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J Child Neurol 1999 14: 368

DOI: 10.1177/088307389901400605

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Molar Tooth Sign in Joubert Syndrome: Clinical, Radiologic, and Pathologic Significance

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ABSTRACT

Joubert syndrome is a rare autosomal-recessive condition characterized by early hyperpnea and apnea, developmental delay, and truncal ataxia. We previously described key ocular motor signs in Joubert syndrome and the molar tooth sign resulting from dysplasia of the isthmic segment of the brain stem, superior cerebellar peduncles, and vermis. In this study, we obtained clinical and developmental data in 61 cases, and radiologic data in 46 of these, to determine the prevalence of the molar tooth sign in a large sample, and to ensure that magnetic resonance images obtained for study were representative of the Joubert syndrome population at large. We studied the morphology of the isthmic segment of the pontomesencephalic junction, the segment of the brain stem derived from the primitive isthmus. Portions of the cerebellum analyzed included the superior cerebellar peduncles, the anterior and posterior lobes of the vermis, and the flocculonodular lobe. In one case, autopsy of the brain was performed. The average age at diagnosis was 33 months. All patients were hypotonic and developmentally delayed. The molar tooth sign was present in 85% of cases with 13% of these showing additional malformations. All patients without the molar tooth sign had other mimicking conditions such as neocerebellar dysgenesis, isolated vermian atrophy, cerebellar aplasia, and cystic dilation of the cisterna magna. Autopsy showed aplasia of the cerebellar vermis with dysplasia of the dentate nucleus, elongated locus coeruleus, and marked dysplasia of the caudal medulla. A better understanding of the clinical, radiologic, and pathologic features of Joubert syndrome should help uncover the genetic basis for the syndrome. (*J Child Neurol* 1999;14:368–376).

In 1969, Joubert et al described a family of four siblings displaying episodic hyperpnea, abnormal eye movements, ataxia, and mental retardation associated with agenesis of the cerebellar vermis.¹ Consanguinity in the family was noted and a genetic basis with autosomal-recessive inheritance was suggested. Several years later, Boltshauser and Isler described an additional three patients with similar findings and coined the name Joubert syndrome.² For many years, hyperpnea and apnea associated with vermian hypoplasia were believed to be the sole clinical hallmarks of Joubert syndrome.^{2–7} In 1990, Kendal et al reported breathing abnormalities in only 44% of that series of 16 patients.⁸

Subsequent studies found additional cases lacking hyperpnea or apnea.^{9,10} Ocular abnormalities such as nystagmus, strabismus, ptosis, and retinal dystrophy have been reported frequently, but as with breathing abnormalities, they have not been found to be a unilateral hallmark of this syndrome.^{8–15} Neonatal hypotonia, developmental delay, and truncal ataxia are found in almost all instances of Joubert syndrome, but are also common to other neurologic disorders and are of limited diagnostic value.¹⁶

To date, only seven studies have used magnetic resonance imaging (MRI) to categorize the underlying pathology of Joubert syndrome.^{8,11,17–21} We previously performed detailed neurologic, neuro-ophthalmologic, and MRI assessments on 15 patients with Joubert syndrome and described a constellation of abnormalities producing the molar tooth sign; specific oculomotor abnormalities correlated with MRI findings.²⁰ We believe that the molar tooth sign is pathognomonic for Joubert syndrome. The purpose of this study was to better characterize the clinical, neurodevelopmental, radiologic, and pathologic findings in Joubert syndrome. The molar tooth sign was present in 85% of

Received August 21, 1998. Received revised Oct 28, 1998. Accepted for publication Nov 10, 1998.

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patients; the remaining 15% of cases had other disorders. Although helpful diagnostically, MRI does not demonstrate the widespread malformations in the caudal medulla detected pathologically, which probably account for respiratory problems and other features of the disease.

MATERIALS AND METHODS

Patients

Clinical and neurodevelopmental data were obtained in 61 cases, and radiologic data in 46 of these, to determine the prevalence of the molar tooth sign in a large sample, and to ensure that MRIs obtained for study were representative of the Joubert syndrome population at large. Patients were recruited for study through a research registry provided by the Joubert Syndrome Foundation. These patients had been diagnosed previously with Joubert syndrome by their neurologist, radiologist, geneticist, or ophthalmologist. Our sample consisted of 36 boys and 24 girls, including six pairs of siblings. This resulted in a 3:2 male-to-female ratio. Their ages ranged from 1.3 to 17.0 years, with a mean of 7.5 years and a standard deviation of 4.3 years. The 61 cases were divided into four groups. Group A consisted of 15 cases previously reported in the original series, from whom we obtained new detailed neurodevelopmental data.²⁰ Group B consisted of 30 new cases, from whom we obtained MRIs and neurodevelopmental data, while group C consisted of 15 new cases from whom MRIs could not be retrieved, but neurodevelopmental data were obtained, and group D consisted of a new case from whom we obtained an MRI, neurodevelopmental data, and autopsy of the brain.

Clinical History

Caregivers of these patients were contacted by telephone and asked a comprehensive battery of questions to provide a detailed history of clinical severity, developmental milestones, and associated conditions. Clinical questions included age at diagnosis, type of physician diagnosing, imaging modality used, history of hyperpnea and apnea, use of apnea monitor, walking ability, ocular and oculomotor findings, and presence of any other associated conditions such as renal abnormalities, polydactyly, tongue tumors or protrusion, congenital heart disease, and microcephaly. The developmental history section included ages at which patients first rolled over, sat up on their own, walked, said their first words, combined a few different words, dressed themselves, and were toilet trained.

Magnetic Resonance Imaging

The neuroradiologist (R.G.Q.) who studied the MRIs from the 46 group A, B, and D patients was blinded to the clinical findings and developmental history. MRIs included at least axial and sagittal short repetition time and short time to echo (T_1 -weighted) spin echo and axial long repetition time and long time to echo (T_2 -weighted) imaging sequences. In six cases, multiple sets of scans were available. These serial scans were analyzed to determine if any significant changes had occurred. The imaging evaluation in this series included analysis of the cerebrum, brain stem, and cerebellum. Cerebral evaluation included a search for the presence of migration abnormalities, delays in myelination, and focal or diffuse atrophy. Lateral ventricle size and location of atrophy were also noted.

Three regions of the brain stem were analyzed: the mesencephalon (midbrain), pontomesencephalic junction (isthmus), and rhombencephalon (pons and medulla oblongata). The isthmus was particularly scrutinized because of its suspected involvement in the spectrum of neuro-ophthalmologic abnormalities found in Joubert syndrome. The isthmic malformation was rated on the depth of depression in the posterior foramen cecum portion of the interpeduncular fossa.

Among the cerebellar structures studied were the cerebellar hemispheres, superior cerebellar peduncles, and anterior and posterior lobes of the vermis. The cerebellar hemispheres were analyzed on the basis of size and level of sulcation. The superior cerebellar peduncles were assessed for thickness and course relative to the brain stem. The evaluation of hypoplasia in the vermis included the presence or absence of the primary fissure, the presence or absence of the archaeocerebellum (flocculonodular lobe), the level of fusion of the left and right sides of the vermis, the differentiation and foliation of the superior vermian lobules (central and culmen), and the differentiation and foliation of the inferior vermian lobules (declive, folium, tuber, pyramis, and uvula).

Autopsy

The sole patient in group D died at age 31 years after being discovered unresponsive submerged in a swimming pool. He was a hypotonic newborn but no hyperpnea or apnea was reported. He had congenital nystagmus and was later noted to have oculomotor apraxia. He rolled at 12 months, sat at 18 months, walked at 42 months, and combined words at 60 months. He protruded his tongue as a young child and was born with a partially cleft palate. He started having seizures at 1 year of age but had been seizure-free for 6 years at the time of death. His gait had always been wide-based and ataxic.

RESULTS

Clinical and Developmental History

Clinical history was available for all 15 group A patients, 28 of 30 group B patients, all 15 group C patients, and the one group D patient. The average age of diagnosis for the 58 group A, B, and C patients was 33 months with a standard deviation of 63 months. All cases were hypotonic in the neonatal period. Forty-one patients ($71\% \pm 14\%$; 95% confidence interval) experienced breathing abnormalities with 32 monitored in infancy. Thirty-two patients ($55\% \pm 17\%$) had hyperpnea, with 20 still experiencing hyperpnea when excited or ill. Thirty-five patients ($60\% \pm 16\%$) had a history of apnea. All but three patients were found to have some type of ocular dysfunction (Table 1). Of the 58 surveyed, 11 ($19\% \pm 23\%$) had retinal abnormalities and 4 were legally blind. Nystagmus was found in 31 patients ($53\% \pm 18\%$) and strabismus in 18 ($31\% \pm 21\%$). Table 2 is a list of associated conditions.

All patients had severe developmental delay. Ninety-one percent of patients were capable of rolling over at an average age of 10.0 ± 1.5 months (95% confidence interval). Seventy-three percent had learned to sit up at 19.2 ± 2.7 months. Fifty percent of patients learned to walk at $47.4 \pm$

Table 1. Ocular and Oculomotor Findings

<i>Ocular</i>	<i>No. of Patients (N = 58)</i>	<i>Oculomotor</i>	<i>No. of Patients (N = 58)</i>
Poor vision	18 (31%)	Nystagmus	31 (53%)
Retinal dystrophy	8 (14%)	Strabismus	18 (31%)
Retinal pigmentary changes	3 (5%)	Ocular motor apraxia	13 (22%)
Congenital ocular fibrosis	1 (2%)	Ptosis	11 (19%)
Farsightedness	3 (5%)		
Nearsightedness	4 (7%)		
Astigmatism	1 (2%)		
Blindness	4 (7%)		

8.3 months, 86% of whom reported an ataxic gait. Sixty-one percent said their first words at 26.1 ± 4.9 months, 75% of whom later combined words at 44.0 ± 17.4 months. Twenty-four percent of patients could dress themselves at 91.3 ± 16.2 months and 35% were toilet trained by 62.6 ± 12.3 months. There was a good deal of variability in developmental delay and physical ability among the 58 patients. No patient had regression in neurodevelopmental parameters.

Neuroradiologic Findings

MRI findings were available for 45 group A and B patients. No significant differences were found in the six sets of serial scans. The majority of patients were found to have morphologically normal cerebrums. Mild atrophy was found in seven patients and moderate atrophy in five. Three patients had an abnormal corpus callosum, while one had an immature brain, and one had lissencephaly. Myelination was delayed in 15 (33%) cases. Mild atrophy was present in the lateral ventricles of 17 (38%) patients, while three had moderate to severe atrophy. MRI analysis showed little or no abnormality in the mesencephalon, with only six patients exhibiting minimal, five moderate, and two marked abnormalities. This was also the case in the region of the rhombencephalon, where MRI showed only five patients with an atrophic pons. However, the isthmus of the brain stem (pontomesencephalic junction) showed an abnormality in 32 (71%) of the cases, consisting of a deeper than normal cleft of the foramen cecum portion of the interhemispheric fissure (Figure 1). The extent of the isthmus abnormality varied among patients: 16 had a mild defect, 14 exhibited a moderately deep isthmus defect, and the remaining 2 exhibited a markedly deep isthmus deformity. The superior cerebellar peduncles were found to be abnormal in all but seven

cases. Thirty-six patients (80%) were found to have superior cerebellar peduncles that were thickened to varying degrees and reoriented into a vertical position relative to the brain stem, while two had smaller than normal peduncles.

Essential to the following observations is the awareness that development of the cerebellar vermis is related to organization, and that it can be defined easily in every lateral scan, including those of newborn infants. Separate superior vermian lobules were well delineated in all cases and five separate inferior vermian lobules could be reasonably well defined, with a mean of 4.5 lobules in age-matched controls. At times, separation of the nodulus, uvula, and pyramis was difficult because of partial volume artifact created by sections including portions of the biventral cerebellar lobules. The vermian folia are also well defined at the time of birth. Thus, degrees of abnormality could effectively be based on failure to form separate vermian lobules, failure to fuse the right and left portions of the vermis, and failure to adequately form the vermian folia. Vermian structures were found to be hypoplastic in all but five cases (Table 3). The right and left sides of the anterior vermis were cleft to varying degrees. The condition of the superior vermis ranged from two normal lobules to one poorly foliated mass, with an average of 1.7 ± 0.1 lobules (Figure 2). Inferior vermian development also ranged from the normal five lobules to one undifferentiated mass, with an average of 2.8 ± 0.4 lobules; two patients exhibited complete agenesis. The primary fissure was absent in five of the 45 patients. The flocculonodular lobe was present in all but three patients; hypoplasia of the flocculonodular fissure was seen, but deemed of minimal significance. Ectasia of the fourth ventricle and a rostral shift of the central velum fastigium were noted in all cases with vermian hypoplasia.

Table 2. Associated Conditions

<i>Condition</i>	<i>No. of Patients</i>	<i>Condition</i>	<i>No. of Patients</i>
Tongue protrusion	26 (45%)	Bradycardia	1 (2%)
Polydactyly	13 (23%)	Heart murmur	1 (2%)
Renal abnormalities	9 (16%)	Skips heartbeat	1 (2%)
Megalocephaly	7 (12%)	Cerebral palsy	1 (2%)
Microcephaly	5 (9%)	Hirschsprung's disease	1 (2%)
Esophageal reflux	5 (9%)	Vocal cord paralysis	1 (2%)
Gastrostomy tube	4 (7%)	Asthma	1 (2%)
Tongue tumors	3 (5%)	Hypothalamus abnormality	1 (2%)
Seizure disorder	2 (4%)	Webbed toes	1 (2%)
Hepatic abnormalities	2 (4%)	Cleft lip	1 (2%)
Pectus excavatum	2 (3%)	Club foot	1 (2%)
Hydrocephalus	1 (2%)		



Figure 1. Axial T_2 -weighted MRI obtained at the pontomesencephalic junction (isthmus) demonstrates a widened interpeduncular fossa, with associated thinning of the brain stem (arrow).



Figure 2. Sagittal T_1 -weighted MRI demonstrates enlarged interpeduncular fossa, ectatic fourth ventricle, and rostrally displaced fastigium. Note that vermian lobules are in a "picket fence" configuration rather than in their usual curvilinear profile.

Molar Tooth Sign

The most consistent region of gross abnormality in this series was located in the structures derived from the primitive isthmus: the pontomesencephalic junction, the superior cerebellar peduncles, and the cerebellar vermis. The molar tooth sign consists of an abnormally deep cleft in the isthmus of the brain stem, thickened and reoriented superior cerebellar peduncles, and vermian hypoplasia. Of the 45 group A and B patients studied radiologically, 37 (82%) were found to exhibit the molar tooth sign with varying degrees of severity in the three key anomalies (Figure 3). Thirty cases exhibited the molar tooth sign with minimal or no other abnormalities of the cerebrum, cerebellum (excluding the vermis), or brain stem.

Joubert Syndrome Plus

Seven patients exhibited the molar tooth sign and additional abnormalities of the cerebrum, cerebellum (exclud-

ing the vermis), or brain stem. This condition was named Joubert syndrome plus. Six of the seven patients with Joubert syndrome plus had the Dandy-Walker malformation. The extent of the superior vermis, isthmus, and superior cerebellar peduncle abnormalities were no greater than in the Joubert syndrome group; however, the addition of Dandy-Walker complex was associated with a greater degree of inferior vermian hypoplasia. Four of the patients with Dandy-Walker malformation also had moderate to marked hypoplasia of the mesencephalon. The one case of Joubert syndrome plus that did not show signs of a Dandy-Walker

Table 3. Abnormalities of the Vermis

	No. of Patients (N = 45)		No. of Patients (N = 45)
<i>Anterior Lobe</i>		<i>Posterior Lobe</i>	
Left and right		Lobules	
Connected	16 (36%)	Five	7 (16%)
Partially split	23 (51%)	Four	9 (20%)
Split	6 (13%)	Three	12 (27%)
Lobules		Two	5 (11%)
Two lobules	31 (69%)	One	10 (22%)
One lobule	14 (31%)	Zero (aplasia)	2 (4%)
Foliation		Foliation	
Normal	6 (13%)	Normal	5 (11%)
Mild	18 (40%)	Mild	10 (22%)
Moderate	6 (13%)	Moderate	13 (29%)
Severe	15 (33%)	Severe	17 (38%)

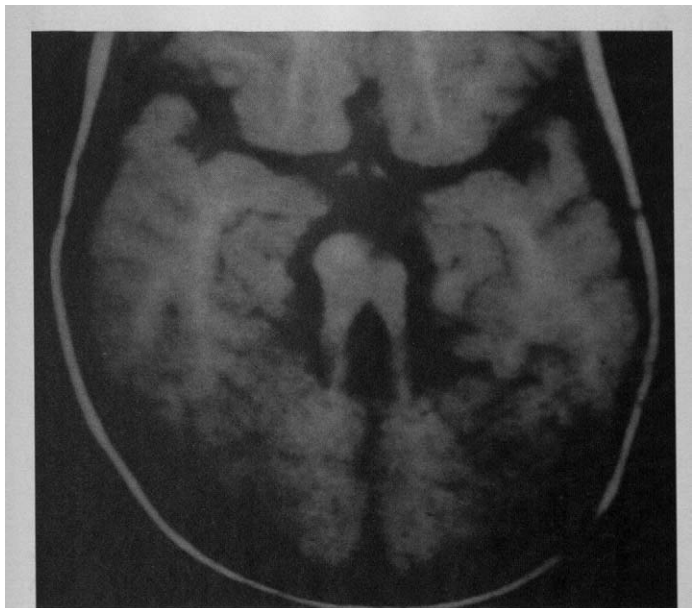


Figure 3. Molar tooth sign. Malformations in the caudal midbrain, superior cerebellar peduncles, and cerebellar vermis combine to give the appearance of a molar tooth on axial MRI through the pontomesencephalic junction.

Table 4. Joubert Mimic Category

Patient	Diagnosis	Abnormalities
1	Neocerebellar dysgenesis	Pachygyriform calcification, decreased volume CC, mild DM, diffuse LVE, small SCP and pons, hypoplastic FN and CH
2	Neocerebellar dysgenesis	Cerebral atrophy, absent CH
3	Marked vermian and cerebellar atrophy	Atrophic CH
4	Elongated isthmus; Dandy-Walker malformation	Immature brain, DM, generalized LVE, abnormal mesencephalon, hypoplastic vermis, FN, CH, and pons
5	Bilateral cerebellar atrophy	Mild DM, atrophic CH
6	Cerebellar aplasia	Mild cerebral atrophy, mild DM, generalized LVE, small SCP, severely hypoplastic vermis, absent CH, hypoplastic pons
7	Partial absence of rostral corpus callosum	Abnormal CC, abnormal tectum colliculi
8	Cystic dilation of the cisterna magna and cerebral atrophy	Moderate cerebral atrophy, generalized LVE, mild cerebellar atrophy

CC = corpus callosum; DM = delayed myelination; LVE = lateral ventricle enlargement; SCP = superior cerebellar peduncles; FN = flocculus and nodulus; CH = cerebellar hemispheres.

malformation did exhibit an abnormal mesencephalon with fusion of the tegmentum and a poorly formed intracranial cistern.

Joubert Syndrome Mimicry

The remaining eight group A and B patients, although clinically and developmentally similar to patients with Joubert syndrome or Joubert syndrome plus, had significantly different radiologic findings (Table 4). The molar tooth sign was absent in all eight cases who were found to have other definable conditions; these patients were called Joubert syndrome mimics. The isthmus, vermis, and superior cerebellar peduncles of five of the eight patients were found to be normal. Six of the eight Joubert syndrome mimic patients had abnormalities of the cerebrum, which included three with atrophy, two with an abnormal corpus callosum, one with pachygyriform calcifications, and one with an immature brain. Seven of the eight cases of Joubert syndrome mimicry also had hypoplastic (three), atrophic (two), or absent (two) cerebellar hemispheres. A Dandy-Walker malformation was present in one of the cases of Joubert syndrome mimicry.

Autopsy

The MRI obtained 6 years before the death of the group D patient showed the presence of a molar tooth sign (Figure 4). The unfixed brain reportedly weighed 1340 grams at the time of autopsy. We received a formalin-fixed brain that had been sectioned previously in the coronal plane with several sections of the cerebral hemispheres and cerebellum having been taken for histologic study. The leptomeninges showed minimal opacification, primarily along the vertex. The cerebral hemispheres were symmetrical with no gross abnormality in the gyral and sulcal pattern. There was focal interdigitation of the frontomedial gyri. The corpus callosum and olfactory bulbs and tracts were present. The basal vasculature was normally formed.

External examination of the brain stem showed severe hypoplasia of the cerebellar vermis with only a rudiment of the rostralmost portion of the superior vermis remaining. The medulla lacked the usual bulges corresponding to the medullary pyramids and inferior olives (Figure 5). Because of this, the XIth and XIIth nerves exited the medulla in a

rather haphazard fashion. Otherwise, the cranial nerves were normal. Examination of serial coronal sections of the cerebral hemispheres showed good demarcation of gray- and white-matter structures. The deep cerebral nuclei were grossly normal. The left hippocampus was slightly smaller than the right, but there were no grossly apparent architectural abnormalities. Coronal sections of the brain stem confirmed and extended the striking findings on external inspection. The fourth ventricle was markedly enlarged due to vermian agenesis. The rostral midbrain was grossly normal with a well-pigmented substantia nigra. However, the caudal midbrain showed an apparent elongation of the iter (rostral extent of fourth ventricle) and of tegmental structures in general. This apparent elongation of the caudal midbrain tegmentum corresponded to the molar tooth appearance on scan (Figure 4). The folia of the lateral cerebellar hemispheres, especially the cerebellar cortex adjacent to the enlarged fourth ventricle, were whitish and firm with poor demarcation of cortex and white matter. The dentate nuclei were indistinct. The basis pontis was small and contained a few large obliquely oriented fiber bundles corresponding to aberrant crossing pontine fibers.

Additional sections through the medulla showed striking abnormalities at caudal levels near the cervicomedullary junction. There was no apparent posterior median sulcus and there was poor demarcation of the posterior columns, nuclei gracilis and cuneatus, and spinal tract and nucleus of the Vth cranial nerve. The inferior olivary nuclei appeared indistinct and possibly hypoplastic. There was no obvious pyramidal decussation. Formalin-fixed, paraffin-embedded tissue sections from multiple levels of the brain stem and cerebellum were examined microscopically with hematoxylin and eosin, cresyl violet, and luxol fast blue stains. In addition, hematoxylin and eosin-stained sections from the thalamus and hippocampus were studied.

Cervical Spinal Cord and Caudal Medulla

There was marked dysplasia of the caudal medulla near the cervicomedullary junction. The posterior median sulcus was absent. The fasciculi gracilis and cuneatus were not separated and formed a peculiar C-shaped structure extending from the dorsomedial aspect to mediolaterally in the medullary tegmentum. The nuclei gracilis and cuneatus

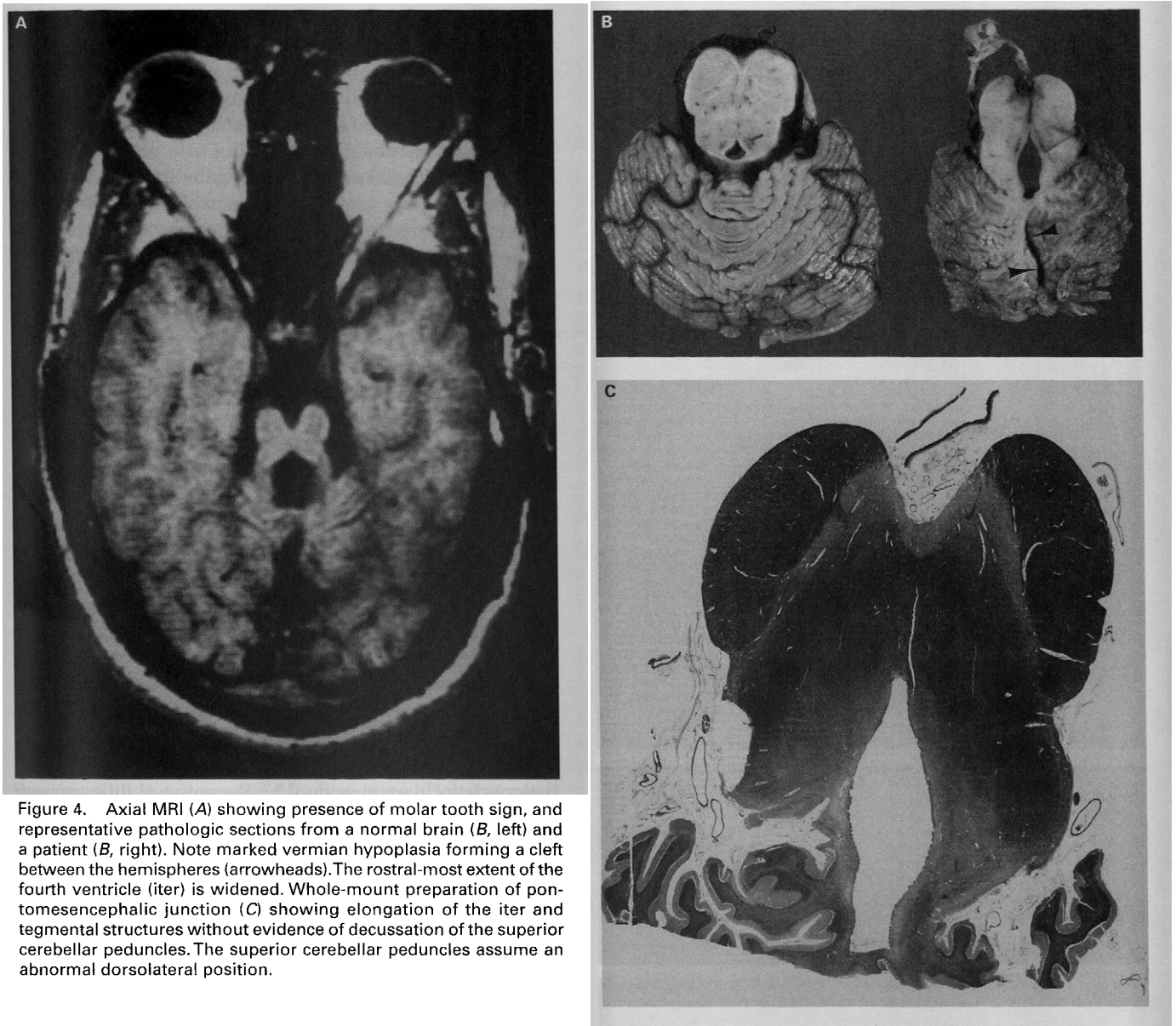


Figure 4. Axial MRI (A) showing presence of molar tooth sign, and representative pathologic sections from a normal brain (B, left) and a patient (B, right). Note marked vermian hypoplasia forming a cleft between the hemispheres (arrowheads). The rostral-most extent of the fourth ventricle (iter) is widened. Whole-mount preparation of pontomesencephalic junction (C) showing elongation of the iter and tegmental structures without evidence of decussation of the superior cerebellar peduncles. The superior cerebellar peduncles assume an abnormal dorsolateral position.

were dispersed in haphazard fashion in most caudal levels while having a more typical arrangement further rostrally. Neurons of these two nuclei were swollen and contained abundant neuronal intermediate filaments. There were many axonal spheroids associated with disorganized tegmental gray matter, the latter representing residual gracile and cuneate nuclei. Axonal spheroids were most striking centrally, just above the residual central canal within the disorganized tegmentum. The nucleus of the spinal tract of cranial nerve V was fragmented and hypoplastic (especially the pars gelatinosa). The solitary nucleus and tracts were not easily identified. A peculiar decussation of the pyramidal tract was characterized by unilateral abnormal scattering of fibers in the most caudal sections of medulla at a point where there should have been a discrete lateral corticospinal tract. There was striking marginal gliosis of the tegmentum that was clearly demonstrated by glial fibrillary acidic pro-

tein (GFAP) immunostaining. Anterior horn cells were normal at this level.

Midmedulla, Rostral Medulla, and Pons

The inferior olivary nuclei were markedly hypoplastic and poorly formed. It was impossible to tell whether accessory olives were present. There was focal cytoplasmic basophilia and hyperchromatism of scattered neurons within the ventral arcuate nucleus. As in lower levels of the medulla, there was a striking circumferential marginal gliosis that was clearly delineated by GFAP immunostaining. There was a decrease in the volume of the medial lemniscus. Neurons of the reticular formation were reduced in number and there was a relative increase in myelin staining of the tegmentum. Crossing pontine fibers were obliquely oriented. There was an apparent reduction in neurons of the pontine base without a significant glial reaction. Clumps of

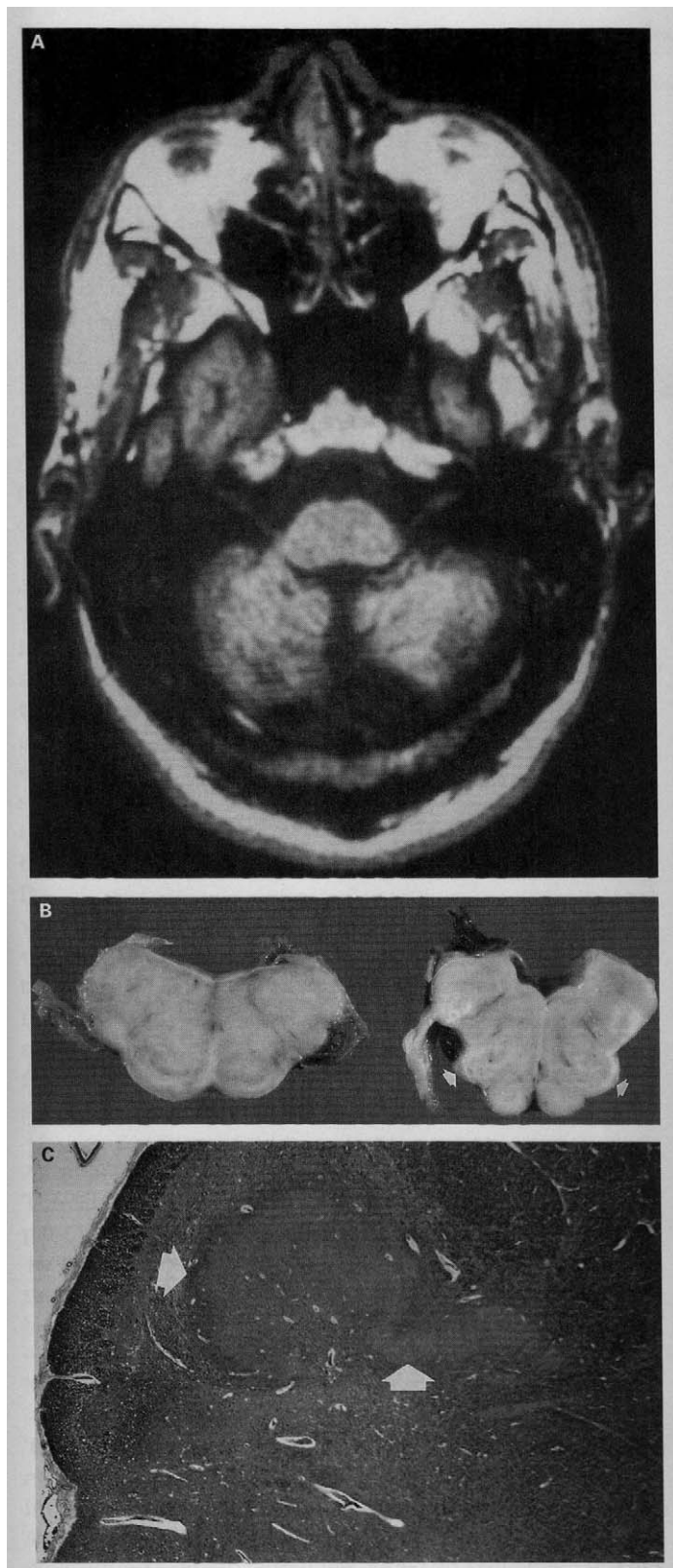


Figure 5. Axial MRI (A) and pathologic section of a patient (B, left) show that the medulla lacked the usual bulges seen in normal brain (B, right), corresponding to the medullary pyramids and inferior olives. In particular, the pyramids in the patient with Joubert syndrome are less well defined than in the normal brain and the inferior olives (well seen in the normal brain; arrows) are not grossly apparent. Microscopic section at the midmedulla level (C) shows marked hypoplasia of the inferior olive (arrows).

large neurons were present in the tegmentum that could represent dysplastic inferior olivary nuclei.

Caudal Midbrain

There was an enlarged slit-like iter and elongated tegmentum. Pigmented neurons corresponding to a dispersed locus coeruleus extended along the elongated iter (ie, the locus coeruleus was elongated along an anterior-posterior dimension and appeared to extend posteriorly toward the tectum). There was no decussation of the superior cerebellar peduncles. The latter assumed an abnormal dorsolateral position.

Cerebellum

The dentate nucleus appeared to be broken up into individual islands or foci of gray matter. Other than this, no obvious heterotopias were identified. Sections of cerebellum showed extensive areas of marked cortical atrophy with Purkinje cell loss and proliferation of the Bergmann glia. A few apparently normal areas of cerebellar cortex also were observed.

DISCUSSION

All patients were found to be developmentally delayed. Gross dysfunction in vision and ocular motility, motor skills, and speech severely impair ability to learn and gather stimulus from the environment.¹⁷ Detailed neuropsychologic reports of patients with Joubert syndrome warn of underestimation of cognitive ability because of the difficulty patients have in expression.^{17,21,22} Receptive abilities appear to be less severely impaired than expressive language and motor functioning. In a recent study, Gitten et al performed a correlational analysis of the severity of posterior fossa abnormalities seen on MRI with level of developmental delay in patients with Joubert syndrome.²¹ No positive correlations were found between developmental delay and the composite score of posterior fossa abnormalities. This finding suggests that radiologically detected abnormalities cannot predict the severity of neuropsychologic dysfunction, and the physiologic or neuroanatomic basis for the mental retardation in Joubert syndrome is still unclear. The one patient from whom neuropathology was obtained had trouble communicating because of expressive language difficulties, but he had learned to read music and enjoyed playing the piano. His MRI and autopsy showed a moderately severe degree of vermian hypoplasia.

The parental report of hyperpnea or apnea in 55% to 60% of patients is consistent with previous observations that not all patients have respiratory abnormalities. The true prevalence of respiratory abnormalities has yet to be defined in a large cohort. It could be that such problems are much more common in Joubert syndrome but are of limited severity in a subset of patients. Longitudinal studies are required to better define the natural history and pathogenesis of breathing problems. Early death has been reported in Joubert syndrome and attributed to apnea. To date no therapy has been shown to be effective in reducing episodes of hyperpnea and

apnea, which seem most severe in the perinatal period but can persist in later childhood.

Ocular and oculomotor findings are common in Joubert syndrome.⁸⁻¹⁵ We previously showed that children with Joubert syndrome have variable delays in initiating ocular saccades and difficulty in cancelling the vestibular-ocular reflex.²⁰ Such oculomotor defects correlated with MRI findings. Children with suspected Joubert syndrome should have a pediatric neuro-ophthalmologic assessment to determine if the characteristic oculomotor abnormalities are present. It is not surprising that only 22% of parents in this series reported the presence of oculomotor apraxia since few patients had undergone detailed examinations. We are not aware of any other condition in which patients have the combination of oculomotor abnormalities reported by Maria et al²⁰ Thus, neuro-ophthalmologic assessment could help distinguish Joubert syndrome from Joubert syndrome mimics. A possible correlation between renal and retinal abnormalities has been reported in Joubert syndrome.²³⁻²⁵ In this study, 19% of patients reported retinal abnormalities and 16% reported renal dysfunction; only 3 of the 17 patients were known to have concurrent renal and retinal abnormalities. Further studies are required to determine the true prevalence of renal abnormalities and if a subset of patients have genetic conditions other than Joubert syndrome.

It has been more than 20 years since Friede and Boltshauser reported the only other pathologic study of the brain of a patient with Joubert syndrome. The neuropathologic findings reported here share some striking similarities with those reported by Friede and Boltshauser.²⁶ Specifically, aplasia of the cerebellar vermis and sequestration of the dentate nucleus into islands were present in both cases. Elongation of the locus coeruleus without other striking midbrain abnormality were common to both cases. A complex malformation of the caudal medulla was observed in the present case and shares some similarities with Friede's case. Specifically, absence of all but minor pyramidal decussation, and anomalies of the descending tract of cranial nerve V, the solitary nucleus and tract, the dorsal column nuclei, and inferior olivary nuclei are common features of both cases. One significant difference between Friede's case and ours was that in the former, the cerebellar hemispheres were judged to be enlarged, while they were small in the present case. One reason for this could have been that the cerebellum was secondarily damaged by seizure activity and by hypoxia in the present case. No apparent structural lesion was identified that might explain the etiology of the seizures.

Genetic and Developmental Considerations

It is likely that the isthmus, cerebellar vermis, and superior cerebellar peduncles are derived from the first rhombomeric component of the developing brain stem.²⁷⁻²⁹ Several studies have discovered that the cerebellum, once thought to be solely a hindbrain structure, is derived from a migration of both mesencephalic and rhombencephalic tissue.^{30,31} This study found that the majority of MRIs demonstrate a nor-

mal midbrain, pons, medulla oblongata, and cerebellar hemispheres, although all who fell into the Joubert syndrome and Joubert syndrome plus categories had abnormalities in the isthmus of the rhombencephalon. In light of the fact that phenotypic expression of abnormalities in the isthmus were so strikingly similar among patients, and that Joubert syndrome is probably autosomal recessive, a genetic mutation in a gene or group of genes expressed in the isthmus portion of the developing brain stem could explain the pathogenesis of malformations. However, pathologic abnormalities in the caudal medulla not detected radiologically suggest the possibility that the genetic mutation(s) result in widespread brainstem and cerebellar vermis malformations. The constellation of abnormalities categorizing Joubert syndrome plus could represent additional mutations in neighboring genes that affect not only the isthmus and medulla but also the midbrain.

Extensive research in vertebrate models such as mice,³² chicks,^{30,31} and zebrafish³³ has isolated several genes that act on the regions of the mid- and hindbrain. Members of the *Engrailed* (*En*),^{34,35} *Wnt*,³⁶⁻⁴⁰ *Hox*,⁴¹ and *Pax*⁴² (paired-box-containing) gene families have been found to regulate pattern formation and segmentation in the developing brain stem. Homozygous mutant mice targeted for the *Wnt1*^{36,37} or *En1*³⁴ genes both experience deletion of the cerebellum and midbrain structures, whereas mutations of the *En2*³⁵ gene lead to less severe abnormalities of cerebellar foliation. Although distinct from Joubert syndrome,³⁸ recent analysis of a less severe *Wnt1* mutant mouse, *swaying*,³⁹ suggests that *Wnt1* is necessary for proper formation of the pontomesencephalic junction. One interesting discovery that could be relevant to Joubert syndrome is that some candidate genes, such as the *Pax* and *Wnt* genes, are expressed in other organ systems. For example, mutation of the *Pax5*⁴² and *Wnt1*⁴⁰ genes lead not only to abnormalities of the brain stem, but also to abnormalities of B-cell and limb development, respectively. A similar mutation could explain the comorbid renal, hepatic, and ocular abnormalities associated with Joubert syndrome. So far, only *Wnt1* has been excluded as the gene causing Joubert syndrome.³⁸ Further genetic research is warranted with an emphasis on genes whose sites of action are associated with the isthmus portion of the developing brain stem and the caudal medulla. The question remains on how genetic defects account for the constellation of clinical, radiologic, and pathologic findings. Discovery of the genetic basis for the abnormalities found in Joubert syndrome through linkage analysis studies underway and the study of candidate genes will aid in diagnosis, genetic counseling, and understanding of the pathogenic basis for the development of widespread brainstem and cerebellar malformations.

Diagnostic neuroimaging with MRI should be obtained in the perinatal period in children with hyperpnea and apnea to search for the presence of the molar tooth sign and vermian hypoplasia. In the absence of perinatal distress, it took some time (mean, 33 months) for the hypotonia and developmental delay to trigger neurology consultation and

diagnostic neuroimaging. Now that the radiologic features of Joubert syndrome are better defined, it should be possible to distinguish Joubert syndrome from mimicking disorders at a very early age. Better characterization of the syndrome is paramount to successful genetic studies to identify the defective gene(s). Much work needs to be done in Joubert syndrome to understand the pathogenesis of breathing dysfunction and mental retardation.

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