Brain Morphometric Analysis in Neurofibromatosis 1

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Rationale and Objectives: To investigate the relationships between brain and skull base growth in patients with neurofibromatosis 1 (NF1) compared with healthy control subjects using brain magnetic resonance imaging (MRI) for morphometric analysis.

Methods: Evaluated patients included children who underwent T1- and T2-weighted or dual-echo proton density axial and T1-weighted sagittal brain MRI from January 1, 1988, to December 31, 1995. Study subjects (n = 27) received a diagnosis of NF1 by accepted National Institutes of Health clinical criteria and were compared with an age- and sex-matched control group (n = 43). Twenty-four predetermined ventricular and brain parenchymal dimensions and area calculations were evaluated. Data were analyzed using 2-tailed t tests, χ² analysis, analysis of variance, and analysis of covariance adjusted for age and sex. Correlational analyses with respect to subject type and age were performed separately.

Results: There were 27 patients (20 boys, aged 1.0-17.7 years; mean age, 8.8 years) and 43 controls (22 boys, aged 0.1-17.7 years; mean age, 5.9 years). The mean ages between groups (boys, girls, and totals) were not statistically different. Significant differences were appreciated for 6 of 24 measures. Patients with NF1 had a significantly larger bicaudate width (P = .002), biatrial width (P<.001), and biparietal diameter (P = .003), but not hemispheric length. They also had significantly increased iter measures (P = .004), descending sigmoid sinus (P<.001), and an age-specific increase in brainstem height (P = .03) not seen in controls.

Conclusions: Patients with NF1 experience dynamic changes in brain morphometry, resulting in a predominant lateral volume expansion of the supratentorial compartment and an increasing velocity of brainstem growth as they age. These data underscore brain-region-specific parenchymal overgrowth potential.

Arch Neurol. 1999;56:1343-1346

NEUROFIBROMATOSIS 1 (NF1) is a relatively common (incidence, 1 in 3000) autosomal dominant disorder with a spontaneous mutation rate of about 60%.1,2 The diagnosis is based on an individual demonstrating at least 2 of the following 7 clinical criteria: 6 or more café-au-lait spots (pubertal-dependent size criteria), 2 or more neurofibromas or plexiform neurofibromas, axillary or inguinal freckling, distinctive osseous lesions, optic nerve glioma, more than 2 iris Lisch nodules, or a first-degree relative with NF1.1,2 The NF1 gene on chromosome 17 encodes for the protein neurofibromin.2 Mutations in the NF1 gene result in the production of a nonfunctional neurofibromin protein or the absence of its expression.

Macrocephaly, a common clinical manifestation in patients with NF1, can be ascribed to several mechanisms that are not mutually exclusive.3,4 This may be secondary to communicating or obstructive hydrocephalus, megalencephaly (large brain), or intracranial mass or fluid collections. Megalencephaly would appear to be the most common identifiable underlying reason for macrocephaly seen in patients with NF1. Owing to the fact that the NF1 gene plays a role in regulating cell growth and differentiation, it is likely that a direct effect on tissue growth and ultimate size is linked to tissue-specific expression of this gene. Since not all cell and tissue types need be dependent on this intracellular regulatory gene product, it is likely that not only a brain-specific effect could be postulated but also that brain-region-specific effects could be identified.

We undertook a morphometric analysis of the brain to clarify the structural relationships of brain and skull base growth with attention to region-specific brain growth patterns in patients with NF1 compared with healthy control subjects. We expected that the analysis would reveal a logical sequence of consistently measurable neural and cranial distortions. These identified regions may correlate further to areas of highest potential for the development of hamartomas or neoplasia.

RESULTS

There were 27 patients with NF1 (20 boys; aged 1.0-17.7 years; mean age, 8.8 years)
SUBJECTS AND METHODS

SUBJECTS AND COMPARISONS

All patients referred to the Neurogenetics Clinic at The University of Connecticut Health Center, Farmington, and Connecticut Children’s Medical Center, Hartford, were considered eligible for evaluation. Entry criteria included the availability of brain magnetic resonance images (MRI) obtained from January 1, 1988, to December 31, 1995. Patients selected for evaluation included study subjects with a diagnosis of NF1 by National Institutes of Health–accepted clinical and radiological criteria and a control group matched by sex and age. Controls were only included if the indication for MRI was for the evaluation of headaches or idiopathic seizures and if results of the clinical examination and MRI were normal. The MRI study was considered complete with a T1- and T2-weighted or dual-echo proton density axial image set and a T1-weighted sagittal image set. Poor-quality studies due to motion or other artifacts excluded the potential control from study. In patients with NF1 who subsequently underwent neurosurgical interventions, only preintervention images were evaluated. The presence or absence of malformations, high-signal-intensity lesions, and masses were noted by location. We were interested in identifying regions of growth or size difference that would be appreciated readily, as they related to observable changes in skull growth. Previous studies indicated increased skull growth in the region of the sella turcica and in each skull dimension (height, length, and width). Previous studies demonstrated excellent correlation between skull base distortion and brain morphology in patients with achondroplasia using these measures and methods, and we therefore applied this approach in our present study.

Magnetic resonance images were examined by one of us who is a neuroradiologist (G.R.R.) and who was unaware of the clinical condition of the subjects. All measurements were confirmed by another of us (F.J.D.). Measurements were made in millimeters to the nearest single millimeter for all linear measures, and angular measures were obtained to the nearest single degree. Twenty predetermined ventricular and brain parenchymal dimensions were evaluated, including foramen magnum anterior-posterior (AP) diameter in sagittal plane, the sinojugular transition zone, and the ascending sigmoid sinus widths in axial plane. In addition, the sum of the maximum width of the left- and right-sided sinojugular transition zones was calculated. The product of the maximum AP and lateral widths of the descending sinuses on the left and right sides was calculated. These products (left and right) were then summed for a combined total. The predetermined anatomical regions examined were identified consistently within the landmark identification key (Figure 1). Lastly, the presence or absence of ventriculomegaly was determined and further quantified as grade 1 (mild), 2 (moderate), or 3 (severe) in the NF1 group. This was done by comparing all axial T1-weighted images together. Controls had no ventriculomegaly by definition.

STATISTICAL ANALYSIS

Data were analyzed using the statistical software SPSS for Windows Release 5.0 (SPSS, Inc, Chicago, Ill, 1992). Analysis of covariance with adjustments for age and sex was used to assess mean differences between groups, whereas Pearson correlational analysis was used to assess the relationship between measures.

Although 15 of the 27 patients with NF1 had MRI high-signal T1-weighted lesions identified during this study, there were no significant differences noted on any measure when separate group analyses of the patients with NF1 with and without high-signal lesions were performed independently. We studied no patients with identified tumors or masses.

OUR ANALYSIS OF MORPHOMETRIC MEASURES SHOWED A SERIES OF PREDICTABLE CONSEQUENCES OF BRAIN GROWTH IN PATIENTS WITH NF1. THE WELL-KNOWN MACROCEPHALY IDENTIFIED IN PATIENTS WITH NF1 CAN BE QUANTIFIED AS HAVING A PRIMARY BASIS IN THE LATERAL VOLUME EXPANSION OF THE CEREBRAL HEMISPHERES. THIS OVERGROWTH (MEGALENCEPHALY) MAY HAVE AN IMPACT ON COGNITIVE FUNCTION AS A CONSEQUENCE OF DETERIORATING ORDERLY NEURONAL PRUNING, NEURONAL HYPERTRPHY, ABNORMAL NEURONAL MIGRATION, MYELIN OVERPRODUCTION, OR OVERABUNDANCE OF DENDRITIC SPROUTING AS POSSIBLE CAUSATIVE FACTORS. THE OCCURRENCE OF T1-WEIGHTED HYPERINTENSITY PARENCHYMAL LESIONS ON MRI IN VARIOUS (BUT OFTEN DEEP GRAY MATTER) NUCLEI, BRAINSTEM, AND CEREBELLAR LOCATIONS ALSO SUPPORTS THE DISORDERED PARENCHYMAL GROWTH.

In our study, brainstem growth rate as measured by brainstem height was found to accelerate over time (Figure 2). This specific brain region has been identified as evolving concomitant gliomas with unique biological be-

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ARCH NEUROL/VOL 56, NOV 1999 WWW.ARCHNEUROL.COM

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haviors that distinguish them from non-NF brainstem tumors.12 Our data suggest that this unique biological behavior and growth potential relate at least in part to this anatomical region’s NF1-specific growth rate, regardless of whether high-signal lesions are evident on MRI.8-15

In a recent case-control study of 22 children with NF1, children with NF1 had significantly larger brain volumes mainly due to white matter enlargement.16 When groups were administered the Judgment of Line Orientation and the Developmental Test of Visual-Motor Integration, significant positive correlations were found between lowered scores in the patients with NF1 and larger white matter volume in patients compared with controls.16 Further data supporting disordered growth regulation manifested in distinct morphometric abnormalities come from a study of corpus callosum regional area measurements.17 When 14 patients with NF1 were compared with a sibling control group, the patients were found to have significantly enlarged midcallosal regions out of proportion to their underlying megalencephaly. Each of these studies underscores the region-specific overgrowth potential inherent in patients with NF1. Regardless of whether these anatomical morphometric differences have clinically identifiable correlates, they serve as the parenchymal substrate on which clinically important events evolve.

The regions we identified as divergent in size and growth rate compared with controls (bicaudate, biatrial, and bipearietal widths and brainstem height) are the parenchymal zones that often correlate with high-signal T2-weighted lesions on MRI.8-15 Patients with NF1 with and without high-signal T2-weighted lesions underwent separate analysis. No significant differences were noted on any measure. This suggests that, although these high-signal lesions are associated with NF1, they do not reflect a greater specificity for parenchymal overgrowth per se but rather reflect other inherent localized tissue quality differences. These differences have been identi-
fied preliminarily as myelin microvascular changes and tissue edema. These observations suggest that although the typical transient nature of these high-signal lesions evolves over time, a more intrinsic structural difference in brain growth potential remains. High-signal lesions may be a nonspecific epiphenomenon or may relate to transitory tissue substrate components, whereas the morphometric distinctions we have identified are more fundamentally related to underlying structural differences in the brains of these patients.

In our study, support for a more generalized potential parenchymal overgrowth exists that is unrelated to the presence or absence of high-signal T2-weighted lesions.

In a recent study by Nordlund et al, immunohistochemical analysis was performed on the brains of 3 patients with NF1 (2 with school learning disabilities) and compared with that of controls. The pattern of neurofibromin expression was enriched in large-projection neurons and to a lesser extent in oligodendrocytes. Microglia, astrocyte, and endothelial cells did not show staining. The intensity of neurofibromin immunoreactivity was similar in healthy human brain and in brains with no gross abnormalities in levels or distribution present within the cortex or cerebellum. Importantly, however, they also found an increase in astrocyte number and cell size within the white and gray matter. Prominent glial fibrillary acidic protein staining was noted throughout the ependymal layer surrounding the ventricles as well as an absolute increase in glial fibrillary acidic protein level per astrocyte in NF1 compared with control brains. At least in part, this is produced by a preferential periventricular astrocytic hypertrophy and proliferation. Brain morphometric differences exist in a number of other somatic overgrowth syndromes. A number of these latter disorders also are associated with coincidental intellectual impairment. Cognitive impairment is a concomitant finding in up to 40% of patients with NF1. The degree of impairment may be related to the type and extent of neuronalanatomical disorganization as it relates to a number of possible underlying mechanisms (eg, defective pruning, neuronal hypertrophy, abnormal neuronal migration, defective neuronal-glial interaction).

In summary, we distinguished a number of specific brain structure–morphometric relationships that derive from the underlying brain growth abnormalities associated with NF1. Patients with NF1 experience dynamic changes in brain morphometry resulting in a predominant lateral volume expansion of the supratentorial compartment in addition to an increasing velocity of brainstem growth as they age. These data underscore brain-region–specific parenchymal overgrowth potential.

Accepted for publication February 8, 1999.

This work was supported in part by a grant from the Health Center Research Advisory Committee, The University of Connecticut, Farmington.

Presented in part as a poster at the Child Neurology Society Meeting, Minneapolis, Minn, September 27, 1996.

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