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Authors

Wang, PP
Hesselink, JR
Jernigan, TL
et al.

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Specific neurobehavioral profile of Williams' syndrome is associated with neocerebellar hemispheric preservation

P.P. Wang, MD; J.R. Hesselink, MD; T.L. Jernigan, PhD; S. Doherty, PhD; and U. Bellugi, EdD

Article abstract—Previous work demonstrated enlargement of the neocerebellar vermis in Williams' syndrome (WS), despite diminished volumes in the cerebral hemispheres. We present the first in vivo volumetric study of any structure within the cerebellar hemispheres. Using MRI, we identified and reliably measured the neocerebellar tonsils in WS subjects; Down's syndrome (DS) subjects matched for age, IQ, and cerebral volume; and age-matched normal controls. WS tonsils were equal in size to control tonsils and larger than DS tonsils. In proportion to the cerebrum, WS tonsils were larger than controls'. These results coincide with the remarkable neuropsychological preservation of language and affect in WS, despite general cognitive impairment. They contrast with the neocerebellar vermal hypoplasia seen in autism, with its communicative and affective deficits. Additionally, two WS subjects showed Chiari type I malformations, but the average tonsillar position in WS was not found to be different than in controls.

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Williams' syndrome (WS) is a genetic disorder characterized by the constellation of peculiar facial features (medial eyebrow flare, malar flattening, elongated philtrum, full lips, upturned nasal tip with low nasal bridge, and other features), frequent supravalvar aortic stenosis and peripheral pulmonic stenosis, dental anomalies, skeletal contractures and synostoses, idiopathic infantile hypercalcemia, other medical markers, and retardation of mental and somatic growth.[1-3] Research from this and other laboratories has shown that WS subjects are also characterized by a unique neurobehavioral profile: they display relative preservation of their linguistic[4-7] and affective[8] skills in the face of general mental retardation.

Jernigan and Bellugi[9] recently reported on the abnormal morphology of the brain in WS. On MRI study, they found an overall reduction in cerebral volume and a typical dolichocephalic shape in WS, while Down's syndrome (DS) subjects had a comparable reduction in volume but a brachycephalic shape. However, the WS subjects demonstrated preservation of posterior fossa volume, while the DS subjects showed cerebellar volume diminution proportional to their cerebral diminution. Specific measurements on the midsagittal image showed that the cross-sectional area of the neocerebellar portion of the vermis, lobules VI and VII, was significantly larger in WS than in either control or DS subjects.

The cerebellar vermal enlargement seen in WS is especially intriguing in light of the growing body of evidence that the neocerebellum may be involved in higher cognitive functions, rather than only motor functions.[10] In addition, neocerebellar abnormalities are present in many (although not all) subjects with autism, on both in vivo neuroimaging studies and postmortem histopathologic studies.[11-14] Behaviorally, the communicative and affective impairment present by definition in autism contrasts diametrically with the pattern in WS.[8] We have therefore undertaken an examination of the neocerebellar hemispheres in WS. This represents the first quantitative study of a subset of the cerebellar hemispheres in living subjects. We focus on the cerebellar tonsils, the most reliably identifiable portion of the neocerebellar hemisphere.

Our study is also motivated by reports of Chiari

From the Laboratory for Cognitive Neuroscience (Drs. Wang, Doherty, and Bellugi), Salk Institute for Biological Studies, La Jolla, CA; the Departments of Radiology (Dr. Hesselink) and Psychiatry (Dr. Jernigan), University of California, San Diego School of Medicine, San Diego, CA; and the Veterans Affairs Medical Center (Dr. Jernigan), San Diego, CA.

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Address correspondence and reprint requests to Dr. Paul P. Wang, The Salk Institute - LCN, 10010 North Torrey Pines Road, La Jolla, CA 92037.

malformation in WS children. Specifically, Kaplan et al[15] reported a 6-year-old WS girl with symptoms of hypertonia and hyperreflexia in the lower extremities, bilateral Babinski's sign, and marked contractures of the left hip and bilateral knee joints. She showed "improvement of neurologic function in the lower limbs" after surgical decompression of a Chiari type I malformation. In the larger WS population, scoliosis, abnormalities of tone and reflex, and cerebellar signs are common.[3,16] These symptoms can result from Chiari malformations.

Methods. MRIs from 11 WS subjects (5 male, 6 female), seven DS subjects (2 male, 5 female), and 18 healthy, unrelated volunteer controls (7 male, 11 female) were analyzed. The WS and DS scans and 17 of the control scans had been obtained previously as part of a large, multidisciplinary study on the neurobiologic basis of language and cognitive development.[9,17] The one remaining control was recruited for studies of psychiatric and neurologic disorders. The groups were matched for age, ranging from 10 to 20 years (mean, 14.7) for WS, 10 to 20 (mean, 15.4) for DS, and 10 to 24 (mean, 15.4) for controls. All subjects were screened with medical and social histories. Informed consent was obtained from all subjects and their parents (for minors and all WS and DS subjects).

MRIs were performed at the University of California-San Diego/AMI Magnetic Resonance Institute, under a 1.5-tesla field, with a Signa/General Electric scanner. A 256 × 256 matrix was employed, with a 24-cm field of view and two excitations. Five-mm-thick slices were obtained, with a 2.5-mm gap between slices. A sagittal sequence was centered on the midsagittal plane. Repetition time (TR) of 600 msec and echo time (TE) of 20 msec were employed for T_1-weighted images. Axial and coronal sequences also were acquired, using an asymmetric, multiple-echo sequence (TR = 2,000 msec, TE = 25 and 70 msec) for proton density- and T_2-weighted images.

Analysis of these original MRI data was performed blind to subject identity, using a computer-assisted method adapted from Jernigan and Bellugi's[9] study of vermal area. The T_1-weighted sagittal images were displayed on a video screen and the tonsils identified, with reference to hard-copy MRIs. A numeric brightness criterion was adjusted downward until all pixels within the tonsil were above the criterion and most of the CSF bordering the tonsil was below it. An electronic mouse was then used to trace the margin of the tonsils; the number of supracriterion pixels within the tracing was the cross-sectional area. Tonsillar "size" was defined as the cumulative cross-sectional area across all images on which tonsil appeared. Determination of the position of the tonsils relative to the foramen magnum also was made. A single best image was selected for identification of the foramen magnum. Contrast and brightness were adjusted to optimally display the basion and opisthion. The line between them defines the foramen magnum. This line was transposed by computer to each image on which tonsil appeared. The lowest point of the tonsil was then designated for each image, and its distance from the foramen magnum calculated.

Utilizing the proton density- and T_2-weighted images, the volume of the cerebrum was estimated by determining the total volume of the supratentorial vault. Details of this technique and the results of this analysis are presented elsewhere.[9,18]

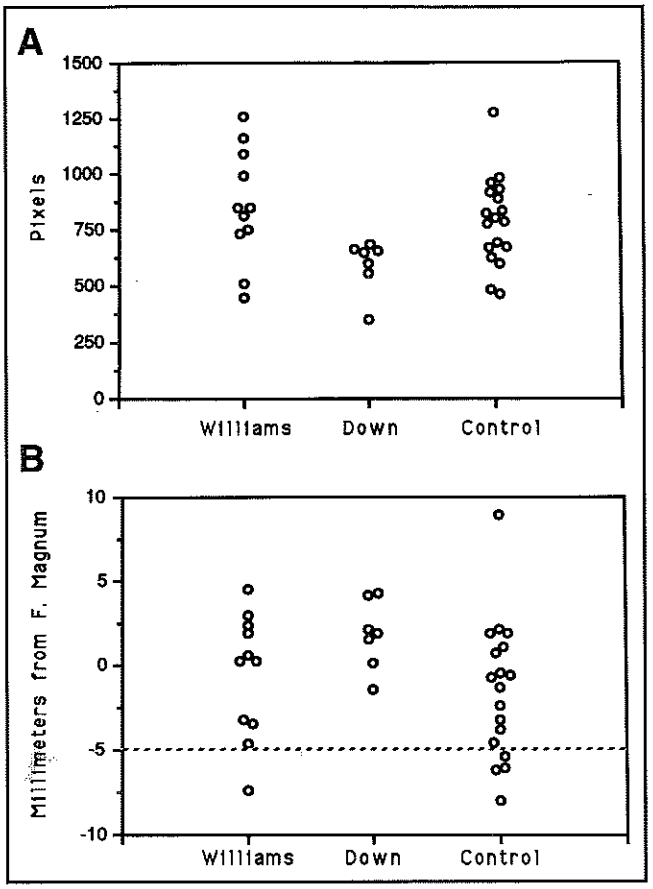

Figure. (A) Size of the neocerebellar tonsils. Datapoints represent the number of pixels within the tonsillar borders, cumulated across all MRIs showing tonsils. Tonsils in Williams' syndrome are significantly larger than in Down's syndrome, and equal in volume to control tonsils. (B) Lowest extent of the tonsils in relation to the foramen magnum. Negative values indicate that the tonsils extend below the foramen. Dashed line indicates the numerical criterion for Chiari type I malformation. The Williams' subject falling marginally above the line received a clinical diagnosis of Chiari malformation. Position of the tonsils in Williams' syndrome as a group was not significantly different than in controls.

All measures were repeated three times. Reliability of the measurements was computed according to a single-factor, repeated-measures ANOVA. Kruskal-Wallis nonparametric ANOVA was performed for multigroup comparisons. Significant results were further explored with Mann-Whitney U tests between each combination of two groups.

Results. Clinical interpretation of the MRIs yielded diagnoses of Chiari type I malformation for two of the WS subjects. These diagnoses were made on the basis of cerebellar tonsillar ectopia (>5 mm below the foramen magnum) with compressive deformation of the tonsils. No other abnormalities of the posterior fossa or spinal cord were noted for these two subjects or for any of the control or DS subjects.

For the experimental measures, intrarater relia-

bility proved to be very good across three repeated measures. For cumulative cross-sectional area of the tonsils (tonsillar size), reliability was 0.995. For distance between tonsil and the foramen magnum, reliability was 0.964.

Figure 1A provides a scatterplot of tonsillar size for each of the three groups. Statistical analysis showed a significant difference among the three groups ($p < 0.05$). Pair-wise comparisons showed the tonsils to be equivalently sized in WS (mean, 858; SD, 256) and control (788 ± 196) subjects, but significantly smaller in DS subjects (591 ± 115) ($p < 0.02$ versus control, $p = 0.02$ versus WS). In proportion to the estimated cerebral volume, the tonsils were significantly larger in WS than among controls ($p < 0.05$).

Figure 1B illustrates the lowest extent of the cerebellar tonsils in relation to the level of the foramen magnum. The DS tonsils were situated more superiorly than tonsils in the other groups. This finding was weakly significant ($p < 0.10$ among all three groups, $p < 0.05$ versus control).

This quantitative analysis of tonsillar position concurred with the clinical diagnosis of Chiari type I in one of the two WS subjects. The second subject's tonsils were measured at only −4.8 mm (below the foramen), but showed the compression characteristic of Chiari malformations. The Chiari subjects' tonsils were the first and fourth largest in size among the 11 WS subjects. Among the normal controls, four were found to have tonsils 5 mm or more below the foramen. Two of these four were considered borderline for the clinical diagnosis of Chiari type I, with minimal compression or pointing of the tonsils. The other two had relatively large foramina, with no tonsillar deformation, and were not diagnosed as Chiari malformations. Tonsil size in these four subjects ranked first, second, fourth, and 11th out of 17 controls. Among the DS scans, no cases of Chiari malformation were identified. No relationship of age to tonsillar volume or position was evident.

Discussion. This is the first example of volumetric analysis of a specific portion of the cerebellar hemispheres. First, we demonstrate good reliability for the computer-assisted method that was employed. Then, we demonstrate preservation of neocerebellar volume in WS, in the face of decreased cerebral volumes. This contrasts with the diminution of both cerebral and neocerebellar volumes in DS. Together with the previous findings on the cerebellar vermis, our findings provide evidence for selective preservation of the neocerebellar system in WS. This neuroanatomic contrast between WS and DS, and between WS and autism, is paralleled by the neuropsychological profiles of these syndromes. In comparison to DS subjects with equal levels of general cognitive impairment, WS subjects show much better linguistic skills.[6,19] Furthermore, the language of WS subjects evidences high levels of affective prosody and is replete with devices used to engage the conversational partner.[8] By contrast, the language of autistics often shows little regard for the listener and is typically characterized by prosodic abnormalities.[20] Furthermore, these contrasts coincide with suggestions that the neocerebellum, which evolved in concert with the frontal lobes, may have an important role in the regulation of emotion and in the coordination of the many cognitive resources necessary for fluent language.[10,21] For example, recent studies using PET have shown activation of the right inferior lateral cerebellum during a word-finding language task.[22]

Given the reliability of the volume measurements, reservations concerning the volume determination must stem primarily from the inability to study tissue in the 2.5-mm gap between images, combined with possible differences in shape between DS and WS (and control) tonsils. However, this effect seems unlikely to account for the large differences found. First, the tonsils are fairly regular in shape. Therefore, as long as no group-specific deformations occur, the nonimaged tissue (tissue in the 2.5-mm gaps) should be proportional to the imaged tissue. Second, any compression due to Chiari malformation would be expected to deform the WS tonsils more than the DS tonsils because the former are situated lower than the latter. Such deformation would increase the lateral extent of the WS tonsils. However, the tonsils do not appear deformed on clinical reading of the images. Furthermore, the tonsils do not extend further laterally in WS than in DS; they are found on an average of 2.5 images in WS and 2.6 in DS.

Our findings on tonsillar position relative to the foramen magnum should be of some clinical interest. We have identified two new cases of Chiari type I malformation in WS, and are aware of two other patients in the United States with both diagnoses. With the case of Kaplan et al,[15] the total number of such cases thus amounts to five. We are in the process of evaluating the clinical neurologic condition of our patients in comparison with normal subjects.

Despite the additional cases of Chiari type I malformation identified, our results do not confirm a statistically significant difference in tonsillar position for the WS population as a whole. Here, we recognize that any ill definition of the anatomic landmarks referenced for position measurements, especially in concert with a relatively small sample size, limits the power of our analysis. Analysis of a more extensive series of subjects might reveal group differences.

Both WS and DS present the opportunity to study genetically determined disorders of neurodevelopment. Investigation that crosses levels of neuroscience—from neurobehavior to neuroanatomy to neurogenetics—holds promise for elucidating the brain systems underlying behavior.

Addendum. Two further cases of Chiari type I malformation in association with Williams' syn-

drome have come to our attention. One of these, a 3.5-year-old girl, suffered from apnea that was relieved by surgical therapy for her Chiari malformation.

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