RADIOLOGIC FINDINGS OF THE HEAD AND SPINE IN NEUROFIBROMATOSIS I (NF1) IN NORTHERN FINLAND

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Abstract
Imaging of the head and spine with CT and/or MRI was performed on 125 Northern Finnish NF1 patients to evaluate the CNS lesions in patients of different ages and their role in diagnosis and follow-up.

Manifestations of NF1 in the head were more common in children than in adults. 77% of the children and 33% of the adults had T2 hyperintense brain lesions. Optic gliomas were present in 29% of the patients, in 44% of the children and 10% of the adults. 8% of the patients had other intracranial tumours. Spinal lesions were seen in 75% of the patients.

Hyperintense T2 lesions were most common in the age group of 5 to 9 years. During follow-up of the children, the lesions diminished in 25%, remained unchanged in 36%, showed mixed behaviour in 20% and disappeared in 10%. In 15% they increased in size and number. In one patient a malignant tumour developed at the site of a T2 lesion.

Optic gliomas were located intraorbitally and/or prechiasmally in 94%, chiasmally and/or at the hypothalamus in 58% and in other optic areas in 14% of the patients. 52% of the intraorbital gliomas were bilateral. The gliomas remained unchanged in 68% of the children and 50% of the adults. Other lesions included plexiform neurofibromas, sphenoid bone dysplasias and hydrops of the optic sheath. Optic glioma was more common in children with T2 hyperintense brain lesions than without them.

The other brain tumours included six astrocytomias, including an affected mother and her son. In one patient the astrocytoma regressed spontaneously. Hydrocephalus was seen in 5% of the patients.

T2 hyperintense brain lesions were more common and numerous in macrocephaly; all macrocephalic children, but only 59% of the normocephalic children were affected. All children without T2 lesions were normocephalic. The brain measurements did not reveal any specific area to be responsible for macrocephaly.

Spinal postural changes and dural ectasias were more common in adults. The spinal cord was affected in two patients. Spinal neurofibromas were seen in 19% of the children and 55% of the adults. Even young children may have severe manifestations. In one family a rare familial type of spinal neurofibromatosis (FSNF) was observed in four adults with bilateral spinal neurofibromas at all levels of the spine.

Although both CT and MRI were valuable in CNS imaging, MRI proved to be the method of choice in detecting T2 hyperintense brain lesions, in evaluating the intracranial extent of optic gliomas and hydrops of the optic sheath and lesions of the spinal cord and nerves. MR imaging proved necessary for evaluating the extent of NF1 manifestations and helpful in the diagnosis, screening and follow-up of NF1 patients.

Keywords: CNS, CT, imaging follow-up, MRI, NF1
To my family
This study was carried out at the Department of Radiology, University of Oulu, in 1994–2003.

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Oulu, September 2003

Eeva-Liisa Leisti
Abbreviations

ADC  apparent diffusion coefficient
CHO, Cho  choline
CNS  central nervous system
CR, Cr  creatine
CSF  cerebrospinal fluid
CT  computed tomography
DNA  deoxyribonucleic acid
FLASH  fast low angle shot sequence
FSE  fast spin echo pulse sequence
FSNF  familial spinal neurofibromatosis
Gd-DTPA  gadolinium dimeglumine-triamine-penta-acetic acid
H  Hounsfield unit
I  iodine
IR  inversion recovery pulse sequence
LOH  loss of heterozygosity
MPNST  malignant peripheral nerve sheath tumour
MR  magnetic resonance
MRI  magnetic resonance imaging
MRS  magnetic resonance spectroscopy
NA, NAA  N-acetyl aspartate
NF (1-2)  neurofibromatosis (types 1-2)
NIH  National Institute of Health
OG  optic glioma
PEG  pneumoencephalography
PET  positron emission tomography
PG  pontine glioma
RAS  oncogene
SE  spin echo pulse sequence
STIR  short-T1 inversion recovery pulse sequence
T  Tesla (unit of magnetic induction)
T1  longitudinal relaxation time
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<tr>
<td>T2</td>
<td>transversal relaxation time</td>
</tr>
<tr>
<td>TE</td>
<td>time to echo</td>
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<td>TR</td>
<td>time of repetition</td>
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<tr>
<td>TSE</td>
<td>turbo spin echo pulse sequence</td>
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<td>VEP</td>
<td>visual evoked potential</td>
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References
1 Introduction

Neurofibromatosis is autosomally dominantly inherited neuro-cutaneous syndromes, which belong to a larger group of hamartomatoses or phakomatoses. Most hamartomatous lesions observed have been explained by aberrations in the migration, growth and differentiation of neural crest cells, which is why the disorders have also been called neurochristopathies (Bolande 1974). The presently known types of neurofibromatosis were characterized in detail relatively late, and the most common ones, NF1 and NF2, have been shown to be caused by mutations in two different genes located in chromosomes 17 and 22, respectively.

Neurofibromatosis 1 or NF1 (von Recklinghausen disease) is one of the commonest single-gene disorders in man, with an incidence of 1 per 2500–4300 and a prevalence of 1 per 4000–4950 individuals (Samuelsson et al. 1981, Huson et al. 1989, Pöyhönen et al. 2000b). Approximately half of the patients represent new gene mutations, while the rest have inherited the gene defect from one of their parents.

NF1 is a clinically highly variable disorder even in members of the same family. Its diagnostic hallmarks, such as café-au-lait macules, cutaneous neurofibromas, iris hamartomas and axillary freckles, affect most patients to some extent, but the phenotype may also be much more complicated (Pöyhönen 2000a). Many patients suffer from plexiform neurofibromas, which have an increased tendency towards malignant transformation. Gliomas, such as astrocytomas, also occur in NF1. About half of the patients present with macrocephaly, and about 40% show some learning difficulties or clumsiness, some even mental retardation. Gliomas of the optic nerve or other parts of the optic system are common. Tibial pseudoarthrosis, scoliosis, spinal tumours, spinal dural ectasias and pheochromocytoma have been described in NF1 patients among many other features. NF1 has rarely been diagnosed before the age of one year, but it is diagnosable in most patients during the first few years of life. NF1 is a progressive disorder, and many of its significant features may appear later in life. Identification of CNS lesions, in either symptomatic or asymptomatic patients with NF1, has become an important part of the treatment and follow-up of these patients. The development of modern neuroimaging methods has greatly facilitated the characterization of the lesions of CNS and related structures in NF1 patients. In cases with suspected NF1, the presence of T2 hyperintensities of the brain, for example, may even be of diagnostic help.
The earliest neuroimaging methods used included plain films, tomography, pneumoencephalography (PEG), angiography, myelography with negative or positive contrast and orbital venography. Development of computerized tomography (CT) in the early 1970’s improved greatly the visualization of the lesions in NF1, e.g. orbital changes or cranial tumors. Magnetic resonance imaging (MRI), which was introduced in the 1980’s, further improved the accuracy of diagnostic imaging, revealing, among others, hyperintense T2 lesions and spinal lesions in NF1. MRI also proved useful in the follow-up of patients because it involved no risk of ionizing radiation. Until the recent years, the high costs and poor availability of MRI have somewhat restricted its use. The examination is also time-consuming, and small children require anesthesia.

Although the CNS changes in NF1 have been subject to numerous studies, only a few follow-up studies have been made on larger groups of patients of different ages, including imaging of both the head and the spine. Even now that imaging of the CNS in asymptomatic patients has become a routine in several centres, more information is needed about the course of the disease and about such features as macrocephaly and its relation to the other central nervous system lesions. Investigations of larger series may also reveal new, as yet undiscovered features of the disease or familial clustering of certain lesions.

The epidemiology and phenotype of NF1 were recently studied in a large Northern Finnish family series (Pöyhönen 2000a, 2000b), where most patients had either undergone neuroimaging earlier for diagnostic purposes or needed to be further characterized for purposes of follow-up. This study was undertaken to investigate more extensively and in more detail the CNS features in Northern Finnish patients, in order to further characterize the CNS lesions found in NF1 and to learn more about the course of the disease.
2 Review of the literature

The earliest descriptions of neurofibromatosis or neurofibromatosis-like disease date back to the thirteenth century in Austria and to the sixteenth century (Mulvihill 1990). In 1822, Wishart, a Scottish surgeon, published the first description of a deaf and blind boy with multiple tumours of the dura and the cranial nerves, which combination has long been recognized as the principal form of neurofibromatosis (Rubinstein 1986). Virchow reported in 1847 the first family with neurofibromatosis in several generations (Huson et al. 1989).

In 1882, Friedrich von Recklinghausen, a German pathologist and professor in Strasbourg, presented in his article "Über die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen" two autopsied patients and recognized the neural origin of the neurofibroma, which is the most common lesion in NF (Crump 1981). This identification caused the disorder also to be known as von Recklinghausen’s disease. The first systematic genetic study of NF was carried out by Thomson in 1900. Borberg (1951) and Crowe (1956) reported the first large clinical studies of neurofibromatosis. They also established the autosomal dominant mode of inheritance of neurofibromatosis and the high penetrance of the disease and showed that about half of the probands represented new mutations. Since then, several clinical and genetic population-based studies of neurofibromatosis have been performed, and the etiology and genetics of the different forms of NF have been evaluated.

The significance of central nervous system symptoms and lesions in neurofibromatosis became apparent soon after the recognition of this disorder. Before the era of CT and MRI, imaging information of the central nervous system was obtained by plain radiographs and tomography of the skull and the orbits. PEG with polytomography, angiography, orbital phlebography and radionuclide scanning were also used, and only secondary signs of pathological conditions could be seen, such as enlargement of the skull and orbital foramina, thinning, erosion or sclerosis of bone, pathological vascular markings, sutural widening or defects, orbital deformities and calcifications. The neuroradiological methods of investigating tumours involving the optic pathways varied according to whether the lesion was intraorbital or intracranial. (Savoiardo et al. 1981). For spinal lesions, plain films, tomography, myelography with either negative or positive contrast medium, angiography and radionuclide scanning were used. Abnormal spinal curvature,
bony anomalies and secondary lesions, such as widening of the intervertebral foramina or the spinal canal, could be easily detected, but it was not possible to decide if the widening was due to a tumour or to dural ectasia.

Several lesions of NF, both cerebral and spinal, have become visible or their visualization has been greatly facilitated by the modern imaging methods, CT and especially MR. T2 hyperintense brain lesions and intramedullary tumours in both NF1 and NF2 have been recognized, and the extent of the lesions, e.g. spinal neurofibromas, can now be easily evaluated with MRI. The use of intravascular contrast agents has further improved the diagnosis of CNS lesions. Imaging of the CNS and follow-up of the disease can be performed with MRI without any risk of ionizing radiation, which is important especially in children.

2.1 Classification and diagnostic criteria of neurofibromatoses

Neurofibromatosis was traditionally divided into two entities, central NF and peripheral NF, until it was established in the 1980’s that these entities represent two entirely different clinical disorders due to mutations in two different genes. The National Institute of Health (NIH) Consensus Development Conference held in 1987 in Bethesda, Md, USA (NIH 1988) suggested, on the basis of clinical features, two distinct types to be differentiated: NF1 and NF2, and defined the diagnostic criteria for both of them. NF1 was synonymous to the classical von Recklinghausen’s disease, while NF2 corresponded to the predominantly intracranial (central) type of neurofibromatosis.

Riccardi (1987) refined the classification further and suggested that neurofibromatosis should be divided into eight subgroups. NF1 (von Recklinghausen NF or peripheral NF) has as its major features multiple café-au-lait spots, peripheral neurofibromas and pigmented iris hamartomas (Lisch nodules). NF2 (central NF or bilateral acoustic neurofibromatosis) is characterized by bilateral acoustic neurinomas, meningiomas and spinal medullary tumors. NF1 and NF2 together account for more than 99% of all cases of neurofibromatosis (Braffman & Naidich 1994).

More recently, Carey and Viskochil (1999) proposed a further classification of NF based on both clinical and molecular genetic criteria. Other forms than NF1 and NF1 are considered as variants of NF, e.g. segmental neurofibromatosis (former NF5) manifests in restricted areas of the body, usually unilaterally.

Of all the different types of neurofibromatosis, NF1 or classical neurofibromatosis or von Recklinghausen’s disease accounts for 90% of all cases (Huson 1987). Its diagnostic criteria were established in consensus meetings in 1987 and 1997, and are now used universally. For the diagnosis of NF1, the patient should fulfill two or more of the following criteria (Gutmann et al. 1997):

1. six or more café-au-lait macules with a diameter of >1.5 cm in postpubertal and > 0.5 cm in prepubertal individuals
2. two or more neurofibromas of any type, or one plexiform neurofibroma
3. multiple freckles in the axillary area or the groins
4. optic glioma
5. two or more Lisch nodules (iris hamartomas)
6. a distinct osseous lesion, such as sphenoid dysplasia or thinning of the bone cortex with or without pseudoarthrosis

7. an affected first-degree relative (parent, sibling, offspring) with NF1

Most of the diagnostic criteria are well visible and easy to use. CNS-related criteria have not been needed, although T2 hyperintensities of the brain have been suggested as an additional diagnostic criterion (Curless et al. 1998, De Bella et al. 2000a)

### 2.2 Genetics and occurrence of neurofibromatoses

NF1 and NF2 have been shown to be entirely distinct disorders with different genetic backgrounds and different clinical and radiological manifestations.

NF1 is an autosomally dominantly inherited disorder, which is caused by mutations of the NF1 gene in chromosome 17. In 1987, the gene was mapped to the long arm of chromosome 17 (locus 17q11.2; Barker et al. 1987), and cloned in 1990 (Cawthon et al. 1990, Wallace et al. 1990). The protein encoded by NF1 gene is neurofibromin, which down-regulates RAS activity. More than 200 mutations of the NF1 gene have been described, and most families have their own mutation, although recurrent mutations have recently been described (Ars et al. 2003). Mutation analysis of the NF1 gene for clinical purposes is complicated, since the gene is very large, composed of 60 exons and spanning 350 kb of genomic DNA. The mutation rate is high, and there seems to be no clear hot spots for mutations (Messiaen et al. 1995). However, if powerful molecular techniques are used, mutation can be detected in 95% of NF1 patients fulfilling the NIH criteria (Messiaen 2003). Patients with deletion of the whole gene have been shown to have a recognisable dysmorphic phenotype, which changes with age, and they also have more neurofibromas (including spinal neurofibromas), learning difficulties and certain malignant tumours (Huson 2003). The penetrance of the gene has been shown to be almost 100% by the age of five years (Huson et al. 1989, Pöyhönen 2000b), but its expressivity is highly variable. About 50% of all patients with NF1 represent new mutations, predominantly ones derived from paternal meiosis (Samuelsson & Axelsson 1981, Huson et al. 1989, Pöyhönen et al. 2000b). The genetic fitness of NF1, i.e. the ability to propagate, has been shown to be reduced to about half of that expected (Pöyhönen et al.2000).

NF1 occurs all over the world among all races, and women and men are equally affected. The birth incidence of NF1 has varied in different studies from 1/2500 to 1/4300 and was shown to be about 1/3700 in Northern Finland, which is a minimum estimate (Pöyhönen et al. 2000b). The prevalence of NF 1 has varied from 1/4600 in Sweden (Samuelsson et al. 1981) to 1/4950 in Wales (Huson et al. 1989). The overall prevalence in Northern Finland was calculated to be 1/4400, which is also a minimum estimate. The highest age-related prevalence was 1/3000 in the age group of 10 to 19 years. NF1 has been an underdiagnosed disorder, and the milder forms may have remained unreported. In Northern Finland, the mean age at diagnosis was 20 (±16) years in the whole population, although the children born in the 1980’s were diagnosed earlier at a mean age of 6 (±4) years (Pöyhönen et al. 2000b).

NF2 is also an autosomal dominantly inherited disease with high penetrance and more limited clinical manifestations, the most important being vestibular schwannomas. It is
much less common than NF1 and usually becomes symptomatic during the second or third decade of life (Evans et al. 1992). Evans et al. in (1992) found its incidence to be approximately 1/33 000–40 000 and prevalence 1/12 000–22 000. The penetrance of the gene is close to 100% by the age of 60. About 50% of the cases have been new mutations. The NF2 gene was located in the long arm of chromosome 22 (22q12) in 1987 (Rouleau et al. 1987, Wertelecki et al. 1988), and the different nature of NF1 and NF2 were thus ascertained.

2.3 Role of radiologic imaging in NF1

2.3.1 CT and MRI in the diagnosis and follow-up of NF1

Since the introduction of CT, and especially MRI, CNS abnormalities in NF patients have been shown to be much more common than it had been thought earlier. Gardeur et al. (1983) found normal CT scans in only 17 out of 77 NF patients, including both NF1 and NF2. Jacoby et al. (1980) found normal CT in 8 out of 29 NF patients, while 21 (72%) had abnormalities of the orbits or brain. Gayet-Delacroix et al. (1995) presented the MRI findings of 40 asymptomatic NF1 patients (mean age 22), pointing out that MRI demonstrated various abnormalities in 24 patients (60%). Shu et al. (1993) found abnormalities in 66 (94%) of their 70 NF patients on cranial MRI examinations.

MR has been recommended as the method of choice for examining the head and spine in NF patients (Menor et al. 1991). It has been found better than CT in detecting and defining many brain and spinal lesions, especially ones in the posterior fossa and spinal cord. MRI has been pivotal in the detection of T2 hyperintensities in the brain, and intramedullary tumours in NF have become more easily visualized. The use of contrast agents in MRI has further improved the detection of lesions in NF1. Gadolinium-DTPA (Gd-DTPA) is over 25 times safer than iodinated contrast agents. The NIH conference report of 1990 (Mulvihill 1990) recommends the use of intravenous contrast enhancement in MRI examinations of patients with neurofibromatosis.

There are only a few real comparisons concerning the sensitivity of CT and MRI. Menor et al. (1991) compared CT and MRI in an evaluation of the incidence of CNS lesions in 41 children with NF1. CT detected 32% globus pallidus lesions which showed hyperintensity on T2-weighted MR images. On T2-weighted images, 51% of the patients showed cerebellar and 42.5% brainstem hyperintensities, which were not visible on CT. One of the four brain tumours did not show on CT, and two cases of Chiari I malformations remained undetected on CT. Involvement of the chiasm or optic radiation were better seen on MRI.

The MRI imaging protocols have varied in different studies. Menor et al. (1991), for example, recommended for brain imaging a MRI protocol consisting of an initial sagittal T1-weighted SE and axial T2-weighted SE sequences as well as a T1-weighted SE study parallel to the hard palate, which is optimal for visualizing the optic pathways. According to them, gadolinium should be reserved for the evaluation of aqueductal stenosis, the posterior extent of the optic pathway and parenchymal tumours and lesions with a mass.
effect or perilesional edema and hypointensity with a tumour suspicion on T1 sequences. In the case of a typical NF lesion, yearly MRI control was recommended, and controls at shorter intervals were to be made only if clinically needed. Lesions with gadolinium uptake should be biopsied or controlled with MRI within less than six months.

There are several advantages in the use of MRI in the imaging of the optic pathways: the intracranial extent of the optic tumour is easier to detect, the anatomic delineation of the optic glioma is visualized better, other than optic pathway lesions are easily detectable on the same examination, no ionizing radiation (or i.v. contrast) is needed, bone and non-ferromagnetic metallic implants produce no artifacts, as they do on CT, and direct coronal, sagittal and oblique imaging is possible (Pomeranz et al. 1987). Parazzini et al. (1995) recommended MRI screening for patients with NF1 to detect clinically silent optic pathway lesions and serial MRI studies to follow up the evolution of these lesions. No aggressive treatment should be undertaken without follow-up, and surgical treatment should be limited to cases that are clinically and radiologically in progression. Listernick et al. (1999), on the other hand, emphasized the importance of yearly ophthalmological examinations of a child with NF1 and regarded radiological screening for optic pathway gliomas as unnecessary.

Balestri et al. (1993) were able to show that the likelihood of detecting imaging abnormalities in patients with NF1 is increased by systematic follow-up. They found three cases of optic glioma, six cases of T2 hyperintensities and a suspected parenchymal tumour in one case at the initial examination. After follow-up for two to four years, they found three more cases of optic glioma and T2 lesions in nine more patients. The authors concluded that systematic follow-up MRI examinations are indicated in NF1 patients, but invasive treatment should be avoided and used only in rapidly progressive and symptomatic lesions.

The NIH Consensus Group on Neurofibromatosis (1988) regarded radiological examinations of asymptomatic NF patients as unnecessary. Nor did Guttmann et al. (1997) recommend routine CT or MRI screening of the CNS of individuals with NF1, whereas patients at risk for NF2 should undergo gadolinium-enhanced MRI of the head and the whole spine, to rule out vestibular schwannomas and spinal tumours.

2.3.2 MR spectroscopic and diffusion studies and PET

Broniscer et al. (1997) analyzed the proton magnetic resonance spectroscopic (MRS) findings of patients with diffuse pontine glioma (PG) with and without NF1 and healthy children. The neuronal markers N-acetyl aspartate (NA) and the vector sum of the metabolites choline and creatine/phosphocreatine (M-CHO-CR) were compared in different groups. The mean NA levels and the mean M-CHO-CR levels did not differ significantly between NF1 patients and controls. Patients in the PG group had significantly lower NA and M-CHO-CR levels than did patients in the control and NF1 groups. Patients with NF1 and symptomatic brainstem enlargement had significantly higher (MRS) values for the variables studied compared to patients with PG. The authors presume the higher NA values to represent preservation of brainstem neuronal elements in NF1 patients, consis-
tent with fewer symptoms upon brainstem involvement, and the results may be helpful in planning appropriate therapy.

Gonen et al. (1999) studied the brains of NF1 children and healthy control subjects with three-dimensional multivoxel proton MR spectroscopy and found distinct metabolic features in normal brain and T2 hyperintense lesions and tumours in children. The T2 hyperintense lesions were characterized by significantly elevated choline (Cho), reduced creatine (Cr), 2>Cho:Cr>1.3 and nearly normal N-acetyl aspartate (NAA) levels. The tumours had Cho:Cr>2 and no NAA. The T2 hyperintense lesions had no intrinsic lipid or lactate signals, and they were more extensive than shown by MRI.

Wilkinson et al. (2001) studied NF1 children with typical T2 hyperintense brain lesions and lesions with atypical or tumorous features and found that MR proton spectroscopy can help to differentiate between T2 hyperintense brain lesions and brain (non-optic/ hypothalamic) glioma. They found a significant increase in choline and myo-inositol in tumours compared to typical T2 hyperintense brain lesions or controls, a reduction in the N-acetyl levels in T2 hyperintense lesions compared to controls, a reduction in N-acetyl in tumours compared to controls and a reduction in glutamate/glutamine in tumours compared to controls. The MR proton spectroscopy findings of Jones et al. (2001) suggested that metabolic changes may be present without visible changes on MRI.

Sener et al. (2000a) and Eastwood et al. (2001) evaluated changes in brain water diffusibility by MRI in different areas of the brain in children with and without NF1. Eastwood et al. measured significant ADC (apparent diffusion coefficient) increases both in hyperintense lesions and in normal-appearing areas of the brain in children with NF1. Sener et al. obtained higher ADC values in optic radiations affected by glioma than values of normal white matter, suggesting relatively high molecular motion in the affected areas, probably due to myelin vacualization. ADC values of thalamic hamartomas were lower, and it might be possible to differentiate optic gliomas from hamartomas.

Balestri et al. (1994) presented four patients with NF1 who underwent cerebral PET with (18F)-2-fluoro-2-deoxy-D-glucose. Widespread hypometabolism was found in three of them. The lesions on MRI, which were localized in the subcortical white matter and grey matter structures had normal rates of glucose metabolism. This suggested that the lesions seen on MRI were not due to defective blood supply

2.4 NF1 as a clinical entity

NF1 is a progressive hamartomatous neurocutaneous disorder, which is limited to more or less cosmetic lesions in most patients, but which causes significant developmental or medical problems in about one third of the patients (Pöyhönen 2000a, Sippel et al. 2001). Learning and behavioural disturbances are common in children, and the psychological problems associated with skin manifestations may be severe. Malignant brain tumours, malignant peripheral nerve sheath tumours (MPNST) and childhood leukemia are the main causes of increased mortality in NF1 (Sorensen et al. 1986, Rasmussen et al. 2001).
2.4.1 Main diagnostic signs

The presence and nature of the main diagnostic signs – café-au-lait macules, freckles, neurofibromas and Lisch nodules – in several population or clinical studies from different countries were recently evaluated by Pöyhönen (2000a).

**Café-au-lait macules.** – Practically all NF1 patients have presented with multiple café-au-lait macules by the age of 5 years. The macules are not seen in newborns, but increase both in number and in size with age. In the Northern Finnish study (Pöyhönen 2000a), macules were seen in all patients under 30 years of age, but in only 75% of those aged over 60 years. The café-au-lait macules do not cause symptoms and have not been reported to predispose to malignant change.

**Freckles.** – Light brown freckles usually occur in the axillae and groins, but may also appear over larger areas of the body. They have not been reported in the newborn, but appear later in 70% to 87% of the patients. In a Welsh study of 135 NF1 patients, axillary freckling was seen in 67% and inguinal freckling in 44% of the patients (Huson et al. 1994). In Northern Finland, about half of the children under 6 years of age showed freckles, and 87% of all patients (n=164) had them.

**Neurofibromas.** – Neurofibromas are benign tumours that may appear as either small, soft cutaneous nodules or, less frequently, as subcutaneous denser lumps along any nerve. They may also be pedunculated or diffuse. They usually involve the skin, but may occur in deep peripheral nerves, in viscera and blood vessels innervated by the autonomic nervous system and in spinal nerves (Riccardi 1981). Neurofibromas are rarely seen in young children – they were seen in only 4% of children aged under 6 years, but in more than 50% of children between 6 and 16 years of age in Northern Finland – but practically all patients are affected in later age. Neurofibromas may cause symptoms, depending on their location.

**Lisch nodules.** – Lisch nodules are melanocytic iris hamartomas derived from neural crest tissue, and they have been shown to be almost pathognomonic to NF1 (Lewis & Riccardi 1981, Huson et al. 1987). Iris hamartomas were first described in connection with neurofibromatosis in 1918 by Waardenburg (Ragge et al. 1993) and later in 1937 by Karl Lisch (Lisch 1937). They are small, multiple nodules and are usually seen in both irises, but may also appear unilaterally. Lisch nodules begin to develop in early childhood – they were seen in 20% of children aged under 6 years and in 65% of those aged under 11 years in the Northern Finnish series. The usefulness of Lisch nodules in the diagnosis of NF1 is well known, and if they are large enough, they are visible to the naked eye, but in young children the nodules are not yet present or are small, and are best seen with a slit lamp.

2.4.2 Other somatic manifestations

**Plexiform neurofibromas** are tumours that grow along nerves and infiltrate into surrounding tissues. They are usually congenital and highly vascularised and may grow superficially or in deep structures. They may lead to localised or segmental hypertrophy of the bone and limb. Plexiform neurofibromas that reach the midline of the body have been
suggested to indicate aggressivity of the tumour or involvement of the spinal cord (Riccardi 1980). Cutaneous hyper-pigmentation or hypertrichosis may be associated with plexiform neurofibromas. Plexiform neurofibromas are almost exclusively associated with NF1 (Klatte et al. 1976, Riccardi 1981, Listernick & Charrow 1990, Peltonen & Jaakkola 1991, Pöyhönen 2000a). They have been reported in 15% to 40% of patients in different studies and were found in 20% of the Northern Finnish patients (Pöyhönen 2000a).

There is an increased risk of both primary and secondary malignancies in NF1 (Jensen et al. 1998). Sorensen et al. (1986) reported a relative risk of 4.0 of developing a malignant neoplasm or a benign central nervous system tumour in probands with NF1 relative to the general population. In addition, about one fifth of the NF1 patients with a primary malignancy developed a secondary malignancy. The following malignancies are especially associated with NF1: malignant peripheral nervous sheath tumours, astrocytomas, rhabdomyosarcomas, pheochromocytomas, carcinoid tumours and childhood leukemia. Hemispheric, brainstem and cerebellar astrocytomas are also more common in NF1 patients than in the normal population. Faravelli et al. (1999) reported a family with brain tumours in seven members, and discussed different hypotheses to explain this unusual recurrence, such as the nature of the mutation or cosegregation of other predisposing genes. Airewele et al. (2001), in their study of 173 NF1 patients, found females to be at a much higher risk for cancer than males. No elevated cancer risk was detected in unaffected first-degree relatives, regardless of whether or not the proband had cancer, suggesting that the malignancy in the proband is not a result of a modifying gene that has a significant impact on the overall cancer risk.

Malignant transformation occurs in about 5% of plexiform neurofibromas. They show a tendency to develop into malignant peripheral nerve sheath tumours (MPNST), the most common of them being neurofibrosarcoma (Rubenstei 1986). Of the 164 NF1 patients from Northern Finland, 11 (7%) had malignant tumours, the most common one being MPNST, which was seen in 5 patients (Pöyhönen et al. 1997b). Hope and Mulvihill (1981) pointed out that neurofibrosarcomas may occur wherever neurofibromas develop, and it has been shown that they arise from established neurofibromas, most often from ones of the large plexiform variety.

Griffiths et al. (1983) presented three patients with NF1, duodenal carcinoid tumour and pheochromocytoma (one bilateral case) and three patients with NF1 and a duodenal carcinoid tumour. Although pheochromocytoma is rare in NF1, it has been thought to occur in about 1% of the patients (Fuller & Williams 1991). The authors also mentioned that the NF1 patients with duodenal carcinoid have a greater risk to develop pheochromocytoma. Wilms' tumour has also been reported in connection with NF1 (Walden et al. 1977, Stay & Vawter 1997).

Bader and Miller (1978) found the risk of childhood leukemia (juvenile chronic myeloid leukemia) to be increased in NF1. An association between NF1, juvenile xanthogranuloma and leukemia has been described (Crepi et al. 1995).

Multiple malignancies (neurofibrosarcoma, pheochromocytoma, breast carcinoma, astrocytoma, adenocarcinoma of the stomach) in a family with NF1 have been described (Landsmeer-Beker et al. 1993).

Dysplastic vascular tumours have been detected in patients with NF1. Mansat et al. (1995) presented five patients with "acute" vascular tumours appearing within one day in
four patients and within several weeks in one patient. An underlying neurofibroma was found in three cases, and an intramuscular injection had preceded the tumour in one case. All tumours were operated on because of suspected malignancy. Histologic examination revealed vascular dysplasia of capillary vessels in four cases and hematoma in one case. The patients were followed up for 4 to 5 years, without recurrence. The pathogenesis of these tumours remained unknown.

Other cutaneous lesions observed in NF1 include both local and generalized hyperpigmentation, presence of hypopigmented macules, pseudoatrophic macules, skin angiomas and juvenile xanthogranulomas.

Short stature is common in NF1 and was recorded in 18 % of the Northern Finnish patients. A markedly asymmetric face was seen in 13/164 patients and other dysmorphic features in 7/164. Macrocephaly is also common in NF1 and will be described in more detail later.

NF1 is often associated with skeletal lesions, such as scoliosis, congenital bowing and thinning of the long bones, pseudoarthrosis and vertebral anomalies, which will be described in more detail later.

Precocious puberty is usually caused by a hypothalamic lesion (Saxena et al. 1970). Guillamo et al. (2002) reported precocious puberty as a main clinical finding in 5 (10%) out of 48 patients with optic glioma. Retardation of growth combined with retarded sexual development and anorexia nervosa has also been found in association with NF1.

Pulmonary manifestations occur in 5 to 10% of NF1 patients. (Fraser et al. 1994). The lesions consist of diffuse interstitial fibrosis (pathologically fibrosing alveolitis) and bullae, either alone or in combination. Thoracic neoplasms, usually neurogenic in origin, may arise in the intercostal nerves, in the mediastinum or in the lungs themselves.

Aortic, celiac, mesenteric and renal arterial stenosis and aneurysms of multiple vessels, including intracranial, have been found in neurofibromatosis (Tomsic et al. 1976).

The association of Noonan’s syndrome with neurofibromatosis has been discussed (Allanson et al. 1985, Meinecke 1987). Both inherited cases and new mutations of NF associated with the Noonan phenotype have been described. It has been suggested that this combination could be a variant of NF1 (Meinecke 1987). Five patients of the Northern Finnish patients had features characteristic of Noonan’s syndrome (Pöyhönen 2000a).

Weaver syndrome (van Asperen et al. 1993), Poland anomaly (Stoll et al. 1993) and gastroschisis (Segre et al. 1993) in combination with NF1 have been reported as coincidental findings.

2.4.3 Neuropsychologic manifestations

Psychomotor retardation, learning difficulties and even mental retardation are known to be associated with NF1 (Ozonoff 1999). In the Northern Finnish study (Pöyhönen 2000a), learning difficulties and developmental delay were observed in 28% of the patients and fine motor co-ordination problems in 39%. Intellectual handicap was identified in 22 patients (13%), and 8 (5%) were mentally retarded (with IQ under 70). A psychiatric disorder, mostly chronic psychosis or depression, had been diagnosed in 19% of the patients.
Only 55% of the adults had passed the school matriculation examination, and 46% of the adults were employed.

In total, 65% of the NF1 patients suffered from one or more symptoms related to NF1 and needed either medical intervention, rehabilitation or follow-up. In only 38% of the cases had the patient’s medical problems been treated before NF1 was diagnosed.

### 2.5 Brain manifestations in NF1

The extent and nature of the different CNS lesions in NF1 have become better known now that computed tomography and magnetic resonance imaging have been applied to both the diagnosis and the follow-up of the patients and their relatives. The use of MRI has shown that T2 hyperintense lesions are the most common brain lesions in NF1, especially in children, and that optic gliomas are the most common tumours. Different types of intraparenchymal benign or malignant tumours and brainstem tumours have been reported to occur in NF1 (Huson et al. 1994, Bilaniuk et al. 1997), and nontumorous hydrocephalus and macrocephaly have also been shown to be features of NF1 (Huson et al. 1994, Spadaro et al. 1986, Gonzales et al. 1990, Menor et al. 1991). Medullary tumours occur, but they are more common in NF2 than in NF1. Spinal neurofibromas and other lesions are well known to be part of the NF1 phenotype (Egelhoff et al. 1992, Thakkar et al. 1999).

#### 2.5.1 T2 hyperintense lesions of the brain

The most common abnormality seen on MR imaging in patients with NF1 are small multiple areas of high signal intensity in the brain on T2-weighted images (Goldstein et al. 1989, Mapstone 1992). These lesions have also been called unidentified bright objects (UBOs; Balestri et al. 1994), unidentified neurofibromatosis objects (UNOs; Pont and Elster 1992), focal areas of signal intensity (FASIs; Cohen et al. 1990–91), neurofibromatosis bright objects (NBOs; Mukonoweshuro et al. 1998) or regional signal hypointensities (RSHs; Steen et al. 2001).

T2 hyperintense lesions are often bilateral and may be symmetric or asymmetric, and there is generally no evidence of a mass effect, surrounding oedema or contrast enhancement. They may appear as either singular or multiple lesions. On T1-weighted images, the lesions usually appear isointense to slightly hypointense (Duffner et al. 1989). The lesions in the globus pallidus may occasionally have a mild mass effect, and they may be bright on T1-weighted images (Aoki et al. 1989, Sevick et al. 1992, Smirniotopoulos & Murphy 1992, Ferner et al. 1993). The lesions in the globus pallidus are usually sharply defined, whereas the lesions in the cerebellum and brainstem tend to be more confluent and may involve the midbrain, pons and medulla contiguously (Goldstein et al. 1989). On CT, there are usually no corresponding abnormalities, although focal areas of hypodensity have been reported in the basal ganglia on CT (Duffner et al. 1989). Menor et al. (1992) compared the visualization of bright lesions in a prospective CT and MRI study of 41
children with NF1. Lesions were detected on MR in 22 (45%) of the patients, but on CT in only 7 patients (17%). The smallest lesion detected on CT measured 0.8 cm, and there was no correlation between the size of the lesions on MR and their visibility on CT. None of the observed lesions enhanced with contrast medium on either MRI or CT.

2.5.1.1 Occurrence, localization and follow-up of T2 hyperintense lesions

The occurrence of T2 hyperintense lesions has been subject to several studies since their early detection in 1989 (Duffner et al. 1989, Goldstein et al. 1989). In contrast to most hamartomatous lesions in NF1, they often disappear or diminish over time, the pathological changes underlying them have not yet been clarified, and their significance has also remained largely unknown.

The prevalence of T2 hyperintense lesions in children with NF1 has been found to be high, ranging from 60% to 93% of affected children in different studies, while their frequency in adults is low (Duffner et al. 1989, Pont & Elster 1992, Sevick et al. 1992, Balestri et al. 1994, Menor et al. 1998) (Table 1). They have been encountered from the early age of about one year onwards, and they have been found useful as an additional diagnostic criterion of NF1. In the study of Menor et al. (1998), MR imaging contributed to a definitive diagnosis of NF1 in 53% of suspected cases, Parazzini et al. (1995) found T2 hyperintense lesions in 100% of their 11 NF1 patients, and Griffiths et al. (1999) found them in 93% of the children examined with MRI.

T2 hyperintense lesions have been reported to be more frequent in NF1 patients with optic gliomas (Hurst et al. 1988, Di Mario et al. 1993). In the study of Aoki et al. (1989), they were found in 89% of the patients with optic glioma but in only 44% of the patients without glioma. In the study of Balestri et al. (1993), the corresponding figures were 67% and 47%. All the seven patients of Van Es et al. (1996) with T2 lesions also had optic glioma. Rosenbaum et al. (1999), on the other hand, found T2 lesions in 86% of the studied children with NF1 (n=31), but were unable to show a correlation between them and optic pathway gliomas.

As listed in Table 1 and also observed in other studies (Hurst et al. 1988, Goldstein et al. 1989, Menor et al. 1992, Di Mario et al. 1993, Ferner et al. 1993, Shu et al. 1993), T2 hyperintense lesions have been encountered at numerous locations of the brain, but most often in the basal ganglia/globus pallidus. The cerebellum and the brainstem have also been common locations for lesions. They have been found in the intracerebral optic regions in 8 to 40% of the patients (Duffner et al. 1989, van Es et al. 1996, Menor et al. 1998). Sener et al. (2000b) found hamartomas of the septum pellucidum in three out of 86 NF1 patients (3.4%). The lesions were especially detectable on fluid attenuation inversion recovery (FLAIR) and proton-weighted images. T2 hyperintense lesions have also been described in hippocampal areas (Turbidy et al. 2001).
Table 1. Occurrence, localization and follow-up of T2 hyperintense brain lesions in NF1 in previous studies.

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<td>43</td>
<td>44</td>
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<td>1–31</td>
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<td>8–16</td>
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<td>16.2</td>
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<td>32/60</td>
<td>34/79</td>
<td>34/77</td>
<td>32/64</td>
<td>56/78</td>
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<td>Sites of T2 lesions (% of patients affected)</td>
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<tr>
<td>basal ganglia</td>
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<td>3.**</td>
<td>88</td>
<td>48</td>
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<tr>
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<td>13</td>
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MRI follow-up T2 lesions

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<th>patients</th>
<th>mean follow-up time (y)</th>
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<th>unchanged</th>
<th>progression</th>
<th>mixed</th>
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<tr>
<td>mean follow-up time (y)</td>
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<tr>
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<td>10</td>
<td>3</td>
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<tr>
<td>unchanged</td>
<td>42/40**</td>
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<td>27/34**</td>
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</tr>
<tr>
<td>progression</td>
<td>25/16***</td>
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<tr>
<td>mixed</td>
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</table>

* = number of sites of lesion, ** = in an order of frequency, *** = % of the patients, basal ganglia/cerebellum and brainstem

The development and follow-up of T2 hyperintensive lesions has been reported in several studies (those in Table 1; Mautner et al. 1995, Carella & Medicamento 1997, Griffiths et al. 1999). Although the patient groups have been relatively small and the mean follow-up times only a few years, it has appeared that these lesions may increase in size and number throughout childhood, but that they often show a tendency to resolve with increasing age and have less often been seen in adults. In the studies of Sevick et al. (1992) and Itoh et al. (1994), the patients showing progression of the lesions had a mean age of 5 and 3.7 years, while the mean ages of the patients showing regression were 13 and 11.4 years, respectively. In addition, some of their patients showed lesions that remained unchanged, and some had mixed-type lesions. In the study of Mautner et al. (1995) of 20 NF1 patients aged 5–51 years, 11 patients (median age 10 years) had unchanged MR images. A reduction in the size or complete resolution of the lesions was found in 9 patients (median age 10 years).
In the study of Menor et al. (1998), the lesions showed progression in children aged under 10 years, but diminished in older patients. 18% of the 44 patients studied presented with atypical unenhanced lesions showing either edema, some mass effect or hypointensity on short TR images; two of the lesions were considered brainstem gliomas. Griffiths et al. (1999) found T2 lesions to be rare in children under 4 years of age, common at 4–10 years of age, and significantly reduced after 10 years of age. Atypical appearance of T2 hyperintense lesions was reported in two patients by Raininko et al. (2001). In an 18-year-old patient, an enhancing lesion was found bulging into the lateral ventricle, but it had almost disappeared after two years’ follow-up. The other patient was an 11-year-old boy who had a non-enhancing lesion in the left cerebellar hemisphere at a location that had been normal in MRI six years previously. The lesion remained stable one and a half years later. Morris et al. (1997) also reported spontaneous disappearance of an enhancing brain lesion in a child with NF1.

2.5.1.2 Nature and significance of T2 hyperintense lesions

The exact nature of T2 hyperintensive lesions is not yet exactly known. This may be partly due to nonspecificity of the bright lesions: prolongation of T2 relaxation occurs with various pathologic lesions, and no specific tissue composition can be deduced on the basis of the visual finding. They have been suggested to represent hamartomas, brain heterotopias, zones of gliosis, glial scars, low-grade tumours, areas of delayed demyelization or areas of vacuolar or spongiotic change. Delayed or abnormal brain maturation in these areas has also been suggested to cause the lesions (Braffman & Naidich 1994, Itoh et al. 1994, Di Paolo et al. 1995). In two NF1 children, Zimmerman et al. (1992) were able to demonstrate microscopically the presence of hyperplastic or dysplastic glial proliferation in the T2 hyperintense areas of the globus pallidus and midbrain peduncles. The bright lesions have also been thought to represent infarcts secondary to vascular occlusive dysplasia, which is known to occur in NF (Crawford et al. 1988), or increased free-water content of the tissue (Mirowitz et al. 1989, Balestri et al. 1993). Normal brain tissue has also been demonstrated at biopsy of T2 high-intensity foci (Di Mario et al. 1993). Because the lesions in the basal ganglia may show a mass effect and be hyperintense even on T1 images (whereas the white matter lesions are generally isointense on T1 images), it has been suggested that the basal ganglia lesions may have a different pathogenesis (Sevick et al. 1992).

Ectopic collections of Schwann cells have been described in NF1 patients, mostly in the spinal cord, but also in the cerebral cortex and basal ganglia (Rubinstein 1986, Mirowitz et al. 1989), and hamartomatous collections of melanocytes in the brain have also been found. Because lesions manifesting as hyperintensities on T1 images are uncommon (lipids, methemoglobin, melanin), the authors suggested that the hyperintensities in NF patients may be caused by dense clustering of myelinated Schwann cells or melanocytes in the basal ganglia, while the small focal signal hyperintensities on T2 images could be caused by other tissues within the hamartomas or could result from reactive gliosis leading to an increased water content. Myelinated areas of the brain appear to have high signal intensity compared to the cortex and white matter on T1 images, and the
high intensity in the case of melanocyte collections could be related to the paramagnetic properties of free radicals in melanin. Similar T1 hyperintensity has been detected in brain metastases of melanoma.

The clinical significance of hyperintense T2 lesions in NF1 patients is unknown. It has been suggested that such lesions could be associated with the increased frequency of mental retardation or specific learning and behavioural problems and seizures in the patients. The studies so far done on the correlation of the high-intensity T2 foci and the neurocognitive deficits in NF1 patients have been contradictory. In an extensive literature review by Ozonoff (1999), a summary of 71 articles from the years 1986 to 1997 on studies of neuropsychological function in NF1 is presented. According to it, the presence of T2 hyperintense lesions of the brain did not show a consistent relationship with the cognitive phenotypes of the patients. In some studies, the presence of T2 hyperintense brain lesions was considered predictive of a lower IQ, while in some reports the total number of brain lesions correlated negatively with cognitive function.

Although the T2 hyperintense lesions have, in most cases, been regarded as innocent changes, development of areas with T2 signal hyperintensity into astrocytoma has been described. Carella and Medicamento (1997) presented a 23-year-old patient with NF1, in whom an anaplastic astrocytoma developed from areas of T2 signal hyperintensity in the cerebellum. Previous follow-up examinations two and three years earlier had not shown any progression or any clue towards an unfavourable outcome. In the 32-year-old patient described by Miaux et al. (1997), glioblastoma multiforme developed from a non-enhancing hyperintense periventricular lesion during a follow-up of three years.

2.5.1.3 Differential diagnosis of T2 hyperintense lesions

Hyperintense cerebral white matter lesions on T2-weighted MR images have been described in conditions other than NF1, and they have thus not been thought to be pathognomonic to NF1. They have been found in ischemia, infections, demyelinating diseases, such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS), Wilson’s disease, dementia and Whipple’s disease, and they have also been found in increasing numbers in otherwise healthy elderly persons along with increasing age (Duprez et al. 1996, Nazer et al. 1993, Yetkin et al. 1993).

Artifacts and normal structures, such as a deep sulcus, substantia gelatinosa, a gyrus or a perivascular Virchow-Robin space, may mimic true white matter lesions. Miyazaki et al. (1991) have described deep white matter lesions mimicking T2 hyperintensive lesions also in cases of tuberous sclerosis, congenital muscular dystrophy, congenital myotonic dystrophy, autism, epilepsy and congenital heart disease.

2.5.2 T1 hyperintense lesions of the brain

Mirowitz et al. (1989) found areas of increased signal intensity relative to cerebral white matter on T1-weighted MR images in the basal ganglia region in seven out of 35 NF1
patients (mean age 12 years). The globus pallidus and portions of capsula interna were involved in all patients, and the posterolateral parts of the thalami were involved in five cases. In addition, one patient had T1 hyperintensities in the corpus callosum. In most patients, the hyperintensities on T2 images were much more limited than the hyperintensities on T1 images. The lesions appeared smoothly marginated, somewhat nodular and with no mass effect, edema or contrast enhancement on all sequencies.

Terada et al. (1996) studied 35 NF1 patients and found hyperintense T1 lesions in 8 patients aged 3 to 17 years. Seven of them showed hyperintense T2 foci in the same areas in the globus pallidus. No enhancement with gadopentate dimeglumine was noted. It was found that, in some patients, the T1 foci developed later than the T2 foci and did not regress during follow-up for up to 90 months, while the T2 foci showed regression. They suggested that the T1 lesions may be characteristic of lesions of basal ganglia only, but not of lesions in the posterior fossa or cerebral white matter.

2.5.2.1 Differential diagnosis of T1 hyperintense lesions

T1 hyperintense lesions of the basal ganglia due to manganese deposition have been reported in patients who have undergone gastrointestinal surgery with perioperative parenteral nutrition (Iwase et al. 2002). T1 hyperintense lesions of the globus pallidus were described in children with portosystemic encephalopathy (Yanai et al. 1995) and also in children with chronic liver disease without obvious hepatic encephalopathy (Ballauf et al. 1994). Similar lesions are also found in patients with melanotic metastases of melanoma (Isiklar et al. 1995), in herpes simplex encephalitis (Shian & Shi 1996), in acute measles encephalitis (Voudris et al. 2002) and in tuberous sclerosis (Wippold et al. 1992) as well as in Tay-Sachs disease (Mugikura et al. 1996).

2.5.3 Brain tumours

CNS tumours in NF1 primarily originate from astrocytes and neurons (Aoki et al. 1989). Optic and parenchymal gliomas are the most usual tumours, and brain gliomas have been reported in 1% to 3% of patients with NF1. They are usually low-grade astrocytomas, appearing earlier than in the general population, and also more often multicentric. Gliomas of the brainstem, hypothalamus and the third ventricle are also relatively common, while diffuse gliomas of the cerebral hemispheres, cerebellum or spinal cord occur rarely (Gardeur et al. 1983, Bogdanno et al. 1988, Huson et al. 1989, Shu et al. 1993). Guillaumo et al. (2002) found 127 CNS tumours in 104 NF1 patients; 48 tumours were optic gliomas, 21 brainstem tumours and 22 tumours in other locations. 21 patients (20%) had multiple tumours. They found extra-optic location, tumour diagnosis in adulthood and symptomatic tumours to be associated with shorter survival. Malignant gliomas are rare in NF, and lobar gliomas have been reported to be more infiltrative than paraventricular ones (Gardeur et al. 1983). Vinchon et al. (2000) had operated on six NF 1 children with radiologically progressive cerebellar astrocytomas, one of them malignant. They found
the tumours associated with NF 1 to have a better prognosis than the non-NF-associated ones. Ependymomas, primitive neuroectodermal tumours, meningiomas and neurofibrosarcomas also occur (Sato 1992, Braffman & Naidich 1994), and pituitary adenomas have been described (Gardeur et al. 1983). Colloid cysts (Bogdanno et al. 1988) and epidermoid cysts (Shu et al. 1993) have also been reported.

In a series of 69 Northern Finnish NF1 patients with histologic tumour verification, Pöyhönen et al. (1997b) reported five patients with malignant brain tumours. These included three children with pilocytic astrocytoma and two adults with glioblastoma multiforme and anaplastic astrocytoma of the cerebellum, respectively.

In the series of van Es et al. (1996), only one patient out of the 50 studied NF1 children had a CNS tumour (ependymoma) other than optic glioma. Menor et al. (1998) reported 8/72 children with NF1 to have a CNS tumour other than optic glioma; of these, two had been verified histologically.

Astrocytic brainstem tumours in NF patients may differ in presentation, histology and natural history from similar-appearing tumours in non-NF1 patients. The tumours in NF patients may progress slowly for an indeterminate length of time, whereas most brainstem tumours in children without NF progress rapidly (Cohen et al. 1990–91). Raffel et al. (1989) suggested that the brainstem tumours in NF1 patients might be extremely slowly growing tumours or static hamartomas, although their nature is difficult to ascertain. Neurofibromatosis-associated brainstem gliomas seemed to have a better prognosis than sporadic gliomas.

Bilaniuk et al. (1997) described 25 NF1 patients shown by MRI to have diffuse (n=12) and focal (n=13) brainstem tumours diagnosed at the mean age of 7.8 years (range 1.1–15.2 years.) In four patients, the tumour was found on routine screening. Medullary enlargement was most frequent (68%), followed by pontine (52%) and midbrain enlargement. In 30% of the patients both brainstem and optic pathway tumours were present. Surgery was performed on four patients and revealed fibrillary astrocytomas, one of which progressed into an anaplastic astrocytoma. Diffuse tumours in patients with NF1 appear to have a much more favourable prognosis than those in patients without NF1.

Molloy et al. (1995) presented 17 NF1 patients with brainstem tumours, located primarily in the medulla in 14 (82%) patients, in contrast to the pontine tumour location in the non-NF1 patients. The mean age of the NF1 patients at tumour diagnosis was 101 months. 5 (29%) patients had neurologic signs and symptoms suggestive of brainstem dysfunction. Contrast enhancement was seen in 7 patients (41%) on MR. 6 (33%) patients showed evidence of radiographic tumour progression, while only three showed clinical progression. In two of these, histological study revealed either fibrillary or anaplastic astrocytomas. 15 (88%) patients remained alive after a median follow-up time of 52 months. The brainstem tumours of the NF1 patients showed less aggressive behaviour than the tumours in the non-NF group. The tumours can be differentiated from non-neoplastic T2 high signal intensities because they exhibit focal or diffuse brainstem enlargement, have a mass effect, may show enhancement with gadolinium and often result in obstructive hydrocephalus.

Some periaqueductal gliomas may mimic the appearance of benign aqueductal stenosis, and it has been suggested that aqueductal stenosis in neurofibromatosis should be considered as suggestive of probable mesencephalic glioma necessitating follow-up examinations (Gardeur et al. 1983).
It is very difficult to differentiate benign, insignificant lesions from true gliomas. The presence of vasogenic edema and mass effect, enhancement with gadolinium, cavitation of the lesion, hypointensity of the lesion on T1 images and increasing size of the lesion on serial scans are suggestive of a glioma in patients with NF (Mulvihill 1990).

Faravelli et al. (1999) presented an unusual clustering of brain tumours in a family with NF1 and various cutaneous features.

2.5.4 Hydrocephalus

Obstructive hydrocephalus associated with NF1 may be caused by infratentorial neoplasms, midline arteriovenous malformations or primary, nontumorous aqueductal stenosis (Spadaro et al. 1986, Huson et al. 1988, Aoki et al. 1989, Gonzales et al. 1990, Menor et al. 1991). The earliest cases were described in 1927 and 1940 (Horwich et al. 1983). Afifi et al. (1988b) presented a series of 289 NF patients collected over 20 years. Of them, hydrocephalus was found in 15 (5%) cases; eight were caused by intracranial tumours, two had Chiari malformation, three had aqueductal stenosis, and two were of undetermined etiology. Pou-Serradell et al. (1989) presented nontumoural hydrocephalus in 9 out of 30 NF1 patients referred to MRI because of neurological problems.

The frequency of nontumorous aqueductal stenosis in NF1 has been 2% according to Riccardi and Einchner (1986). In most cases, nontumoural aqueductal stenosis has been detected in the first or second decade of life. Afifi et al. (1988a) found a total of 28 NF1 patients with nontumoural aqueductal stenosis in the literature.

Afifi et al. (1988a) studied three cases of nontumoural aqueductal stenosis in children with NF1. In them, MRI revealed an area of high intensity in the tectal and periaqueductal regions, and the findings remained stable during follow-up for one year. On T1-weighted images, kinking of the aqueduct without surrounding hypodense lesions was found. The hyperdense areas on T2-weighted images were assumed to represent hamartomas.

The pathogenesis of aqueductal stenosis in NF1 is heterogeneous but has been suggested to be due to direct expression of the NF1 gene. Periaqueductal gliosis has been found in some cases of stenosis, and septum formation and forking of the aqueduct have also been detected (Horwich et al. 1983, Spadaro et al. 1986, Schreiber & Quade 1990). Also, polyp-like growths of ependymal granulation tissue obstructing the aqueduct have been seen (Horwich et al. 1986). In MR images, Braffman & Naidich (1994) were able to show hydrocephalus, bulbous dilatation of the third ventricle, fusion of soft tissue of the midbrain with resultant obstruction of the aqueduct and absence of the CSF flow-void sign in their patients with NF1.

Afifi et al. (1988b) presented two adult NF1 patients with ventriculomegaly and Chiari type 1 malformation. Both patients had similar anomalies of the cranio cervical junction: hypoplastic occipital condyles, a short basiocciput and an invaginated dens with compression on a low-lying medulla.

It is important to differentiate between instances of hydrocephalus due to aqueductal stenosis and macrocephaly, which is common in NF1. Macrocephaly usually appears without neurological symptoms, and the patient’s head circumference remains constantly at or above the 97th centile, whereas in cases of obstructive hydrocephalus, there is an
increase of the head circumference over time relative to the growth curves (Horwich et al. 1986).

### 2.5.5 Other lesions of the brain

Mild ventricular supratentorial dilatation has been detected commonly in NF patients (Gardeur et al. 1983, Spadaro et al. 1986). Maki et al. (1981), using CT scans on NF patients (mostly NF1), demonstrated mild dilatation of the lateral ventricles without periventricular hypodensity in 44% of the 18 children. 60% of the 21 adult patients showed slight dilatation of the lateral ventricles, and one third of them also had dilatation of the third ventricle. In some of these patients, ventricular stasis without a block was found on radioisotope cisternography. Altogether 55% of the children and 85% of the adults had abnormal findings on CT, mild ventricular dilatation being the most common finding. Callosal agesis, cavum septi pellucidi and atrophic changes in brain were also found in some patients.

Enlargement of the quadrigeminal cistern, cisterna magna or subarachnoid spaces or subarachnoid cysts may be seen in NF1 (Menor et al. 1991, Di Mario et al. 1993, Ruggieri et al. 1995). Chiari I and II type malformations have been reported in a few cases of NF1 (Bognanno et al. 1988, Menor et al. 1991, Ruggieri et al. 1995), and hypoplasia of the temporal lobe has been detected in some patients (Imana Martinez & Martinez San Millan 1993). Porencephaly (Ruggieri et al. 1995) and localized megalencephaly, polymicrogyria and pachygyria have also been found (Gardeur et al. 1983). The cerebral ischemia described in NF1 may be due to arterial dysplasia.

Enlargement of the internal auditory canal due to dural ectasia may be seen in NF1 patients (Sarwar & Swischuk 1977, Aoki et al. 1989, Shu et al. 1993, Braffman & Naidich 1994). This may cause audiologic dysfunction. On MRI scans, the seventh and eighth cranial nerves appear normal in the enlarged auditory canal and there is no enhancement with gadolinium.

Agenesis of the corpus callosum has been described in association with NF1 (Jacoby et al. 1980, Maki et al. 1981). Atlas et al. (1988a) presented total agenesis of the corpus callosum and gyral malformations on MRI examinations of identical twins with NF1. Hypoplasia and lipoma of the corpus callosum have also been reported (Shu et al. 1993). In a patient with NF1, thin corpus callosum detected on MR scans was associated with microcephaly (Di Mario et al. 1993). Ruggieri et al. (1995) found two patients with NF1 with partial agenesis of corpus callosum on MRI. A cyst of the corpus callosum was reported in a patient with NF1 by Duffner et al. (1989).

Huson and Hughes (1994) have summarized the malformative CNS lesions detected by several investigators in autopsy studies of NF1 patients. These have included abnormal architecture of the cerebral cortex, hypertrophic gliosis of the optic nerve, hyperplastic proliferative gliosis, subependymal gliofibrillary nodules, which are histologically indistinguishable from small subependymal pilocytic astrocytomas and have been associated with aqueduct stenosis in NF1, meningoencephalic cerebellar gliosis, micronodular vascular proliferation in the nervous system and the visceral organs (vascular neurofibromatosis) and hydromyelia.
Pathologic intracranial calcifications occur in 10% of NF patients (Galanski and Benz 1978), mostly in ones with NF2 with meningiomas. Laminated type of unilateral cerebellar calcification in CT examinations has been found in NF1 (Jacoby et al. 1980), and the calcification was thought to be due to hamartomatous lesions. Suprasellar extensions of optic gliomas in NF1 may sometimes show calcification, which may simulate craniopharyngeoma (Davidson 1966). Arts and Van Dongen (1986) found multiple subependymal nontumorous calcifications without contrast enhancement or expansivity in three patients with NF2. On the basis of this finding and the literature referred to, they suggested that nontumorous intracranial calcifications may be a rare sign of both NF1 and NF2.

2.5.6 Vascular lesions of the head and neck

Both occlusive lesions and aneurysms of cerebral arteries have been described as associated with NF1 in occasional patients. In the occlusive disease of cerebral arteries described by several authors (Tomsick et al. 1976, Taboada et al. 1979, Crawford et al. 1988), the angiographic findings have included occlusion of the supraclinoid internal carotid artery, the proximal anterior cerebral and middle cerebral arteries and, less commonly, the more distal branches of these arteries. Occlusion of the posterior cerebral artery has been reported, although involvement of the posterior circulation is rare. Basal teleangiectasias producing a moyamoya appearance have been described to be associated with occlusions of the major intracranial vessels.

The occlusive disease of the cerebral arteries in NF has been found most often in children, in whom it has often been associated with cerebral infarction and has not been progressive. The occlusive lesions have been thought to be caused by intimal smooth muscle cell proliferation. Intracranial aneurysms (Tomsick et al. 1976) and arteriovenous malformations and aneurysms of cervical arteries have been described in patients with NF1 (Deans et al. 1982, Westacott et al. 1988, Schiewinck & Piepgras 1991, Hoffman et al. 1998). These lesions usually manifest in the fifth or sixth decade of life, and they are more common in female than male patients. The vertebral arteries are most commonly affected.

The generalized mesenchymal dysplasia in NF1 may cause structural weakness of the arterial wall and predispose the patient to aneurysm formation. (Deans et al. 1982). Mechanical factors (chiropractic manipulation, etc.) have also been thought to play a role in the formation of vertebral aneurysms. The primary weakness of the arterial wall in NF1 could lead to the development of an arteriovenous fistula through rupture of a preexisting aneurysm or direct rupture of the artery into adjacent veins.
2.6 Manifestations of the optic pathways and orbits in NF1

Optic pathways are commonly affected in patients with NF1. Lisch nodules or iris hamartomas occur in a majority of the patients, and they are commonly used as diagnostic markers of the disease. Optic gliomas, on the other hand, are the most common tumours in children with NF1. Plexiform neurofibromas also appear both intra- and extraorbitally. In patients with NF1, many other ophthalmologic lesions have been described, including choroidal hamartomas, prominent corneal nerves, iris heterochromia, secondary glaucoma due to infiltration of the angle by a neurofibroma that obstructs aqueous flow or maldevelopment of the anterior chamber eye, strabismus and neurofibromas of the conjunctiva and ciliary nerves. (Ragge et al. 1993). Combined hamartomas of the retina and retinal pigment epithelium and retinal capillary hemangiomas also occur. The lens is usually normal in patients with NF1 (Sippel et al. 2001).

Dural ectasia of the sheath of the optic nerve is a benign manifestation of NF1 (Lövblad et al. 1994, Doi et al. 1997), which can be clearly demonstrated with MRI as a dilatation of the perioptic dural sheath without tumorous involvement of the optic nerve. Hydrops of the optic sheath (Jinkins et al. 1987) is also described as a dilatation of the perioptic subarachnoid space caused by different pathologic conditions, such as tumours, trauma and inflammation, and the optic sheath may be thickened in, for example, inflammatory processes.

Dysplasia of the greater wing of the sphenoid bone may cause pulsating enophthalmos in NF1 (Savino et al. 1977), and exophthalmos has been reported to be caused by intraorbital tumors. Uveal malignant melanoma has been reported as a rare complication of NF1 (Antle et al. 1990). Enlargement of the eye globe with glaucoma has been reported in up to 50% of NF1 patients with ocular plexiform neurofibroma (Reed et al. 1986).

2.6.1 Anatomy and imaging of the optic pathways

From the retina, the visual pathways extend anteroposteriorly as the optic nerves, chiasm, optic tracts and optic radiations and terminate in the striate cortex on the medial aspect of the occipital lobe. The optic tracts are located at the posterolateral aspects of the chiasm. The lateral bundles of the optic tract end in the lateral geniculate body and contain the visual fibres. The axons from the lateral geniculate body run in the lateral wall of the occipital horn of the lateral ventricle, called the tapetum. These fibers terminate in the occipital cortex (Hollander et al. 1999).

Imaging of the optic pathways has usually been done by CT or MRI scanning, the latter of which has become the method of choice in the study of NF1. On CT scans, the intraorbital and prechiasmal intracranial and chiasmal parts of the pathway can be visualized, but the intracanalicular and posterior parts of the optic pathways are difficult to evaluate. On CT, the optic nerve sheath cannot be discerned from the nerve itself. Calcifications or bony changes can be seen better on CT than on MRI.

On T1- and T2-weighted MR images, the optic nerve appears similar in intensity to cerebral white matter. On T2-weighted images, the high signal intensity CSF is demon-
strated within the normal optic nerve sheath surrounding a string-like, low signal intensity structure representing the optic nerves. (Weber et al. 1996).

On conventional T2 images, the optic nerve and the surrounding CSF may be nearly isointense with orbital fat. The lacrimal gland is nearly isointense with the adjacent orbital fat and fat within the medullary cavity of the adjacent bone.

On conventional T1-weighted images, the high signal intensity of fat disturbs the visualization of the optic nerve as distinct from CSF and the dural sheath. The intracanalicular margins of the nerve are often indistinct because of the adjacent high signal intensities from bone marrow. The intraorbital muscles are poorly distinguishable from their fibrous sheaths, and the wall and contents of the globe contrast poorly with the adjacent structures. The chemical shift misintegration artifacts, are observed as bands of high and low intensity parallel to the long axis of the optic nerve sheath and muscles on the axial images, and above and below the nerve and muscle on coronal images. The fat suppression technique applied to similar T1 sequences results in better visualization of the optic nerve, muscle and lacrimal gland, due to the increased positive contrast between the optic nerve with low-intensity CNF, the nerve sheath and orbital fat. The chemical shift artifact is decreased, and the true anatomic borders of the anatomic structures are visualized (Simon et al. 1988).

The selection of the MR imaging sequence in the suprasellar and chiasmal regions is different at different strengths of the magnetic fields, because the crossover points, at which the chiasm and brain become isointense with CSF, vary.

2.6.2 Optic pathway gliomas

Gliomas of the optic pathways are among the most common tumours in patients with NF1. Histologically, they are classified as low-grade pilocytic astrocytomas (grade I). Although slowly growing and benign in nature, they are the most important cause of visual disturbance in patients with NF1. In some patients, more aggressive behaviour of gliomas has been observed, but spontaneous involution of the tumour has also been reported.

Although the association was reported earlier, optic gliomas were only considered as part of NF1 in 1940 (Mulvihill et al. 1990). They may affect any part of the visual pathway uni- or bilaterally and usually appear before the age of ten years. Kornreich et al. (2001) found the orbital optic nerve to be the most common site of involvement in NF1 patients A female preponderance of the tumour has been suggested (De Potter et al. 1995). Bilateral optic nerve tumours have been considered pathognomonic of NF1 (Chattel et al. 2001). Gliomas, however also appear unassociated with NF1. NF1 patients with optic gliomas have a tendency to develop a second primary neoplasm of the CNS (Sörensen et al.1986, Singhal et al. 2002). Kuenzle et al. (1994) found 52% of their NF children with optic gliomas to develop an additional cerebral tumour an average of four years after the diagnosis of the optic glioma.
2.6.2.1 Imaging of optic gliomas.

Because MRI has superior contrast resolution and multiplanar imaging capability, it has been the method of choice for evaluating especially the intracranial extent of optic glioma. High-resolution CT has been, for a long time, the best method for imaging the intraorbital contents, because most conventional orbital MR imaging strategies have some limitations related to fat, but imaging with the surface coil and fat suppression techniques has improved the visualization of intraorbital anatomic details (Holman et al. 1985, Albert et al. 1986, Brown et al. 1987, Atlas et al. 1988b, Simon et al. 1988).

For CT scans of the anterior optic pathway, the following criteria of optic glioma have been suggested by Byrd et al. (1978): 1 diffuse thickening of the intraorbital optic nerve, 2. fusiform enlargement of the optic nerve and 3. a discrete focal mass arising from the optic nerve or chiasm with moderate contrast enhancement. Small lesions may appear as fusiform widening of the optic nerve, but larger ones may be eccentric or multilobular. An optic nerve with a tumour may present as an elongated curving structure. The baseline density of smaller lesions is about the same as that of a normal optic nerve, but larger masses may present with higher density values. Enhancement after intravenous contrast administration has varied from imperceptible to moderate (Peyster et al. 1983). Byrd et al. (1978) reported the approximate Hounsfield numbers associated with optic nerve gliomas to be 28–35 HU in unenhanced and 40–55 HU in enhanced tumours. Calcification is seen occasionally. The optic nerve cannot be differentiated from the tumour mass. Enlargement of the optic canal can be seen if the tumour extends intracranially. Cyst formation due to necrosis has also been found in gliomas, and Jacobiec et al. (1984) found mottled radiolucencies within the tumours, correlating with the extensive mucin deposition that is highly distinctive for pilocytic astrocytomas.

Fletcher et al. (1986) described three diagnostic CT patterns for chiasmal gliomas: 1) tubular thickening of the optic nerve and chiasm, 2) suprasellar tumour with contiguous optic nerve expansion and 3) suprasellar tumour with optic tract involvement.

The MRI manifestations of optic gliomas are usually an increase in size, a mild to strong hyperintensity on T2- and proton density-weighted images and a hypointensity on T1-weighted images (Aoki et al. 1989). Enhancement after an intravenous injection of Gd-DTPA is markedly variable. The use of a fat suppression technique with enhancement was recommended by Hendrix et al. (1990) to improve the delineation of optic nerve lesions from fat and to differentiate nerve sheath meningiomas from optic nerve gliomas.

Gliomatous tissue has long T1 and T2 relaxation times due to its high water content, which causes it to appear bright on T2-weighted images and dark on T1-weighted images (Brodsky 1993). An optic nerve glioma associated with neurofibromatosis has a different histopathologic pattern of tumour growth compared to an isolated non-neurofibromatous optic glioma (Stern et al. 1980). The perineural arachnoid gliomatosis surrounding the central core of an optic nerve with cellular features of glioma has been shown to be characteristic of neurofibromatosis-associated orbital optic glioma (Brodsky 1983, Seifff et al. 1987, Imes & Hoyt 1991), and this causes the double signal on MR imaging: an outer signal that is indistinguishable from cerebrospinal fluid and a sharply demarcated inner signal of opposite intensity corresponding to the optic nerve.
Menor et al. (1991) found contrast enhancement to be absent or minimal in most cases with optochiasmal involvement; while marked enhancement was seen in cases of posterior optic pathway tumours.

The normal chiasm appears on MRI as smoothly contoured, homogeneous in texture, isodense with cerebral tissue and non-enhancing after intravenous contrast administration. Chiasmal gliomas are primarily either isodense or hyperdense with normal brain tissue and do not enhance, although contrast enhancement has been found occasionally. To visualize the chiasm, thin sections nearly parallel and perpendicular to the Reid base line are optimal, the optic nerves are best seen at an angle of –10° with respect to the Reid line, and the optic tracts are seen best at angles of 0–30°.

2.6.2.2 Occurrence and localization of optic gliomas

The occurrence, localization and development of optic pathway gliomas in NF1 have been subject to several imaging studies with CT and/or MRI. The findings of nine larger studies from 1984 to 2001 are presented in Table 2.

Optic pathway gliomas have been encountered in 14% to 36% of patients with NF1 (Huson & Hughes 1994, Listernick et al. 1989, De Potter et al. 1995). They have usually been diagnosed before school age, and often even earlier if the child has had ophthalmological symptoms. In their study of 33 NF1 patients with optic glioma, Listernick et al. (1994) found the mean age at diagnosis to be 5.3 years in children without symptoms versus 1.9 years in children with symptoms. Mean age at diagnosis varied from 4.2 to 16 years in the studies presented in Table 2. According to Listernick et al. (1994) and de Potter et al. (1995), optic gliomas are more common in females than in males, while Lewis et al. (1984) and Aoki et al. (1989) were unable to show any gender-related differences.

The localization and extent of optic gliomas have varied in different individuals with NF1. In the study of Menor et al. (1998) on 20 individuals affected by optic glioma, 10 patients showed unilateral optic nerve glioma (five with associated chiasmal glioma), five had bilateral optic nerve glioma (one also chiasmal glioma), five had chiasmal glioma only, and two patients had glioma of the chiasm and the optic radiation. In the study of Listernick et al. (1994), too, the optic nerves were more commonly affected than the chiasm, and unilateral affliction was more common. In 15/33 (45%) of the affected individuals the glioma was purely intraorbital. Duffner et al. (1989) paid special attention to the involvement of the hypothalamus, which was affected by glioma (together with chiasmal involvement) in 8 patients. This association was also noticed by van Es et al. (1996) in 3/7 NF1 patients with optic glioma.
Table 2. Occurrence, localization and follow-up of optic glioma in NF1 in previous studies.

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<td>53</td>
<td>47</td>
<td>43</td>
<td>38</td>
<td>176</td>
<td>50</td>
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<td>1–78</td>
<td>0.8–18</td>
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<td>10</td>
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<td>Mean age at diagnosis</td>
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<td>not reported</td>
<td>10/23</td>
<td>6/16</td>
<td>33/19</td>
<td>7/14</td>
<td>20/18</td>
<td>43</td>
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</tbody>
</table>

Sites of OG (pt’s affected)
- optic nerve
- optic nerve unilateral
- optic nerve bilateral
- optic nerve + chiasm
- chiasm only
- chiasm + hypothalamus
- optic nerve/chiasm + optic radiation
- introrbital only

Follow-up of optic glioma
- patients (n)
- mean follow-up time (y)
- progression
- unchanged
- regression

*Chiasm with or without optic nerve affliction. **All postchiasmal afflictions
2.6.2.3 Natural history of optic gliomas

The clinical course of optic gliomas is variable in different individuals. Gliomas may be asymptomatic and non-progressive, but they may also enlarge rapidly or even behave aggressively with leptomeningeal metastasis (Bruggers et al. 1991). About half of the patients with radiologically verified optic gliomas have had visual disturbances (Listernick et al. 1997).

In the three studies concerning mainly pediatric patients with NF1, referred to in the Table 2, most of the observed optic gliomas did not show evident progression. The mean follow-up time in the 7 patients of Aoki et al. (1989) was 1.8 years, and progression was only seen in one patient. Similarly, one of the 6 patients reported by Balestri et al. showed progression after a mean follow-up time of 2.6 years (1993). Two of the 26 children studied (7.7%) by Listernick et al. (1994) showed progression during a mean follow-up of 2.4 years.

Kuenzle et al. (1994) observed progression of optic glioma in three of 13 children with NF1 who had not been operated on. The mean duration of follow-up in their patient series of altogether 21 patients was 9.0 years. Deliganis et al. (1996), in their study on childhood optic gliomas, followed 16 children with NF1 for 10.2 years. Tumour progression was seen in five patients (31%). In the study of Schroder et al. (1999), 29 patients with NF1 and optic glioma, of whom 25 were children under 11 years of age, were followed for a mean of 6.5 years. The lesions remained stable in 11 children, but progression with substantial loss of vision was observed in 14 (56%). Grill et al. (2000), in their study of 51 symptomatic children with NF1, found out that 47% of the patients with progression showed this progression after the age of 6 years.

Optic gliomas in NF1 may also regress or show spontaneous involution in children. Brzowski et al. (1992) described spontaneous regression of optic glioma involving the left intracranial optic nerve and chiasm in a 23-month-old girl during follow-up for 32 months. Manfre et al. (1998) presented four NF1 children (aged 4 to 6 years) with spontaneous regression of presumed chiasmal glioma on repeated MRI. Reduction of size and normalization of the signal changes seen in chiasmal lesions were detected, and the previously found contrast enhancement also disappeared. Similar reports include those of Parazzini et al. (1995) on 4 children, Zuccoli et al. (1998) on a 3-year-old child after 9-month follow-up, Rossi et al. (1999) on two children aged 21 and 32 months after follow-up for 4 and 5 years, Gottschalk et al. (1999) on two children aged 1 y 11m and 3 y 2m with chiasmal/hypothalamic masses during follow-up for 12 months and 15 months, respectively, and Parsa et al. (2001) on three children aged 3 months, 3 years and 11 years, respectively. Schmandt (2000) also described spontaneous regression of a biopsy-proven hypothalamic/chiasmal low-grade astrocytoma in a child during follow-up for four years. The tumour first regressed, then progressed and was biopsied. After the biopsy, spontaneous regression was seen.
2.6.2.4 Clinical significance of optic gliomas

Although most optic gliomas are benign and grow slowly, they may lead to visual disturbances through pressure on or infiltration of the optic pathways. The most common disturbance is reduced vision, and abnormal pupillary function, optic atrophy, decreased colour vision and proptosis have also been reported. Endocrinological abnormalities, including precocious puberty and growth hormone deficiency, have been shown to be associated with optic glioma in some patients (Cnossen et al. 1997).

In the large series of Lewis et al. (1984), only 33% of the 33 patients with optic glioma had abnormal visual fields, and 20% had ophthalmoscopic evidence of optic atrophy. Two-thirds of the radiologically determined tumours were clinically silent, and this was valid for tumours of both the optic nerve and the chiasm. The presence of normal visual acuity, pupil function and healthy optic nerves in ophthalmoscopy did not exclude the presence of glioma in the anterior visual pathway.

The follow-up study of Schroder et al. (1999) on 29 patients with NF1 included neurological, ophthalmological, MRI and visual evoked potential (VEP) examinations. The lesions remained stable in 11 children, while progression resulting in substantial loss of vision was seen in 14. The children with unfavourable course had a lower age at diagnosis (3.2 vs. 5.8 years) and more frequently strabism, optic atrophy, visual field defects and involvement of the optic chiasm (11/14 vs. 3/11) than the children with a stable condition. Optic gliomas that become symptomatic in early childhood (under the age of 6 years) grow rapidly and require frequent ophthalmologic assessments and MRI scanning. Tumours diagnosed in late childhood (after the age of 6) do not progress, allowing gradual prolongation of the intervals between ophthalmological investigations. – Grill et al. (2000) found that the children with symptomatic optic gliomas had progressive tumours later during follow–up (47% after the age of 6 years) compared to the non-NF-children, and that they also had more often proptosis and infiltrating tumours, but less often nystagmus or increased intracranial pressure. In the less symptomatic group, progression occurred more often in the non-NF children.

In 43 pediatric patients with NF1 and optic pathway gliomas (Balcer et al. 2001) involvement of the optic tracts and other postchiasmal structures at tumour diagnosis was associated with a significantly higher probability of visual acuity loss. Visual loss was noted in 20/43 patients (47%) at a median age of 4 years, but three patients developed visual acuity loss in adolescence. Fletcher et al.’s (1986) study of chiasmal gliomas, including eight with NF1, showed a poor correlation between tumour enlargement and progression of visual loss. Chiasmal and retrochiasmal tumours appear to have a more aggressive course and a poorer prognosis based on the findings of Pomeranz et al. (1987).

In the study of Chatall et al. (2001), 11 of the 14 NF1 patients with optic glioma did not have specific neurological symptoms, two had decreased visual acuity, and one had exophthalmos and papilloedema. VEPs were abnormal in all cases.

In the Northern Finnish series of Mustonen et al. (1997), gliomas of the optic nerve and/or chiasm were seen in 23 (24%) of the 96 NF1 patients studied with CT and/or MRI, fourteen (61%) of them being children. Reduced visual acuity and visual field defects were detected unilaterally in three and bilaterally in eight cases. Follow-up of 17 patients without therapy for 1–14 years (median 5.3 years) did not reveal any progression clinically or neuro-ophthalmologically.
2.6.2.5 Differential diagnosis of optic gliomas

Both neoplastic and nonneoplastic lesions need to be taken into consideration in differential diagnosis of optic nerve enlargement. Neoplastic lesions include, in addition to optic glioma, meningioma, neurinoma, hemangioblastoma, metastatic lesions and leukemia, and non-neoplastic conditions include increased intracranial pressure, optic neuritis, Graves’ disease, orbital pseudotumour, toxoplasmosis, tuberculosis, sarcoidosis, central retinal vein occlusion and traumatic hematoma of the optic nerve sheath (Peyster et al. 1983).

Meningiomas of the optic nerve sheath are seen most often in middle-aged women. In children, they are more common than intracranial meningiomas, and especially bilateral optic meningiomas are usually associated with neurofibromatosis (Byrd et al. 1978, Peyster et al. 1983), but bilateral meningiomas in children without neurofibromatosis have also been described (Jacobiec et al. 1984). In them, the enlargement of the nerve may be fusiform, but uniform thickening of the sheath is more common. (Peyster et al. 1983, Johns et al. 1984). The normal optic nerve running through the tumour is often visualized as a "tram track" pattern of the low-density nerve surrounded by the higher-density tumour on axial views (Daniels et al. 1982, Peyster et al. 1983, Johns et al. 1984). The "tram track" sign is not to be confused with the small degree of optic nerve dural enhancement normally seen after infusion of contrast medium (Johns et al. 1984). Calcification is more commonly seen in meningiomas than in gliomas. Optic nerve sheath meningiomas enhance with contrast, although less intensely than intracranial meningiomas. Optic canal widening and hyperostosis of adjacent bones may be seen (Daniels et al. 1982, Peyster et al. 1983). Arachnoid hyperlasia is a meningeal response, which is often seen in association with gliomas of the anterior visual pathways, and which may be falsely interpreted as a primary optic nerve meningioma (Cooling & Wright 1979).

Optic neuritis is usually idiopathic, but may be associated with other inflammatory diseases, and is often a manifestation of multiple sclerosis. Enlargement and contrast enhancement of the optic nerve can occasionally be seen secondary to edema and increased vascular permeability. The changes are reversible (Howard et al. 1980, Peyster et al. 1983). Optic nerve/sheath enlargement may be seen in patients with Graves’ disease, but these findings occur only during the advanced stages, when muscle enlargement is readily identified with CT (Peyster et al. 1983).

Orbital pseudotumour is an idiopathic disease that may involve any of the intraorbital structures. Pathologically, a nonspecific infiltrate is seen, and on CT, enlargement and contrast enhancement of the optic nerve/sheath may be visible (Peyster et al. 1983).

Toxoplasmosis, tuberculosis, sarcoidosis, central retinal vein occlusion and traumatic hematoma may also cause optic nerve/sheath enlargement visible on CT scans (Som et al. 1982, Peyster et al. 1983). Rare intraneural lesions, such as von Hippel’s tumour, juvenile xanthogranuloma and metastatic carcinomatosis of the meninges, have also been described (Jacobiec et al. 1984).

The optic subarachnoid space may dilate (optic hydrops) uni- or bilaterally due to various diseases involving the orbit, optic canal, sella and paresellar regions (Doi et al. 1997, Jinkins 1987). In some cases, such as orbital inflammation and sheath tumours, the optic sheath is also thickened. On CT, a clearly enlarged margin of hypodensity is seen between the sheath and the nerve, indicating dilation of the perioptic subarachnoid space. The
optic hydrops seems to be limited to either malignant or aggressive-benign lesions of the orbit and parasellar regions. This phenomenon has not been found in benign, slowly progressing conditions, such as osteopetrosis with optic canal constriction. Optic meningocoele is a condition of primary thickening and dilatation of the optic nerve sheath, and dural ectasia of the optic nerve sheath is considered appropriate for describing the condition of dilatation of the optic nerve sheath alone (Doi et al. 1997).

### 2.6.3 Orbital plexiform neurofibromas

Plexiform neurofibromas are the most common orbital masses found in patients with NF1, and the most severe involvement of the orbit tends to occur in the youngest patients (Reed et al. 1986). Plexiform neurofibromas usually arise in the lateral portion of the upper eyelid, and are present congenitally although the signs in a newborn are subtle. 25% of the tumours of the lids extend intraorbitally (Sippel 2001). The most serious symptom is the development of glaucoma in the ipsilateral eye in up to 50% of the affected patients. Both nodular and plexiform neurofibromas may arise in the orbit. Nodular neurofibromas are less strongly associated with NF1 than plexiform neurofibromas. In the orbit, nodular neurofibromas arise from the ophthalmic division of the trigeminal nerve, they are not encapsulated but well circumscribed. They usually present in the superior orbit, most commonly in young to middle-aged adults. Schwannomas are rare. The optic nerve, being part of the central nervous system, cannot be affected by plexiform neurofibromas.

### 2.7 Bony lesions of the skull in NF1

Cranial changes in NF1 are uncommon as compared to involvement of the axial and peripheral skeleton (Davidson 1966). These changes have been divided into three classes (Galanski & Benz 1978): 1. mesodermal dysplastic changes (sphenoid wing dysplasias, bone defects along sutures, dysplasias of temporal and facial bones), 2. secondary changes (enlargement of the optic foramina, orbits and internal acoustic canals) and 3. non-specific changes (macrocephalia).

Although rare, *sphenoid wing dysplasia* has been considered the most characteristic bony change of the skull bones in NF1, and it manifests as hypo- or aplasia of the greater wing of the sphenoid bone and as hypoplasia and upward displacement of the lesser wing of the bone. The dysplasia can be seen on a plain film as an "empty orbit", and it may lead to pulsating exophthalmos. Hunt and Pugh (1961) found 13 cases (7%) of such dysplasia in 192 patients with peripheral neurofibromatosis (NF1). Gardeur et al. (1983) found sphenoid wing dysplasias in 6 patients (8%) in a group of 77 patients, including both NF1 and NF2. Lewis et al. (1984) detected dysplasia of sphenoid bones, orbits or facial bones in 4.6% of 127 patients with NF 1 on CT.

*Sutural defects* are most common in the left lambdoid suture (Holt 1978). Sutural defects may be quite large, and they are irregular in shape but sharply demarcated, and the
rims are thin and without sclerosis. Sutural defects are usually not associated with overlying cutaneous or underlying intracranial tumours (Galanski & Benz 1978).

Dysplasias of facial bones are nonspecific, and they occur most often in the vertical part of the mandible and in the zygomatic bones and arches (Hunt and Pugh 1961). Asymmetry of the skull and basilar impression have also been seen in neurofibromatosis (Hunt & Pugh 1961, Gardeur et al. 1983). Maki et al. (1981) found remarkable thickening of the skull in their CT study on Japanese patients with neurofibromatous changes in the face, head and neck.

Secondary bony changes have been seen in association with tumours of the optic nerve and chiasm, which may cause excavation of the chiasmal sulcus with erosion of the tuberculum sellae. Arterial aneurysms of the basal brain arteries may also occur in NF and cause sellar erosion. Intraorbital plexiform neurofibromas may similarly cause erosion and enlargement of the orbit. Neurofibromas may further cause widening of the foramen magnum, and in NF1 patients, tumours of even other cerebral nerves may rarely cause enlargement of their foramina in the skull.

2.8 Macrocephaly in NF1

Macrocephaly, which is relatively common, has been considered a nonspecific finding in NF1. Weichert et al. (1973) were the first to suggest that macrocranium may be a manifestation of neurofibromatosis. They measured the breadth, height, length and circumference of the skull on the radiographs of 34 NF children. Cases with intracranial tumours or hydrocephalus were excluded. Eight out of 27 patients (30%) had macrocranium by virtue of their head circumference, and 18 out of 24 (75%) based on Haas’ skull measurement criteria (Haas 1952).

For practical purposes, macrocephaly may be defined as a condition where head circumference is above the 97th percentile (> + 2 SD) for age and sex. Riccardi et al. (1981) found the mean head circumference of their NF1 patients to be around the 70th percentile, the median to be at the 75th centile, and 27% of the patients to have a head circumference above the 97th centile. They suggested that macrocephaly in NF1 has a postnatal onset because, in children between two and six years of age, head circumference increased from the 48th to the 77th percentile, at which level it remained in all the older patients. In a population study of 135 NF1 patients, Huson et al. (1988) found macrocephaly in 52/115 (45%) individuals with NF1. Patients with CNS tumours, aqueductal stenosis and large facial plexiform neurofibromas had been excluded. In the Northern Finnish study of Pöyhönen (2000), clinically verified macrocephaly was present in 47/164 patients (29%), being more common in males (36%) than in females (22%). Patients with hydrocephalus were excluded.

The etiology and pathogenesis of macrocranium and macroencephaly in NF1 are not known, if tumours and aqueductal stenosis are excluded. They have been suggested to be secondary to increased glial cell production, which causes a symmetric or asymmetric increase in brain size (Holt 1978, White et al. 1986, Latchaw 1991).
2.8.1 Morphometric studies

In order to understand the process of exceptional head growth, the roles of the different parts of the brain have been evaluated morphometrically in several studies. Holt & Kuhns (1978) found that 44% of 52 neurofibromatosis patients had cranial capacities over the 95th percentile (70% were above 50th percentile). Four patients above the 95th percentile had normal pneumoencephalograms and angiograms, indicating that the cause of macrocranium might be macrencephaly rather than expansion of the CNF spaces. Volumetric measurement of the sella turcica in 27 patients showed idiopathic enlargement of the sella to be rare in neurofibromatosis.

DiMario et al. (1993) studied selected anthropometric measurements performed on plain skull roentgenograms (29 measurements, 9 qualitative assessments and 3 area/volume calculations), to find out whether these would be useful in the diagnosis of NF1. They compared the findings of 14 patients with NF1, 15 with probable NF1 and 29 healthy controls, both children and adults. Both diagnosed NF1 and probable NF1 patients could be distinguished from the controls by measurements of the height and depth of the sella turcica and the width, length, height and volume of the skull.

Mott et al. (1996) measured the midsagittal area of corpus callosum and brain on T1-weighted MR images of 14 NF1 children and their unaffected siblings. They found that the NF1 children with macrencephaly had an exceptionally large corpus callosum, which was most prominent in the midcallosal region. Dubovsky et al. (2001) also measured the surface area of the corpus callosum and the intracranial skull surface on midsagittal T1-weighted MR images of 43 children with NF1 and 43 healthy control subjects. They found a statistically significant increase in the mean corpus callosum surface area in pediatric patients with NF1. The large corpus callosum was never an isolated finding in NF1 patients; all of these patients also had the characteristic T2 signal abnormalities. None of the patients had abnormal signals within the corpus callosum. The midsagittal intracranial skull surface was also significantly increased. Kayl et al. (2000) also showed in their MRI study of 34 children with NF1 that the patients had a significantly larger total corpus callosum area and significantly larger regional measurements in 3/7 areas than the controls.

The increased size of the corpus callosum was further verified by Moore et al. (2000) in 52 NF1 patients.

Said et al. (1996) measured the volumes of cerebral grey and white matter in 22 children with NF1 and 20 controls by using axial brain MRI scans. The overall cerebral hemisphere volume was greater in patients than in controls, and this increase was thought to be primarily due to an increase in the white matter volume, particularly in girls. It was suggested that macrencephaly in NF1 is largely a result of increased white matter volume, possibly due to glial cell proliferation. In a subsequent study on 34 NF1 children and 35 controls (Greenwood et al. 1997), the increase in white matter volume was shown to be greater than that in grey matter volume (23% vs. 10%) in the children with NF1 as compared to the controls. Moore et al. (2000) in their study of 52 children and adults with NF1 concluded that especially the grey matter contributed to the increase in brain volume. This was more prominent in younger subjects. Steen et al. (2001), on the other hand, found macrocephaly to be associated specifically with enlargement of white matter in their study of 18 asymptomatic children with NF1.
In a morphometric study of 27 NF1 children and 43 age- and sex-matched controls with MRI, DiMario et al. (1999) evaluated several ventricular and brain parenchymal parameters. Significant differences between the two groups were observed for 6 of the 24 measures. Patients with NF1 had significantly larger values of mean bicaudate width, bictrial width and biparietal diameter than the controls. They also had significantly increased iter measures and antero-posterior dimensions of the descending sigmoid sinus, and an age-specific increase in brainstem height was observed in NF1 patients. The authors concluded that patients with NF1 experience dynamic changes in brain morphometry, resulting in predominant lateral volume expansion of the supratentorial compartment and an increasing rate of brainstem growth as they age. No significant differences were seen on any measure in a comparison of NF1 patients with and without T2 hyperintense lesions of the brain.

2.8.2 Significance of macrocephaly

Macrocephaly in NF1 has previously been considered an incidental finding with no correlation with impaired intelligence, seizures or electroencephalographic changes (Rubenstein et al. 1985). More recent studies have shown that some features of NF1 could be related to quantitative differences in brain morphology. Said et al. (1996) reported a significant relationship between right hemisphere grey matter volume and visuo-spatial and developmental performance in NF1 patients, with greater grey matter volume signifying better performance. In the study of Moore et al. (2000), 52 children and adolescents with NF1 were studied both neuroanatomically and neuropsychologically. It was found out that the grey matter volume was related to the degree of learning disability, and that diminished academic performance and visuo-spatial and motor skills were associated with a greater regional corpus callosum size. Kayl et al. (2000) in their study of corpus callosum morphology and the attention-deficit hyperactivity disorder in children with NF1, noticed that increased severity of attention problems was associated with smaller total callosal areas. Cutting et al. (2000) did not find a close relationship between the impairment of cognitive functions and macrocephaly. The macrocephalic patients, however, showed significant verbal impairment relative to the normocephalic patients.

The correlation of macrocephaly with T2 hyperintense lesions has also been considered. In the series of DiMario et al. (1999), 15 of the 27 NF1 patients showed T2 hyperintense lesions, but no significant differences were seen on any brain measures. Cutting et al. (2000) also came to the conclusion that macrocephaly does not appear to be related to the presence or absence of T2 hyperintense lesions in NF1.

2.9 Spinal manifestations in NF1

Lesions of the spine and related structures are quite common in NF1 (Table 3). The presence of osseous, spinal nerve and cord lesions in NF1 have been known for a long time, and plain radiographs have been sufficient to visualize many of the skeletal changes. CT
and MRI have, however, yielded more reliable information about soft tissue tumours and CNF spaces and their relations to adjacent structures.

**Table 3. Occurrence, localization and follow-up of spinal lesions in NF1 in previous studies.**

<table>
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<tr>
<td>Age range (y)</td>
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<td>6-60</td>
<td>children +adults</td>
<td>5-56</td>
<td>0.9-18</td>
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<tr>
<td>Mean age</td>
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<td>not reported</td>
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<td>Patients with neurofibromas (n/%)</td>
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<td>15/38</td>
<td>20/10</td>
<td>35/65</td>
<td>7/13</td>
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<td>Sites of neurofibromas (n)</td>
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<tr>
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<tr>
<td>patients</td>
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<tr>
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<td>no progression</td>
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<td>10</td>
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* (1) lateral meningocele

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### 2.9.1 Lesions of the bony spine

Skeletal changes have been seen in 51 to 71 % of NF1 patients. (Casselman & Mandell 1979). They can be classified as: 1) bony erosions caused by a tumour, 2) osteomalacia from a genetic tubular defect, 3) congenital abnormalities, such as macrocranium, and 4) mesodermal dysplasias, such as pseudoarthrosis of the extremities, local gigantism and scoliosis.

Most commonly, bony abnormalities occur in the spine (Yaghmai 1986). Absence and hypoplasia of the vertebral pedicles, hypoplasia of the bodies, spinous and transverse processes of the vertebrae and posterior and anterior scalloping of the vertebral bodies have been considered as primary hypoplastic changes due to mesodermal hypoplasia. Scoliosis and lateral meningoceles are secondary to hypoplastic bone changes. The overgrowth of the pedicles and arches present hyperplastic changes due to mesodermal dysplasia, and mixed hypo- and hyperplastic forms may occur.

Intradural, extradural and paravertebral nerve sheath tumours may cause, as a pressure effect, widening of the intervertebral foramina and the spinal canal, and erosion of bones
and displacement of adjacent organs. Malignant schwannomas and metastatic lesions may cause erosion of adjacent bones.

Some degree of abnormal spinal curvature has been reported in 10-41% of NF patients (Klatte et al. 1976, Holt 1978). More than 80% of these changes appear before the age of 16 years, the majority between 11 and 16 years of age. A short segment of angular scoliosis with five or fewer vertebrae primarily involved, usually located in the lower thoracic region, has been thought to be diagnostic of the disease. Concurrent local dysplastic changes in individual vertebrae (scallop
ing, hypoplasia of pedicles, etc.) may be found, and the presence of adjacent "twisted-ribbon" ribs is also said to be diagnostic (Holt 1978).

_Kyphosis_ of varying degrees is seen in association with scoliosis, and kyphosis has been considered a poor prognostic sign because of its tendency to rapid progression and resistance to all types of treatment. Isolated thoracic or lumbar kyphosis in neurofibromatosis is not a usual finding (Holt 1978). Kyphoscoliosis occurs in at least 2% of NF1 patients (Riccardi 1981). Winter et al. (1979) found 80 of their 102 NF1 patients with vertebral deformities to have abnormal curvatures of the spine with specific dystrophic changes in the vertebrae and ribs. 31 of the patients had kyphoscoliosis. The associated dystrophic changes and adjacent soft tissue neurofibromas were found to be highly significant for prognosis and management. Spinal cord or cauda equina compression was noted in 16 patients. In the study group of Egelhoff et al. (1992) (Table 3), 16 of the 23 NF1 patients studied presented with spinal bony abnormalities.

The etiology of kyphoscoliosis is not known. Neurofibromatous tissue is not usually found at the site of the vertebral anomaly, but dural ectasia associated with kyphoscoliosis is always seen in these patients (Klatte et al. 1976).

Yong-Hing et al. (1979) found cervical spine abnormalities in seventeen (30%) out of 56 neurofibromatosis patients with a mean age of 14 years. Four of them had abnormalities of the bones (enlarged foramina, dysplasia or scalloping of vertebral bodies), while thirteen had abnormalities of alignment. Cervical abnormalities occurred more often in patients with thoracic and thoraco-lumbar kyphoscoliosis than in ones with scoliosis only. Seven patients were asymptomatic.

### 2.9.2 Dural ectasias and meningocele

Dural ectasia with enlargement of the spinal canal is also a relatively common finding in neurofibromatosis. Egelhoff et al. (1992) found dural ectasia in three out of 28 patients in their study. Dural ectasia may be localized, or, more often, several segments of the spine may be involved. It is most commonly found in the lumbar area, but also appears in the lower thoracic region (Baltzell et al. 1974). Increased interpediculate distance, thinning of pedicles and pedicular clefts may be found in association with dural ectasia (Braffman & Naidich 1994). On plain films, dural ectasia can be suspected on the basis of vertebral scalloping or concavity of vertebral bodies. Vertebral scalloping may also be seen in connection with other disorders, such as the Marfan syndrome, the Ehlers-Danlos syndrome, long-standing communicating hydrocephalus and slow-growing intraspinal masses (Klatte et al. 1976).
The cause of dural ectasia is possibly a congenital weakness of the dura, in which case the constant pulsation of cerebrospinal fluid causes progressive enlargement of the dural sac with resultant scalloping of the posterior portions of the vertebral bodies and erosion of the pedicles (Klatte et al. 1976, Casselman & Mandell 1979). Another explanation for scalloping has been thought to be primary bone dysplasia, which results in a softened, weakened centrum, which is slowly eroded by normal pulsations of cerebrospinal fluid. A combined effect of the two mechanisms has also been suggested. Lateral and anterior scalloping of the vertebral bodies can also be seen in patients with NF (Casselman & Mandell 1979). Vertebral scalloping may also be caused by adjacent neurofibromas, but the typical scalloping caused by dural ectasia is hardly ever associated with a tumour. Myelography, CT and MRI can be used to confirm dural ectasia rather than a tumour as the cause of vertebral scalloping. Schonauer et al. (2000) presented in their report on two NF 1 patients with lumbosacral dural ectasia that the dura in the area of the ectasia is extremely thin and fragile and predisposes surgical patients to high morbidity.

Saccular protrusion of the meninges (meningocele, arachnoid cyst) along the course of the nerve roots through the intervertebral foramina or eroded vertebral has been described in patients with NF1 (Egelhoff et al. 1992, Braffman & Naidich 1994, Drevelengas & Kalaitzoglou 1995). The most commonly involved region is the thoracic spine, where the meningocele displaces the pleura and forms a posterior mediastinal mass called intrathoracic or lateral meningocele. Lumbar meningocele has also been described (Drevelengas & Kalaitzoglou 1995).

Intrathoracic meningoceles with neurofibromatosis are usually lateral or anterolateral in relation to the vertebral column, in contrast to the posterior meningoceles associated with spinal dysraphism (Nakasu et al. 1991). 85% of thoracic meningoceles have been associated with neurofibromatosis, and most of them are asymptomatic and small, accidental findings on chest radiograms (Erkulwratr 1979). They may manifest at any age, but are most commonly found in middle-aged patients (Klatte et al. 1976). Both dural and vertebral dysplasias have been thought to contribute to the formation of meningoceles. Rupture of the meningocele is very rare (Drevelengas & Kalaitzoglou 1995).

CT myelography demonstrates a cystic lesion freely communicating with the thecal sac and water-soluble contrast medium passing into the meningeal protrusion. CT also demonstrates well the associated bony abnormalities and tumours. MRI is superior for assessing soft tissue lesions. On MR images, a meningocele has the same intensity as cerebrospinal fluid. Cardiac-gated cine MRI demonstrates pulsatile signal changes in the cyst and CSF (Drevelengas & Kalaitzoglou 1995).

### 2.9.3 Neurofibromas

The spinal nerve sheath tumours seen in NF1 patients are benign neurofibromas (Halliday et al. 1991). They consist of fibroblasts, nerve sheaths and nerve cells. The nerve cells are incorporated into the tumour mass, which complicates surgical removal of the tumour. The spinal nerve root neurofibromas in NF 1 have been generally considered asymptomatic (Mapstone 1992). Neurofibromas account for 23% of all spinal tumors in NF and sporadic cases (Levy et al. 1986), and multiple spinal neurofibromas are often a
Malignant nerve sheath tumours are uncommon, but a sudden increase in size may be a sign of malignant change. Malignant degeneration is most common in multiple lesions.

Fusiform neurofibromas of spinal nerves are usually bilateral, extend to the branch fibers of the nerve and exceed 30 cm in length. They are seen on CT scans as tumours of low attenuation with areas of higher density, which enhance with intravenous contrast medium. These tumours have an endoneural myxoid matrix, which represents the unenhanced areas on CT (Yaghmai 1986). Varma et al. (1992) reviewed retrospectively the MR images of 32 histologically proven extracranial nerve sheath tumours, with 12 patients having NF1. On T1-weighted images, the tumours were isointense or slightly hyperintense compared to muscle, and on T2 images and enhanced T1 images, a target pattern with a peripheral hyperintense rim and central low intensity was seen in 52% of the benign tumours, but not in the malignant ones. This pattern corresponded histologically to peripheral myxomatous tissue and central fibrocollagenous tissue, and the pattern was absent in lesions with cystic, hemorrhagic or necrotic changes, which were hyperintense and variably inhomogeneous on T2-weighted images. MRI did not distinguish neurinomas from schwannomas, and benign tumours may mimic malignant tumours whenever cystic, necrotic or hemorrhagic changes are present. The target pattern together with the localisation of the tumours may facilitate differential diagnosis.

Benign nerve sheath tumours usually have intradural extramedullary location. They may extend extradurally and have a dumb-bell configuration through the intervertebral foramen in as many as half of the cases. Individual nerves may be involved by solitary tumours, or multiple nerves may be involved in a plexiform fashion. The tumours are usually multiple, appear at different levels and show different stages of growth. They appear more frequently in the second and third decades of life, and the cervical and thoracic segments are primarily affected (Tatagiba et al. 1994). The distribution of intradural extramedullary spinal nerve sheath tumours has been found to be relatively equal throughout the spine. Intramedullary neurofibromas are unusual (Egelhoff et al. 1992).

Thakkar et al. (1999; see Table 3) found on MRI spinal tumours in 35 of their 54 patients with NF1 aged 5-56 years. Intramedullary tumours were seen in 3 (6%), intraspinal extramedullary tumors in 18 (33%) and intraforaminal tumours in 31 (57%) of the patients. 24 of the 54 patients had such symptoms as sensory impairment or paralysis. Altogether 23 (96%) of the symptomatic patients and 12 (40%) of the 30 asymptomatic ones had spinal tumours. The cervical, thoracic and lumbar segments were similarly affected. 12 patients were operated on, and all extramedullary intraspinal tumours proved to be neurofibromas, while one patient had a thoracic intramedullary pilocytic astrocytoma.

In the MRI study of 28 NF1 patients (Egelhoff et al. 1992), spinal intradural extramedullary neurofibromas predominantly in the lumbar spine were found in 5 patients, one NF1 patient had cervical extradural neurofibromas, and there were four cases of intramedullary involvement (a cervical low-grade astrocytoma in one, a widened cord in two and a nonhomogeneous signal in one case). Ravegnani et al. (1993) had found intradural extramedullary spinal tumours in 20% of the 145 NF1 children they studied, 45% of whom were asymptomatic at the time of diagnosis. Fera et al. (1995) found on MRI paraspinal neurofibromas in 15 (38%) out of 38 NF1 patients, of whom 9 were asymptomatic. The size and number of the tumours varied, and very large tumours and wide-
spread bilateral spinal nerve involvement were also found. In the large patient series of Barbo et al. (1998), only three patients had abnormal medullary findings suggesting intramedullary disease. Khong et al. (2003) found spinal neurofibromas in 13.2% of 53 symptomless children with NF1 who underwent MRI. The tumours were located in the thoracic and lumbar areas, no cervical lesions were detected, and no intramedullary tumours were found. Three children had lateral meningoceles, and 72% had scoliosis. Follow-up was available for ten patients, but no progression of the lesions was seen.

Differential diagnosis of neurofibromas includes meningeomas and, especially in children, subarachnoidal metastases of intracranial malignant tumours, including medulloblastoma, ependymoma, primitive neuroectodermal tumour and malignant gliomas. In adults, melanoma and carcinoma of the lung may also metastasize into the subarachnoid space. Epidural metastases are most often due to lung and breast carcinoma and lymphoma, and spinal bone metastasis to carcinoma of the lung, breast, prostate and thyroid or lymphoma (Zimmerman & Bilaniuk 1988).

The patient’s age and sex and the location and multiplicity of the lesions are helpful in differential diagnosis.

**2.9.4 Spinal nerve plexiform neurofibromas**

Plexiform neurofibromas may involve long segments of the spinal nerves and extend into the spinal cord. These plexiform neurofibromas have a potential for malignant degeneration (Huson & Hughes 1994). Less than 5% of NF1 patients develop neurofibrosarcomas, which are often the major cause of death in NF1. In most instances, malignant progression of the fibroblast component appears to be responsible for the development of malignancy, and molecular genetic studies suggest that inactivation of the p53 tumour suppressor gene is a critical factor in the sarcomatous progression of neurofibromas.

**2.9.5 Intramedullary tumours**

Intramedullary tumours are uncommon in NF1. In the study of Egelhoff et al. (1992), four of the 28 NF1 patients had intramedullary manifestations on MRI. A low-grade astrocytoma was detected in one, a widened cord in two and an inhomogeneous signal in one. Fera et al. (1995) found one patient with intramedullary astrocytoma among their 38 NF1 patients. In Thakkar et al.’s study (1999), 3 of the 54 patients scanned with MRI had an intramedullary tumour, one a proven astrocytoma. Khong et al. (2003) found no spinal tumours in 53 symptomless children with NF1 examined with MRI. 95% of all intramedullary tumours are gliomas, which account for 20-25% of the tumours involving the spinal cord and canal. Approximately 65% of intramedullary glial tumours are ependymomas, 30% astrocytomas and 3% oligodendrogliomas. Cervical and thoracic intramedullary ependymomas are not distinguishable from astrocytomas in myelography, intrathecally enhanced CT, intravenously enhanced CT or MR imaging (Zimmerman & Bilaniuk 1988).
2.9.6 Other spinal manifestations

Syringomyelia and hydromyelia in connection with NF1 have been reported. Heffner (1969) presented a patient with the classic symptoms of NF1 and hydromyelia, but without spinal tumours. According to Mulvihill (1990), syringomyelia is probably secondary to an intramedullary tumour or tumorous compression of the spinal cord rather than a primary defect.

Dysraphia of the spinal cord between the third and seventh thoracic vertebrae has been reported (Baltzell et al. 1974). According to the authors, the T3-7 segment is the one most commonly involved in NF1 patients with scoliosis and meningoceles. T2 hyperintense lesions of the cord were reported in some NF1 patients by Katz and Quenser (1989).

2.9.7 Familial spinal neurofibromatosis (FSNF)

The possible existence of a special subtype of neurofibromatosis, familial spinal neurofibromatosis, was already speculated on by Mulvihill (1990). Weinstock et al. (1995) presented eight patients with multiple spinal and peripheral tumours, and none of them met the NIH criteria for NF1 or NF2. MRI examinations of all of these eight patients showed intradural extramedullary tumours: seven had multiple spinal cord tumours and four had evidence of cranial nerve tumours. No vestibular schwannomas were present. Family history was positive for a similar distinctive type of neurofibromatosis in five cases. Pulst et al. (1991) described two families with spinal neurofibromas, with café-au-lait spots in four generations in one family, and only spinal neurofibromas in two generations in the second family. Other signs of NF1 or NF2 were absent, and no brain lesions were found on CT or MRI examinations. One individual in both families developed a neurofibrosarcoma. Using genetic linkage analysis with polymorphic DNA-markers, the authors were able to demonstrate that, in the first family, the phenotype was linked to the NF1 gene, whereas no linkage to either the NF1 or the NF2 gene was seen in the second family.

Ars et al. (1998) also reported a three-generation family with five members affected by spinal neurofibromatosis. All the affected members had multiple spinal neurofibromas at all levels of the spine and café-au-lait macules, one had cutaneous NF, and some members had other signs of NF1. Genetic analysis of this family revealed a mutation in the NF1 gene. Kaufmann et al. (2001) presented spinal neurofibromatosis without café-au-lait macules in two families with null mutations of the NF1 gene. In Northern Finland, a three-generation family with familial spinal neurofibromatosis has also been reported (Pöyhönen et al. 1997).
3 Aims of the study

The purpose of the present study was to evaluate radiologically the lesions of the head and spine in patients with neurofibromatosis (NF1) in a population-based Northern Finnish NF1 patient and family series. The investigations included both CT and MRI scanning of patients at different ages. Specifically, the study aimed:

1. to evaluate the types and extent of the lesions of the brain, optic pathways and spine in NF1 patients,
2. to evaluate the development and changes of the lesions of the brain, optic pathways and spine over time,
3. to evaluate macrocephaly and its association with the other CNS changes seen in patients with NF1.
4 Patients and methods

4.1 Patients

The patients examined radiologically (n=125) belonged to a larger group of NF1 patients (n=197) referred for a clinical and genetic analysis of NF in Northern Finland up till the end of the year 1996 (Pöyhönen 1999). The patients came from the catchment area of Oulu University Hospital, which comprises the provinces of Lapland and Northern Ostrobothnia and the northernmost parts of the province of Western Finland (altogether ca. 730 000 inhabitants). The study subjects had been systematically traced from amongst the patients seen in the departments of Oulu University Hospital and in the four central hospitals within the study area, through inquiries presented to physicians of different specialties in the area and by reviewing hospital records. Many of them had been identified from among the close relatives of previously known NF1 patients at the Department of Clinical Genetics, where the clinical evaluation of these patients had been done during the years 1989 to 1996. The clinical evaluation of most patients had included an examination by a clinical geneticist, neuro-ophthalmologist, neurologist or pediatric neurologist.

Full clinical data were available for 164 patients who fulfilled the diagnostic criteria of NF1 (NIH Consensus Development Conference 1988; see page 15). 125 (90%) of the 164 NF1 patients had undergone either CT examinations (since 1980) and/or MRI (since 1990) of the central nervous system or were examined by the author for this study during the years 1994 to 2000. All the imaging findings were analyzed by the author, and the hospital records were reviewed for clinical data. With a few exceptions, the radiological examinations had been done at the Department of Radiology of Oulu University Hospital. Imaging studies either were not available or could not be performed in 39 cases. The neuroradiological examinations were done as part of the clinical evaluation of the patients and their affected relatives after informed consent from the patient and, in the case of children, their parents. The study was approved by the ethical committee of the Medical Faculty of the University of Oulu.

The 125 patients belonged to 100 families, of which 21 had NF1 in two generations and 2 in three generations. Two twin pairs were concordant for NF1, and two twin pairs were discordant for the disease. 58 (46%) of the studied patients were female and 67
(54%) male. The mothers of three NF1 patients suffered from segmental neurofibromatosis. 59 of the patients were children (aged under 18 years) at time of the initial CT/MRI scanning, while 66 were adults. The mean age of the radiologically examined patients was 23.6 years with a range of 0.2 to 66.4 years.

59 patients (47%) had inherited the disease from one of their parents, and 31 (53%) of them were female and 28 (47%) male. In 66 patients (53%) the disease was considered to represent new mutations.

4.2 Radiologic methods

4.2.1 Computed tomography (CT)

The CT examinations were performed variably with four sets of equipment: Somatom 2 (Siemens) from 1980 to 1992; SYTEC 3000 + (General Electrics) from 1992 onwards; Toshiba TCT-80A (Toshiba) from 1984 to 1993; and HiSpeed Advantage RP (General Electrics) from 1993 onwards. For the contrast-enhanced examinations done on 80/88 patients (91%), intravenous non-ionized contrast medium was used (2ml/kg, 300-350 mg iodine/ml).

The basal parts of the brain were imaged with 4-5 mm thick axial slices parallel to the orbitomeatal line up to the sella turcica, and the more cranial parts with 8-10 mm thick slices. The orbits were examined with thin axial and/or coronal slices of 1 to 4 mm thickness, depending on the equipment. Two-dimensional reconstructed slices in different directions were obtained as needed.

The spine was examined at the suspected levels with 3 to 5 mm thick axial slices, using computerized reconstructions as needed.

4.2.2 Magnetic resonance imaging (MRI)

The MRI examinations were mainly performed with Magnetom 1.0 T 42 SP (Siemens; since 1990), with the exception of a few scans obtained with other equipment. For contrast studies, intravenous Gd-DTPA 0.1 ml/kg was used for 31/92 patients (34%).

The brain was imaged mainly with T1-weighted sagittal slices (TR 570, TE 15, slice thickness 5 mm) and T2-weighted axial slices (TR 3500, TE 95, slice thickness 5 mm) and with proton density images (TR 3500, TE 19). In addition, the orbits were imaged with T1-weighted coronal slices (TR 500, TE 15, slice thickness 3 mm) and occasionally with the short-T1 inversion recovery (STIR) (TR 1500, TE 20) and fat-suppression sequences. No separate orbital coil was obtainable. For contrast imaging of the brain and orbit, T1-weighted images (TR 600, TE 15, thickness 3-5 mm) were used.

The cervical, thoracic and lumbar sections of the spine were examined with T2-weighted sagittal slices (TR 2300, TE103, slice thickness 3-5 mm), T1-weighted coronal slices (TR 500, TE 15, slice thickness 3-5 mm) and axial slices with the fast low-angle
shot (FLASH) technique (TR 500, TE 18). Intravenous contrast (Gd-DTPA) was used only occasionally as needed.

4.2.3 Plain X-rays, myelography and PEG

Plain films of the spine were available for almost all of the adult patients. Myelography was done on 8 patients, and PEG on one patient. The intrathecal contrast medium consisted of 10-15 ml of nonionized contrast (180-240mg iodine/ml) in six and oxygen in two patients.

4.2.4 Cerebral measurements

Cerebral measurements were performed on a workstation on MR images of the axial and sagittal slices of 14 NF1 patients with macrocephaly and 14 age- and sex-matched patients without macrocephaly. The parameters measured are shown in Fig. 1.

![Fig. 1. The brain measurements of MRI images in macrocephaly (see Table 13).](image)

4.2.5 Statistic methods

Pearson’s chi-square test was used in all statistic evaluations. p-values of less than 0.05 were considered significant.
5 Results

5.1 General

Of the 125 NF1 patients examined, 124 (99%) underwent CT and/or MR imaging of the head and 76 (61%) corresponding imaging of the spine. Both the head and the spine were examined in 75 patients (60%). One patient was imaged for her spine only.

The clinical symptoms were recorded from the hospital records. Of the 125 patients, 29 had headache, 60 had visual impairment and 8 had ocular symptoms. 24 patients were reported to have speech problems, 12 learning difficulties and 4 problems in concentration or attention deficit disturbances. Seven patients were mentally retarded and 10 had convulsions. 33 patients had macrocephaly.

23 patients were short in stature and one had hemi-hypertrophy. Back pain was reported by 10 patients, 17 had scoliosis, one patient had peroneal paresis and one subluxation of the hip. Four patients had pseudoarthrosis of the tibia, 5 bowing of the tibia and fibula and one asymmetry of the lower extremities. Ten patients had malignant tumours. Atopic skin changes were mentioned by 11 patients.

5.1.1 CT and MRI of the head

MRI and/or CT imaging of the head was done on 124 patients: 92 patients underwent MRI and 96 CT. MRI was the primary imaging method in 31 (25%) and CT in 93 (75%) patients. Intravenous contrast medium was used in 94% of the CT examinations and in 39% of the MRI examinations. The ages of the patients ranged from 0.2 to 66 years.

Patients aged under 18 years underwent an average of 2.9 (from 1 to 10) CT examinations. 28 of them had 1 to 2 examinations and only three patients had 9 to 10 examinations. The mean number of MR examinations performed was 1.8 (1 to 9); 43 patients underwent 1 to 2 MR examinations, and only two patients had seven or more examinations. As a whole, each of these NF1 patients underwent 3.9 (1 to 11) CT/MRI examinations.
Correspondingly, the adult patients (> 18 years) underwent an average of 1.6 (1 to 5) CT examinations; 40 of them had 1-2 examinations and 9 had 3-5 examinations. The average number of MRI examinations was 1.1 (1 to 4), and 39 patients had only one MRI examination done. As a whole, each adult patient underwent 1.9 (1-5) examinations. Of all the patients, 64 (52%; 39 children and 25 adults) had both CT and MRI done, while 28 (23%; 12 children and 16 adults) had only MRI and 32 (26%; 8 children and 24 adults) only CT done.

### 5.1.2 CT and MRI of the spine

76 (61%) of the 125 NF1 patients underwent radiologic imaging of the spine. 73 (93%) patients had MRI, 11 (15%) had CT, 9 (12%) had both CT and MRI, and one patient had only myelography. 31 (41%) of the patients were under 18 years old at the time of the first examination, and 45 (59%) were older. Eight patients (11%) underwent myelography, two of them with negative contrast medium (oxygen). All of the 31 children underwent imaging of the cervical and thoracic spine, and 23 of the examinations were done as MRI. Eight children (26%) underwent imaging of the whole spine, 6 with MRI. One patient had only myelography of the whole spine, and another child had MRI of the cervical and thoracic areas and CT of the lumbar spine done.

44 (98%) adults underwent imaging of the cervical spine, 43 (96%) of the thoracic spine and 23 (51%) of the lumbar spine. 22 (49%) adults had their whole spine scanned. Follow-up imaging was available for 20 (56%) of the 36 children with T2 hyperintense lesions, and the mean follow-up time was 2.1 years (from 0.7 to 3.6 years). One adult was followed up for 3.4 years. Optic gliomas were followed up radiologically in 33 (96%) of the 36 affected patients, with a mean follow-up time of 6.4 years for the children and 5.5 years for the adults (from 0.7 to 16.5 years for all patients with optic glioma).

### 5.2 Imaging findings of the head and brain in NF1

#### 5.2.1 General

Pathological imaging findings of the head, including pathological lesions of the brain, were observed in 53 (90%) of the children and 42 (65%) of the adult patients. 17 of the affected children (32%) had only one pathological lesion, 19 (36%) had two, and 17 children (32%) had three or four lesions of different types in CT/MRI. As a whole, 95 (77%) of the patients with NF1 had abnormal findings of the head, and the average number of observed lesions was 2.1 for all affected patients (2.2 for children and 2.0 for adults). The abnormal imaging findings are shown in Table 4; of them, T2 hyperintense lesions, optic lesions, other orbital findings, intracranial tumours, other cranial findings and changes associated with macrocephaly will be described in more detail below.
5.2.2 T2 hyperintense lesions of the brain

T2 hyperintense lesions of the brain were most typically seen bilaterally in the globus pallidi (Fig. 2), but they also occurred elsewhere (Fig. 3). They appeared as sharply demarcated lesions in the globus pallidi, but were more diffuse elsewhere. Their sizes varied from a few millimeters up to a few centimeters in diameter. T2 lesions were detected in 51 (55%) of the 92 NF1 patients who underwent MRI scanning. They were significantly more common in children (36 affected; 77%) than in adults (15 affected; 33%) (p=<0.001). The lesions were equally common in females (n=21, 54%; 13 children and 8 adults) as in males (n=30, 57%; 23 children and 7 adults). Nine of the adults (20%) had other than NF1-related T2 lesions, mainly degenerative, while the children showed only hyperintense lesions with NF1. The more detailed age and sex distribution of the patients with T2 hyperintense lesions is shown in Table 5. They were most frequent in the age group of 5 to 9 years, where 94% of the 18 children showed T2 lesions. Their appearance diminished along with age; in the age group of 18 to 24 years they were seen in 60%, but in the age group of 45 to 54 years in only 20% of the patients. None of the patients older than 55 years showed T2 hyperintense lesions.
Fig. 2. Typical T2 hyperintense lesions (thick arrows) bilaterally in the globus pallidus and a small lesion behind the trigonum of the right lateral ventricle on axial MRI scans of a 13-year-old girl with NF1. A plexiform neurofibroma on the left side frontally (thin arrow). – (a) T2-weighted image (SE, 2200/80, 5 mm); (b) proton density image (2200/15); (c) T1-weighted image (600/15). A= anterior, R= right.

Fig. 3. Multiple T2 hyperintense lesions (arrows) in an 11-year-old boy with NF1. There are diffuse cerebellar lesions, lesions in the pons and crus cerebelli (a,b), a lesion in the right globus pallidus (c) and sharply demarcated lesions anteriorly in the corpus callosum (c,d). – T2-weighted axial MR images (TSE, 3500/93, 5 mm).
Table 5. Appearance of T2 hyperintense lesions in NF1 patients examined with MRI, including 39 females and 53 males.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Patients studied</th>
<th>Affected females</th>
<th>Affected males</th>
<th>All affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>&lt; 18 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>10</td>
<td>2</td>
<td>100%</td>
<td>5</td>
</tr>
<tr>
<td>5-9</td>
<td>18</td>
<td>6</td>
<td>100%</td>
<td>11</td>
</tr>
<tr>
<td>10-17</td>
<td>19</td>
<td>5</td>
<td>83%</td>
<td>7</td>
</tr>
<tr>
<td>All</td>
<td>47</td>
<td>13</td>
<td>93%</td>
<td>23</td>
</tr>
<tr>
<td>&gt; 18 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>5</td>
<td>2</td>
<td>50%</td>
<td>1</td>
</tr>
<tr>
<td>25-34</td>
<td>13</td>
<td>3</td>
<td>38%</td>
<td>1</td>
</tr>
<tr>
<td>35-44</td>
<td>17</td>
<td>3</td>
<td>38%</td>
<td>4</td>
</tr>
<tr>
<td>45-54</td>
<td>5</td>
<td>0</td>
<td>0%</td>
<td>1</td>
</tr>
<tr>
<td>&gt;55</td>
<td>5</td>
<td>0</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td>45</td>
<td>8</td>
<td>32%</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>21</td>
<td>30%</td>
<td>51</td>
</tr>
</tbody>
</table>

5.2.2.1 Localization of T2 hyperintense lesions

T2 hyperintense lesions were mostly seen bilaterally. 14 of the affected children (39%) and 11 adults (42%) showed hyperintense lesions at only one location, mostly either uni- or bilaterally in the globus pallidi (Table 6). Seven children (19%) and 3 adults (20%) had them at two, and 15 children (42%) and 1 (7%) adult at three of more locations of the brain, respectively. On an average, the children had 3.5 and the adults 1.3 T2 lesions/patient. The average number of T2 lesions was 3.1 per affected patient among females and 2.9 among males. Localization of T2 hyperintense lesions in the globus pallidus and putamen was more common in females than in males (p=0.018).

Table 6. Localization of T2 lesions in 36 affected NF1 children according to sex.

<table>
<thead>
<tr>
<th>Localization</th>
<th>Females (n=13)</th>
<th>Males (n=23)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Globus pallidus, putamen</td>
<td>13</td>
<td>100%</td>
<td>13</td>
</tr>
<tr>
<td>Parietal/occipital/temporal</td>
<td>4</td>
<td>31%</td>
<td>12</td>
</tr>
<tr>
<td>Thalamus, hypothalamus</td>
<td>4</td>
<td>31%</td>
<td>7</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>2</td>
<td>15%</td>
<td>2</td>
</tr>
<tr>
<td>Optic tract, optic radiation</td>
<td>0</td>
<td>0%</td>
<td>3</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>1</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>5</td>
<td>38%</td>
<td>9</td>
</tr>
<tr>
<td>Crus cerebelli, pons</td>
<td>4</td>
<td>31%</td>
<td>10</td>
</tr>
</tbody>
</table>

The average size of T2 hyperintense lesions was larger in children than in adults. All but one of the adult patients (93%) had a T2 lesion smaller than one centimeter in diameter, while the corresponding percentage for children was 61% (n=22). 13 children (36%)
presented with diffuse lesions located in the temporal areas and the optic tracts. Four adult patients (27%) had diffuse lesions, which were located in the temporal, occipital and optic tract areas. One adult patient had T2 hyperintense lesions on the hippocampal areas bilaterally (Fig. 4).

Three (15%) children had hypodense areas visible on their CT scans (Fig. 5) corresponding to the T2 hyperintensities seen on MRI. In the globus pallidus, lesions were visible in one patient on CT and MRI at the age of 6 years and in another patient on CT at the age of 7 and on MRI at the age of 11 years. In the third patient the internal capsules were seen to be affected on CT and MRI at the age of three years, and he also had T2 lesions elsewhere in the brain (globus pallidus and cerebellum) not visible on CT. In a fourth child, hypodense areas were observed anterior to and in both thalami on CT at the ages of 4 and 8 years, but no lesions were detected at the age of 18 years on MRI. All the four patients also had glioma of the optic pathway.

Nine adults had other than NF1-related hyperintense T2 lesions, which were mostly degenerative. These lesions were located in the parietal periventricular areas in 7 (78%) patients, and in the thalamus or internal capsule in 2 patients.
5.2.2.2 Changes in T2 hyperintense lesions over age

The possible changes in the appearance of T2 hyperintensities in relation to the patients’ age were estimated by studying their visibility in successive individual MRI scans or by comparing their visibility in MRI scans taken from patients belonging to different age groups.

Successive MRI scans were available for 20 children (56%) and one adult (7%). The mean follow-up time for the children was 2.1 years (from 0.7 to 3.6 years) and that for the adult 3.4 years. Among the children, the T2 lesions remained unchanged in 7 children (35%); their ages ranged from 5.7 to 16.9 years (mean 9.5 years) with a mean follow-up time of 1.7 years (range 0.3–3.3 years). The size and/or number of the lesions diminished in 5 children (25%), whose ages ranged from 3.0 to 12.7 years (mean 9.0 years) and whose mean follow-up time was 2.7 years (range 1.3–3.5 years) (Fig. 6). Further, 4 children aged 3.2 to 13.6 (mean 6.8 years) years showed both unchanged and diminished lesions. Their mean follow-up time was 2.3 years (range 1.5–3.6 years). The lesions disappeared completely in one patient who, at the age of 4.5 years, showed two lesions in the crus cerebelli, and whose MRI scan was normal at the age of 5.2 years already. In one case, MRI was normal at the age of 4.4 years, T2 lesions were detected bilaterally in the lentiform nuclei two years later, and the lesions disappeared another two years later. Increase in the size or number of lesions was observed in three children (15%) aged 3.0, 3.4 and 9.4 years (mean 5.3 years), all of whom had multiple, differently behaving lesions during a mean follow-up time of 2.5 years (1.9 to 3.3 years) (Fig. 7). The lesions in the cerebellum, pons and crus cerebelli of the 18-year-old adult patient remained unchanged both in size and in number during a follow-up of 3.4 years.
The appearance of T2 hyperintensities in the different age groups is shown in Tables 5 and 7. They were already present in 70% of the children in the youngest age group of up till 5 years of age, who had an average of 3.7 lesions each. Three children aged 0.2, 1.7 and 2.7 years did not show any T2 lesions on MRI, while the remaining 7 children in this age group (aged 3.0 to 4.4 years) were all affected. In the age group of 5 to 9 years, 17/18 children showed T2 lesions, and only one child aged 7.1 years had no lesions. Of the patients aged 10 to 17 years, 12/15 (80%) had T2 hyperintense lesions. The oldest patient with T2 lesions was a 47-year-old male. The overall frequency of T2 hyperintense lesions in the affected patients over 18 years was 33%.

Fig. 6. Reduction of T2 hyperintense lesions during three-year follow-up in a boy with NF1. Several lesions (thick arrows) are seen in both the cerebrum (a, b) and the cerebellum (c) on MR images taken at the age of 3.1 years. On control scans (d, e, f) taken three years later, only small lesions are seen in the cerebellum (thin arrows). A chiasmal tumour (arrow) is also seen (e). – Axial T2-weighted images (SE, 2200/80, 5 mm).
Fig. 7. Variably behaving T2 hyperintense lesions (thick arrows) in a girl with NF 1 during follow-up for 3.7 years (a, b, c, d, e). A tumour (thin white arrow) diagnosed as glioblastoma multiforme developed in the frontal horn of the right lateral ventricle. – T2-weighted axial MR images at the ages of 3.0 (a), 5.2 (b), 5.3 (c), 6.3 (d) and 6.7 (e) years; TSE, 3500/93, 5 mm. The same patient also had a widespread optic glioma (Fig. 7). The intraventricular tumour seen on a non-enhanced T1-weighted axial image (f) (SE, 600/15).

Table 7. Mean number of T2 hyperintense lesions per affected NF1 patient according to age and sex (n=51).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
<th>All affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean</td>
<td>n</td>
<td>mean</td>
<td>n</td>
</tr>
<tr>
<td>0-4</td>
<td>2</td>
<td>4.5</td>
<td>5</td>
<td>3.0</td>
<td>7</td>
</tr>
<tr>
<td>5-9</td>
<td>6</td>
<td>4.2</td>
<td>11</td>
<td>4.0</td>
<td>17</td>
</tr>
<tr>
<td>10-17</td>
<td>5</td>
<td>2.8</td>
<td>7</td>
<td>2.8</td>
<td>12</td>
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<tr>
<td>All</td>
<td>13</td>
<td>3.8</td>
<td>23</td>
<td>3.3</td>
<td>36</td>
</tr>
<tr>
<td>18-24</td>
<td>2</td>
<td>2.5</td>
<td>1</td>
<td>2.0</td>
<td>3</td>
</tr>
<tr>
<td>25-34</td>
<td>3</td>
<td>2.3</td>
<td>1</td>
<td>2.0</td>
<td>4</td>
</tr>
<tr>
<td>35-44</td>
<td>3</td>
<td>1.7</td>
<td>4</td>
<td>1.0</td>
<td>7</td>
</tr>
<tr>
<td>45-54</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>&gt;55</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td>8</td>
<td>2.1</td>
<td>7</td>
<td>1.3</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>3.1</td>
<td>30</td>
<td>2.9</td>
<td>51</td>
</tr>
</tbody>
</table>
The number of T2 lesions observed was highest in the age group of 5 to 9 years with an average of 4.1 lesions per individual (Table 7). Their number dimished gradually with increasing age, being only 1.7 lesions per individual in the patients over 35 years of age. The number of lesions was slightly higher in females than in males in all age groups.

5.2.2.3 Association of T2 hyperintense lesions with other abnormalities of the head

In addition to the observed associations of optic gliomas, 5 (14%) children with T2 hyperintense lesions had additional abnormalities: 2 patients had hydrocephalus due to aqueductal stenosis. One child had glioma of the hypothalamus, one a suspected astrocytoma, and one had a post-hemorrhagic scar. Three (20%) adult patients had further abnormalities in addition to T2 hyperintense lesions: one had optic glioma and hypothalamic-thalamic glioma, another had plexiform neurofibroma of the orbit and sphenoid bone dysplasia, and a third had a small venous malformation and a small midline lipoma.

Of the patients with degenerative T2 lesions, one had an optic glioma, and another a hypophyseal tumour.

5.2.3 Manifestations of the optic pathways and orbits

Optic gliomas comprised either intraorbital or intracranial (prechiasmal) thickening and/or tortuosity of the optic nerve, thickening of the chiasm or lesions of the optic tract and optic radiation. The thickening of the nerve and the presence or absence of tortuosity were estimated by visual inspection. Optic gliomas were detected in 36 (29%) of the 124 NF1 patients. They were statistically significantly (p=<0.001) more common in children (26 children affected, 44%) than in adults (10 affected, 15%). There was no significant difference between women and men (p=0.98). Their presence in the different age groups is shown in Table 8.

Table 8. NF1 patients affected with optic glioma according to sex and age at the time of initial CT/MRI imaging (n=124).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Studied patients</th>
<th>Affected females</th>
<th>Affected males</th>
<th>All affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>0-4</td>
<td>27</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>5-9</td>
<td>22</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>10-17</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>All</td>
<td>59</td>
<td>10</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>18-24</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25-34</td>
<td>21</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>35-44</td>
<td>23</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>45-54</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;55</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All</td>
<td>65</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>17</td>
<td>19</td>
<td>36</td>
</tr>
</tbody>
</table>
25/36 patients (69%) were imaged with both CT and MRI, 8 patients (22%) with MRI only and 3 patients (8%) with CT only. As a whole, every patient with optic glioma underwent 3.9 CT/MRI examinations; an average of 4.5 examinations were made on the children and 2.3 on the adults. In 28 patients (78%) the primary diagnosis of optic glioma was made on their first CT/MR imaging and in 8 patients on the second examination. The diagnosis was made with CT in 20 patients, with MRI in 15 patients and with PEG in one patient.

5.2.3.1 Localization of optic gliomas

The intraorbital and/or prechiasmal optic nerves were affected in 34 (94%) of the patients with optic glioma, including 25 children (96%) and 9 adults (90%) (Fig. 8). Chiasmal and/or hypothalamic lesions were seen in 21 patients (58%) (Fig. 9, 10), including 16 children (62%) and 5 adults (50%), with six of them (29%) having both chiasmal and hypothalamic lesions. Lesions of other areas of the optic system were diagnosed in 5 patients (14%), 4 children and 1 adult. More detailed data on the location and extent of the lesions in relation to the age and sex of the patients are given in Table 9.

Fig. 8. A thickened and tortuous left optic nerve (arrow) (a,c) and an asymmetrically enlarged optic chiasm (asterix) (b) in a 3-year-old girl with NF1. – T1-weighted sagittal (a) and coronal (b) MR images (SE, 570/15, 5 mm) and a proton density axial image (2300/15) (c). S= superior, A= anterior, R=right.
Fig. 9. An optic glioma affecting the intracanalicular (arrows) (a) and prechiasmal (arrows) (b) parts of the optic nerves of a 16-year-old boy with NF1. The chiasma (arrow) (c) is also affected. The prechiasmal parts of the nerves and the chiasm are slightly hyperdense. The intraorbital optic nerves (thin arrows) (d) appear thin. Bilateral papillary atrophy had been detected three years earlier. – Non-enhanced axial CT scans (4 mm).

Fig. 10. An enhancing hypothalamic tumour (arrows) (a,b) compressing the third ventricle in a 3.2-year-old boy with NF 1. Two years after radiotherapy, no signs of the tumour were visible (c). – Non-enhanced (a) and enhanced (b, c) coronal T1-weighted images (SE, 690/15, 5 mm; Magnevist 3 ml i.v). The patient also had bilateral optic nerve glioma (Fig. 12) and multiple T2 hyperintense brain lesions.
Table 9. Localization and extent of optic lesions in 36 NF1 patients with optic glioma according to age and sex. (F= female, M= male, ch= chiasm, ht= hypothalamus, o.n. = optic nerve, o.tr. = optic tract)

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Age &lt;18 y</th>
<th></th>
<th>Age &gt;18 y</th>
<th></th>
<th>All ages</th>
<th></th>
<th>Both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Intraorbital optic nerve</td>
<td>9 90%</td>
<td>8 50%</td>
<td>4 57%</td>
<td>2 67%</td>
<td>13 76%</td>
<td>10 53%</td>
<td>64%</td>
</tr>
<tr>
<td>Prechiasmal optic nerve</td>
<td>8 80%</td>
<td>13 81%</td>
<td>4 57%</td>
<td>2 67%</td>
<td>12 70%</td>
<td>15 79%</td>
<td>75%</td>
</tr>
<tr>
<td>Chiasm</td>
<td>5 50%</td>
<td>10 63%</td>
<td>3 43%</td>
<td>2 67%</td>
<td>8 47%</td>
<td>12 63%</td>
<td>56%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>2 20%</td>
<td>5 31%</td>
<td>0</td>
<td>0</td>
<td>2 12%</td>
<td>5 26%</td>
<td>19%</td>
</tr>
<tr>
<td>Optic tract/radiation</td>
<td>1 10%</td>
<td>3 19%</td>
<td>1 14%</td>
<td>0</td>
<td>2 12%</td>
<td>3 18%</td>
<td>14%</td>
</tr>
<tr>
<td>Extent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic nerve only</td>
<td>5 50%</td>
<td>2 13%</td>
<td>3 43%</td>
<td>1 33%</td>
<td>8 47%</td>
<td>3 16%</td>
<td>31%</td>
</tr>
<tr>
<td>Orbital o.n. + ch or ht</td>
<td>3 30%</td>
<td>2 13%</td>
<td>1 14%</td>
<td>1 33%</td>
<td>4 24%</td>
<td>3 16%</td>
<td>19%</td>
</tr>
<tr>
<td>Prechiasmal o.n. + ch or ht</td>
<td>1 10%</td>
<td>8 50%</td>
<td>2 29%</td>
<td>1 33%</td>
<td>3 18%</td>
<td>9 47%</td>
<td>33%</td>
</tr>
<tr>
<td>O.n. + ch + ht</td>
<td>1 10%</td>
<td>3 19%</td>
<td>0 0</td>
<td>0 0</td>
<td>1 6%</td>
<td>3 16%</td>
<td>11%</td>
</tr>
<tr>
<td>O.tr. or o.n. + ht</td>
<td>0</td>
<td>1 6%</td>
<td>1 14%</td>
<td>0 0</td>
<td>1 6%</td>
<td>1 5%</td>
<td>6%</td>
</tr>
<tr>
<td>All</td>
<td>10 16%</td>
<td>7 3%</td>
<td></td>
<td></td>
<td>17 19%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The most common localizations of optic gliomas were the prechiasmal (intracranial) optic nerve (75% of the affected patients), the intraorbital optic nerve (64%) and the chiasm (56%). The hypothalamus was affected in 19% and the optic tract and radiation in 14% of the affected patients, respectively. As to the extent of the changes, the optic nerve alone was affected in about one third of the patients (31%), and the combination of prechiasmal optic glioma with chiasmal changes was seen in a similar number (33%). There was no statistically significant difference in the localization or extent of the lesions between children or adults (p=0.142-0.97) or between females and males (p=0.10-0.90). A widespread optic glioma is presented in Fig. 11.

Fig. 11. A widespread optic glioma in a 20-year-old male NF1 patient. Tortuous, slightly thickened optic nerves (black arrows) up to the enlarged optic chiasm (white arrow) are seen (a, b, c). There is a diffuse T2-hyperintense lesion (asterix) (b) in the right optic tract at the site of the calcified area (black arrow) seen earlier on CT (d). None of the lesions enhanced with contrast, and they remained unchanged during MRI follow-up for three years. Thickening of the optic nerves (black arrows) had not progressed since the previous CT over 12 years earlier (d). – T2-weighted axial MR image (a) (FSE, 3500/88, 5 mm), proton density images (b, c) (3500/14), and enhanced CT images (d, e) (4 mm, Urografin 60% U/ml 40 ml i.v.).
Uni- or bilaterality of the abnormalities was assessed in all cases of optic nerve and chiasmal gliomas. Of the intraorbital gliomas, 52% were bilateral (Fig. 12), and the corresponding percentages for prechiasmal and chiasmal gliomas were 41% and 70%, respectively. The bilateral changes were somewhat more common in males than in females (75% vs 62%).

Fig. 12. Bilateral optic thickening with an enhancing tumour of the right optic nerve (thick arrow) and ectatic dilatation of the left optic sheath (long arrow) (a) in a 2.9-year-old boy with NF 1. Enhancement of the right, 12 mm thick tortuous optic nerve is mostly peripheral (short arrows, b), whereas the left, 8 mm thick nerve is surrounded by a hypodense zone that corresponds to the ectatic optic sheath. The patient also had a thickened chiasm, a hypothalamic tumour (see fig. 10) and several T2 hyperintense brain lesions. – Axial non-enhanced (a) and enhanced (b) CT images (2mm; Ultravist 300 mg I / ml 30 ml i.v.).

Hydrops of the optic sheath was seen in 5 patients (four children and one adult) studied for the presence of optic gliomas on MRI (Fig. 13). Hydrops was unilateral in three patients aged 4.4, 3.0 and 4.2 years and bilateral in two patients aged 7.3 and 29 years,
respectively. On CT, the nerves appeared thickened and optic glioma was suspected; MRI revealed a normal optic nerve surrounded by hydrops.

Fig. 13. Ectatic dilated optic sheaths (thick arrows) and thickening of the posterior part of the right intraorbital optic nerve (thin arrow) in a 5.4-year-old boy with NF 1. The finding remained unchanged during follow-up for two years. – T2-weighted axial MR image (TSE, 3500/93, 5 mm).

5.2.3.2 Changes in optic gliomas during follow-up

Changes in the lesions of the optic system were estimated either by studying successive imagings of singular patients or by comparing the abnormalities in the CT and/or MRI scans of patients in different age groups. The youngest patients diagnosed with optic glioma were 3.0 years old in the CT group and 3.4 years old in the MRI group. The most advanced ages at imaging-based diagnosis were 56 years and 57 years, respectively. The mean age at the diagnosis of optic glioma was 23.2 years.

Successive CT and/or MRI scans were obtained for 33 (92%) patients with optic glioma, including 25 (96%) children and 8 (80%) adults. The mean follow-up time for children was 6.4 years (0.7 to 16.5 years) and that for adults 5.5 years (1.8 to 13.8 years). Seven patients were followed up for more than ten years, 9 for more than five years and 17 for less than five years, most of them for less than two years.

The imaging methods used were CT and MRI for children and CT for adults. In altogether 14 of the patients who had been examined with both CT and MRI (56%), the findings of the two methods complemented each other.

In 21 (84%) of the patients, i.e. in 17 children (81%) and in all of the 4 adults, the observed optic lesions remained unchanged during the follow-up. Regression of the lesions was detected in 3 (14%) children and in none of the adults, which accounts for 12% of all patients. One patient, a 4.4-year-old child, showed progression of the lesions during a follow-up period of 1.2 years. Both optic nerves were affected on the first exami-
nation, and a chiasmal tumour was found in the follow-up examination. Subsequent MRI scans showed regression of both lesions.

In 8 (24%) patients (5 children and 3 adults), the primary examination (CT) was normal, while the subsequent MRI examinations showed optic lesions. The mean period between the CT and MRI examinations in these children was 3.8 years (1.1-8.5 years), and the pathological findings were made at a mean age of 9.2 years (7.2-10.8 y). These consisted of a thickened prechiasmal optic nerve in 2 children, a thickened prechiasmal optic nerve and affected chiasm/hypothalamus in 2 children, and a thickened optic nerve with hydrops of the optic sheath in one child. Thickening of the optic nerves was found in 2 adults and T2 signal hyperintensities in the optic tracts in one adult. The intervals between the CT and MRI examinations in these cases were from 2.3 to 3.3 years, and the lesions were detected at the ages from 29.4 to 35.6 years, respectively.

In 3 children and one adult, the primarily suspected optic changes on CT could not be seen or verified on subsequent MRI scans. These changes included slight asymmetry or thickening of the prechiasmal optic nerve and/or the chiasm. The interval between the CT and MRI examinations performed on these children was 1.8 years (0.3-4.3 years), and the children’s mean age at the time of the primary CT was 9.7 years (5.2-17.8 y). The adult patient was primarily studied at 52.7 years of age, and her MRI was performed 8.3 years later. In one patient, an optic tract calcification was seen on CT at 7.7 years of age, and later, at the age of 16.9 years, a T2 hyperintensity was detected on MRI in the same area (Fig. 11). In a 29-year-old patient, thickened optic nerves were identified on CT; at the age of 43 years, normal optic nerves and hydrops of the optic sheath were detected on MRI.

5.2.3.3 Contrast enhancement of optic gliomas on CT and MRI

Contrast enhancement was used either to improve the visibility and differential diagnostics of already detected changes or as a routine method to evaluate the orbital structures of NF1 patients. All of the 36 patients with optic glioma had intravenous contrast enhancement done. These included all of the 28 patients examined with CT and 17 (52%) of the 33 patients examined with MRI. 25 patients underwent both CT and MR, and in 12 of them both CT and MRI were enhanced.

Enhancement (increased density or intensity) of the optic gliomas was detected in 6 children, in two of them both on CT and on MRI, and in one patient only on CT (with no enhancement on MRI). Of the remaining 3 patients, two were enhanced on MRI and one on CT. The two patients with enhancement in both examinations were 3-year-old boys, in whom the whole optic nerve, chiasm and hypothalamus were affected with glioma (fig. 10 and 12). In one of them the optic nerves were enhanced. These changes diminished after an operation on the right blind eye and radiation of the chiasm and the hypothalamus. In the other boy, the chiasm was enhanced; his left thickened optic nerve and hypothalamus were irradiated, which resulted in subsequent regression of the lesions. He also had right sphenoidal dysplasia (Fig. 14). The other four patients were a 5-year-old girl with enhancement of the optic nerve on CT (but not on MRI), an 8-year-old girl with enhancement of the chiasm on CT, a 7.3-year-old boy with enhancement of the thickened...
right optic nerve on MRI and a 4.4-year-old girl with enhancement of the chiasm on MRI.

Two patients with hyperdense lesions on CT did not show enhancement with contrast medium. These were a 7.7-year-old boy with a dense prechiasmal optic nerve and chiasm.

Fig. 14. Thickening and tortuosity of the whole left optic nerve (thick black arrows), asymmetry of the bony orbits and edema of the upper right eyelid are seen on axial CT images (3 mm) (a, b) in a three-year-old boy with NF 1. On the right, the optic foramen and the superior orbital fissure were fused (asterix). On contrast-enhanced CT images (5 mm, Omnipaque 300 mg I/ml) (c, d) enhancement of the prechiasmal optic nerves and the chiasm is seen (white arrows). The affision of the left optic nerve and chiasm (white arrows) is well demonstrated on enhanced T1-weighted MR images (SE, 600/15, 5 mm, Magnevist 4 ml i.v.) (f, g). The patient also had several T2 hyperintense brain lesions (Fig. 6).
and a 4.2-year-old girl with a bilaterally dense intraorbital and unilaterally dense prechiasmal optic nerve.

5.2.3.4 Other orbital findings

11 of the 124 patients (9%) had orbital findings other than lesions of the optic system, and three of them also suffered from optic glioma. Plexiform neurofibromas were found in three children and three adults (Fig. 15). In four patients the tumours were at least partly intraorbital, one appeared on the upper eyelid and one in the corner of the eye. The tumours appeared as homogeneous enhancing masses separate from the optic system. A 3-year-old boy also had sphenoid bone dysplasia and glioma of the optic nerve, and a 32-year-old male had sphenoid bone dysplasia and an enhancing tumour of the cavernous sinus.

![Fig. 15. Bilateral plexiform neurofibromas (arrows) lateral to the orbits in a 44-year-old female patient with NF 1. – T2-weighted axial MR image (TSE, 3500/ 95, 5 mm).](image)

Enlarged lacrimal glands were seen in a 3.8-year-old boy who also had optic glioma. A 32-year-old man presented with optic glioma and dense, non-enhancing intraorbital fatty tissue. A 15-year-old boy had a suspected intraorbital plexiform neurofibroma and thickened intraorbital upper rectus and levator palpebrae muscles. A 28-year-old male had small enhancing tumours in the posterior parts of the ocular bulbi. In a 48-year-old female, CT did not reveal the malignant conjunctival melanoma that was found in a clinical examination. One additional patient presented with symmetrically thickened superior rectus muscles in both orbits.

Sphenoid bone dysplasias were found in two (1.6 %) of the 124 NF1 patients, and both also had orbital plexiform neurofibromas.
5.2.3.5 Association of optic gliomas with other abnormalities of the head

A total of 25 (69%) patients with optic lesions showed other pathological findings of the orbit, brain or head.

Of the 33 patients examined with MRI who had optic glioma, 28 (85%) showed T2 hyperintensities, 23 being children (96%) and 5 adults (56%). The other way round, optic glioma was observed in 20/36 (56%) of the children with T2 lesions, while only 1/11 child (9%) without T2 lesions presented with a suspected optic glioma. In adults, optic gliomas were found in seven out of 15 (47%) cases with T2 lesions, but only 1/30 one patient (3%) had an optic glioma without T2 lesions.

The other lesions detected in patients with optic glioma included 2/36 instances of plexiform neurofibroma (6%), one of them intraorbital with sphenoid bone dysplasia and one in the neck with destruction of the mandibular angle. These cases represented 2/6 (33%) of the patients with plexiform neurofibroma. Astrocytoma of the brain was seen in 2/36 patients with optic glioma (6%), who accounted for 33% (2/6) of the patients with astrocytoma. Singular findings with optic glioma were detected in 5/36 individuals, including suspected epidermoid tumour of parietal bone, enlarged lacrimal glands, dense intraorbital fatty tissue, vascular malformation and asymmetric cavernous sinuses.

Minor structural abnormalities (ventricular asymmetry, etc.) were seen in 14 (39%) patients with optic glioma. Intracranial calcifications were detected in 3 (8%) patients; in the globus pallidus bilaterally, in the chiasm and crus cerebelli and in the chiasm, respectively. One of the 9 patients with degenerative T2 lesions had optic glioma.

5.2.4 Other brain tumours

Ten patients, 6 males and 4 females, presented with intracranial tumours other than tumours of the optic system. The main findings of six patients with brain gliomas are presented in Table 10.

Table 10. Histologically verified brain tumours in six patients with NF1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Type of tumour</th>
<th>Localization</th>
<th>Imaging method</th>
<th>Other observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>male</td>
<td>7</td>
<td>pilocytic astrocytoma gr I</td>
<td>frontoparietal</td>
<td>CT, MRI</td>
<td>no recurrence in 10 years</td>
</tr>
<tr>
<td>2</td>
<td>female</td>
<td>6</td>
<td>glioma gr IV</td>
<td>lateral ventricle</td>
<td>MRI</td>
<td>multiple T2 lesions, OPG</td>
</tr>
<tr>
<td>3</td>
<td>male</td>
<td>8</td>
<td>pilocytic astrocytoma enhancing lesions</td>
<td>left temporo-hypothalamic</td>
<td>CT, MRI</td>
<td>enlarged chiasm histology: normal brain tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td>right temporo-hypothalamic</td>
<td>CT, MRI</td>
<td>site of an earlier stable T2 lesion</td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>17</td>
<td>glioblastoma multiforme</td>
<td>parieto-occipital</td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>female</td>
<td>36</td>
<td>astrocytoma gr III</td>
<td>trigonum</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>male</td>
<td>53</td>
<td>astrocytoma gr II</td>
<td>cerebellum</td>
<td>CT, MRI</td>
<td>hydrocephalus</td>
</tr>
</tbody>
</table>
Six patients had a verified astrocytoma (patients 1–6). Their ages ranged from 6 to 53, and patient 1 was the son of patient 5. In one patient, astrocytoma was suspected radiologically, but was later shown to be normal brain tissue histologically.

The astrocytomas differed in radiological appearance in the different patients. In patient 1, a slowly growing, small, enhancing tumour with a surrounding enlarging cyst in the right frontoparietal region was shown on operation at the age of 10 years to be a grade 1 pilocytic astrocytoma. Biopsy performed at the age of 8 years had not revealed any specific changes. During the follow-up of 12 years, no progression of the tumour was detected. In patient 2 with numerous T2 hyperintense lesions and severe OPG, a progressively growing tumour was detected in the frontal horn of the lateral ventricle at the age of 4 years (see Fig. 7). On operation at the age of 6 years 8 months, a grade IV glioma was verified. Patient 3 was shown to have an enhancing tumour in the left temporo-hypothalamic region on CT at the age of 8 years, which was shown to be a low-grade pilocytic astrocytoma on stereotactic brain biopsy. At the same time, a smaller lesion was detected on the right side. During the follow-up (Fig. 16) the size of the lesions fluctuated, and a biopsy of the enlarged right-sided lesion revealed normal brain tissue. By the age of 20 years, the lesions had finally disappeared. The findings have been reported separately (Leisti et al. 1996).

![Fig. 16. A spontaneously regressing pilocytic astrocytoma in a boy with NF 1. On a contrast-enhanced CT image (10 mm, Urografin 60% 50 ml i.v.) (a) of the boy at the age of 8.3 years, an enhancing mass lesion (short arrow) surrounded by edema is seen on the left side. Biopsy revealed a pilocytic astrocytoma. On the CT scan (b) at the age of 9.7 years, the left-sided lesion has almost disappeared, and there is a new mass lesion (long arrow) on the right (normal brain tissue at biopsy). Both lesions are nearly invisible on CT taken at the age of 11.3 years (c), and on T2-weighted (SE, 3500/95, 5 mm) MR images (d, e) at the age of 20 years, only small hyperintense areas on both sides, consistent with brain biopsy sites, are seen (arrows).]
In the patients 4, 5 and 6, the tumours presented as more or less hypodense lesions enhancing variably with contrast medium and surrounded by oedema. In patient 4, the tumour was located partly in the region of the left optic radiation (Fig. 17), where a T2 hyperintense lesion persisted for several years of follow-up.

Fig. 17. Development of a malignant tumour at the site of a previous T2 hyperintense lesion in a boy with NF 1. A the age of 6.6 years, only slight asymmetry of the lateral ventricles is seen on CT (a). On MR images at the ages of 12.3 and 16.5 years, diffuse hyperintensity (arrow) in the right trigonal area is visible (b, c), and dilatation of the lateral ventricles had developed. The patient also had diffuse hyperintensity around the cerebral aqueduct (Fig. 18). Six months later, MRI revealed a 5 cm tumour (black arrow) surrounded by edema (glioblastoma multiforme at operation) (d). – Enhanced CT image (8 mm, Omnipaque 300 mg I/ ml 30 ml i.v.) (a), T2-weighted MR image (SE, 3500/93, 5 mm) (b), T2-weighted MR images (SE, 4000/114, 4 mm) (c,d).
A 9-year-old girl had MRI findings of a non-expansive, non-enhancing T2 hyperintense lesion following the gyri and affecting both white and grey matter frontally on the left, which was suspected to be an astrocytoma. It was about 5 cm in diameter but had been visible on CT since the age of four years as a smaller hypodense lesion. Biopsy yielded nothing but normal brain tissue. On follow-up, the lesion remained unchanged for 5.4 years. The patient had additionally T2 hyperintense lesions of the basal ganglia and the cerebellum.

A 36-year-old male patient had a minor lipoma in the interpeduncular cistern. In a 54-year old female, a 16 mm high enhancing hypophyseal tumour was detected on MRI. The tumour enlarged during six months of follow-up, and an adenoma was found on operation. A small enhancing residual tumour was detected a year later. A 32-year-old male had an enhancing lesion in the sinus cavernosus on MRI; the nature of this lesion remained unknown.

### 5.2.5 Other manifestations of the head

**Minor extraparenchymal abnormalities** (ventricular asymmetry, large cisterna magna, slight dilatation of the basal liquor spaces and cavum septi pellucidi) or **slight central and/or cortical brain atrophy** were detected in 43 patients (35%; see Table 4). Ventricular asymmetry was found in 12 adults and nine children, cavum septi pellucidi in five adults and two children. Six children had large cisterna magna, six had slight dilatation of the fourth ventricle or the lateral ventricles without signs of atrophy or increased intracranial pressure. Slight dilatation of the basal cisterns was detected in two children. Ten adult patients (14%), but none of the children, showed atrophic changes.

**Hydrocephalus** was detected in four children and two adult patients (4.8%). In two children, hydrocephalus was due to aqueductal stenosis, which was detected at the ages of 11 and 12 years and associated with diffuse high-signal intensity around the aqueduct (Fig. 18). Both children had had normal CT findings at the ages of 3 and 6 years, respectively. A 3-year-old boy developed hydrocephalus subsequent to an inoperable opticus glioma, and a 6-year-old girl had an intraventricular glioma as the cause of her hydrocephalus. Hydrocephalus was also present in a 42-year-old male without NF-specific intracranical changes or increased intraventricular pressure and in a 53-year-old male patient, who had a cerebellar astrocytoma and developed obstruction of the fourth ventricle and subsequent hydrocephalus.

**Intracranial calcifications** were found in five patients (4%). A 16-year-old boy showed bilateral small calcifications in the globus pallidus, and a 7-year-old boy had calcifications in the optic tract. Two adult patients had nonspecific small calcifications frontally and parietally, respectively, and a 23-year-old male with an inoperable optic glioma showed calcifications in the chiasm and optic tract bilaterally.
Fig. 18. Hyperintensity (arrow) around the upper part of the aqueduct is seen on a T2-weighted image (TSE, 3500/93, 5 mm) (a) a boy aged 12.3 years. Dilated third and lateral ventricles are seen. Hydrocephalus is also seen in a T1-weighted sagittal image (b) (SE, 570/15, 5 mm), no tumorous lesions are seen around the aqueduct (arrow).

Lesions of cranial bones probably related to NF1 were detected in three children and four adults (7%). Two patients had sphenoidal dysplasia, and one of them also had local thinning of the parietal bone. Sclerotic dysplasia and thickening of the medial part of the frontal sinus were found in one adult and sclerotic margins of the coronary sutures in a 16-year-old adolescent. Local thinning of the occipital bone was seen in an adult patient, and another had an oval high-intensity lesion of the medial part of the left parietal bone on T2 images, suspected to be a dermoid tumour. One patient suffered from an arteriovenous malformation and subsequent destruction of the basal osseous cranium. The other cranial bone lesions observed included anomaly of the dens and clivus in one patient, anomalous location of the posterior arch of the atlas (C1) in one patient and an enlarged foramen magnum in one patient.

Plexiform neurofibromas of the head and neck were found in 8 children and 6 adults (11%); and six of these had been verified histologically. In three children and three adults, the tumour was located in the orbital region, while four of the tumours were totally or partially intraorbital. A 13-year-old child presented with a T1-hyperintense lesion in the left frontal sinus, which was histologically proven to be a plexiform neurofibroma. A 7-year-old boy showed an enhancing lesion 3 cm in diameter in the basis of the cranium suspected to be a plexiform neurofibroma. A 4-year-old girl had a large tumour in the left parotic region extending to the mandibular angle and causing bone destruction. Five patients showed either uni- or bilateral cervical plexiform neurofibromas.

Vascular lesions were detected in 5 adult patients. A 38-year-old female had a large arteriovenous malformation with bone destruction of the basal cranium. Two male patients had small venous angiomas, and a female patient had a small cavernous hemangioma in the right area perforata. A 31-year-old female suffered from elevated blood pressure and bilateral carotid dissection.
5.2.6 Macrocephaly

Macrocephaly was observed in 33 (27%) of the 124 studied patients: 20 children (34%) and 13 adults (20%). In 21 patients (17%) head circumference was within the range of +2–+2.4 standard deviation (SD) for age and sex, while in 3 patients (2.4%) it was +2.5–2.9 SD, in 8 patients (6.4%) +3.0–+3.4 SD and in one patient +4 SD. Macrocephaly was more common in male (n= 22; 33%) than in female patients (n=11; 19%).

5.2.6.1 Cerebral measurements in children with macrocephaly

Cerebral measurements on axial and sagittal MR images were performed on 14 NF1 children with macrocephaly, including 10 boys aged 3 to 14 years and 4 girls aged 7 to 13 years. The degree of macrocephaly in them varied from +2 SD to +4 SD for age and sex. The controls consisted of 14 NF1 children (10 boys and 4 girls) whose head circumferences were normal.

The results of the measurements, which are the means of two separate measurements in each case, are presented in Table 11. Pearson’s chi-square test was used in the analysis, and p-values <0.05 were considered statistically significant.

Table 11. Comparison of mean brain measurements in 14 macrocephalic and 14 sex- and age-matched normocephalic children with NF1.

<table>
<thead>
<tr>
<th>Measured brain parameter</th>
<th>Macrocephalic</th>
<th>Normocephalic</th>
<th>p-value1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Width of frontal horns</td>
<td>39.83 2.68</td>
<td>36.49 3.34</td>
<td>0.025*</td>
</tr>
<tr>
<td>Frontal horn/brain width index</td>
<td>0.35</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>2. Corresponding brain width</td>
<td>113.50 5.78</td>
<td>107.82 5.74</td>
<td>0.041*</td>
</tr>
<tr>
<td>Distance between caudate nuclei</td>
<td>14.72 5.95</td>
<td>11.33 3.49</td>
<td>0.124</td>
</tr>
<tr>
<td>4. Width of 3rd ventricle</td>
<td>5.86 2.68</td>
<td>4.89 1.64</td>
<td>0.202</td>
</tr>
<tr>
<td>5. Corresponding brain width</td>
<td>129.38 8.00</td>
<td>126.57 6.35</td>
<td>0.412</td>
</tr>
<tr>
<td>3rd ventricle/brain width index</td>
<td>0.05</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>6. Maximum brain width</td>
<td>135.84 4.53</td>
<td>130.50 5.49</td>
<td>0.048*</td>
</tr>
<tr>
<td>7. Width of 4th ventricle</td>
<td>16.61 2.13</td>
<td>16.34 3.45</td>
<td>0.825</td>
</tr>
<tr>
<td>8. Corresponding brain width</td>
<td>105.55 6.71</td>
<td>100.94 5.29</td>
<td>0.030*</td>
</tr>
<tr>
<td>4th ventricle/brain width index</td>
<td>0.16</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>9. Midline sagittal brain length</td>
<td>184.29 5.43</td>
<td>175.68 7.74</td>
<td>0.004**</td>
</tr>
<tr>
<td>10. Right hemisphere sagittal length</td>
<td>181.99 5.90</td>
<td>173.59 8.44</td>
<td>0.003**</td>
</tr>
<tr>
<td>11. Left hemisphere sagittal length</td>
<td>184.04 5.17</td>
<td>174.78 8.65</td>
<td>0.001***</td>
</tr>
<tr>
<td>12. Corporal width of lateral ventricles</td>
<td>36.32 5.49</td>
<td>32.08 6.55</td>
<td>0.121</td>
</tr>
<tr>
<td>13. Corresponding brain width</td>
<td>129.20 4.85</td>
<td>125.88 5.67</td>
<td>0.179</td>
</tr>
<tr>
<td>Corpus/brain width index</td>
<td>0.28</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>14. Maximal midline sagittal brain stem width</td>
<td>25.56 2.35</td>
<td>23.37 2.22</td>
<td>0.009**</td>
</tr>
<tr>
<td>15. Maximal peduncular width</td>
<td>40.41 6.34</td>
<td>42.19 4.84</td>
<td>0.429</td>
</tr>
<tr>
<td>16. Width of pons</td>
<td>32.24 3.65</td>
<td>29.51 3.68</td>
<td>0.094</td>
</tr>
<tr>
<td>17. Width of medulla oblongata</td>
<td>16.91 1.81</td>
<td>15.87 1.95</td>
<td>0.091</td>
</tr>
</tbody>
</table>

1 chi square test, p-values <0.05 were considered statistically significant. ** p-value <0.01, * p-value <0.05
The left, right and midline sagittal hemispheric measurements of the brain were significantly larger in the macrocephalic group than in the control group (p = 0.001–0.004), the left hemispheric dimension being the only one statistically highly significant. The maximum width of the brain was, on an average, 5.3 mm greater in the macrocephalic group than in the controls (p = 0.048). The width of the frontal horns, the brain width at the corresponding level, and the brain width at the level of the fourth ventricle were significantly wider in macrocephalic children. Also the maximal midline sagittal brain stem width was significantly wider in the macrocephalic group.

5.2.6.2 Associations between macrocephaly, optic gliomas and T2 hyperintense brain lesions

Macrocephaly was found to be associated with T2 hyperintense lesions in children: of the 20 children with macrocephaly who underwent MRI, all had T2 hyperintense lesions, while of the 13 adults with macrocephaly, only two (15%) had these lesions. Of the 27 normocephalic children examined with MRI, 16 (59%) showed T2 hyperintense lesions. The other way round, 14 of the 36 children with T2 hyperintensities (39%) and 4 of the 15 adults (27%) had macrocephaly. Of the 11 children without T2 hyperintense lesions, none had macrocephaly.

Optic glioma was diagnosed in 11 (55%) of the children with macrocephaly. Optic gliomas were less common in mildly affected patients (head circumference in the +2 SD to --+2.5 SD range; 4/10 children) than in the more severely affected ones (head circumference +2.5 SD to +4 SD, 7/10 children). On the other hand, of the children without macrocephaly, 14 of the 36 children with T2 hyperintensities (39%) and 4 of the 15 adults (27%) had macrocephaly. Of the 11 children without T2 hyperintense lesions, none had macrocephaly.

Nine (27%) of the macrocephalic patients had both T2 hyperintense lesions and optic glioma, including eight children (40%) and one young adult (8%) with macrocephaly. 5 (45%) of them had head circumference of +3 SD or more.

5.3 Imaging findings of the spine in NF1

5.3.1 General

Pathologic lesions of the spinal area were detected in 16 (52%) of the 31 children examined and 41 (91%) of the 45 adults, i.e. in altogether 57 (75%) out of the 76 individuals examined. 21 (68%) of the children and 21 (47%) of the adults suffered from neck- or back-related symptoms. Of the specific lesions, postural changes of the spine, changes in the CNF spaces and neurofibromas were most common (Table 12). The frequencies of postural abnormalities, CSF space changes and neurofibromas did not differ statistically between children and adults, whereas other lesions (vertebral anomalies etc.) were more common in adults than in children (p = <0.001).
The affected children had an average of 1.7 spine-related lesions, while the affected adults had 1.8 lesions, respectively. Eight children showed only one type, six showed two types and two showed three types of spinal lesions simultaneously.

Table 12. Spinal abnormalities seen in 76 NF1 patients examined with CT and/or MRI in children (<18 years, n=31) and adults (18 years or older, n=45).

<table>
<thead>
<tr>
<th>Type of abnormality</th>
<th>&lt;18 y</th>
<th></th>
<th>&gt;18 y</th>
<th></th>
<th>All</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Postural abnormality</td>
<td>9</td>
<td>29</td>
<td>20</td>
<td>44</td>
<td>29</td>
<td>38</td>
</tr>
<tr>
<td>CSF space changes</td>
<td>6</td>
<td>19</td>
<td>16</td>
<td>36</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>Neurofibromas</td>
<td>6</td>
<td>19</td>
<td>15</td>
<td>33</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>Other lesions</td>
<td>6</td>
<td>19</td>
<td>31</td>
<td>69</td>
<td>37</td>
<td>49</td>
</tr>
</tbody>
</table>

5.3.2 Manifestations of the bony spine

Postural changes (scoliosis, kyphosis or kyphoscoliosis) were seen in nine children (29%) and 20 adults (44%). The postural changes were mild in most patients, and only two patients had been operated on. These were a 7-year-old girl with severe progressive thoracolumbar scoliosis and a 31-year-old woman who had been operated at the age of 7 years for severe thoracic kyphoscoliosis.

In all of the 9 children, scoliosis/kyphosis affected the thoracic spine, while the cervical spine was additionally affected in one and the lumbar spine in another child. In the adults, the thoracic spine was affected in 17 individuals (85% of those affected) and the cervical spine in 9 (45%). None of them showed postural lesions of the lumbar spine.

Lesions of single vertebrae included anomalous dens of the CII in one child and an asymmetric thoracic vertebra in another. Affected adults included a patient with a block vertebra of C6-7, a patient with narrow and high vertebrae C6-7, two patients with wedge-shaped thoracic vertebrae and one patient with an anomalous spinous process and lumbar spina bifida. One additional patient showed enlarged foramen magnum. Other bony lesions included a hemangioma in a thoracic vertebra, Sheuerman disease of the thoracic spine and lesions caused by spondylitis in lumbar vertebrae in singular patients. The bony lesions associated with widened CSF spaces will be described separately.

5.3.3 Dural ectasias

Dural ectasias in the patients with NF1 included widened and deformed CSF spaces, which were associated with either concavities of the vertebral bodies or widened intervertebral foramina. They were observed in 6 children (19%) and 16 adults (36%).

Of the children examined, the cervical spine was affected in two (6%), the thoracic spine in four (13%) and the lumbar spine in three (38%). One child showed lesions in both the thoracic and the lumbar spine and another had lesions in all the three segments of the spine. The corresponding figures for the adults were 4 for the cervical spine (9%), 4 for the thoracic spine (9%) and 10 for the lumbar spine (43%). Two adults showed lesions
in two regions: one in the cervical and lumbar and another in the thoracic and lumbar areas.

The *cervical ectasias* varied in severity and could be found along the cervical spine at the level of several vertebrae simultaneously (Fig. 19). In milder cases, only widening of the CSF spaces was seen, while concomitant concavity of the vertebrae was observed in more advanced cases. Postural changes of the cervical spine were seen in all patients with more advanced lesions, as shown by Fig. 26. The spinal cord was, however, only affected in two patients, a 24-year-old male who had widespread intra- and extramedullary tumours in the cervical region and an 18-year-old male with mild thickening of the cord at the level of C3-4 and bilateral neurofibromas of the cervical nerve roots.

The *thoracic ectasias* were mostly milder than the cervical ones and less often involved concavity of the vertebrae. They varied in location and extended over several vertebrae, but only involved the whole thoracic spine in one patient. Postural changes (scoliosis) was present in two children and two adults with ectasias of the thoracic area. None of the patients showed changes of the thoracic spinal cord, with the exception of a 47-year-old male, whose cord extended exceptionally caudally to the second lumbar vertebra.

Fig. 19. Dilated cervical CSF spaces (long arrows) and concavity of the posterior parts of the vertebral bodies (short arrows) in a symptom-free girl aged 10.8 years (a), and a male aged 37 years (b). The spinal cords were normal. In patient (b), thoracic kyphoscoliosis was also found. -T2-weighted sagittal MR images (SE, 2300/103, 3 mm).
Lumbar ectasias were most common and varied from mildly widened CSF spaces to extensively widened spaces with prominent bony excavations of the posterior parts of the vertebral bodies. The changes usually extended over the whole lumbar spine and appeared more pronounced in the lower parts. The youngest patient with lumbar ectasias was a 4-year-old boy with muscular hypotonia and clumsiness, in whom myelography had shown widened liquor spaces and prominent concavity of the vertebrae (Fig. 20). At the age of 16 years, more prominent lordosis and more concave vertebrae were seen on MRI.

![Fig. 20. Dilated lumbar spinal canal with a wide dural sac and concavity of the posterior parts of the vertebral bodies (arrows) are seen on a plain film (a) and myelography (b) at the age of 4.6 years in a boy with NF 1. The same finding is shown on a sagittal T2-weighted MR image (TSE, 2500/103, 4 mm) (c) of the same patient at the age of 16.7 years.](image)

5.3.4 Spinal neurofibromas

5.3.4.1 Neurofibromas

Spinal neurofibromas were seen in 21 patients (28%), including 6 children (19%) and 15 adult patients (33%). They appeared as nerve root-associated tumours, which were most often located outside the spinal canal, but could extend intraspinally, widen the intervertebral foramina and compress the cord. They could appear at different levels of the vertebral column either uni- or bilaterally, and they were usually multiple. The size of the tumours varied from a diameter of a few millimeters to several centimeters, and the largest ones were located in the lumbar area.

Neurofibromas were not discernible on plain X-rays, but their presence could be suspected on the basis of widened intervertebral foramina. On CT, they appeared as tumours isodense or slightly hypodense compared to muscle tissue, and in the only case examined
with intravenous contrast medium, they were slightly enhanced. On T2-weighted MR images the tumours appeared hyperintense compared with the cord, while on T1-weighted images they were hypointense. Their contrast enhancement in MRI varied.

The cervical spine was affected in five of the studied children (16%) and in 10 adults (23%, including four females with spinal neurofibromatosis, see below). The youngest patients with cervical neurofibromas were two 11-year-old children. The thoracic spine was affected in three children and nine adults, and the lumbar spine in one child and eight adults. Fig. 21 shows the multiple extra- and intraspinal tumours seen in a 24-year-old NF 1 patient on MRI. Compression of the cervical cord due to tumours was seen in five patients, four of them with familial spinal neurofibromatosis (FSNF).

5.3.4.2 Familial spinal neurofibromatosis (FSNF)

In a family with neurofibromatosis in three generations, multiple spinal neurorofibromas were detected on MR imaging in the 61-year-old mother and her three adult daughters. The two grandchildren who also had neurofibromatosis were not imaged. The neurofibromas detected were distributed symmetrically at the cervical, thoracic and lumbar levels of the spine in all of the four patients (Fig. 22). The patients had only relatively few cutane-
ous café-au-lait-spots, and only one had mild axillary freckling. Dermal neurofibromas were suspected in two patients. No Lisch nodules were detected on neuro-ophthalmologic examination, and no signs of either NF1 or NF2 could be seen.

Fig. 22. a-c. Coronal T1 weighted non-enhanced MR images (SE, 500 /15, 3 mm) (a, b) of the cervical spine of four adult female patients (1-4) in the family with familial spinal neurofibromatosis show several bilateral extradural intraspinal neurofibromas (white arrows) compressing the spinal cord. Extraspinal tumours are also seen in all patients. Several small bilateral extradural neurofibromas (white arrows) are seen in the middle and lower parts of the thoracic spine in all of the four patients on T1-weighted MR images (c). Patient 2 also has a paraspinal mass on the right (c 2.2).
Fig. 22. d-e. T1-weighted coronal (d) and T2-weighted sagittal MR images (SE, 5000/105, 4 mm) (e) of the lumbar spine of the same patients show numerous bilateral extradural intra- and/or extraspinal tumours (black arrows) in all patients. There is a dumb-bell type of tumour (small white arrows) (d 3) and scalloping of the posterior parts of the vertebral bodies (e). – Not all tumours are marked.

The 32-year-old female proband who had no back-related symptoms had widespread spinal neurofibromas, the largest of them causing compression of the spinal cord at the C5-6 level. Her 37-year-old sister had been operated on several years earlier because of a symptomatic cervical neurofibroma compressing the cord, and later reoperated for tumours at the level of C5-7. The 38-year-old sister had had mild pain and weakness of the upper extremities, and MRI revealed several spinal neurofibromas, which caused compression of the cord at the C6-Th1 levels. She underwent surgery to remove the tumours at the C 7-8 levels. The mother of the family had been suffering from back pain and paraparesis for many years, and multiple thickened nerve roots had been found on previous CT. On MRI, several symmetrical neurofibromas at all levels of the spine were detected, and lumbar duralectasias were also found.

MR imaging of the head was normal in three of the patients, but the 38-year-old sister had a suspected small T2 lesion in the cerebral peduncle and a suspected frontal tumour 5 mm in diameter.
A linkage study of the family suggested close linkage to the NF 1 locus and excluded it from the NF 2 locus. DNA analysis of the histopathologically verified spinal neurofibromas in two of the patients showed no evidence of LOH at 17q.11.2. The family has been reported separately (Pöyhönen et al. 1997). The gene mutation of this as well as 2 other families with familial spinal neurofibromatosis has recently been verified (Messiaen et al. 2002), and the mutation in the NF 1 gene has been shown to be different in different families.
6 Discussion

6.1 General

The present study on the radiological findings of the central nervous system in patients with NF1 confirms NF1 to be a clinically highly variable disorder and shows that it often manifests in the CNS even before any related symptoms appear. CNS imaging is an indispensable method in the early detection of both clinically significant lesions and T2 hyperintense and other brain lesions that are diagnostically useful. CNS imaging has not only been necessary in the follow-up of the observed lesions but also in the follow-up of patients at an increased risk to develop CNS lesions later. Although CNS imaging has been extensively used for the diagnosis of NF1 in Finland, this is the first attempt to evaluate CNC lesions more extensively in a Finnish patient series.

The present series of 125 patients was derived from a population-based study of NF1 in Northern Finland (Pöyhönen 1999), which attempted to identify all NF1 patients in the study area. Not all of the clinically studied 164 patients had undergone CNS imaging or were able to participate. The series differs to some extent from those drawn from speciality clinics, which usually tend to comprise patients in need of medical help. The Northern Finnish series also includes less severely affected individuals and ones in an early stage of the disease, including ones identified among the healthy relatives of the patients in family studies. The present study group included individuals of different ages and with a wide variety of clinical manifestations, and it can be considered to represent relatively well the possible spectrum of radiological manifestations of NF1. The patients also underwent careful clinical and neuro-ophthalmologic evaluation, and individuals without clear evidence or a diagnosis of NF1 were excluded.

From the radiological point of view, the present series allowed both an age-related evaluation and a follow-up of the CNS changes by CT and/or MRI. The radiological equipment and methods used are ones commonly applied in the imaging of the CNS. Invasive approaches were not used routinely in order to avoid the slight risks involved, but they were used whenever more detailed diagnostic information was needed. Previously taken CT scans and, in some cases, MRI scans were available from several patients,
but most of the MRI studies were done during the study period from the year 1994 till 2000.

6.2 Presence of CNS lesions in NF1

The prevalence figures for different CNS lesions vary in different studies and depend on many factors, such as the selection and size of the patient series, the age of the participating patients and the imaging methods. In earlier years, the prevalence figures for CNS lesions were derived from CT findings, while the more recent studies are based on MRI. In the studies including mostly children, T2 hyperintensities of the brain and optic gliomas have been more frequent, while spinal and brain tumours have been more common in adults. Similarly, most of the diagnostic signs of NF1 (café-au-lait spots, Lisch nodules, etc.) have shown age-dependent frequencies in the reported series, including Northern Finnish patients (Pöyhönen 2000a). Another factor affecting the frequencies of the lesions in NF1 is whether the individuals examined have been symptomatic and seen for a medical consultation, or whether they have been seen in the presymptomatic stage, e.g. for genetic counselling, which was the case in the present series.

Lesions of the head were found in 95 patients (77%), including 53 children (90%) and 42 adults (65%). The commonest brain lesions were T2 hyperintense brain lesions, which were observed in 77% of the children and 33% of the adults examined with MRI, i.e. altogether in 51% of the patients. Optic gliomas were observed in 44% of the children and 15% of the adults, which accounts for 29% of the whole series. These figures are comparable with those reported previously from other countries (Tables 1 and 2). Of the 76 patients examined for spinal lesions, 57 (75%) were affected, including 52% of the children and 91% of the adults. In the present study, 19% of the children and 33% of the adults, i.e. 28% of all patients, had neurofibromas. The previously reported frequencies have ranged from 21% to 65% (Table 3).

Although the present patient series is relatively large, more accurate frequencies for CNS lesions will be published in the future, as soon as more systematic follow-up protocols are available for wider use and comparable information has been collected into international databases, such as that of Friedman et al. (1993).

6.3 Brain manifestations in NF1

Before the development of MRI, the most common brain lesions seen on CT and sought for were optic and other brain tumours. T2 hyperintense lesions were recognized as common lesions in NF1 only after 1989, when the MRI techniques superseded CT scanning in the imaging of the brain in NF1. On CT, some changes had been observed as hypodensities in the basal ganglia, but their significance had remained unknown, until it was shown that hypodense areas on CT correspond to hyperintense areas on MRI (e.g.. Menor et al. 1998, Duffner et al. 1989). In the present study, three patients with hyperintense T2 lesions on MRI showed hypodensities in the same areas on CT. In one child, bilateral tha-
lamic hypodensities were found on CT, but no pathological lesions on MRI were seen ten years later. These hypodensities had probably been lesions corresponding to the T2 hyperdensities on MRI. Part of the discrepancies in the observations on CT and MRI may be due to the fact that minor lesions may have remained undetected in CT if they were not specifically looked for.

6.3.1 T2 hyperintense brain lesions: localization, appearance and development

The preferential localization of T2 hyperintense brain lesions has been the basal ganglia in most studies (Duffner et al. 1989, Itoh et al. 1994, van Es et al.1996, Menor et al. 1998), as also in the present study (79% of the affected children). Lesions in the basal ganglia were more common in girls (100%) than in boys (57%), a finding that has not been reported earlier. Other common localizations have been the cerebellum, brainstem, supratentorial white matter and optic areas (Table 1). Affection of the hippocampus was not specifically searched in the present study, but it may be quite common (Turbidy et al. 2001). In the present study, the supratentorial white matter was affected in 44%, the cerebellum in 39% and and the cerebellar crus and pontine areas in 39%.

T2 hypertense brain lesions were more frequent in children than adults (3.5 and 1.3 lesions/affected patient, respectively), as has been reported previously (Aoki et al. 1989, Griffiths et al. 1999), and no differences were noticed between females and males. 39% of the children and 45% of the adults had T2 lesions only in one area, mostly in the pallidal globes either uni- or bilaterally.

On T2-weighted MRI images, the hyperintense lesions were seen as relatively sharply demarcated areas, especially in the basal ganglia, but they could also appear as more diffuse lesions, especially in the optic tracts, as has been reported previously (see Van Es et al. 1996). The size of the lesions varied, and they were larger on an average in children than in adults; only one adult had a lesion larger than 1 cm in diameter. Diffuse lesions were found in 36% of the children and 27% of the adults, and they were located in the temporal and optic tract areas in most cases, but were also seen in the cerebellum.

T2 hyperintense lesions are typically childhood manifestations of NF1, although they could be seen in adults. In the present study, they were most common in the youngest age groups of 0–4 years and 5–9 years, with 70% and 94% of the patients affected, respectively. Of all children under 18 years of age, 77% were affected, while the corresponding figure for adults was 33%. The number of affected cases diminished along with age, and none of the patients over 55 years of age had T2 hyperintense lesions. Similar findings have been reported from elsewhere (Aoki et al. 1989, Itoh et al. 1994). Griffiths et al. (1999) found lesions to be rare in children under the age of four years – the exact age(s) at which T2 lesions appear is(are) actually not known. In the present study, 7 out of 10 patients in the age group of 0–4 years had T2 hyperintensities (the youngest patient was three years old), and the three children without them were aged 0.2, 1.6 and 2.7 years.

In follow-up studies, T2 hyperintense lesions have shown a tendency to diminish or even totally disappear before adulthood, and mixed-type behaviour of these lesions may
occur in the same patient. In previous MRI studies, including mostly children (table 1) followed up for 2 to 5 years, most lesions remained unchanged or diminished, and mixed behaviour or progression was less common. This was also seen in the present study, where the mean follow-up time of the 21 patients was 2.1 years for the children and 3.4 years for the only adult. The lesions remained unchanged in 35% and diminished in 25% of the children (mean ages 9.5 and 9 years, respectively). In 20% of the children, both stable and diminishing lesions were seen (mean age 6.8 years). Mixed-type behaviour, including progression of the lesions, was seen in 15% of the patients (mean age 5.3 years). The lesions disappeared completely in one patient (5%) at the age of 5.2 years, only eight months after they had first been seen on MRI. Thus, in the present series, stable and decreasing lesions were more commonly seen in older children than mixed ones, as also reported by Itoh et al. (1994), Van Es et al. (1996), Menor et al. (1998) and Sevick et al. (1992). In the young adult patient the lesions remained unchanged. No follow-up imaging for the T2 lesions was available in older patients. According to Itoh et al. (1994), the lesions in the cerebellum disappear earlier than those in the basal ganglia and the brainstem.

6.3.2 Significance of T2 hyperintense brain lesions

The pathophysiology or structural features of T2 hyperintense lesions have not yet been fully elucidated. From the clinical point of view, they have usually been regarded as benign lesions. In rare cases, malignant evolution of the lesions has also been reported (Griffiths et al. 1999, Miaux et al. 1997, Carella et al. 1997), and the borderline between neoplastic and non-neoplastic lesions has not always been clear (Raininko et al. 2001). Szudek and Friedman (2002) came to the conclusion that the presence of T2 hyperintensities correlated with central system neoplasms other than optic gliomas. In one of the present patients, glioblastoma multiforme appeared at the site of a hyperintense lesion affecting partly the optic radiation, which had remained unchanged for many years.

The correlation of T2 hyperintense lesions of the brain with learning difficulties, behavioural problems, seizures and mental retardation has been widely studied, but the results have been contradictory (Ozonoff 1999).

The high prevalence, localization and behaviour of T2 hyperintense lesions are so characteristic of NF1 that these features have been suggested to be pathognomonic to this disorder (Duffner et al. 1989, Menor et al. 1998) and have been considered useful in the diagnosis of NF1. In the study of DeBella et al. (2000b), including both NF1 and non-NF1 patients with hyperintense T2 lesions, additional use of T2 lesions as a diagnostic criterion permitted the diagnosis of 30% of young patients with NF1 who did not yet fulfill the diagnostic NIH criteria. In the present study, too, T2 lesions were common and typical of the youngest age groups and could have been used to confirm the diagnosis of NF1. MRI could thus be used for diagnostic purposes in cases where a strong suspicion of NF1 is based on the presence of only limited diagnostic criteria.
6.3.3 Brain tumours

Optic and brain gliomas are the most common CNS tumours in patients with NF 1, and brain tumours, mostly low-grade astrocytomas, occur in 1-3% of patients with NF1. Brainstem gliomas and hypothalamic tumours have also been found to be relatively common. Spontaneous regression of especially hypothalamic tumours has been described.

Brain gliomas were found in 6 (5%) of the present study subjects. Four patients died because of the tumour. In addition, hypothalamic tumours were found in seven children, but all were extensions of optic gliomas. Of the brain tumours, four were histologically astrocytomas; in one of the two children affected with pilocytic astrocytomas the tumour disappeared spontaneously (Leisti et al. 1996). Of the two adult patients, a woman with grade III astrocytoma had a son who developed astrocytoma at the age of 7 years. Astrocytoma was suspected on the basis of the imaging findings in one further child, but biopsy revealed normal brain tissue. Two patients had malignant gliomas; one was a child who had an intraventricular grade IV glioma and who had also optic glioma and widespread T2 hyperintense lesions. In another patient, a 17-year-old male, multiform glioblastoma developed rapidly in a region where T2 hyperintensities had remained unchanged for several years.

Although NF1 predisposes to the development of malignant tumours (e.g. Pöyhönen et al. 1997b), their location and development cannot be predicted. Predisposing factors, such as an increased tendency for brain tumours to occur in individuals with optic gliomas (Friedman & Birch 1997) or T2 hyperdense lesions (Szudek & Friedman 2002), may be possibly related to the expression of NF1 gene mutations. Hereditary factors may also play a role, and unusual clustering of brain tumours and various cutaneous features have been previously reported in a family with NF1 (Faravelli et al. 1999). If early imaging of the brain is performed as a baseline study after the diagnosis, to evaluate the optic tracts, for example, useful background information for possible future need is obtained. Screening for brain tumours may be warranted in children with severe optic tract lesions and extensive T2 hyperintense brain lesions.

6.3.4 Other manifestations of the brain and head

Cerebral lesions other than T2 hyperintensities and brain tumours also occur with a higher frequency in NF1 patient than in the general population. They have been either developmental defects (e.g. vascular malformations) or manifestations of a slowly or rapidly developing disease process (e.g. obstructive hydrocephalus). Radiological findings may confirm the clinical suspicions of a lesion, but in many cases they are detected incidentally.

In the present study, five patients (4%) (four adults and one child) presented with cerebral vascular lesions in MRI, including a rapidly progressing large arteriovenous malformation, two venous angiomas, cavernous hemangioma and carotid dissection. Aneurysms, arteriovenous malformation and occlusive disease of the cerebral arteries have been reported in association with NF1 (Deans et al. 1982, Hoffman et al. 1998, Crawford
et al. 1988). In single cases, however, it is difficult to show whether the vascular changes are related to NF1 or not.

Exact frequencies of minor extraparenchymal abnormalities, such as cavum of the septum pellucidum, minor structural variants or mild brain atrophy, in NF1 have not been reported in the literature. Lewis et al. (1984) found cortical atrophy in 0.9% of their 217 NF1 patients aged from 0.1 to 69 years. In the present series, minor structural abnormalities, including variants, and/or cortical atrophy were detected in 43 (35%) patients. They were all incidental findings, and their association with NF1 could not be determined, as similar lesions are also common in patients without NF1.

Mild supratentorial ventricular dilatation has been found to be common in NF1. In the study of Maki et al. (1981), for example, 44% of the children and 60% of the adult NF patients (most of them with NF1) were found on CT to have mild ventricular dilatation without periventricular hypodensity. In the present study, mild ventricular dilatation without signs of increased intracranial pressure or atrophy was found in six (10%) of the NF1 children, but in none of the adults. Ten adults (15%) had mild ventricular dilatation, considered as an atrophic change, associated with cortical atrophy.

Hydrocephalus was detected in four children and two adults (4.8% of the present patients). In two children (ages 11 and 12 years) the cause of the hydrocephalus was aqueductal stenosis due to diffuse T2 hyperintensity surrounding the aqueduct. The imaging findings had been normal at the ages of 3 and 6 years, respectively. In three patients, hydrocephalus developed due to a glioma, and no specific cause was detectable in one adult. These findings are comparable with the previous studies, where hydrocephalus due to various causes has been reported in 2% to 5% of the patients with NF1 (Riccardi & Eichner 1986, Afifi et al. 1988).

Nontumorous intracranial calcifications, which have rarely been reported in NF1, were found on CT in three patients (2.4%; one child and two adults). In the 16-year-old boy, bilateral small calcifications were found in the globus pallidiae, possibly at the site of previous T2 hyperintense lesions. In addition, the calcifications in one child and one adult were associated with optic glioma.

Bony lesions of the head were found in seven patients (6%). Two (2%) had sphenoid dysplasia, which is a well-known bony lesion encountered in NF1 with frequencies reported between 4% to 8% (van Es et al. 1996, Gardeur et al. 1983). Thin or sclerotic areas of bone were found in four patients (3%) without any associated tumours. Bony anomalies were found in two patients at the junction of the skull and the cervical spine. Bone destruction secondary to an arteriovenous malformation was seen in one adult patient.

The bony changes and intracranial calcifications were all detected in CT imaging. It is therefore possible that small changes may remain unnoticed in the patients in whom MRI was used as the only imaging method.
6.4 Manifestations of the optic pathways and orbits in NF1

6.4.1 Optic gliomas

Optic gliomas are the most common tumours in children with NF1, with reported frequencies varying from 14% to 43% (Table 2; Balcer et al. 2001). They have been the most important target for CNS imaging in NF1, especially in children. In the present study, optic gliomas were found in 36 (29%) of the 124 NF patients, in 26 children (44%) and in 10 adults (15%). Visual acuity was normal in 20 (56%) patients, bilaterally reduced in 8 (22%) and unilaterally reduced in 8 (22%). Papillary atrophy was seen in 9 patients (25%), two of whom were unilaterally blind. No significant difference in the appearance of optic gliomas between men and women was observed. Optic gliomas were also significantly more common in children than in adults in this study.

Optic gliomas have been reported in NF1 patients during the first year of life already (Listernick et al., 1994) or at 1 to 2 years of age (Deliganis et al. 1996, Balcer et al. 2001), even in children who were asymptomatic. In the present study, the patients’ ages at the diagnosis of optic glioma ranged from 3 years (in three patients) to 57 years, with a mean age of 23.2 years. The mean age at diagnosis was, however, much lower in the younger age groups, being 9.6 years in those born in the 1970’s, 7.0 years in those born in the 1980’s and only 3.8 years in those born in the 1990’s. This trend reflects the changing practices in the ophthalmologic screening and imaging of children with NF1, which has also been pointed out elsewhere. Age at diagnosis was not affected by whether CT or MRI was used as the primary imaging method. In general, optic gliomas have been diagnosed earlier in symptomatic than asymptomatic patients. In the present study, the primary imaging finding of the optic system (CT) had been normal in eight patients (five of them children), but MRI revealed optic gliomas later. Similar cases have been reported by, for example, Massry et al. (1997) and Menor et al. (1998).

The localization and extent of optic gliomas in the present patients varied; intraorbital and/or prechiasmal optic nerve gliomas were most common, affecting almost all patients (94%). Chiasmal and/or hypothalamic lesions were seen in 21 (58%) patients and lesions of the posterior parts of the optic system in 5 (14%). In the study of Balcer et al. (2001), 49% of the NF1 patients had the postchiasmal structures affected. In the present patients, the optic nerve was solely affected in 31% of the patients, and combined prechiasmal and chiasmal affision with normal postchiasmal structures was seen in 33%. Although unilateral optic gliomas have been more common in some studies (Menor et al. 1998), most of the present cases were bilateral, with only prechiasmal gliomas being more common unilaterally (59%).

The radiologic behaviour of optic gliomas was found to be variable, as reported previously. Successive imaging was done on 33 patients with a mean follow-up time of 6.4 years for the 25 children and 5.5 years for the 8 adults. The optic gliomas remained unchanged in 21 patients (84%), i.e. 81% of the children and all adults. In the study of Listernick et al. (1994), optic gliomas remain unchanged in 92% of the 26 NF1 patients through a mean follow-up of 2.4 years. Pascual-Castroviejo et al. (1994) noticed that optic gliomas hardly grew at all during follow-up for up to 20 years.
Spontaneous regression of an optic nerve glioma was seen in one child between the ages of 7.4 and 13.2 years. Two children showed postoperative regression of their gliomas. One child with bilateral optic nerve gliomas showed first progression of the lesions to the chiasm, followed by regression.

Spontaneous regression of both optic nerve gliomas and gliomas of the chiasm or hypothalamus has been reported (Brzowski et al. 1992, Parsa et al. 2001), and it has been suggested that this could be due to an (unknown) factor also related to the regression of T2 hyperintense lesions of the brain.

In the present study, only one child showed progression of optic nerve glioma, but 8 patients (5 children and 3 adults) developed optic glioma after a normal initial finding on CT. These gliomas were found later on MRI after mean follow-up times of 3.8 and 2.8 years, respectively. Deliganis et al. (1996) found progression of optic gliomas in 31% of the patients after a follow-up of 10.2 years and Schroeder et al. (1999) in 56% of their child patients after a follow-up of 6.5 years. In the latter study, the children with progression had been diagnosed earlier than those without progression (3.2 years vs. 5.8 years) and they had more symptoms. Grill et al. (2000) reported 47% progression in a series of symptomatic children with NF1 observed at the age of over 6 years. Balcer et al. (2001) found progression of the optic gliomas to occur even during adolescence after the development of visual symptoms.

Although optic gliomas have a benign course in most patients, gliomas have been found even in very young children, and progression and later development of optic gliomas occur. Optic gliomas and T2 hyperintense brain lesions have shown a positive correlation, and baseline imaging of young children would reveal, in addition to optic gliomas, also these lesions and other manifestations. Clinical and neuro-opthalmological follow-up of patients is important, but the precise size and extent of the glioma is best seen in MRI. In the present study, four patients were primarily suspected to have optic gliomas (mild thickening of the optic nerve) on CT, which finding, however, could not be verified later on MRI. The nature of these minor changes remained unexplained.

In two further patients in the present study, MRI yielded additional information other than the optic lesions. In one patient, a hyperintense diffuse lesion was found in the area of a calcified optic tract lesion detected earlier on CT, and in another, the widened optic nerves on CT turned out to be normal nerves surrounded by ectatic dilatation of the optic sheath. Thickening of the optic nerves due to dilatation of the optic sheath is a known differential diagnostic feature (Jinkins et al. 1987), which is better demonstrated on MRI than on CT. In this study, altogether five patients (14%), four children and one adult, had hydrops of the optic sheath on MRI.

Contrast enhancement of the optic lesions has been found to be variable. In this series, enhancing optic lesions were detected in 6 children (11%). Further two children had non-enhancing, primarily hyperdense lesions on CT.

6.4.2 Other orbital findings

Other orbital imaging abnormalities are relatively rare in NF1. Sphenoid bone dysplasias are the most characteristic bony lesions, and they have been reported in 4–8% of patients
with NF 1 (Gardeur et al. 1983, Van Es et al. 1996). Sphenoid dysplasia was found in two (1.6%) of the present patients, and both of them also had plexiform neurofibromas of the orbital region. CT was found to be better able than MRI to detect bony (and calcified) lesions.

Orbital plexiform neurofibromas have been reported in 4% of NF 1 patients (Lewis et al. 1984), and six of the present patients (5%) were affected. In four of them, the tumour was partly intraorbital and partly facial, in one patient the plexiform neurofibroma was located in the upper eyelid. In one patient the tumor was located in the corner of the eye, being associated with sphenoid dysplasia and optic glioma.

6.5 Macrocephaly in NF1: Nature and associations with other CNS manifestations

Macrocephaly (head circumference more than 2 SDs over the mean for age and sex) is a common and well documented feature in NF1, with the reported frequencies varying from 27% to 45% (Riccardi et al. 1981, Huson et al. 1988). In the present study, 33 (27%) of the NF1 patients, 34% of the children and 20% of the adults, had macrocephaly, with 33% of the male and 19% of the female patients being affected. In about two thirds of the patients, macrocephaly was mild (head circumference from +2 SD to +2.4 SD for age and sex), and only one patient had a head circumference of +4 SD.

Both the origin and the clinical significance of macrocephaly have been subject to several studies. Di Mario et al. (1999), for example, found significant differences in 6 of the 24 ventricular and brain parameters measured on the MR images of NF1 patients and control subjects. There were no significant differences in any measures between patients with and without T2 hyperintense lesions. They suggested that lateral volume expansion of the supratentorial compartment and an increasing rate of brainstem growth along with aging were the predominant causes of macrocephaly in NF1. Increase of the surface area of the corpus callosum and the midsagittal area of the brain were reported by, for instance, Dubovsky et al. (2001) and Steen et al. (2001).

In the present study, cerebral measurements of 17 different parameters of the brain MRI scans were done on 14 macrocephalic and 14 normocephalic age- and sex-matched children with NF1. Four parameters indicating brain width, the maximum width of the brain, the width of the frontal horns and corresponding brain width and the brain width at the level of the fourth ventricle, were significantly wider in macrocephalic than in normocephalic children. The sagittal and midsagittal dimensions of the brain and the maximal midsagittal brain stem width were also significantly wider in the macrocephalic group. These results suggest, that no specific area or structure was responsible for the increased growth of the brain in the macrocephalic patients. No volumetric measurements were available.

In a volumetric study, Said et al. (1996) showed that the overall cerebral hemispheric volume was greater in NF1 patients than in normal subjects, and that this increase was due to an increase in the white matter volume. Similar observations on the role of white matter were made by Greenwood et al. (1997) and Steen et al. (2001). Cutting et al.
(2002), in their study on patients with NF1-related macrencephaly, reported that all patients had larger total and frontal white matter volumes than normal controls. The total volume of grey matter was also enlarged, but not in the patients with the attention deficit hyperactivity disorder (ADHD). On the other hand, Moore et al. (2000) found that especially grey matter contributed to the increase of brain volume, and that it was more prominent in young patients.

The possible association of macrocephaly with T2 hyperintense lesions and also optic gliomas was studied by DiMario et al. (1999) and Cutting et al. (2000), who did not find any differences in the brain measures of macrocephalic patients with or without T2 hyperintense lesions. In a recent large study on the associations of clinical features in NF1 (Szudek et al. 2003), macrocephaly, optic glioma and other neoplasms had a tendency to occur together more often than expected.

In the present study, all the 20 macrocephalic children examined with MRI had T2 hyperintense lesions, while 59% of the 27 normocephalic children were affected. Of the 13 adults with macrocephaly, only two (15%) had these lesions, and in the group of 51 normocephalic adults, T2 lesions were seen in 24%. The other way round, 39% of the children and 27% of the adults with T2 hyperintense lesions had macrocephaly, but none of the 11 children without T2 lesions were macrocephalic. These results suggest that a possible association between macrocephaly and T2 hyperintensities may exist, and that a common etiologic factor may play a role in both of them.

The presence of optic glioma was not found to be associated with macrocephaly; the lesion was found in 56% of the normocephalic and 55% of the macrocephalic children, respectively.

Macrocephaly was earlier considered an incidental finding without clinical significance, but the most recent studies have established a tentative relationship with clinical features. Said et al. 1996 noticed better visuo-spatial and developmental performance in the patients with greater right-hemispheric grey matter volume. Moore et al. (2000) also found that the grey matter volume was related to the degree the learning disability, and that diminished academic performance and visuo-spatial and motor skills were associated with greater regional corpus callosum size. Kayl et al. (2000) found the increased severity of attention problems to be associated with smaller total callosal areas. Cutting et al. (2000) found macrocephalic patients to show significant verbal impairment relative to normocephalic patients.

6.6 Spinal manifestations in NF1

In the present study, 76 patients (31 children, 45 adults) were scanned with CT and/or MRI. 55% of the patients had back-related symptoms (68% of the children and 47% of the adults). Young children, if symptomless, were not scanned equally often as adults because anesthesia would have been needed. Pathological lesions were seen in 75% of the patients, with 52% of the children and 91% of the adults being affected. The frequencies of postural and CSF space abnormalities and neurofibromas did not differ statistically in children and adults, but other lesions were more common in adults than in children (p=<0.001). All of the the last-mentioned manifestations are not necessarily related to
NF1, but may be occasional findings. In the study of Egelhoff et al. (1992), including both symptomatic and asymptomatic patients, 61% of the 28 NF1 patients were affected by spinal lesions.

6.6.1 Manifestations of the bony spine and CSF spaces

In previous studies, skeletal changes, including scalloping of the vertebrae associated with dilated CSF spaces, have been reported in 51% to 71% of the patients with NF1 (Casselman & Mandel 1976). Egelhoff et al. (1992) found bony lesions on MRI in 57% and dural ectasias in 11% of the patients with NF1 at a mean age of 15 years. In the present study, postural changes, including scoliosis, kyphosis or kyphoscoliosis (mostly mild), were seen in 29% of the children and in 44% of the adults. Among the patients with postural changes, the thoracic spine was affected in all children and 45% of the adults. Two patients suffered from severe childhood onset scoliosis/kyphoscoliosis and had been operated on. Vertebral anomalies were seen in seven patients (9%). Dural ectasias were detected in 29% of the patients, in 19% of the children and 36% of the adults, and the lumbar area was mostly affected, as described previously (Baltzell et al. 1974). Two young children had quite prominent dural ectasias of the lumbar or cervical areas. Four of the patients had abnormal CSF spaces at more than one level of the spine. The size of the spinal canal and the degree of associated scoliosis and/or kyphosis varied, and the thoracic area was most mildly affected. Follow-up was available for only one patient, who showed progression of both the dural ectasias, the concavity of the vertebral bodies and scoliosis in the lumbar area from four to sixteen years of age.

Some degree of abnormal curvature of the spine was reported in 10–41% of the NF patients (Riccardi 1981), and in more than 80% of the cases, scoliosis was found to appear before the age of 16 years. Scoliosis often affects a short segment of the lower thoracic spine, as in the present study, and is associated with anomalies of the adjacent vertebrae. Kyphoscoliosis has been seen in 2% of NF1 patients, and it has often been associated with dural ectasias (Klatte et al. 1976, Riccardi 1981). Cervical abnormalities have been seen more often in patients with kyphoscoliosis than in those with scoliosis only (Ken Yong-Hin et al. 1979).

Most of the present patients examined with CT or MRI had plain skeletal films also taken, in which the skeletal changes, such as postural changes, posterior scalloping of the vertebrae and widening of the spinal canal and the neural foramina, were adequately diagnosable. CT and MRI were, however, found to be superior in differentiating whether the bony lesions were due to tumours or widened CSF spaces.

6.6.2 Spinal neurofibromas

Spinal neurofibromas are relatively common in NF1, and their frequency has been reported to vary between 13% and 65% (Table 3). Thakkar et al. (1999) found spinal tumours in 65% of 54 NF1 patients examined with MRI (the tumours in three were intramedul-
The tumours were more common in symptomatic than asymptomatic patients, and different levels of the spine were similarly affected. In the present study, spinal neurofibromas were detected in 28% of the patients, 19% of the children and 33% of the adults, and the cervical area was most commonly affected, followed by the thoracic and lumbar areas, as in the study of Tatagiba et al. (1994). In the MRI study of Khong et al. (2001) on 53 NF1 children, 13% had spinal neurofibromas, but they were located predominantly in the thoracic and lumbar areas.

The extent and size of the spinal neurofibromas seen in the present study varied, and the largest ones were detected at the lumbal level, as in the study of Egelhoff et al. (1992). The tumours were either uni- or bilateral and usually multiple. The most severely affected young male patient with NF1 also had multiple intramedullary tumours. The cervical spinal cord was affected in only one additional patient with mild thickening of the cord. Intramedullary tumours, mostly astrocytomas, have also been rare in previous studies, the reported frequencies varying from 3% to 14% (Table 3). Compression of the cord by nerve sheath tumours was seen in 5 patients, four of them with FSNF. One adult patient had a relapsing cervical plexiform neurofibroma attaching to the nerve roots at the level C4-C6.

### 6.6.3 Familial spinal neurofibromatosis (FSNF)

In one family, exceptional spinal imaging findings were observed in four adult patients, which allowed delineation a new clinical type of NF1, called familial spinal neurofibromatosis, FSNF (Pöyhönen et al. 1997a). The family was discovered through an apparently healthy female and her two children affected by numerous café-au-lait macules but without Lisch nodules. The patient, her two sisters and their mother all showed widespread spinal neurofibromas on MRI; the children were not imaged. The mutation in this family has recently been localized to the exon 8 of the NF1 gene (Messiaen et al. 2003).

Characteristically, MRI in this family, as in those reported by others (Pulst et al. 1991, Weinstock et al. 1995, Ars et al. 1998 and Kaufmann et al. 2001), showed bilateral spinal neurofibromas at all levels of the spine, compression of the cervical cord, and lumbar dural ectasias in the adult patients. Although symmetrical spinal neurofibromas are seen in patients with NF1, they are less common than in the group with FSNF, where all adult patients were affected and in whom neurofibromas were detected at all levels of the spine. Compression of the spinal cord with subsequent symptoms, which is common in FSNF, is also rare in NF1. The absence of Lisch nodules was characteristic of all FSNF patients.

The experience so far obtained about FSNF suggests that spinal MRI may be helpful in the diagnosis of neurofibromatosis in individuals with relatively scant diagnostic signs, and that imaging of the whole spine may be indicated when symmetrical neurofibromas are found in one region of the spine.
6.6.4 Other spinal manifestations

Intramedullary tumours were seen in only one patient with severe NF1 with extensive manifestations. Several patients showed single lesions, such as vertebral anomalies and enlarged foramen magnum. The vertebral hemangioma and Scheuerman disease in some patients may rather represent occasional abnormalities.

6.7 Role of radiologic imaging in the study and diagnosis of NF1

NF1 is a genetic disorder that is still primarily diagnosed on the basis of its clinical features by using the widely accepted diagnostic NIH criteria, as in all cases of the present study. A diagnosis of NF1 in a patient always signifies a risk of having CNS manifestations at the time of diagnosis already or developing them at a later age. In children, the main diagnostic concern is the risk for optic gliomas.

The present study confirms that NF1 is, both clinically and radiologically, a highly heterogeneous disorder. Pathologic lesions of various types can be found practically anywhere in the CNS, either in the nervous tissue itself or in the neighbouring structures. Radiologic imaging can often detect the cause for the CNS-related symptoms, but it also reveals unexpected lesions, whose significance may need to be evaluated by further studies.

Although both CT and MRI have been established as valuable tools in detecting CNS manifestations, MRI is the method of choice for studying T2 hyperintense lesions of the brain, the intracranial extent of optic gliomas and lesions of the spinal cord and nerves and for differentiating optic nerve tumours from hydrops of the optic sheath. Because of a lack of ionized radiation, MRI is also suitable for repeated imaging when needed. The use and timing of CNS imaging in the diagnosis, screening and follow-up of NF1 patients has, however, remained somewhat controversial, because the clinical criteria of the disease are sufficient for the diagnosis of NF1 in most patients, and the most common manifestations of the disease, namely optic gliomas and T2 hyperintense lesions of the brain, have a benign course in most cases. Listerick et al. (1997), who considered regular clinical and neuro-ophthalmologic examination of symptomless optic gliomas necessary, suggested imaging only when symptoms occur. On the other hand, T2 hyperintense lesions have even been recommended as one of the criteria of NF1 in cases where the clinical criteria have not been met. In the study of Menor et al. (1998), MRI contributed to a definitive diagnosis of NF1 in 53% of the suspected cases and was recommended to confirm the diagnosis in young patients who did not fulfil the NIH criteria. The present study has also shown the significance of T2 hyperintense lesions in NF1 in children, in many of whom they confirmed the diagnosis. NF1 patients have an increased risk for brain and other malignancies, and malignant evolution of T2 hyperintense brain lesions on other than typical sites does occur. Screening studies have revealed specific variants of NF1, such as FSNF in Northern Finnish patients, and families with several members affected by brain tumours have been described, such as the mother and her son with brain astrocytomas. There is a trend to use MRI imaging more extensively and at an earlier age in the evaluation of NF1 patients, but CNS imaging should be considered on an individual basis.
by the multidisciplinary team which is responsible for the clinical follow-up of the patient.

The use of intravenous contrast medium has been recommended by several authors (Bonawitz et al. 1998) both in MRI and CT. In the present study, contrast medium was used when necessary in CT and MRI for diagnostic purposes, but not in patients screened for CNS lesions. In the latter group, only rare patients needed MRI scanning with contrast enhancement in order to obtain further information.

In general, the role of CT has diminished because of the risks caused by ionized radiation especially to the lens in orbital studies, but also because of the need for repeated follow-up examinations. The availability of MRI is, however, still limited, and the examination is time-consuming and expensive. The risks related to anesthesia and the use of contrast medium also need to be considered in the case of both CT and MRI.

The present study reflects the developing diagnostic and follow-up practices of NF1 in a modern university hospital setting. The new methods being developed, such as MR spectroscopic and diffusion studies and PET, have already shown promising results in the differentiation between benign and malignant or potentially malignant lesions in NF1.
7 Summary and conclusions

In the present study, the radiologic features of the CNS were analyzed with CT and/or MRI scanning in a series of 125 patients with neurofibromatosis 1 (NF1) from Northern Finland. The patient series was well representative of this hereditary disorder, and it consisted of patients with a wide age range and marked clinical variability. The patients belonged to a larger group collected for an epidemiologic and clinical study and also included some milder cases discovered in family studies.

The present study, which is the first extensive radiologic analysis of Finnish NF1 patients, confirms that NF1 is, even radiologically, an extremely variable disorder, with the CNS affected in most patients. Although certain lesions are common in NF1, the radiologist may encounter and need to explain unexpected findings, of which FSNF is a good example.

1. Of the 124 patients with imaging of the head, 77% showed pathologic findings. T2 hyperintense lesions seen on MRI were the most common findings, with 77% of the children and 33% of the adults affected. Optic gliomas were seen in 29% of the patients: in 44% of the children and 15% of the adults. Other manifestations of the head included intracranial tumours, bony lesions and plexiform neurofibromas. Spinal changes were detected in 75% of the 76 patients studied: in 52% of the children and 91% of the adults. Postural changes were most common (38% of the patients), followed by CSF space changes (29%) and neurofibromas (28%). Other, less common spinal lesions were seen in 49% of the patients.

T2 hyperintense lesions were most common in children in the age group of 5 to 9 years and usually appeared bilaterally in the pallidal globes. In some cases they could have been used as a diagnostic aid, although all patients in this study had been diagnosed clinically before the MRI scanning. T2 hyperintense lesions were equally common in females and males, but lesions in the globus pallidus and putamen were more common in females. On CT, the corresponding lesions were seen as hypodense areas only in a few patients.

Age at the diagnosis of optic gliomas had dropped from 9.6 years in the patients born in the 1970s to 3.8 years in those born in the 1990s. For the purposes of radiologic diagnosis, both CT and MRI were reliable, but MRI is more accurately able to visualize the lesions of the optic tracts and hydrops of the optic sheet. The intraorbital and/or prechiasmal optic nerve was affected in 94% of the patients, the chiasm and/or hypothalamus in
58% and the posterior parts of the optic system in 14%. Optic gliomas were bilateral in most cases, although prechiasmal gliomas were more common unilaterally. Gliomas were equally common in females and males.

Brain tumours other than optic gliomas were found in 8% of the patients, including astrocytomas (5%). In one family, both the mother and a son were affected. In one patient, a verified astrocytoma disappeared spontaneously.

Spinal lesions were more common in adults than in children, but even young children could be severely affected: two children had severe scoliosis requiring operation, and two had quite prominent dural ectasias of the cervical/lumbar level. A young man had widespread neurofibromas of the spinal nerves and multiple medullary tumours. Medullary affilions were rare. Postural changes were mostly mild and commonest in the thoracic spine. Dural ectasias were most common in the lumbar area. Spinal neurofibromas varied in extent and size, and the largest tumours were found in the lumbar area. An exceptional family with rare familial spinal neurofibromatosis (FSNF) in four adult individuals in two generations were characterized by MRI. In them, the main radiological feature was the presence of bilateral multiple neurofibromas at all levels of the spine. Compression of the cord was seen in five patients, four of them with FSNF.

2. At follow-up, T2 hyperintense lesions (mean follow-up time 2.1 years) remained unchanged in 35% and diminished in 25% of the children. Stable and diminishing lesions, which were more common in older children, were found in 20% and mixed-behaviour lesions in 15% of the children. The number and size of the lesions were larger in children than in adults. In one patient, a glioblastoma appeared at the site of a T2 hyperintense lesion, suggesting that the development of these lesions should be followed radiologically, especially when their location is atypical.

During a mean follow-up of 6.4 years for the children and 5.5 years for the adults, the optic gliomas remained stable in 84% of the patients. Regression was seen in three children, and one child showed first progression and then regression of the glioma. Eight patients with normal initial CT findings were found to have an optic glioma on the following MRI, usually with a slight thickening of the optic nerve.

In a boy with spinal lesions, progression of the dural ectasias and scalloping of the posterior parts of the vertebrae were seen during follow-up for 12 years.

The variable appearance of the CNS changes in the different age groups and the follow-up data show that NF1 is not a stable disorder, but that different lesions in different individuals show variable behaviour. The exact time of appearance of the lesions is not known, but they mostly appear in early childhood. Some lesions, such as T2 hyperintense lesions, are transient, while lesions such as optic gliomas tend to remain stable. Malignant development of a hamartomatous CNS lesion may occur unexpectedly at any age, even at the site of a benign T2 hyperintense lesion. The present study confirms that radiologic follow-up of NF-related lesions of the head and spine seems warranted in some cases as part of the clinical follow-up of the patients.

3. Macrocephaly was found in 27% of the present patients, which percentage is of the same magnitude as reported previously. Brain measurements of 14 macrocephalic and 14 age- and sex-matched normocephalic patients indicated that no specific area or structure of the brain could be considered responsible for the increased growth of the brain.
It was observed that all studied macrocephalic children had T2 lesions (mean number 5.6/patient), while 59% of the normocephalic children were affected (2.6 lesions). On the other hand, the children without T2 hyperintense lesions did not have macrocephaly, while 27% of those affected with them had macrocephaly. The positive correlation between the appearance of macrocephaly and T2 hyperintense lesions may signify the presence of a common pathogenic factor in their development. No corresponding association between optic gliomas and macrocephaly was observed.

Because NF1 is a progressive and highly variable disorder, the role of the radiologist is not limited to the diagnosis or follow-up of the patient, but also includes the detection and interpretation of unexpected lesions at any level of the CNS. Radiologic studies with MRI therefore also include elements of screening and early detection – or exclusion – of possible clinically significant lesions. Early screening for the lesions of the head with MRI is useful, and can recommended in most cases for newly diagnosed NF1 patients in order to obtain an overview of the extent of the disease. The presence of T2 hyperintense brain lesions confirms the diagnosis, and the presence and extent of optic gliomas will be revealed. Follow-up studies are necessary in patients with T2 hyperintense lesions at exceptional sites and in patients with optic gliomas with symptoms. As there is a tendency to concentrate the primary studies and follow-up of patients with NF1 into multidisciplinary centers, the role of the radiologist will be crucial in proper planning of follow-up.
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