Minor disease features in neurofibromatosis type 1 (NF1) and their possible value in diagnosis of NF1 in children ≤6 years and clinically suspected of having NF1


Abstract

Objective—To establish the frequency of minor disease features in children with neurofibromatosis type 1 (NF1) and to evaluate the value of minor disease features in children ≤6 years with a suspected diagnosis of NF1, considering that the disease is virtually 100% penetrant at 6 years of age.

Design—During this 10 year, prospective, multidisciplinary, follow up study, 209 children suspected of having NF1 were examined; 150 were diagnosed with NF1 and 59 were not. The present analysis included children in whom NF1 was considered to be present at 6 years of age (n=85) and children without NF1 at 6 years of age (n=42).

Results—The minor disease features macrocephaly (52.9%), short stature (24.7%), hypertelorism (63.5%), and thorax abnormalities (37.6%) were highly prevalent in children with NF1 and significantly associated with a diagnosis of NF1 at 6 years of age. In addition, the mean number of minor disease features was significantly higher in children with NF1 at 6 years of age compared to the group without a diagnosis at 6 years of age (mean 1.8 ± 0.8, p<0.001). Moreover, children with three or more minor disease features were all diagnosed with NF1 under the age of 6 years. Multivariate analysis using a logistic regression model showed that macrocephaly, short stature, hypertelorism, and thorax abnormalities were all independently associated with the presence of NF1 at 6 years of age.

Conclusion—In children with insufficient diagnostic criteria aged ≤6 years, documentation of minor disease features may be a helpful aid in predicting the diagnosis of NF1 in years to come. (J Med Genet 1998;35:624–627)

Keywords: neurofibromatosis type 1; minor disease features; macrocephaly; short stature

Type 1 neurofibromatosis, NF1, is a common genetic disorder with autosomal dominant inheritance. Half of all patients represent sporadic cases. Diagnostic criteria were established by the National Institutes of Health (NIH) and two or more criteria must be present for the diagnosis. In cases where a first degree family member is affected, only one additional criterion is sufficient for a diagnosis. The penetrance of the disease is regarded as virtually 100% at 5 years of age and the diagnostic criteria have been shown to be applicable in children from 6 years of age.

Although the NF1 gene was cloned in 1990, mutations in this large and complex gene are detected in only 10-20% of NF1 patients using classical methods such as polymorphic markers, single strand conformational analysis (SSCP), and Southern analysis on DNA from lymphocytes. Accordingly, mutation analysis is not available as a diagnostic tool and in the majority of NF1 patients a diagnosis will still be based on the presence of two or more clinical criteria.

In addition to the diagnostic signs, physical characteristics such as macrocephaly, short stature, hypertelorism, and thorax abnormalities are observed more frequently in NF1 patients than in the general population. As such, these characteristics are considered minor disease features.

In this study, we aimed to assess the frequency of minor disease features in children with NF1 and to evaluate the association of the presence of minor disease features with a diagnosis of NF1 in children at 6 years of age. We hypothesised that in contrast to the diagnostic criteria which develop with age, macrocephaly, short stature, hypertelorism, and thorax abnormalities are present from birth and therefore may be of value in predicting NF1. In this way, parents of children suspected of NF1 and younger than 6 years of age can be informed of the necessity for diagnostic follow up and both parents and children may benefit from the knowledge that many of the child’s symptoms are the result of an underlying disorder.

Patients and methods

STUDY POPULATION

Between July 1985 and January 1996, a multidisciplinary NF1 team in the Sophia Children’s University Hospital in Rotterdam, including a paediatrician, dermatologist, paediatric neurologist, ophthalmologist, and clinical geneticist, evaluated children suspected of having NF1. Children were referred with a suspected diagnosis of NF1 by general practitioners and medical specialists. Age at referral was variable.
Minor disease features in neurofibromatosis type 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=85)</th>
<th>Group 2 (n=42)</th>
<th>OR  95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% males)</td>
<td>42.4</td>
<td>38.1</td>
<td>(-0.22; 0.143)</td>
<td>0.39</td>
</tr>
<tr>
<td>Positive family history (%)</td>
<td>52.9</td>
<td>52.4</td>
<td>(-0.19; 0.18)</td>
<td>0.953</td>
</tr>
<tr>
<td>Mean age at first examination (y)</td>
<td>3.9</td>
<td>7.7</td>
<td>(-5.25; -2.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age at last examination (y)</td>
<td>8.3</td>
<td>10.8</td>
<td>(-3.99; -0.97)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Mean follow up time (y)</td>
<td>4.4</td>
<td>3.1</td>
<td>(-0.11; 2.79)</td>
<td>0.070</td>
</tr>
<tr>
<td>Macrocephaly (%)</td>
<td>52.9</td>
<td>51.0</td>
<td>(-0.40; -0.04)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Short stature (%)</td>
<td>24.7</td>
<td>4.8</td>
<td>(-0.31; -0.85)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hypertelorism (%)</td>
<td>63.5</td>
<td>31.0</td>
<td>(-0.50; -0.15)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Thorax abnormality (%)</td>
<td>37.6</td>
<td>9.5</td>
<td>(-0.42; -0.14)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

CI = confidence interval; *significant at level p < 0.05.

UNIVARIATE ANALYSIS
Table 2 presents the frequencies of minor disease features in patients with and without NF1 at 6 years of age. Macrocephaly was present in 52.9% of children with NF1, short...
stature in 24.7%, hypertelorism in 63.5%, and thorax abnormalities in 37.6%. Comparison of the frequencies of minor disease features between both patient groups showed that macrocephaly, short stature, hypertelorism, and thorax abnormalities were significantly associated with the presence of NF1 at 6 years of age (table 2).

Hypothetically, if the associations between minor disease features and a diagnosis of NF1 at 6 years of age were the result of an excess of minor disease features in children with NF1 and aged ≤3 years at the time of diagnosis, the additional value of minor disease features in diagnosing children ≤6 years of age would be minimal. Therefore, subgroup analyses were performed excluding children diagnosed at ≤3 years of age. Although sample numbers decreased, the results were similar. The association between minor disease features and the presence of NF1 was still significant (data not shown).

The number of children with multiple minor disease features was significantly higher in group 1 than in group 2. The mean number of minor disease features was 1.8 and 0.8 respectively (table 3). Children with three or more minor disease features were all diagnosed with NF1 under the age of 6 years. The cumulative percentages of children with two or more minor disease features were also significantly higher among patients in group 1 (67.1%) compared to group 2 (19.1%). In addition, 12.9% of children had no minor disease features in group 1, compared to 42.8% of children in group 2. This difference was also highly significant (median test, p<0.001).

MULTIVARIATE ANALYSIS

Table 4 shows the results of the multivariate logistic regression analysis. Each minor disease feature was independently associated with the presence of NF1 at 6 years of age. Odds ratios varied from 2.1 for macrocephaly to 8.0 for short stature. Short stature (OR=8.0, 95% CI=6.45-9.59) and thorax abnormalities (OR=5.7, 95% CI=4.42-6.90) were the most important independent predictors of the presence of NF1 at 6 years of age.

For the same reasons as mentioned above, we constructed a logistic regression model excluding children diagnosed ≤3 years of age. Odds ratios were similar to those computed in the overall analysis, although confidence intervals were wider, but did not include OR=1.

Discussion

The minor disease features macrocephaly, short stature, hypertelorism, and thorax abnormalities are very common in children with NF1, ranging from 24.7% for short stature to 63.5% for hypertelorism. A significant association was found between their presence and a diagnosis of NF1 at 6 years of age. Furthermore, the mean number of minor disease features in children diagnosed with NF1 at 6 years of age is significantly higher than in children without NF1 at 6 years of age. Multivariate analyses showed odds ratios varying from 2.1 for macrocephaly to 8.0 for short stature, confirming an independent association between each variable and NF1 diagnosis at 6 years of age. The highest odds ratios were observed for short stature (8.0) and thorax abnormalities (5.7).

Our findings suggest that, in the practice of a multidisciplinary clinic, the probability of developing NF1 in the presence of insufficient diagnostic criteria may be predicted on the basis of minor disease features. We have attempted to quantify this probability in order to define a group of children in which follow up is essential as the risk of developing NF1 is substantial. In this way, parents of children suspected of having NF1 and younger than 6 years of age can be informed of the necessity for diagnostic follow up and both parents and children may benefit from the knowledge that many of the child’s symptoms are the result of an underlying disorder.

Minor disease features could be of special importance to children with a de novo mutation in the NF1 gene as they may be diagnosed at a later age than children with an affected relative. The importance and applicability of the diagnostic criteria in children is generally accepted. Korf et al showed that 24 of 41 (58%) children went on to develop NF1, according to NIH criteria, after an initial visit during which only café au lait spots were observed. Almost all children in this study were diagnosed within three years of follow up and before 5 years of age. Obringer et al classified 151 out of 160 children (94%) under 6 years of age on the basis of the diagnostic criteria, including 80% of children with a negative family history. We emphasise that minor disease features should only be used to predict the likelihood of NF1 diagnosis when children have been checked thoroughly for the presence of conventional diagnostic criteria by NF1 specialists.

In the Welsh study, similar prevalences were reported of macrocephaly (45%) and short stature (31.5%). Riccardi also reported short stature (more than one-third below the 5th centile) and pectus excavatum (31%) to be present in a high percentage of his patients. As such, the association between minor disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>OR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Constant</td>
<td>-10.6</td>
<td>1</td>
<td>(1.92-2.97)</td>
</tr>
<tr>
<td>Macropahaly</td>
<td>0.73</td>
<td>2.1</td>
<td>(6.45-9.59)</td>
</tr>
<tr>
<td>Short stature</td>
<td>2.08</td>
<td>8.0</td>
<td>(6.45-9.59)</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>1.15</td>
<td>3.1</td>
<td>(2.26-4.03)</td>
</tr>
<tr>
<td>Thorax abnormality</td>
<td>1.73</td>
<td>5.7</td>
<td>(4.42-6.90)</td>
</tr>
</tbody>
</table>

β=coefficient; OR=odds ratio; CI=confidence interval.
features and NF1 is not surprising. However, the possible value of these variables in diagnosing NF1 has so far not been discussed.

We realise that the group of children without NF1 at 6 years of age may still contain children with an NF1 gene mutation. Particularly, children with one diagnostic criterion other than a positive family history in combination with several minor disease features remain suspect. Atypical NF1 patients have been described with reduced penetrance10 or late expression of the disease.11 In addition, cases of germline and somatic mosaicism have been reported.16-18 Follow up of the children not diagnosed with NF1 at 6 years of age may result in additional diagnoses. Nevertheless, associations between minor disease features and a diagnosis of NF1 at 6 years of age would not be influenced by these cases, as omitting them would only make the association stronger.

The data on hypertelorism are crude as we did not use physical measurements. Therefore we recommend validation of the associations and the logistic model in a similar setting in which hypertelorism is measured. Furthermore, although children were referred suspected of NF1, it is possible that they were referred on the basis of insufficient diagnostic criteria and minor disease features, leading to an underestimation of the odds ratios. In contrast, an overestimation may have been made owing to referral at a later age, with insufficient diagnostic criteria and fewer minor disease features.

Eaton et al9 presented evidence that modifying genes may play a major role in the variability of NF1 within families. Presumably, modifying genes may also be of influence on the presence of minor disease features in NF1 patients. In time, minor disease features may be of importance in discovering loci for these modifying genes. As mutation analysis becomes more important in diagnosing (atypical) NF1 patients, minor disease features may also gain importance in isolating those (atypical) patients suspected of an NF1 gene mutation. It remains difficult to perceive that a positive family history in a child with a reduced expression of the disease and aged >6 years will lead to a diagnosis and the same expression in a child (>6 years) without affected family members will not. In the future, it may clarify matters to exclude a positive family history from the diagnostic criteria for NF1. Basically, disease mechanisms are dependent on the gene mutation, synthesis of mRNA and protein, the genetic background, and environmental factors and independent of a positive family history.

Diagnoses other than NF1 should always be considered in children with insufficient diagnostic criteria for NF1. In our study one of the 14 children >6 years, with only one (clinical) diagnostic criterion, was diagnosed as having neurofibromatosis type 2 during follow up (dermal neurofibromas, bilateral vestibular schwannomas), one child was diagnosed as having Leopard syndrome, and a third child was diagnosed as having Proteus syndrome. No minor disease features were present in these three children. No alternative diagnoses could be made in the remaining children. Other studies include Bannayan-Riley-Ruvalcaba syndrome, McCune-Albright syndrome, urticaria pigmentosa, multiple lipomas, congenital generalised fibromatosis, and steatoctystoma multiplex in the differential diagnosis.8,13

In conclusion, in children with insufficient diagnostic criteria, under the age of 6 years, and examined in a multidisciplinary NF1 clinic, documentation of minor disease features may be a helpful aid in diagnosing NF1.

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