Clinical Risk Factors for Mortality in Patients With Neurofibromatosis 1

A Cohort Study of 378 Patients

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Objective: To identify the main clinical features associated with mortality in patients with neurofibromatosis 1.

Design: Cohort study.

Setting: Referral center for neurofibromatosis.

Patients: Three hundred seventy-eight patients with neurofibromatosis 1 who had more than 1 year of follow-up in the center.

Main Outcome Measures: Mortality. Clinical features, especially dermatological, were evaluated as potential factors associated with mortality.

Results: Factors associated independently with mortality were the presence of subcutaneous neurofibromas (odds ratio, 10.8; 95% confidence interval, 2.1-56.7; \( P < .001 \)), the absence of cutaneous neurofibromas (odds ratio, 5.3; 95% confidence interval, 1.2-25.0; \( P = .03 \)), and facial asymmetry (odds ratio, 11.4; 95% confidence interval, 2.6-50.2; \( P < .01 \)).

Conclusions: Some features that can be found by a routine clinical examination are associated with mortality in patients with neurofibromatosis 1. Clinical follow-up should be focused on patients with subcutaneous neurofibromas and/or the absence of cutaneous neurofibromas and/or facial asymmetry.

Arch Dermatol. 2003;139:187-191

Neurofibromatosis 1 (NF1) is a common human genetic disease with an estimated birth incidence of 1 in 2500 to 3300 infants, an autosomal dominant mode of inheritance, and a high rate of new mutations.1 Neurofibromatosis 1 is characterized by multiple brown skin macules (café au lait spots), intertriginous freckling, iris hamartomas (Lisch nodules), and multiple cutaneous neurofibromas.2 The morbidity and mortality caused by NF1 are dictated by the occurrence of complications that involve any of the body systems. Neurofibromatosis 1 can be associated with optic gliomas, spinal and peripheral nerve neurofibromas, neurologic or cognitive impairment, scoliosis and other bone abnormalities, malignant tumors of the nerve sheath, pheochromocytoma, and vasculopathy.3 The disease is fully penetrant by the age of 8 years,4 but expressivity is variable.5 Manifestations of NF1 vary at different times in an individual’s life. Substantial variability also exists among affected members of a single family. This variability confounds clinical management and genetic counseling. Indeed, the evolution and occurrence of complications in patients with NF1 seems to be unpredictable.

In the French NF network, the Réseau NF-France, clinical follow-up is recommended for each patient with NF1.6,7 Therefore, clinical predictive factors for mortality would be helpful to target the follow-up for susceptible patients. We designed a study to identify the main clinical features associated with mortality.

METHODS

Patients, Data Description, and Definitions

The study was performed using clinical data from the database of our Neurofibromatosis Clinic, the Réseau NF-Mondor. The Réseau NF-Mondor is a multidisciplinary referral center for adult patients with NF. Most patients, mainly adults (about 85%), are referred by specialists (45%) (in dermatology, neurology, pediatrics, genetics, or orthopedic and plastic surgery), the French NF lay group (20%), general practitioners (10%), and miscellaneous sources (10%); 15% of the patients are self-referred.
Four hundred thirty-three patients with NF1, according to established criteria, were ascertained prospectively between June 1, 1995, and June 30, 2001, using the software of the National Neurofibromatosis Foundation International Database, Vancouver, British Columbia. Each patient with NF1 was offered a clinical follow-up according to the standard protocol described previously. One annual standardized clinical examination was recommended, unless a particular symptom or a complication required more frequent consultation and/or further investigations. Among the 433 patients with NF1 in the database, those with a follow-up of more than 1 year were included in the present study.

The database includes demographic characteristics, clinical features, symptomatic complications, mortality, and causes of patients’ death (Table 1). Clinical features were selected as potential factors associated with mortality. Most of the clinical features were easily identified by physical examination, with the exception of Lisch nodules that were diagnosed or excluded by a slitlamp examination. Dermatological features were particularly detailed: count of café au lait spots (0, 1, 2, 3, 4, 5, and ≥7), localization of intertriginous freckling (axillary or diffuse), and count of subcutaneous neurofibromas (0, 1, and ≥2) and of cutaneous neurofibromas (0, 1-10, 11-99, and ≥100). Other items were coded as absent or present. Short stature was coded as present if the subject’s height was 2 SDs or more below the age- and sex-matched population mean. Macrocephaly was coded as present if the subject’s head circumference was 2 SDs or more above the age- and sex-matched population mean. During the follow-up period, symptomatic complications systematically assessed by clinical examination were as follows: symptomatic internal neurofibromas, symptomatic glomus, scoliosis, orthopedic complications, spinal compression, seizures, hydrocephalus, hypertension, and malignancy.

### Statistical Analysis

First, the characteristics of the population (clinical features, symptomatic complications, and mortality) were described. Because the prevalence of some features of NF1 are dependent on age (number of café au lait spots and cutaneous and subcutaneous neurofibromas), the potential relationships between patients’ age and these variables were also analyzed. For that purpose, mean age was compared by analysis of variance and linear regression models were used for quantitative data. Comparisons of clinical features between deceased and living patients were performed to identify factors associated with mortality. The odds ratios (ORs) with their 95% confidence intervals (CIs) were also calculated separately for each variable using unconditional logistic regression models, forcing patients’ age into all models. Exact CIs were estimated when appropriate. Multivariate logistic models were thereafter obtained to take into account all potential predictive factors of mortality. Variables to include in these final multivariate models were selected among those emerging from univariate models with P<.15. Then, final backward step-by-step regression analyses were conducted. P≤.05 indicated statistical significance. All significance tests were 2-tailed.

Continuous data are presented as mean±SD. Data were analyzed using BMDP computer software (StatXact-4 and LogXact; University of California, Berkeley).

### Study Population

Among the 433 patients in the database, 378 with NF1 were included in our study: 166 males and 212 females. Their mean age was 32.7 years (SD, 13.5 years; range, 7-75 years). Of the 378 patients, 34 were children (<17 years). Neurofibromatosis 1 was familial in 148 patients (39%) and considered sporadic in 230 (61%). The median follow-up of this cohort of patients was 53.1 months (range, 12-72 months).

Table 1 summarizes the characteristics of the population, the prevalence of the 18 clinical features included in the analyses, and the number of deceased patients. Eleven patients died during the follow-up. The causes of death were astrocytoma (n=1), malignant peripheral nerve sheath tumors (n=6), spinal compression (n=3), and carcinoid tumor (n=1).

### Relationship Between Age and Clinical Variables

Strong relationships were observed between age and number of café au lait spots and number of cutaneous neurofibromas. The number of small and large café au lait spots significantly (P<.001) decreased with age (linear regression coefficient, 0.22 and 0.17, respectively). The number of cutaneous neurofibromas significantly increased with age (Table 2). No significant relationship was observed between age and subcutaneous neurofibromas (Table 2). The age of deceased (n=11) and living (n=367) patients was 27.7 ± 13.5 and 32.9 ± 13.5 years, respectively (range, 7-75 years). Mortality was not associated with age (t test, P=.21).
RISK FACTORS FOR MORTALITY

The comparisons of the characteristics and the clinical features of dead vs alive patients are summarized in Table 3. In univariate analyses, the following features were associated with mortality (with P< .15) and were entered into multiple logistic regression models: presence of 2 or more subcutaneous neurofibromas, absence of cutaneous neurofibromas, and facial asymmetry. The presence of subcutaneous NF was strongly associated with mortality.

Variables independently associated with mortality in multivariate analyses are as follows: the presence of 2 or more subcutaneous neurofibromas (OR, 10.8; 95% CI, 2.1-56.7; P <.001), the absence of cutaneous neurofibromas (OR, 5.3; 95% CI, 1.2-25.0; P =.03), and facial asymmetry (OR, 11.4; 95% CI, 2.6-50.2; P <.01) (multivariate ORs were age adjusted).

Neurofibromatosis 1 is associated with substantial morbidity and mortality.11-14 In a recent study15 based on US death certificates, persons with NF1 seem to have a decrease in life expectancy of about 15 years compared with the general population. Indeed, certain kinds of malignancy (especially brain tumors and malignant neoplasms of connective and other soft tissues) seem to occur more frequently than expected in people who die with NF1. Such malignancies and vascular diseases (especially cerebrovascular disease) seem to contribute disproportionately to mortality in children and young adults with NF1. Other problems that can lead to early death in patients with NF1 include acute hydrocephalus, severe seizures, progressive spinal cord encroachment by plexiform neurofibromas or unstable dysplastic scoliosis, and complications of hypertension. The morbidity of patients with NF1 is determined by many factors. It is obvious from simple clinical observation that some patients with NF1 have a debilitating or even fatal disease early in life, while others live to an advanced age with only mild manifestations. To provide an assessment of overall disease severity, some clinicians use graded scales based on the clinical features of NF1 present in a particular patient at a given time in the patient’s life. Severity scales, such as the scale of Riccardi and Kleiner,16 provide a relatively easy way to describe the clinical status of a patient, but their general usefulness is limited because they do not predict the future course of the disease. Indeed, regarding the occurrence of complications, to our knowledge, there are no known factors that predict that any complication will definitely occur in a given patient. One or two factors increase the probability for a given complication occurring, but we do not know the exact risk for a given individual. For example, we know that most malignant nerve sheath tumors occur in preexisting lesions, but the risk to a given individual is unknown. Large databases using uniform ways of assessing and grading NF1 can help to solve unanswered questions.17

To determine clinical risk factors for mortality, we prospectively assessed a large cohort of patients with NF1. The features of our patients with NF1 were found in the same proportion as in the main series and databases,3,15 except for the prevalence of short stature, macrocephaly, xanthogranulomas, and café au lait spots that is generally higher than in our study. Indeed, the prevalence of café au lait spots was less than expected. One possible explanation is that most of our patients were adults, and the number of café au lait spots decreased with age in our series. Mortality was about 3% during the follow-up period, and causes of death, mainly malignancies (especially brain tumors and malignant neoplasms of connective and other soft tissues), were those reported in the literature.6,19 Each of our patients was offered clinical follow-up according to published guidelines.2,6 Therefore, our study was focused on clinical features as risk factors for mortality. The prevalence of many features of NF1 is influenced by age. For example, the number of cutaneous neurofibromas increased with age while the number of café au lait spots decreased. Taking into account these characteristics of NF1, we systematically adjusted any feature for age in our analyses. We identified independent risk factors for mortality: the presence of 2 or more subcutaneous neurofibromas, the absence of cutaneous neurofibromas, and facial asymmetry.

In patients with NF1, from a clinical perspective, 4 types of neurofibromas may be distinguished: (1) discrete cutaneous neurofibromas of the dermis or epidermis, (2) subcutaneous neurofibromas that lie deeper in the skin, (3) deep nodular neurofibromas, and (4) diffuse plexiform neurofibromas. Subcutaneous neurofibromas arise along peripheral nerves under the skin and tend to be firm to palpation. They may present clinically as beadlike nodules along the length of a nerve. These discrete neurofibromas can occur along nerves deeper within the body. Tumors that arise from spinal nerve roots may grow through the neural foramen, assuming a dumbbell shape. These may cause nerve root compression or compression of the spinal cord. Nerve root compression will lead to radicular symptoms, including pain, weakness, or sensory loss. The presence of subcutaneous neurofibromas could be correlated with the presence of deep nodular neurofibromas. Most deep nodular neurofibromas are asymptomatic.20 Nevertheless, some of them may cause serious long-term morbidity and un-
timely death among patients with NF1. Malignant peripheral nerve sheath tumors arise mostly from nodular and plexiform neurofibromas. The occurrence of deep nodular neurofibromas within or adjacent to vital organs can cause obstruction or compression. A major cause of death in our series was malignant peripheral nerve sheath tumors and spinal compression.

The absence of cutaneous neurofibromas is the second risk factor for mortality in our study. The presence of 2 or more neurofibromas of any type is a diagnosis criterion for NF1. Consequently, the absence of cutaneous neurofibromas is uncommon in patients with NF1. Hu

<table>
<thead>
<tr>
<th>Variable *</th>
<th>Deceased (n = 11)</th>
<th>Living (n = 367)</th>
<th>OR (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial case (n = 378)</td>
<td>3 (27)</td>
<td>145 (40)</td>
<td>0.6 (0.2-2.2)</td>
<td>.61</td>
</tr>
<tr>
<td>Male sex (n = 378)</td>
<td>7 (64)</td>
<td>159 (43)</td>
<td>2.2 (0.6-7.7)</td>
<td>.20</td>
</tr>
<tr>
<td>Short stature (n = 367)</td>
<td>0</td>
<td>45 (13)</td>
<td>0 (0-3.0)</td>
<td>.49§</td>
</tr>
<tr>
<td>Macrocephaly (n = 292)</td>
<td>1 (9)</td>
<td>40 (14)</td>
<td>0.6 (0.1-4.7)</td>
<td>.60</td>
</tr>
<tr>
<td>&gt;6 Cafe au lait spots</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (n = 370)</td>
<td>7 (64)</td>
<td>264 (72)</td>
<td>0.6 (0-2.2)</td>
<td>.47</td>
</tr>
<tr>
<td>Large (n = 378)</td>
<td>6 (55)</td>
<td>248 (68)</td>
<td>0.5 (0-1.1)</td>
<td>.26</td>
</tr>
<tr>
<td>Freckling (n = 378)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>10 (91)</td>
<td>324 (88)</td>
<td>1.3 (0-10.6)</td>
<td>.79</td>
</tr>
<tr>
<td>Diffuse</td>
<td>6 (55)</td>
<td>165 (50)</td>
<td>1.2 (0-4.0)</td>
<td>.77</td>
</tr>
<tr>
<td>Subcutaneous neurofibromas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present (n = 376)</td>
<td>11 (100)</td>
<td>182 (50)</td>
<td>2.5 (–)</td>
<td>.001§</td>
</tr>
<tr>
<td>≥2 (n = 371)</td>
<td>9 (82)</td>
<td>128 (36)</td>
<td>8.3 (1-39.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Absence of cutaneous neurofibromas (n = 378)</td>
<td>5 (45)</td>
<td>54 (15)</td>
<td>5.0 (1-16.7)</td>
<td>.04</td>
</tr>
<tr>
<td>Plexiform neurofibromas (n = 376)</td>
<td>5 (45)</td>
<td>142 (39)</td>
<td>1.4 (0-4.6)</td>
<td>.61</td>
</tr>
<tr>
<td>Hemangiomas (n = 377)</td>
<td>0</td>
<td>29 (9)</td>
<td>0 (0-4.9)</td>
<td>.82§</td>
</tr>
<tr>
<td>Xanthogranulomas (n = 377)</td>
<td>0</td>
<td>4 (1)</td>
<td>0 (0-38.9)</td>
<td>.99§</td>
</tr>
<tr>
<td>Depigmented areas (n = 377)</td>
<td>1 (9)</td>
<td>25 (7)</td>
<td>1.4 (0-11.1)</td>
<td>.79</td>
</tr>
<tr>
<td>Hyperpigmented areas (n = 377)</td>
<td>2 (18)</td>
<td>29 (8)</td>
<td>2.9 (0-14.4)</td>
<td>.23</td>
</tr>
<tr>
<td>Itching (n = 378)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>1 (9)</td>
<td>98 (27)</td>
<td>0.3 (0-2.6)</td>
<td>.22</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>20 (5)</td>
<td>0 (0-7.5)</td>
<td>.99§</td>
</tr>
<tr>
<td>Lisch nodules (n = 259)</td>
<td>5 (71)</td>
<td>216 (66)</td>
<td>0.5 (0-2.5)</td>
<td>.40</td>
</tr>
<tr>
<td>Pseudarthrosis (n = 377)</td>
<td>0</td>
<td>7 (2)</td>
<td>0 (0-25.7)</td>
<td>.99§</td>
</tr>
<tr>
<td>Congenital tibia bowing (n = 376)</td>
<td>0</td>
<td>8 (2)</td>
<td>0 (0-21.8)</td>
<td>.99§</td>
</tr>
<tr>
<td>Noonan phenotype (n = 378)</td>
<td>0</td>
<td>6 (2)</td>
<td>0 (0-21.8)</td>
<td>.99§</td>
</tr>
<tr>
<td>Facial asymmetry (n = 378)</td>
<td>4 (36)</td>
<td>29 (8)</td>
<td>6.5 (1-24.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Hypertension (n = 378)</td>
<td>0</td>
<td>39 (11)</td>
<td>0 (0-3.5)</td>
<td>.52§</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
*Values in parentheses are based on available data from patients.†Percentages may not compute because of missing data.
‡The ORs were age adjusted.
§Exact CI.

burs affected by familial spinal NF; only 1 member had cutaneous neurofibromas. Poyhonen et al described a family in which 7 members in 3 generations were affected; only 2 had possible dermal neurofibromas. What is unusual is the occurrence of neurofibromas of multiple spinal nerve roots. These tumors may cause serious neurologic deficits. As in our center, no systematic imaging was performed in adult patients with no or few cutaneous neurofibromas; it is premature to conclude that patients with a severe outcome and lack of cutaneous neurofibromas have an entity related to spinal NF.

The third feature associated with mortality was facial asymmetry. Dysplasia of the bones of the skull and face is common in patients with NF1, ranging from simple skull asymmetry to localized defects. About 9% of our patients had facial symmetry. The most consistent craniofacial bone dysplasia in patients with NF1 involves the sphenoid wings. Facial asymmetry can be associated with plexiform neurofibromas and intracranial tumors, causes of substantial morbidity and mortality. Nevertheless, facial asymmetry did not seem to be related to causes of death in our patients.

Predictive factors for mortality were strong. The phenotype, which is associated with subcutaneous neurofibromas, an absence of cutaneous neurofibromas, and fa-
cial asymmetry, has a high risk for mortality. Nevertheless, our conclusion should be limited to the adult population with NF1 that constitutes the study cohort. Factors that influence the NF1 phenotype are not known. The phenotypic similarities observed in families with NF1 are consistent with the hypothesis that modifying genes influence the NF1 phenotype. The NF1 protein, neurofibromin, interacts with many other proteins, including tubulin, kinases, and Ras. Functional variants of these proteins might also influence the NF1 phenotype.

Our study demonstrates that some features that can be found by a routine clinical examination are associated with mortality in adulthood. Clinical follow-up should be focused on patients with subcutaneous neurofibromas and/or the absence of cutaneous neurofibromas and/or facial asymmetry. Further clinical and epidemiological studies are necessary to confirm our data, but our investigations provide hope that some serious complications of NF1 can be predicted.

Accepted for publication May 21, 2002.

This study was supported in part by the Association Neurofibromatoses et Recklinghausen, Blagnac, France.

This study was presented in part at the Journées Dermatologiques de Paris, Paris, France, December 6, 2001.

We thank Ariane Dunant, MSc, for her collaboration in the statistical analysis; and Patricia Birch, MSc, and Jan Friedman, MD, PhD, for their comments on the scientific aspect and on the style.

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