CASE REPORT

An elusive ciliopathy: Joubert syndrome

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SUMMARY

The police brought a 65-year-old female patient to the EADU after being found 'roaming the streets' in an apparent state of confusion. This was her third admission under the same circumstances during the last 3 years. Neurological examination revealed (1) cognitive impairment, (2) oculomotor apraxia, (3) abnormal cancellation of vestibular ocular reflex, (4) mild ataxia and (5) mild hypotonia. Renal function was abnormal and liver function was normal. No retinal disturbance was found. The head CT on admission was normal for stroke and the lumbar puncture was negative for encephalitis. Her brain MRI showed 'molar tooth sign', suggestive of Joubert syndrome, which was confirmed by genetic testing showing anomalous *NPHP1* gene

caravan house, apparently because 'she lost her keys to her house'. In the AE, her blood investigations revealed: white cell count $16 \times 10^9/L$, haemoglobin 110 g/L, platelets $335 \times 10^9/L$, random glucose 6.7 mmol/L, bilirubin $47 \mu\text{mol/L}$ (0–22 $\mu\text{mol/L}$), alkaline phosphatase 85 U/L, alanine transaminase 9 U/L, total protein 66, albumin 32 g/L, globulins 34 g/L, calcium 2.3 mmol/L, sodium 147 mmol/L, potassium 3.8 mmol/L, urea 9.5 mmol/L (1.7–7.1 mmol/L) and creatinine $106 \mu\text{mol/L}$ (45–84 $\mu\text{mol/L}$). Going back 3 years, her renal function was noted to be consistently abnormal: urea ranging from 8.8 to 9.3 mmol/L and a creatinine from 96 to 100 $\mu\text{mol/L}$. A head CT scan did not show any signs of ischaemia, oedema or haemorrhage; however, it revealed bilateral superior cerebellar peduncle elongation (figure 1). This prompted a review of an MRI done in 2013, during her first admission, which had been reported simply as 'cerebellar atrophy'. Interestingly, on the axial image (figures 2 and 3) it showed bilateral cerebellar peduncle elongation, a deep interpeduncular fossa and a severe hypoplasia of the cerebellar vermis (molar tooth sign); the vermian hypoplasia is more evident on the coronal view (figure 4). On the sagittal view (figure 5), it showed an abnormally displaced fourth ventricle and a severely hypoplastic cerebellar vermis. These findings led to a radiological diagnosis of Joubert syndrome.

On examination, her general physical appearance gave the impression of chronic self-neglect (facial hair, overweight, long fingernails, lack of most dentures and so on). She had signs of peripheral vascular disease, chronic cellulitis in both lower limbs, ankle varicose veins and multiple small haematomas in both forearms. Her body mass index was 35, blood pressure 150/90 mm Hg, RR 19, pulse 89 and temperature of 37 degrees. Heart auscultation revealed a mild aortic systolic murmur (2/5) with no diastolic friction rub and no jugular vein distension; on lung auscultation, there was bilateral, lower lobe crepitus and upper lobe expiratory wheezing. Abdominal examination was normal (no hepatomegaly or splenomegaly, no pain or ascites). A CT scan of chest–abdomen–pelvis showed small cystic-like lesions in the right hepatic lobe (figures 6 and 7).

She was able to understand simple, straightforward ideas and questions, however, more complex situations became immediately more difficult for her. If the required task was too complex, she would remain silent, yet not distraught. Although she appeared apathetic and disengaged with her surroundings, she was able to respond—although very slowly—to verbal and non-verbal prompts

BACKGROUND

1. This is an atypical presentation of a very rare disease.
2. Joubert syndrome is usually diagnosed in childhood; however, in this case, the patient was 65 years old, living independently, without any obvious cerebellar dysfunction (it only becomes obvious on a detailed physical examination).
3. Despite being 65 years old, with the new diagnosis, she has been able to access high-quality social care, appropriate multidisciplinary follow-ups (ophthalmology, neurology, nephrology, gastroenterology, psychology and psychiatry) and we will be able to improve her comorbidities as best as possible (and reduce readmissions).

CASE PRESENTATION

Previous to her most recent admission, this 65-year-old female patient had been found wandering on the street twice (once in 2013 and then, 1 month before her last admission, in September 2016). She was confused and agitated, and was brought to the Accident and Emergency department (AE) for admission. She was discharged on the first occasion with a diagnosis of 'viral encephalitis on a background of learning difficulties'; however, there was no cerebrospinal fluid abnormality. On the second admission, she was discharged with a diagnosis of 'heat exhaustion and learning difficulties', treated with thiamine 100 mg once a day, risperidone 1 mg once a day, citalopram 10 mg once a day and ceterizine 10 mg once a day and referred to a local mental health hospital for further management.

On her third (present) admission, she was found by the police once again 10 miles away from her

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Figure 1 CT head: bilateral superior cerebellar peduncle elongation.

and stimuli. There was a lack in blink frequency resulting in a sustained—non-intentional—gaze, associated with exophthalmos. Neurologically, her strength was mildly hypotonic in all four limbs; all sensory modalities (pinprick, light/crude touch, proprioception, vibration, temperature and pain) were preserved in all four limbs, as in the face and thorax. No cranial nerve dysfunction was elicited. Both patellar reflexes were brisk (+++/++), ankle reflexes were absent and no Babinski or Hoffman sign could be elicited. Upper limb reflexes were normal (++/++) and no frontal-lobe or lower brainstem reflexes were elicited. Cerebellar evaluation revealed a very subtle upper and lower limb dysmetria, predominantly on the right side and also, marked adiadocokinesia of the left hand. There was left-hand and right-hand apraxia for fine-motor movements. She presented a wide-based gait without lateropulsion and a negative Romberg test. Ophthalmological examination revealed normal retina and nerves (figure 8), although vision slightly reduced at 6/12 in each eye corrected. Eye movements were abnormal with hypometric saccades and a tendency to head thrust to initiate saccades (oculomotor apraxia). She also presented abnormal cancellation of vestibulo-ocular reflex (VOR).

Following these findings, with permission of the patient, we requested genetic testing to confirm the clinical and radiological diagnosis. Genetic testing demonstrated NPHP1 mutation which fell within the previously described subtypes.

Figure 2 MRI axial: bilateral cerebellar peduncle elongation, a deep interpeduncular fossa and a severe hypoplasia of the cerebellar vermis (molar tooth sign).

Figure 3 Deep interpeduncular fossa.

INVESTIGATIONS

1. MRI scan.
2. Blood investigations (including antinuclear antibodies, anti-cytoplasmic neutrophil antibodies, erythrocyte sedimentation rate, C reactive protein, protein electrophoresis, Ca, P, K, Na).
3. Ophthalmology evaluation in clinic.
4. Genetic testing.

DIFFERENTIAL DIAGNOSIS

1. Joubert syndrome-related disorders
2. Dandy-Walker malformation
3. Cerebellar vermian hypoplasia
4. Oligophrenia
5. Congenital ataxia
6. Arima syndrome
7. Leber's congenital amaurosis

TREATMENT

There is no curative treatment for this condition, only supportive measures. For the patient, her management consisted in secondary prevention of renal, liver and ocular morbidity and making sure that her living conditions do not impair her current medical state.

Figure 4 Coronal view: the vermian hypoplasia is more evident on the coronal view.

Figure 5 Sagittal view: it showed an abnormally displaced fourth ventricle and a severely hypoplastic cerebellar vermis.

OUTCOME AND FOLLOW-UP

The patient has been on follow-up in clinic and has remained medically stable. Her social condition and overall well-being has greatly improved.

DISCUSSION

The diagnosis of Joubert syndrome is mainly based on radiological evidence and genetic confirmation.¹ Clinically, it can present with a wide spectrum of manifestations, none of which are pathognomonic. Usually, the first suspicion arises at birth or during the initial stages of childhood.^{2–4} In this case, however, we describe a patient who is 65 years of age and whose symptoms were so subtle that she managed to go undiagnosed until the later stages of her life. The key for diagnosing her was the brain MRI, which revealed a characteristic ‘molar tooth sign’ which results from the combination of:

1. Deeper-than-normal posterior interpeduncular fossa at the level of the isthmus and upper pons.
2. Prominent superior cerebellar peduncles.
3. Vermian hypoplasia or dysplasia.

Other radiological signs were also evident in this patient and aided in the diagnosis. These were more easily visualised on the coronal and sagittal imaging: (1) abnormally shaped (and rostrally displaced) fourth ventricle and (2) mild clefting of the vermis.

Figure 6 CT scan of chest–abdomen–pelvis showed small cystic-like lesions in the right hepatic lobe.

Figure 7 Small cystic lesions in liver.

The authors found that her radiological manifestations were more revealing than her clinical presentation. Having lived 65 years ‘independently’ (or with minimal assistance), this implied that her cognitive impairment was not severe and that her overall mobility was not greatly impaired. The typical findings—usually detected at birth and early childhood—of episodic hyperpnoea, ataxia, mental retardation and abnormal eye movements were only mildly manifested. She had no breathing difficulties, her gait was wide-based but no overt-limiting ataxia was noted (she was able to walk unassisted, although slowly), her cognitive capacities were limited (yet not disabling) and her eye movements were clearly abnormal. It was the latter which proved to be one of the most helpful clinical aids in her diagnosis; she presented with: (1) oculomotor apraxia (OMA), with hypometric saccades, (2) abnormal cancellation of the VOR and (3) horizontal nystagmus.^{8,9} No intraocular abnormalities were noted on examination. These neuro-ophthalmological manifestations are directly linked to the hypoplastic cerebellar vermis and the elongated superior cerebellar peduncles visualised on the MRI.

Her cognition was impaired, mainly for executive functions and complex, multitask commands. However, she was able to carry out simple, linear thought processes. The full breadth of her memory was difficult to assess; however, she was able to provide excellent recall for recent events, dates and people and she was

Figure 8 Ophthalmologic examination revealed normal retina and nerves.

Table 1 Comparative table representing the six different subtypes of Joubert-related syndromes

	'Classical' Joubert syndrome ¹⁰
	1. Molar tooth sign
	2. Intellectual impairment/developmental delay of variable degree
	3. Hypotonia in infancy
	4. One or both of the following (not required but helpful): irregular breathing in infancy and/or abnormal eye movements (nystagmus and/or ocular motor apraxia)
Type 1	
Type 2	Joubert syndrome + retinopathy ¹¹
Type 3	Joubert syndrome + renal disease ¹²
Type 4	CORS or Senior-Loken syndrome ¹³
Type 5	COACH ¹⁴
Type 6	Oral-facial-digital syndrome VI ^{15 16}

COACH, oloboma, oligophrenia, ataxia, cerebellar hypoplasia and hepatic fibrosis; CORS, cerebello-oculo-renal syndrome.

also capable of remembering long-term events. She was also able to copy simple geometric forms and to complete a dotted-line examination.

We also investigated for other potential multisystem manifestations, yet found none. After performing a CT scan of her chest, abdomen and pelvis, we found the following:

1. Renal system was intact (no signs of cystic dysplasia or nephronophthisis). No findings suggestive of Dekaban-Arima syndrome were found either.
2. Liver had small cysts; however, these were not of clinical relevance. No dilation of intra or extra hepatic ducts was noted. No hepatic fibrosis was noted either, ruling out COACH syndrome (coloboma, oligophrenia/developmental delay, ataxia, cerebellar vermis hypoplasia and hepatic fibrosis).
3. No small or large bowel abnormality was noted.
4. Lungs were greatly intact, no major finding was noted.

Furthermore, we did not find skeletal defects (such as polydactyl, epiphyseal defects, and so on) or endocrinology problems. Of the six phenotypic subtypes that have been described, from a clinical and radiological point of view (confirmed genetically), we ruled out all but type 1, that is pure Joubert syndrome. Table 1 has a summary of the six phenotypes.

The clinical and radiological diagnosis was further confirmed by genetic testing. The authors also debated on why exactly there was such variability between the manifest radiological findings and the subtle clinical presentation. The phenotypic variability is due to mainly two factors: (1) genetic heterogeneity (with >20 genes to date implicated) and (2) pleiotropic nature of the implicated genes. In the case of the latter, one particular gene can cause a multitude of symptoms and even syndromes.

Contributors All authors contributed to this case. The assessment in clinic was done by all three in different times and we then gathered in five occasions to discuss our findings and write down our interpretation of our ideas. The conception of the design was done during these meetings and the overall interpretation of laboratory data and clinical findings was done by CC and BB with the assistance of the trainee AM. All three authors obtained different reference articles and research papers regarding the patient independently and then gathered to discuss and contrast the content of each article. CC followed up the patient in neurology clinic and BB followed up the patient in ophthalmology.

Learning points

- If Molar tooth sign is seen on the MRI or CT scan, Joubert syndrome (and related disorders) must be considered. It is highly suggestive of such diagnoses.
- A full and detailed physical examination in such cases is very important in order to assure a clinical-radiological correlation, as best as possible.
- Joubert syndrome is the result of brainstem and cerebellar malformations, manifesting clinically as: hypotonia, ataxia, oculomotor apraxia and ataxia.
- There are >20 implicated genes and 6 clinical phenotypes in Joubert syndrome (and Joubert syndrome-related disorders).
- The molar tooth sign is very suggestive of Joubert syndrome, however, it may also be found in other conditions such as Dandy-Walker malformation.

Competing interests None declared.

Patient consent Obtained.

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