Genetics of adolescent idiopathic scoliosis

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SUMMARY A genetic family study was undertaken by photofluorography of the first, second, and third degree relatives of 116 index patients with adolescent idiopathic scoliosis (AIS). The index patients were ascertained in the course of an epidemiological screening. The pattern of familial clusters and the recurrence risk related to the number of affected relatives and to the severity of the disorder in the index patients support the theory of polygenic inheritance, a multifactorial-threshold aetiological model. The recurrence risk table for first degree relatives, prepared by computerised data processing and analysis, may contribute to the early diagnosis and prevention of the disorder.

The aetiologic evaluation of scoliosis rests upon 5 main points.

(1) Scoliosis is of heterogeneous origin. Thus, it can be a symptom of various syndromes and disorders, and can also appear as an independent nosological entity (Ponseti and Friedman, 1950; James, 1966, 1967; Beals, 1973; Scheier, 1975). This type is termed idiopathic scoliosis.

(2) On the basis of the clinical symptoms and epidemiological characteristics, idiopathic scoliosis can be subdivided into 3 types: infantile, juvenile, and adolescent (Wynne-Davies, 1968; Riseborough and Wynne-Davies, 1973). The present paper discusses the genetic problems of adolescent idiopathic scoliosis (AIS).

(3) AIS belongs to the group of common disorders. Prevalence in a representative Hungarian sample of persons over 14 years of age was 0.51 to 0.54 ± 0.05% (Bellyei et al., 1977a). If only clinical cases with more than 10° deviation were included, a prevalence of 0.29 ± 0.035% was found. In 1974 to 1975, 22 624 microfilms from a definite geographical and administrative area were examined in several stages. (i) The phthisiologist selected cases with the slightest signs of scoliosis; (ii) the microfilms of 413 selected cases were examined by 2 orthopaedists independently, and in 223 cases a distinctly visible curve was found on each microfilm by them both; (iii) these 223 scoliotic patients were asked to come for radiological and genetic examinations; of these, 5 died and 14 did not appear even after repeated requests; (iv) a detailed clinical examination was made and a full-size x-ray of the spine in the standing position was taken for each of the 204 patients. The angle of curvature was determined according to Cobb’s method (Neugebauer, 1972).

(4) Some environmental factors have a definite role in the aetiology of AIS. Our epidemiological survey indicated that occurrence was higher among children of families working in agriculture and living in rural districts, particularly among those who had been of low birthweight (Bellyei et al., 1977b).

(5) Genetic factors, too, have to be taken into consideration in the aetiology of AIS. Early twin studies (Faber, 1936), and two more recent ones (Fisher and De George, 1967; Wynne-Davies, 1968), showed that the concordance of AIS in homozygotes (73%) was considerably higher than in dizygotic twins (30%). Accordingly, the H value can be estimated at 60%. Familial clusters have also suggested the importance of heredity in idiopathic scoliosis (Faber, 1936; Fisher and De George, 1967; Wynne-Davies, 1968; Filho and Thompson, 1971; Cowell et al., 1972). In a Boston study, occurrence was found to be 11.1%, 2.4%, and 1.4% in the first, second, and third degree relatives of AIS cases (Riseborough and Wynne-Davies, 1973). Thus, there is a 55, 12, and 7 times higher affection rate among relatives than in a given population (0.2%). It has been suggested that idiopathic scoliosis is inherited by the autosomal dominant mode (Garland, 1934; Faber, 1936; Gilly et al., 1963), the X-linked dominant mode (Cowell et al., 1972; MacEwen, 1973), and by polygenic inheritance (De George and Fisher, 1967; Wynne-Davies, 1968; Filho and Thompson, 1971; Riseborough and Wynne-Davies, 1973).
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This study is based on the photofluorography of the relatives of 116 AIS cases. To the best of our knowledge, this is the first attempt to evaluate the genetic indices of AIS in randomly selected persons by the use of epidemiological screening.

Materials and methods

In the district of Dombóvár, after a careful examination of photofluorographs of 22,624 people (4 to 14 films per person) taken in 1971, 413 people suspected of having scoliosis were selected. The films were then analysed by two orthopaedists independently. As a result, the diagnosis of scoliosis was made in 223 cases. These people were asked to attend for clinical and x-ray examination in 1975. Of the 204 people (92%) presenting for examination, scoliosis was not found in only 3. In 116 of the 201 index patients, the diagnosis of AIS was unequivocal. Detailed pedigrees of the first, second, and third degree relatives, histories, and epidemiological, sociological (with matched control), and clinical data were collected for all cases.

Later, an attempt was made to undertake photofluorography in all the relatives over 14 years of age. The results are shown in Table 1. As the first degree relatives predominated in the sample, we concentrated on examining them. Over 80% of the relatives of AIS cases were included in the study, which seems a satisfactory rate. In general, only people with scoliosis exceeding 10° deviation were included in the evaluation.

Results and discussion

The expected occurrence of AIS in the first, second, and third degree relatives of our index patients, according to the modified version of the Edwards formula (Czeizel and Tusnády, 1972), was 8.34 ± 0.37%, 2.00 ± 0.17%, and 0.84 ± 0.07%, respectively. However, sex-modified values have to be considered when a precise evaluation is made. In first degree male relatives, the expected occurrence rate was 6.1%, and in the females, 10.2%. The 5.24% found in fathers, brothers, and sons, and the 6.22% in mothers, sisters, and daughters correspond to the expected values, if the effect of environmental factors is also taken into account (Table 2). An affection rate of 1.36% (6/440) and 0.77% (3/389) was found in the second and third degree relatives, respectively.

Overall heritability (h2) was 88% in first degree relatives, 70% in relatives of the male index patients, and 107% in the relatives of females. However, the rates may be raised on account of the common environment.

Table 1 Number of first, second, and third degree relatives of index patients with AIS

<table>
<thead>
<tr>
<th>Relation</th>
<th>No.</th>
<th>Unknown (dead; under 14; emigrated, etc.)</th>
<th>Remainder</th>
<th>Examined No.</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>116</td>
<td>75</td>
<td>41</td>
<td>33</td>
<td>80-49</td>
<td>28-45</td>
</tr>
<tr>
<td>Mother</td>
<td>116</td>
<td>39</td>
<td>77</td>
<td>69</td>
<td>89-61</td>
<td>59-48</td>
</tr>
<tr>
<td>Brother</td>
<td>195</td>
<td>48</td>
<td>147</td>
<td>115</td>
<td>78-23</td>
<td>58-97</td>
</tr>
<tr>
<td>Sister</td>
<td>163</td>
<td>60</td>
<td>103</td>
<td>89</td>
<td>86-41</td>
<td>54-60</td>
</tr>
<tr>
<td>Son</td>
<td>213</td>
<td>159</td>
<td>54</td>
<td>43</td>
<td>79-63</td>
<td>20-19</td>
</tr>
<tr>
<td>Daughter</td>
<td>167</td>
<td>92</td>
<td>75</td>
<td>67</td>
<td>89-33</td>
<td>40-12</td>
</tr>
<tr>
<td>Total</td>
<td>970</td>
<td>473</td>
<td>497</td>
<td>416</td>
<td>83-70</td>
<td>42-89</td>
</tr>
</tbody>
</table>

Table 2 Affected persons with more than 10° deviation among 1st degree relatives of index patients with AIS

<table>
<thead>
<tr>
<th>Sex</th>
<th>p value (%)</th>
<th>Father M/m</th>
<th>Mother M/m</th>
<th>Brother M/m</th>
<th>Sister M/m</th>
<th>Son M/m</th>
<th>Daughter M/m</th>
<th>Total M/m</th>
<th>q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0-13</td>
<td>0/16</td>
<td>0-00</td>
<td>0/11</td>
<td>0-00</td>
<td>4/67</td>
<td>5-97</td>
<td>2/14</td>
<td>14-29</td>
</tr>
<tr>
<td>Female</td>
<td>0-46</td>
<td>1/17</td>
<td>5-88</td>
<td>3/58</td>
<td>5-17</td>
<td>4/48</td>
<td>8-33</td>
<td>7/75</td>
<td>9-33</td>
</tr>
<tr>
<td>Total</td>
<td>0-29</td>
<td>1/33</td>
<td>3-03</td>
<td>3/69</td>
<td>4-35</td>
<td>8/115</td>
<td>6-96</td>
<td>9/89</td>
<td>10-11</td>
</tr>
</tbody>
</table>

M, no. of patients with AIS; m, no. of examined relatives; q, rate of affected relatives (M/m%); p, sex specified population prevalence; k, q/p.
Table 3  Recurrence among 1st degree relatives of index patients with different degrees of severity of AIS

![Image of Table 3](http://jmg.bmj.com/)

Table 4  Recurrence in 1st degree relatives related to sex of index patients and of relatives

![Image of Table 4](http://jmg.bmj.com/)

Table 5  Recurrence risk of AIS

![Image of Table 5](http://jmg.bmj.com/)
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When both parents were affected, AIS was diagnosed in 40% of the children. When only one of the parents was affected, recurrence was 29.3%. When the parents of the index patients were unaffected, the recurrence risk was 17.7% for the sibs. Thus, the recurrence risk increases with the number of affected relatives.

In general, recurrence risks are also related to the severity of the polygenic disorder of the index patient. This seems to be true in AIS, but only in regard to the total figures. It is not always evident in the part figures, because of the small number of cases, and because of many environmental factors, for example, the possible influence of treatment and the age of onset of AIS (the earlier it starts the worse it becomes) (Table 3).

Sex can influence the results in the following ways.

(a) The male/female ratio in AIS cases with more than 10° deviation is 1:3-4; thus, there is a marked female preponderance.

(b) On the basis of a presumed polygenic inheritance, the highest recurrence is to be expected in the daughters of affected fathers, the lowest in the sons of affected mothers (Carter, 1976). In contrast to this theory, we found an essentially similar occurrence in both groups. Other surveys yielded the same results (Table 4). Highest recurrence was consistently manifested in the sisters of female index cases.

(c) The mean deviation in children with AIS of the 3 affected fathers was 13.3°, and that of the offspring of the 8 affected mothers was 11.9°. This suggests that the disorder is more severe in the offspring of the less affected sex, though the results have to be interpreted with caution because of the small number of cases. When both parents had scoliosis, the deviation of the affected children amounted to 21°.

Our material included one case of marriage between first cousins, and another between second cousins. The 0-9% prevalence rates are three times greater than is normal in the Hungarian population (0-3%) (Czeizel et al., 1976).

Based on the presumed multifactorial-threshold aetiology of AIS, a computerised table (Smith, 1972) was prepared to estimate the recurrence risk for first degree relatives (Table 5). The female h² value was adjusted to 88%, a percentage justified by the part figures. Table 5 can be of value in genetic counselling, in assisting the early diagnosis of the disorder and helping to avoid triggering factors.

References


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