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Familial Aggregation in Idiopathic Subglottic Stenosis

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Abstract

Objective.—To evaluate inheritance patterns and define the familial clustering rate of idiopathic subglottic stenosis (iSGS).

Study Design.—Retrospective observational study.

Setting.—International multicenter collaborative of >30 tertiary care centers.

Methods.—Patients with a clinically confirmed iSGS diagnosis within the North American Airway Collaborative's iSGS[1000] cohort consented between 2014 and 2018 were eligible for enrollment. Patient demographics and disease severity were abstracted from the collaborative's iSGS longitudinal registry. Pedigrees of affected families were created.

Results.—A total of 810 patients with iSGS were identified. Positive family history for iSGS was reported in 44 patients in 20 families. The rate of familial clustering in iSGS is 2.5%. Mean age of disease onset is 42.6 years. Of the 44 patients with familial aggregation of iSGS, 42 were female and 2 were male; 13 were mother-daughter pairs and 2 were father-daughter pairs. There were 3 sister-sister pairs. There was 1 niece-aunt pair and 2 groups of 3 family members. One

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Supplemental Material

Additional supporting information is available in the online version of the article.

pedigree demonstrated 2 affected mother-daughter pairs, with the mothers being first-degree paternal cousins. Inheritance is non-Mendelian, and anticipation is present in 11 of 13 (84%) parent-offspring pairs. The mean age of onset between parents (48.4 years) and offspring (36.1 years) was significantly different ($P = .016$).

Conclusion.—This study quantifies the rate of familial clustering of iSGS at 2.5%. Inheritance is non-Mendelian, and disease demonstrates anticipation. These data suggest that there may be a genetic contribution in iSGS.

Keywords

idiopathic subglottic stenosis; laryngotracheal stenosis

Idiopathic subglottic stenosis (iSGS) is a rare (1:400,000 people per year)[1] but devastating fibroinflammatory airway disease that occurs almost exclusively in adult Caucasian women.[2] The disease is characterized by mucosal inflammation and localized fibrosis resulting in luminal obstruction of the upper airway.[3] Because of high recurrence rates, many patients with iSGS will require multiple surgical procedures following their initial diagnosis.[4] Given the significant emotional, physical, and financial costs associated with recurrent airway obstruction,[5] most research efforts have focused on surgical techniques to improve patency rates. Highly focused scientific approaches to identify key elements of iSGS disease pathophysiology are critical to developing improved therapies.

Given the homogenous demographic and clinical characteristics of the iSGS patient population, several authors have postulated a genetic basis for disease.[3] While clinical experience does not demonstrate a Mendelian inheritance pattern (diseases transmitted through generations in predictable ratios that are consistent with single-gene inheritance), a genetic contribution to disease susceptibility or severity cannot be excluded and warrants further investigation.

The first step in studying the genetic contribution to disease is through examining familial aggregation. Clustering of disease within a family may be due to genetic or environmental factors, but by studying affected individuals and their affected family members, attention may be placed on detecting shared exposures or potential inheritance patterns of the disease.[6] Although there are limited data regarding familial clustering of iSGS, some familial aggregation has been reported. In 2013, 2 pairs of sisters and a mother and daughter with iSGS were described.[7] However, the study reported only 6 patients with no iSGS prevalence data. To examine the prevalence of familial aggregation in iSGS, we utilized the North American Airway Collaborative (NoAAC) iSGS^{1000} cohort.[2] We identified patients with iSGS with affected family members and analyzed their pedigrees to define the rate of familial clustering in iSGS.

Methods

This multicenter observational study was performed in accordance with the Declaration of Helsinki, good clinical practice, and applicable regulatory requirements. The study and clinical review of patient data were approved by the Institutional Review Board at all sites.

Participants

Patients with iSGS who met established diagnostic criteria were candidates in this study.[2,8] Included were adult patients (> 18 years of age) with pathology and narrowing of the subglottis without vasculitis or positive autoimmune titers. Excluded were patients with known airway injury (intubation, caustic, or thermal), patients with a tracheostomy within the past 2 years, and patients without a confirmable index surgical procedure date.[9] A set of monozygotic twins was excluded as they are considered genetically identical.

Setting

Patients were recruited by clinicians in the NoAAC network, which consists of 30 participating tertiary care centers throughout the United States and internationally that are referral centers for iSGS.[2,4,10–13] Patients were also identified via online communities and patient advocacy groups, who directly contacted the study coordination team and subsequently consented to participate in the trial.

Study Protocol

Patient clinical characteristics and demographic information were extracted from the medical record. Demographic information included age, race, sex, body mass index (BMI), birth year, and medical comorbidities.

Statistical Analysis

Data management and analysis were performed with Prism 8 (GraphPad) and Microsoft Excel. Univariate analyses were performed with the Student's *t* test, Fisher's exact tests, and chi-square tests to compare 2 populations when examining difference in demographic factors, including age, ethnicity, BMI, as well as disease severity (defined as the interval between operative procedures to restore luminal caliber) and age of disease onset. Statistical significance was considered when the 2-sided *P* value was <.05.

The rate of familial clustering was defined as the number of representative familial groups divided by the total number of patients with iSGS. In parental pairs, disease onset intervals were calculated with age and year of symptom onset. The difference in year of onset is defined by subtracting the year in which a patient developed symptoms of iSGS from the year of onset of the affected family member. The relative difference in age of onset is calculated by subtracting the parent's age of onset from the offspring's age of onset; a negative number indicates that offspring presented at an earlier age than the parent. Disease severity was measured by the interval between operative procedures to restore luminal caliber. This interval was calculated by dividing the period (in months) from the date of disease onset to the date of last follow-up by the number of operative interventions performed.[2] Patients with only 1 intervention recorded were excluded from this calculation.

Results

Demographic Data

Of 1056 patients in the NoAAC iSGS[1000] cohort, 810 with iSGS met inclusion criteria. Table 1 demonstrates the baseline clinical characteristics of patients with iSGS and familial

aggregation as compared with those with iSGS and no affected family members. The rate of familial clustering in our study was 2.5%. We identified a total of 44 patients in 20 groups with a positive family history of iSGS. All but 2 patients in our cohort are female, and all patients report Northern European ancestry. Of note, 2 sets of affected identical twins were found in the NoAAC but were excluded from this study, since they are considered genetically indistinguishable. There were no significant differences in the percentage of female patients, mean age at onset, ethnicity, BMI, or disease severity.

Table 2 demonstrates the clinical characteristics of pairings and groups of patients with iSGS and familial aggregation. For each parent-offspring pair, we evaluated whether disease presented at a similar time by calculating the difference in year of onset; the mean ± SD was 8.9 ± 10.9 years. Difference in age of onset was also calculated for each pair. The relative difference in age of onset was −12.3 ± 15.8 years. Dilation intervals ranged from 2.6 to 72 months. Anticipation, defined as whether a child presented at a younger age than the affected parent, is indicated by a negative value for relative difference in age of onset. This occurred in 11 out of 13 parental pairs (84.6%; Table 3). The mean age of onset between parents (48.4 years) and offspring (36.1 years) was significantly different ($P = .016$).

The most frequent medical comorbidities were gastroesophageal reflux disease (6 of 31, 19.4%), asthma (5 of 31, 16.1%), and hypothyroidism (5 of 31, 16.1%).

Figure 1 displays representative pedigrees of affected relatives. Figure 1A displays a lineage with 2 motherdaughter affected pairs who are related paternally. Figure 1B is an example of sisters with iSGS. Figure 1C shows a pedigree with a mother and daughter who are affected. Figure 1D shows a pedigree with an affected father-daughter pair. A comprehensive compilation of pedigrees for all affected groups is displayed in Supplemental Figure S1 (available online).

Discussion

Our study represents an initial investigation into familial iSGS by studying pedigrees, patterns of disease onset, and disease severity in 20 familial groups. We define the rate of familial aggregation in iSGS as 2.5%, and pedigree analysis shows a non-Mendelian pattern of inheritance. Disease is not present in every generation in an autosomal dominant fashion, nor does it necessitate 2 alleles for disease expression as an autosomal recessive disease. The cohort had a range of disease severity, as represented by the mean dilation interval, which suggests variable expression of disease. Furthermore, disease inheritance patterns exhibit anticipation, as offspring in parent-daughter pairs developed disease earlier than their parents. These findings suggest a hereditary basis for familial iSGS, although other determinants may modulate disease development.

Epidemiologic studies have characterized the patient population of iSGS as being demographically homogenous. The disease tends to present in perimenopausal Caucasian females without comorbid disease. In addition to demographic uniformity, iSGS is geographically restricted and rarely seen in areas such as Mediterranean Europe, Asia, and Africa.[3] The new finding of familial clustering in iSGS is evidence of a genetic component

of disease. We subsequently explored other clinical characteristics in our cohort to elucidate a potential genetic pathogenesis of iSGS.

While the demographics of our familial iSGS cohort are consistent with previously described homogeneity,[3] disease severity, as measured by mean surgical interval for each individual, varied widely. The mean interval between surgical interventions ranged from 2.6 to 72 months (Table 2). This variation of disease severity among individuals with a potentially genetic disease underscores the complexity of disease inheritance. Expressivity is the result of variation in allelic composition. In many genetic diseases, an allele may not be fully penetrant, and this leads to inconsistency and diversity in phenotype.[14] There are several hypotheses for differential expression of disease, including microRNA that regulates genes at a posttranscriptional level and affect phenotypic outcomes.[15] The finding of variable expression in familial iSGS indicates that there are likely additional determinants that regulate phenotypic manifestation of disease.

A second clinical finding of anticipation suggests that familial iSGS may be genetic. In anticipation, the disease becomes more severe and assumes earlier expression in each generation. This phenomenon is due to expanded triplets: repetitive DNA sequences that show a high degree of mutation.[16] These unstable DNA sequences, which comprise 30% of eukaryotic DNA,[17] increase in number from one generation to the next and result in variable expression of disease. Anticipation has been well characterized in neurodegenerative disorders, most notably Huntington's disease,[18,19] as well as genetically complex disorders, including autoinflammatory conditions such as Crohn's disease[20] and psoriasis.[21] In cases of genetic anticipation, parental sex can influence disease severity. While men rarely present with iSGS,[2] our study included 2 men with daughters who developed stenosis at an age 22 years younger than their fathers' presentation age. This pattern in the 2 father-daughter pairs with iSGS parallels Huntington's disease, in which descendants of affected males have an earlier onset of the disease when compared with descendants of affected women.[22]

A third clinical characteristic studied in each familial pair was year of disease onset to consider the possibility of an external environmental exposure as a cause of iSGS. In the absence of gene-environmental studies, such as family-based monozygotic and dizygotic twin studies, estimates of genetic and environmental contributions to disease phenotypes and the interactions between them are difficult to partition and quantify. It is suggestive of a simultaneous exposure if disease onsets are temporally congregated, similar to acquisition of an infectious disease. The interval between successive cases of a disease is a measure used to interpret epidemiologic spread of disease.[23] To investigate potential temporal association, we examined year of onset of disease. There was no consistent interval identified; years ranged from as few as 2 years between diagnosis to 35 years, suggesting that iSGS is not solely caused by an environmental exposure.

We hypothesize that familial patients with iSGS may possess a genotype rendering them more susceptible to disease initiation, which may explain the lack of full penetrance throughout generations. Depending on an individual's inherited genotype, perhaps an external exposure may provide the "second hit" and create the iSGS phenotype in these familial groups. Both the underlying genotype and the identity and/or role of a "second hit"

remain undefined. In other more prevalent fibrotic airway diseases that have been studied in greater depth, such as idiopathic pulmonary fibrosis, most patients do not have an affected family member. For these sporadic patients, weaker genetic risk alleles may contribute to the pathogenesis of fibrosis. Less commonly, patients with idiopathic pulmonary fibrosis have similarly affected family members and share more highly penetrant genetic risk alleles.[24] These hypotheses may be generalized to patients with iSGS. We anticipate future studies identifying genes of interest in familial iSGS that may then be validated in a sporadic iSGS cohort.

Our study has limitations. Our cohort is small and reflects the rare prevalence of familial iSGS. Even so, these data are strengthened by our large multi-institutional collective of patients with iSGS. Broadly speaking, diseases characterized by progressive fibrosis, especially those of late onset, are complex and difficult to study. Environmental triggers are challenging to define. While we did study the year of disease onset in familial pairs as a proxy for an environmental cause, we were not able to evaluate patients' and family members' living locations at the time of disease onset, limiting our evaluation of geographically shared exposures. It will be beneficial to consider these factors as patient data are collected prospectively. Even with this constraint, the identification of these familial pairs facilitates future genetic studies to identify alleles that portend greater risk of disease.

In conclusion, this study reports novel clinical data about familial aggregation of iSGS and informs our understanding of iSGS. We define the rate of familial aggregation as 2.5%. We also provide data supporting a non-Mendelian pattern of disease inheritance and demonstrate anticipation in 11 of 13 parental pairs. The presence of anticipation is suggestive of a genetic contribution to familial iSGS. Further studies are necessary investigating the genomic composition of these familial pairs. Future directions include whole exome sequencing for comparison of affected family members to nonaffected relatives to identify candidate genes. Candidate genes uncovered in the familial pairs described in this work can then be validated in the larger iSGS^{1000} cohort to confirm their impact on iSGS disease pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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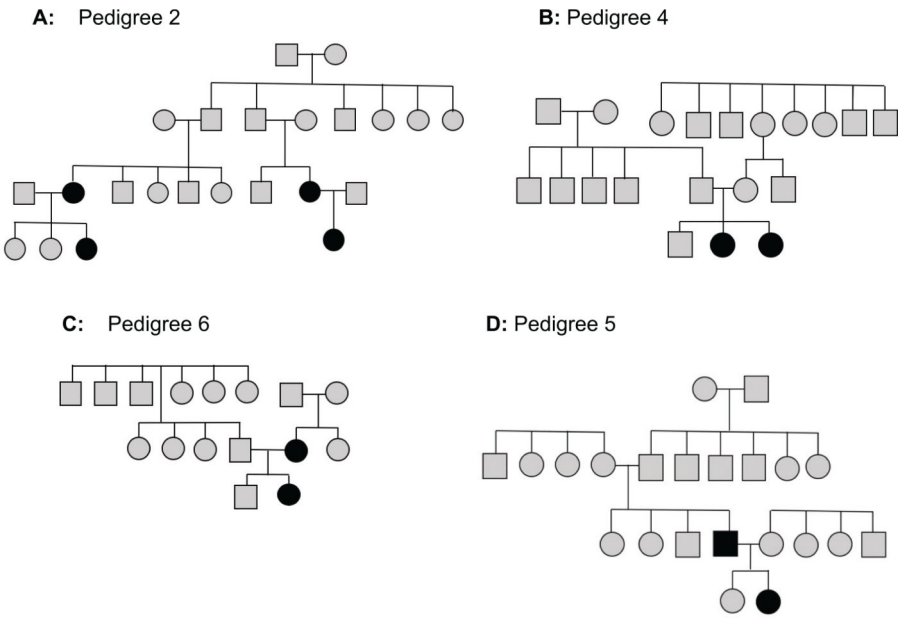

Figure 1.

Sample pedigrees. A filled-in marker denotes idiopathic subglottic stenosis. (A) Paternally related mother-daughter pairs. (B) Affected sisters. (C) A mother-daughter pair. (D) A father-daughter pair.

Table 1.

Clinical Characteristics of Patients With iSGS: Comparison Between Those With and Without Affected Relatives.[a]

	Familial iSGS	iSGS without affected relatives	*P* value
Patients	44 (5.4)	766 (94.6)	
Familial groups	20 (2.5)		
Female sex	42 (95.5)	756 (98.7)	.08
Age at onset, y	42.6 ± 11.8	43.7 ± 12.6	.36
Ethnicity			
Caucasian	44 (100)	743 (97.0)	.24
Hispanic	0 (0)	17 (2.2)	
Black	0 (0)	1 (0.1)	
Other	0 (0)	5 (0.7)	
Body mass index, kg/m^2	26.9 ± 5.2	29.3 ± 9.9	.17
Dilation interval, mo	18.4 ± 20.0	19.4 ± 16.8	.81
Pairs			
Mother-daughter	13		
Sister-sister	3		
Father-daughter	2		
Niece-aunt	1		
Group of 3			
Niece, aunt, cousin	1		
Mother, 2 daughters	1		

Abbreviation: iSGS, idiopathic subglottic stenosis.

[a]Values are presented as No. (%) or mean ± SD.

Table 2.

Clinical Characteristics of Patients With Idiopathic Subglottic Stenosis and Paired Affected Family Members.

Pair/group: relationship	Sex	Birth year	Onset year	Onset age, y	Anticipation present?	Difference in year of onset, y	Relative difference in age of onset, y	Dilation interval, mo
1								
Daughter	F	1971	2008	37	Y	4	−18	38
Mother	F	1949	2004	55				7.5
2								
Daughter	F	1970	2011	41	Y	9	−1	
Mother	F	1950	1992	42				6
Paternal cousin	F							
Daughter of paternal cousin	F							
3								
Daughter	F	1974	2015	41	Y	3	−15	
Mother	F	1956	2012	56				6.3
4								
Sister	F	1980	2016	36	NA	3	NA	
Sister	F	1981	2013	32				4.7
5								
Daughter	F	1978	2008	30	Y	4	−22	
Father	M	1952	2004	52				6
6								
Daughter	F	1969	2014	45	N		+2	
Mother	F			43				
7								
Daughter	F							
Mother	F							
8								
Daughter	F	1979	2005	26	Y	5	−22	
Father	M	1952	2000	48				
9								

Pair/group: relationship	Sex	Birth year	Onset year	Onset age, y	Anticipation present?	Difference in year of onset, y	Relative difference in age of onset, y	Dilation interval, mo
Daughter	F	1956	2012	56	Y	22	−2	
Mother	F	1932	1990	58				51
10								
Daughter	F	1950	2005	55	N	35	+12	
Mother	F	1927	1970	43				
11								
Daughter	F	1973	2016	43				
Mother	F							
12								
Niece	F	1973	2013	40	NA			3.5
Maternal aunt	F							
Cousin	F							
13								
Paternal aunt	F	1979	2013	34	NA			9
Niece	F							
14								
Sister	F	1963	2005	42	NA	2		
Sister	F	1965	2007	42				16.8
15								
Daughter	F	1998	2012	14	Y	2	−40	2.6
Mother	F	1960	2014	54				6.5
16								
Daughter	F	1977	2005	33	Y	13	−4	
Mother	F	1955	1992	37				72
17								
Daughter	F	1952	1994	42				39.4
Mother	F							
18								
Daughter	F	1985	2017	32	Y	26	−1	5.3
Daughter	F	1987	2011	24	Y	20	−9	15.8

Pair/group: relationship	Sex	Birth year	Onset year	Onset age, y	Anticipation present?	Difference in year of onset, y	Relative difference in age of onset, y	Dilation interval, mo
Mother	F	1957	1991	33				22.4
19								
Daughter	F	1965	2000	35	Y	11	−40	
Mother	F	1936	2011	75				
20								
Sister	F							
Sister	F							
Mean ± SD				42.6 ± 11.8	84.6%	8.9 ± 10.9	−12.3 ± 15.8	18.4 ± 20.0

Abbreviation: NA, not applicable.

Table 3.

Parental Pairs: Age of Onset Comparison.

	Age, y	
Pair	**Parent**	**Offspring**
1	55	37
2	42	41
3	56	41
5	52	30
6	43	45
8	48	26
9	58	56
10	43	55
15	54	14
16	37	33
18	33	32
18	33	24
19	75	35
Mean ± SD[a]	48.4 ± 11.3	36.1 ± 11.4

[a] $P = .016$.