

Special Article

Cognition, Behavior, and Development in Joubert Syndrome

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ABSTRACT

This article reports on a series of studies of children with Joubert syndrome who were examined in three investigations from 1994 through 1998. Neuropsychologic screening of 10 of 40 children showed a variety of deficits in cognition, verbal memory, visuomotor, motor, and language-related tasks. Parent report of developmental attainments revealed only 3 of 40 children functioning in the borderline range, with the rest scoring in the severely impaired range. Parent reports of behaviors revealed problems in temperament, hyperactivity, aggressiveness, and dependency, as well as problems in physical development and care that were felt to be related to their neurologic handicaps. Future directions of research with this rare disorder are suggested. (*J Child Neurol* 1999;14:592-596).

Joubert syndrome is a multidimensional syndrome, characterized by neuroanatomic, physical, and neurobehavioral components. Autosomal-recessive inheritance is suggested by its occurrence in both males and females (in a male to female ratio of 2:1), its elevated expression among sibships, and consanguinity found among approximately 20% of patients' parents.¹⁻³

In their original report, Joubert et al⁴ indicated that agenesis of the cerebellar vermis was a common structural abnormality affecting four siblings in whom a syndrome including episodic hyperpnea, abnormal eye movements, ataxia, and mental retardation had been discovered. Structural abnormalities, found through advanced imaging techniques, continue to be used to support clinical findings of features of Joubert syndrome. Specifically, reports indicate that patients with Joubert syndrome show abnormalities of the midline cerebellum. One of the most consistently found radiologic abnormalities is dysgenesis or complete agenesis of the cerebellar vermis, with dysgenesis occurring predominantly in the posterior-inferior region, the final

embryonic region to develop. Other commonly found neurologic abnormalities include enlarged and maloriented peduncles as well as a dysmorphic or asymmetric midbrain. Together, these neuroradiologic findings have been referred to as the "molar tooth sign."⁵ Central nervous system abnormalities extending beyond the cerebellum also have been described, including a hypoplastic brain stem, cortical atrophy, delayed myelination, and an enlarged 4th ventricle.⁶ In Joubert syndrome cases in which the 4th ventricle is enlarged, an associated disorder, Dandy-Walker malformation, also can be present. Like Joubert syndrome, Dandy-Walker malformation is characterized by dysplasia of the cerebellar vermis, as well as hydrocephalus and dilation of the 4th ventricle.

Characteristic clinical symptoms and signs further define Joubert syndrome. These symptoms and signs include ocular, motor, and respiratory abnormalities.⁷ Some neonates experience respiratory difficulties described as episodes of apnea alternating with tachypnea, which have been described as similar to the panting of a dog.¹ Other early clinical manifestations described form a range of ocular abnormalities, including nystagmus (oculomotor apraxia), abnormal saccades or gaze palsy (oculomotor ataxia), and decreased visual acuity.^{5,7} Reported motor abnormalities include psychomotor retardation, poor coordination, and hypotonia.¹ Subjects with Joubert syndrome have been described as displaying other anomalies, including polydactyly of the fingers or toes, tumors of the tongue, rhythmic protrusions of the tongue, polycystic kidneys, hepatic fibrosis, and facial spasms.⁷⁻⁹

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Until recently, the neurobehavioral development of children with Joubert syndrome has not been well described. The original report of the disorder included the term "mental retardation" as part of a constellation of symptoms comprising the syndrome.⁴ Mental retardation in children with Joubert syndrome was again indicated by Boltshauser and Isler⁷; however, neither report included assessment information. While reports continued to include terms such as mental retardation and developmental delay to represent a consistent characteristic of Joubert syndrome,^{6,9} others began to question whether the mental abilities of children with Joubert syndrome had been underestimated.¹⁰ It was argued that the cognitive abilities of children with Joubert syndrome would be difficult to recognize because of severely impaired fine and gross motor movements, abnormal eye movements, deficient speech, and breathing difficulties, each causing barriers to interaction. However, a more comprehensive evaluation by Maria et al⁵ of 11 children with Joubert syndrome indicated that these children were impaired on measures of attention, motor, visuospatial, language, and social functioning. Through their investigation of children with sporadic nonsyndromic cerebellar hypoplasia, Shevell and Majnemer¹¹ also concluded that cerebellar hypoplasia could be a marker for developmental disability. Developmental disability in this study included delays in motor, language, intellectual, memory, perceptual, and social skills.

The literature on Joubert syndrome comprises mainly general descriptions of a small number of cases. Although research on patients with Joubert syndrome reports some level of developmental delay, neurobehavioral development has not been well characterized. Research on other disorders involving cerebellar malformations suggests that the cerebellum plays a significant role in psychomotor development. Our goal was to assess a large sample of children with Joubert syndrome, using measures of neurobehavioral functioning and development, to more specifically define the deficits as well as abilities seen in these children.

NEUROBEHAVIORAL INVESTIGATIONS

Initial Neurobehavioral Study

Our first investigation of children with Joubert syndrome began at a meeting of the Parents in Touch Network in Orlando, Florida, in 1994. A brief neuropsychologic battery was selected to evaluate the children. The battery consisted of the Information and Picture Completion subtests from the Wechsler Intelligence Scale for Children-III (WISC-III).¹² Memory was assessed by means of the digit span subtest from the WISC-III; immediate and delayed recall of stories read to the children were assessed by the Wide Range Assessment of Memory and Learning.¹³ Motor functioning was assessed by means of Denckla's test of finger and foot movements.¹⁴ The Beery-Buktenica Test of Visuomotor Integration¹⁵ was used to measure fine motor copying skills. Finally, a measure of verbal fluency was administered to assess the child's ability to generate words to target letters (F, A, and S).¹⁶

In addition to the neurobehavioral measures, we asked the parents to complete a problem behavior questionnaire developed at the Psychology Clinic of the University of Florida (UF Child Diagnostic Screening Scale). Parents also completed the Child Development Inventory,¹⁷ which is a parent report measure of developmental attainments of their child across the domains of language comprehension, expressive language, social development, gross motor skills, fine motor skills, self-help behaviors, and letter and number knowledge. There also is a summary scale measuring general development.

Subjects

Nine boys and two girls were assessed. Four of the children were right-handed, one was left-handed, four were ambidextrous, and one child had no clear hand preference. Three of the children were so profoundly impaired that only the parent questionnaires could be accomplished. Two of the children were below the age limits of the neuropsychologic test battery, so only the parent questionnaires were obtained. For the remaining six children, neuropsychologic testing and parent report questionnaires were administered. Scores were calculated according to the tests' standard methods, then categorized broadly as impaired (greater than two standard deviations below age-appropriate mean scores) or unimpaired.

Results of Neuropsychologic Testing

Cognitive functioning was impaired in the majority of children who completed the WISC-III subtests of Information and Picture Completion.¹² While only 20% of the children were impaired on tests of immediate recall of digits forward, 67% were impaired on digits backward. Furthermore, 75% of the children tested were impaired on tests of immediate and delayed recall of age-appropriate story passages. Motor impairments were present in the majority of cases, with 100% demonstrating problems in finger movements, 87% impaired on toe movements, and with no child able to successfully perform on heel-toe movements. Similarly, all children assessed scored in the impaired range on both the Test of Visuomotor Integration and tests of verbal fluency.

Parent Questionnaires

Table 1 presents the most frequent problem behaviors reported by the parents on the University of Florida Child Diagnostic Screening Scale. While many reflect symptoms consistent with the child's neurologic handicaps, a number of problematic behaviors were also

Table 1. Problem Behaviors Reported by Parents of Children With Joubert Syndrome

| Problem | Percentage Reported |
|--|---------------------|
| Clumsy, fine motor problems | 100 |
| Demanding, strong willed | 100 |
| Clumsy, walking problems | 75 |
| Vision problems | 50 |
| Speech difficult to understand | 50 |
| Hyperactive, can't sit still | 50 |
| Unhappy, cries a lot | 50 |
| Growth problems | 50 |
| Dependent, clingy, upset at separating | 25 |
| Eating problems | 25 |
| Overly aggressive | 25 |

reported reflecting temperament difficulties, hyperactivity, aggressiveness, and dependency. Results of the Child Development Inventory, previously reported by Maria et al.,⁵ documented that all of the children examined attained general development domain scores in the severely delayed range (more than 30% below chronologic age).

Second Neurobehavioral Study

In a second data collection effort, 32 parents attending a meeting of the Parents In Touch Network in Chicago completed the Child Development Inventory.¹⁷ Magnetic resonance imaging (MRI) scans of 17 of the children also were available for examination.

Subjects

The children ranged in age from 14 months to 17 years, with a mean age of 5 years, 9 months. Most of the caregivers who completed the Child Development Inventory were the mothers (78%). The parents ranged in age from 24 to 52 years.

Questionnaire Results

Raw scores on each of the nine scales were converted to scores reflecting the percentage below chronologic age. The average developmental age for each of the scales ranged from 12 to 37 months, which is well below the group's average chronologic age of 5 years, 9 months. The average developmental age for the composite General Development Scale was 19 months, reflecting the severity of developmental delay for this group of 32 children.

Magnetic Resonance Imaging and Developmental Questionnaires

As reported in Gitten et al.,¹⁸ we examined the relationship between several MRI markers of brain pathology and scores on the General Development Scale of the Child Development Inventory. Chi square analyses were used to examine the frequency of three abnormalities seen on the MRIs (cerebral atrophy, enlarged lateral ventricles, and delayed myelination) and severe impairment on the Child Development Inventory. No significant relationships were found. This suggested that degree of developmental delay (as measured by the Child Development Inventory) did not predict the frequency of three different MRI abnormalities.

Third Neurobehavioral Study

Our third investigation of children with Joubert syndrome took place in conjunction with a meeting of the Joubert Syndrome Foundation (formerly Parents In Touch Network) in Salt Lake City, Utah, in 1998. There, we collected Child Development Inventories from eight new families and conducted neurobehavioral testing on three young children.

Subjects

Children tested ranged in age from 2 years, 3 months to 11 years, 7 months. One child was Italian; his bilingual parents acted as translators during testing, which may have compromised the results. Testing of one additional child was attempted but discontinued after she became agitated at being presented with test materials.

Test Procedures

We used a modified version of the Peabody Picture Vocabulary Test-Revised to assess vocabulary.¹⁹ To enhance visual clarity for the children, we enlarged the picture plates by 30%. Similarly, a modified version of the Bracken Basic Concept Scale²⁰ also was used. Here again, the picture stimuli were enlarged by 30%. Otherwise, both tests were administered and scored according to standardized procedures. The Beery-Buktenica Test of Visuomotor Integration¹⁵ was again employed to measure fine motor copying ability. The Trail Making Test²¹ was used to measure speed of processing. Finally, Denckla's test¹¹ of repetitive and successive finger movements was again used to measure motor speed. Parents of eight children not previously evaluated also completed the Child Development Inventory.¹⁷

RESULTS

Neurobehavioral Test Results

We will describe the results of the testing of the two native-English-speaking children only. The older child (11 years, 7 months) obtained an age equivalent score of 7 years, 7 months on the Peabody Picture Vocabulary Test (1st percentile) and a concept age of 6 years, 7 months on the Bracken Basic Concept Scale (16th percentile). In contrast, the younger child (4 years, 11 months) obtained an age-equivalent of 4 years on the Peabody Picture Vocabulary Test (20th percentile) and a concept age of 4 years, 10 months (50th percentile) on the Bracken Basic Concept Scale. Both children scored more than two standard deviations below age norms on tests of finger movements. The older child scored at the 1st percentile on the Test of Visuomotor Integration, while the younger child was too impaired to successfully draw any lines on this test. On the Trail Making Test, the older child performed in the impaired range on Trails A (greater than three standard deviations below age norms) and could not understand the concept of alternating between numbers and letters on Trails B. The younger child was below the age norms on the Trail Making Test.

Questionnaire Results

For the eight children whose parents completed the Child Development Inventory, scores on the nine scales were consistent with those reported by Gitten et al.¹⁸ Developmental age on the scales ranged from 21% to 79% below chronologic age. Mean score of the group for the composite General Development Scale was 45% below chronologic age. One child's scores fell in the borderline range (20% below chronologic age), while the remainder scored in the severely impaired range (more than 30% below chronologic age).

DISCUSSION

Joubert syndrome is a rare disorder with a number of associated clinical signs and symptoms, structural central nervous system abnormalities, and the frequent finding of significant developmental delays across a variety of domains

of functioning.¹⁸ Since 1994, we have had the opportunity to examine a number of children with this disorder.^{5,18,22} Our efforts have been directed at describing key neurologic, neuroimaging, and neurodevelopmental findings in this diverse group. Developmental outcome in such children is variable, consistent with Steinlin and colleagues' recent follow-up report of 19 children.²³ They suggest that outcomes in Joubert syndrome can be divided into three courses: (1) children who die young; (2) patients who survive but are severely developmentally delayed and have a variety of visual and motor handicaps; and (3) patients whose developmental quotients fall within the mildly delayed range (70 to 80).

In our studies, parents described most of the children (94%) as functioning at developmental levels at least 30% below chronologic age. With the least handicapped children we examined, younger children appeared to be less impaired than older children. However, we were unable to determine whether this reflects a true age difference, a sampling bias, or a difference in the rate of acquisition of age-related skills between the younger and older children examined. Only a small percentage (25%) of the children seen were able to undergo brief neuropsychologic examinations. Among these children, cognitive deficits in verbal fluency, verbal memory, picture recognition vocabulary, and response sequences were noted for the majority. All children had impairments on tasks that tapped motor or visuomotor skills, consistent with their neurologic handicaps.

Neuropsychologic testing of physically and cognitively handicapped children is a challenging undertaking. While our batteries were designed to tap aspects of behavior associated with cerebellar functioning, testing was still limited by time constraints and the ability of the children to tolerate testing procedures. While the Child Development Inventory allowed parents to describe their child's developmental progress, here too, considerable variation in the degree of delay was noted. Of interest is the fact that these delays were not predicted based on neuropathologic findings on the child's MRI.¹⁸

By using a second problem behavior questionnaire, we were able to elicit from parents a report of actions that affected their ability to manage their child's physical and emotional needs. As Table 1 suggests, children with Joubert syndrome display hyperactivity, aggressiveness, dependency, and temperaments that are stressful for parents to manage.²⁴ (See Leusher et al in the October 1999 issue.) To our knowledge, these data are the first of their type to be collected from parents of children with Joubert syndrome and suggest that an additional focus of care for these children is on managing these problematic behaviors.

Reflecting on our own experiences, we would like to propose some future directions for research: (1) A more comprehensive and systematic assessment of the neurobehavioral profile of children with Joubert syndrome is needed. This could be accomplished if funding were available for a multisite research grant to support studies of these children.

(2) We have relatively little information regarding the developmental course of children with Joubert syndrome. Longitudinal studies are needed to chart the growth and change in cognitive, social, and physical development. (3) Further research on the problem behaviors shown by some children might lead to the development of specific behavioral interventions to help parents manage or modify these behaviors as children mature. (4) Future investigations of children with Joubert syndrome should begin to differentially characterize the findings according to a subtyping approach. Such an approach has been helpful in describing the differences in developmental course and outcome in other childhood disorders, including learning disabilities, autism spectrum disorders, traumatic brain injuries, and childhood epilepsies.²⁵ With such a subtyping approach more precise relationships between structural abnormalities and their specific neurobehavioral manifestations can be accomplished.

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Discussion

Dr Maria: Do cerebellar abnormalities account for the cognitive defects in Joubert syndrome?

Dr Fennell: Based on current knowledge, I don't think we can exclude cerebral microdysgenesis and processing problems as explanations for cognitive problems.

Dr Maria: Mutism has been reported postoperatively in children with posterior fossa tumors. It has been shown recently that cerebral perfusion defects in language areas are present in such patients.

Dr Dennis: I am not comfortable with the notion that the posterior fossa malformation in Joubert syndrome can fully account for cognitive defects. For example, the magnitude of the developmental impairment is not consistent with that of the Dandy-Walker malformation.

Dr Maria: In our study of Dandy-Walker malformation, we found that children with isolated posterior fossa abnormalities did very well developmentally. Children with associated cerebral malformations had significant learning difficulties.

Dr Boltshauser: I want to be provocative and mention that children with nonsyndromic, nonprogressive, congenital ataxia have

marked impairment in school performance. One half have normal neuroimaging. Many have epilepsy.

Dr Dobyns: Neuropathologic studies in Arima syndrome show the presence of frank cortical dysplasias that could account for the mental retardation.

Dr Rorke: The prevalence of cortical dysplasia is high in children with intractable epilepsy. Using special immunohistochemical techniques, one can document abnormalities of orientation and lamination and peculiarity of the neurons. However, in routine autopsy material, we are now discovering a high incidence of unsuspected microscopic dysplasia.

Dr Barkovich: There is a recent paper in the *American Journal of Neuroradiology* showing that T₂-weighted thin section magnetic resonance images (MRIs) demonstrate brainstem nuclei in the neonate. If a child is suspected of having Joubert syndrome at birth, an early MRI with thin sections and heavy T₂-weighting could show brainstem nuclei and abnormalities that correlate with pathologic findings.