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Development of the Brainstem and Cerebellum in Autistic Patients[1]

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Studies of magnetic resonance images have revealed morphological disorders of the brainstem and cerebellum in autistic children and adults. When we studied development of the brainstem and cerebellum in autistic patients, we found that although the brainstem and cerebellum significantly increased in size with age in both autistic patients and controls, these structures were significantly smaller in autistic patients than in controls. The speed of development of the pons, the cerebellar vermis I–V and the cerebellar vermis VI–VII was significantly more rapid in autistic patients than in the controls. However, the speed of development of the other brain structures in the posterior fossa did not differ between autistic patients and controls. The regression intercepts of the brainstem and cerebellum as well as those of their components were significantly smaller in autistic patients than in controls. Results suggest that brainstem and vermian abnormalities in autism were due to an early insult and hypoplasia rather than to a progressive degenerative process.

INTRODUCTION

There is a growing acceptance of infantile autism as an organically based neurodevelopmental disorder involving both cognitive and social deficits. Pathologic studies have demonstrated a loss of neurons (Purkinje and granular cells) from the cerebellar hemisphere and vermis (Arin, Bau-

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man, & Kemper, 1991; Bauman, 1991; Bauman & Kemper, 1985; Ritvo et al., 1986; Williams, Hauser, Purpura, DeLong, & Swisher, 1980). Although no neuropathologic changes have been found in the brainstem in autism (except for one case) (Bauman, 1991), physiologic studies such as auditory brainstem evoked potentials and short latency somatosensory evoked potentials have revealed some brainstem dysfunction (Hashimoto, Tayama, & Miyao, 1986; Ornitz, 1985, 1987, 1988; Thivierge, Bedard, Cote, & Maziade, 1990). The majority of recent neuroradiological studies have demonstrated cerebellar hypoplasia and/or a small brainstem, including the midbrain, pons, and medulla oblongata, in autistic patients (Ciesielski et al., 1990; Courchesne, Saitoh, et al., 1994a; Courchesne, Townsend, & Saitoh, 1994b; Courchesne, Yeung-Courchesne, Press, Hesselink, & Jernigan, 1988; Gaffney, Kuperman, Tsai, & Minchin, 1988; Gaffney, Tsai, Kuperman, & Minchin, 1987; Hashimoto, Murakawa, Miyazaki, Tayama, & Kuroda, 1992a; Hashimoto, Tayama, Miyazaki, Murakawa, & Kuroda, 1993a; Hashimoto et al., 1993b; Hashimoto, Tayama, et al., 1992b; Kleiman, Neff, & Rosman, 1992; Murakami, Courchesne, Yeung-Courchesne, & Hesselink, 1989; Piven et al., 1992). A minority of studies, however, have not found any abnormalities in the posterior fossa structures of the brain (Garber & Ritvo, 1992; Hsu, Yeung-Courchesne, Courchesne, & Press, 1991). Except for three studies (Courchesne et al., 1994a, 1994b, Hsu et al., 1991), the number of autistic subjects in MR studies of the posterior fossa has been small and the effect of brain development has not been studied. Differing results may therefore have been related to small study samples and a failure to understand the role of brain development.

The aim of this study was to investigate the neuroradiologic development of the brainstem and cerebellum in a large number of autistic patients from early infancy to adulthood and to compare the developmental patterns of autistic patients with those of mentally normal controls without autistic behavior.

SUBJECTS AND METHOD

Subjects were 102 autistic patients ranging in age from 6 months to 20 years ($M = 6.10 \pm 4.70$ years) and 112 controls from 3 months to 20 years ($M = 7.10 \pm 5.38$ years). Forty-five autistic and 59 control subjects were the same as those appearing in the author's previous reports (Hashimoto et al., 1992a, 1992b, 1993a, 1993b). The autistic patients and controls were divided into nine age groups (Group 1, 0–< 2 years; Group 2, 2–<

4; Group 3, 4–< 6; Group 4, 6–< 8; Group 5, 8–< 10; Group 6, 10–< 12; Group 7, 12–< 14; Group 8, 14–< 16; and Group 9, 16–20).

The autistic patients were diagnosed by two clinicians according to the criteria of the American Psychiatric Association, DSM-III-R. All 102 autistic patients met DSM-III-R criteria, and both clinicians agreed on the diagnosis. Twenty-nine patients who were identified prior to their 3rd birthdays, including 10 infants, were formally diagnosed as autistic when they reached the age of 3. An assessment of autistic behavior in autistic children was performed in each child using a checklist for the autistic child (CLAC; Makita & Umezu, 1972). The autistic group contained 76 males and 26 females, with more male subjects in the autistic group than in the control group ($p < .02$). Seventeen autistic children were high functioning, having IQ (DQ) greater than or equal to 80. Thirty-five were mildly retarded, IQ (DQ) 79–60. Thirty-three were moderately retarded, IQ (DQ) 59–30. Seventeen of the autistic children were severely retarded. IQ (DQ) < 29. Mean IQ (DQ) of autistic patients was 59.5 ± 25.0. Developmental quotient (DQ) was assessed in all subjects by the Tsumori-Inage development test and IQ by the Suzuki-Binet test. A chromosome examination (G-band method) was performed in all autistic patients with three or more minor anomalies. Patients with large ear lobe deformity and mental retardation were also evaluated for the fragile X chromosome. However, no abnormalities of the X chromosome were found in these patients. Other tests such as serum antibody titer for cytomegalovirus, serum uric acid, lactate, pyruvate, urinary amino acid, and mucopolysaccharide screening test were all normal. An electroencephalogram (EEG) was performed in all autistic patients, and in 25 patients the EEG revealed epileptic discharge. Of 102 autistic patients, 41 were right-handed, 8 were left-handed, and 53 were ambidextrous. A neuroradiologist determined that no autistic patient exhibited major structural abnormalities on magnetic resonance (MR) imaging. The control group used in this study consisted of children who had MR examinations performed for evaluation of headache or evaluation of head trauma, as well as employees and their younger siblings recruited at Tokushima University Hospital. The group consisted of 65 males and 47 females ranging in age from 3 months to 20 years ($M = 7.10 \pm 5.38$ years). Normal healthy volunteers were 41: 7 in Group 1, 6 in Group 2, 3 in Group 3, 5 in Group 4, 4 in Group 5, 4 in Group 6, 3 in Group 7, 5 in Group 8, and 4 in Group 9. The behavior of the control children was assessed on medical examination. The learning ability of school-aged controls was assessed from their school records and was at least average in each case. The learning ability of preschool aged children was assessed by their ability to read a short sentence written in Japanese character "Hiragana," write their

Table I. Demographic Data for Autistic and Control Groups

	Autism (n = 102)	Control (n = 112)
Age		
Range	6 months–20 years	3 months–20 years
$M \pm SD$ (years)	6.1 ± 4.7	7.1 ± 5.4
Sex (F/M)[a]	26/76	47/65
DQ(IQ)		
Range	10–129	-
$M \pm SD$	59.5 ± 25.0	-

[a]The ratio of M/F was significantly higher in the autistic group when compared to the control group (χ^2 test, $p < .02$).

full name, correctly count at least 10 pennies, copy triangles, and name four or more colors. The control patients exhibited no neurologic or behavioral abnormalities and also did not meet the diagnostic criteria for attention deficit hyperactivity disorder from DSM-III-R. The control subjects under 3 years of age revealed normal DQ. However, the follow-up assessments of their development were not performed. Their MRI scans were reported as anatomically normal by a neuroradiologist. Of the 112 controls, 67 were right-handed, 6 were left-handed, and 39 were ambidextrous. Demographic data and IQ (DQ) of the subjects studied appear in Table I.

Magnetic resonance imaging was performed using a Toshiba MRT-50A 0.5 T. and a Siemens Magnetom 1.5T superconducting magnet system both with a 256 × 256 acquisition matrix. Sections were 5- and 7-mm thick, respectively. With the Toshiba MRT-50A, sagittal MR images were obtained with a field-echo sequence (TR 300 ms, TE 14 ms), and axial images were obtained with both a field-echo (TR 300 ms, TE 14 ms) and a spin-echo (TR 2000 ms, TE 30 ms, and 100 ms) sequence. With the Siemens Magnetom, sagittal images were obtained with a spin-echo sequence (TR 200 ms, TE 15 ms) and axial images were obtained with a spin-echo (TR 510 ms, TE 15 ms, and TR 2000 ms, TE 90 ms and 22 ms) sequence. Before the MR imaging was performed, most of the autistic patients, and those control children under the age of 6 years were sedated with triclofis sodium, 50–100 mg/kg, after informed consent had been obtained from subjects and/or their parents.

Measurements of brain structure area were made independently by two clinicians (T.H. and K.M.) using the medical image file system, TDIS-FILE-500 (Toshiba). Six autistic cases were excluded from measurement of the cerebellar vermis because the midsagittal image of the cerebellar vermis

had not been performed correctly. One of us (M.M.) outlined the midbrain, pons, medulla oblongata, and cerebellum on the midsagittal T1-weighted MR images developed on X-ray film without knowing the diagnosis. The outlined film was fed into the TDIS-FILE-500 (Toshiba) for digitization and measurement of area using a film digitizer. The areas of the cerebellum and brainstem were calculated using computer-aided design software. Regions of interest were magnified so as to differentiate these from surrounding structures. The outlined brainstem and cerebellum are shown in Figure 1. The midbrain was bounded by a line drawn from the caudal margin of the mammillary bodies through the posterior commissure rostrally and by a line drawn from the caudal margin of the inferior colliculus to the bisection point between the pons and midbrain on the ventral side (the midbrain included the superior and inferior colliculi and the aqueduct of Sylvius). This method differed from that used by Gaffney et al. (1988) and Hsu et al. (1991). The caudal margin of the pons was bounded by a line drawn from the inferior pontine notch of the IVth ventricle to the bisection point between the pons and the medulla oblongata on the ventral side. Only the entire pons was measured, as described by Gaffney et al. (1988) and Hsu et al. (1991). The area of the ventral pons was not measured. The caudal margin of the medulla oblongata was bounded by a line bisecting the area (caudal border of the decussation pyramidum) where the medulla oblongata tapered to the cervical spinal cord according to the method of Gaffney et al. (1988); this point was the intersection of two tangent lines of both the cervical spinal cord and the decussation pyramidum on the ventral side and was roughly at the inferior border of the cerebellum. The cerebellum was divided into three parts: anterior vermis (vermian lobules I to V), superior posterior vermis (vermian lobules VI to VII) and inferior posterior vermis (vermian lobules VIII to X). The method of defining vermis boundaries followed that of Courchesne et al. (1988). The boundary between the anterior vermis and the superior posterior vermis was defined as the line joining the anterior aspect of the primary fissure to the apex of the IVth ventricle. The boundary between the superior posterior vermis and the inferior posterior vermis was defined as the line joining the anterior aspect of the prepyramidal fissure to the apex of the IVth ventricle.

The means of two measurements were used. Measurements were made blindly for both the autistic and control groups (by M.T. and T.H.). For the neuroanatomic structures mentioned here, the interrater and intrarater correlations were more than .98. The interrater and intrarater correlation was calculated from data on 35 autistic patients and 45 controls. The brain structures were measured on midsagittal MR images. Data are reported as mean ± standard deviation. The intraclass correlation was used to examine

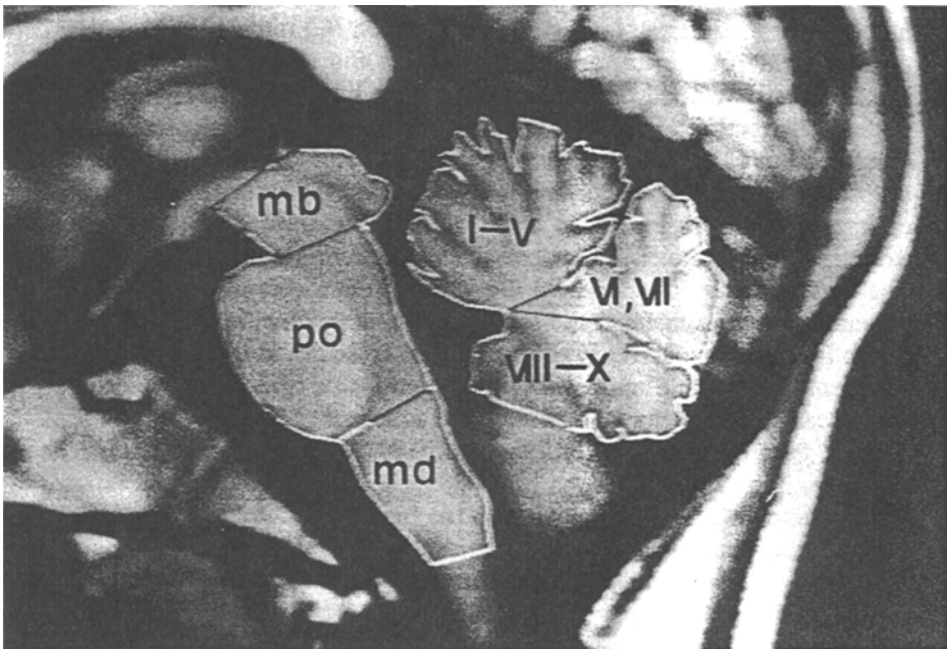

Fig. 1. The cerebellar and brainstem areas are outlined. mb = midbrain; po = pons; md = medulla oblongata; I through X = vermian lobules I through X.

the inter- and intrarater reliability. Student's t test and χ^2 test were used to determine the statistical significance of data for autistic and control groups. Pearson's correlation coefficient was used to examine the relationship between age and areas of the posterior fossa brain structures in both the autistic and control groups. A z transformation was used to test the statistical significance of the correlations between the autistic and control groups. Analysis of variance (ANOVA; two-factor factorial and nonrepeated measures) in the Stat View II was used as the test of statistical significance. Student's t test was used to examine the statistical significance of the comparison of regression slopes and intercepts in each brain structure between autistic and control groups.

RESULTS

The area of the brainstem and its three components (midbrain, pons, and medulla oblongata) increased with development and revealed a statistically significant correlation coefficient with age (autistic group: brainstem, $r = .789$, midbrain, $r = .673$, pons, $r = .776$, and medulla oblongata, $r =$

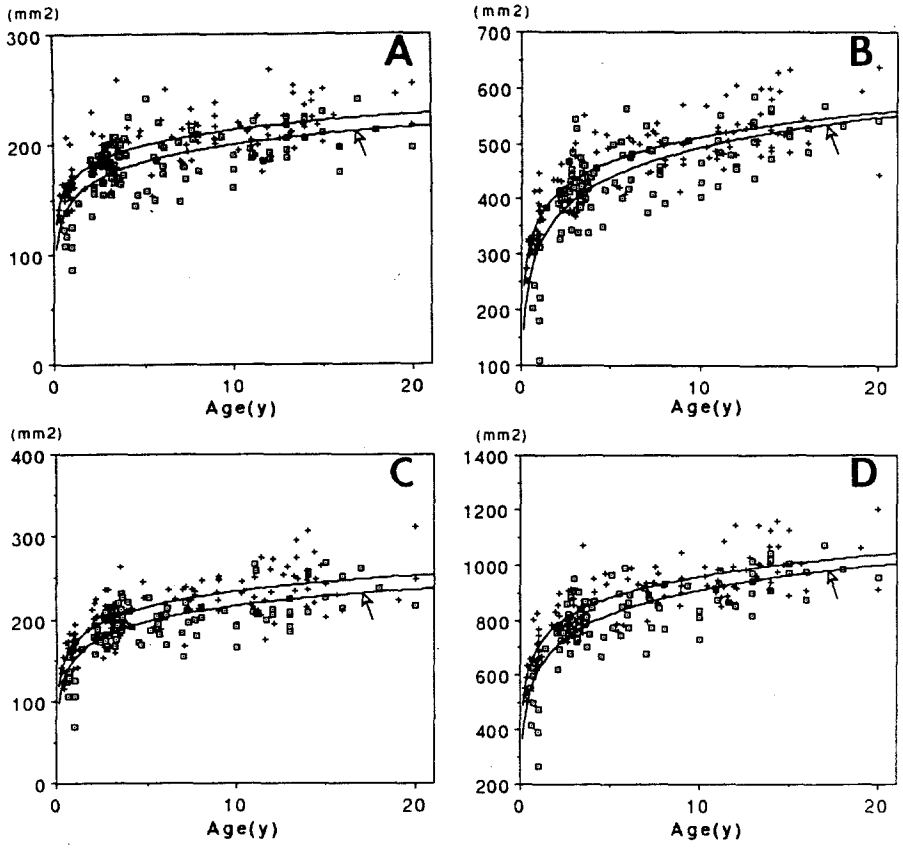

Fig. 2. The changes in area of the brainstem and its components (midbrain, pons, and medulla oblongata) with age is shown with the fitting curves. The open arrow points to the fitting curve for the autistic group. + = control group; □ = autistic group; A = midbrain; B = pons; C = medulla oblongata; D = brainstem. Formulas for the fitting curves were as follow: midbrain, autistic group y = 148.05 + 52.36log(x), r = .673, control group y = 167.12 + 46.64log(x), r = .765; pons, autistic group y = 314.50 + 179.12log(x), r = .776 control group y = 365.89 + 146.34log(x), r = .857; medulla oblongata, autistic group y = 152.15 + 64.78log(x), r = .718, control group y = 171.40 + 62.97log(x), r = .795; and brainstem, autistic group y = 614.70 + 296.27log(x), r = .789, control group y = 704.41 + 255.95log(x), r = .865.

.718; and control group: brainstem, r = .865, midbrain, r = .765, pons, r = .857, and medulla oblongata, r = .795) ($p < .001$ for the brainstem and its components in both autistic and control groups). The r values for each structure did not differ significantly between autistic and control groups (Figure 2, A, B, C, D). The area of the entire cerebellar vermis and its

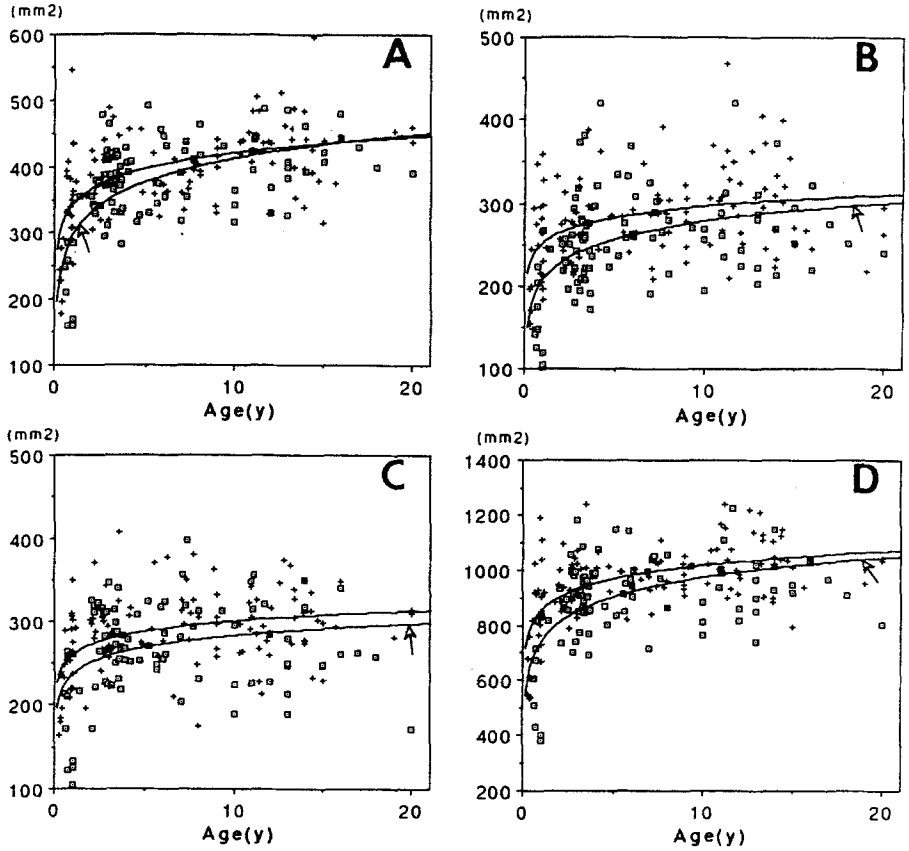

Fig. 3. The changes in area of the cerebellar vermis and its components (vermian lobules I–V, VI–VII and VIII–X) with age is shown with the fitting curves. The open arrow points to the fitting curve for the autistic group. + = control group; □ = autistic group; A = vermian lobules I–V; B = vermian lobules VI–VII; C = vermian lobules VIII–X; D = cerebellar vermis (entire). The fitting curves were as follow: vermian lobules I–V, autistic group y = 295.19 + 117.77log(x), r = .635, control group y = 341.82 + 79.31log(x), r = .582; vermian lobules VI–VII, autistic group y = 208.00 + 70.51log(x), r = .437, control group y = 252.53 + 44.01log(x), r = .400; vermian lobules VIII–X, autistic group y = 235.99 + 47.70log(x), r = .327, control group y = 259.88 + 41.32log(x), r = .430; and cerebellar vermis (entire), autistic group y = 740.03 + 234.99log(x), r = .549, control group y = 854.22 + 164.64log(x), r = .598.

three components (vermian lobules I–V, vermian lobules VI–VII and vermian lobules VIII–X) also increased with development and revealed a statistically significant correlation coefficient with age (autistic group: entire cerebellar vermis, r = .549, vermian lobules I–V, r = .635, vermian lobules VI–VII, r = .437, and vermian lobules VIII–X, r = .327; and control group:

entire cerebellar vermis, $r = .598$, vermian lobules I–V, $r = .582$, vermian lobules VI–VII, $r = .400$, and vermian lobules VIII–X, $r = .430$) ($p < .001$ in the cerebellar vermis and its components of both autistic and control groups). The r values for each structure did not differ significantly between autistic and control groups (Figure 3, A, B, C, D).

Thee areas of the brainstem, cerebellar vermis, and their components in each age group in both autistic and control groups are shown in Table II. The results of a two-factor (disorder and age) ANOVA on measurements of the posterior fossa brain structures showed a statistically significant difference between autistic and control groups. In both autistic and control groups, the areas of the posterior fossa brain structures increased with age. However, the areas of the posterior fossa brain structures in the autistic group were significantly smaller than those in the control group (Table III).

The regression slopes for the pons, vermian lobules I–V, and vermian lobules VI–VII were significantly larger in the autistic group than in the control group. The regression slopes for the brainstem, midbrain, medulla oblongata, entire cerebellar vermis, and vermian lobules VIII–X did not differ significantly between autistic and control groups. The regression intercepts of the posterior fossa brain structures were significantly smaller in the autistic group than in the control group (Table IV).

DISCUSSION

In the present study, the areas of the brainstem, the entire cerebellar vermis and their components were smaller in the autistic group than in the control group. This constitutes morphological evidence not only of brainstem involvement in autism in accordance with the findings of Gaffney et al. (1988) and Hashimoto et al. (1992a, 1992b, 1993a, 1993b) but also of involvement of the cerebellar vermis in autism in accordance with the findings of Courchesne et al. (1988).

It has been reported that in autistic children the fourth ventricle is larger than in control subjects (Gaffney, Kupperman, Tsai, Minchin, & Hassanein, 1987) and that the pons is smaller than in control subjects (Gaffney et al., 1988). We too found a reduction in pontine measures, but contrary to Gaffney et al. (1988), we additionally found midbrain and medulla oblongata reduced in midsagittal area. Hsu et al. (1991) and Piven et al. (1992) did not find brainstem abnormalities in their quantitative studies. Difference in results may have been due to our use of both younger and less intelligent subjects or differences in the measurement methods and the number of subjects. In autopsy studies, Bauman (1991) had demonstrated

Table II. Areas ($M \pm SD$, mm^2) of Posterior

Age group (years)	Brainstem		Midbrain		Pons		Medulla oblongata	
	Autism	Control	Autism	Control	Autism	Control	Autism	Control
1 (0–< 2)	526.47 ± 130.37(11)	666.77 ± 83.59(25)	130.52 ± 25.47(11)	158.78 ± 18.99(25)	264.49 ± 79.39(11)	347.12 ± 51.26(25)	131.47 ± 30.77(11)	160.86 ± 20.37(25)
2 (2–< 4)	790.94 ± 65.80(42)	823.85 ± 86.85(20)	180.47 ± 17.07(42)	192.21 ± 22.46(20)	416.50 ± 46.30(42)	428.46 ± 49.42(20)	193.72 ± 18.12(42)	203.18 ± 26.79(20)
3 (4–< 6)	834.71 ± 103.64(10)	869.21 ± 88.83(7)	185.95 ± 34.60(10)	192.93 ± 23.47(7)	454.93 ± 60.82(10)	466.88 ± 47.83(7)	193.83 ± 17.77(10)	209.40 ± 21.99(7)
4 (6–< 8)	835.12 ± 70.08(11)	928.37 ± 54.28(12)	186.33 ± 19.10(11)	209.70 ± 20.72(12)	454.71 ± 44.82(11)	496.20 ± 31.08(12)	194.08 ± 20.38(11)	222.47 ± 20.08(12)
5 (8–< 10)	875.22 ± 91.84(3)	930.83 ± 57.88(8)	197.73 ± 18.65(3)	214.41 ± 13.10(8)	468.33 ± 66.76(3)	481.75 ± 45.36(8)	209.16 ± 6.80(3)	234.68 ± 16.63(8)
6 (10–< 12)	815.35 ± 179.04(8)	937.42 ± 60.82(15)	189.10 ± 17.35(8)	203.71 ± 14.63(15)	468.00 ± 48.59(8)	506.42 ± 36.03(15)	210.75 ± 34.54(8)	227.29 ± 24.55(15)
7 (12–< 14)	921.33 ± 77.04(8)	1010.80 ± 75.71(12)	202.13 ± 14.13(8)	221.33 ± 24.01(12)	508.56 ± 54.33(8)	538.42 ± 43.65(12)	210.64 ± 21.25(8)	251.05 ± 27.04(12)
8 (14–< 16)	981.45 ± 57.28(4)	1031.74 ± 92.23(9)	222.14 ± 8.30(4)	229.17 ± 15.66(9)	518.81 ± 37.44(4)	554.53 ± 57.42(9)	240.50 ± 27.12(4)	248.03 ± 31.89(9)
9 (16–20)	973.19 ± 70.69(5)	1022.84 ± 141.20(4)	204.89 ± 24.50(5)	229.34 ± 25.77(4)	531.63 ± 30.46(5)	544.99 ± 88.50(4)	236.67 ± 20.91(5)	248.50 ± 44.70(4)

[a]Number of cases shown in parentheses.

Table III. Results of ANOVA for a Two-Factor Analysis of Variance on Measurements of the Posterior Fossa Brain Structures

Brain structure source	*df*	*F*	*p*
Brainstem			
Disorder	1	25.314	.0001
Age group	8	54.723	.0001
Midbrain			
Disorder	1	24.676	.0001
Age group	8	29.797	.0001
Pons			
Disorder	1	13.397	.0003
Age group	8	48.380	.0001
Medulla oblongata			
Disorder	1	26.763	.0001
Age group	8	35.222	.0001
Cerebellar vermis (entire)			
Disorder	1	12.356	.0005
Age group	8	15.185	.0001

Fossa Brain Structures in Each Age Group[a]

Cerebellar vermian							
Entire		Lobules I–V		Lobules VI–VII		Lobules VIII–X	
Autism	Control	Autism	Control	Autism	Control	Autism	Control
598.35 ± 181.24(11)	824.82 ± 171.29(25)	239.14 ± 70.30(11)	329.98 ± 84.24(25)	168.69 ± 58.09(11)	247.96 ± 59.83(25)	188.73 ± 59.75(11)	246.87 ± 47.31(25)
905.83 ± 104.29(37)	967.30 ± 106.46(20)	376.47 ± 42.85(37)	397.72 ± 48.46(20)	252.39 ± 48.96(37)	274.21 ± 43.20(20)	276.96 ± 39.07(37)	295.37 ± 43.19(20)
958.75 ± 127.69(10)	975.50 ± 80.28(7)	381.80 ± 57.48(10)	395.26 ± 50.44(7)	301.46 ± 63.90(10)	281.43 ± 40.39(7)	275.49 ± 30.95(10)	298.81 ± 37.99(7)
963.38 ± 99.79(10)	978.69 ± 68.27(12)	392.33 ± 43.51(10)	382.93 ± 23.69(12)	272.80 ± 36.86(10)	287.85 ± 49.79(12)	298.26 ± 55.08(10)	307.90 ± 50.23(12)
979.04 ± 100.45(3)	959.31 ± 61.37(8)	437.96 ± 23.39(3)	391.56 ± 38.89(8)	255.33 ± 34.44(3)	279.91 ± 31.28(8)	285.75 ± 47.08(3)	287.83 ± 56.71(8)
965.89 ± 153.66(8)	1035.95 ± 98.26(15)	402.06 ± 57.33(8)	436.05 ± 40.35(15)	279.29 ± 66.33(8)	317.59 ± 59.61(15)	284.52 ± 62.90(8)	282.31 ± 35.20(15)
913.34 ± 127.70(8)	1049.00 ± 121.06(12)	395.41 ± 56.63(8)	431.29 ± 53.50(12)	267.12 ± 55.95(8)	300.83 ± 55.52(12)	250.82 ± 41.24(8)	316.89 ± 35.03(12)
952.01 ± 43.40(4)	1017.74 ± 104.35(9)	404.09 ± 12.98(4)	422.82 ± 77.26(9)	256.97 ± 33.95(4)	302.71 ± 53.88(9)	290.95 ± 52.01(4)	292.21 ± 41.38(9)
949.67 ± 96.88(5)	1016.80 ± 43.34(4)	429.1200 ± 35.64(5)	448.48 ± 9.86(4)	261.57 ± 39.21(5)	254.38 ± 32.68(4)	258.99 ± 59.74(5)	313.94 ± 27.52(4)

Table III. Continued

Brain structure source	*df*	*F*	*p*
Cerebellar vermian lobules I–V			
Disorder	1	4.621	.0328
Age group	8	16.404	.0001
Cerebellar vermian lobules VI–VII			
Disorder	1	8.665	.0036
Age group	8	6.906	.0001
Cerebellar vermian lobules VIII–X			
Disorder	1	11.410	.0009
Age group	8	8.187	.0001

evidence of inferior olivary nucleus abnormalities in autism, but Bauman's findings in the inferior olive would not necessarily be expected to produce a reduction in brainstem size. Moreover, to our knowledge no anatomic

Table IV. Comparison of Two Regression Slopes and Intercepts Between Autistic and Control Groups

	Slope				Intercept			
	Autism	Control	t	p	Autism	Control	t	p
Brainstem[a]	296.27	255.95	1.4286	< .2	614.70	704.41	4.1372	< .001
Midbrain[a]	52.36	46.64	0.8447	< .4	148.05	167.12	3.6670	< .001
Pons[a]	179.12	146.34	2.0247	< .05	314.50	365.89	4.1314	< .001
Medulla oblongata[a]	64.78	62.97	0.2317	< .9	152.15	171.40	3.1956	< .005
Cerebellar vermis lobules (entire)[b]	234.99	164.64	1.5757	< .2	740.03	854.22	3.2662	< .005
Cerebellar vermian lobules I–V[b]	117.77	79.31	2.3949	< .02	295.19	341.82	3.7081	< .001
VI–VII[b]	70.51	44.01	4.1762	< .001	208.00	252.53	8.9620	< .001
VIII–X[b]	47.70	41.32	0.4860	< .7	235.99	259.88	2.3241	< .05

[a] $df = 210$.
[b] $df = 204$.

evidence exists showing abnormalities of the midbrain and pons. However, the results of neurophysiologic experiments suggest that the brainstem is involved in autism. Short-latency somatosensory evoked potentials in autistic patients show a remarkably increased central transmission time indicative of a brain stem abnormality (Hashimoto et al., 1986). A large number of auditory brainstem response (ABR) studies have been designed to test the integrity of the auditory brainstem pathway in autism (Klin, 1993). The results reported have been contradictory, involving prolongation, shortening, and no abnormalities in central transmission latencies. At present, ABR studies can be seen as only suggestive, rather than supportive, of brainstem involvement in autism (Klin, 1993).

In our previous study, we reported that the sizes of the midbrain and medulla oblongata of high-functioning autistic children were smaller than those of control children. However, the size of the pons did not differ between autistic and control children (Hashimoto et al., 1993b). In retarded autistic children, the size of the brainstem including the midbrain, pons, and medulla oblongata was smaller than in control children (Hashimoto et al., 1993a). The brainstem results in the present study are consistent with the latter results, probably because the subjects of the present study included both high- and low-functioning autistic patients, with a mean IQ (DQ) that was rather low. The low IQ (DQ) may be related to the small size of the brainstem, especially the pons. Murakawa, Hashimoto, Miyazaki, and Kuroda (1991) have found a small brainstem, using MR imaging, in mentally retarded nonautistic children. Ieshima, Kisa, Yoshino, Takashima,

and Takeshita (1984) have observed morphometric changes on computed tomography (CT), such as a small pons, in patients with Down syndrome.

The sizes of the cerebellar vermis and its components was smaller in the autistic group when compared to the control group. This result was consistent with the cerebellar hypoplasia that Courchesne et al. (1988, 1994a, 1994b), Ciesielski et al. (1990), and Piven et al. (1992) have observed in autism. Reanalysis of the Kleiman et al. (1992) results also show clear evidence of cerebellar hypoplasia in autism (Courchesne et al., 1994a, 1994b). Pathologic studies have demonstrated a reduced number of neurons (Purkinje and granular cells) from the cerebellar hemisphere and vermis (Arin et al., 1991; Bauman, 1991; Bauman & Kemper, 1985; Ritvo et al., 1986; Williams, Hauser, Purpura, DeLong, & Swisher, 1980). However, in two MR imaging studies, Garber and Ritvo (1992) did not observe decreased cerebellar size in autism. In our previous studies, the size of the cerebellar vermis in autistic subjects varied from statistically no smaller than control subjects to hypoplastic (Hashimoto et al., 1992a, 1993a, 1993b), although it tended to be smaller in autistic children. The size of the cerebellar vermis was smaller in younger autistic subjects. However, the intelligence of the subjects was unrelated to the size of the cerebellar vermis. These conflicting results may first be explained by a difference in measurement methods. Second, in our present study the number of subjects was larger than in the studies of Garber and Ritvo (1992) and our previous reports (Hashimoto et al., 1993a). In such smaller previous studies the size of the cerebellar vermis tended to be smaller without reaching a statistically significant difference. Third, the difference in the ages of subjects may have affected the results. Finally, the differing results from various investigations may reflect the heterogeneity of the autistic populations evaluated.

The size of the cerebellum and the brainstem increased with development in both autistic and control groups. The pattern of their development was consistent with results of Hayakawa et al. (1989) and Hashimoto, Tayama, Miyazaki, and Kuroda (1991) in control children. This suggests that the changes in the posterior fossa brain structures in the autistic group are not a progressive degenerative process and that after birth the development of the posterior fossa brain structures is relatively smooth. The intercepts of the fitting curves between age and area for each posterior fossa brain structure were smaller in the autistic group than in the control group. In autism, risk factors are frequently present in the prenatal or perinatal period (Tsai, 1987). Although the cause of the autism is unknown in many cases, many prenatal factors such as chromosomal abnormalities, intrauterine viral infection, metabolic disorders, and so on have been thought to be causes (Gillberg & Colman, 1992). If one such cause acts on brain in early pregnancy, the growth of the posterior fossa brain struc-

tures may be affected. As a result, hypoplasia of the brainstem and cerebellum may occur. In animals, brain anomalies have resulted from chemical agents, irradiation, viral infection, and anoxia during pregnancy. Recently, cortical and white matter volume loss has been reported in autism (Courchesne, Press, & Yeung-Courchesne, 1993; Piven et al., 1990). The brain abnormalities responsible for this disorder have their origin during the first 6 months of gestation. Courchesne et al. (1988), in their MRI study of autism, hypothesized that the neocerebellar hypoplasia they observed might be a result of granular cell and/or Purkinje cell loss in the cerebellum, perhaps occurring as early as the 3rd and 5th months prenatally. Thus, the small intercept found in our present study may reflect intrauterine maldevelopment of the posterior fossa brain structures in the autistic group.

The slope of the fitting curve between age and area for the posterior fossa brain structures (pons, cerebellar vermian lobules I–V, and vermian lobules VI–VII) was steeper in the autistic group than in the control group. These results suggest that in the autistic group, with time the development of these structures may gradually catch up to the control group. However, while the size of the midbrain, medulla oblongata, and cerebellar vermian lobules VIII–X increased with age in the autistic group, differences between the autistic and control groups did not decrease. The cause of this difference in development is unknown. However, the following may contribute to this difference. First, the midbrain and medulla oblongata may be damaged and cause a delayed development in autism. So, a difference between autistic and control groups may not decrease. Hashimoto et al. (1992b, 1993b) have reported that in autism without mental retardation the midbrain and medulla oblongata were smaller than those in control group. Although the pons and cerebellar vermis tended to be smaller in the autistic group than in the control group, the statistical results varied from significance to no significance (Hashimoto et al., 1992a, 1993a, 1993b). Second is a matter of neuroanatomy. In our method, the development of the corticospinal tract and the corticopontine tract, which increase in myelination and fiber diameter after birth, did not affect the area of the midbrain in the midline, but could have affected the midline area of the pons. The pontocerebellar tract terminates in the neocerebellar cortex of both hemispheres and the vermis, by way of the middle cerebellar peduncle. Other afferent tracts terminate in the cerebellar cortex by way of the middle and inferior cerebellar peduncles. So, with development the difference in the size of these brain structures (pons and cerebellar vermian lobules I–V and VI–VII) between autistic and control subjects may be very subtle. For cerebellar vermian lobules VIII–X, the vestibulocerebellum is coextensive with the flocculonodular lobe. This region receives its input from the vestibular

nuclei in the medulla and projects directly back to them. Thus, a decrease in the size of one area (medulla oblongata) is likely to be associated with loss of cellular material in another area (cerebellar vermian lobules VIII–X). Through the afferent and efferent conditions with the vestibular nuclei, the vestibulocerebellum governs body equilibrium during stance and gait (Ghez, 1991). In autism, balance disturbance has been reported (Kohen-Raz, Volkmer, & Cohen, 1992). The hypoplasia of the cerebellar vermian lobules VIII–X may partially explain such results and be related to small medulla oblongata.

Moreover, as Ornitz (1985) and Courchesne et al. (1988) have pointed out, both the brainstem and cerebellum have connections with, and affect the function of, the limbic system, an area implicated in infantile autism. This suggests that widespread brain abnormalities of neural circuits are involved in autism. Although the theories are speculative, such abnormalities could be caused by aberrant prenatal development or early brain injury resulting in brain tissue loss. Neurotransmitters such as serotonin, noradrenaline, and dopamine have received special attention in autism. These neurotransmitter systems arise mainly in the brainstem, and project into the limbic and cortical structures and basal ganglia (Cooper, Bloom, & Roth, 1978). In animal experiments, the developmental disruption of these systems has severe behavioral consequences (Brodal, 1981; Geyer, Puerto, Menkes, Segal, & Mandel, 1976) as well as morphologic consequences on the brain (Brenner, Mirmiran, Uylings, & Van der Gugten, 1983).

The present study had a few limitations. First, 71 of the 112 control subjects were also medical patients. It may be argued that a nonmedical control group should have been used. However, entirely normal control children could not be studied because of the ethical constraints on exposing healthy children to a procedure that may require sedation. The clinical data for the control patients were reviewed, and those patients with a history of learning disability, convulsions, or other neurologic diseases (except for psychogenic headache and mild head trauma) were excluded. The medical control subjects were neurologically normal. Therefore we feel that the brainstem and cerebellar vermis in the control subjects in this study were not affected by pathologic lesions, and they could therefore be used as control subjects. Second, the percentage of male subjects was greater in the autistic group than in the control group. Hayakawa et al. (1989) found no sex difference in the size of the pons and cerebellar vermis. On the other hand, Hashimoto et al. (1991) reported that for the age group of 10–16 years the brainstem was larger in males than in females. However, in the present study, the autistic group contained more males but still had a smaller brainstem area. Therefore, our results do not appear to be affected by the sex ratio difference. Finally, two kinds of MRI machine were

used, with two different slice thicknesses, 5 and 7 mm. This could have caused a considerable volume averaging error. However, development of the posterior fossa brain structures was consistent with the data of Hayakawa et al. (1989). In particular, the area measures of the cerebellar vermis in the present study are similar to their results and similar to area measures of controls from many other studies of the vermis. Furthermore, the standard deviation for each area of each structure was not large. We believe that our results reflect a real difference in the size and development of the posterior fossa brain structures in the autistic group compared with the control group.

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