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Original Article

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ABSTRACT

Research on children with Joubert syndrome has focused on brain structural abnormalities and associated clinical symptoms. The degree of developmental delay has not been objectively reported. We investigated the neurobehavioral development of children with Joubert syndrome through neurobehavioral assessment in the largest sample to date. Thirty-two parents of children with Joubert syndrome completed the Child Development Inventory and magnetic resonance imaging (MRI) data was gathered on 17 of these children. Results indicate that 94% were severely impaired according to the Child Development Inventory, with age being positively correlated with degree of neurobehavioral impairment. The average developmental age of our sample was 19 months (63% below chronological age). Severity of illness as measured by the General Development scale of the Child Development Inventory and severity of illness as measured by MRI (overall severity rating) did not yield consistent data regarding severity of the midbrain and cerebellar malformations. Similarly, markers of abnormal cerebral development such as cortical atrophy and delayed myelination were independent of severity of illness ratings on the Child Development Inventory. The degree of developmental delay in Joubert syndrome and the severity of gross central nervous system malformations appear independent. (*J Child Neurol* 1998;13:391–397).

Joubert syndrome is a rare neurogenetic disorder characterized by the presence of specific structural abnormalities in the brain as well as by characteristic clinical symptoms and signs. Joubert, Eisenring, Robb, and Andermann first described this disorder based upon four affected siblings from a family with six children in Montreal.[1] This original description as well as subsequent reports of children with Joubert syndrome has indicated that children with this disorder have abnormalities of the midline cerebellum. These abnormalities include dysgenesis or complete agenesis of the vermis (the posterior-inferior region of the cerebellum is the final region to develop during embryonic development), maloriented and enlarged cerebellar peduncles, and a dysmorphic or asymmetric midbrain.[1–4] A hypoplastic brain stem has also been described. Other central nervous system abnormalities may include cortical atrophy, delayed myelination, and an enlarged fourth ventricle. In cases in which the fourth ventricle is enlarged, an associated disorder, Dandy-Walker syndrome, may also be present. Dandy-Walker syndrome is a sporadic disorder characterized by hydrocephalus associated with enlargement of the posterior fossa, a cyst-like dilation of the fourth ventricle and, similar to Joubert syndrome, dysplasia of the cerebellar vermis.[5]

Ocular and motor abnormalities in Joubert syndrome include nystagmus, gaze palsy, reduced visual acuity, ataxia, psychomotor retardation, poor coordination, and hypotonia.[1,2,6] Neonates with this disorder may have episodic apnea alternating with tachypnea, commonly described as similar to the panting of a dog. This breathing abnormality may subsequently improve and disappear with increasing age.[1,2,7] Other anomalies in children with Joubert syndrome include polydactyly of fingers and toes, continuous and rhythmic protruding tongue movements, fleshy tumors on the tongue, and polycystic kidneys.[6,8–10] Joubert syndrome is inherited in an autosomal recessive fashion and consanguinity of the children's parents has been found in approximately 20% of the reported cases.[8] Considerable variability of outcome in Joubert syndrome has also been reported, with symptoms

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ranging from death in infancy to severe disability including mental and motor function deterioration to lack of clinical symptoms at follow-up.[7,11] Joubert syndrome has been more commonly reported in males in a 2:1 ratio.

Detailed descriptions of the behavioral and developmental outcome associated with Joubert syndrome have largely been left out of previous reports. In their original description, Joubert et al[1] included mental retardation as an associated symptom. Others have included terms such as developmental delay, mental deterioration, or cognitive impairment in their list of characteristic symptoms associated with Joubert syndrome.[2,8,9] Although mention of behavioral or developmental status is made, neurobehavioral development is not well characterized. Previous research relied upon general descriptions of a small number of cases.[7,12,13] Reference to specific measures for quantification of impairment was not included. One report attempted to link Joubert syndrome with autism.[14] In that report, the behavioral characteristics of a brother and sister were described as including stereotypic behavior, impaired social interaction, diminished communication, and perseveration. The cognitive development of those children was reported as significantly better than previous descriptions of children with Joubert syndrome. However, in opposition to the link between Joubert syndrome and autism, it has been argued that children with Joubert syndrome who display difficulties with communication due to symptoms such as cognitive delay, limited gross and fine motor coordination, and abnormal eye movements, may appear autistic due to their physiologic limitations rather than a specific link between the behavioral syndrome of autism and cerebellar abnormalities.[15]

AIMS AND HYPOTHESES

The first goal of this study was to describe the neurobehavioral development of children with Joubert syndrome through the use of formal testing using the Child Development Inventory in a large sample covering a wide range of ages. The second goal was to correlate radiologic data with neurobehavioral data in order to ascertain the relationship between severity of central nervous system malformations characterized with magnetic resonance imaging (MRI) with information obtained through psychological assessment. We hypothesized that percentage scores (indicating how far below expected neurobehavioral developmental level each child is scoring), as measured by the Child Development Inventory, would correlate with age. Previous literature notes that mental and motor deterioration occurs across the life span of children with Joubert syndrome. Therefore, it was expected that older children would fall developmentally further behind their age-matched peers. We further hypothesized that a rating of developmental impairment as measured by the Child Development Inventory would positively correlate with a rating of the severity of central nervous system malformations.

METHODOLOGY

Subjects

Our study involved 32 caregivers of children previously diagnosed with Joubert syndrome by the child's neurologist. Radiologic information was also obtained on a subset of 17 children. Following the expected 2:1 male to female ratio, our sample consisted of 22 males and 10 females diagnosed with Joubert syndrome. Their ages ranged from 14 to 204 months with a mean of 68.7 months and a standard deviation of 50.5 months. The sample consisted of 94% European American children and 6% Asian American children. Of the caregivers responding, 78% were mothers of children with Joubert syndrome while the remaining 22% were fathers of the children with Joubert syndrome. The ages of the caregivers ranged from 24 years to 52 years with a mean of 34.59 years and a standard deviation of 7.48 years.

Procedure

Caregivers were recruited for participation either at a national Joubert syndrome conference or through phone contact from information supplied through a research registry. Families of children with Joubert syndrome have formed a network referred to as the Parents-In-Touch Network (P-I-T-N). This network includes international membership of over 125 families of children with Joubert syndrome and other cerebellar abnormalities currently living in Australia, Arabia, Brazil, Canada, Columbia, England, Iceland, Italy, The Netherlands, Switzerland, and the United States. If interested, members of the network may become part of a research registry established to allow for collaboration between families and researchers. The network also organizes a national convention every 2 years where families may obtain medical, educational, and psychosocial information. Of families contacted for participation in the present study, 63% returned their mail delivered packets or participated at a conference.

Measures

Parents completed a battery of questionnaires including the Child Development Inventory (CDI), Family Assessment Device (FAD), Ways of Coping Checklist–Revised (WCCL-R), Caregiver Strain Index (CSI), and Achenbach Child Behavior Checklist (CBCL). Information obtained from the Child Development Inventory is the focus of this paper.

Child Development Inventory

The Child Development Inventory is an updated version of the Minnesota Child Development Inventory (MCDI), an inventory originally designed to help identify and describe children with a variety of developmental problems based upon parent report.[16] The inventory was designed for use with children between the ages of 12 months and 6-years 3-months or for use with older children expected to score significantly below their chronological age on measures of development. The Child Development Inventory contains 270 age-discriminating items answered either true or false by the caregiver. The questions are divided to form nine scales: social, self-help, gross motor, fine motor, expressive language, language comprehension, letters, numbers, and general development. The social scale includes items about both individual and group interactions with

family, peers, and other adults. The self-help scale addresses adaptive behaviors such as eating and bathing as well as other indices of independence. Items on the gross motor scale cover activities such as walking, climbing, jumping, balance, and coordination. Alternatively, items on the fine motor scale address activities involving hand-eye coordination. Expressive language items include gestural, vocal, and verbal behavior, while language comprehension items range from simple comprehension to understanding of concepts. Items on the letters and numbers scales cover ability to print and read and knowledge of quantity, respectively. Finally, the general development scale is a 70-item scale based upon the most age-discriminating 10 items each from the social, self-help, gross motor, fine motor, expressive language, and language comprehension scales and 5 items each from the letters and numbers scales.[16] Normative data for the measure was collected on over 500 children from 12 months to 6-years 3-months of age from south St. Paul, Minnesota. This normal group was primarily European American (95%) and of similar make-up to our population (94% European American).

For each scale, raw scores were calculated that were then converted into developmental age scores. Finally, percentage scores were calculated, which indicated the percentage below chronological age that each child scored. Percentage scores were established as more appropriate for evaluation than difference scores (between chronological age and developmental age) because percentage scores equate large difference scores obtained on older children with proportionally equal yet smaller difference scores obtained by younger children. According to the Child Development Inventory manual, a score less than 20% below chronological age is considered normal. Scores between 20% and 30% below chronological age are defined as borderline or mildly delayed. Children scoring greater than or equal to 31% below their chronological age are considered developmentally delayed.

Magnetic Resonance Imaging

MRI data was collected on a subset of the children in this study with Joubert syndrome. This data involved abnormality ratings on the midbrain-pontine region (isthmus), the superior cerebellar peduncles, and the vermis. This constellation of malformations is thought to distinguish Joubert syndrome from other cerebellar disorders.[3,4] The midbrain malformation was rated as mild or marked based on the degree of isthmic segment midline depression in the region of the posterior foramen cecum portion of the interpeduncular fossa (Figure 1). In the marked midbrain malformation, the defect reached the floor of the fourth ventricle and could pass through the median longitudinal fasciculus. The grading system for malformation of the superior cerebellar peduncles included assessment of thickness and course relative to the brain stem. The grading system used to assess vermic dysplasia was based upon three markers: the formation of the primary fissure, the development of the superior (central and culmen) and inferior (declive, folium, tuber, pyramis, and uvula) lobules, and the formation of the vermic folia (ie, the degree of vermic sulcation) (Figure 2). For example, mild vermic dysplasia was defined if the primary fissure was present, both the culmen and central lobules could be distinguished, but the folia were poorly formed and sulcation was minimal. Furthermore, the right and left sides of the superior vermis were at least partially fused. Alternatively, marked dysplasia was defined if the primary fissure was present but the lobules of the superior vermis were indiscernible, remaining fused into one mass of tissue. The MRI data covered other measures of development, including degree of myelination, and the presence or absence of cortical atrophy plus a rating of overall severity of midbrain and cerebellar malformations in Joubert syndrome. The MRI rating for overall level of severity of Joubert syndrome was a subjective composite rating of midbrain, cerebellar peduncle, and vermian malformations established and read by the neuroradiologist amongst the authorship (R.G.Q.) who was unaware of the subject's clinical state. Again, in order to increase the power of analyses, this single composite MRI rating was employed as representative of the other specific neuroanatomical abnormalities of the midbrain, vermis, and superior cerebellar peduncles. Of the 17 children with radiologic information, 88.24% of the children had their information based upon MRI administered between 1 and 12 months of age. The two remaining children received their MRI during their 12th year. Information from more than one MRI was available for three children. The length of time between scans ranged from 9 to 28 months. Interpretation of repeat scans indicated minimal or no change to radiologic ratings of severity. Based on the observation that the neuroanatomical abnormality is nonprogressive, we assumed that the age at which the MRI was taken would not have an effect on the composite rating.

RESULTS

Primary analyses were aimed at determining the level of development that children with Joubert syndrome have achieved. As indicated, raw scores were obtained on each scale for each child by tallying the total number of statements marked true by the child's parent. Raw scores were then converted to developmental age scores using the Child Development Inventory profile form. Figure 3 shows the means for each subscale of the Child Development Inventory obtained by the full sample of 32 children. The average developmental age on each of the six subscales and one composite scale (rounded to the nearest month) was between 12 and 37 months. From the mean profile, it appears as if the letters and numbers scales represent strengths for children with Joubert syndrome. However, raw scores of zero on these two scales result in developmental age scores of 25 and 18 months. Therefore, the floor effect may cause an overestimation of ability within these areas. The greatest amount of impairment was seen on the GM scale, which shows a mean developmental age score of 12 months for the sample. This pattern of impairment is consistent with expectations from children with cerebellar malformations. As indicated, the mean chronological age of the sample was 68.7 months; therefore, a mean general developmental age of 19 months indicates severe impairment.

Next, percentage scores were calculated for each child. In order to increase the power of analyses, the general development scale was used as a single comprehensive measure of development from the Child Development Inventory. Of the 32 children in our sample, no children scored

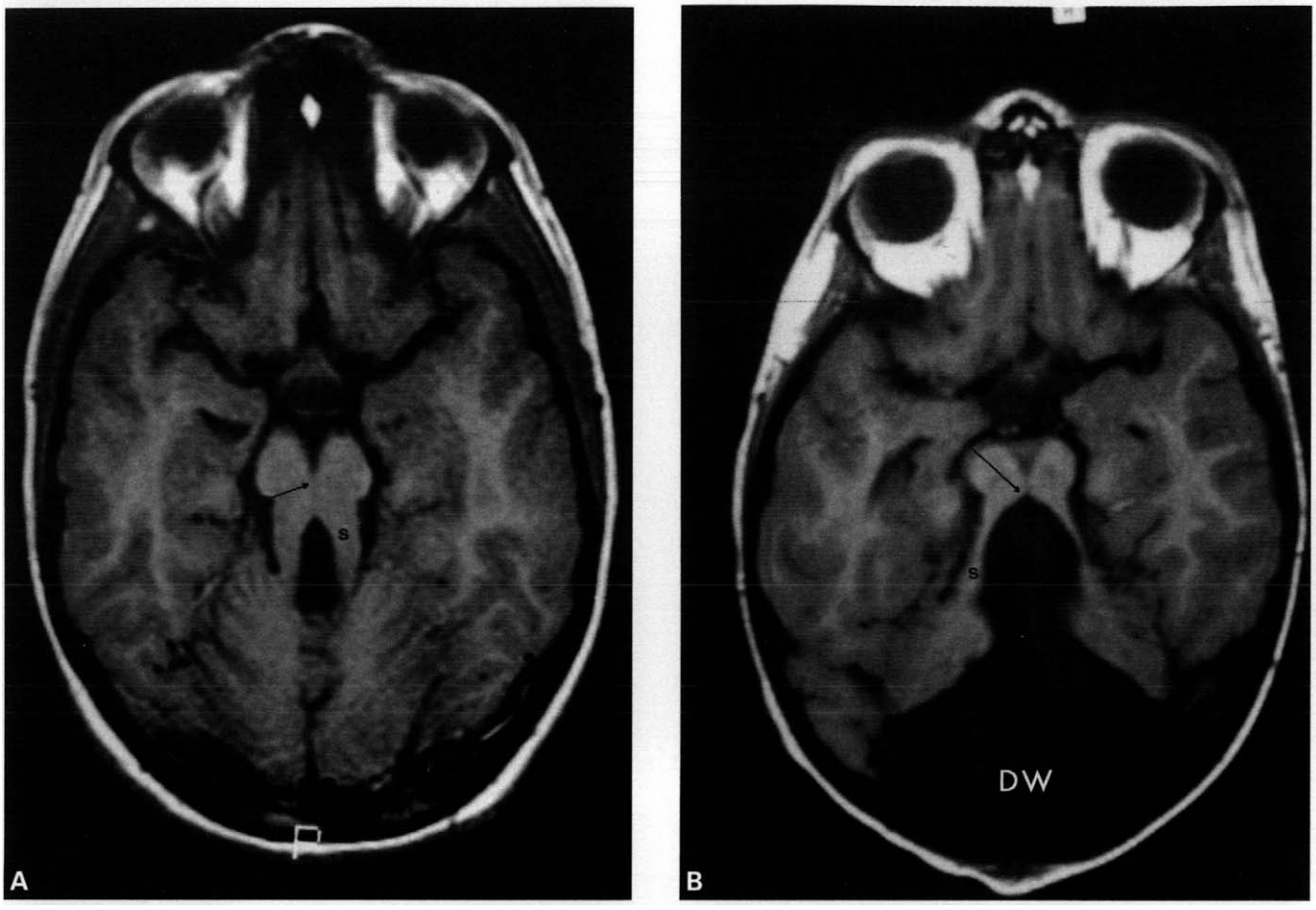

Figure 1. Two T_1-weighted axial images from two different patients illustrating mild and marked isthmic abnormalities. Similar changes were evident in virtually every case of Joubert syndrome and represent an important morphologic abnormality characterizing the Joubert syndrome patient group. *A,* Mild isthmic segment midline depression in the region of the posterior foramen cecum portion of the interpeduncular fossa. Note also the thickened (dysmorphic) superior cerebellar peduncles that are also characteristic of Joubert syndrome. *B,* Marked isthmic segment midline depression in the region of the posterior foramen cecum portion of the interpeduncular fossa. In this instance, the defect appears to reach the floor of the fourth ventricle. In that location the depression is likely to pass through the median longitudinal fasciculus helping to account for clinical evidence of ocular motility symptoms. There is an associated Dandy-Walker malformation evident in this case. This is an example of a patient exhibiting features of Joubert syndrome with additional abnormalities.

in the normal range (<20% below chronological age), two children scored in the borderline range (20–30% below chronological age), and 30 children scored in the significantly delayed range (≥31% below chronological age). The degree of impairment on the General Development scale ranged from 21% to 91% below chronological age. The mean degree of general developmental impairment was 63% below chronological age. However, beyond 31% impairment, there are no further meaningful breakpoints in degree of developmental delay; all children scoring >31% below their chronological age are judged to be severely impaired.

All further analyses were conducted using SPSS for Windows: Professional Statistics, 6.1. A Pearson correlation conducted on chronological age and level of developmental impairment (measured as percent below chronological age on the General Development scale of the Child Development Inventory) revealed a significant positive correlation ($r = .681$, $P < .01$). This correlation suggests that older children's developmental age scores, as calculated on the Child Development Inventory general development scale, fall further below their chronological age than younger children's developmental age scores.

As previously indicated, MRI data was collected on a subset of 17 children from the original sample. A Pearson correlation conducted on chronological age and overall level of severity of the malformations characterized by MRI was not significant, indicating that there does not appear to be a significant relationship between the age of a child and his or her severity of midbrain and cerebellar malformations.

With the second goal of the study to compare impairment according to the Child Development Inventory with impairment indicated by the MRI, analyses were conducted on the relationship between severity of neurodevelopmental delay as measured by the Child Development Inventory (general development) and severity of the central nervous system malformation as measured by MRI (overall severity rating). Given more severe ratings of the central nervous system malformations, more severe development delay might

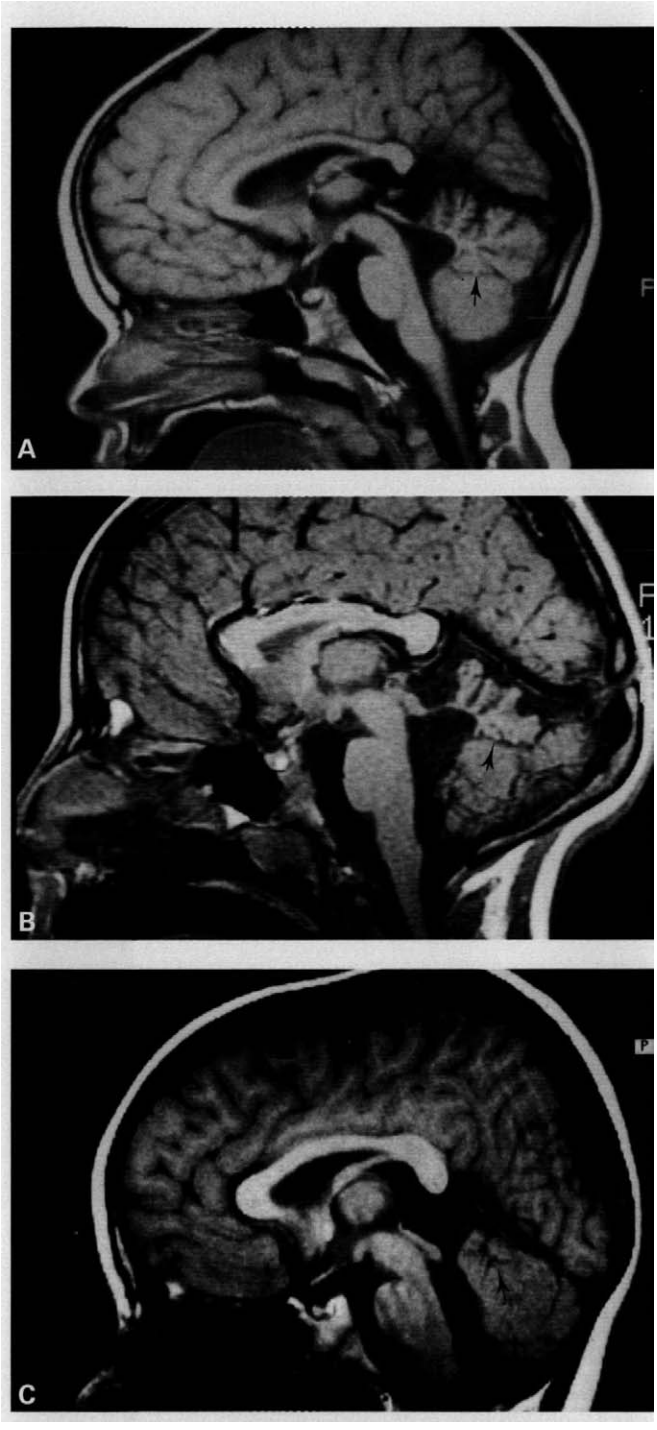

Figure 2. Sagittal T_1-weighted image series of three patients illustrating the range of vermic dysplasia (or incomplete formation anomalies). *A*, Mild vermic dysplasia. The inferior (or posterior vermis) segmentation is incomplete and the entire vermis is smaller than normal. The fourth ventricle is ectatic and the fastigium is shifted rostrally. The vermic lobules have the appearance of being arranged in a row along the dorsal surface of the fourth ventricle. *B*, Moderate vermic dysplasia. The lobules of superior vermis are preserved but the sulcation is reduced. The lobules of the inferior vermis are poorly separated. The vermic size is reduced, while the fourth ventricle is even more ectatic than seen in *A*. Again the lobule arrangement is linear along the dorsal fourth ventricular surface. *C*, Marked vermic dysplasia. The primary fissure is present but anomalous, and the lobulation of the superior and inferior vermis is virtually absent. Sulcation has not begun. The mesial margins of the fully developed cerebellar hemispheres have closed into the midline, filling the void left by the small vermis.

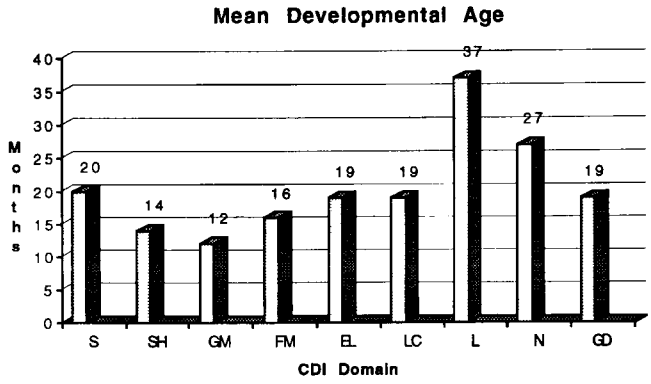

Figure 3. The mean developmental age (expressed in months), for each subscale of the Child Development Inventory, obtained by the full sample of 32 children.

be expected. Due to the small sample size ($n = 17$) and the limitation of working with nonparametric data, χ^2 analyses were conducted and found to be nonsignificant. A lack of significant relationship between MRI and Child Development Inventory data suggests that these two forms of evaluation do not necessarily yield consistent information about the severity of the Joubert syndrome in a child.

In order to further evaluate the relationship between degree of impairment according to the Child Development Inventory with the degree of central nervous system malformations indicated by MRI, three more analyses were conducted comparing the relationship between severity of illness as measured by the Child Development Inventory (general development) and markers of abnormal cerebral hemisphere development including atrophy of cerebral hemispheres, enlargement of lateral ventricles, and delayed myelination. Again, χ^2 analyses were conducted and found to be nonsignificant. Although we violated the assumption that at most 20 percent of the cells have expected frequencies less than five, review of the raw data shows that subjects who received a score indicating severe developmental delay on the Child Development Inventory were split evenly between receiving ratings of no cerebral atrophy or moderate atrophy of the hemispheres. Similarly, children scoring within the severely impaired range on the Child Development Inventory were split evenly between receiving ratings of no increase in lateral ventricle size or moderate enlargement of the lateral ventricles. Finally children found to be severely developmentally impaired according to the Child Development Inventory were split between being found to have delayed myelination or not. Alternatively, all children with severe atrophy of the cerebral hemispheres or marked enlargement of the lateral ventricles ($n = 2$ and 1, respectively) were severely developmentally delayed on the Child Development Inventory.

DISCUSSION

This study describes the neurobehavioral development of children with Joubert syndrome through the use of formal testing, specifically the Child Development Inventory, in

the largest sample to date ($n = 32$). The questionnaire return rate of 63% suggests that the sample analyzed in the current research is representative of the population of children diagnosed with Joubert syndrome.

Our results support previous statements that children with Joubert syndrome are severely developmentally delayed. This significantly delayed development is seen across a variety of domains, including adaptive behaviors, motor, language, and general development. One limitation of using the Child Development Inventory to describe a population such as children with Joubert syndrome, who show extensive impairment, is that all children scoring ≥ 31% below their chronological age are classified as severely impaired. Future research may attempt to delineate the type and level of impairment within this broadly defined group by creating a measure of development designed specifically for severely impaired children.

The positive correlation found between age and level of impairment as measured by the Child Development Inventory also appears to support previous findings that mental and motor deterioration occurs across the life span of children with Joubert syndrome. This finding of mental and motor deterioration in children with Joubert syndrome does not imply that this disease is a progressive one. Rather, because the child has failed to reach cognitive milestones, as the child grows older, he or she falls further behind age matched peers. Therefore, repeat testing of a child's neurobehavioral development would appear to be a useful tool for evaluating a child's current level of functioning and appropriate needs. Of note, another limitation of using the Child Development Inventory as a measure of general development is that a floor effect occurs with younger children. Children close to 12 months of age cannot score significantly below their chronological age because any developmental age scores below 12 months (0–11 months) receive a score of 11 months. Therefore, it is possible that with a measure of development that allows for the proper classification of severely delayed infants, the correlation between age and level of her or his severity of illness may not appear as strong. Although the newest revision of the Bayley Scales of Infant Development[17] may be used among severely delayed infants, it could not be used across the age span of the children who comprise the present sample of patients with Joubert syndrome.

In order to accurately evaluate whether the correlation between age and degree of neurobehavioral impairment is due to a floor effect in the developmental measure employed in this research or a result of a relative decline in functioning as the child grows older, longitudinal research is necessary. According to this study's MRI ratings, Joubert syndrome does not appear to be a progressive disease, yet older children with Joubert syndrome appear to be more developmentally impaired than younger children with this disease. Therefore, future longitudinal research employing repeat neurobehavioral and developmental testing of children with Joubert syndrome seems warranted. Although we recognize that detailed studies of children with severe developmental delays are difficult to accomplish due to limitations in available measurement instruments, such an approach may help to better characterize neurobehavioral subtypes of patients with Joubert syndrome that map onto their neuroanatomical abnormalities.

There does not appear to be a relationship between the age of a child and his or her severity of central nervous system malformations characterized by MRI. This finding is consistent with previous information that the malformations do not increase over time. However, it is possible that the radiologic rating of severity may not correlate with age if older children in the sample showed less severe structural impairment initially compared with the younger children in our sample. As noted, children with Joubert syndrome may not live into adulthood. Therefore, it is possible that children who are able to live longer start out with less severe structural abnormalities. Again, in order to address this issue, a longitudinal study is important. This study should incorporate multiple MRIs (with the initial MRI taken within the child's first year of life) and involve evaluation of the child's degree of initial impairment.

The strong return rate discussed earlier supports the stated sentiment of the P-I-T-N that families are highly motivated to participate in research in order to further understanding of Joubert syndrome. This return rate also suggests that these families may be willing to participate in further research in this area (ie, repeat testing for longitudinal studies).

The lack of a significant relationship between degree of developmental impairment (as measured by the Child Development Inventory) and severity of the central nervous system malformations suggests that a child's ability to function cannot be estimated directly from radiologic study. Although it has been generally implied that children with Joubert syndrome show significant developmental delay, the lack of a significant relationship between degree of developmental delay and MRI findings indicates that neuropsychological data is required to evaluate functional severity and that the MRI in and of itself does not provide prognostic information on neurodevelopment in Joubert syndrome.

Finally, the lack of a significant relationship between the degree of developmental delay and the neuroanatomy of cerebral hemispheres further supports our conclusion that a child's ability to function cannot be estimated directly from radiologic ratings. Again, these findings suggest the importance of including neuropsychological assessments in the evaluation of a child with Joubert syndrome in order to have an accurate understanding of his or her deficits and abilities.

Future research looking at the cognitive and behavioral development of children with Joubert syndrome might also address other factors that affect the degree of impairment aside from brain malformations. These factors may include, but are not limited to, rehabilitative therapies received, special education acquired, and family demographic variables. Further research is currently underway to address caregiving issues in the Joubert syndrome population.

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