Brain Morphometric Analysis in Neurofibromatosis 1

Francis J. DiMario, Jr, MD; Gale R. Ramsby, MD; Joseph A. Burleson, PhD

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 = .04), 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
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 in 6 of 24 measures (Table). Patients with NF1 had a significantly enlarged bicaudate width ($P=0.002$), biatrial width ($P<0.001$), and biparietal diameter ($P=0.003$), but not hemispheric length. Patients with NF1 also had significantly increased iter measures ($P=0.004$) and AP dimension of the sigmoid sinus ($P<0.001$). Finally, there was an interaction between patient group and age such that the occurrence of T2-weighted hyperintensity lesions in patients with NF1 was positively associated with age ($P=0.03$). For the NF1 group, the older the patient, the larger the brainstem height was; for control patients, age and brainstem height were not significantly correlated (Figure 2).

We noted in our control group a larger range of normal for the distance of the the iter to the incisural line (iter distance) than that previously described in adults (0-8.0 mm). The $T_2$-weighted parasagittal image was included in the analysis for each of the 3 possible pairs of measures, ie, optic tract angle, foramen magnum AP diameter, and iter distance, and found no significant relationships. Separate 0-order correlations within the subject and control groups reflected a similar pattern.

Although 15 of the 27 patients with NF1 had MRI high-signal $T_2$-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 defective neuronal pruning, neuronal hypertrophy, abnormal neuronal migration, myelin overproduction, or overabundance of dendritic sprouting as possible causative factors. The occurrence of $T_2$-weighted hyperintensity parenchymal lesions on MRI in various (but often deep gray matter) nuclei, brainstem, and cerebellar locations also supports the disordered parenchymal growth. The occurrence of T2-weighted hyperintensity parenchymal lesions on MRI in various (but often deep gray matter) nuclei, brainstem, and cerebellar locations also supports the disordered parenchymal growth.
baviors 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.

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, bivalvular, and biparietal 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 ependymal and choroid plexus. 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.

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.

Reprints: Francis J. DiMario, Jr, MD, Department of Pediatrics, Connecticut Children’s Medical Center, 282 Washington St, Hartford, CT 06106 (e-mail: jdmari@cmckids.org).

REFERENCES


Figure 2. Graph depicting relationship between brainstem height and age in healthy control group (mean age, 5.9 years) and patients with neurofibromatosis 1 (NF1; mean age, 8.8 years).