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Scoliosis severity does not impact risk of scoliosis in family members

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Abstract

Does scoliosis severity increase scoliosis risk or severity in relatives? In a cohort of 1257 severe idiopathic scoliosis patients, the percentage with at least one affected relative was compared across the categories of patient gender, major curve severity (Cobb angle), and treatment method. In total, 11% (138/1257) of patients had at least one affected first-degree relative and 5% (59/1257) had at least one affected second-degree relative. As expected, males were more likely to have affected first-degree relatives than females (18% versus 10% with a risk difference of -0.0864 [95% CI, -0.14, -0.03; $p=0.0002$]). However, the major curve severity of the patient ($<25^\circ$, $25-49^\circ$, and 50°) did not impact the prevalence of having at least one affected relative ($p=0.69$). Surgically-treated patients had no greater risk than non-surgically treated patients of having either an affected relative or a surgically-treated relative [11% vs 11% (OR, 0.912; 95% CI, 0.640–1.299, $p=0.61$), 6% vs 5% (OR, 0.788; 95% CI, 0.485–1.280, $p=0.34$), respectively]. Therefore, our data suggest that scoliosis severity does not independently influence risk of either scoliosis or its severity in family members.

Keywords

scoliosis; adolescent; juvenile; fusion; familial

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is the most common type of scoliosis, affecting as many as 4 in 100 adolescents [1]. AIS is strongly influenced by genetic factors as evidenced by the higher concordance rate in identical twins compared to non-identical twins [2]. Up to 50% of AIS patients report a family history of scoliosis [3], though the prevalence varies considerably depending upon method of ascertainment, definition and evidence required to confer affected status, and degree of relatedness [4].

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While risk factors for curve progression, including gender, menarcheal status, Risser sign, and curve type, have been studied [5–7], past investigations into the heritability of curve severity have yielded variable results. A large Swedish study of 1463 idiopathic scoliosis patients found a difference in maximum curve between those with one or more affected relatives and those with no affected relatives [8], though the curve difference was small (35° versus 32°). A systematic study of Utah familial data provided little evidence to support heritability of curve severity [9] and Miller et al also found no association between patient's curve severity and the proportion of affected relatives [10]. In the latter study, a correlation existed between mean curve severity of all affected family members and the proportion of affected relatives, but the correlation was weak.

Patients with surgically treated scoliosis have concerns that their children will be at greater risk for developing scoliosis as a consequence of their own severity. Furthermore, they worry that their children will also be at greater risk for severe, progressive scoliosis. Past studies into the heritability of scoliosis severity included relatively few patients from this severe patient population. In addition, many prior studies defined scoliosis as curve >10° in order to obtain maximal estimates of the scoliosis heritability and therefore were not designed to address the familial recurrence risk of severe scoliosis. To achieve the goal of the current study, which is to specifically determine the heritability of severe scoliosis, we studied a large population of idiopathic scoliosis patients recruited from two tertiary surgical referral centers.

METHODS

Patients

This study was approved by the Institutional Review Board and consent was obtained from all participants and/or their parents. Patients were recruited from tertiary referral pediatric spine deformity clinics between 2005 and 2016 at St Louis Children's Hospital and Shriners Hospital for Children, St Louis. Inclusion criteria included a diagnosis of either adolescent idiopathic scoliosis (AIS) or juvenile idiopathic scoliosis with spinal curves measuring 10°. Patients were recruited from clinics with a high proportion of surgically treated patients, and due to research coordinator time constraints, patients with severe curves were preferentially recruited when multiple patients were evaluated simultaneously in clinic, leading to a cohort that was skewed toward larger Cobb angles. Patient data, including date of birth, gender, maximum Cobb angle, and treatment was recorded. Curve measurements are reported for the maximum lateral spinal curve using the Cobb method. All patients with non-surgical range curves at the time of enrollment were followed until either reaching skeletal maturity or undergoing spinal fusion surgery. Patients with congenital and infantile scoliosis, as well as patients with known underlying disorders such as Marfan syndrome, or co-morbidities such as Chiari malformation, were excluded, resulting in 1257 patients with adolescent or juvenile idiopathic scoliosis (Table 1). Of these, 1036 were female and 221 were male. The median Cobb angle was 48° and 50% required surgical treatment for their scoliosis.

Family history was recorded at the time of recruitment as a three-generation pedigree by the research coordinator. The research coordinators had extensive training and experience in

obtaining accurate family histories from scoliosis families as well as drawing pedigrees. Relatives were recorded as affected with scoliosis only if they self-reported a Cobb angle of 25° , or if they self-reported treatment with either bracing or surgery. The number of first- and second- degree relatives affected with scoliosis was recorded for each patient. First-degree relatives include parents, siblings, and children while second-degree relatives include grandparents, grandchildren, aunts, uncles, nieces, nephews, and half siblings. When multiple affected family members were treated at our institution, only one person was considered “the patient” so that duplicate data was not entered.

Analyses

Because very few individuals had more than one affected first- or second-degree relative with scoliosis, rather than reporting the number of affected relatives, the data was dichotomized to indicate percentage of patients with or without affected relatives. Collected data was sorted by patient Cobb angle into bins of mild ($<25^\circ$), moderate ($25\text{--}49^\circ$), and severe ($\geq 50^\circ$) idiopathic scoliosis. The percentage of patients with a first-, second-, or combined first- and second-degree affected relatives was compared across these categories. All statistical analyses were performed in SAS 9.4 software. χ^2 tests of independence were utilized in frequency analyses. The Wilcoxon Rank Sum test was used for skewed two sample analyses. The significance threshold was $p=0.05$.

RESULTS

Among all patients in this study, 14% had at least one first- or second-degree relative who had braced or surgically treated scoliosis, or a curve $\geq 25^\circ$. More specifically, 11% had at least one affected first-degree relative and 5% had at least one affected second-degree relative. The percentage of males having at least one affected relative was higher compared to females in all categories, including first-degree relatives, second-degree relatives, or both (Table 2).

There was no difference in the prevalence of the patient having an affected first- or second-degree relative based on patient Cobb angle of $<25^\circ$, $25\text{--}49^\circ$, and $\geq 50^\circ$ ($p=0.69$) (Table 3). The same trend was observed in males ($p=0.92$) and females ($p=0.51$), demonstrating that the risk to family members was independent of curve severity in both genders. When first-degree or second-degree relatives were considered separately, there was also no effect of curve severity on the frequency of affected relatives with scoliosis ($p=0.60$ and $p=0.50$, respectively) (Table 3). The median Cobb angle of patients with at least one affected family member was 48° compared to 48° with no affected family members ($p=0.3942$).

To determine whether scoliosis severity was heritable within families, we evaluated the treatment concordance among affected family members. Surgically treated patients did not have a greater risk of having a surgically treated relative compared to non-surgically treated relative (Table 4). We identified 97 patients (7.7% of our cohort) who had an affected parent, of which 23 were concordant surgically treated parent-child pairs (1.8% of all patients) (Table 5). Treatment concordance between parent and child was not greater than expected by chance ($p=0.57$) (Table 5).

DISCUSSION

Patients with severe scoliosis are primarily concerned about passing on the risk of *severe* scoliosis to their children. To focus on severe scoliosis that concerns both parents and clinicians the most, we used a more strict definition of scoliosis in relatives (curve treated by bracing or surgery, or a curve with a Cobb angle of $\geq 25^\circ$) than in the patient (curve $>10^\circ$). Strict definition in relatives was also used to minimize overestimation of the presence of scoliosis in this population because we could not obtain documentation from each and had to rely upon self-report of scoliosis, curve magnitude, and treatment. As a consequence of this definition, the proportion of idiopathic scoliosis patients with at least one first- or second-degree relative in our study may be lower than affected relative proportions in some studies, but is remarkably consistent with Riseborough and Wynne-Davies, who reported curves >20 degrees in 11.1% of all first-degree relatives who were subjected to radiographic diagnosis [4]. Using this definition of scoliosis, we found no significant relationship between curve severity in a patient and the presence of severe scoliosis in family members. This is particularly meaningful for patients who have severe scoliosis and are concerned about the outcomes of their children who are known to be at an increased risk for scoliosis. Overall, a relatively small percent (7.7%) of our cohort also had a parent with scoliosis and only 1.8% consisted of concordant surgically treated parent and child. The number of concordant surgically treated parent-child pairs would likely have been much smaller if we had recruited our patient cohort from a community setting or general orthopedics clinic as half of our patients had surgery.

Our data are largely in agreement with previous studies that provided little evidence to support heritability of curve severity [9,10]. Miller et al found no association between a patient's curve severity and the proportion of affected relatives, although there was a weak correlation between mean curve severity of all affected family members and the proportion of affected relatives [10]. Heritability of curve severity was supported by a large Swedish study of 1463 patients that found a small difference in curve severity based on family history, however the curve difference was small (35° versus 32°), and no difference was noted between the maximum curve size when only first-degree affected relatives were considered [8]. Notably, these studies differed from the current study not only in their definition of affected status of family members, but also in the inclusion of patients with a broader range of curve severities. Overall, this demonstrates that even when vastly different cohorts are studied, there is little clinical evidence supporting a major role for heritability of curve severity in population-based studies.

While our data suggests that genetic factors contribute minimally to curve severity on a population level, we cannot exclude the possibility that severe scoliosis may be heritable within select families. For example, a recent study showed an increased prevalence of rare genetic variants in *FBNI*, the causative gene for Marfan Syndrome, in patients with AIS [11]. While that study found that few idiopathic scoliosis patients actually fulfilled criteria for Marfan Syndrome, patients with *FBNI* rare genetic variants had larger spinal curves, were taller, and had slightly higher Ghent systemic feature scores compared to individuals without *FBNI* variants, suggesting that they had milder mutations that did not predispose to the full syndrome or risk of aortic aneurysm. Interestingly, severe, treatment-resistant

scoliosis is a relatively common feature of Marfan syndrome [12] and scoliosis was similarly manifest in AIS patients with *FBN1* variants who had, on average, more severe scoliosis. Future genetic studies on families with highly concordant severe scoliosis are likely to identify additional mechanisms conferring susceptibility to severe scoliosis.

A limitation of the current study is that the majority of scoliosis patients were treated with bracing which may have limited our ability to detect a correlation between genetic factors and curve severity. The current study and all other previously published studies evaluating the heritability of curve severity occurred during an era when bracing treatment is not only widely used but also shown to be effective [13]. However, bracing treatment may have been applied differently across generations within families. Therefore, we cannot exclude the possibility that the lack of correlation between genetic factors and curve severity was due to robust response and differential use of bracing across generations.

While no relationship between curve severity and risk of scoliosis in relatives was seen in our data, we replicated previous studies demonstrating a robust effect of gender on risk to family members. A significantly higher percentage of male patients have affected relatives compared to females [4,9,14] supporting the Carter effect, in which ‘resistant’ males require more genetic loading of susceptibility genes to become affected compared to females [15]. The Carter effect specifically points to polygenic inheritance of a sexually dimorphic disorder, and aptly describes the inheritance pattern of adolescent idiopathic scoliosis. Because males with scoliosis presumably carry a larger number of susceptibility gene variants, they are therefore more likely to have a greater number of affected relatives.

In conclusion, we find no relationship between curve severity and increased risk of severe scoliosis to family members in our population-based data. Scoliosis severity does not influence risk of scoliosis to family members, and severity is poorly concordant among affected family members. At least in the modern era of aggressive bracing, risks for scoliosis susceptibility appear to be distinct from risks for curve progression, as proposed by Cheng et al [16]. Only rarely does severe scoliosis occur repeatedly in families, and these unusual families may be rich for genetic studies aimed at understanding mechanisms of curve progression.

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Table 1

Descriptive data of adolescent/juvenile idiopathic scoliosis probands

	Total	Male	Female
N	1257	221(18%)	1036 (82%)
Median curve (IQR)	48° (28 °)	50 ° (30 °)	48 ° (28 °)
Surgical treatment (%)	630 (50%)	113 (51%)	517 (50%)
Curve severity			
<25°	157 (13%)	31 (14%)	126 (12.2%)
Median Curve (IQR)	19° (5°)	19° (8°)	19.5° (4°)
25–49°	489 (39%)	79 (36%)	410 (40%)
Median Curve (IQR)	36° (14°)	35° (14°)	37° (14°)
50°	611 (49%)	111 (50%)	500 (48%)
Median Curve (IQR)	60° (15°)	60° (12°)	60° (15°)

IQR=interquartile range

Table 2

Family history of scoliosis by gender

	Total (N=1257)	Male (N=221)	Female (N=1036)	Risk Difference (95% CI)	χ^2 p-value
Any first-degree affected relative	138 (11%)	40 (18%)	98 (10%)	-0.0864 (-0.14, -0.03)	0.0002
Any second- degree affected relative	59 (5%)	16 (7%)	43 (4%)	-0.0309 (-0.07, 0.005)	0.0487
Any first- or second-degree affected relative	181 (14%)	48 (22%)	133 (13%)	-0.0888 (-0.15, -0.03)	0.0006

Table 3

Family history of scoliosis by curve severity

Curve severity	N	Any first-degree family history	Any second-degree family history	Any first- or second- degree family history
Total				
<25°	157	17 (10.8%)	10 (6.4%)	25 (15.9%)
25–49°	489	59 (12.1%)	20 (4.1%)	73 (14.9%)
50°	611	62 (10.2%)	29 (4.8%)	83 (13.6%)
χ^2 p-value		0.60 ^a	0.50 ^b	0.69 ^c
Males				
<25°	31	5 (16.1%)	3 (9.7%)	7 (22.6%)
25–49°	79	14 (17.7%)	5 (6.3%)	16 (20.3%)
50°	111	21 (18.9%)	8 (7.2%)	25 (22.5%)
χ^2 p-value		0.93	0.83	0.92
Females				
<25°	126	12 (9.5%)	7 (5.6%)	18 (14.3%)
25–49°	410	45 (11.0%)	15 (3.7%)	57 (13.9%)
50°	500	41 (8.2%)	21 (4.2%)	58 (11.6%)
χ^2 p-value		0.36	0.64	0.51

^aComparison of first-degree family history prevalence between <25°, 25–49°, and 50° groups.^bComparison of second-degree family history prevalence between <25°, 25–49°, and 50° groups.^cComparison of first- or second-degree family history prevalence between <25°, 25–49°, and 50° groups.

Table 4

Family history of scoliosis by surgical treatment

	Non-surgically treated probands (N=627)	Surgically treated probands (N=630)	OR (95% CI)	p-value
First-degree relative affected	66 (11%)	72 (11%)	0.912 (0.640, 1.299)	0.61
First-degree relative treated surgically	31 (5%)	39 (6%)	0.788 (0.485, 1.280)	0.34
Second-degree relative affected	33 (5%)	26 (4%)	1.291 (0.762, 2.184)	0.34
Second-degree relative treated surgically	18 (3%)	16 (3%)	1.134 (0.573, 2.245)	0.72

Table 5

Affected parent-child pairs by surgical treatment

	Proband non-surgical (N=46)	Proband surgical (N=51)
Parent non-surgical (N=41)	23 (26%)	18 (21%)
Parent surgical (N=46)	23 (27%)	23 (27%)
X ² P-Value	0.57	
Relative Risk (95% CI)	1.12 (0.76, 1.67)	0.8780 (0.56, 1.38)