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Disease associations in alpha-1-antitrypsin deficiency

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Summary
Introduction: In addition to emphysema alpha-1-antitrypsin deficiency (AATD) has been shown to be associated with several inflammatory conditions, including bronchiectasis, vasculitis, (in particular Wegener's granulomatosis), and panniculitis, suggesting neutrophil proteinases also play a role in their pathophysiology. However, it remains unknown whether other inflammatory diseases are also more prevalent in AATD than the general population. The current study describes the prevalence of other co-morbidities in AATD with particular emphasis on inflammatory bowel disease.
Methods and results: The case notes of 651 PiZZ or PiZnull patients attending the UK national centre for AATD between 1996 and 2011 were reviewed. The prevalence of inflammatory bowel disease (1.5%) was higher than that predicted in the UK (0.4%). Ten patients had a confirmed diagnosis of ulcerative colitis, and 1 had Crohn's disease. In 2 cases there was a family history of inflammatory bowel disease and all but 1 patient were ex or never smokers. There was also a higher prevalence of hypothyroidism in this patient group than expected for the UK population – 26 cases (7.2% of females and 1.3% of males).
Conclusions: The current study of the UK cohort of patients with AATD confirmed a higher prevalence of ulcerative colitis than would be expected in the general population, providing further evidence of a potential link between these 2 conditions. In addition, the data suggested a potential link between hypothyroidism and AATD.

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Introduction

Co-morbidities are becoming increasingly recognised in patients with usual COPD. Cardiovascular disease, the metabolic syndrome and osteoporosis all occur more frequently than expected and may have a common inflammatory pathway [1].

Alpha-1-antitrypsin deficiency (AATD) of the PiZZ genotype has a prevalence of 1 in 2500 in the UK and is the only widely recognised genetic factor that increases susceptibility to develop COPD [2]. This severe form of the deficiency results in a critically low level of AAT that reduces the ability to protect tissues from the bystander damage caused by proteolytic enzymes from the neutrophil, including neutrophil elastase and proteinase 3 [3,4]. This excessive damage may be central to the processes seen in panniculitis and arteritis which are both neutrophilic conditions [5] and more frequent in subjects with AATD [6] suggesting cause and effect.

Little is known about other co-morbidities in AATD that have a neutrophilic pathophysiology although there has been a suggested link with inflammatory bowel disease [7].

The UK registry for AATD has comprehensive physiological and radiological data but also documents co-morbidities and their temporal relationship to the diagnosis of AATD. The current project was undertaken to determine the frequency of other co-morbidities with an inflammatory basis in patients with AATD.

Methods

The ADAPT programme is the UK national centre for patients with AATD, established in 1996, which documents the patients in detail, including past and present medical history.

A retrospective review was undertaken of the first 651 consecutive patients joining the registry with the PiZZ or PiZnull phenotypes from 1996 to September 2011. AATD phenotype and genotype was confirmed in all patients based on dried blood spots by a single laboratory (Heredilab, Salt Lake City, Utah).

Data on all co-morbidities was extracted from the case notes for each of the patients. It was noted that 2 co-morbidities appeared to be more prevalent than anticipated; namely inflammatory bowel disease and hypothyroidism, therefore they were selected for further analysis for the current report. In those in whom a diagnosis of IBD was recorded, confirmation was sought from the individual patients' primary care physician, together with the date of diagnosis, where the diagnosis was made, and whether any family history of inflammatory bowel disease was known.

In the patients in whom a diagnosis of hypothyroidism had been recorded, confirmation of the diagnosis was also sought from the patients' primary care physician, including date of diagnosis and the presence or absence of thyroid autoantibodies. Where autoantibodies were not documented thyroid peroxidase (TPO) autoantibodies were measured in the patients' stored plasma using a fluorescence enzyme immunoassay (FEIA — a sandwich immunoassay) and expressed as a value in arbitrary units (au).

Other demographic data for patients with IBD or thyroid disease was extracted directly from the registry database.

Data analysis was undertaken using Microsoft Excel 2007 and SPSS version 17 (Chicago Ill). Ethical approval for the study was approved by the South Birmingham Ethics Committee (LREC number 3359), and all patients gave written informed consent.

Results

IBD

There were 11 patients from this UK cohort who had a diagnosis of IBD documented in the case notes (2 of whom also had a family history of IBD). The diagnosis was of UC in 10 patients, and Crohn's disease in the remaining patient. In each case, the patients' primary care physician confirmed both the diagnosis and the date of diagnosis. There was one further patient who had a diagnosis of IBD made in secondary care, and had undergone a surgical resection of the large bowel, but in whom the definitive diagnosis of UC or Crohn's was not made. Data from this individual was therefore excluded from the UC series, in the current study. The demographic data for the 10 patients with confirmed UC and AATD are presented in Table 1.

There were 4 male and 6 female patients, which is consistent with the even sex distribution of UC in the general population. The overall prevalence rate of UC in this patient cohort was 1.5% (10 of 651 patients), which is equivalent to

Table 1 Demographic data for the 10 patients with AATD and UC.

Male (%)	4 (40)
Age at UC diagnosis	37.4 (5.1)
Age at AATD diagnosis	35.1 (6.4)
AAT level (μm)	4.1 (1.2)
FEV_1 (L)	2.7 (1.8)
FEV_1% predicted	98.0 (45.8—117.8)
FVC (L)	4.9 (3.94—6.0)
FVC% predicted	123.2 (22.8)
FEV_1/FVC ratio	56.3 (23.2)
TLC (L)	6.8 (1.7)
TLC% predicted	120.9 (8.2)
KCO mmol/min/kPa/L	1.2 (0.3)
KCO% predicted	73.3 (15.8)
RV/TLC%	41.9 (1.8)
Smokers (%)	7 (70)
Pack year history	9.5 (3.7)
CT emphysema alone (%)	3 (30)
CT bronchiectasis (%)	1 (10)
CT emphysema and bronchiectasis (%)	3 (30)
SGRQ impact	28.7 (9.3—42.5)
SQRG activity	50.4 (18.1—80.9)
SGRQ symptoms	62.8 (41.8—61.2)
SGRQ total	42.7 (19.5—58.6)

Data are shown as mean values with SD in parentheses or median with IQR in parentheses, apart from the proportion of males, smokers and those with CT abnormalities shown as number and % in parentheses.