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ORIGINAL ARTICLE

The familiarity of idiopathic scoliosis: statistical analysis and clinical considerations

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Abstract
Purpose The etiology of idiopathic scoliosis (IS) has been the subject of extensive research, and the current opinion is in favor of a multifactorial pathogenesis with an important genetic component. The aim of this study is to investigate the pattern of inheritance over generations of IS and its possible risk factors.
Methods A total of 70 patients affected by IS was selected and studied up to the third generation for an overall cohort of 2,055 subjects. The genealogy was investigated and correlated for scoliosis.
Results The outcomes showed that 73 % of the patients had an age between 12 and 15 years. The 60 % of the mothers had an age between 20 and 29 years and 57 % of the patients were "first born". The 5.8 % of the brothers and the 12.7 % of the sisters were affected by scoliosis. From the analysis of the total sample, it is clear that in 53 % of the families, there is at least another scoliotic besides the patient.
Conclusion The statistical analysis revealed three different types of transmission: autosomic dominant, autosomic recessive and multifactorial. When this last mode of inheritance is involved, female sex and firstborn resulted as risk factors of IS.

Keywords Idiopathic scoliosis · Genetic · Multifactorial · Risk factors

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Introduction

Idiopathic scoliosis (IS) is a structural lateral curvature of the spine, which affects otherwise healthy patients. Prevalence of IS in the pediatric population is 1–3 % between 10 and 16 years of age [1]. There are multiple causes of spine deformity, including congenital, neuromuscular, traumatic, intraspinal abnormalities, syndromic, and so on, and it is essential to exclude other causes before labeling a curvature as idiopathic. Its etiology is still unknown but the current opinion is in favor of a complex genetic disorder, with one or more genes interacting with the environment to result in spinal deformity [2]. The mode of inheritance has been investigated by many Authors, and evidence for autosomal dominant inheritance with partial penetrance, X-linked inheritance, and a complex trait or multifactorial mode of inheritance have been described [3–9]. Moreover girls are affected more commonly than boys with a female/male ratio of 8:1 [10]. Finally, family surveys have indicated that 11 % of first-degree relatives are affected, as are 2.4 and 1.4 % of second- and third-degree relatives, respectively [5]. In the present study, we performed an analysis of genealogical data from our patients not only to evaluate the patterns of inheritance over generations, but also to detect some possible risk factors for IS.

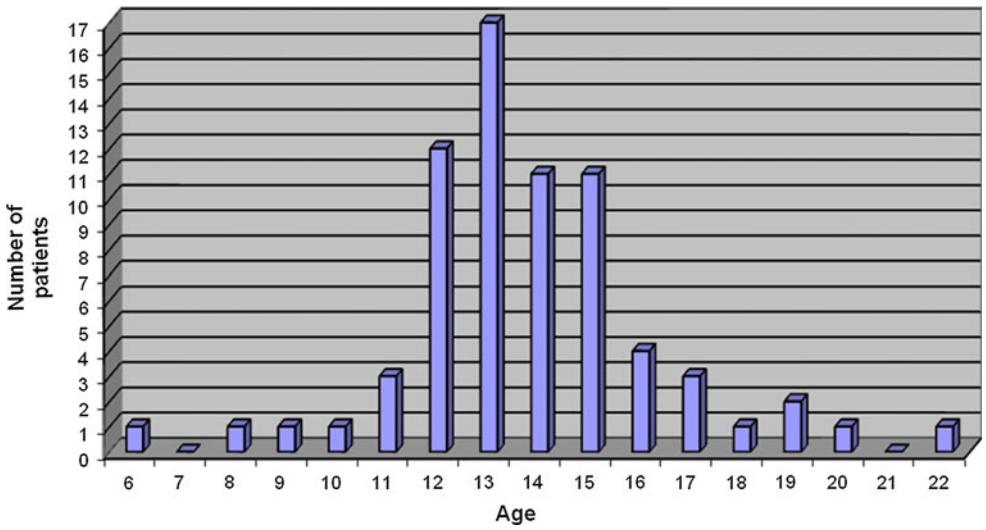

Fig. 1 Age of patients at first observation

Materials and methods

The study cohort consists of families (up to the third degree relationship) of 70 patients with IS admitted to the Orthopedic Department of A. Gemelli University Hospital of Rome. In order to make the sample as homogeneous as possible only females, representing the majority of patients, were considered. A total of 2,055 subjects were enrolled in the study including:

- 70 patients;
- 272 first-degree relatives (fathers, mothers, brothers and sisters);
- 746 second-degree relatives (uncles and grandparents);
- 967 third-degree relatives (cousins).

For all probands, a genealogic tree of at least three generations was constructed, and for each tree, the presence of any other scoliotic patient and the degree of consanguinity have been identified.

First-degree relatives underwent to direct physical examination, while second- and third-degree relatives have been visited only if affected by IS or if there were uncertain anamnesis.

Full-spine standing radiographs were required only in case of positive clinical examination with hump exceeding 5 mm. A structural lateral curvature of over 20° by the Cobb method was regarded as pathologic since minor curves could pass undetected compromising the analysis of results. In addition, the following parameters were evaluated:

- patient's age at the first observation;
- site of curvature;
- age of parents at patient's birth.

Dead or unavailable relatives, representing 2.48 % of the total sample, mainly patients' grandparents, were considered unaffected.

Results

At first observation, 73 % of patients had an age between 12 and 15 years (Fig. 1), and the most frequent site of spine curvature was at dorsal level (Fig. 2). The 57 % of patients were the first-born and 60 % of mothers had an age between 20 and 29 years. Moreover, 5.8 and 12.7 % of brothers and sisters, respectively, were affected by scoliosis, even considering that 55 % of male and 54 % of female were younger than 15 years old. Fathers with scoliosis were 7.1 %, while the mothers were 8.6 % (Table 1). The distribution of scoliosis cases in the second- and third-degree relatives was, respectively, 2.1 and 2.3 % (Fig. 3).

These two samples were first divided by ancestry in maternal and paternal relatives and then by gender in order to identify any different incidence in these subgroups. In particular, IS incidence was significantly higher in the group of female relatives, especially in those of mother's side (second degree = 4.9 % and third degree = 4 %). On the other hand, in the group of male relatives, as well as a lower morbidity, a higher percentage of scoliosis in

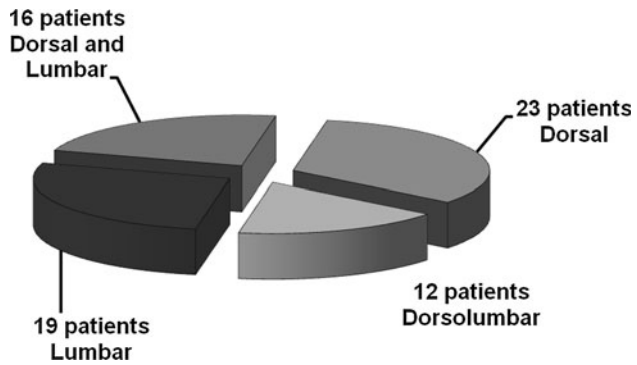

Fig. 2 Spine curvature site

Table 1 Characteristics of study cohort

Total of patients	70
Mean age	13.8
Scoliotic parents	7.8 %
Male/female	7.1 %/8.6 %
Affected siblings	9.1 %
Male/female	5.8 %/12.7 %
II and III degree relatives	2.2 %

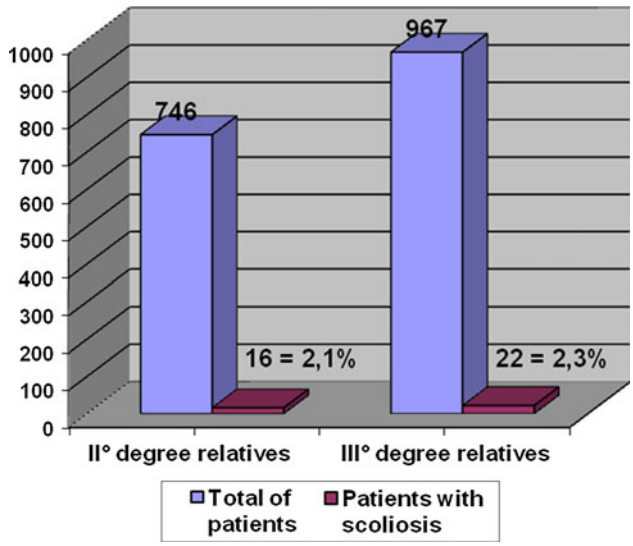

Fig. 3 Characteristics of second- and third-degree relatives

relatives of paternal side has been shown (second degree = 1 % and third degree = 1.2 %).

Analysis of the total sample has also highlighted that in 53 % of families, there was at least a scoliotic subject besides our patient, while in remaining 47 %, she was the only one affected.

Regarding furthermore genealogic trees, our analysis have demonstrated that in 11 cases, an autosomal dominant vertical transmission involving both males and females was present, while in nine cases, there was an autosomal recessive horizontal transmission characterized by healthy parents and two or more affected siblings. The remaining cases, corresponding to 50 patients, were sporadic or characterized by a multifactorial mode of inheritance.

Discussion

IS affects more than 2 % of the pediatric population and results in more than 600,000 physician visits annually. More severe curves occur in 0.2–0.5 % of children; both the incidence and severity are greater in girls [11]. Although the specific cause of IS has not been determined, the role of genetic factors in the development of this condition is widely accepted. Early clinical observations and population studies have documented a higher prevalence of scoliosis among relatives of affected individuals than in the general population [12]. In our sample, IS incidence resulted of 6.4 and 3.1 % considering only affected relatives. These data are underestimated because we considered all deceased or untraceable relatives (2.48 %) as healthy and because we counted only curves of at least 20° since the limit of 10°, suggested by many Authors, are too difficult to identify through an anamnestic and clinical assessment.

The most frequent site of spine curvature was at dorsal level. In effect, since patients with IS have a flatter thoracic kyphosis than normal children, it has been hypothesized that in these patients, the equilibrium between anterior and posterior column growth is disturbed, resulting in hypokyphosis or lordosis of the thoracic spine by relative anterior spinal overgrowth. In addition, asymmetrical anatomy of the thoracic organs and, in particular, the eccentric position of the thoracic aorta that is in close relationship to the vertebral column is likely to play an important role in the development of this preexistent rotational tendency [13–15]. In first-degree relatives, fathers and mothers showed a similar incidence of IS (7.1–8.6 %). In our opinion, these data, apparently conflicting with the well-known prevalence of scoliosis in the female population, are due to the fact that they express not a percentage of affected people, but a risk factor: the father is able to transmit one o more "altered" genes in the same way as the mother.

A similar distribution of IS was found in the maternal and paternal ascendancy. The second- and third-degree relatives with scoliosis are both in the paternal side (47 %) and in the maternal side (53 %). Analyzing the sex-related incidence, males with scoliosis were 28 % in the paternal side and 5 % in the maternal one, while females were, respectively, 72 and 95 %. Clinical manifestations of disease prevail in female sex, while the paternal line and male are involved in transmission of scoliosis. This can be considered a multifactorial mode of inheritance with partial penetrance and variable expressivity.

Moreover:

- at least another brother or sister with scoliosis was present in 11 % of the families without other scoliotic forebears;
- in 47 % of the families, there were no other scoliotic relatives except the patient (overall incidence of 3.55 %);
- in the remaining 53 %, there are relations of particular interest:
  a. the incidence of IS in families with two scoliotic subjects was 7.2 %;

b. the incidence of IS in families with three scoliotic subjects was 9.3 %;
c. the incidence of IS in families with more of three scoliotic subjects was 15.4 %.

In this last group are included two families with an overall IS incidence equal to 22 % out of 50 relatives and 29.4 % out of 17 relatives.

However, careful analysis of pedigrees suggests an heterogeneous etiology. In particular, we found that 11 trees (15.7 %) had a structure that strongly suggests a Mendelian autosomal dominant inheritance, while nine trees (12.8 %) were characterized by an autosomal recessive horizontal transmission. In these families with Mendelian inheritance, scoliosis may represent the first sign of phenotypes more articulate, particularly those that involve different forms of collagen, elastin and fibrillin. In particular, in cases of autosomic dominant or recessive transmission, cardiac abnormalities or even events related to musculoskeletal laxity of ligaments can make us think of connective tissue disorders such as Marfan syndrome. On the other hand, signs like hypotony or weakness, cramps and/or muscle stiffness suggest the presence of neurological or myopathic disorders [16, 17].

Conclusion

The data of this study confirm that IS is a multifactorial disorder characterized by an important genetic component. In particular, we have identified three different types of transmission: autosomic dominant, autosomic recessive and multifactorial. When this last mode of inheritance is involved, female sex and firstborn resulted as risk factors of IS.

It is unclear whether families that showed a Mendelian mode of inheritance actually represented hidden conditions in which syndromic scoliosis may be the first sign of more complex phenotypes. Before defining the risk of recurrence is useful to ascertain whether it is an idiopathic or syndromic scoliosis, in particular, those that involve alternated forms of collagen, elastin or fibrillin. It is also important to carefully evaluate the patient's family and build up a family tree.

Even if no chromosomal studies were carried out in our sample, considering our results, we believe that it is possible in future to investigate the genetic component of IS in families with numerous members affected by IS. In fact, despite the phenotypic and genetic heterogeneity of IS, it remains crucial to identify susceptibility genes for this disorder, to better understand and manage it.

Conflict of interest No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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