Oesophageal disease in systemic sclerosis: does heritability play a role?

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ABSTRACT

Objective. *In systemic sclerosis (SSc) the most common gastrointestinal tract (GIT) complaint is gastroesophageal reflux disease (GERD), which may contribute to oesophagitis, stricture, Barrett's oesophagus, and oesophageal adenocarcinoma. We used a genealogical resource the Utah Population Database (UPDB) to analyse SSc pedigrees for hereditability of oesophageal disease.*

Methods. *SSc, GERD, oesophagitis, stricture, Barrett's, and oesophageal adenocarcinoma were defined by ICD Ninth and Tenth Revision codes. Familial aggregation, relative risk (RR) of the GIT disease in SSc proband and their relatives was estimated by Cox regression model. The model (adjusted for sex and birth year) was used to evaluate the effects of having or being related to, a case or control for SSc, on GIT diseases.*

Results. *We identified 2,227 unique SSc patients and 11,136 randomly selected controls matched by birth year, gender, and whether born in Utah, in an approximately 1:5 ratio. A SSc proband had a significant high risk of GERD (RR: 3.28), dysphagia (RR 5.58), oesophageal stricture (RR: 5.16), oesophagitis (RR: 4.86), and Barrett's (RR: 4.52) all with significant p-values <2e-16. First-degree relatives of a SSc proband were at elevated risk of GERD (RR: 1.14, p=6.85e-05), dysphagia (RR: 1.22 p=0.002), and oesophagitis (RR: 1.37, p=2.10e-06). First cousins (RR: 1.09, p=0.03) and spouses (RR; 1.37, p=0.02) were at increased risk of oesophagitis and dysphagia.*

Conclusion. *These data suggest that independent of GERD, oesophagitis in SSc patients and their relatives may have both a hereditable and environmental aetiology. There does not seem to be a heritable component to Barrett's oesophagus.*

Introduction

Gastrointestinal tract (GIT) problems are the presenting disease feature in 10% of, occurs during disease course in up to 95% of, and is responsible in 6-12% of mortality in SSc patients (1). The oesophagus is the most common visceral organ involved in SSc and is associated with quality of life and mortality in large cohorts of early, diffuse SSc (2, 3). The aetiology of oesophageal involvement and symptomatic gastroesophageal reflux disease (GERD) in SSc is unknown, however autoimmunity, vasculopathy, and fibrosis are suspected to result in progressive oesophageal structural change (4). Management of oesophageal involvement in SSc is guided by whether there are features of serious disease and empiric management of suspected (GERD) is started prior to diagnostic studies in this patient population (2). Eosinophilic oesophagitis, which is requires oesophagogastroduodenoscopy (EGD) for diagnosis, can result in chronic oesophagitis, has a higher occurrence in SSc patients, and has a familial association (5-7). The role of hereditability of oesophageal symptoms (such as dysphagia and heartburn), and oesophageal diseases (such as oesophagitis, stricture, Barrett's oesophagus, and oesophageal adenocarcinoma) are unknown in SSc patients.

The purpose of this study was to determine heritable risk of gastrointestinal tract disease within SSc subjects and their extended family members to identify possible shared genetic aetiology of oesophageal symptoms in SSc families. We anticipate that identification of diseases with shared genetic aetiology may improve risk stratification of oesophageal symptoms and facilitate a targeted use of diagnostic testing and screening in SSc patients.

Methods

Utah Population Database

The Utah Population Database (UPDB) offers a unique opportunity to study in individual medical records linked to genealogical data from collected in Utah since the 1840s. The UPDB is a shared research resource between the Pedigree and Population Resource of the Huntsman Cancer Institute and the University of Utah. The UPDB resource links inpatient and outpatient electronic medical records from 1995 to the present drawn from the University of Utah Health Sciences Center and Intermountain Healthcare and statewide medical data collected by the Utah Department of Health linked to 1.6 million genealogy records of early Utah immigrants provided by the Genealogical Society of Utah. This resource has successfully created SSc pedigrees for analysis of possible hereditable aspects of disease pathogenesis (8, 9). This study was approved by the University of Utah institutional review board and the Utah Resource for Genetic Epidemiological Research, which oversees the usage of UPDB. All of the data involved in this project were de-identified, and waivers of informed consent were granted by the institutional review board.

Study subjects

All SSc probands were identified by International Classification of Diseases Ninth and Tenth Revision codes (ICD-9 710.1 and ICD-10 M34.0, M34.1, and M34.9). In the SSc pedigrees, each family member was assessed for diagnostic codes for SSc, GERD (ICD-9 530.1 and ICD-10 K21.9), dysphagia (ICD-9 787.20), oesophageal stricture (ICD-9 530.3 and ICD-10 K 22.2), Barrett's oesophagus (ICD-9 530.85 and ICD-10 K22.7), and oesophageal adenocarcinoma (ICD-9 150.9 and ICD-10 C15.9). Five matched controls were selected randomly from the UPDB population database without replacement. The controls were matched on gender, birth year, and whether they were born in Utah.

Statistical analysis

Using kinship analysis tools (KAT), a statistical software developed by the UPDB the magnitude of familial risk for GIT in SSc patients was estimated. A Cox regression model was used to estimate the relative risk of GIT disease in SSc proband and their relatives. Time at risk was measured from birth to the age of diagnosis, or death, or at the age of the end of the study, whichever occurred first. The model was adjusted for sex, birth year and used to evaluate the effects of being, or being related to, a case or control for SSc, on other GIT diseases. In order to accommodate the dependence of the data, a cluster was defined, which consists of all the relatives of the case or controls. High risk pedigrees were defined by having the familial standardised incidence rate (FSIR) >2 with p-value <0.05.

Table I. Diagnosis code sources from the Utah Population Database.

Diagnosis	UUHSC	IHC	Inpatient
SSc	1252	1435	1182
GERD	89678	276307	NA
Dysphagia	15472	41036	42040
Stricture	42040	36485	NA
Barrett's Oesophagus	2827	9416	13081
Oesophageal adenocarcinoma	NA	NA	180

NA: not applicable (data code not found).

Results

The data distribution from the individual data sets for SSc pedigrees is shown in Table I. A total of 2,227 unique SSc patients and 11,136 controls were identified.

Using the KAT we identified numbers of high risk SSc pedigrees with at least 4 SSc patients in the pedigree, FSIR >2 with p-value <0.05. The number of descendants of the high risk pedigrees ranged from 1,804 to 80,787. We extended our selection by taking into account the high number of GIT patients in these pedigrees. The population attributable risk analysis result indicated that approximately 15% of the SSc cases were familial. The family with the highest number of both SSc and reflux had 22 affected members and 78,992 descendants. Thus, the absolute risk was 0.028%.

The RR of each gastrointestinal tract symptom or disease in shown in Table II. Cox proportional hazard analysis result shows SSc proband had a significant high risk of oesophageal diagnoses: GERD (RR: 3.28), dysphagia (RR 5.58), oesophageal stricture (RR: 5.16), oesophagitis (RR: 4.86), and Barrett's (RR: 4.52 (all p<2e-16). First-degree relative of a SSc proband were at elevated risk of GERD (RR: 1.14, p=6.85e-05), dysphagia (RR: 1.22 p=0.002), and oesophagitis (RR: 1.37, p=2.10e-06). First cousins (RR: 1.09, p=0.03) and spouses (RR; 1.37, p=0.02) were also at increased risk of oesophagitis and dysphagia. There were no significant findings of any of these GIT codes among second degree relative of SSc proband. These results suggested that both genetics, as indicated by increased risk in relatives, and similar exposures, as indicated by increased risk of spouses, may play a role in pathogenesis. Oesophageal stricture and Barrett's oesophagus do not appear to be hereditable and were also not seen in spouses. None of the SSc cases had oesophageal adenocarcinoma.

Discussion

While SSc has a well-recognised heritable component to its pathogenesis (10), the aetiology of gastrointestinal disease in this disease is unknown. Nonetheless, gastrointestinal disease is an important aspect of SSc morbidity and a critical focus for research (11, 12). The UPDB, which is linked to over 7 million medical records, allowed us to study the pedigrees of 2,276 unique SSc patients. In our study, the SSc proband had a significant presence of oesophageal symptoms of GERD and dysphagia, as well oesophageal disease oesophageal stricture, oesophagitis, and Barrett's, which supports the concept of the importance of assessing for oesophageal involvement in this patient population.

Table II. Oesophageal hereditability in systemic sclerosis pedigrees.

Relationship	Gastroesophageal reflux disease	Dysphagia	Oesophageal stricture	Oesophagitis	Barrett's oesophagus
Proband	**3.28 (3.05-3.53)**† ***p*<2e-16***	**5.58 (4.9-6.35)** ***p*<2e-16***	**5.16 (4.35-6.12)** ***p*<2e-16***	**4.86 (4.21-5.62)** ***p*<2e-16***	**4.52 (3.41-6)** ***p*<2e-16**
1st degree	**1.14 (1.07-1.21)** ***p*=6.85e-05***	**1.22 (1.07-1.39)** ***p*=0.002***	1.09 (0.93-1.28) *p*=0.284	**1.37 (1.2-1.56)** ***p*=2.10e-06**	1.19 (0.92-1.53) *p*=0.18
2nd degree	1.04 (0.99-1.09) *p*=0.17	1.09 (0.98-1.21) *p*=0.10	0.91 (0.81-1.03) *p*=0.15	**1.12 (1-1.25)** ***p*=0.048***	1.22 (0.97-1.53) *p*=0.08
3rd degree	1.03 (0.99-1.07) *p*=0.18	1.09 (1.01-1.18) *p*=0.031*	1.01 (0.92-1.1) *p*=0.89	**1.09 (1-1.19)** ***p*=0.04***	1.11 (0.94-1.3) *p*=0.21
Spouse	1.09 (0.97-1.23 *p*=0.15	1.37 (1.05-1.8) ***p*=0.019***	1.14 (0.83-1.56) *p*=0.42	**1.57 (1.19-2.09)** ***p*=0.002***	1.2 (0.73-1.97) *p*=0.47

†Relative risk (confidence interval); *Statistical significant.

Progressive oesophageal involvement in SSc results in smooth muscle atrophy of the inner circular layer of the muscularis propria and fibrosis of the distal two thirds of the oesophagus (2, 13).Previous pathological sample analysis reveal inconsistent ischaemic or inflammatory processes, thus the cause of the patulous oesophagus remains unknown (13). Nonetheless, the importance of understanding oesophageal disease in SSc is underscored by the higher incidence of Barrett's and oesophageal adenocarcinoma that is seen in this patient population (14). Proper characterisation of risk in the population can guide treatment and diagnostic considerations. In our study we did not find oesophageal stricture or Barrett's oesophoagus to be hereditable. However, none of our SSc cases had oesophageal adenocarcinoma.

We also found that oesophagitis and dysphagia are statistically significant in first degree relatives and first cousins as well as in spouses. This result may suggest that both genetics and environment (possibly similar diets) may play a role in pathophysiology of SSc oesophageal symptoms. As such, lifestyle modifications, such as not eating a certain number of hours before repose, head of bed elevation, and avoidance of exacerbating food groups in order to reduce symptomatology is likely important advice to give all patients with GERD symptoms. The proper duration of empiric reflux medications and appropriate timing of diagnostic tests for oesophageal complaints becomes somewhat more challenging in this patient population, however our data suggests due to the familial component of oesophagitis and dysphagia, that EGD should be considered in all patients with persistent GERD.

In conclusion, this study supports that the aetiology of reflux in SSc is likely multi-factorial with both heritable and exposures playing a role in pathogenesis. The UPDB is a robust research tool that allows comparable hereditability in SSc pedigrees to be studies in detail. Future studies of SSc pedigrees may help better delineate whether SSc clustering of unrelated probands can better identify environmental influences on the gastrointestinal aspect of this disease.

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References

1. GYGER G, BARON M: Gastrointestinal manifestations of scleroderma: recent progress in evaluation, pathogenesis, and management. *Current Rheumatol Rep* 2012; 14: 22-9.
2. HANSI N, THOUA N, CARULLI M *et al*.: Consensus best practice pathway of the UK scleroderma study group: gastrointestinal manifestations of systemic sclerosis. *Clin Exp Rheumatol* 2014; 32 (Suppl. 86): S214-21.
3. DOMSIC RT, NIHTYANOVA SI, WISNIEWSKI SR *et al*.: Derivation and External Validation of a Prediction Rule for Five-Year Mortality in Patients With Early Diffuse Cutaneous Systemic Sclerosis. *Arthritis Rheumatol* 2016; 68: 993-1003.
4. KIRBY DF, CHATTERJEE S: Evaluation and management of gastrointestinal manifestations in scleroderma. *Current Opin Rheumatol* 2014; 26: 621-9.
5. ROTHENBERG ME: Biology and treatment of eosinophilic esophagitis. *Gastroenterology* 2009; 137: 1238-49.
6. FRECH TM, BOYNTON K, DOWNS-KELLY E, JONES B, KRIESEL JD, PETERSON K: Eosinophilic Esophagitis in Two Patients with Systemic Sclerosis. *Case Rep Rheumatol* 2016; 2016: 6410-421.
7. PETERSON K, FIRSZT R, FANG J, WONG J, SMITH KR, BRADY KA: Risk of Autoimmunity in EoE and Families: A Population-Based Cohort Study. *Am J Gastroenterol* 2016; 111: 926-32.
8. FRECH T, KHANNA D, MARKEWITZ B, MINEAU G, PIMENTEL R, SAWITZKE A: Heritability of vasculopathy, autoimmune disease, and fibrosis in systemic sclerosis: a population-based study. *Arthritis Rheum* 2010; 62: 2109-16.
9. FRECH TM, PIMENTEL R, MINEAU G, SAWITZKE A, PENMETSA G, WONG J: Parental influence on systemic sclerosis. *Arthritis Care Res* 2015; 67: 310-2.
10. BOSSINI-CASTILLO L, LOPEZ-ISAC E, MARTIN J: Immunogenetics of systemic sclerosis: Defining heritability, functional variants and shared-autoimmunity pathways. *J Autoimmun* 2015; 64: 53-65.
11. KARAMANOLIS GP, DENAXAS K, PANOPOULOS S *et al*.: Severe oesophageal disease and its associations with systemic sclerosis. *Clin Exp Rheumatol* 2017; 35 (Suppl. 106): S82-5.
12. BARSOTTI S, STAGNARO C, D'ASCANIO A, DELLA ROSSA A: One year in review 2016: systemic sclerosis. *Clin Exp Rheumatol* 2016; 34 (Suppl. 100): S3-13.
13. ROBERTS CG, HUMMERS LK, RAVICH WJ, WIGLEY FM, HUTCHINS GM: A case-control study of the pathology of oesophageal disease in systemic sclerosis (scleroderma). *Gut* 2006; 55: 1697-703.
14. WIPFF J, CORIAT R, MASCIOCCHI M *et al*.: Outcomes of Barrett's oesophagus related to systemic sclerosis: a 3-year EULAR Scleroderma Trials and Research prospective follow-up study. *Rheumatology* (Oxford) 2011; 50: 1440-4.