Prevalence of Neurofibromatosis 1 in German Children at Elementary School Enrollment

Marga Lammert, MD; Jan M. Friedman, MD; Lan Kluwe, PhD; Victor F. Mautner, MD

Objective: To determine the prevalence of neurofibromatosis 1 (NF1) among 6-year-old children in Germany.

Setting and Patients: A total of 152,819 children aged 6 years in 6 German states were screened for NF1 during routine medical examinations at elementary school enrollment in cooperation with local health departments in 2000 and 2001.

Main Outcome Measure: The prevalence of NF1 among 6-year-old German children was estimated to be 1:2996 (95% confidence interval, 1:2260 to 1:3984).

Results: Fifty-one NF1 cases were identified and confirmed by evaluation by appropriate medical specialists. Seven other children were found to have multiple café au lait spots without other apparent features of NF1. A minimum estimate of the crude prevalence was 3.0 per 10,000 (95% confidence interval, 2.3-4.0 per 10,000 population). The incidence of NF1 in this population was probably in the range of 30 to 38 cases per 100,000 live births.

Conclusion: Our study obtained a nearly unbiased birth incidence of NF1 of approximately 1 in 2600 to 1 in 3000 and demonstrates that NF1 can be diagnosed by age 6 years in most cases by routine physical examination with special attention to the disease-associated skin stigmata.

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Neurofibromatosis 1 (NF1) is an autosomal dominant disease characterized by multiple café au lait spots, intertriginous freckling, and neurofibromas. Cerebral and spinal tumors, skeletal dysplasias, and ophthalmological abnormalities are also frequent in affected patients. About half of children with NF1 have learning disabilities. The median age at death among NF1 patients is about 15 years younger than that of the general population. Early diagnosis of NF1 is important for optimal management, especially for treatment of neuropsychological problems in affected children.

Neurofibromatosis 1 is caused by mutations of the NF1 gene on chromosome band 17q11.2. Estimates of the prevalence of NF1 have ranged from 1.0 to 10.4 per 10,000 in various populations, but the prevalence has not been studied in Germany.

Neurofibromatosis 1 is infrequently diagnosed at birth because most of the disease-associated signs and symptoms develop later. This makes estimates of the incidence of NF1 at birth dependent on extrapolations from prevalence figures determined later in life. However, some patients with NF1 die early, so the prevalence decreases with increasing age, complicating efforts to obtain accurate estimates of the birth incidence.

Although the multiple cutaneous neurofibromas that give NF1 its name are infrequent before puberty, multiple café au lait spots are clearly visible in more than 95% of children with NF1 by age 6 years. Intertriginous freckling, another pigmentation abnormality characteristic of NF1, can be seen in more than 85% of patients with NF1 by age 6 years. The presence of these 2 features is sufficient for diagnosis of the disease by standard clinical criteria.

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In most parts of Germany, all children are required to have a medical examination at age 6 years, prior to enrollment in elementary school. We used these routine examinations to perform a population-based study of the prevalence of NF1 and to estimate the incidence of NF1 at birth.

Methods

Children in Germany are required to undergo a medical examination for enrollment in elementary school at age 6 years. This examination is usually performed by a physician for
schoolchildren from the local public health department, but in some areas the official examination can be performed by another physician or is not required for children with disabilities or mental retardation. To avoid underascertainment of children with NF1, we restricted our study to areas of Germany in which all children are examined by a physician from the local health department prior to enrollment in elementary school. A total of 6 German federal states fulfill these criteria—5 in eastern Germany (Brandenburg, Mecklenburg-Vorpommern, Sachsen, Sachsen-Anhalt, and Thüringen) and 1 in western Germany (Saarland). Non-German ethnicity in these states is estimated to be 4%.

In 1999, we contacted all 117 local public health departments in the 6 selected German federal states, explaining the purpose of our study and asking for support and cooperation. All of the departments agreed, and we sent them information regarding the diagnostic criteria for NF1 according to the National Institutes of Health (NIH). Because of the limited nature of the routine preschool examinations, Lisch nodules and optic gliomas could not be identified. Cutaneous neurofibromas were not considered because they are rare in 6-year-old children. Although plexiform neurofibromas may develop additional features of NF1 within the next few years. About 5% of children who subsequently can be diagnosed with NF1 will also turn out to have NF1. This prevalence measured in 2000 and 2001 was similar: 1:3072 and 1:2938, respectively (Table 1). Combining these data, we estimate the prevalence of NF1 among 6-year-old German children to be 1:2996 (95% confidence interval, 1:2260 to 1:3984).

In addition, 7 other children were reported to have had more than 6 café au lait spots larger than 5 mm in greatest diameter but no other signs of NF1. These children are not included among the 51 diagnosed cases for children met the diagnostic criteria for NF1 with 2 or more of the following features: 6 or more café au lait spots larger than 5 mm in greatest diameter, axillary or inguinal freckling, pseudarthrosis of the tibia, or history of a first-degree relative with NF1. The health departments reported that the diagnosis of NF1 was confirmed in all 51 children by a neurologist or other appropriate specialist. The prevalence measured in 2000 and 2001 was similar: 1:3072 and 1:2938, respectively (Table 1). Combining these data, we estimate the prevalence of NF1 among 6-year-old German children to be 1:2996 (95% confidence interval, 1:2260 to 1:3984). In addition, 7 other children were reported to have had more than 6 café au lait spots larger than 5 mm in greatest diameter but no other signs of NF1. These children are not included among the 51 diagnosed cases for the estimation of prevalence. However, most, if not all, of these children probably also have NF1. Some of these patients may already have Lisch nodules, optic gliomas, or other cardinal clinical features that would not have been identified in this study, and most of the other children with multiple café au lait spots are likely to develop additional features of NF1 within the next few years. About 5% of children who subsequently can be diagnosed with NF1 do not meet the standard diagnostic criteria on complete examination by age 6 years, although almost all of these children have multiple café au lait spots. In our study, 51 (88%) of the 58 children with more than 6 café au lait spots at age 6 years met the diagnostic criteria for NF1. A maximal estimate of the prevalence of NF1 among the 6-year-old children in this study can be obtained by assuming that all 7 children noted to have 6 or more café au lait spots but not diagnosed as having NF1 will also turn out to have NF1. This would give an estimated prevalence of 58 in 152819 or 1:2635 (95% confidence interval, 1:2023 to 1:3439). Our estimate of prevalence of NF1 among 6-year-old children in Germany is similar to that found in most previous studies of other populations (Figure). The striking exception is the study by Garty et al,14 which found a

### RESULTS

A total of 152819 children aged 6 years were examined for features of NF1 in 6 German federal states over a period of 2 years (Table 1). According to reports provided by the participating health departments, 51 of these children met the diagnostic criteria for NF1 with 2 or more of the following features:

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Participating Public Health Departments</th>
<th>No. of Children Studied</th>
<th>Neurofibromatosis 1 Cases</th>
<th>Crude Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>84</td>
<td>67602</td>
<td>22</td>
<td>1:3072</td>
</tr>
<tr>
<td>2001</td>
<td>110</td>
<td>85217</td>
<td>29</td>
<td>1:2938</td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>152819</td>
<td>51</td>
<td>1:2996</td>
</tr>
</tbody>
</table>

### COMMENT

Our estimate of prevalence of NF1 among 6-year-old children in Germany is similar to that found in most previous studies of other populations (Figure). The striking exception is the study by Garty et al,14 which found a
prevalence of NF1 among 17-year-old Israeli military recruits that was several times higher than that observed in this or any other population-based study that has been reported. Whether this difference reflects a higher prevalence of NF1 among Jewish people or some other factor is unclear.

Our study provides an excellent opportunity to generate an unbiased estimate of the incidence of NF1 at birth. Most infants who carry an NF1 mutation cannot be identified at birth because few of the clinical features of NF1 are apparent at that time. By age 6 years, the diagnosis of NF1 can be made in about 95% of affected children using the standard NIH criteria. An even higher proportion of affected individuals can be identified clinically in adolescence or early adulthood, but the prevalence decreases with age because premature death is much more frequent in adolescents and young adults with NF1 than in the general population. This is not true for young children with NF1. Thus, most children with NF1 can be identified by physical examination at age 6 years, and very few members of this birth cohort will have died as a result of NF1 or its complications. The criteria used for diagnosis of NF1 in this study are simple, and the examinations were carried out in a standard fashion by public health department physicians. It therefore seems likely that the incidence of NF1 at birth is very similar to the prevalence we measured at age 6 years—between 33 and 38 per 100,000 population. Only a few estimates have previously been made of the incidence of NF1 at birth.

Neurofibromatosis 1 is clearly one of the most common autosomal dominant diseases in humans. Our study and all previous studies of NF1 prevalence and incidence at birth involve populations of mainly European origin, and it is not known whether the frequency of NF1 differs in other populations. This question is of considerable interest, given the high mutation rate that has been calculated for the large NF1 gene.

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Correspondence: Lan Kluwe, PhD, Laboratory for Tumor Biology and Development Disorders, Department of Maxillofacial Surgery, University Hospital Eppendorf, Martinistr 52, 20246 Hamburg, Germany (kluwe@uke.uni-hamburg.de).

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Table 2. Estimates of the Incidence of NF1 at Birth

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Estimated Incidence of NF1 at Birth (per 100 000 Live Births)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>30-40</td>
<td>Ascertainment based on hospital admissions or residence in an institution for the mentally retarded in Michigan, 1941-1950; diagnosis based on clinical features similar (but not identical) to NIH criteria; prevalence equated to birth incidence without consideration of differential mortality of NF1</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>Multiple ascertainment of cases with diagnosis based on clinical features similar (but not identical) to NIH criteria; population-based study in southeast Wales, 1969-1986; estimate of birth incidence based on prevalence observed among the population aged &lt;20 years, corrected for underascertainment on the basis of the proportion of sporadic cases</td>
</tr>
<tr>
<td>13</td>
<td>23</td>
<td>Ascertainment through genetic counseling service in northeast Italy, 1980-1986; diagnosis based on clinical features similar (but not identical) to NIH criteria; incidence at birth assumed to be the same as prevalence observed in the 0- to 9-year-old age group</td>
</tr>
<tr>
<td>17</td>
<td>27</td>
<td>Multiple ascertainment of cases with diagnosis by NIH criteria; population-based study in northern Finland, 1960-1985; direct calculation from observed numbers of cases and live births in region; differential mortality of NF1 not considered</td>
</tr>
<tr>
<td>Present study</td>
<td>33-38</td>
<td>Population-based study of 6-year-old children examined prior to school entry in Germany, 2001-2002; diagnosis based on a subset of NIH criteria (see text); incidence at birth assumed to be the same as prevalence at age 6 years</td>
</tr>
</tbody>
</table>

Abbreviations: NF1, neurofibromatosis 1; NIH, National Institutes of Health, Bethesda, Md.

REFERENCES

10. Samuelsson B, Axelsson R. Neurofibromatosis: a clinical and genetic study of


18. Ohringer AC, Meadows AT, Zackai EH. The diagnosis of neurofibromatosis 1 in the child under the age of 6 years. AJDC. 1989;143:717-719.


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**ARCHIVES Web Quiz Winner**

Congratulations to the winner of our October quiz, Maj Brett Sloan, USAF, MC, PGY-4 Dermatology, San Antonio Uniformed Services Health Education Consortium, San Antonio, Tex. The correct answer to our October challenge was nevus sebaceous containing syringocystadenoma papilliferum. For a complete discussion of this case, see the “Off-Center Fold” section in the November ARCHIVES (Ang GC, Lee JB. A pigmented verrucous plaque on the cheek. Arch Dermatol. 2004;140: 1393-1398).

Be sure to visit the Archives of Dermatology Web site (http://www.archdermatol.com) to try your hand at the Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of The Art of JAMA II.