

MRI in neurofibromatosis 1. The nature and evolution of increased intensity T2 weighted lesions and their relationship to intellectual impairment

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Abstract

Thirty eight patients with neurofibromatosis 1 (NF1) had neurological examinations, intellectual assessments and MRI scans. Increased intensity lesions on T2 weighted images were found in 13 patients. These abnormalities were more common in patients aged under 18 years. The lesions occurred predominantly in the basal ganglia, brainstem and cerebellum, and were multiple in 11 patients. They did not produce symptoms or neurological deficit in any patient and did not enhance with gadolinium-meglumine-triamine-pentacetic acid contrast medium (Gd-DTPA). In 2 patients, however, the abnormalities exerted mass effect distorting the brain and in 3 patients they occurred in conjunction with known gliomas. The lesions remained unchanged over a three year follow up period. The nature of the lesions is uncertain but the fact that they may produce mass effect and occur in association with gliomas suggests that they have malignant potential. There was no correlation between the presence of these abnormalities and intellectual impairment.

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Neurofibromatosis 1 is a common autosomal dominant disease with a minimum prevalence of 1 in 5000.¹ Diagnostic criteria formulated by the National Institutes of Health Consensus Development Conference² are set out in table 1. The complications of the disorder are legion and neurological manifestations range from gliomas to intellectual impairment. The majority of patients have an IQ in the low average range. Specific learning problems such as attention deficit, visual-spatial problems and reading difficulties, occur in between 40-60% of sufferers.³⁻⁴

Table 1 Diagnostic features of neurofibromatosis 1²

- 1 Café au lait spots
- 2 Two or more neurofibromas or one plexiform neurofibroma
- 3 Axillary or groin freckling
- 4 Lisch nodules
- 5 Optic nerve glioma
- 6 A first degree relative with NF1
- 7 A distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the long bone cortex with or without pseudarthrosis

2 or more criteria are required for diagnosis.

The cause of the intellectual difficulties has not been established. However, Rosman and Pearce⁵ showed in a post mortem study that patients with NF1 and intellectual impairment had heterotopias in the subcortical and deep white matter and disordered cerebral architecture. Patients with NF1 and average intelligence had similar less severe changes but these abnormalities were absent in control subjects. They proposed that the intellectual problems were linked to migrational abnormalities in the brain of the developing fetus.

MRI is now the investigation of choice for visualising the distinction between grey and white matter in the brain. Increased intensity lesions have been detected on T2 weighted MRI brain scans in children and young adults with NF1. They occur predominantly in the basal ganglia, brainstem and cerebellum.⁶⁻⁹ They do not show mass effect and do not enhance with Gd-DTPA. The nature of the abnormalities is uncertain, but it has been suggested that they may be hamartomas or slow growing gliomas. The lesions are distinguishable from those in multiple sclerosis and vascular disease by their larger size and different location. Another possibility is that these lesions represent grey matter heterotopias. Mirowitz *et al* observed that 7 of 35 patients with NF1 had increased signal intensity lesions in the basal ganglia which were more prominent on T1 than on T2 weighted MRI. They suggested that the signal characteristics and morphology were compatible with grey matter heterotopias containing Schwann cells and/or myelin.¹⁰ Sevic *et al* reported that the lesions increase in frequency in early childhood but tend to resolve with increasing age.⁹

Two recent studies have attempted to correlate the presence of these lesions with learning problems in children with NF1. Duffner *et al*⁷ found increased intensity T2 weighted lesions in 29 of 47 children and Dunn and Roos¹¹ detected these abnormalities in 16 of 31 children. There was, however, no correlation between the presence of increased intensity lesions on MRI and learning difficulties in the children studied.

As part of a larger study on intellectual impairment in NF1, we performed brain MRI on 38 adults and children with NF1. We evaluated the scans for the occurrence of general neuroradiological abnormalities and increased intensity T2 weighted lesions. We determined whether the presence of these T2 weighted abnormalities was age related and scans were performed at intervals to assess

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the evolution of the lesions. We also considered whether intellectual impairment is related to the presence of T2 weighted abnormalities in this patient group.

Methods

We are reporting all MRI head scans carried out on 38 patients with NF1 in our hospital between 1987–91 are reported. These included 32 patients from a study of 100 patients attending our neurofibromatosis clinic and taking part in a study of intellectual impairment. The subjects included 16 children and their ages ranged from 3–63 years (mean 25 years). Neurological and psychometric assessment.

All patients had general medical and neurological examinations. Twenty eight patients had formal IQ testing with the Wechsler IQ scales.^{12 13} Estimates of intellectual ability were based on school performance and occupational history in the remaining 10 subjects.

MRI

MRI brain scans were carried out with a 1.5 Tesla superconducting system (Philips Gyroscan S15, Philips Medical Systems). Images were taken in the axial, coronal and sagittal planes, with a slice thickness of 5 mm to 8 mm and an interscan distance of 0.5 mm to 0.8 mm. T1 weighted Spin Echo images were obtained with a Repetition Time (TR) of 500 ms and Echo Time (TE) of 20 ms. T1 weighted scans were performed following the administration of Gd-DTPA paramagnetic contrast medium in 16 cases. Initially T1 Inversion Recovery sequences were used on the first 19 patients with a TR 1500 ms, TE 30 ms and TI 300 ms to look for grey matter heterotopias. T2 weighted Spin Echo images were carried out using TR of 2000 ms to 3000 ms and TE 50/100 ms to 20/120 ms. Follow up scans were available in ten patients. A Chi square test was used to assess the relationship between the presence of increased intensity T2 weighted abnormalities on the scans and intellectual impairment.

Post mortem studies

A neuropathological study of two brains was carried out. The post mortem brains were both immersion fixed and sliced. The first was sliced in the coronal plane and the second case was sliced in the sagittal plane to correspond with images taken on MRI.

Statistics

Differences between proportions were tested with Chi squared or Fisher's exact tests and two-tailed probabilities are quoted.

Results

Abnormalities on MRI head scans were present in 28 of 38 patients (table 2). No grey matter heterotopias were found in any of the 19 patients on whom T1 Inversion Recovery sequences were used.

Increased intensity lesions on T2 weighted

Table 2 Abnormalities on MRI head scans in 38 patients with NF1

Known associations		Other associations	
Increased intensity T2 weighted lesions	13	Multiple sclerosis	2
Optic nerve glioma	6	Vascular disease	2
Parenchymal glioma	3	Cerebral atrophy	1
Dilated ventricles	4	Chromophobe adenoma	1
Increased intensity T1 weighted lesions	1	Posterior fossa arachnoid cyst	1
		Meningeal dysplasia	1
		Venous malformation arising from corpus striatum vessels	1
Total patients affected	24	Total patients affected	10
Total number of patients with abnormal scans = 28 normal scans = 10			

Note: Some patients had more than one abnormality

Table 3 Sites of increased intensity lesions on T2 weighted scans

Sites	Number of patients
Basal ganglia	11
Cerebellum	4
Brainstem	3
Lateral ventricle wall	2
Cerebral peduncle	2
Corpus callosum	2
Frontal lobe	1
Parietal lobe	1
Internal capsule	1
Optic tract	1
Insular cortex	1

images were noted in 13 patients. In 3 cases the lesions were single and were found in the basal ganglia, cerebellum and deep white matter adjacent to the insular cortex. Ten patients had multiple lesions which occurred predominantly in the basal ganglia, particularly the globus pallidus (table 3, fig 1). The lesions did not cause symptoms or neurological deficit in any patient and did not enhance with Gd-DTPA. However, in 2 cases the lesions produced mass effect and distorted

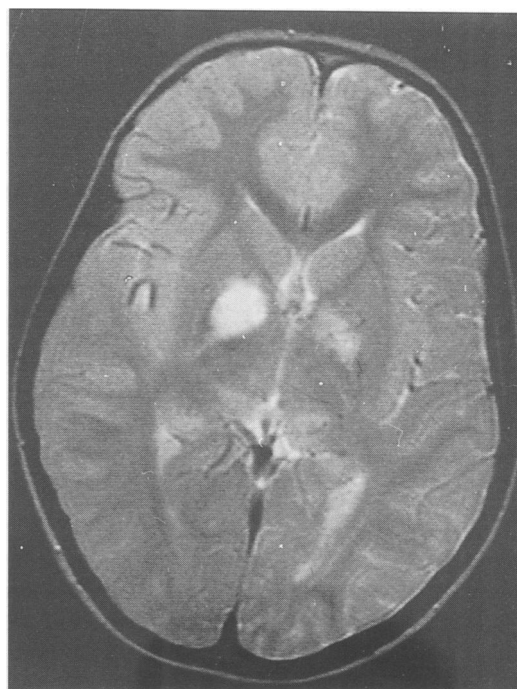


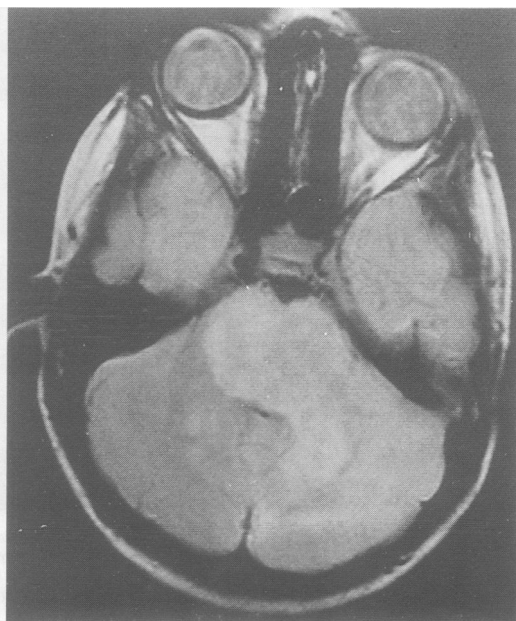
Figure 1 Axial T2 weighted image (TRSE 2000, TE 80) in an asymptomatic patient with NF1. There are bilateral increased intensity lesions in the globus pallidus more marked on the right. They did not enhance after intravenous injection of Gd-DTPA.

Figure 2 Axial T2 weighted image through the brainstem (TRSE 2000, TE 80) in an asymptomatic 17 year old boy with NF1. There is an increased intensity lesion on the left side of the pons and cerebellum which is distorting the fourth ventricle and deviating it to the right. The lesion did not enhance with Gd-DTPA and has remained unchanged for 3 years.



the brain. A 17 year old man had a lesion on the left side of the pons which distorted the fourth ventricle (fig 2). An eight year old girl was found to have a lesion in the brainstem which produced mass effect but did not evolve over a 2 year period (fig 3). Six other patients had interval scans over the same period which did not show changes in the lesions. One patient had asymptomatic increased intensity lesions in the basal ganglia and cerebellum in addition to a known brainstem glioma. Two patients had asymptomatic lesions in the cerebellum, basal ganglia, and internal capsule in association with an optic nerve glioma. Although follow up scans showed an increase in the size of the gliomas

Figure 3 Axial T2 weighted image through the brainstem (TRSE 2000, TE 80) in an asymptomatic eight year old girl with NF1. There is an extensive area of increased signal in the pons and middle cerebellar peduncles especially the left. The lesion is causing swelling and distortion of the fourth ventricle and displacing it to the right. The lesion did not enhance with Gd-DTPA and remained unchanged for 2 years.



the other lesions remained unchanged over a 3 year period. Eight of 16 children had increased intensity signals on T2 weighted MRI scans compared with 5 of 22 adults ($p = 0.16$).

Four patients were mentally retarded with a full scale IQ range between 51 and 67. One of these subjects had a single increased intensity T2 weighted lesion in the region of the right insular cortex as described above. Nineteen patients had an IQ in the range 70–89. Increased intensity lesions on T2 weighted images were seen in 8 of this group and were found predominantly in the basal ganglia, cerebellum and brainstem. Thirteen patients had an IQ range 91–112. Six had increased intensity T2 weighted lesions in the basal ganglia, cerebellum, cerebellar peduncle, and optic tract. There was therefore no significant association between the presence of T2 weighted lesions and intellectual impairment ($p = 0.79$).

Twenty five of 38 patients had macrocephaly defined as a head circumference greater than the 98th centile. Increased intensity T2 weighted lesions were present in 10 of these patients with macrocephaly and in 3 of the 13 with normal head circumferences. Among the 25 patients without T2 weighted abnormalities, 15 had macrocephaly and 10 had a normal head circumference. There was no statistically significant relationship between the presence of increased intensity lesions and macrocephaly.

Post mortem studies were carried out on 2 patients, a 59 year old male whose IQ had been 60 and a 61 year old female who had been a lawyer. In the first case a T2 weighted MRI scan had shown multiple high intensity lesions in the brainstem, basal ganglia and periventricular regions, which were considered to be infarcts, a diagnosis which was confirmed at post mortem. The MRI of the second patient showed multiple high signal lesions on T2 weighted images which were seen in the periventricular areas, pons and cerebellum. The lesions and clinical history were consistent with multiple sclerosis which was verified by the neuropathological examination. No evidence of heterotopias, gliomas or hamartomas was found in either patient.

Discussion

The most significant findings were high signal intensity lesions in the basal ganglia, brainstem and cerebellum on T2 weighted MRI scans in 8 of a selected population of 16 children with NF1, in agreement with previous studies.^{6–9} All the lesions in our series appeared to be asymptomatic. This fact, the lack of enhancement following Gd-DTPA, and the observation that similar lesions are less common in adults (only being present in 5 of 22 in our series) would suggest that the lesions are benign and might be hamartomatous. However, in 2 of our cases the lesions produced mass effect and in another 3 cases the lesions were associated with gliomas elsewhere in the brain which suggests that the

lesions may have malignant potential. It is possible there are two different types of lesion, one which will regress and one which may develop into a glioma. Further follow up and rescanning of our patients should resolve this question. In the meantime we do not advocate that patients should be screened for the presence of these lesions as all of our patients have remained asymptomatic. Patients need to be scanned only in accordance with clinical indications. When these lesions are encountered in NF1, patients can be reassured that they are usually benign, but follow up is necessary. The nature of the high signal intensity lesions on T2 weighted MRI scans might be resolved by appropriate post mortem studies.

We also observed the usual range of abnormalities associated with NF1. The high frequency of optic nerve gliomas in this study can be attributed to the selection of cases by referral to our neurologically orientated Neurofibromatosis Clinic. However optic nerve gliomas are a recognised association with NF1 and were reported in 15% of 217 cases from a Neurofibromatosis Clinic with a more general orientation.¹⁴ These optic nerve gliomas may be asymptomatic, as in 2 of our 6 cases, but may also cause visual failure and hydrocephalus. The three parenchymal gliomas in our series were located in the brainstem and thalamus: the possibility arises that they had originated in the optic tract and that the glial tissue of the anterior and posterior optic pathways has a particular potential for gliomatous change. Four patients had dilated ventricles and these were due to aqueduct stenosis, a tumour impinging on the foramen of Munro, cerebral atrophy and idiopathic ventriculomegaly. We detected occasional examples of other abnormalities with NF1 which have not been previously associated and may be coincidental (table 3). Macrocephaly is recognised as a feature of NF¹⁴ but it did not correlate with the presence of abnormalities found on T2 weighted MRI scans in our series, and it is not associated with intellectual impairment in NF1.⁴

No differences were discovered between the MRI scans of those patients who were mentally retarded and those who were not, although patients with parenchymal gliomas showed the deterioration in cerebral function anticipated from the sites of their lesions. A post mortem study had shown that grey matter heterotopia was common in the brains of

patients with NF1.⁵ Grey matter heterotopias have been demonstrated in the non-NF1 population with MRI scans.¹⁵ We did not identify any grey matter heterotopias during the study period. However, since then we have identified bilateral T1 weighted lesions in the basal ganglia, similar to those described by Mirowitz *et al*,¹⁰ in one patient with a low average IQ. We were unable to find a correlation between the presence, number, size and sites of T2 weighted abnormalities and the occurrence of mental retardation in children or adults. The cause of mental retardation in NF1 deserves further investigation which might profitably be pursued with studies of cerebral metabolism by positron emission tomography.

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