

## ORIGINAL ARTICLES

# A prospective 10 year follow up study of patients with neurofibromatosis type 1

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## Abstract

**Objective**—To establish the prevalence and incidence of symptoms and complications in children with neurofibromatosis type 1 (NF1) and to assess possible risk factors for the development of complications.

**Design**—A 10 year prospective multidisciplinary follow up study.

**Patients**—One hundred and fifty children diagnosed with NF1 according to criteria set by the National Institutes of Health.

**Results**—In 62 of 150 children (41.3%) complications were present, including 42 (28.0%) children with one complication, 18 (12.0%) with two complications, and two (1.3%) with three complications (mean (SD) duration of follow up 4.9 (3.8) years). Ninety five of the 150 children presented without complications (follow up, 340.8 person-years). The incidence of complications was 2.4/100 person-years in this group. An association was found between behavioural problems and the presence of complications.

**Conclusion**—This is the largest single centre case series of NF1 affected children followed until 18 years of age. Children with NF1, including those initially presenting without complications, should have regular clinical examinations.

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Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder affecting one in every 3300 individuals. Half of all cases are sporadic cases.<sup>1</sup> Symptoms are highly variable and severity cannot be predicted, even within families. Diagnostic criteria for NF1 were established by the National Institutes of Health consensus development conference (NIH) in 1987.<sup>2</sup>

Characteristic features of the disease include café au lait spots, axillary and inguinal freckling, neurofibromas, and Lisch nodules. Minor disease features seen in NF1 patients are macrocephaly, short stature, hypertelorism, thorax abnormalities, and learning, speech, motor, and behavioural disorders. In child-

hood, various complications can occur such as mental retardation, tumours of the central nervous system (optic and chiasm gliomas), orthopaedic abnormalities, endocrinological disorders, and malignancies.<sup>3 4</sup>

Previously, only the prevalence of symptoms and complications have been reported in NF1 patients. In this study, which includes the largest reported series of children with NF1, we determined both overall prevalence and incidence rates of symptoms and complications in 150 children. Subsequently, we analysed possible risk factors for the development of complications.

## Methods

### PATIENTS AND FOLLOW UP

Since 1985, a multidisciplinary NF1 team in the Sophia Children's University Hospital in Rotterdam including a paediatrician, dermatologist, paediatric neurologist, ophthalmologist, and clinical geneticist, has evaluated children suspected of having NF1. At first visit, clinical evaluations, x rays of the cranium and the entire spine, and a visual evoked potential were performed. In all NF1 affected children, irrespective of presence of complications, follow up consisted of periodic clinical evaluations supplemented by additional studies as required. In this study, follow up was calculated from first examination date with an NF1 diagnosis.

Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were only performed on indication—ophthalmological abnormalities (optic atrophy, relative afferent pupillary defect, abnormal Ishihara colour vision test, or abnormal visual evoked potential), endocrinological disorders, mental retardation, and various other neurological abnormalities.

### DEFINITIONS

Individual symptoms and complications were defined as follows: mental retardation was defined as attendance at a school for the mentally disabled; learning difficulties were defined as attendance at a special school, other than a school for the mentally disabled. Accordingly, prevalence of mental retardation and learning difficulties were established in children 6 years and older (n = 110). Speech abnormalities

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were variable and often included late onset of speech as well as articulatory problems. Counselling by a speech therapist was recorded. Motor problems were defined as clumsiness on evaluation by a paediatric neurologist; support by a physiotherapist was reported. Behavioural problems varied from attention deficit hyperactivity disorders to aggressive behaviour and depression requiring psychiatric help.

Optic pathway gliomas reported in this study were detected on CT/MRI scans of the brain. Plexiform neurofibromas were defined as either a large, soft swelling with ill defined borders (diffuse plexiform neurofibroma) or a firm, spherical or ovoid shaped swelling (nodular plexiform neurofibroma).<sup>4</sup> Plexiform neurofibromas were interpreted as complications on the basis of either localisation or symptomatology. Threatening localisations included the head and neck, the vertebral column, paravertebrally and/or the perineum. Plexiform neurofibromas causing severe symptoms (pain, functional disorders, neurological deficits, and cosmetic disfigurement) were also considered to be complications.

Severe scoliosis was defined as a vertebral column abnormality requiring treatment, such as surgery or corset.

#### PREVALENCE RATES

Prevalence was calculated on the basis of a symptom or complication on 1 January 1996 in children (younger than 18 years of age) diagnosed with NF1 according to NIH criteria. Nine children examined before 1985 by all specialists on a regular basis were also included in this study. This population will be referred to as group A (n = 150).

The prevalence of symptoms and complications at initial presentation can be calculated easily by subtracting the number of occurring symptoms/complications (n) from the overall prevalence rate.

#### INCIDENCE RATES

Incidence rates of symptoms and complications were established on 1 January 1996 in children (younger than 18 years of age) without complications at presentation who were diagnosed with NF1. This group of children, which is a subset of group A, will be called group B (n = 95). These patients presented solely with café au lait spots, freckling, Lisch nodules, and/or dermal neurofibromas. Person-years, the denominator of the incidence rate, was defined by the first examination date with NF1 diagnosis and last examination date. Children reaching the age of 18 years before January 1996 were considered withdrawn alive.

Incidence rates of newly presenting complications were also computed in children with one or two complications at presentation. This group will be referred to as group C (n = 55) and is also a subset of group A. Person-years were defined by first examination with NF1 diagnosis and complication(s) and last examination date. Complications were defined as new when occurring more than one year after the presenting complication(s).

*Table 1 NIH diagnostic criteria in neurofibromatosis type 1 (NF1). Two or more of the criteria are necessary for a diagnosis of NF1*

<i>Clinical signs</i>	
Six or more café au lait spots over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals	
Two or more neurofibromas of any type or one or more plexiform neurofibroma	
Freckling in the axillary or inguinal region	
Optic or chiasma glioma	
Two or more Lisch nodules (iris hamartomas)	
A distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bone cortex, with or without bowing and pseudoarthrosis	
<i>Family history</i>	
A first degree relative (parent, sibling, or offspring) with NF1 by the above criteria	

#### ANALYSIS

Clinical data were obtained from medical records and registered on a standardised form. Data were analysed with Dbase IV and SPSS 6.0. Associations between specific symptoms and the presence of complications were assessed by univariate analysis with the  $\chi^2$  test ( $p = 0.05$ , two sided). Risk factors tested included sex; age at NIH diagnosis; physical characteristics observed in children with NF1, such as macrocephaly, short stature, hypertelorism, thorax abnormalities, and mild scoliosis; as well as a variety of symptoms such as learning difficulties, motor disorders, behavioural problems and speech disorders.

#### Results

During this prospective follow up study, 209 children were examined for a suspected diagnosis of NF1. NF1 was diagnosed according to NIH criteria (table 1) in 150 children (64 girls, 86 boys). Five children (3.3%) died of malignancies during the follow up period. Almost half of the NF1 affected children (46%) were referred by either a general practitioner or other primary health care worker. The others were referred by medical specialists.

#### PREVALENCE RATES

Prevalence rates of diagnostic criteria and complications in group A are depicted in table 2. Mean (SD) age at last examination date was 10.4 (5.1) years. Mean (SD) duration of follow up was 4.9 (3.8) years.

#### Diagnostic criteria

Six or more café au lait spots of the required diameter were found in 96.7% of NF1 affected children (mean age at presentation of sign, 3.1 (3.1) years). Freckling was found in 85.3% (mean age at presentation of sign, 6.3 (4.2) years). Dermal neurofibromas were found in 40.0% (mean age at presentation of sign, 8.9 (4.5) years). Plexiform neurofibromas were found in 26.6%, Lisch nodules were found in 52.0% (mean age at presentation of sign, 8.8 (3.6) years), and a distinctive osseous lesion (sphenoid dysplasia, thinning of long bone cortex) was seen in 7.8% of NF1 affected children (table 2). In addition, scalloping of the vertebral bodies was seen in five (4.0%) children and widened foramina of the vertebral

Table 2 Prevalence rates of diagnostic criteria, symptoms, and complications in 150 unselected neurofibromatosis type 1 (NF1) children (group A)

	% (n)	Huson and colleagues <sup>7</sup> (%)	Obringer and colleagues <sup>8</sup> (%)
<b>Diagnostic criteria</b>			
Café au lait spots	96.7 (145)	97–100	97.0
Freckling	85.3 (128)	70.0	81.0
<b>Neurofibromas</b>			
Dermal	40.0 (60)	0–40	15.0
Plexiform*	26.6 (40)	25.7	–
Lisch nodules	52.0 (78)	79–85	30.0
Distinctive osseous lesion†	7.8 (11)	–	6.0
<b>Complications</b>			
Mental retardation	17.2 (19)	2.9	–
Optic pathway glioma	11.3 (17)	5.1	4.0
Epilepsy	0.7 (1)	5.1	–
Plexiform neurofibroma‡	18.0 (27)	12.8	–
Bowing	2.7 (4)	–	–
Pseudoarthrosis	2.0 (3)	7.8	6.0
Hemihypertrophy	2.7 (4)	–	–
Severe scoliosis	2.0 (3)	2.6	–
Aqueduct stenosis	0.7 (1)	2.1	–
Atlantoaxial dislocation	0.7 (1)	–	–
Endocrinological disorder	4.6 (7)	–	–
Central precocious puberty	2.0 (3)	–	–
Growth hormone deficiency	2.0 (3)	–	–
Diencephalic syndrome	0.7 (1)	–	–
Malignancy§	4.0 (6)	1.5**	5.0
Neurofibrosarcoma	2.0 (3)	–	–
Malignant brain tumour	2.7 (4)	–	–

\*Total number of plexiform neurofibromas; †sphenoid and occipital dysplasia (number of x rays/computed tomography scans of skull = 138) and congenital bowing; ‡plexiform neurofibromas considered as complications; §one child was diagnosed with both an astrocytoma and a neurofibrosarcoma; ¶If available, percentages shown in NF1 patients ≤ 18 years (n = 39); \*\*both rhabdomyosarcomas.

bodies was seen in 10 (7.8%) children. In 74 of 150 (49.3%) cases one or more family members were also diagnosed with NF1.

#### Minor disease features

Learning difficulties, speech abnormalities, behavioural problems, and motor disorders were seen in 33.0%, 58.7%, 47.3%, and 49.3% of children, respectively. A speech therapist was treating 76% of the children with speech abnormalities. Support by a physiotherapist was recorded in 66% of the children with motor disorders. Data on macrocephaly, short stature, hypertelorism, and thorax abnormalities have been reported elsewhere.<sup>5</sup>

#### Complications

In summary, 62 group A patients (41.3%) had one or more complication, including 42 (28.0%) children with one complication, 18 (12.0%) with two complications, and two (1.3%) children with three complications. In 88 of 150 (58.7%) children no complications had been diagnosed at last examination date.

Ophthalmological symptoms were seen in 10 of the 17 children with an optic pathway glioma (58.8%). Three of the 17 (17.6%) children with an optic pathway glioma received radiotherapy owing to progressive visual loss. All but one child with an optic pathway glioma had abnormal visual evoked potentials at first presentation. Children with an endocrinological disorder after radiotherapy for an optic pathway glioma were excluded from this analysis (n = 2).

Three of four children with bowing of the tibia developed pseudoarthrosis. One child presented with bilateral bowing and unilateral pseudoarthrosis, which is a rare condition. Histology reports of malignant brain tumours

Table 3 Incidence rates of complications in 95 children presenting without complications (group B)

	Incidence rates/ 100 person-years (n)
Optic pathway glioma	1.2 (4)
Plexiform neurofibroma	0.6 (2)
Atlantoaxial dislocation	0.3 (1)
Endocrinological disorder	0.3 (1)

Table 4 Incidence rates of subsequent complications in 55 children presenting with one or two complications (group C)

	Incidence rate/ 100 person-years (n)
Optic pathway glioma	0.3 (1)
Plexiform neurofibroma	0.3 (1)
Severe scoliosis	0.3 (1)
Atlantoaxial dislocation	0.3 (1)
Endocrinological disorder	0.9 (3)
Malignancy	0.9 (3)

included two astrocytomas, one medulloblastoma, and one oligodendroglioma (grade III).

#### INCIDENCE RATES

##### Symptoms and complications

The total number of person-years in children presenting without complications was 340.8. The incidence of complications in group B is depicted in table 3. In group B, 2.4 complications developed for each 100 person-years. Complications developed in seven children (one complication developed in six children and two complications developed in one child). Incidence rates were highest for optic pathway glioma and plexiform neurofibroma. Univariate analysis for possible risk factors in group B showed an association between behavioural problems and the presence of complications ( $\chi^2$  test,  $p < 0.05$ ).

Subsequent complications in children with one or two complications at presentation are depicted in table 4. The total number of person-years in this subset was 322.6. In group C, 3.0 complications developed for each 100 person-years. Most second/third complications were endocrinological or a malignancy. One patient with cervical dysplasias at presentation experienced atlantoaxial dislocation after surgery for a plexiform neurofibroma (Cnossen *et al*, unpublished data). There was no significant difference between the number of complications that developed in group B and group C (95% confidence intervals (CI), -0.05, 0.07;  $p > 0.05$ ).

#### Discussion

This study presents prevalence and incidence rates of symptoms and complications, recorded during a prospective follow up study of a large group of NF1 affected children (n = 150). Huson and colleagues<sup>7</sup> documented the age range of presentation and prevalence of major complications in a smaller group of 39 NF1 patients who were younger than 18 years. Long term prospective follow up of children with NF1 was determined necessary to define the natural history of the disease. An analysis of the prevalence and applicability of the diagnostic criteria in children 6 years old and younger was

given by Obringer and colleagues.<sup>6</sup> However, descriptions of complications were not included.

#### PREVALENCE RATES OF SYMPTOMS AND COMPLICATIONS

Strikingly, in the study population as a whole, complications were observed in 42%; moreover, one third of these children had two or more complications of the disease.

The prevalence of the diagnostic criteria and severe scoliosis were similar to those reported in other studies.<sup>2 6 7</sup>

Prevalence rates of learning difficulties, motor disorders, behavioural problems, and speech disorders were similar to those reported in other studies.<sup>8 9</sup> The high percentages of these problems emphasises the necessity of following up NF1 affected children and informing their parents about the association of these symptoms with the disease, so that educational and supportive measures can be taken.

The prevalence of optic pathway glioma has been variously reported, depending on the indication for brain imaging: 19%, if carried out routinely<sup>10</sup>; 11.3%, if performed because of suspected central nervous system tumours, eye problems and/or endocrinological abnormalities (this study); 5.1%, if carried out because of suspected eye problems.<sup>7</sup> We agree that routine neuroimaging for optic pathway glioma is not indicated because only half of the detected optic pathway gliomas in our study were symptomatic; one third of these presented with progressive visual loss. One of the three children in this series had central precocious puberty and an optic pathway glioma was found on MRI examination. This is in contrast with earlier observations of concurrence of chiasma glioma in all NF1 patients with central precocious puberty.<sup>11</sup>

Distinct from Huson and colleagues,<sup>7</sup> none of the NF1 patients in this series had a rhabdomyosarcoma. Therefore, our data suggest that this is a rare complication. Prevalence of epilepsy, pseudoarthrosis, and aqueduct stenosis were higher in the Welsh study. Contrastingly, except for two patients with delayed puberty, Huson did not observe any children with endocrinological disorders.<sup>7</sup>

#### INCIDENCE RATES OF SYMPTOMS AND COMPLICATIONS

In the group presenting without complications, 2.4 complications developed for each 100 person-years. By way of illustration, follow up of 20 children presenting without complications for five years would lead to the discovery of more than two complications in the total group. This may not seem impressive but the complications in NF1 are severe and cause both serious morbidity and mortality. We feel that follow up of children is indicated on the basis of these data.

The incidence rate of subsequent complications in children presenting with one or two complications was 3.0/100 person-years, not significantly higher than in the group presenting without complications.

Because this is the first study on incidence rates of symptoms and complications in NF1

patients, there are no comparative data available. Although most of those with plexiform neurofibromas (88.9%) and optic pathway gliomas (70.6%) presented with symptoms at initial examination, they might also develop symptoms later on and present during follow up. Accordingly, optic pathway gliomas have been reported to develop in patients without abnormalities on MRI scan at presentation.<sup>12</sup>

However, most endocrinological disorders (57.1%) presented during follow up (table 4). Therefore, deviations from the growth velocity curve and premature manifestations of puberty should be recognised as possible endocrine complications of NF1. Malignancies were all acquired during follow up. Half of the presenting tumours developed in pre-existing plexiform neurofibromas.

An association was found between behavioural problems and the development of complications. However, behavioural problems may also be a consequence of complications in children and as such cannot be considered a risk factor.

#### FUTURE PROSPECTS AND RECOMMENDATIONS

Our data indicate that routine *x* rays of the cranium and the entire spine are unnecessary, unless symptoms indicate these investigations. The observation of one case of atlantoaxial dislocation in a patient with cervical dysplasias and the 11.8% prevalence of this condition in NF1 leads to our recommending complete bidirectional cervical vertebral column *x* rays in all NF1 patients undergoing anaesthesia and/or surgery. Visual evoked potentials were a valuable addition to the ophthalmological examination at first presentation. Although the specificity of this test is low, sensitivity is high,<sup>13</sup> leading to detection and treatment of progressive optic pathway glioma at an early stage.

Our data provide justification for follow up of NF1 patients because they give the prevalence of complications at presentation, the increase of complications (incidence rate), and the overall prevalence of specific complications. We conclude that NF1 is a disease that is associated with various psychomotor problems and severe complications during childhood. The children merit regular surveillance by an experienced paediatrician, paediatric neurologist, and ophthalmologist. Factors predisposing children with NF1 towards the development of complications remain to be determined. Children without complications should be seen every one to two years, unless problems arise earlier. Children with complications at presentation should be examined more frequently. These children do not have a higher risk of subsequent complications than children presenting without complications. We hope that our prospective follow up study will be useful for physicians and clinical geneticists caring for NF1 patients and informing families about the nature and progress of the disease.

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