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Anomalous Brain Morphology on Magnetic Resonance Images in Williams Syndrome and Down Syndrome

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• **Quantitative studies of brain morphology in a group of subjects with Williams syndrome revealed a distinctive pattern of dysmorphology unlike that observed in another form of mental retardation, Down syndrome. Reduced cerebral size but normal cerebellar size was observed in Williams syndrome, in contrast to reductions in both brain components in Down syndrome. Examination of cerebellar vermal morphology suggested significantly increased area of neocerebellar vermal lobules in Williams syndrome, with low-normal size in the paleocerebellar vermal lobules. Thus, a highly selective effect on brain development appears to accompany Williams syndrome, with some brain subsystems, possibly later-developing ones, relatively spared.**

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In 1961, Williams et al[1] described a pediatric syndrome characterized by supravalvular aortic stenosis, growth deficiency, mental retardation, and so-called elfin/pixie facial features. Subsequent descriptions specified key features, eg, broad forehead, medial eyebrow flare, stellate iris pattern, flat nasal bridge, long smooth philtrum, and wide mouth.[2,3] The disorder has been associated with elevated serum calcium levels in infancy, and medical studies also suggest a defect in calcitonin production[4]; however, the cause is not yet fully understood. As part of a broad program investigating the neuropsychological, neurophysiologic, and neuroanatomic characteristics of Williams syndrome (WS), recent studies have described an unusual profile in which specific cognitive deficits coincide with remarkably preserved linguistic abilities.[5-8]

In the present study, we examined gross brain morphology in a group of subjects with WS using magnetic resonance imaging (MRI). Comparison is made with a group of normal individuals and a small group of age-matched subjects with Down syndrome (DS).

SUBJECTS AND METHODS

Of 8 MRI examinations of subjects with WS, 2 examinations yielded axial images degraded by motion artifact. The remaining 6 subjects with WS ranged in age from 10 to 20 years (mean, 15.8 years). Of four examinations of subjects with DS, 1 was degraded by motion. The remaining 3 subjects were aged 14 to 17 years (mean, 16 years). These groups were compared with 14 normal controls aged 8 to 32 years (mean, 19.0 years). Five of 14 normal controls, 4 of 6 subjects with WS, and 2 of 3 subjects with DS were female. All subjects with WS and DS, as well as 7 normal subjects under age 12 years, were participants in a large multidisciplinary study of neurodevelopmental disorders of language and cognition. They were screened by medical and social histories and underwent a full neurologic examination and extensive behavioral testing. Seven adult normal controls (over age 25 years) were recruited for studies of psychiatric and neurologic disorders and were also screened by medical and psychiatric interviews. They were all employed or attending school. Informed consent was obtained in all cases.

Imaging Protocol

The MRI was performed with a 1.5-T superconducting magnet (Signa; General Electric, Milwaukee, Wis) at the University of California–San Diego/AMI Magnetic Resonance Institute. A standard protocol was adopted for the acquisition of MRI brain images to be analyzed by the Brain Imaging Laboratory in the Department of Psychiatry. Three consecutive spin-echo pulse sequences were used to obtain images in each of three orthogonal planes (Fig 1). Using a T_1-weighted (repetition time, 600 milliseconds; echo time, 20 milliseconds) sequence, sagittal images centered at the midsagittal plane were acquired to visualize the corpus callosum, brain stem, and other medial hemisphere surface landmarks. Subsequently, proton-density-weighted and T_2-weighted images were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (repetition time, 2000 milliseconds; echo time, 25 and 70 milliseconds). The sequence was used twice to obtain images of the entire brain in the axial and coronal planes in each subject. Slice thickness was 5 mm, with a 2.5-mm gap between successive slices in all instances. A 256 × 256 matrix and 24-cm field of view were used in all examinations.

Image Analysis

A detailed description of the image analysis method is given in a separate article.[9] For each axial brain section imaged, a computed matrix was produced in which pixels were classified as most resembling (in signal strength) gray matter, white matter, cerebrospinal fluid (CSF), or signal hyperintensities. The full series of axial images was analyzed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex. Blinded to subject age or diagnosis, operators manually separated cerebellar from cerebral areas and cortical from subcortical regions using a stylus-controlled cursor on the displayed image. In this way, separate estimates of the four classes of pixels could be made for these areas. The fully processed images are illustrated in Fig 2. Different pixel classes are color-coded as follows: right hemisphere

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cortical gray matter is yellow and subcortical gray matter is light blue; left hemisphere cortical gray matter is white and subcortical gray matter is magenta. Fluid is red, white matter is black, and signal hyperintensities are blue; however, subcortical and cortical fluid and hyperintensities are measured separately. Volumes of cerebellum and cerebrum were estimated by summing pixels in infratentorial and supratentorial zones, respectively, over all sections. A ratio of the cerebellar to the cerebral volume was also computed. Other measures were obtained by summing pixels in given classes, for each region, over all axial sections. An overall measure of cerebral volume loss was computed by expressing the total number of non-CSF pixels as a proportion of the supratentorial cranium. This measure will be referred to as the cerebral proportion. A similar measure of cerebellar volume loss was computed for the infratentorial areas and will be referred to as the cerebellar proportion. Other measures examined include signal hyperintensities in cortical and subcortical zones and in cortical gray matter, all expressed as proportions of the supratentorial cranial volume.

An additional analysis of the structure of the cerebellar vermis was conducted using a midsagittal section. The method was modified from Courchesne et al.[10,11] Subjects were excluded if motion artifacts or an eccentric plane of section rendered the vermal landmarks indistinct. A suitable section, showing the primary and prepyramidal fissures, was available for four of the subjects with WS, two of the subjects with DS, and all of the controls. With the section displayed on the screen, an operator adjusted a numerical criterion until pixel values in the vermal area were all above the criterion while the fluid surrounding the vermis was below it. No attempt was made to exclude the vermal sulci, most of which were partially volumed CSF and tissue. Vermal lobules I through V were then circumscribed with a polygon designated using a stylus-controlled cursor. Next, vermal lobules VI and VII were similarly circumscribed. The numbers of pixels with values above the criterion and falling within the polygons were taken as the vermal I through V and vermal VI and VII areas, respectively. A ratio of vermal VI and VII to vermal I through V areas was also computed. Figure 3 illustrates the method.

Statistical Analysis

Groups were compared using Kruskal-Wallis nonparametric analyses of variance for three-group comparisons, and Mann-Whitney *U* tests for two-group comparisons. These statistics were chosen because they do not require assumptions about the distributions of the measures. When the sample size is small, application of parametric tests to nonnormal measures may yield spurious results.[12] Since the distributions of the morphological measures are not well established, and the samples were small, nonparametric tests were deemed more appropriate.

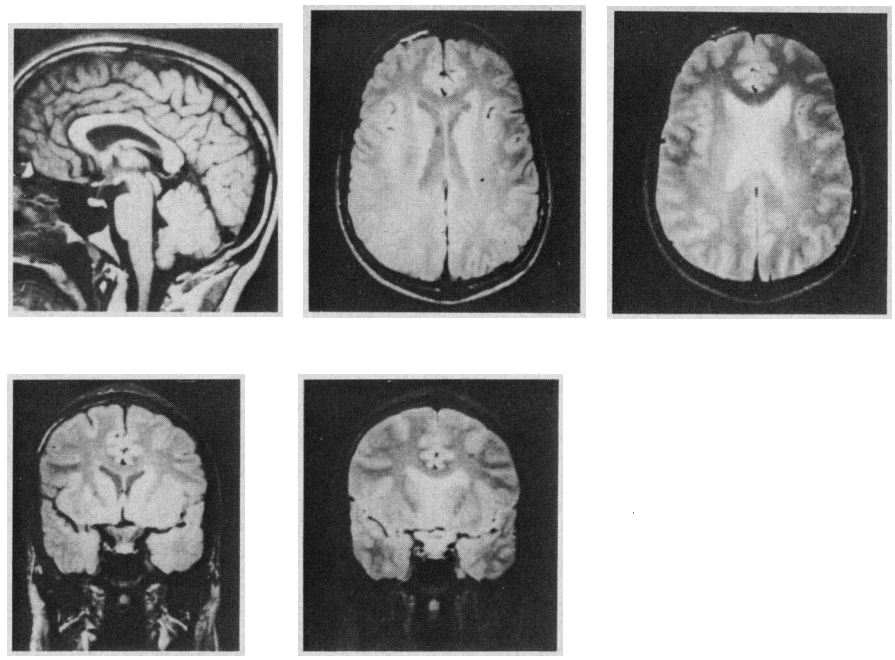
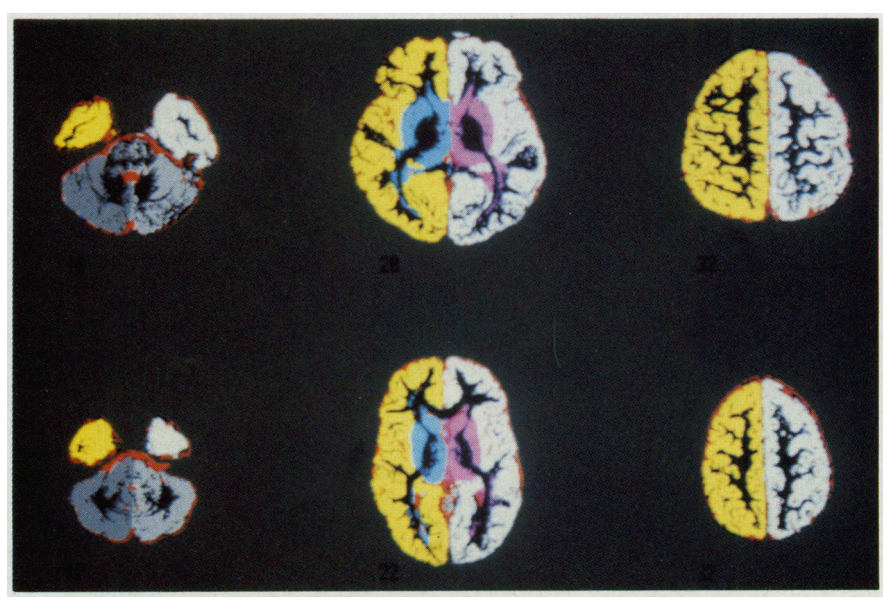


Fig 1.—Representative images from the standard protocol. Top left, Sagittal section (spin-echo [SE], 600/20 milliseconds). Top center, Axial section (SE, 2000/25 milliseconds; proton-density-weighted in text). Top right, Axial section (SE, 2000/70 milliseconds; T_2-weighted in text). Bottom left, Coronal section (SE, 2000/25 milliseconds; proton-density-weighted in text). Bottom right, Coronal section (SE, 2000/70 milliseconds; T_2-weighted in text). All sections were 5 mm thick; the matrix was 256 × 256; All series had a 2.5-mm gap between images.[9]

Fig 2.—Representative, fully processed images. Pixels are classified and zones have been manually designated. The gray matter pixels have been color-coded to display the zone designations: right hemisphere cortical is yellow and subcortical is light blue; left hemisphere cortical is white and subcortical is magenta; and cerebellar is gray. Cerebrospinal fluid and white matter pixels in all zones are displayed in red and black, respectively; however, these pixels are coded separately by zone so that regional measures may be computed. The three sections in the upper row are from a normal subject, and the three comparable sections in the lower row are from a subject with Williams syndrome. Note the reduced size and elongated shape of the cerebrum in the subject with Williams syndrome.



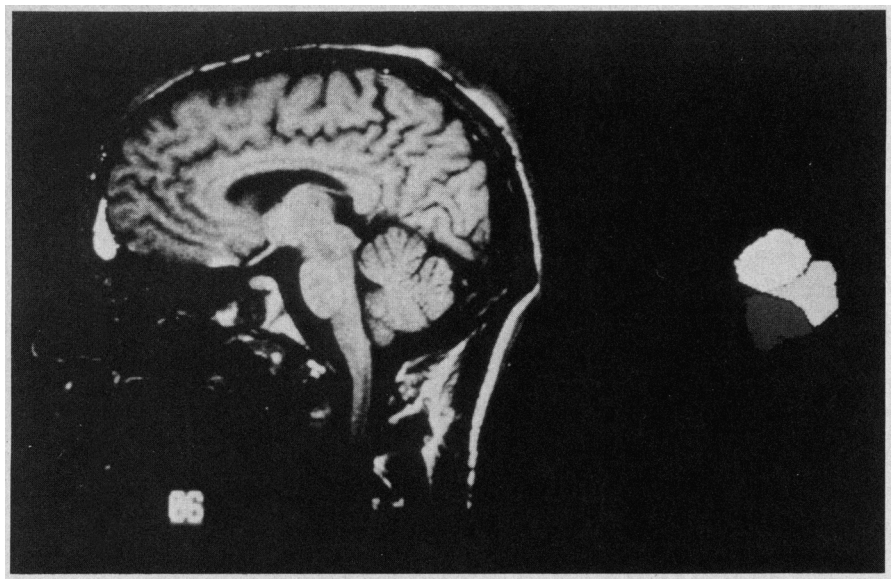


Fig 3.—Illustration of vermal measurement technique. Primary and prepyramidal fissures are visually identified on a midsagittal section displayed on the console screen as seen at left. With a stylus-controlled cursor, a polygon is designated that circumscribes first vermal lobules I through V and then vermal lobules VI and VII. At right, all pixels designated as vermal I through V are shown in white, and those designated as vermal VI and VII in light gray. Areas reported here are total pixel counts of these regions.

Results of Quantitative Analyses*

	Groups			Statistical Tests			
					Mann-Whitney *U*		
	C	WS	DS	K-W	C/WS	WS/DS	C/DS
Axial analyses†							
No.	14	6	3	...	...	...	...
Cerebral volume, voxels	201 102	160 517	150 409	15.0‡	82.0‡	NS	42.0§
Cerebellar volume, voxels	26 490	24 842	18 649	8.1‖	NS	18.0‖	41.0‖
Volume ratio	0.132	0.156	0.124	9.7§	6.0§	17.0‖	NS
Cerebral proportion	0.92	0.92	0.89	NS	NS	NS	NS
Cerebellar proportion	0.11	0.14	0.16	6.7‖	21.0¶	NS	4.0‖
Cortical gray proportion	0.50	0.51	0.52	NS	NS	NS	NS
Cortical hyperintensity	0.0016	0.0047	0.0096	10.9§	10.0§	NS	3.0‖
Subcortical hyperintensity	0.0024	0.0032	0.0034	NS	NS	NS	NS
Vermal analyses							
No.	14	4	2	...	...	...	...
Vermal I through V area	577	514	422	7.5‖	44.0¶	8.0¶	28.0‖
Vermal VI and VII area	344	436	307	9.4§	1.0§	8.0¶	NS
Vermal ratio	0.60	0.85	0.73	11.5§	0.0§	8.0¶	2.0¶

*C indicates control; WS, Williams syndrome; DS, Down syndrome; K-W, Kruskal-Wallis analysis of variance; and NS, not significant.

†Derivation of proportions is explained in the "Image Analysis" section.

‡$P < .001$.

§$P < .01$.

‖$P < .05$.

¶$P < .1$.

RESULTS

Routine clinical readings of the MRI examinations were performed. The reported subjective impressions were as follows: punctate signal hyperintensities in the centrum semiovale were noted in one male and one female subject with WS. Focal right temporal horn dilatation was noted in another female subject with WS. No abnormalities were noted in the remaining three subjects with WS. A high signal abnormality in the glomus of the left lateral ventricle was noted in one male subject with DS. This was considered to represent subacute hemorrhage, possibly related to a small vascular malformation in this location. Mild diffuse atrophy was noted in a female subject with DS. No abnormalities were noted for the remaining subjects with DS.

A right cerebellar venous angioma was noted in a normal 9-year-old boy. Moderate volume loss, with a single small punctate hyperintensity, was noted in a normal 32-year-old woman. A single punctate focus of signal hyperintensity in the frontal lobe was noted in another normal 32-year-old woman. No abnormalities were noted in the remaining 11 controls.

Results of the quantitative analyses of the images are summarized in the Table. Significant group differences were observed in the measures of cerebral and cerebellar volume, in the cerebellum-to-cerebrum volume ratio, in the cerebellar proportion, in the measure of cortical signal hyperintensities, in vermal I through V and VI and VII areas, and in the vermal ratio.

Both groups of retarded subjects showed reduced cerebral volumes compared with normal controls. The distributions of the values for each group are shown in Fig 4, left. Cerebellar volumes were reduced in the subjects with DS, but no suggestion of such a decrease was observed in the subjects with WS, and indeed subjects with WS had significantly larger cerebellar volumes than subjects with DS (Fig 4, center). The cerebellum-to-cerebrum volume ratio was significantly higher in the subjects with WS relative to both other groups (Fig 4, right). No differences were observed in the cerebral proportion; however, subjects with DS had significantly reduced cerebellar proportions, and a similar trend was noted in the subjects with WS, although it did not reach statistical significance. Both groups had increased numbers of hyperintense pixels in the cortical region compared with controls.

Analyses of the vermal measure-

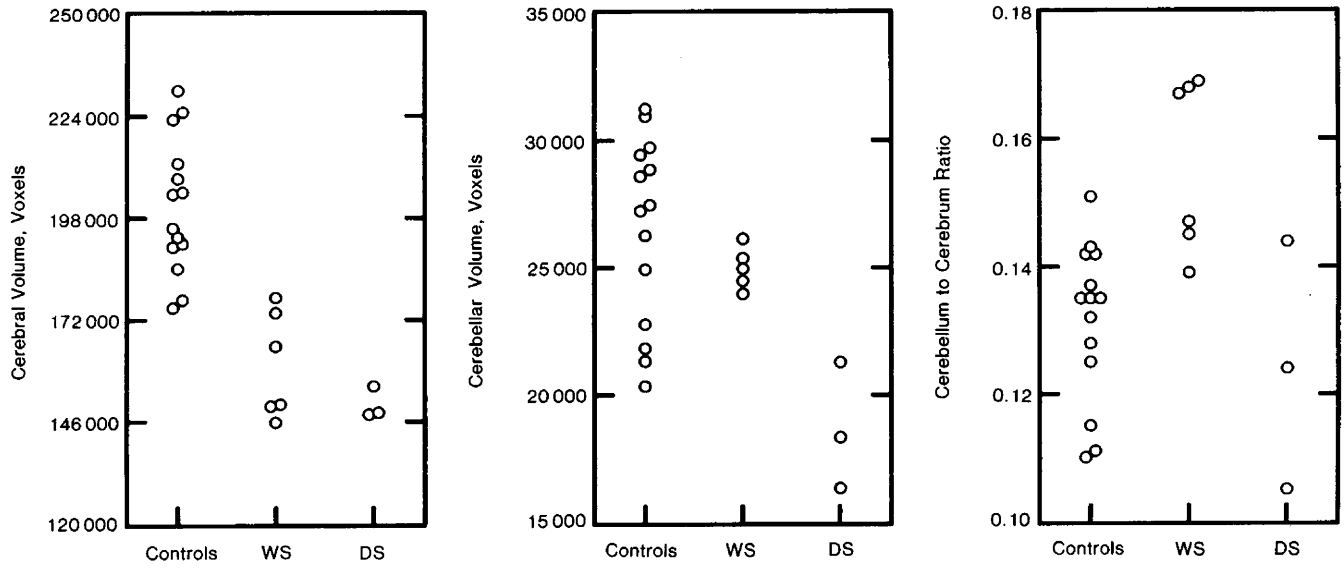


Fig 4.—Distributions of values for the three groups on estimated cerebral and cerebellar volumes and ratio of cerebellar to cerebral volume. Values are in units called "voxels," measuring 0.94 × 0.94 × 7.5 mm (ie, the pixel dimensions multiplied by the section-to-section interval). Left, Distributions show reduced cerebral size in both retarded groups. Center, Reduced cerebellar volume is present in subjects with Down syndrome (DS) but not in those with Williams syndrome (WS). Right, Cerebellum-to-cerebrum ratio is increased in subjects with WS.

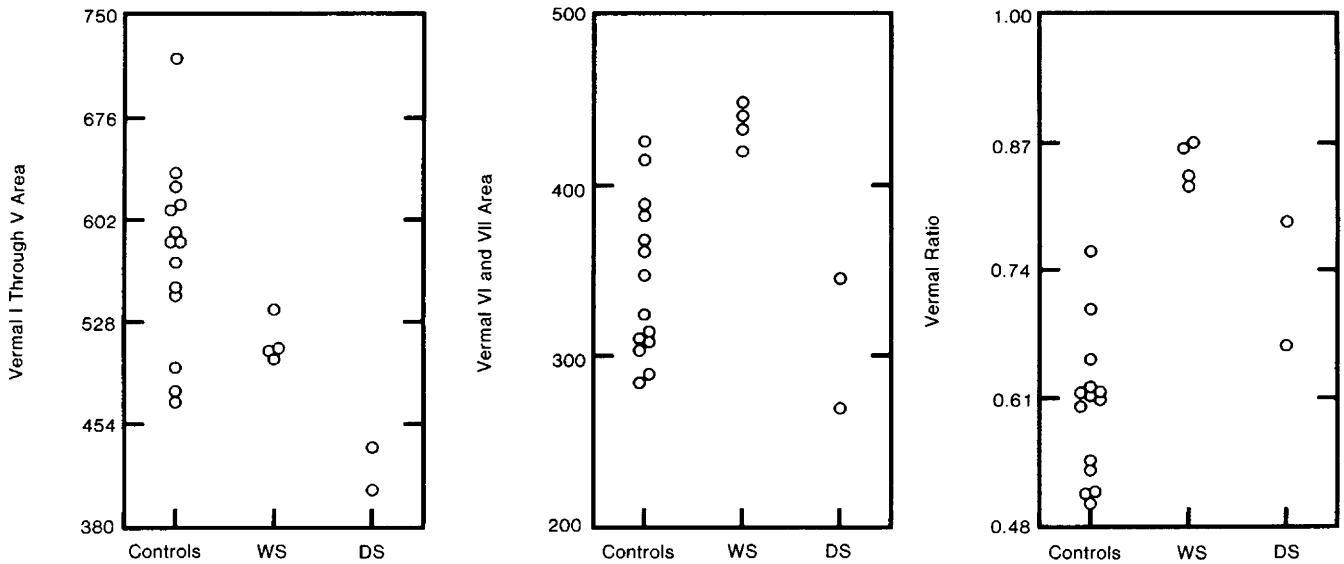


Fig 5.—Distributions of values for the three groups on areas of vermal lobules I through V and VI and VII and on the vermal ratio. Left, Vermal I through V areas are decreased in subjects with Down syndrome (DS) and are slightly, but not significantly, smaller in subjects with Williams syndrome (WS). Center, Vermal VI and VII areas are increased in subjects with WS. Right, The vermal ratio is increased in subjects with WS.

ments focused on the comparison of subjects with WS with control subjects, since only two subjects with DS could be studied. The vermal VI and VII area was significantly larger in the subjects with WS, as was the vermal ratio. The distributions of values for controls, subjects with WS, and subjects with DS are shown in Fig 5 for the vermal I through V area, the vermal VI and VII area, and the vermal ratio.

COMMENT

These results suggest an unusual pattern of brain dysmorphology in WS. The smaller cerebral volume observed in our retarded subjects was consistent with the reported microcephaly of DS and WS.[2,13-15] Further analyses of the cerebral measures suggested that, although it is smaller in the retarded groups, the cerebrum has a proportion of gray matter similar to that observed in the normal controls, and that no gross cerebral volume loss, as reflected in increased CSF proportion, is present in either of these small groups of subjects. There is evidence of increased areas of signal hyperintensity in the cortical zone for both groups, but the significance of this is unknown.

A significant reduction of the vol-

ume of the posterior fossa, as well as the cerebrum, was observed in the subjects with DS. This is consistent with the findings of Crome et al,[12] suggesting that in DS, the cerebellum and brain stem are more dramatically reduced in size than is the cerebrum. Interestingly, there was also a greater proportion of CSF in the posterior fossa, suggesting some volume loss in the cerebellum (in addition to the hypoplasia reflected in a smaller fossa). In striking contrast, subjects with WS showed no suggestion of a reduction in the overall size of posterior fossa structures. This at first appears surprising, since the cerebellum is often described as growing later, and most factors affecting cerebral growth would be expected to affect the later cerebellar growth as well. Studies by Dobbing and Sands,[16] however, suggest that while the cerebellum grows later, it also grows faster, and obtains its full complement of cells earlier than the forebrain. Although these authors consider that the neuronal cell population is complete as early as 18 weeks' gestation, they note that because of differences in the rate of cell multiplication in the glial populations responsible for most of the brain growth spurt, the cerebellum achieves adult cell numbers at about age 18 months, when the forebrain has only about 60% of its full complement of cells. Since the cause of WS is still unknown, the unusual findings reported here may have some implications for candidate mechanisms, either environmentally or genetically mediated, by which development of the brain is affected.

Prompted by recent studies by Courchesne et al[10,11] showing significant differences in vermal morphology in autistic subjects, we examined the posterior fossa structures of our subjects more carefully, using similar methods. In the earlier studies of autistic subjects, vermal I through V areas were comparable with those in controls; however, vermal VI and VII areas were reduced, and in some cases, the hypoplasia was pronounced. The present results in WS showed a surprising reversal of the pattern observed in autism. The vermal I through V area was, as in autism, not significantly different from that in controls, although it tended to be slightly smaller in WS; however, the vermal VI and VII area in WS was significantly larger than in controls, and the vermal ratio showed no overlap between normal controls and subjects with WS. Thus, an anomalous pattern is suggested, with neocerebellar vermal lobules VI and VII preserved, and possibly hyperplastic, in the context of low-normal paleocerebellar vermal development and significantly reduced forebrain size. This, of course, presumes that changes in cross-sectional areas of the vermal lobules reflect altered volume of the cerebellar regions. Since neocerebellar areas of the cerebellum compose a larger proportion of this structure than do paleocerebellar regions, hyperplasia of these regions might be expected to produce an overall increase in cerebellar volumes. No significant increase was observed in the present study. One explanation is that the increased vermal VI and VII area is due to a change in shape of the cerebellum rather than hyperplasia. For example, reduction in lobules I through V may have altered the shape of preserved lobules VI and VII so that they appear larger in cross section. Another possibility is that reduced paleocerebellar size sufficiently offsets the increase in neocerebellar size to prevent an overall increase that is detectable with four subjects. Further studies may help to resolve this question.

Unfortunately, it is not clear at this point whether the observed reduction in cerebral volume is due to diffuse factors or to the reduction of specific cerebral subsystems. It is possible that cerebral structures linked anatomically to the neocerebellar vermis, such as thalamus and frontal cortex, or cerebral structures developing in close temporal contiguity with the neocerebellum, may also show selective preservation. Further studies to address this question are under way.

In the present study, most of the mentally retarded subjects were teenagers. In contrast, controls were drawn from two groups: children aged 8 to 10 years, and adults aged 26 to 32 years. Although, ideally, subjects should be individually age-matched, it seems reasonable to assume that values on morphological variables in teenagers will be intermediate between those in children and those in young adults. The relationship of cerebellum to cerebrum observed here is abnormal in WS relative to either subgroup of controls, as is the vermal ratio. Thus, the results do not appear to be attributable to imperfect age-matching.

It is unclear whether the unusual preservation of specific linguistic capacities in WS, in the context of marked retardation in other cognitive domains,[5] may be related to the observed preservation of cerebellar structures in the context of cerebral maldevelopment. Further studies are under way to examine the specific relationships between the neuropsychological characteristics of WS and the morphological anomalies here noted.

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