

Molar Tooth Sign of the Midbrain–Hindbrain Junction: Occurrence in Multiple Distinct Syndromes

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The Molar Tooth Sign (MTS) is defined by an abnormally deep interpeduncular fossa; elongated, thick, and mal-oriented superior cerebellar peduncles; and absent or hypoplastic cerebellar vermis that together give the appearance of a “molar tooth” on axial brain MRI through the junction of the midbrain and hindbrain (isthmus region). It was first described in Joubert syndrome (JS) where it is present in the vast majority of patients with this diagnosis. We previously showed that the MTS is a component of several other syndromes, including Dekaban–Arima (DAS), Senior–Löken, and COACH (cerebellar vermis hypoplasia (CVH), oligophrenia, ataxia, coloboma, and hepatic fibrosis). Here we present evidence that the MTS is seen together with polymicrogyria, Váradi–Papp syndrome (Orofaciodigital VI (OFD VI)), and a new syndrome with encephalocele and cortical renal cysts. We also present a new patient with COACH syndrome plus the MTS. We propose that the MTS is found in multiple distinct clinical syndromes that may share common developmental mechanisms. Proper classification of

patients with these variants of the MTS will be essential for localization and identification of mutant genes. © 2003 Wiley-Liss, Inc.

KEY WORDS: Joubert; molar tooth; Váradi–Papp; OFD-VI; COACH; Senior–Löken; Dekaban–Arima; cerebellar vermis; hypotonia; ataxia; oculomotor apraxia; kidney cysts; nephronophthisis; hepatic fibrosis; Leber congenital amaurosis; polymicrogyria; coloboma; encephalocele

INTRODUCTION

The Molar Tooth Sign (MTS) is a constellation of anatomic brain abnormalities that together result in the brainstem isthmus and upper pons taking the appearance of a “molar tooth” on axial brain MRI. These abnormalities include a deep interpeduncular fossa at the level of the isthmus and upper pons, elongated, thick and mal-oriented superior cerebellar peduncles, and hypoplasia/aplasia/dysplasia of the superior cerebellar vermis, i.e., cerebellar vermis hypoplasia (CVH) [Maria et al., 1997]. The MTS is identified on axial MRI through the midbrain–hindbrain junction and is not evident on images that are above or below this junction. Although CVH is a key component of the MTS, the CVH may better be appreciated on more caudal images or on coronal images through the cerebellum, and thus many authors will report the MTS separately from the CVH.

The MTS was first described in patients with suspected Joubert syndrome (JS) and was subsequently found in the vast majority of patients with this syndrome. JS is a clinically and radiographically defined syndrome consisting of CVH and the clinical features of neonatal apnea/hyperpnea, oculomotor

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apraxia, hypotonia, ataxia, and mental retardation [Joubert et al., 1968; Boltshauser and Isler, 1977]. In a study of forty-five patients with JS, the MTS was seen in 37 (82%) [Maria et al., 1997], suggesting a high frequency of occurrence in JS. This observation prompted MRI analysis of the first patients to be reported by Dr. Marie Joubert to determine if the MTS was part of the syndrome, because the initial clinical description was before the availability of MRI. These patients displayed the MTS, providing evidence that it is a cardinal feature of the syndrome [Andermann et al., 1999]. However, it remains unclear whether the MTS is pathognomonic of JS or a component of other syndromes that may overlap with JS.

Genome-wide analysis carried out in a large set of JS families largely defined by the presence of the MTS and CVH failed to identify a specific chromosomal locus for this disorder [Chance et al., 1999]. A genome-wide linkage analysis and subsequent homozygosity mapping in consanguineous Arab pedigrees detected one locus for JS on 9q34.3 in two of four families [Saar et al., 1999]. This finding, coupled with failure to demonstrate linkage to 9q34.3 in other pedigrees [Blair et al., 2002], suggests that JS may be genetically heterogeneous. One possibility for the lack of significant linkage among JS families is that the current clinical and radiographic criteria for diagnosis of JS may encompass multiple distinct genetic syndromes. Consistent with this hypothesis, we have previously identified the MTS as a component of several additional syndromes including Dekaban–Arima (DAS), Senior–Löken, and COACH [Satran et al., 1999], indicating that the MTS is not pathognomonic for JS.

As the majority of previously identified patients with the MTS were ascertained as part of an assessment for JS, we hypothesized that there may be additional clinical syndromes of which the MTS is a component. In this study we ascertained patients with the MTS through a worldwide registry of patients with midbrain–hindbrain malformations, and assessed for both the MTS as well as other radiographic and clinical features. We define three new radiographic/clinical entities that include the MTS as a component and report an additional patient with classical features of COACH syndrome with the MTS. These data, together with previously published data, allows for the creation of a classification system for patients with the MTS.

METHODS

Patients with midbrain–hindbrain malformations were recruited through the Child Neurology Bulletin Board (<http://www.waisman.wisc.edu/child-neuro/e-mail.html>), the Lissencephaly Network (<http://www.lissencephaly.org/>), our JS research project recruitment (<http://gleesongenetics.ucsd.edu/>), the Joubert Syndrome Foundation, Inc. (<http://www.joubertsyndrome.org/>), and physicians seeking an opinion on a brain MRI through one or more of the authors. All testing was performed as part of the standard clinical evaluation. A hard copy of the MRI was generally reviewed together with the clinical information, which was obtained under

a protocol of informed consent for each of the authors' respective institutions. We reviewed MRI scans from approximately 100 individuals with posterior fossa abnormalities for this study, and selected cases for presentation that appeared to be clinically and radiographically distinct from previously described patients with a diagnosis of JS.

RESULTS

Cortical Polymicrogyria + MTS

Patient 1 is a 5-year-old male born at term to non-consanguineous Caucasian parents. He was transferred to the neonatal intensive care unit after birth for persistent apnea that was treated with theophylline for several months. Brain MRI showed extensive bilateral cortical dysplasia with polymicrogyria and the MTS (Fig. 1). Neurological examination at 6 weeks of age revealed significant hypotonia and a presumptive diagnosis of JS was made. There was no history of seizures. Ophthalmological evaluation, kidney ultrasound, karyotype (550 band resolution) were normal, and there was no evidence of dysmorphic features.

Patient 2 is an 8-month-old male born at term to non-consanguineous Caucasian parents. There were no prenatal abnormalities. He was born via emergency caesarian-section following a failed vaginal delivery. He displayed neonatal hypotonia and poor respiratory effort with dusky spells. A sleep-study at 5-days-of-age showed many hypoxic episodes. Physical examination was notable for significant hypotonia. There was no history of seizures. Facial appearance was significant for down-turned corners of the mouth and tenting of the upper lip. Abdominal ultrasound and ophthalmological examination were not performed. A karyotype (550 band resolution) was normal. Brain MRI showed the MTS. The cortical gray matter was moderately thickened, particularly in the perisylvian region, and there was an extended sylvian fissure, typical for polymicrogyria (Fig. 2).

COACH Syndrome

Patient 3 is a 7-year-old male born at 28 weeks gestation after premature labor to non-consanguineous Caucasian parents. He was treated for apnea but the parents do not recall episodes of hyperventilation or panting respirations during the first year. Facial appearance showed a normal forehead, mildly deep-set eyes, and a mildly hypoplastic philtrum. At 3 years of age elevated liver transaminase levels were found on routine monitoring, and a liver biopsy showed fibrosis and cirrhosis, but he was asymptomatic. However, at 5 years of age he presented with hematemesis, esophageal varices, and portal hypertension. Ophthalmological evaluation showed exotropia and bilateral optic nerve coloboma. Renal ultrasound showed small calcifications but no cysts. His developmental level approximates half of that expected for his chronological age. Brain CT (Fig. 3) and MRI showed the MTS without other cortical or subcortical malformations. A karyotype was not performed.

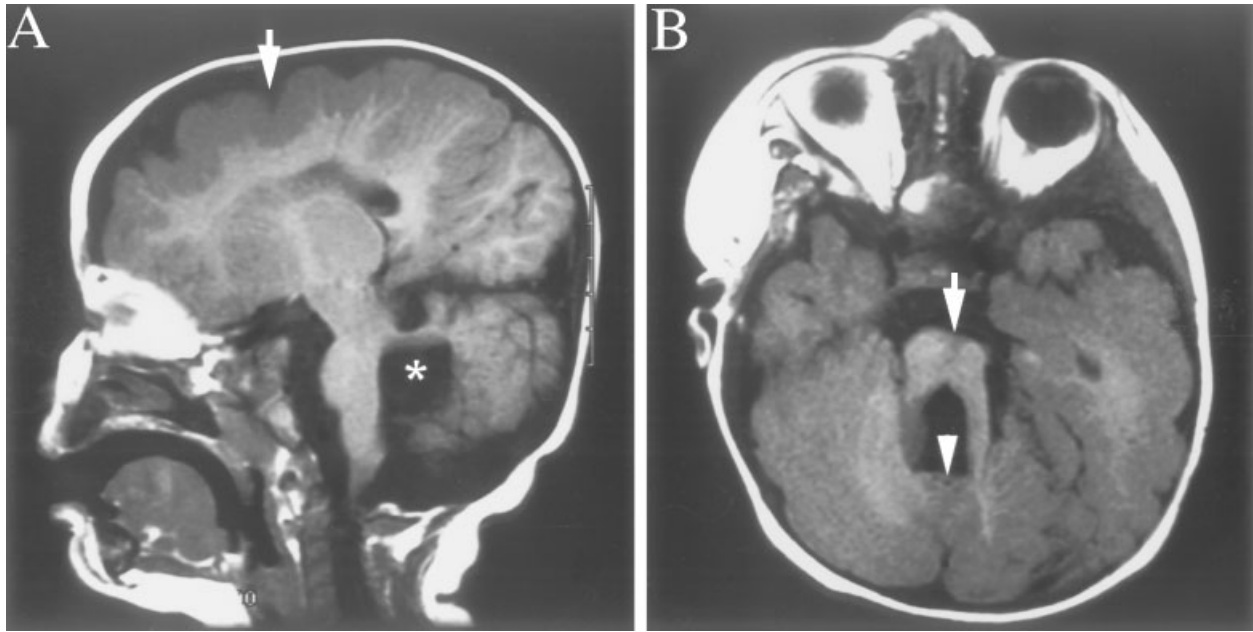


Fig. 1. Patient 1. **A:** Sagittal MRI showing cortical dysplasia (arrow) with thickened gray matter and polymicrogyria. Asterisk highlights the 4th ventricle. **B:** Axial image showing the Molar Tooth Sign (MTS) (arrow) and CVH (arrowhead).

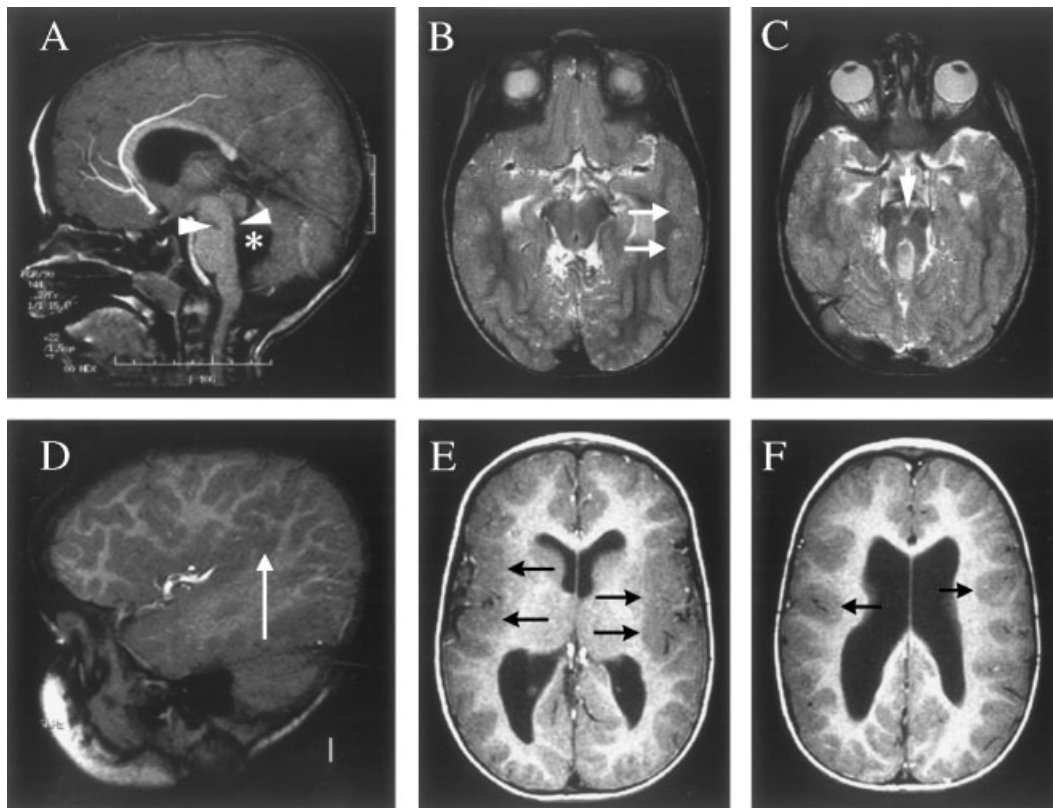


Fig. 2. Patient 2. **A:** Midline sagittal T1 image showing a narrow isthmus (region between arrowheads), large 4th ventricle (asterisk), and dysplastic cerebellum. The vermis is small, but difficult to distinguish from the cerebellar hemispheres. **B:** T2-weighted axial image shows cortical gray matter thickening (arrows). **C:** MTS (arrow). **D:** T1-weighted sagittal image

through the left lateral hemisphere demonstrates an extended left sylvian fissure (arrow) and mildly thickened cortex typical of polymicrogyria. **E–F:** T1-weighted images showing an abnormal gyral pattern with moderately thick cortex (arrows) typical of polymicrogyria.

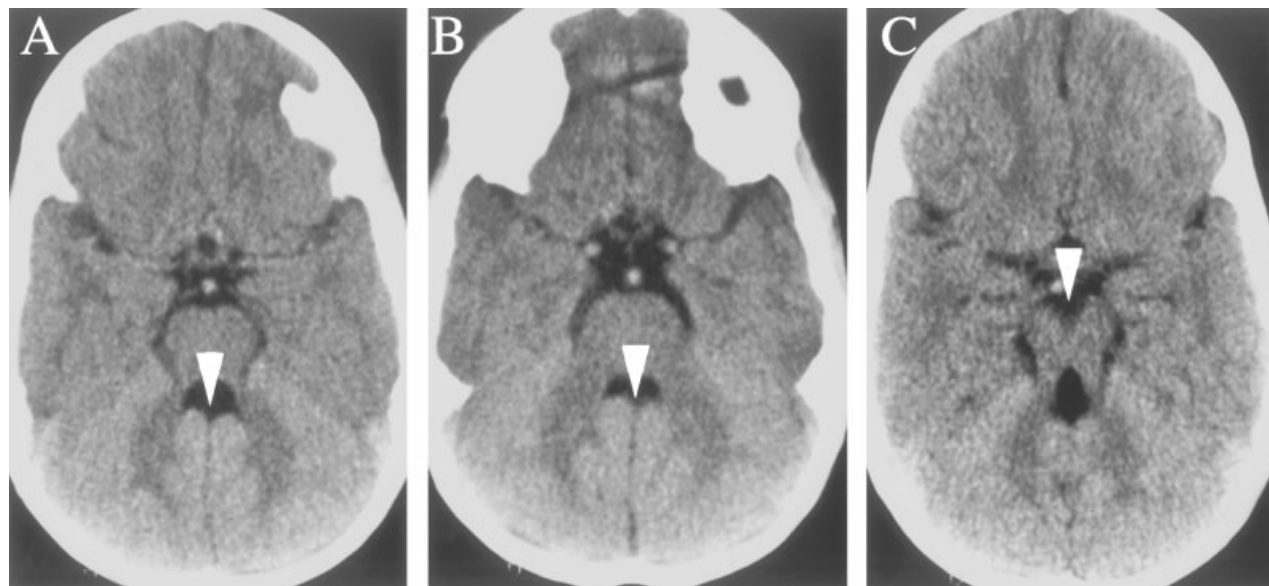


Fig. 3. Patient 3. **A–B:** Axial CT images through upper (A) and lower (B) pons showing CVH (arrowhead). **C:** Axial CT image through the isthmus showing the MTS (arrowhead).

Váradí–Papp Syndrome (Orofaciodigital VI) + MTS

Patient 4 is a 7-month-old male born at term to non-consanguineous Caucasian parents. He had neonatal apnea that spontaneously resolved. Examination showed a broad nasal bridge, midline notch of the upper lip, and multiple soft-tissue nodules on the inferior and superior aspects of the tongue (Fig. 4). There was partial syndactyly on both hands and feet. The hands had six bony metacarpals and digits with a “Y” shaped central metacarpal on the right that together suggested the diagnosis of Váradí–Papp syndrome (also known as oral-facial-digital syndrome type VI) [Váradí et al., 1980; Munke et al., 1990]. Brain MRI showed the MTS and cerebellar vermis aplasia with fusion of the two hemispheres at the midline. There was no evidence of hypothalamic abnormalities or masses, epilepsy, congenital heart defect, or anal atresia as are found in some patients with Váradí–Papp syndrome [Stephan et al., 1994]. No abdominal ultrasound, karyotype, or ophthalmological examinations have been performed to date.

Patient 5 is a 4-year-old male born to non-consanguineous Hispanic parents. Several dysmorphic features were noted, including short limbs, large head, hypertelorism, lobulated tongue with multiple hamartomas, multiple alveolar frenula, cleft palate, notched midline upper lip, absent epiglottis, and postaxial/insertional polydactyly of the hands with bilateral duplicated halices of the feet (Fig. 5). As a result of these malformations, he required tracheostomy and gastrostomy tubes. He had diffuse hypotonia, dysconjugate eye movements, and episodic hyperpnea. MRI at 4 weeks of age showed absent posterior cerebellar vermis and the MTS, together suggesting a diagnosis of Váradí–Papp syndrome. Partial agenesis of the corpus callosum was also noted. He had a normal echocardiogram but

unexplained bradycardia. Brainstem auditory evoked response testing demonstrated profound sensory neural hearing loss. A renal ultrasound was normal and an eye exam showed an optic nerve coloboma. Seizures started in infancy and were refractory to treatment with phenobarbital and topiramate. He was diagnosed with hypothyroidism that was responsive to replacement therapy. At 2 years of age, he was hospitalized for acute renal failure, and a repeat ultrasound showed nephrocalcinosis with out cystic changes, suggesting toxicity associated with topiramate. A karyotype was not performed.

MTS + Hydrocephalus + Occipital Encephalocele + Cortical Renal Cysts (Malta Syndrome)

Patient 6 is an 18-month-old male born to non-consanguineous parents from the island of Malta in the Mediterranean. Prenatal ultrasound showed microcephaly. At birth an occipital myelomeningocele leaking CSF was noted. The defect was surgically repaired and shunted. Parents report recurrent episodic tachypnea as well as pendular nystagmus that have decreased but not disappeared with time. Additionally, there has been temperature instability with episodes of hyperpyrexia up to 105°F. Neurological evaluation revealed moderate spontaneous activity, response to voice with calming, truncal hypotonia, slightly brisk reflexes, ability to touch toes with hands and suck fingers, but inability to sit or walk. Further diagnostic evaluation revealed congenital left-sided microphthalmia, microcornea, and inferior choroidal coloboma with dysplastic discs and absent visual evoked responses bilaterally. There were no notably dysmorphic features except for bilateral ptosis. Liver ultrasound was normal but the kidneys showed numerous bilateral 2 mm cortical cysts (Fig. 6).

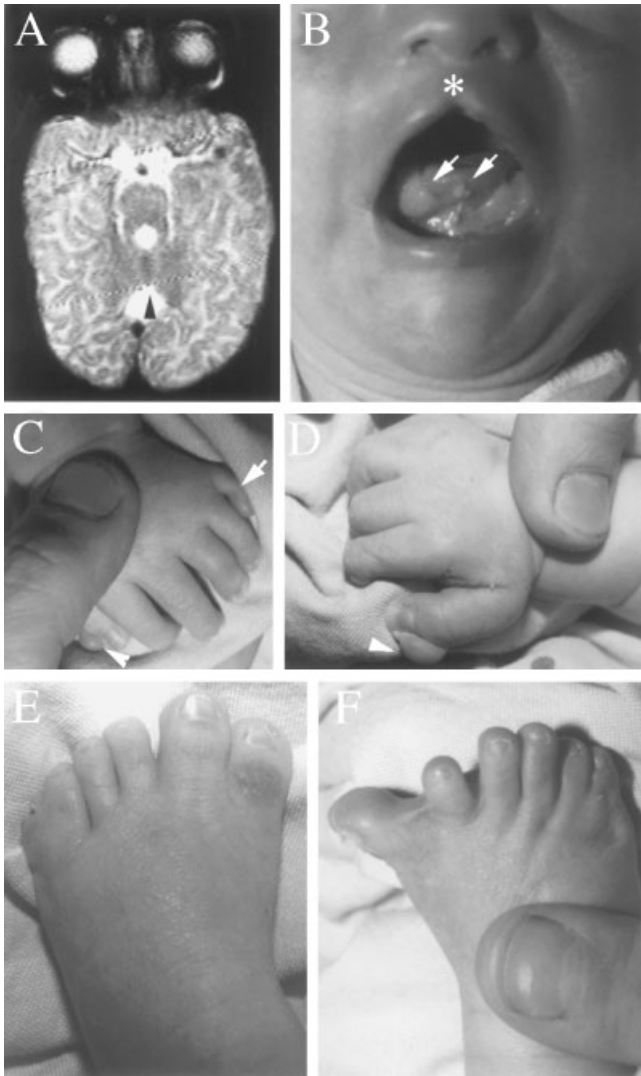


Fig. 4. Patient 4. **A**: Axial MRI showing the MTS and absent vermis, with partial fusion of the cerebellar hemispheres (arrowhead). **B**: Multiple lingual tumors (white arrows) and notched upper lip (asterisk). **C–D**: Left and right hand, respectively, showing postaxial polydactyly (arrow) and soft-tissue tumors on both thumbs (arrowheads). **E–F**: Left and right foot, respectively, demonstrating preaxial polydactyly and partial syndactyly.

Brain MRI revealed the repaired occipital encephalocele, with stretching of the tectum and superior cerebellum towards the torcula. Spatial distortion made it impossible to evaluate the corpus callosum or cortical morphology. There was dilatation of the lateral and 3rd ventricles, and a small dysplastic vermis together with the MTS. A karyotype was not performed.

Patient 7 is a female cousin of the Patient 6 with a nearly identical presentation of occipital encephalocele, and findings including absent visual evoked responses and bilateral cortical renal cysts. An electroretinogram demonstrated bilateral grossly attenuated signal, consistent with Leber congenital amaurosis (LCA). A detailed family history revealed no evidence of a consanguinity loop in the previous three generations, but more distal consanguinity could not be excluded. A karyotype was not performed.

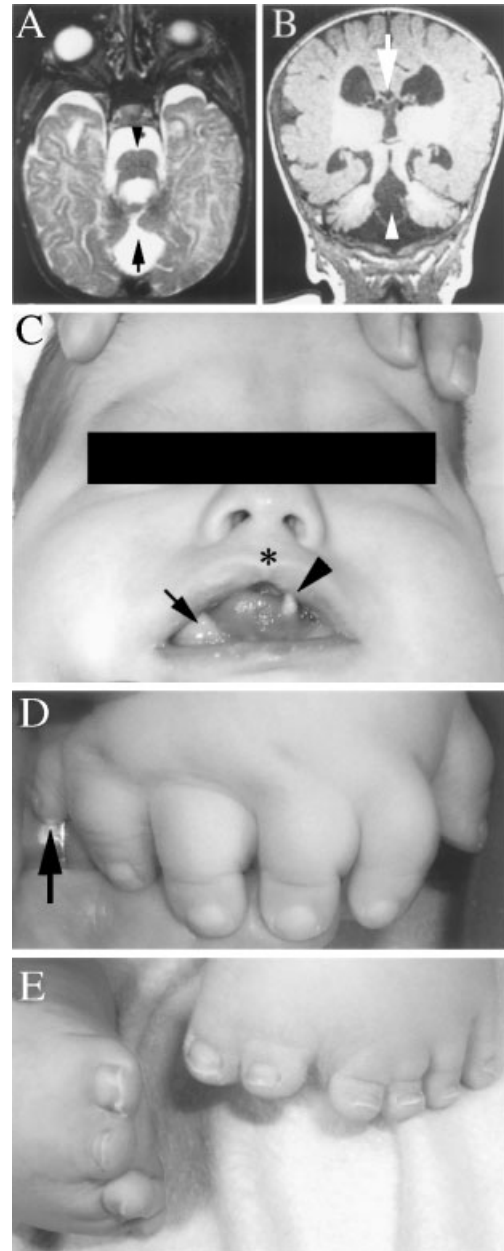


Fig. 5. Patient 5. **A**: Axial MRI showing the MTS (arrowhead) and absent cerebellar vermis (arrow). **B**: Coronal MRI showing absent cerebellar vermis (arrowhead) and thin corpus callosum (arrow). **C**: Face showing hypertelorism, lobulated tongue (arrow) with hamartomas (arrowhead), and notched upper lip (asterisk). **D**: Right hand showing postaxial polydactyly. **E**: Feet showing bilateral duplicated halices and partial syndactyly.

Patient 8 is a 4-year-old Hispanic girl from non-consanguineous parents who presented with an encephalocele at birth requiring excision and ventriculo-peritoneal shunting for hydrocephalus. There were no dysmorphic features. CT demonstrated the MTS and absence of the vermis (Fig. 7). Neonatal apnea required monitoring and caffeine. She has mild subvalvar and valvar pulmonary stenosis not requiring surgical intervention. Kidney ultrasound demonstrated left-sided hydronephrosis and a simple renal cyst in the right

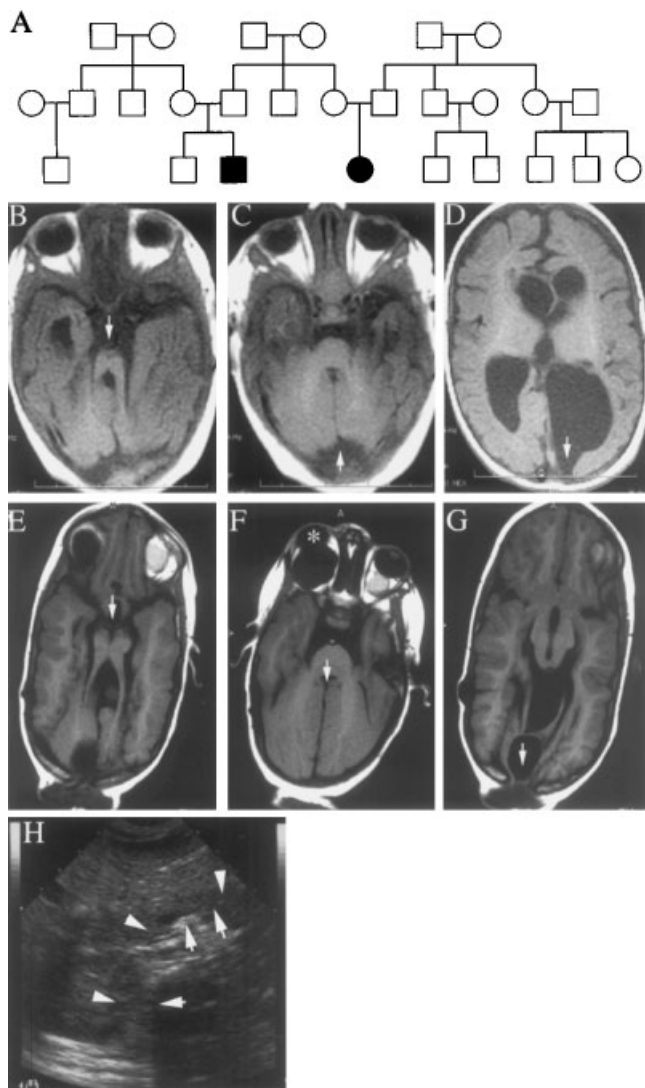


Fig. 6. Patients 6 and 7. **A**: Family tree showing the first-cousin affected individuals. **B–G**: Axial MRI from the male (**B–D**) and female (**E–G**) showing the MTS (**B, E**), absent vermis (**C, F**) and occipital encephalocele (**D, G**) highlighted by arrows. The asterisk in **F** highlights the coloboma. **H**: Kidney ultrasound from the male showing the outline of the kidney (arrowheads) and multiple 2–3 mm cysts at the cortico-medullary junction (arrows).

upper pole, and she has had frequent episodes of pyelonephritis. Diuretic scintigraphy using technetium(99)-mercaptoacetyl triglycine (MAG3) showed severely impaired clearance from the left kidney. Seizures began at 1 year of age and were treated with carbamazepine. No visual tracking was present and dilated ophthalmoscopy did not reveal coloboma or retinal degeneration. A karyotype was not performed.

DISCUSSION

We describe ten patients displaying the MTS with clinical features that appear to distinguish them from classical JS. All patients display the MTS in addition to many of the key clinical diagnostic features of neonatal respiratory alternating hyperpnea/apnea, hypo-

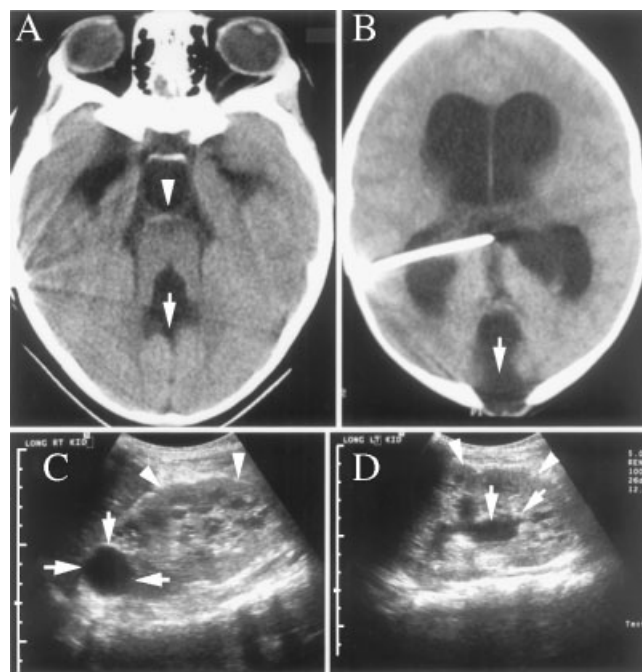


Fig. 7. Patient 8. **A**: Axial CT image showing the MTS (arrowhead) and CVH (arrow). **B**: Axial CT image showing the repaired encephalocele (arrow). Mild ventriculomegaly and an indwelling ventricular-peritoneal shunt tip (white) are also seen. **C–D**: Kidney ultrasound images showing the right and left (**C–D**, respectively) outline of the kidney (arrowheads) and cysts (arrows).

tonia, developmental delays, oculomotor apraxia, and ataxia consistent with a diagnosis of JS. However, additional striking features suggest that these patients should be classified into distinct genetic syndromes both to improve diagnosis and for future genetic mapping studies.

Patients 1 and 2 display extensive cortical polymicrogyria together with clinical and radiographic features of JS including the MTS. Some genetic forms of polymicrogyria have been mapped, including autosomal recessive diffuse polymicrogyria and X-linked perisylvian polymicrogyria [Piao et al., 2002; Villard et al., 2002], but no previously reported patients have displayed the MTS or vermis aplasia. Our data suggests that the two conditions may be seen together. While seizures are a frequent presenting feature in patients with polymicrogyria, neither of these two patients had a history of epilepsy.

We believe that the MTS is a frequent component of Váradi–Papp syndrome (OFD VI), based on the findings in our two patients and on the partially characterized posterior fossa abnormalities previously reported in this condition. This syndrome was initially described as the combination of polydactyly (typically mesaxial, with a “Y” shaped metacarpal, but also preaxial and occasionally postaxial), cleft lip/palate or lingual nodules or lumps, prominent oral frenula, and psychomotor retardation [Váradi et al., 1980]. Congenital heart defects, generally conotruncal defects [Váradi et al., 1980] and hypothalamic hamartomas [Stephan et al., 1994] have been described. The spectrum of the syndrome was later

recognized to include CVH and some of the clinical features of JS [Munke et al., 1990; Smith and Gardner-Medwin, 1993; Haug et al., 2000]. However, these studies did not evaluate for the presence of the MTS. Attempts to re-evaluate these previously reported patients for evidence of the MTS have been unsuccessful as the scans were unavailable and the families lost to follow-up. Patients 4 and 5 display many of the characteristic features of Váradi–Papp syndrome, including mesaxial polydactyly or “Y” shaped metacarpal that are the most characteristic feature of this syndrome. These plus a notched upper lip, tongue hamartomas, and CVH distinguish OFD VI from other OFD syndromes.

Patients 6–8 display a constellation of features not previously described, and therefore we suggest the assignment of these patients to a distinct syndrome that we have named “Malta syndrome.” This constellation includes the MTS, occipital encephalocele with hydrocephalus, and cortical renal cysts, with or without coloboma and LCA. We considered that these children might be classified under DAS (OMIM 243910) as we have previously found an overlap between JS and DAS [Satran et al., 1999]. However, DAS has not been reported to include hydrocephalus or occipital encephalocele. We also considered that these patients might be classified under Meckel–Gruber syndrome (MGS) (OMIM 24900), an autosomal recessive condition with encephalocele plus renal cysts, with variable features including hepatic ductal dysplasia and polydactyly. The overlap between and JS and MGS has been previously reported [Casamassima et al., 1987]. However, coloboma and the MTS have not been reported in this condition. Additional studies will be required to determine if there is phenotypic or genotypic overlap between these syndromes.

Based on our evaluations, one possibility is that the features displayed by patients 6–8 represent a distinct clinical entity. However, a different possibility is that encephalocele/hydrocephalus is a variable feature in JS and the MTS, and may be seen in any of the variants that have been described. Indeed, in the initial pedigree described by Joubert et al., one of four patients displayed occipital encephalocele [Joubert et al., 1968]. Likewise, in a recently reported set of monozygotic twins with JS and the MTS, only one displayed occipital encephalocele [Raynes et al., 1999]. We are aware of at least three other sibling pairs with features of JS that are discordant for occipital encephalocele (MAP, IAG, unpublished observation). Therefore, occipital encephalocele may be an inconsistent finding among siblings or even identical twins, so it may not be helpful in syndrome delineation. A second possibility is that the MTS may be due to the encephalocele as hindbrain contents herniate through the calvarial defect [Chapman et al., 1989], but the discordant finding of encephalocele in siblings and in twins argues against this possibility. Preliminary mapping studies assuming an autosomal recessive inheritance pattern in the family of patients 6 and 7 exclude linkage to the only known JS locus on 9q34.3 as well as the three known MGS loci: (8q, 11q, 17q (JGG, LCK, unpublished observations)), but no loci for DAS have been described to test for genetic overlap.

SYNDROME DELINEATION

Many of the features described here have been previously reported to exist in JS, but our data suggests that the current classification system for patients with the MTS is inadequate. Previous studies have indicated coexistence of JS with polydactyly [Egger et al., 1982; Kher et al., 1994], ocular coloboma [Lindhout et al., 1980; Kher et al., 1994; Dahlstrom et al., 2000], LCA [King et al., 1984a; King and Stephenson, 1984b; Houdou et al., 1986; Ivarsson et al., 1993], renal cysts [Ivarsson et al., 1993; Silverstein et al., 1997], or nephronophthisis [Satran et al., 1999; Apostolou et al., 2001], hepatic fibrosis [Lewis et al., 1994], and soft-tissue tongue tumors [Pellegrino et al., 1997]. These variable findings were corroborated in larger numbers of JS patients [Chance et al., 1999]. King et al. [King et al., 1984a; King and Stephenson, 1984b] differentiated two forms of JS: Type I was described as CVH with the clinical triad of neonatal breathing abnormalities, oculomotor apraxia, and hypotonia. Type II included these features plus retinal and renal involvement, as it was previously demonstrated that among a cohort of 29 patients, retinal dystrophy was never absent in JS when renal cysts were present [Saraiva and Baraitser, 1992].

We propose a revised classification for patients with the MTS that encompasses the previous classification system [Maria et al., 1999a], most previously reported patients and patients reported in the current study (Table I). We refer to these as JS and related disorders (JSRD). There are at least eight distinct syndromes in which the MTS occurs, although there is some overlap among the different syndromes and some may eventually prove to be allelic disorders. For several of these syndromes including classical Joubert, Senior–Löken, DAS, and COACH syndromes, the coexistence of the MTS has been previously documented [Maria et al., 1997, 1999b; Satran et al., 1999].

For this classification system, we consider the diagnosis of classical JS to include patients with encephalocele, as this feature displays remarkably variable expressiveness within families [Joubert et al., 1968] and even in identical twins [Raynes et al., 1999]. Likewise, postaxial polydactyly may be seen in only one of the affected children in a family [Houdou et al., 1986] or in only one of two hands in individual patients (J.G.G., M.A.P. unpublished observation), suggesting further variability. The inclusion of patients with Dandy–Walker malformation (DWM) in this group also seems appropriate. There is confusion both in clinical practice and in the literature on the difference between CVH/MTS and DWM, and many patients with Joubert are misdiagnosed as displaying a “Dandy–Walker variant.” The two conditions can be distinguished in the majority of cases based on the presence of a cystic dilatation of the 4th ventricle in DWM, which is absent in CVH/MTS [Patel and Barkovich, 2002]. Nevertheless, we have encountered rare cases in which it is impossible to distinguish between the two and where DWM appears to be more of a continuum of disease occasionally encompassing the MTS [Barkovich et al., 1989; Chance et al., 1999; Soto-Ares et al., 2000].

TABLE I. JS and Related Disorders (JSRD) of Midbrain/Hindbrain Formation

	Classical Joubert	Joubert + LCA or retinal dystrophy	Dekaban-Arima syndrome	Senior-Löken syndrome	COACH/Gentile syndrome	Váradí-Papp syndrome (OFD VI) ^a	Joubert + Polymicrogyria ^a	Malta syndrome ^a
MTS	+	+	^b +	^b +	+	+	+	+
Clinical features of MTS	+	+	^b +	^b +	+	+	+	^c +
Postaxial polydactyly	+/-	+/-	-	-	+/-	+/-	-	-
Encephalocele	+/-	+/-	+/-	+/-	+/-	+/-	^c -	+
Coloboma	+/-	+/-	+/-	+/-	+/-	+/-	^c -	+
LCA or retinal dystrophy	-	+	+	+	-	-	-	+
Cystic dysplastic kidneys	-	-	+	+	-	-	-	+
Nephronophthisis	-	-	-	+	-	-	-	-
Hepatic fibrosis	-	-	-	+	+	+	-	-
Tongue tumors	-	-	-	-	-	-	-	-
Mesaxial polydactyly	-	-	-	-	-	+	-	-
Polymicrogyria	-	-	+/-	-	-	-	+	-

Revised classification for patients with Joubert syndrome and related disorders (JSRD), including the MTS and CVH. Clinical features, neonatal apnea/hyperpnea, oculomotor apraxia, hypotonia, ataxia, and mental retardation, which are seen in all or nearly all patients with the MTS. Only a subset of patients with DAS or SLS have been evaluated for JSRD, so the presence of the MTS and clinical features is listed as +/- . In SLS, cystic dysplastic kidneys is seen early, and nephronophthisis is usually identified later in the disease.

MTS, molar tooth sign; LCA, Leber congenital amaurosis; COACH, CVH, Oligophrenia, Ataxia, Coloboma, Hepatic fibrosis; OFD VI, Orofaciodigital VI syndrome.

^aFirst described in this report.

^bFurther delineation required.

^cToo few patient ascertained to make conclusive statements.

The association of classical JS with renal disease has been widely recognized, where it takes one of two forms: cystic dysplastic kidney disorder or nephronophthisis (characteristic renal histological triad of tubular basement membrane disintegration, tubular atrophy with cyst development, and interstitial cell infiltration with fibrosis). JS with renal disease is very often associated with LCA [Saraiva and Baraitser, 1992] a severe form of retinal dystrophy characterized by blindness from birth and absent electroretinal responses. In some published cases, differentiation between LCA and retinal dystrophy based on an electroretinogram has not been made, and thus LCA/retinal dystrophy are considered as a single entity in this study. This data delineates two syndromes: (1) DAS consisting of JS with LCA plus cystic dysplastic kidneys [King et al., 1984a; Ivarsson et al., 1993]. (2) Senior-Löken syndrome consisting of JS with LCA and/or retinitis pigmentosa plus juvenile nephronophthisis [Chance et al., 1999; Satran et al., 1999]. There is some discussion that autosomal recessive cystic dysplastic kidney disorder may not be distinct from juvenile nephronophthisis [Hildebrandt and Omram, 2001], suggesting that DAS and Senior-Löken syndromes may be part of a spectrum. Neurological impairment that is classical for JS and CVH were described in the original paper by Dekaban [1969] and many patients with DAS display these features [Kubota et al., 1991; Saraiva and Baraitser, 1992]. Contrarily, review of the published cases indicates that clinical features of JS are only rarely present in Senior-Löken syndrome. Mutations in the *NPHP1* gene at 2q13 and the *NPHP4* gene at 1p36 have been identified in individuals with nephronophthisis alone and in some pedigrees with Senior-Löken syndrome, but the MTS was not described in these patients [Hildebrandt et al., 1997; Mollet et al., 2002; Otto et al., 2002]. Adding further complexity, some patients with nephronophthisis and oculomotor apraxia without retinal or cognitive problems have been found to have mutations in the *NPHP1* gene [Betz et al., 2000]. Clearly, there is overlap between these cerebello-oculo-renal conditions and JS, particularly JS associated with retinal and/or renal manifestations. However, no mutations in nephronophthisis-related genes have been reported in individuals with JS or the MTS.

JS plus LCA is included as a separate syndrome, although further analysis may indicate that it is part of the DAS/Senior-Löken syndrome complex. There have been patients reported with JS plus LCA without mention of renal involvement [King and Stephenson, 1984b; Houdou et al., 1986], but because the kidney may only be involved later in the disease it is possible that such patients would eventually develop kidney disease.

Gentile et al., reported two brothers with features of COACH syndrome including CVH, congenital ataxia with oculomotor apraxia and hepatic fibrosis, but excluding renal involvement or coloboma [Gentile et al., 1996]. MRI images across the brainstem isthmus are not available for review in these patients, so it is not possible to determine if the MTS is present in these patients. It is possible that they represent a unique syndrome, but because of the similarity between the descriptions of

patients with Gentile syndrome and COACH, we have included them as a single entity.

The finding of cortical dysplasia of the polymicrogyria type in patients with features of JS suggests that the two conditions may occur together, and may explain the not-infrequent coexistence of seizures in patients with the MTS [Kubota et al., 1991; Haug et al., 2000].

The description of Váradi–Papp and Malta syndrome are also presented here as new subtypes of JSRD.

While JS without additional features accounts for the majority of patients with the MTS, it is critical to obtain screening evaluations in patients with the MTS for these co-existent features for correct classification. More detailed analyses of midbrain and hindbrain anatomy with high-resolution imaging and quantitative methodologies are needed to better define overlapping and distinct neuroanatomical features of genetically discrete conditions. As retinal, renal, and hepatic complications can develop with time in individuals with JSRD, regular evaluation for these findings is important. It is hoped that these distinctions will aid in identification of causative genes given the known genetic heterogeneity in these conditions.

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