Specific learning disability in children with neurofibromatosis type 1:
Significance of MRI abnormalities

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Article abstract—To determine whether previously reported areas of increased T_2 signal intensity on MRI examination in children with neurofibromatosis type 1 (NF 1) are associated with deficits in development and learning common in this population, we evaluated 51 children with NF 1 (aged 8 to 16 years). Forty children completed the full assessment protocol (MRI, medical, psychometric, speech therapy, and occupational therapy assessments). The mean Full Scale IQ scores for the entire study population showed a left shift compared with the normal population, and the distribution of IQ scores was bimodal, suggesting that there are two populations of patients with NF 1—those *with* and those *without* a variable degree of cognitive impairment. There was no association between lower IQ scores and any clinical variable. Areas of increased T_2 signal intensity unidentified bright objects (UBO+) were present in 62.5% of the study population, and their presence was not related to clinical severity, sex, age, socioeconomic status, macrocephaly, or family history of NF 1. However, compared with children without areas of increased T_2 signal intensity (UBO−), the UBO+ group had significantly lower mean values for IQ and language scores and significantly impaired visuomotor integration and coordination. Children with areas of increased T_2 signal intensity were at a much higher risk for impaired academic achievement. Children without increased T_2 signal on MRI (UBO−) did not significantly differ from the general population in any measure of ability or performance. Areas of increased T_2 signal on MRI represent dysplastic glial proliferation and aberrant myelination in the developing brain and are associated with deficits in higher cognitive function. The presence of these abnormal signals on MRI divides the NF 1 population into two distinct groups anatomically and developmentally (UBO+ and UBO−). These two groups should be considered separately in the assessment and management of learning disability in children with NF 1.

NEUROLOGY 1994;44:878-883

Neurofibromatosis type 1 (NF 1) is the most common single gene disorder to affect the human nervous system, with an estimated prevalence of one in 4,000.[1] The physical features of NF 1 are well characterized.[1-3] The most common neurologic complication of the disorder in childhood is specific learning disability (SLD), defined as a major discrepancy between *ability* (intellect or aptitude) and *achievement*.[4] SLDs occur in 30% to 45% of children with NF 1, which is three to four times the prevalence of learning disability in the general population.[1,2,4,5] Previous studies of cognitive function in patients with NF 1 have noted a left shift in Full Scale IQ values,[5,6] with mean IQ scores remaining within the normal range. The pathogenesis of learning disability and cognitive deficits in children with NF 1 remains obscure.

Focal areas of high signal intensity on T_2-weighted MRI are pathognomonic of NF 1 in children and may, in the future, be considered as one of the diagnostic criteria[3,7] (figure 1). These areas do not exert a mass effect, have no surrounding edema, do not enhance with gadolinium, are not visible on CT, and are not associated with focal neurologic deficits.[8] They most commonly occur in the basal ganglia, cerebellum, brainstem, and subcortical white matter and are of uncertain etiology.[7,9-13] The reported frequency of areas of increased T_2 signal intensity on MRI varies from 43% to 79%,[7,8,10-13] and their clinical significance is undetermined. They have been called hamartomas, heterotopias, or unidentified bright objects (UBO).[9]

We hypothesized that areas of increased T_2 signal intensity on MRI may be associated with the frequent occurrence of SLD in patients with NF 1, and evaluated a population of children with NF 1 to test this hypothesis.

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Supported by the Children's Hospital Fund and the Clive and Vera Ramaciotti Foundation.

Received July 19, 1993. Accepted for publication in final form November 3, 1993.

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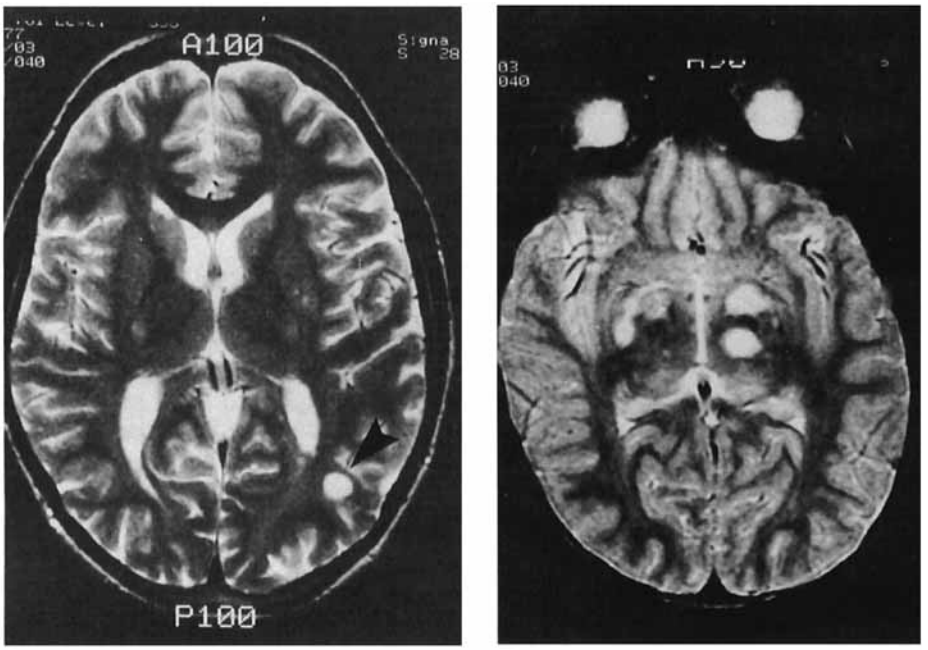

Figure 1. Areas of increased T_2 signal intensity on MRI. (A) Single lesion in left occipital lobe (arrow). (B) Multiple lesions in basal ganglia bilaterally.

Methods. *Study population.* The Neurofibromatosis Clinic at The Children's Hospital, Sydney, aims to provide general medical review and genetic counseling for families with NF 1 (both adults and children). Patients are referred primarily from the Sydney Metropolitan Region (approximate population 3 million) with some additional referrals from elsewhere in the state of New South Wales. In the 18-month period of March 1991 to September 1992, 204 individuals with NF 1 were assessed. All individuals satisfied the diagnostic criteria for NF 1.[14] A total of 51 children aged 8 to 16 years (inclusive) were seen in the Neurofibromatosis Clinic during this period and enrolled in the study.

All children were assessed by a neurologist and a geneticist and underwent an initial evaluation including full medical history and examination, vision and hearing assessment, and other tests as indicated for specific problems. All first-degree relatives were examined to determine a family history of NF 1. For each child, a grading of clinical severity of disease complications was made (as per Riccardi[15]) as follows: grade 1 = minimal disease, 2 = mild, 3 = moderate, and 4 = severe disease complications. At the time of initial assessment, parents completed a questionnaire concerning their child's overall school performance and need for special education. In addition, a questionnaire rating the school performance, level of education, and employment status of the child's first-degree relatives was administered to determine socioeconomic status (SES)[16] and family history of learning disability.

Children were excluded from further assessment if additional variables were present that might affect test performance. Seven children were excluded because of CNS pathology (hydrocephalus in three children, epilepsy in two, cranial irradiation in one, sudden hearing loss in one). Patients with asymptomatic untreated optic gliomas were not excluded (visual acuity was normal in all cases). One child did not adequately understand English to complete testing, and two additional children were excluded after Wechsler Intelligence Scale for Children-Revised (WISC-R) assessment because of Full Scale IQ scores less than 70 (ie, their learning disability was not *specific*). Parental consent was refused for one child. Informed parental consent was obtained for the remaining 40 children. The final sample size is adequate for drawing statistical conclusions from the results.[17]

None of the 40 children who completed the full assessment protocol had significant visual or hearing impairment or intracranial pathology (apart from asymptomatic optic gliomas in three cases). Only two children in the study group were initially diagnosed as having NF 1 because of school performance problems. The majority of children were referred to the clinic because of multiple café au lait spots or a family history of NF 1. Parents and referring doctors were unaware of the research interest of the clinic at the time of referral. The study protocol was approved by the Children's Hospital Ethics Committee.

Study protocol. Developmental assessment. All children were assessed during two half-day sessions by the same psychologist, speech pathologist, and occupational therapist using the same protocol to study different areas of *ability* (intellect, language, visuomotor function, and coordination) and *performance* (academic achievement). The test protocol included the WISC-R,[18] Clinical Evaluation of Language Fundamentals-Revised (CELF-R),[19] Peabody Picture Vocabulary Test (PPVT-R),[20] Beery Developmental Test of Visual-Motor Integration (VMI),[21] Henderson Test of Motor Impairment (TOMI),[22] Neale Analysis of Reading Ability,[23] number skills (Differential Ability Scale),[24] and the Test of Written Spelling.[25] Detailed neuropsychological assessment was also completed for each child, the results of which will be reported separately.

Cranial imaging. MRI was performed in each child. Each MRI was reported independently by two neuroradiologists (M.dS., K.M.) blinded to the results of clinical examination and cognitive testing. Results of MRI examination were not known at the time of clinical or developmental assessment unless intracranial pathology was

present that would exclude the child from the study. For each MRI, site, size, number, and lateralization of areas of increased T_2 signal intensity were noted.

MRI included axial T_1- and axial T_2-weighted sequences followed by axial T_1-weighted imaging after intravenous administration of gadopentalate dimeglumine at 0.1 mmol/kg (Magnevist; Berlex Laboratories). Typical imaging parameters were 500/16 (TR [repetition time] msec/TE [echo time] msec) for axial T_1 images, and 580/29 (TR msec/TE msec) for sequences after gadolinium enhancement. Twenty-seven patients had conventional spin-echo axial T_2 sequences (2500/30,85 [TR msec/TE msec]), and in the latter part of the study, dual-contrast fast spin-echo (FSE) axial T_2-weighted images (3270/18,108 [TR msec/pseudo-echo time msec]) were performed in 12 patients.[26] All imaging sequences were obtained with 5-mm-thick sections with 2-mm spacing, 20-cm field of view, a 256 × 192 matrix (256 × 256 for FSE sequences), and one to two excitations. MRIs were performed on a superconducting magnet operating at 1.5 tesla (Sigma, General Electric Medical Systems, Milwaukee, WI).

Analysis of results. Mean standard scores for the study group (n = 40) were calculated for tests of intellectual function, language, and visuomotor integration. In the TOMI (assessing manual dexterity, balance, and ball skills), children were rated as *average* or as having *mild, moderate,* or *severe* problems with coordination.[22] For tests of academic achievement, impaired performance on reading and spelling tests was defined by a reading age or spelling age more than 2 years below chronological age. In mathematics, scores more than 1.96 SD below the mean were rated as impaired.

The effects of clinical variables such as age, gender, disease severity, macrocephaly (defined as head circumference greater than or equal to the 95th percentile), family history of NF 1, SES, and family history of learning difficulties on performance in tests of *ability* and *achievement* were assessed using an unpaired *t* test or chi-square analysis as appropriate.[27,28] The association of clinical variables with areas of increased T_2 signal intensity on MRI were evaluated using a chi-square analysis.[28]

Patients were divided into two groups: those with areas of increased T_2 signal intensity on MRI studies (UBO+) and those with no abnormal areas of increased T_2 signal (UBO−). For each group, the mean test scores in each test of *ability* (intellect, language, visuomotor function) were determined and compared using an unpaired *t* test.[27] For the TOMI, the comparison between UBO+ and UBO− groups was determined using the Mann-Whitney test.[27] In each group, the number of children with impaired performance in tests of academic achievement was calculated and compared using a chi-square analysis.[28] For parental report of special educational needs, the association with MRI abnormalities was determined using Fisher's exact test.[29]

Results. For the 40 children studied, there was an equal sex incidence and a representative distribution in ages between 8 and 16 years (mean age, 11.99 years; median, 11.96 years). Fourteen children were clinical severity grade 1 (minimal disease), six were grade 2 (mild), 17 were grade 3 (moderate), and three were grade 4 (severe).[15] Twenty children were macrocephalic. Nineteen of the 40 patients had a family history of NF 1, and in 21 patients no other family member was affected. Seven children were SES II, seven were SES III, 11 were SES IV, and 15 were SES V. There was a family history of learning difficulties in at least one first-degree relative in 40% of children. In 10% of families, the relative with learning disability also had NF 1.

Developmental assessment. For the study group (n = 40), WISC-R results indicated a general lowering of Verbal, Performance, and Full Scale IQ in association with NF 1, but mean scores remained within 1 SD of the population mean (mean 100, SD 15).[18] The mean Verbal IQ score was 92.6 (SD 13.4; range, 65 to 124), the mean Performance IQ score was 95.4 (SD 12.9; range, 67 to 133), and the mean Full Scale IQ score was 93.3 (SD 12.6; range, 74 to 131). The individual IQ scores for the study group did not follow a normal distribution; two peaks were evident, one at 85 and the other at 100. There was no significant discrepancy between the Verbal and Performance IQ.

Receptive, expressive, and total language scores (CELF-R), receptive vocabulary (PPVT-R), and the VMI also showed a left shift compared with normative data for the population (mean 100; SD 15).[19-21] On the CELF-R, the mean receptive language score was 91.4 (SD 13.6; range, 63 to 120), the mean expressive language score was 90.8 (SD 18.3; range, 54 to 130), and the mean total language score was 90.3 (SD 16.2; range, 55 to 121). The mean score for the PPVT-R was 92.7 (SD 16.0; range, 56 to 139), and the mean score in the VMI was 92.4 (SD 10.4; range, 71 to 119). In the TOMI,[22] 9/40 children (23.5%) rated at an *average* level of ability, 11/40 (27.5%) had *mild*, 7/40 (17.5%) had *moderate*, and 13/40 (32.5%) had *definite* problems with coordination.

On tests of reading accuracy, 45% of children performed more than 2 years below chronological age and 47.5% had impaired performance on reading comprehension tasks. In spelling, 32.5% of the group had impaired performance while 27.5% of children had math scores more than 1.96 SD below the mean. There was a significant association between lower IQ scores and impaired academic achievement in all areas.

Clinical correlates. Clinical severity, age, macrocephaly, and a family history of NF 1 were not significantly associated with mean IQ values, scores of language and visuomotor function, incoordination, or impaired performance in tests of academic achievement. There was no significant association between IQ scores, gender, or SES. However, male gender and lower SES (IV and V) were associated with impaired academic achievement, particularly in reading and spelling. There was also a significant association ($p < 0.05$ on chi-square) between family history of learning disability and poor performance in tests of reading accuracy and spelling. This association lost its statistical significance when first-degree relatives with learning disability *and* NF 1 were excluded from the analysis.

Table. Mean scores in tests of intellectual, language, and motor function: Comparison with results of MRI examination

	UBO+ (n = 25)			UBO− (n = 15)			*p* Value (*t* test)
	Mean	SD	Range	Mean	SD	Range	
Verbal IQ	86.3	9.8	65-98	103.0	12.1	81-124	0.0001
Performance IQ	90.4	10.8	67-112	103.8	11.8	90-133	0.0013
Full Scale IQ	87.0	8.4	74-104	103.7	11.7	87-131	0.0001
Language (CELF-R)							
Expressive score	83.1	14.3	54-108	103.5	17.5	59-130	0.0008
Receptive score	85.0	10.8	63-105	101.9	11.1	78-120	0.0001
Total score	82.7	12.1	55-107	103.0	14.2	67-121	0.0001
PPVT-R	85.9	13.6	56-127	104.1	13.2	85-139	0.0002
Visual-Motor Integration	89.0	8.4	71-102	97.9	11.2	79-119	0.015

UBO+ Areas of increased T_2 signal present on MRI.
UBO− No abnormal signal on MRI.

The UBO+ group has significantly lower mean test scores on objective assessment of cognitive, language, and visual-motor function.

MRI findings. Areas of increased T_2 signal intensity (UBO) were present on the MRI examinations of 25/40 children (62.5%) (figure 1). These areas were not evident on T_1-weighted images and did not enhance with gadolinium. In 22/25 children (88%), the areas of increased T_2 signal were present at multiple (two or more) sites. In three patients, areas of increased signal were present at a single site only. The lesions occurred most commonly in the optic tracts (64%) and basal ganglia (60%). The brainstem (44%), cerebellum (28%), and cortex (16%) were also involved. Three children in the study population had asymptomatic optic gliomas—in one patient the tumor was intraorbital, and in two patients there was enlargement of the optic chiasm. In all three patients, areas of increased T_2 signal intensity were present at multiple sites, *including* the optic tracts in two patients. There was no significant relationship between the presence of areas of increased signal intensity and any other clinical variable (disease severity, age, gender, SES, macrocephaly, family history of NF 1, or family history of learning disability).

Developmental assessment and MRI findings (table). The 40 patients were divided into two groups on the basis of the presence (UBO+, n = 25) or absence (UBO−, n = 15) of areas of high T_2 signal intensity on MRI. There was no significant difference in age, gender, or SES distribution between the two groups. The mean IQ scores of the UBO− group did not differ significantly from normative values for the general population (mean 100; SD 15).[18] The UBO+ group had significantly lower mean Verbal IQ, Performance IQ, and Full Scale IQ when compared with the UBO− group. These results were not altered by the inclusion of the IQ scores of the two children who were excluded from the overall study because of Full Scale IQ scores <70. The bimodal distribution of IQ scores for the entire group was due to the shift to the left in IQ scores for the UBO+ group (mean Full Scale IQ = 87) compared with the UBO− group (mean Full Scale IQ = 103.7) (figure 2).

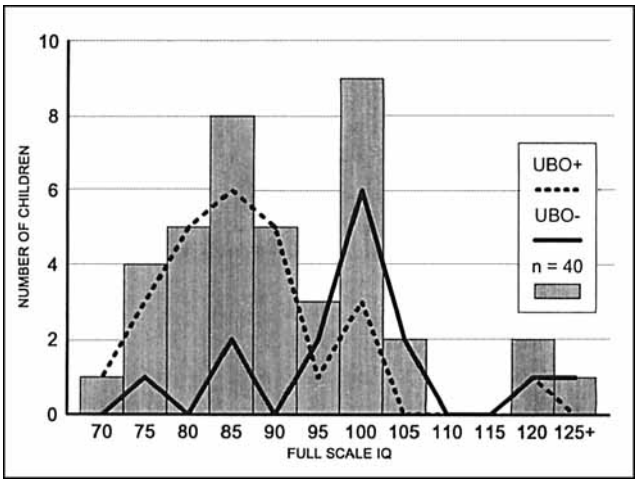

Figure 2. Full Scale IQ scores for the study population and association with areas of increased T_2 signal (UBO+) on MRI examination. The presence or absence of areas of abnormal signal (UBO+/UBO−) divides the study population into two distinct groups. The UBO− group has a mean IQ score of 103.7, which does not differ significantly from normative values for the general population. The UBO+ group has a mean IQ score of 87.0 and significantly lower performance in tests of cognitive function.

In the UBO+ group, the expressive, receptive, and total language scores as well as the mean scaled standard score for the VMI were significantly lower than the mean for the UBO− group. The presence of *definite* motor impairment (TOMI) was significantly associated with the presence of increased T_2 signal on MRI ($p = 0.03$ using Mann-Whitney).

On formal testing of academic achievement, the majority of children with impaired performance were in the UBO+ group. Ninety-two percent of children with impaired performance in spelling

were in the UBO+ group, 89% for reading accuracy, 79% for reading comprehension, and 73% for mathematics. The UBO effect was independent of any other clinical variable, including male gender and SES. From parent questionnaires concerning their child's school performance, 18/40 children were receiving some form of special educational assistance (eg, special class, integration aide, speech or occupational therapy). Seventeen of these 18 children had areas of increased T_2 signal intensity on MRI (level of significance compared with UBO− group, $p = 0.0001$ using Fisher's exact test).

Children with fewer areas of increased T_2 signal intensity on MRI did not appear to have better test performance than children with multiple lesions. For example, the three children with lesions at single sites had Full Scale IQ scores of 83, 85, and 86. Conversely, the three children in the UBO+ group with IQ scores over 100 had multiple areas of increased T_2 signal intensity.

Discussion. The mean Full Scale IQ of our entire study population showed a left shift compared with the normal population, consistent with previous studies of intellectual ability in patients with NF 1.[2,5,6] The distribution of Full Scale IQ scores was bimodal, suggesting that there are two populations of patients with NF 1—those *with* and those *without* a degree of cognitive impairment. There was no significant association between lower IQ scores and any clinical variable. However, children with areas of increased signal intensity on MRI (UBO+) had significantly lower IQ scores than children without these lesions, suggesting that the areas of increased T_2 signal are associated with the presence of a cognitive deficit. Scores in tests of language function, visuomotor integration, and coordination were also significantly lower in the UBO+ group. The performance of the UBO− group did not differ significantly from normative data for the general population in any area assessed.

The frequency of learning disability in the study population was much higher than expected for the general population. Impaired performance on at least one test of academic achievement was present in 65% of children, and 18 of the 40 children (45%) were already receiving some form of educational assistance. Impaired performance in tests of academic achievement was associated with lower IQ scores, male gender, and lower SES (IV and V). The majority of children with impaired performance in tests of academic achievement had areas of increased T_2 signal on MRI. This association was independent of gender and SES but may be a secondary effect of the lower mean IQ scores in the UBO+ group.

Previous attempts to establish a link between MRI abnormalities and cognitive function have been largely unsuccessful, but the relevance of the findings was limited by lack of uniform methodology and inadequate definition of learning disability. Some studies[8,11] were based on small populations, covered a wide age range (9 months to 20 years), and did not include quantitative assessment of cognitive function. These studies also included a large number of children with CNS pathology (such as epilepsy and intracranial tumors) which could have an additional effect on cognitive function.

Only one study has correlated MRI findings with pathologic data. Zimmerman et al[7] performed autopsies on two pediatric patients and studied histologically five areas of brain tissue (two globus pallidus and three midbrain peduncles) that correlated with areas of high T_2 signal intensity on MRI examinations performed on these patients prior to death. The five areas examined had similar histologic appearances. These consisted of atypical glial infiltrate with bizarre hyperchromatic nuclei, foci of microcalcification associated with perivascular gliosis, areas of dysmyelination, and spongy change in the white matter at the periphery of the lesions.

Recent observations concerning the natural history of areas of increased T_2 signal on MRI suggest that the pathology underlying the abnormal signal changes over time.[12,13] Aoki et al[13] found that areas of increased T_2 signal were rare over the age of 20 years. Sevick et al[12] followed 18 patients with increased T_2 signal on serial MRI examinations and found that in all patients over the age of 10 years, the lesions remained static or decreased with time, but in none had the lesions completely disappeared by the age of 16 years. They proposed that areas of increased T_2 signal intensity represent the formation of chemically abnormal myelin that is subsequently broken down by normal metabolic processes to be replaced by myelin with a more stable conformation. Zimmerman (personal communication) also postulated that the MRI abnormal signal may disappear with further maturation of white matter and replacement of abnormal myelin.

Seizinger[30] proposed that mutations of the NF 1 gene result in aberrant control of cell growth and differentiation in a variety of tissues, particularly in the central and peripheral nervous systems. On this basis, we propose a model for the pathogenesis of SLD in NF 1. Mutations of the NF 1 gene may result in abnormal cell differentiation in the brains of a subgroup of patients with NF 1. Areas of dysplastic gliosis and aberrant myelination disrupt important neuronal circuits involved in higher cognitive processing and, in turn, these areas appear as increased T_2 signal intensity on MRI.

In this and previous studies, areas of increased T_2 signal intensity were located principally in the basal ganglia and subcortical white matter of the brain. The basal ganglia are involved in the regulation of complex cognitive functions.[31,32] We postulate that disruption of these subcortical neuronal pathways in NF 1 results in the left shift in intellectual function and SLD rather than global intellectual handicap.

In our study, the frequency of areas of increased T_2 signal on MRI did not seem related to the degree of cognitive impairment in the individual. How-

ever, if the abnormal signals on MRI are merely a radiologic marker for aberrant cellular differentiation and dysplastic brain development in some patients with NF 1, then the lesions themselves may be more extensive.

Whether the dysplastic changes persist or resolve at a microscopic level and whether there is improvement in cognitive function with time is unknown. Riccardi[2,33] noted a major age discrepancy in cognitive function in patients with NF 1. On formal testing, the average IQ (on WISC-R) for children aged 6 to 17 years (n = 67) was at or near 90 (SD 17), compared with a mean IQ (on the Wechsler Adult Intelligence Scale) of 99.3 (SD 15.6) for patients 17 years or older (n = 89). There was also an improvement in coordination with age. This finding may be significant in light of the similar changes reported for areas of increased T_2 signal on MRI.[12,13] However, there have been no systematic longitudinal studies to confirm this improvement in function with time. The natural history of areas of increased T_2 signal on MRI and their relationship to development and learning in the individual with NF 1 requires further study.

The significance of areas of increased T_2 signal on MRI has major implications for the assessment and management of learning disabilities in children with NF 1. Children with areas of increased T_2 signal on MRI are at a much higher risk for learning disability and need for special educational assistance than children without these lesions. The presence or absence of these abnormal signals on MRI divides the NF 1 population into two distinct groups anatomically and developmentally, and these two groups should be considered separately in further studies of learning disability in children with NF 1.

Acknowledgments

We thank Dr. Craig Mellis for helpful suggestions in study design, and the staff of the Department of Medical Genetics, particularly Drs. Robert Ogle, Leslie Ades, and Bronwyn Kerr for their assistance in the medical assessment of the patients in this study. We also thank A/Prof. Robert Ouvrier, Dr. Peter Procopis, and Prof. James McLeod for their critical review of the manuscript, and Ms. Suzanne Smith for coordinating the MRI examinations.

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Neurology 1994;44;878
DOI 10.1212/WNL.44.5.878