Cerebral and Cerebellar Motor Activation Abnormalities in a Subject With Joubert Syndrome: Functional Magnetic Resonance Imaging (MRI) Study

ABSTRACT

Joubert syndrome is an autosomal recessive disorder characterized by hypotonia, ataxia, developmental delay, and a distinctive hindbrain malformation involving the cerebellum and brain stem, visualized radiographically on magnetic resonance imaging (MRI) as the "molar tooth sign." In postmortem brains from subjects with Joubert syndrome, there is an apparent absence of decussation of both corticospinal and superior cerebellar tracts, although the functional significance has not been elucidated. We sought to explore the cerebral and cerebellar activation pattern elicited by finger tapping in an adolescent with Joubert syndrome and in a normal control subject using functional MRI. In contrast to the typical highly lateralized activation seen in our control subject, the subject with Joubert syndrome demonstrated striking bilateral activation of the sensorimotor and cerebellar cortex. Although our functional MRI data do not indicate a clear absence of decussation, the abnormal activation pattern observed suggests altered brain functional organization in relation to anatomic differences. Malformation of the hindbrain could result in recruitment of alternative pathways, similar to what has been observed following ischemic injury to the developing or mature central nervous system. (*J Child Neurol* 2004;19:214–218).

Joubert syndrome is a rare autosomal recessive neurologic disorder characterized by cerebellar vermis hypoplasia, neonatal hypotonia, ataxia, developmental delay, and, often, oculomotor apraxia and/or neonatal breathing abnormalities consisting of episodic tachypnea and apnea.[1-3] The characteristic neuroradiologic finding is the "molar tooth sign" on axial magnetic resonance imaging (MRI) through the pontomesencephalic junction (brainstem isthmus), which consists of an abnormally deep cleft anterior to the isthmus of the brain stem (a deepened interpeduncular fossa), thick and straight superior cerebellar peduncles, and cerebellar vermis hypoplasia. Other anomalies include an increased rostrocaudal lengthening of the isthmus and a cleft in the vermis.[4,5] The specific genetic abnormalities in Joubert syndrome have not been identified, although one locus in two Arab families has been mapped to chromosome 9q34.[6]

Postmortem neuropathologic reports of the brains of patients with Joubert syndrome are limited. Those available describe, in addition to hypoplasia and clefting of the cerebellar vermis, anomalies of the dorsal column nuclei, solitary tract, and cranial nerve V tract; abnormal elongation of the locus ceruleus; and hypoplasia of the inferior olives.[7-9] However, one of these references also describes pronounced cerebral malformations consisting of extensive nodular heterotopias without documentation of the molar tooth sign,[9] in contrast to the other postmortem descriptions. These studies demonstrate absence of decussation of the superior cerebellar peduncles and medullary pyramids,[7,8] as well as abnor-

mal orientation of pontine crossing fibers,[5] findings supported by limited MRI studies.[5,10] Recent high-resolution MRI of the postmortem brain of a child with Joubert syndrome and the molar tooth sign showed that the superior cerebellar peduncles did not cross the midline at the level of the isthmus, thus accounting for the narrowing of the isthmus and corresponding deepening of the interpeduncular fossa. Hypoplasia of the inferior olives was also visualized with high-field MRI.[11] In this study, we sought to determine if absent or defective motor tract decussation in Joubert syndrome was associated with changes in cortical organization of motor system function. We obtained functional MRIs during finger tapping in a patient with Joubert syndrome and the classic molar tooth sign and compared the cerebral and cerebellar activation patterns with those of normal control subjects.

Methods

Subjects

Informed consent for this study was obtained under a protocol approved by the Human Subjects Division of the University of Washington.

We studied an 18½-year-old left-handed female patient with the diagnosis of Joubert syndrome since 7 years of age. She had oculomotor apraxia, rotatory and vertical nystagmus, ataxia, hypotonia, developmental delay, and cerebellar vermis hypoplasia. She had surgery for strabismus and has myopia but no renal or retinal abnormalities. Cranial MRI confirmed the presence of the molar tooth sign (Figure 1). Intelligence testing by the Wechsler Adult Intelligence Scale-III (WAIS-III) at the age of 18 years revealed a Performance IQ of 65, a Verbal IQ of 76, and a Full-Scale IQ of 69. Her family history is notable for a 14-year-old brother with the same diagnosis and similar findings that also include postaxial polydactyly but no other affected family members.

The control subject was a 24-year-old right-handed female with normal cognitive function.

MRI Acquisition

Images were acquired on a GE Signa 1.5-Tesla system. Subjects were placed on the scanner bed, pillow under knees, and wore prescription-adjustable, fiberoptic goggles through which the instructions were viewed. High-resolution anatomic images were obtained in plane with functional images, with a slice thickness of 6 mm (1 mm gap) and in-plane resolution of 0.94 mm. The functional MRI used a gradient echo, echoplanar pulse sequence with T_2-weighting for blood oxygenation level-dependent contrast, with a TR of 2000 milliseconds, a TE of 40 milliseconds, 20 axial brain slices of 6 mm thickness with a 1 mm gap, and in-plane resolution of 3.75×3.75 mm. Each functional MRI consisted of six sequential cycles, each with 20 seconds of right index finger tapping, followed by 20 seconds of left index finger tapping and then 20 seconds of rest. The scans began with a 10-second lead-in period to establish magnetic field homogeneity and to account for hemodynamic lag. During scanning, subjects wore a splint to keep wrists and other fingers immobile.

Although the subject with Joubert syndrome is significantly nearsighted (OD −12.5 diopters, OS −8.5 diopters), her vision was correctable with goggles, and the instructions during tasks were very large and easy to read. She did not demonstrate weakness in her hands or fingers. Verification that the subject tapped only the correct finger on the designated side was accomplished by visual observation from the console room by one of the authors (J.D.P.). Both subjects had been trained to tap at 2 Hz, but the subject with Joubert syndrome tapped at approximately 4 Hz during functional MRI.

Data Analysis

For each functional MRI data set, all images were motion-corrected to a standard volume using the Automated Image Registration and MEDx 3.41 (Sensor Systems, Sterling, VA). Images were linear-detrended, using rest as a
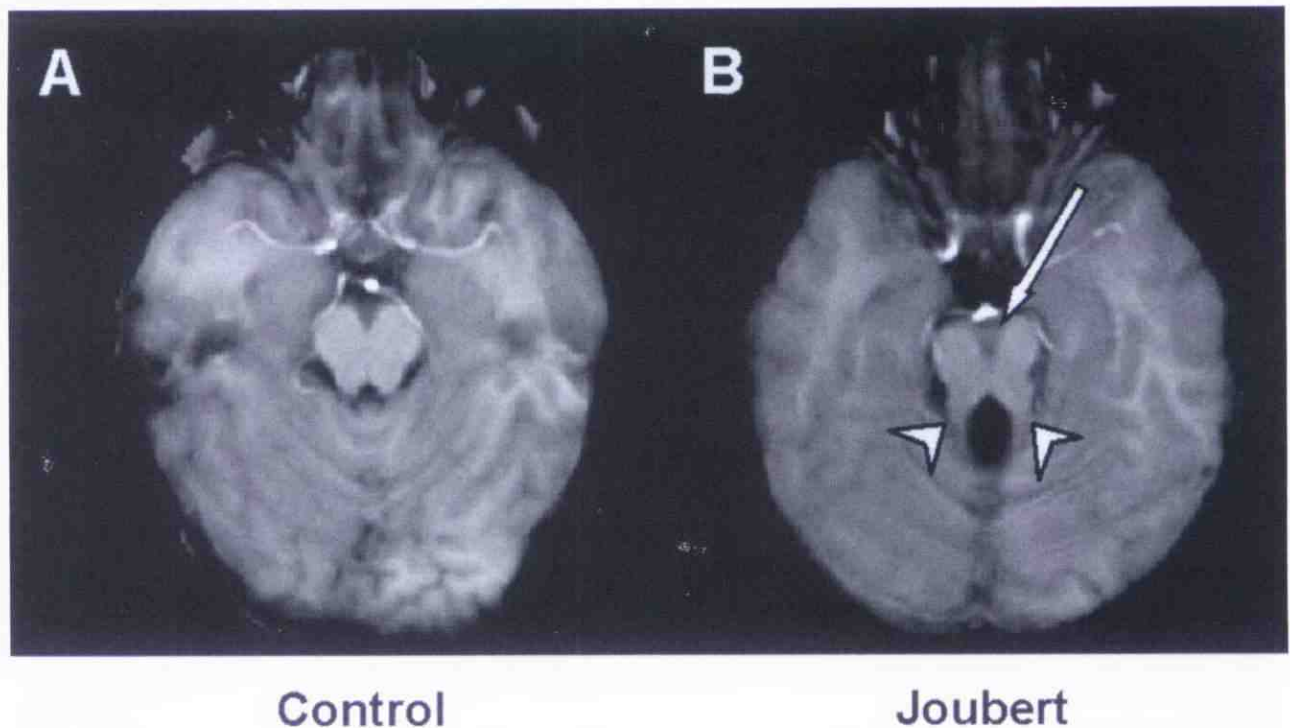
Figure 1. Anatomic magnetic resonance images illustrating (A) a normal control subject on axial section through the brain stem and cerebellum and (B) the presence of the molar tooth sign in a subject with Joubert syndrome. The individual with Joubert syndrome has cerebellar vermis hypoplasia with a deep interpeduncular fossa (*white arrow*) and thick and straight superior cerebellar peduncles (*white arrowheads*).

baseline. A *t*-test was performed on each voxel, contrasting the rest ("off") and right or left finger-tapping ("on") states, with results expressed as a Z-map. Each subject's activation Z-map was spatially smoothed with a 4 mm gaussian filter. The resulting maps were transformed into Talairach standard stereotaxic space.

The number of significantly activated voxels was measured within two regions on each side of the brain: the primary sensorimotor cortex, consisting of the precentral + postcentral gyri, and the cerebellar hemisphere. These gyri were identified relative to the central sulcus; the central sulcus was identified as being immediately posterior to the precentral sulcus, which was defined as previously described.[12] Activated voxels with Z > 3 and belonging to an activation cluster with a size greater than that expected by chance (*P* < .05) were identified.[13] This method considers the significance of activation in the voxel of interest and in adjacent voxels to identify a voxel as significantly activated and also corrects for multiple comparisons. The number of significantly activated voxels belonging to such significant clusters was then counted in both the left and right sensorimotor cortex and cerebellum. These regions were defined on the high-resolution anatomic scans in-plane with functional images and guided by the volumetric images plus brain atlases. The laterality index was calculated for the activation volume in each brain region by the following formula: (left − right)/(left + right), where left and right refer to regional activation volumes.

The laterality index data from the subject with Joubert syndrome was compared with a data set that combined the current control subject with seven right-handed normal young control subjects under the age of 50 years, who have been described previously[14] and who also performed 2 Hz right index finger tapping under the same acquisition and analysis methods as in the current study.

Results

The anatomic MRI from the individual with Joubert syndrome, in contrast to that of the normal control subject, demonstrates a hindbrain malformation consisting of the molar tooth sign, with the "roots" of the "tooth" represented by the malformed superior cerebellar peduncles (see Figure 1).

With right-sided finger tapping, the normal control subject showed cerebellar activation almost exclusively in the ipsilateral (right) hemisphere. In contrast, the subject with Joubert syndrome demonstrated some bilateral cerebellar activation with an ipsilateral activation that was more robust than that of the control subject, particularly in the superior cerebellum. These results are reflected by the voxel counts shown in Table 1.

For the normal control during right-sided finger tapping, activation in the primary sensorimotor cortex was predominantly on the left, within the precentral gyrus (Figure 2A). These results are very similar to findings in young controls previously described.[15] The cortical activation pattern for the subject with Joubert syndrome

Table 1. Voxel Counts at Z > 3 Threshold

Region of Brain Activation	Joubert Syndrome Subject	Control Subject(s)
Left sensorimotor cortex	90	35
Right sensorimotor cortex	77	0
Left cerebellum	48	0
Right cerebellum	93	11
Laterality index*		
Sensorimotor cortex	0.08	1.0 (0.87)†
Cerebellum	−0.32	−1.0

*Laterality index was calculated by (left − right)/(left + right).
†When data are pooled from a total of eight control subjects (the one control in this study and seven additional controls under age 50 years,[14] the mean laterality index for the sensorimotor cortex is 0.87 ± 0.12, with a range of 0.72 to 1.0. See the text for details.
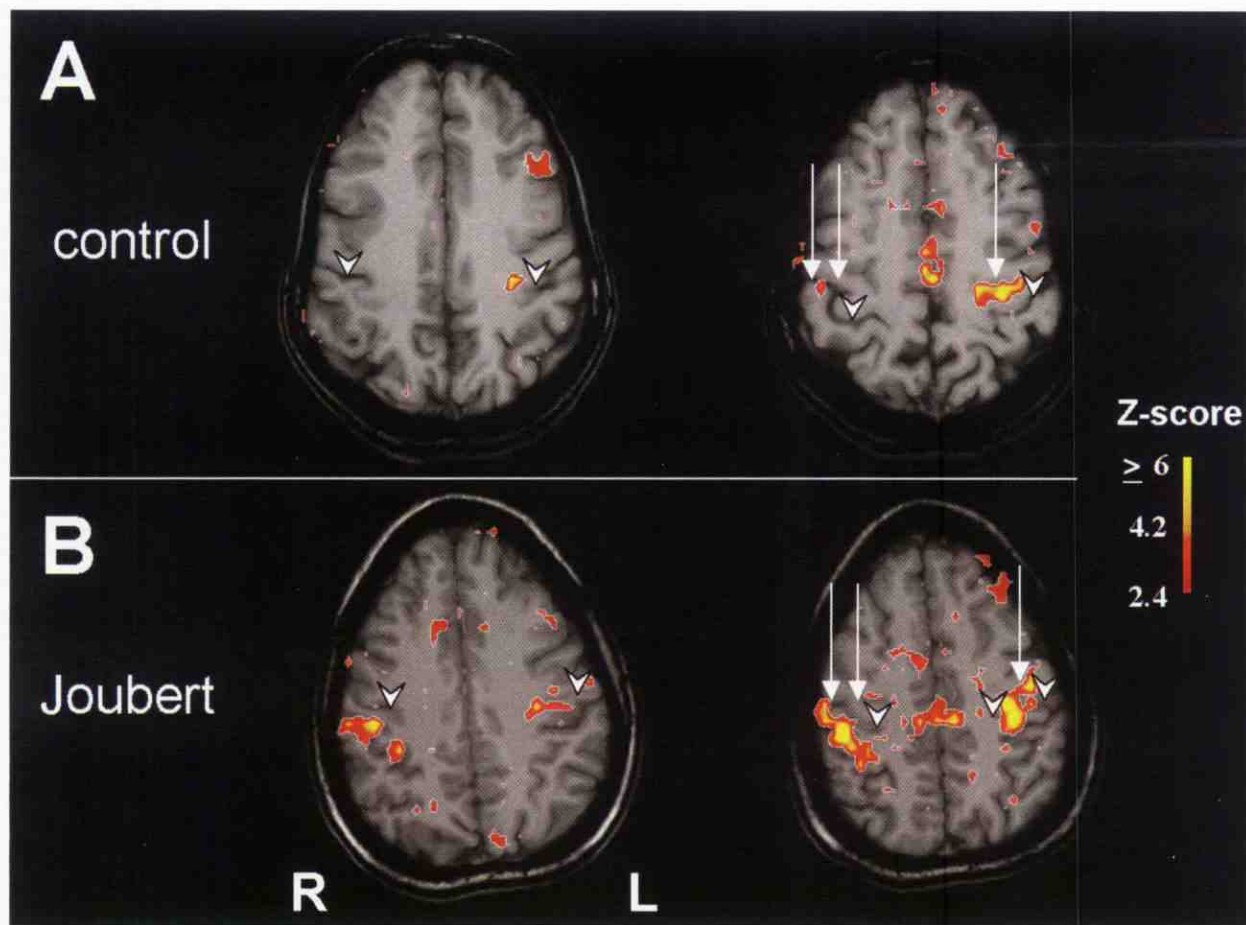
Figure 2. Functional magnetic resonance imaging activation patterns during right index finger tapping in a control subject and in a subject with Joubert syndrome. Functional images are superimposed on anatomic images and presented in a radiologic orientation, with the left side of the brain on the right side of the figure. For each subject, selective representative slices at the same level are shown. *A*, Selected cortical activation images from a 24-year-old right-handed female control comparing 2 Hz right index finger-tapping to rest. *Left panel:* Pattern of activation in sensorimotor cortex, with the central sulcus indicated by *arrowheads*. *Right panel:* Activation in the primary sensorimotor cortex is predominantly on the left on the precentral gyrus (*long arrow*). *Double long arrows* indicate minimal activation in the right hemisphere, ipsilateral to the tapping finger. *B*, Selected cortical activation images from an 18½-year-old left-handed female with Joubert syndrome comparing 4 Hz right index finger tapping to rest (the patient was trained and instructed to tap at 2 Hz). *Left panel:* Pattern of activation in the sensorimotor cortex, with the central sulcus indicated by *arrowheads*. Activation in the primary sensorimotor cortex is bilaterally distributed. *Right panel:* On the left side (*long arrow*), activation is primarily on the precentral gyrus, anterior to the central sulcus (indicated by *arrowheads*). On the right, ipsilateral to the tapping finger, activation is larger than in the control and is also primarily posterior to the central sulcus (*double long arrows*). Activation in the midline supplementary motor area is similar in both subjects. Note that regions in the "precentral gyrus" are motor and those in the "postcentral gyrus" are sensory.

with right finger tapping showed a bilateral distribution of signal intensity in the primary sensorimotor cortex (Figure 2B). In the left primary sensorimotor cortex, activation was predominantly in the precentral gyrus, anterior to the central sulcus, similar to the normal control (Figure 2B, right panel). However, on the right side, ipsilateral to the tapping finger, activation was primarily posterior to the central sulcus, in the S1 and S2 sensory areas. The activation pattern in the midline supplementary motor area was similar in both control subjects and the subject with Joubert syndrome.

The cluster analysis derived from voxel counts is summarized in Table 1. The laterality index in the cerebellum was less negative in the subject with Joubert syndrome, as expected for a subject with bilateral rather than purely ipsilateral activation. The laterality index in the sensorimotor cortex for the subject with Joubert syndrome was markedly less than that of the control subject,

indicating significant ipsilateral activation in this region. In fact, a comparison of the laterality index in the sensorimotor cortex in our subject with Joubert syndrome (0.08) with the average from eight normal control subjects (the one included here plus seven from a previous study[14]; 0.87 ± 0.12) demonstrates that the laterality index of the subject with Joubert syndrome is clearly more than 2 SD below the normal group mean.

Discussion

Normal control subjects, when tapping the right index finger, have a predominantly contralateral motor activation consistent with pyramidal decussation, as well as some minor ipsilateral motor and sensory activations but at an order of magnitude less. They also demonstrate ipsilateral cerebellar activation. Our patient with Joubert syndrome had clear differences in the brain activa-

tion pattern with finger tapping in both the sensorimotor cortex and the cerebellum.

The pattern of sensorimotor cortex activation in the subject with Joubert syndrome during right finger tapping showed a much more bilateral distribution of activity compared with the primarily contralateral pattern of activation seen in normal subjects. When the ipsilateral motor strip is activated during finger tapping in normal subjects, the pattern of activation is usually smaller and shifted anteriorly.[12] Our subject with Joubert syndrome had essentially equal bilateral magnitudes, but the ipsilateral side was predominantly more posterior, with activation in the sensory cortex, S1, as well as the inferior parietal S2 area. With regard to cerebellar activity, the subject with Joubert syndrome demonstrated cerebellar activation that was more bilateral compared with that of the control. This might reflect a compensatory mechanism to recruit additional cerebellar pathways given the reduced size of the cerebellar vermis and abnormal crossing of cerebellar tracts in individuals with Joubert syndrome.

The increased extent to which sensorimotor cortex and cerebellar activation was bilaterally organized in the subject with Joubert syndrome might simply reflect a change arising from the anatomic abnormalities in the cerebellum and brain stem in this condition. The finding might also indicate aberrant sensory processing. Finally, a number of studies have shown that in patients recovered from paresis-inducing stroke, there is an increase in the extent to which sensorimotor cortex activation is bilaterally organized.[16-18] The significance of this change after stroke is a matter of ongoing discussion. Some authors have emphasized its correlation with visible mirror movements,[16] which were absent in the subject with Joubert syndrome. Some have provided evidence from transcranial magnetic stimulation methods that this activation could, in part, be a passive disinhibition arising from injury to callosal inhibitory fibers.[17] Others have suggested a direct participation in movement control by the sensorimotor cortex ipsilateral to movement.[18] Thus, it is also possible that Joubert syndrome–related differences in sensorimotor cortex organization represent the same adaptive events that are related to maintenance of sensorimotor function in adults recovered from stroke.

One of the limitations of this study is the inclusion of only one subject because there is known phenotypic heterogeneity in Joubert syndrome and there are likely to be at least two (or more) causative genes for Joubert syndrome.[6,19,20] Given this heterogeneity, we expect that future studies including several subjects with Joubert syndrome might show a spectrum of abnormalities in the activation patterns in this and other motor tasks. Another limitation of this study is that the subject with Joubert syndrome was left-handed, in contrast to controls. However, this concern is reduced by prior observations that right-hand motor task performance is not associated with substantial differences in lateralization of motor cortex activation when comparing left-handed and right-handed subjects.[21] Additional limitations arise from further differences between the subject with Joubert syndrome and controls. The patient with Joubert syndrome had ataxia. The reduction of IQ could be consistent with differences in attention during scanning, known to change functional MRI activation.[22] The differences in tapping rate could also have influenced final results.[23]

However, none of these limitations likely account for the observed difference in the laterality index (see Table 1).

In this study, we did not use MRI methods with sufficient resolution to determine whether pyramidal decussation was normal in the subject with Joubert syndrome, so the precise relationship between functional reorganization and pyramidal tract anatomic abnormalities related to Joubert syndrome cannot be determined. We hypothesize that some subjects could show evidence for a complete lack of decussation or, as in our subject, demonstrate findings consistent with abnormalities in the development of corticospinal pathways or of laterality. It is possible that specific functional abnormalities can, in fact, be predictive of the specific gene defect responsible for Joubert syndrome in an individual, and these genes are likely to developmentally regulate the patterning and organization of the hindbrain. Our study shows a clearly abnormal activation pattern, which raises the possibility that functional MRI could be used for future genotype-phenotype studies. High-resolution correlative studies, including volumetric MRI and diffusion-tensor imaging to specifically trace white-matter tracts, will be important to establish structure-function relationships.[24]

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Thrombophilia Interpretation in Childhood Stroke: A Cautionary Tale

ABSTRACT

Several authors have reported a link between childhood stroke and inherited thrombophilia in recent years. The impact of such a relationship on management and outcome is yet to be determined, as is the potential cost-benefit ratio associated with the performance of thrombophilic screening in children presenting with ischemic stroke. We present a case that highlights the need for clinical and radiologic examinations to remain the definitive criteria used to diagnose stroke in children. The diagnosis should not be influenced by the finding of a thrombophilic marker. (*J Child Neurol* 2004;19:218–219).

A number of studies have shown a relationship between childhood stroke and inherited thrombophilia.[1,2] The clinical significance of this relationship and the cost benefit of thrombophilic testing in children presenting with stroke remain uncertain. Additionally, the interpretation of thrombophilic markers in children is difficult, and age-appropriate reference intervals for thrombophilic markers must be used. We report a case that highlights the potential danger of overinterpretation of thrombophilic markers in children presenting with presumed stroke.

A previously well 5-year-old Arabic boy presented after being found pale, unresponsive, and aphasic and having been incontinent of urine. The symptoms and signs resolved over the following 12 hours. A postictal electroencephalogram (EEG) performed the following day identified left-sided slow-wave activity. A clinical diagnosis of a postictal state following a focal seizure was made. The patient recovered fully and was discharged. A magnetic resonance image performed 2 weeks later showed a low signal lesion in the left insula cortex (7 mm diameter), likely representing an old infarct (Figure 1). The lesion did not have the signal characteristics of cortical edema associated with a recent seizure. An extensive thrombophilia screen was performed, including protein C, protein S, antithrombin, lupus anticoagulant, anticardiolipin, and activated protein C ratio. All results were reported as normal, apart from reduced total protein S, 56% (laboratory reference