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Neurofibromatosis Type 1: The Evolution of Deep Gray and White Matter MR Abnormalities

Takashi Itoh, Silvia Magnaldi, Robert M. White, Martha Bridge Denckla, Karen Hofman, Sakkubai Naidu, and R. Nick Bryan

PURPOSE: To investigate the evolution of deeply located high-signal-intensity abnormalities of the brain on T2-weighted MR images of patients with neurofibromatosis type 1 (NF-1). **METHODS:** The study consists of two patient groups: 1) retrospective evaluation of MR scans of 24 symptomatic NF-1 patients, 10 of whom were sequentially studied, and 2) prospective MR evaluations of 20 asymptomatic NF-1 subjects from 14 families; 2 of these families were sequentially studied. **RESULTS:** Deeply located, high-signal-intensity abnormalities on T2-weighted images were noted in 34 of 44 NF-1 subjects (77%). If NF-1 patients are grouped according to age, 28 of 30 subjects (93%) younger than 15 years had the lesions, whereas 4 of 7 subjects (57%) between 16 and 30 years, and 2 of 7 subjects (29%) older than 31 years had lesions. High-signal lesions in basal ganglia and brain stem were demonstrated in all decades with relatively high frequency. Lesions in the cerebellar white matter and dentate nuclei were mainly found in the patients younger than 10 years, and never found after the third decade. In 13 sequential studies (mean interval, 24 months), lesions appeared to increase in size in 3, remain unchanged in size in 2, and decrease in size in 7. One subject showed a mixed pattern of lesion size change. **CONCLUSIONS:** Deeply located high-signal-intensity lesions on T2-weighted MR images are more evident in young NF-1 patients. The underlying brain abnormality, while pathologically unproved, is probably transient.

Index terms: Neurofibromatosis; Brain, high-intensity lesions; Brain, magnetic resonance; Phakomatoses

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Neurofibromatosis (NF) is the most common phakomatosis. It is a congenital disease characterized by dysplasias and/or tumors of tissues and organs derived from embryonic ectoderm, mesoderm, and endoderm. It most frequently presents with nervous system and cutaneous lesions (1, 2). There are two types of NF, the more frequent of which is type 1, also known as von Recklinghausen disease or NF-1.

Although the general presentation of NF-1 is well known, some of its manifestations have not been completely explained. In particular, the significance of deep gray and white matter abnormalities reflected by altered magnetic resonance (MR) signal intensity is still unclear (2–9). The aim of this paper is to show the evolution of these areas of altered signal intensity.

Subjects and Methods

This study consists of two patient groups. The first involves a retrospective study of 24 symptomatic NF-1 patients who had one or more cranial MR examinations for clinical reasons. The 24 subjects (10 female and 14 male) ranged from 1 to 37 years of age (mean age, 13). Sixteen patients were younger than 15 years and 8 were older. The second group of this study consists of prospective MR evaluations of 20 asymptomatic NF-1 subjects from 14 different families (in 6 of which NF-1 affected a parent and a child; in the other 8 only a child was affected). These

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From the Johns Hopkins University School of Medicine, Division of Neuroradiology (T.I., S.M., R.M.W., R.N.B.) and Neurology (M.B.D., K.H., S.N.), Baltimore.

Address reprint requests to: R. Nick Bryan, MD, PhD, Division of Neuroradiology, The Johns Hopkins University School of Medicine, 600 N Wolfe St, Baltimore, MD 21205.

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subjects are included in a learning disability research study of NF-1 patients. These 20 subjects (4 female and 16 male) ranged from 6 to 50 years of age (mean age, 19.4). Fourteen patients were younger than 15 years and 6 were older.

The evaluation of the MR examinations considered the presence or absence of contrast abnormalities on T2-weighted images (reflected by areas of increased signal intensity and lack of mass effect), as well as the size and anatomic location of the lesions. The volume of abnormal areas was measured three-dimensionally in the familial group. Quantitative volumetric measurements are performed on an ISG Digital Image Workstation. The T2-weighted data set is loaded into the workstation. Lesions are initially defined by visual inspection of the sections by the reader. Lesions are characterized by regions of abnormally increased T2-weighted signal intensity greater than normal gray matter and which have no mass effect. The lesions are digitally defined as regions of interest by manually thresholding the raw images to exclude normal brain and cerebrospinal fluid, leaving only the bright lesions visible. For each section, a seed-based segmentation algorithm is then initiated by placing a "seed" in the center of each lesion. The algorithm then automatically floods the similar, contiguous region using a local histogram analysis and an edge detection protocol. The algorithm then attempts to drop a seed automatically into similar regions on adjacent sections and perform the same lesion segmentation operation. The algorithm allows editing of lesion identification and boundary definition by the reader. That is, a seed selection inside a threshold area allows the filling in of a contiguous area that falls within the segmentation threshold levels and boundary criteria, while allowing adjustment of the final region of interest by the operator, if desired. After the lesion regions of interest are performed on each section, a 3-D object (or volume of interest) of each lesion is reconstructed from the segmented sections by linear interpolation of the original multisection, two-dimensional data set into a 512 × 512 × 512 3-D data set. The volume of the 3-D lesion object is calculated in mm^3. Up to 12 volumes of interest in the same 3-D data set can be simultaneously managed. For this application, NF-1 lesion identification, the semiautomatic tissue segmentation algorithm of the ISG workstation should be considered only as an operator aid, because the final volumes of interest determination must be confirmed by the reader's eyes. Two neuroradiologists separately analyzed each case for lesion presence. There was no disagreement on lesion identification. Lesion volumes were calculated by the first reader and visually confirmed by the second reader. Ten subjects in the retrospective group and three in the prospective group had follow-up studies. The mean time interval between the first and last study was 24.1 months (range, 11 to 38 months).

All the MR scans were obtained with a superconducting magnet operating at 1.5 T, using a head coil. The section thickness was 5 mm, with 1.5 to 2.5 mm intersection gaps. Images were acquired with a 256 × 256 matrix, 1 or 2 excitations, and a field of view of 20 to 24 cm. In all patients, a T2-weighted spin-echo sequence (2000–3333/70–100 [repetition time/echo time]) in the axial plane was performed. MR examinations were reviewed by three neuroradiologists who knew only that the examinations were from subjects with a possible clinical diagnosis of NF-1 by recently established criteria (10). In general (90% of cases) there was agreement among the three observers. In the remaining cases the presented data are the result of the consensus of the observers.

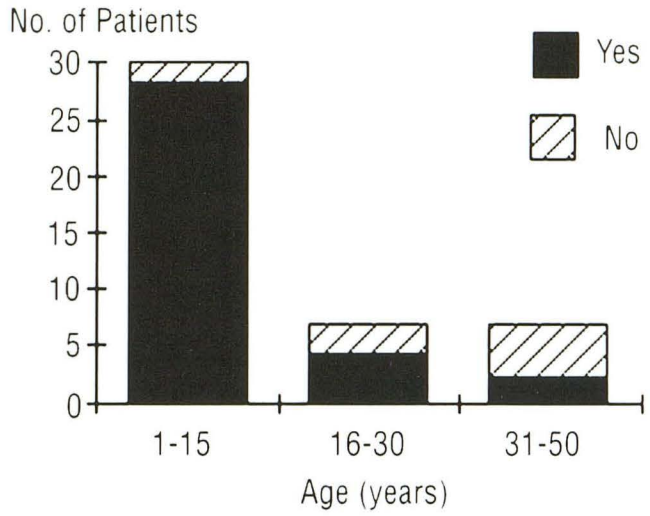

Fig 1. Presence of high-signal-intensity lesions on T2-weighted MR images. Prevalence of lesions is extremely high (93%) in the subjects younger than 15 years.

Results

Frequency of Deep Gray and White Matter Abnormalities

Thirty-four (77%) of 44 patients had deep gray and/or white matter abnormalities reflected by increased T2-weighted signal intensity. If NF-1 patients are categorized according to age, 28 (93%) of 30 patients younger than 15 years (mean age, 8.7 range 1–14) had lesions, whereas 4 (57%) of 7 patients between 16 and 30 years (mean age, 22) and 2 (29%) of 7 older than 31 years had these lesions (Fig 1). In the prospective group, 1 of the 6 NF-1 parents and 12 of the 14 NF-1 children had MR signal abnormalities. In the older patients the lesions were small and unilateral; in the younger subjects the lesions were larger and bilateral.

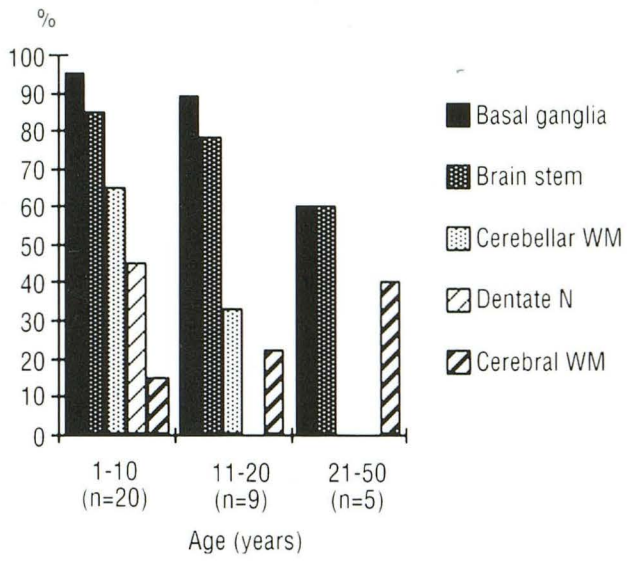

Fig 2. Anatomic distribution of lesions by age, in percent of patients with NF-1. There are many lesions in different locations in younger subjects. Cerebellar lesions are mainly found in the patients younger than 10 years. WM indicates white matter; N, nuclei.

Anatomical Locations of Deep Gray and White Matter Abnormalities

The high-signal lesions on T2-weighted images were demonstrated in the basal ganglia, brain stem (midbrain, pons, and cerebellar peduncles), cerebellar white matter, dentate nuclei of the cerebellum, and cerebral white matter (in 88%, 79%, 47%, 26%, and 21% of patients with NF-1, respectively). Figure 2 reveals the relation of patient age to anatomic locations of the abnormalities. The high signal lesions in the basal ganglia and the brain stem were demonstrated in all decades with relatively high frequency (95% and 85% in mean age 7.3, 89% and 78% in mean age 12.7, 60% and 60% in mean age 33, of patients with NF-1, respectively). Those in the cerebellar white matter and the dentate nuclei were mainly found in the patients younger than 10 years (65% and 45% in mean age 7.3, 33% and 0% in mean age 12.7, respectively), and never found after the third decade.

Relation of Patient Age to Total Volume of the High-Signal Lesions (in Children in the Prospective Group)

There is no correlation between the patient age (mean age, 9.8 years; range, 6 to 14) and total volume of the high-signal lesions.

Follow-up Studies

Changes in size of lesions in each anatomic location were evaluated on follow-up examinations in 13 subjects (Table). Lesions appeared to increase in size in 3 (initial study mean age, 3.7 years; range, 1 to 6) (Fig 3), were unchanged in size in 2 (initial study mean age, 6; range, 5 to 7), disappeared or decreased in size in 7 (initial study mean age, 11.4; range, 7 to 17) (Fig 4). In one subject (initial study age 10), lesions showed a mixed pattern of size change, some lesions increased and some decreased in size.

Changes in lesion size over time

Name	Age, y/Sex	Period, mo	Basal Ganglia	Brain Stem	Dentate Nuclei	Cerebellar White Matter	Cerebral White Matter
M.S.M.	1/F	37	Inc	Inc	App	App	. . .
E.N.	4/F	28	App	NC	NC	NC	. . .
H.E.	5/M	11	NC	NC	. . .	NC	. . .
R.J.	6/M	29	Inc	NC	NC	Inc	. . .
C.D.	7/M	29	NC	NC	NC	NC	. . .
L.M.	7/F	12	Dec	Dec	NC	NC	. . .
G.K.	10/F	30	Inc	Dec	. . .	. . .	Dec
D.G.	10/M	23	Dis	Dec	. . .	Dec	. . .
F.T.	10/F	20	Dec	. . .	. . .	Dec	. . .
D.F.Jr.	11/M	29	Dec	Dec	. . .	. . .	. . .
W.W.	12/M	10	Dec	. . .	. . .	. . .	Dis
R.K.	13/F	10	Dec	. . .	. . .	Dec	. . .
P.J.	17/M	38	. . .	Dis	. . .	. . .	. . .

Note.—Inc indicates increase; Dec, decrease; App, appeared; Dis, disappeared; and NC, no change.

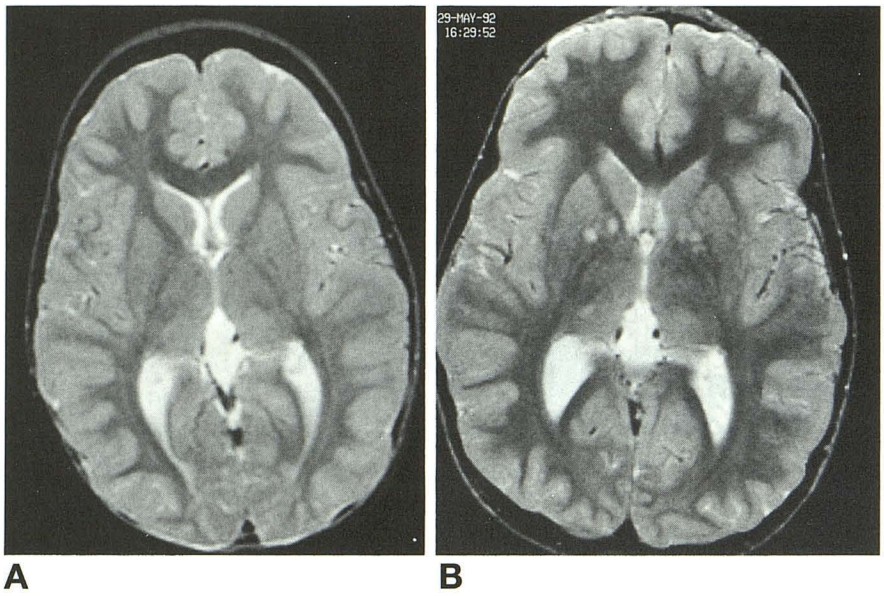

Fig 3. T2-weighted images (spin-echo 3000/100) of NF-1 patient.

A, Initial study at the age of 4 years reveals no abnormality in the basal ganglia.

B, High-signal lesions appear in the basal ganglia with follow-up study (28 months later).

Discussion

The genetic transmission, pathogenesis, clinical appearance, and the most common MR manifestations of NF have been well described by several authors (1, 4–6, 11–18). Although NF is the most common phakomatosis (3, 5, 13, 19), it is an uncommon disease, thought to be without racial or ethnic preference (20). Type 1 is approximately 10 times more frequent than type 2. The nervous system lesions in NF can be divided into neoplastic (including optic gliomas and acoustic neuromas) and nonneoplastic. Nontumorous deep gray and white matter abnormalities, often called "hamartomas," were evaluated in this study (5, 6, 19, 21–23). With the extensive clinical use of MR in NF patients, areas of altered signal intensity have been increasingly described in the deep gray matter, and less frequently in the deep white matter. The most frequent locations of these lesions include the globus pallidus and putamen, the cerebellar peduncles, the pons, the midbrain, the thalamus, the cerebellar white matter, the dentate nuclei of the cerebellum, and, less frequently, the internal capsule and the periventricular white matter (3, 5, 6–9, 15, 21, 22).

Regarding their MR appearance, the majority of authors agree that most lesions appear isointense on T1-weighted images and hyperintense on T2-weighted images (3, 5–7, 15, 21, 22). Such signal behavior is common in many pathologic processes and might be caused by increased water content or the presence of "gliosis." However, these lesions, especially the lesions in the basal ganglia, can sometimes appear hyperintense on T1-weighted images as well (2, 3, 15). Such behavior could be explained by other hypotheses regarding their composition: ectopic Schwann cells, clustering of myelinated fibers, accumulation of melanocytes or melanin, or even iron or calcium-containing areas generating abnormal signal (3, 6, 24, 25). Some authors have suggested that the lesions in basal ganglia may be different from lesions in the white matter (6, 23). We are not sure whether this opinion is correct, and have focused on the lesions of both deep gray and white matter.

Hypotheses regarding the pathogenesis of these deeply located abnormalities are numerous, but unproved. Some authors maintain that they are hamartomas (9, 15, 19, 21), which are areas of altered composition and/or organization of otherwise normal tissue types. Others believe them to be heterotopias (ie, areas of gray matter abnormally located in the white matter) (5, 8, 13, 21), zones of gliosis (3), glial scars (2), or low-grade tumors (15, 19). Still others consider them to be areas of delayed or disordered myelination (6, 23). Their presence predominantly in young NF-1 subjects (6, 9, 19, 21, 23) suggests as a further hypothesis, delayed or abnormal brain maturation in these areas.

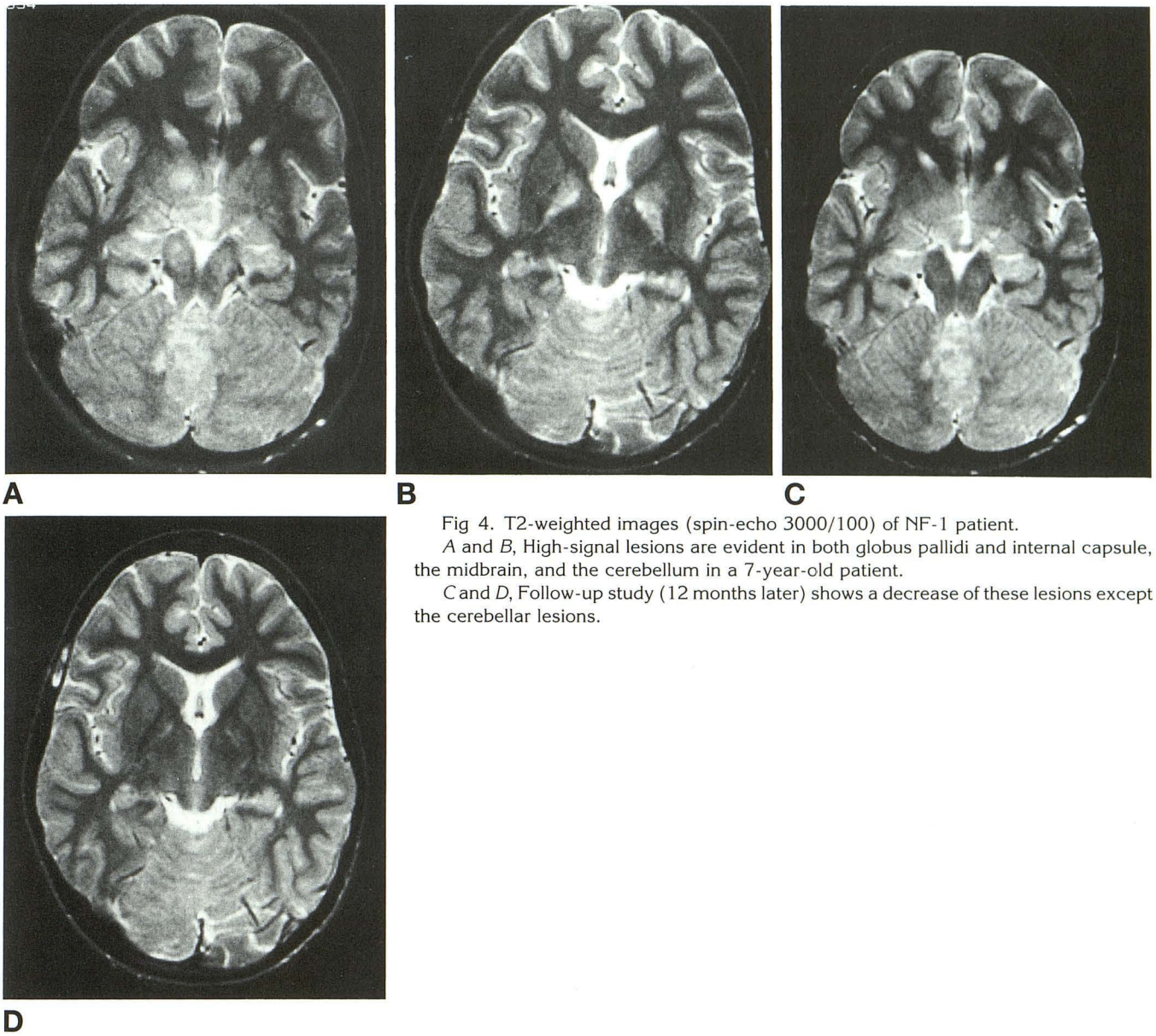

Fig 4. T2-weighted images (spin-echo 3000/100) of NF-1 patient.

A and *B*, High-signal lesions are evident in both globus pallidi and internal capsule, the midbrain, and the cerebellum in a 7-year-old patient.

C and *D*, Follow-up study (12 months later) shows a decrease of these lesions except the cerebellar lesions.

We believe that these deep gray and white matter lesions are transient: this hypothesis is based on three observations. First, the lesions were present more frequently in patients less than 15 years of age (93%) than in those older than this age (43%). Second, in the families included in the NF-1 learning disability research program, deep gray and white matter abnormalities were found in 86% of the affected children, but in only 17% of the affected parents. Third, many lesions showed a decrease in size in follow-up studies, though some lesions revealed an increase in size in very young patients (mean age, 3.7 years). Thus, these lesions appear to diminish or disappear with age. This result is compatible with previous reports (6, 23). According to our study, the lesions in the cerebellum disappear earlier than those in the basal ganglia and brain stem.

If these lesions are transient, they would not be consistent with developmental abnormalities such as hamartoma, heterotopia, or other malformative lesions. Nor would they be consistent with neoplasia. The paucity of previous neuropathologic observations of these lesions is consistent with their being transient lesions, because most pathologic reports have involved adult cases (20, 23, 26). Unfortu-

nately, even these limited reports do not define clearly the nature of these lesions. In the only pathologic report on lesions documented to be abnormal by MR, tissue from the region of the globus pallidus and cerebral peduncle consisted of "atypical glial infiltrate with bizarre hyperchromatic nuclei, foci of microcalcification associated with perivascular gliosis, and a spongy change in the white matter at the periphery of the lesions (26)." These findings were thought to be consistent with hyperplastic or dysplastic glial proliferation.

It is possible that these lesions may represent areas of disordered myelin maturation secondary to abnormal or delayed glial differentiation. The NF-1 gene has recently been identified and located in the long arm of chromosome 17. This gene encodes for a protein designated as neurofibromin. The function of this protein is not clearly defined, but is postulated to act as an effector of rasGTP and sends a signal related to cell differentiation. These putative functions may be related to certain tumorgenic features of NF-1 (27). We speculate that neurofibromin may also be involved in the maturation of certain central nervous system cells—including glia which are responsible for myelination. A mutation of the gene in NF-1 subjects resulting in abnormal neurofibromin could result in disordered myelinization which might explain the MR signal changes we and others have described. Presumably the cells expressing the abnormal gene later mature and correct the myelin abnormality. More radiologic-pathologic correlations are necessary for proving this hypothesis.

In young patients, up to 15 years of age, there was no correlation of patient age to total volume of abnormal areas. When analyzed only in terms of binary categories (lesions present or absent, mental retardation present or absent) these deep lesions have not been shown to correlate with neuropsychological disturbances (2, 9, 19, 21, 22) that affect up to 40% of NF-1 patients (13, 17). However, the question about a possible correlation between behavior disturbances and deep gray and white matter abnormalities in NF-1 patients is still open. Correlation of the volume and/or number of the abnormal high signal lesions and psychointellectual disturbances in children with NF-1 is the subject of an ongoing NF-1 learning disability research program.

We conclude that deep gray and white matter abnormalities are frequently found in NF-1 patients (77%), especially in patients younger than 15 years of age (93%). The majority of these lesions appear to be transient and their presence is not well explained by any of the previously published etiologic hypotheses.

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