

CME Article

Clinics in diagnostic imaging (118)

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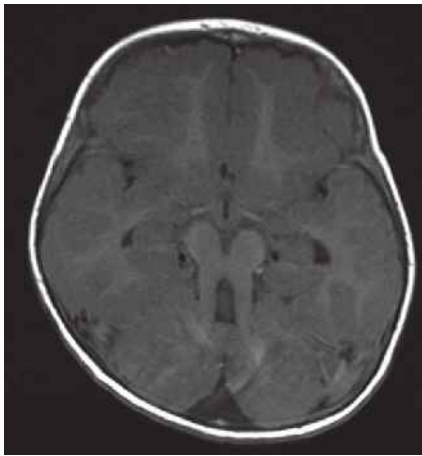


Fig. 1 Axial T1-W image of the brain taken at the level of the cerebellar peduncle.

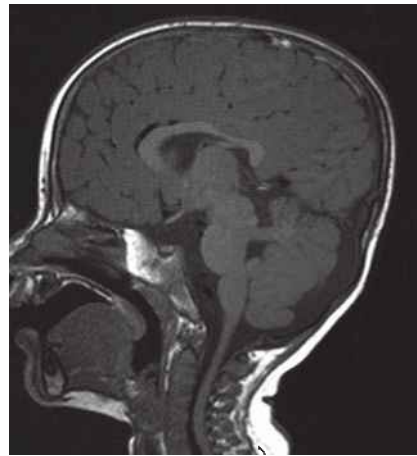


Fig. 2 Parasagittal T1-W image of the brain.



Fig. 3 Mid-sagittal T1-W image of the brain.

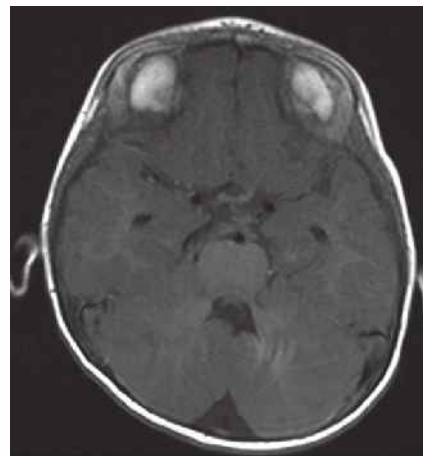


Fig. 4 Axial T1-W axial image taken at the level of the fourth ventricle.

CASE PRESENTATION

An 18-month-old boy presented to the paediatric outpatient clinic with delayed milestones and a recent episode of seizure. There was no history of birth asphyxia. On examination, the child had strabismus in his right eye. The head circumference was normal. The muscle tone

was reduced. There was delay in speech and language development; however, the child could localise auditory stimuli. He could stand with support but he had difficulty in walking. Magnetic resonance (MR) imaging of brain was done (Figs. 1–4). What is your diagnosis?

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IMAGE INTERPRETATION

Axial MR image revealed the molar tooth sign (Fig. 1) due to an abnormally-oriented and thickened superior cerebellar peduncle. Sagittal MR image showed a thickened cerebellar peduncle lying perpendicular to the brain stem (Fig. 2). MR image also showed thinning of isthmus with a widened interpeduncular cistern (Fig. 3) and hypoplastic cerebellar vermis. The fourth ventricle was enlarged with a bat-wing configuration on the axial MR image (Fig. 4). The posterior fossa was mildly enlarged. The clinical and MR imaging features were diagnostic of Joubert syndrome.

DIAGNOSIS

Joubert syndrome

CLINICAL COURSE

The child was started on physiotherapy for the strengthening of his muscles. Antiepileptic drugs were prescribed. Renal function tests and renal ultrasonography are being performed at regular intervals as these patients may have cysts in the kidneys and suffer from poor renal function. Routine ocular examination has also been advised because retinal dystrophy may be associated with this syndrome. The prognosis has been explained to the parents. The risk of recurrence and the need for prenatal counselling in future pregnancies were also explained.

DISCUSSION

Marie Joubert, a French neurologist, first reported this syndrome in five children who had episodes of abnormal breathing and eye movements, ataxia, mental retardation in association with vermian agenesis.⁽¹⁾ This syndrome is an autosomal recessive disorder, with characteristic abnormalities in the cerebellar vermis and pontomesencephalic junction.⁽¹⁾ Affected children have facial dysmorphism with mild epicanthus, high rounded eyebrows, broad nasal bridge, low set ears and triangular-shaped open mouth. They have developmental delay and decreased muscle tone. Other associated features are coloboma of retina and retinal dystrophy in 50%, renal cystic disease in 30% and polydactyly in 15% of the patients.⁽²⁾ Presence of retinal dystrophy in these patients is associated with increased prevalence of multicystic kidney disease and they have decreased survival rates.⁽³⁾ The molecular and biochemical abnormalities in these patients have not been established and no specific chromosomal locus has been identified.⁽⁴⁾

Maria et al proposed revised diagnostic criteria for the diagnosis of Joubert syndrome.⁽⁵⁾ These include hypotonia, ataxia, global developmental delay and molar tooth sign on imaging. Other associated abnormalities which have been included in their diagnostic criteria are facial dysmorphism, breathing abnormalities, ocular

abnormalities (such as retinal dysplasia, coloboma, nystagmus, strabismus and ptosis), oculomotor apraxia and renal microcystic disease. Seizure is not a part of this syndrome, though it was seen in the present patient. Pathological studies in these patients have shown abnormalities in the cerebellar vermis and pontomesencephalic junction.⁽⁶⁾ The cerebellar vermis is hypoplastic and the dentate nucleus is fragmented. The pontomesencephalic junction is dysplastic, with abnormal decussation of the superior cerebellar peduncle and elongation of rostral fourth ventricle. There is a reduction in neurons of the basis pontis and reticular formation. In the medulla, the inferior olivary nucleus, tractus solitarius, the nucleus and spinal tracts of trigeminal nerves are hypoplastic. The posterior median sulcus and pyramidal decussation are absent. In addition, there is neuronal swelling seen in the nucleus gracilis and cuneatus.

Quisling et al studied the MR imaging features in 44 patients with Joubert syndrome.⁽⁷⁾ They reported various morphological abnormalities in the isthmus and rostral brain stem. The characteristic MR imaging features seen in these patients were: (1) thinning of the isthmus with widened interpeduncular fossa; (2) thickened superior cerebellar peduncles lying perpendicular to the dorsal pons; (3) hypoplasia of the vermis with enlargement of the fourth ventricle and rostral shift of the fastigium; and (4) sagittal vermian cleft due to incomplete fusion of the two halves of vermis. These patients had normal cerebellar hemisphere volume suggesting a normal neocerebellar formation. The characteristic MR imaging findings were present in 35 patients in their study. In the other nine patients, there was either tecto-cerebellar dysplasia or the Dandy-Walker malformation, in addition to the characteristic MR imaging features of Joubert syndrome. They classified these patients as having the Joubert plus syndrome.

Supratentorial abnormalities were uncommon and two-thirds of the patients in their study had normal cerebral hemispheres. Prominent subarachnoid spaces and ventriculomegaly were seen in one third of patients. Delayed myelination was noted in ten patients. The molar tooth sign is seen on the axial MR images, due to thickened and abnormally-oriented superior cerebellar peduncles, isthmus dysgenesis and vermian hypoplasia. It was first described by Maria et al.⁽⁸⁾ This sign is not specific for Joubert syndrome. It may be seen in other syndromes, such as the Dekaban-Arima, Senior-Loken, COACH, Varadi-Papp, Joubert with polymicrogyria, and Malta syndromes.⁽⁹⁾ Although the molar tooth sign and other key clinical features of the Joubert syndrome, such as neonatal respiratory abnormality, hypotonia, developmental delay, ataxia and ocular motor apraxia, may be seen in these syndromes, they usually have additional striking features.

The Dekaban Arima syndrome is associated Leber

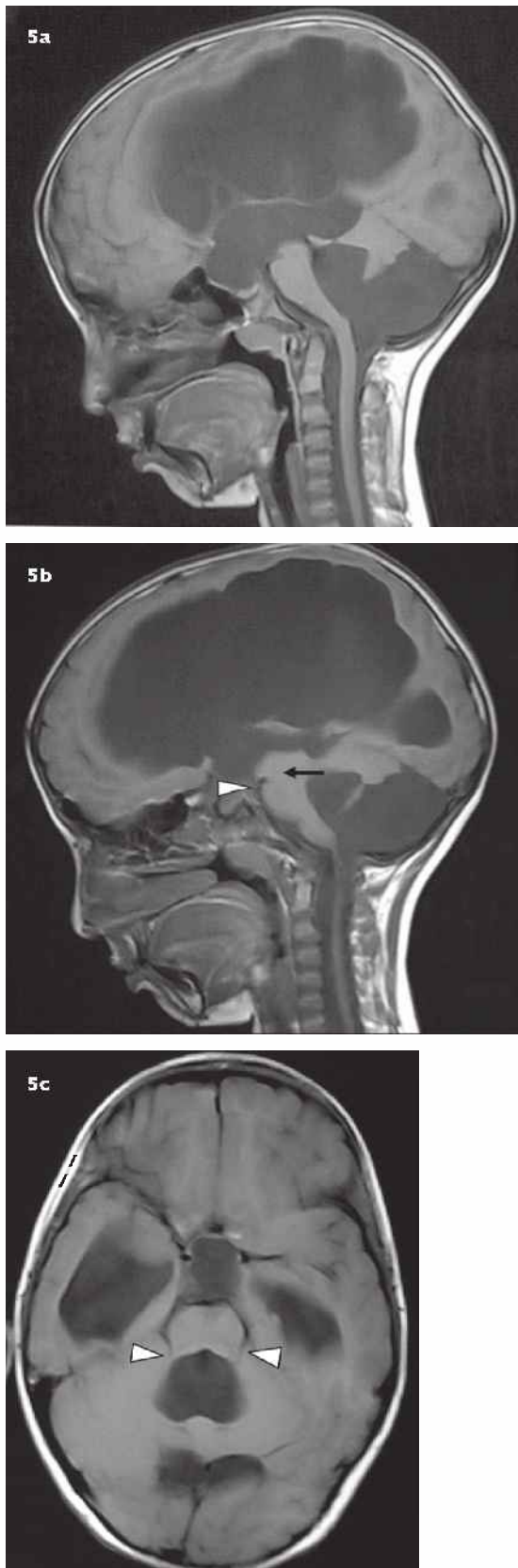


Fig. 5 Dandy-Walker malformation. MR imaging appearances. (a) The vermis is hypoplastic. However, the fourth ventricle is enlarged and communicates with a cyst in the posterior fossa. In addition, there is hydrocephalus. (b) The pontomesencephalic junction (arrow) and interpeduncular fossa (arrowhead) are normal. (c) The superior cerebellar peduncle is normal in thickness (arrowheads).

congenital amaurosis and cystic dysplastic kidneys,⁽⁹⁾ whereas the Senior-Loken syndrome is associated with Leber congenital amaurosis, retinitis pigmentosa and juvenile nephronophthisis. Patients with COACH syndrome have hepatic fibrosis, bilateral coloboma and renal calcification, and in the Varadi papp syndrome there is mesaxial polydactyly, Y-shaped metacarpal, cleft lip or cleft palate, lingual hamartomas and vermian hypoplasia.⁽⁹⁾ In the Malta syndrome, the affected patients have the molar tooth sign, occipital encephalocele, hydrocephalus, cortical renal cysts with or without coloboma, and Leber congenital amaurosis.⁽⁹⁾ Some patients may have features of Joubert syndrome and polymicrogyria. None of the additional features were seen in the present patient. Cerebellar vermian abnormality may be seen in other conditions such as the Dandy Walker malformation and rhombencephalosynapsis.⁽³⁾ In Dandy Walker malformation, the inferior part of the vermis is hypoplastic. However, the fourth ventricle is enlarged and communicates with a cyst in the posterior fossa (Fig. 5a). In addition, the pontomesencephalic junction, interpeduncular fossa (Fig. 5b) and superior cerebellar peduncle (Fig. 5c) are normal. In rhombencephalosynapsis, the cerebellar hemispheres are fused, whereas in Joubert syndrome, there is clefting of vermis.⁽³⁾

The prognosis of these patients is poor, with a five-year survival rate of only 50%.⁽²⁾ Renal and retinal dysfunction can be progressive. In patients with retinal anomalies, the renal function should be monitored regularly and ultrasonography should be done to detect cystic renal disease.⁽¹⁰⁾ Genetic counselling is required in these patients. As the recurrence rate is 25%, prenatal counselling and screening with ultrasonography are required. These patients are also sensitive to respiratory depressant effects of anaesthetic agents, like opiates and nitrous oxide.⁽¹¹⁾ Hence, the use of these anaesthetic agents should be avoided in these patients.

ABSTRACT

An 18-month-old boy presented with delayed milestones, hypotonia, strabismus and an episode of seizure. Magnetic resonance (MR) imaging of the brain revealed abnormally-oriented and thickened superior cerebellar peduncle, giving rise to the characteristic molar tooth sign on axial images. The isthmus was thinned out, with widened interpeduncular cistern and hypoplastic vermis. The clinical and MR imaging features were diagnostic of Joubert syndrome.

Keywords: congenital brain abnormalities, hypoplastic cerebellar vermis, Joubert

**syndrome, magnetic resonance imaging,
molar tooth sign**

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME
Multiple Choice Questions (Code SMJ 200709B)

	True	False
Question 1. Regarding the clinical features of Joubert Syndrome:		
(a) Affected children have breathing abnormalities, ataxia, mental retardation and oculomotor apraxia.	<input type="checkbox"/>	<input type="checkbox"/>
(b) It is an autosomal dominant disorder.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Retinal dystrophy and renal cystic disease may be seen in these patients.	<input type="checkbox"/>	<input type="checkbox"/>
(d) The specific chromosomal abnormality has been identified.	<input type="checkbox"/>	<input type="checkbox"/>
Question 2. Regarding the pathological findings in Joubert Syndrome:		
(a) The cerebellar vermis is hypoplastic and pontomesencephalic junction is abnormal.	<input type="checkbox"/>	<input type="checkbox"/>
(b) There is reduction in neurons of basis pontis and reticular formation.	<input type="checkbox"/>	<input type="checkbox"/>
(c) The superior cerebellar peduncle and fourth ventricle are normal.	<input type="checkbox"/>	<input type="checkbox"/>
(d) In the medulla, pyramidal decussation and posterior median sulcus are normal.	<input type="checkbox"/>	<input type="checkbox"/>
Question 3. Regarding the MR imaging findings in Joubert Syndrome:		
(a) Characteristic MR imaging findings are thinning of isthmus with widened interpeduncular fossa, thickened superior cerebellar peduncles, vermian hypoplasia, and vermian cleft.	<input type="checkbox"/>	<input type="checkbox"/>
(b) The cerebellar hemispheres are hypoplastic.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Supratentorial abnormalities are common.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Tectocerebellar dysplasia and Dandy walker malformation is seen in all patients.	<input type="checkbox"/>	<input type="checkbox"/>
Question 4. Regarding the molar tooth sign on MR imaging:		
(a) It is seen in coronal MR image due to thickened and abnormally oriented superior cerebellar peduncle, isthmus dysgenesis and vermian hypoplasia.	<input type="checkbox"/>	<input type="checkbox"/>
(b) It is specific for Joubert Syndrome.	<input type="checkbox"/>	<input type="checkbox"/>
(c) It is seen in COACH syndrome, which is associated with hepatic fibrosis, bilateral coloboma and renal calcification.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Occipital encephalocele, hydrocephalus, cortical renal cysts are seen in addition to this sign in Malta Syndrome.	<input type="checkbox"/>	<input type="checkbox"/>
Question 5. Regarding the clinical outcome of these patients:		
(a) These patients have good prognoses.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Renal and retinal dysfunction can be progressive.	<input type="checkbox"/>	<input type="checkbox"/>
(c) They are sensitive to respiratory depressant effect of anaesthetic agents, like opiates and nitrous oxide.	<input type="checkbox"/>	<input type="checkbox"/>
(d) In patients with retinal anomalies, the renal function should be monitored regularly and an ultrasonogram should be done to detect cystic renal disease.	<input type="checkbox"/>	<input type="checkbox"/>

Doctor's particulars:

Name in full: _____
MCR number: _____ Specialty: _____
Email address: _____

SUBMISSION INSTRUCTIONS:

(1) Log on at the SMJ website: www.sma.org.sg/cme/smj and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

RESULTS:

(1) Answers will be published in the SMJ November 2007 issue. (2) The MCR numbers of successful candidates will be posted online at www.sma.org.sg/cme/smj by 15 November 2007. (3) All online submissions will receive an automatic email acknowledgment. (4) Passing mark is 60%. No mark will be deducted for incorrect answers. (5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.

Deadline for submission: (September 2007 SMJ 3B CME programme): 12 noon, 25 October 2007