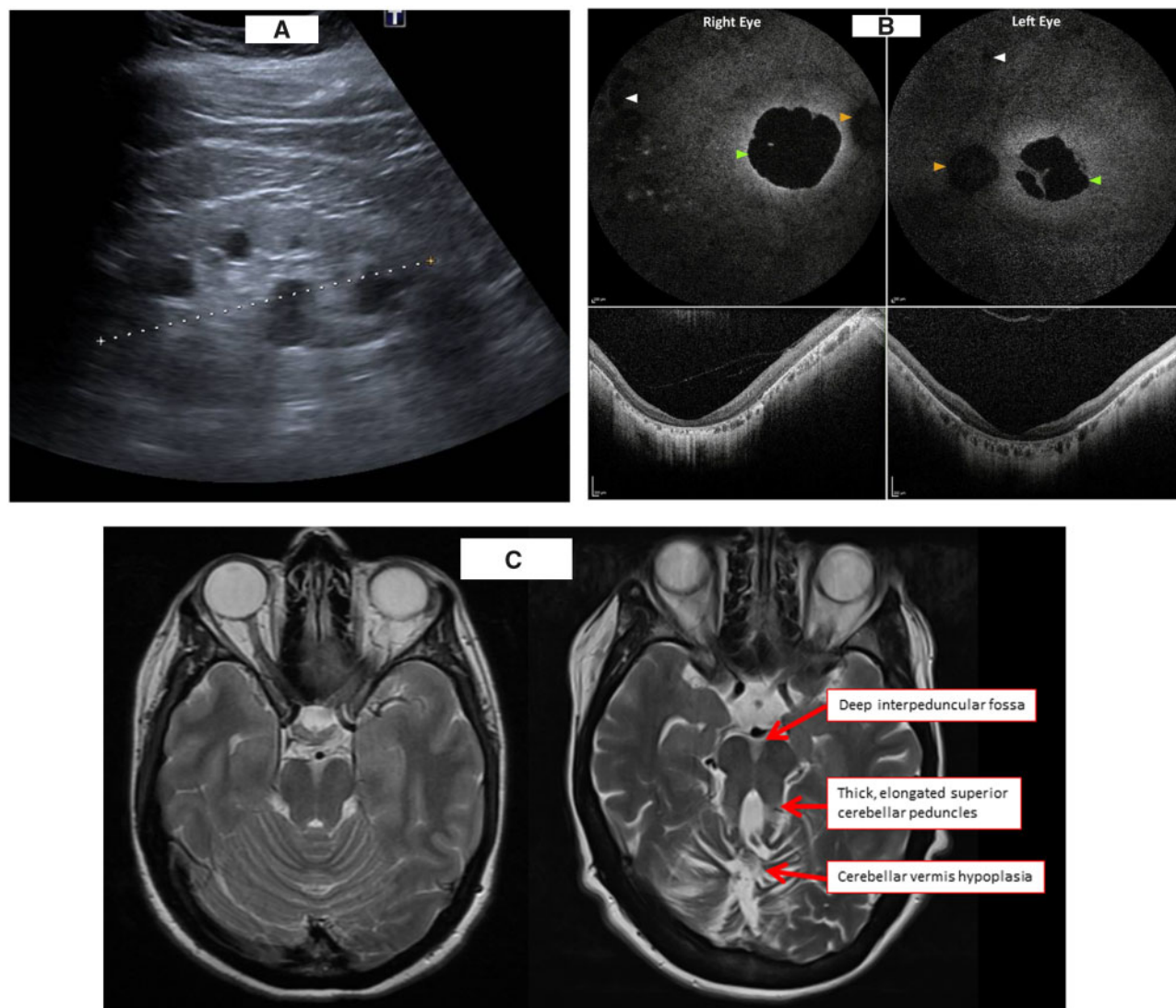
### CASE REPORT

The patient was initially seen in the nephrology clinic at the age of 56 years after her general practitioner had noted progressive decline in estimated glomerular filtration rate (eGFR) over the previous 5 years. Prior to this, she had been treated for essential hypertension from her early 40s with bendroflumethiazide and nifedipine. Her eGFR at the age of 51 years was 57 mL/min/1.73 m<sup>2</sup> [serum (S) creatinine 91 µmol/L] by Modification of Diet in Renal Disease study equation. This had steadily declined to 24 mL/min/1.73 m<sup>2</sup> (S creatinine 189 µmol/L) at first nephrology assessment. She had never smoked and her BMI at the age of 56 years was 30.8 kg/m<sup>2</sup> (height 1.58 m, weight 76.8 kg), and urine protein–creatinine ratio was 67 mg/mmol. Review of previous records showed normal kidney function at the age of 34 and 41 years (S creatinine 73 and 84 µmol/L, respectively). After initial nephrology assessment, the clinical diagnosis was chronic kidney disease of uncertain cause. Further details

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**FIGURE 1:** (A) Image from ultrasound performed at the age of 56 years showing abnormal echogenicity and cysts in left kidney. (B) Detailed retinal imaging of the patient at 56 years of age illustrating the generalized retinal degeneration. Visual acuity was 6/60 in both eyes. Top row: imaging identified bilateral multiple areas of retinal atrophy at the macula (green arrow heads), around the optic nerve (orange arrow heads) and mid-peripheral retina (white arrow heads). Bottom row: cross-sectional imaging identified the prominent widespread outer retinal atrophy, with profound macular thinning and posterior bowing (staphylomata) in both eyes. (C) Axial T2 image from patient's MRI brain scan at the age of 58 years showing components of the molar tooth sign. Image in the same plane from a normal individual is shown on the left for comparison.

of clinical course are available in [Supplementary data, Table S1](#). Her first ultrasound at the age of 56 years showed increased echogenicity of the kidneys, loss of corticomedullary differentiation and multiple, bilateral small cortical cysts ([Figure 1A](#)), consistent, in hindsight, with nephronophthisis. Renal lengths were 11.1 cm (left) and 9.1 cm (right). She had a history of moderate learning difficulties and retinal dystrophy, but these were initially thought to be unrelated to the kidney disease.

Her parents had noted a shallow and fast breathing pattern in early infancy, but no episodes of apnoea, and this was not investigated further. Nystagmus was also noted in infancy, but cerebral palsy was thought to be the cause of her failure to meet early developmental milestones. She made slow progress at a special needs school. There were no further medical problems in childhood, but visual impairment was identified in her late 20s and a diagnosis of retinal dystrophy (rod-cone dystrophy) was made at the age of 32 years. She had surgery for bilateral

cataracts in her 40s. Images from recent ophthalmology assessment are shown in [Figure 1B](#).

A retinal dystrophy gene panel test was requested when she was 57 years, and identified compound heterozygous loss-of-function variants in *AHI1* c.703dupA, p.(Arg235LysfsTer12) and c.2212C>T, p.(Arg738Ter). An MRI brain scan performed soon afterwards showed the classical molar tooth sign ([Figure 1C](#)), confirming a diagnosis of Joubert syndrome. She commenced hospital haemodialysis at the age of 58 years when her S creatinine had reached 490  $\mu\text{mol/L}$  and is awaiting a renal transplant.

## DISCUSSION

The prevalence of Joubert syndrome is between 1:80 000 and 1:100 000. The genetic basis is heterogeneous, with >35 known genes, nearly all inherited in an autosomal recessive manner. Variants in *AHI1* account for ~7% of Joubert syndrome cases

and are associated either with 'pure' Joubert syndrome, or Joubert syndrome plus renal and/or retinal disease [2].

In a large prospective study, renal disease occurred in 30% (29/97) of patients with Joubert syndrome of diverse genetic aetiology and manifested as: (i) nephronophthisis; (ii) an overlapping phenotype of autosomal recessive polycystic kidney disease/nephronophthisis; (iii) unilateral multicystic dysplastic kidney; and (iv) indeterminate-type cystic kidney disease [3]. Thirteen of these 29 patients with renal involvement progressed to ESRD at a median age of 11.3 years. Nephronophthisis due to disease-causing *AHI1* variants has a slightly later age at ESRD (teens or 20s) than other genetic causes of juvenile nephronophthisis [4, 5]. Presentation with nephronophthisis, from any cause, at the age of 51 years is highly unusual. This case also extends the retinal phenotype associated with Joubert syndrome, as typically the retinal dystrophy is evident from birth/early infancy.

Most *AHI1* variants cause protein truncation, leading to loss of protein function, and cluster in exons 6–19 [3–5]. Our patient had later than usual onset of both retinal and renal disease despite two truncating variants, which adds further support to the lack of predictive genotype–phenotype correlations for *AHI1*-associated disease.

Joubert syndrome should be considered in anyone with a neurodevelopmental disorder associated with unexplained renal disease and/or retinal dystrophy. Increasing availability of large genetic testing panels and, more recently, whole exome and genome sequencing means that the genetic heterogeneity (or atypical presentation) of Joubert syndrome is no longer a barrier in establishing a precise molecular diagnosis.

Importantly, patients with a diagnosis of Joubert syndrome should have lifelong renal function monitoring, as renal impairment can develop in older adults.

## PATIENT CONSENT

The patient gave informed consent for the publication of this case.

## SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST STATEMENT

None declared. We declare that the results presented in this article have not been published previously in whole or part, except in abstract format.

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