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ORIGINAL RESEARCH

Spanish Registry of Patients With Alpha-1 Antitrypsin Deficiency; Comparison of the Characteristics of PISZ and PIZZ Individuals

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Abstract

Alpha-1 antitrypsin deficiency (AATD) is associated with an increased risk of pulmonary emphysema and liver disease. The growing interest in this deficiency in Spain led to the development of the Spanish Registry of Patients with Alpha-1 Antitrypsin Deficiency (REDAAT) in 1993. At present, the REDAAT is a network of more than 350 health care professionals and the database includes a total of 511 individuals. The adult population included consists of 469 individuals (91.8% of the total) and their phenotype distribution is: 348 Pi*ZZ (74.2%), 100 Pi*SZ (21.3%) and 21 carriers of rare variants (4.5%). The most frequent diagnosis is lung disease (74.6%). Patients with chronic obstructive pulmonary disease (COPD) registered in the REDAAT constitute approximately 15% of the expected cases of AATD-related COPD in Spain. Pi*ZZ showed more severe impairment in lung function and younger age at baseline compared with Pi*SZ. The mean decline in FEV_1 in the Pi*ZZ subgroup was –23 ml/year (SD:142.8), being –18 ml/year (SD:108.8) in Pi*SZ. Forty-five percent of the Pi*ZZ individuals received augmentation therapy. A total of 61 deaths was recorded. The characteristics of the REDAAT population demonstrate some differential trends compared to other series: distribution of phenotypes, inclusion of children and patients treated with replacement therapy. Patients with the Pi*SZ phenotype were older and had milder lung function impairment. The most important challenge of this registry is to collect good quality long-term data that will allow better understanding of the natural history of the disease in real life.

Introduction

Alpha-1 antitrypsin deficiency (AATD) is the most frequent hereditary condition in adults and is associated with an increased risk of pulmonary emphysema and liver disease. Severe deficiency is usually associated with the homozygous Pi*ZZ allele combination, but the clinical expression of other deficient allele combinations is less well characterised, with Pi*SZ being the most frequent among these combinations (1).

It is generally accepted that the Z mutation appeared in the North-east of Europe around 2000 years ago (2). In contrast, the S mutation is believed to originally come from the Northwest of the Iberian Penninsula (3). In Spain, it has been calculated that the frequency of the Pi*S gene is of 104/1000 inhabitants and that of the Pi*Z gene is of 17/1000 inhabitants, with a total of 145,000 Pi*SZ and 12,000 Pi*ZZ individuals having been estimated (4).

Therefore, because of the high prevalence of the S allele, the Spanish registry offers a unique database of individuals with the Pi*SZ phenotype that

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allows the investigation of the clinical characteristics of this group of subjects and comparison with severe deficient Pi*ZZ patients.

History of the Spanish Registry of Alpha-1 antitrypsin deficiency

The first two cases of emphysema due to AATD receiving augmentation therapy with intravenous AAT in Spain were reported in 1991 (5). Following the description of these cases, growing interest in the deficiency resulted in the development of the Spanish Registry of Patients with Alpha-1 antitrypsin deficiency (REDAAT), which was founded in 1993 as a task force of the Spanish Society of Respiratory Medicine and Thoracic Surgery (SEPAR) (6–10). The aim of the REDAAT has always been to increase the scientific knowledge about the deficiency and its treatment through basic and clinical research, raise awareness about the deficiency, and provide support for the diagnosis of the deficiency through phenotyping and genotyping (11–15).

The REDAAT recruited individuals diagnosed with deficient phenotipes Pi*ZZ, Pi*SZ and carriers of rare deficient variants. Follow-up information was requested every six months until death or transplantation (9,16).

Initially the data were sent by regular mail to the coordinator centre located in the Hospital Vall d'Hebron in Barcelona (6,7). The REDAAT participated in the founding of the Alpha One International Registry (AIR), and the Spanish dataset was modified to be compatible with the AIR database (9,17). The Spanish data are regularly uploaded to the AIR. Simultaneously, a new data collection system included in the official SEPAR website was implemented (www.separ.es/air) (9).

To improve the quality of the data collected and reduce the queries generated by missing data, a real-time validation process was also implemented. Upon notification of a new case, an automatic alert is sent to the website manager who reviews and validates the information before it is definitively recorded in the database. This system allows the manager to correct typing errors and to contact the referring physician if relevant information is missing or even delete inappropriate registrations (non-deficient phenotypes or patients with incomplete or non-confirmed diagnoses).

The full process of moving from the first paper-based database to the electronic registry was prolonged until 2006. Of a total number of 301 cases registered until 2001 only 130 (43%) were fully updated into the new online database. Therefore, at the end of 2006 the REDAAT included 291 patients (including the previously registered individuals and those newly diagnosed after 2001) (9). In 2008 the REDAAT database moved to a new independent internet server and obtained its own website domain (www.redaat.es).

At present, the REDAAT is a network of health care professionals with an interest in AATD and consists of more than 360 registered collaborators, 34% of whom have at least one case registered. The website and database are directed by an advisory board including 10 pulmonologists, 3 paediatricians and 3 basic researchers. Apart from the database, the website includes educational materials for patients and health carers, information about diagnosis and contact details of the local experts in AATD, and a real-time summary of the basic characteristics of the cases registered is also available for registered collaborators. The REDAAT is also linked with the Spanish Rare Diseases Registry and provides information about AATD in its website (18). The expertise of the REDAAT has been useful for the development of guidelines for the diagnosis and treatment of individuals with AATD (11,19).

Characteristics of patients included in the Registry

In January 2014, the REDAAT database included a total of 511 individuals. Since 2001 a mean of 39.3 new cases per year have been included (Interquartile range (IQR): 8-102). The mean average of registered patients per physician collaborator was 4 (standard deviation (SD):8), (Table 1).

Forty-two individuals were diagnosed in childhood (8.2%), 25 (59.5%) of whom are males. The phenotype distribution in children is: 32 (76.2%) Pi*ZZ; 7 (16.7) Pi*SZ and 3 (7%) carriers of a rare variant. The mean age at diagnosis is 7.3 years (SD:6.2) and 33.3% are asymptomatic. The reason for diagnoses was liver disease in 47.6% followed by 28.6% of family screening. The adult population consists of 469 individuals (91.8% of the total) with a phenotype distribution of: 348 Pi*ZZ (74.2%), 100 Pi*SZ (21.3%) and 21 carriers of rare variants (4.5%). The most frequent diagnosis is lung disease (74.6%).

According to the prevalence of deficient alleles reported in previous studies, an estimated number of 144 827 Pi*SZ individuals (IC95%: 107,227-195,038) and 12,026 Pi*ZZ individuals (IC95%:7,788–18,493) is expected in Spain (20). Therefore, the REDAAT population represents only the 0.1% of the expected Pi*ZZ and Pi*SZ in the Spanish population. However, the penetrance of the deficiency in terms of developing emphysema is incomplete, and it is estimated that only 60% of severe deficient individuals will develop significant lung disease. Consequently, the patients with chronic obstructive pulmonary disease (COPD) registered in the REDAAT constitute approximately 15% of the expected cases of AATD-related COPD in Spain (20).

Table 1. Distribution of registered cases and collaborators

Cases/collaborator	Cases	Collaborators
1–2	113 (22.1)	87 (70.2)
3–10	136 (26.6)	27 (21.8)
11–40	128 (25)	7 (5.60)
>40	134 (26.2)	3 (2.4)
Total	511 (100)	124 (100)

Data reported as n (%).

The adult population of carriers of rare variants includes 21 (4.5%) individuals; 14% are composite heterozygous of the normal variant M and a rare variant; 47.6% are composite heterozygous of a frequent deficient allele (S or Z) and a rare allele and 33% carry a combination of two rare variants.

Comparison of the characteristics of PiZZ and PiSZ individuals

The cohort of adults includes 448 patients: 348 (74%) Pi*ZZ and 100 (21.3%) Pi*SZ. Male is the predominant gender including 269 (60%) individuals. The most frequent reason for AAT diagnosis in both groups was lung disease (73.6% and 46%, respectively) followed by family screening (17.8% and 22%, respectively).

A total of 364 (81%) reported having lung disease being especially frequent in the Pi*ZZ group with 305 (87.6%) compared to 59 (59%) Pi*SZ ($p < 0.001$). A more severe impairment in lung function is observed at baseline in Pi*ZZ compared with Pi*SZ. A detailed description of the baseline characteristic of PiZZ and PiSZ and their comparison is shown in Table 2.

Forty-five percent of Pi*ZZ individuals have received augmentation therapy at any time after inclusion in the REDAAT.

Table 2. Baseline characteristics of the Pi*ZZ and Pi*SZ individuals included in the Spanish AATD Registry

Variable	Pi*ZZ (n = 348)	Pi*SZ (n = 100)	Total (n = 448)	*p*
Age (years)	57.6 (11.3)	57 (14.8)	57.4 (12.2)	0.71
Gender (males)*	213 (61.2)	56 (56)	269 (60)	0.34
BMI (kg/cm^2)	25.2 (3)	25.8 (3)	25.3 (3)	0.18
Smoking status:				
Never-smoker	51 (14.7)	22 (22)	73 (16.3)	
Current-smoker	25 (7.2)	15 (15)	40 (8.9)	0.006
Former-smoker	272 (78.2)	63 (63)	335 (74.8)	
Pack-years*	24.4 (15.8)	36 (29.8)	26.8 (20)	0.009
Age at diagnosis (years)	46.5 (11.7)	49.7 (15.1)	47.3 (12.7)	0.056
Reason for diagnosis				
Lung disease	256 (73.6)	46 (46)	302 (67.4)	
Liver disease	13 (3.7)	20 (20)	33 (7.4)	
Other disease	5 (1.4)	4 (4)	9 (2)	<0.001
Other reasons	74 (21.3)	30 (30)	104 (23.2)	
Clinical presentation				
Chronic bronchitis	143 (41.1)	32 (32)	175 (39)	0.10
Emphysema	273 (78.4)	41 (41)	314 (70)	<0.001
Asthma	60 (17.2)	20 (20)	80 (17.9)	0.52
Bronchiectasis	112 (32.2)	18 (18)	130 (29)	0.006
Other	37 (10.6)	10 (10)	47 (10.9)	0.85
Main symptoms				
Non-productive cough	10 (3.4)	7 (8)	17 (4.4)	
Productive cough	42 (14.1)	11 (12.6)	53 (13.8)	
Dyspnoea at rest	11 (3.7)	0	11 (2.9)	<0.001
Dyspnoea on exertion	201 (67.5)	33 (37.9)	234 (60.8)	
Dyspnoea attack	17(5.7)	7 (8)	24 (6.2)	
No symptoms	17 (5.7)	29 (33.3)	46 (11.9)	
Previous pneumonia	95 (27.3)	18 (18)	113 (25.2)	0.059
Mean FEV_1 (L) at baseline	1.9 (1.03)	2.75 (1.3)	2.1 (1.2)	<0.001
Mean FEV_1 (%) at baseline	59.1 (32.1)	82.9 (34.2)	64.4 (34)	<0.001
Replacement treatment	158 (45.4)	5 (5)	163 (36.4)	<0.001
Transplantation	14	0	14	–
Death	54	4	58	0.002

Data expressed as mean (SD) except (*) expressed as n (%).
Statistical analysis: Frequency and valid percentage have been calculated for qualitative variables. Quantitative variables have been analysed using mean, quartiles and typical deviation. Comparison between Pi*ZZ and Pi*SZ individuals: Chi-squared test has been used for qualitative variables (Fisher's test if observed frequencies lower than 5). Student's *t*-test has been used for quantitative variables (Mann–Whitney U-test if variables were not normally distributed). ANOVA test has been used in those quantitative variables including more than two categories.

Follow-up of patients in the Registry

Follow-up data of 343 (67%) patients were available. The FEV_1 decline (ΔFEV_1) was calculated in a total of 266 Pi*ZZ and 62 Pi*SZ subjects. The mean ΔFEV_1 in the Pi*ZZ subgroup was –23 ml/year (SD:142.8) and in the Pi*SZ was –18 ml/year (SD:108.8).

Sixty-one deaths were recorded (54 Pi*ZZ, 4 Pi*SZ and 3 carriers of rare variants). The mean age at death was 59 years (SD: 10), 74% being males. The age at diagnoses was significantly higher in individuals who died compared to those alive during the follow-up (51.2 years (SD: 12.2) versus 45.8 years (SD: 11.5), ($p < 0.001$). The baseline lung function values were significantly lower in the individuals who died after the inclusion compared with those who were alive at the end of the study period (mean baseline FEV_1 1.23 L (SD: 0.62) vs FEV_1 2.04 (SD: 1.04); $p < 0.001$). The mean survival of Pi*ZZ individuals was 131.8 months (95%CI: 112.2–149.8).

Discussion

The Spanish Registry of Patients with Alpha-1 antitrypsin Deficiency (REDAAT) has more than 20 years of evolution and currently includes 511 patients. Its population consists mainly of Pi*ZZ individuals but also includes a high percentage of Pi*SZ and some rare deficient variants. The REDAAT has helped to understand the epidemiology of AATD in Spain and increase the awareness and detection rates of this underdiagnosed disease (13,14,21). From an initial small group of experts and a database it has become a network of collaboration among physicians and researchers that has developed research in different areas of the disease, including international collaborations.

The REDAAT is an open database in which any clinician is allowed to include their cases. This makes it different from other European countries with central registries run by a unique group at reference centres or even from the American Registry of the Alpha One Foundation (AOF) in which the patients are allowed to register themselves (22,23).

The population included is only a small proportion of the individuals expected to have AATD. However, the REDAAT was not designed as a population-based registry, and the inclusion of patients is voluntary, and therefore does not reflect the real situation of the epidemiology of AATD in Spain. In contrast, it probably reflects the interest of physicians in different areas of Spain with a particular interest in the disease that translates into higher rates of detection and reporting to the REDAAT.

Our patient population consists mainly of adults with lung disease. This is a selection bias related to the background of the collaborators registered, mainly pulmonologists, since the most frequent morbidity associated with the deficiency is pulmonary emphysema.

The most prevalent phenotype is Pi*ZZ, but up to a 25% of the cases are carriers of other deficient variants. The higher number of Pi*SZ and rare variants in the REDAAT is most likely related to a higher prevalence of the S allele in the Spanish population or even some of the rare alleles as in other Mediterranean areas (21,24,25). For example, the AIR has 11% of Pi*SZ and only 1% of rare variants and the AOF registry includes 70% of Pi*ZZ, but heterozygotes MZ are also included (22,23). In contrast, among subjects with severe AATD researchers from the Italian Registry observed a prevalence of 11% of deficient genotypes other than Pi*ZZ and P*SZ (26).

The characteristics of the individuals registered are similar to those previously published in terms of gender, predominant lung disease and reason for AATD diagnosis, age at symptom onset and delay of diagnoses (22,23,27,28). Lung function impairment is higher in the Pi*ZZ individuals compared with the Pi*SZ, even with a less tobacco consumption and a younger age at quitting, probably due to the earlier onset of symptoms in PiZZ individuals. In a comparison between PiZZ and PiSZ individuals performed recently with data derived from the Spanish and Italian registries, the speed of decline in lung function in relation to tobacco consumption was different between the two phenotypes.

The FEV_1(% predicted) fell abruptly with the first 20 pack-years of smoking in PiZZ subjects and then slowed down, whereas the speed of decline in PiSZ was more constant in relation to pack-years of smoking, with a continuous difference of approximately 20% FEV_1(%) more in PiSZ compared with PiZZ for the same amount of tobacco consumption. The incidence of previous diagnosis of asthma is similar between the two phenotypes and the frequency of asthma-COPD overlap syndrome (ACOS) is 8.6%, being lower that that observed in non-AATD-related COPD (29).

In summary, the REDAAT is a network of health care professionals with an interest in AATD and has collected data for more than 20 years. The REDAAT population currently includes 511 subjects and their characteristics have some differential trends compared to other series in terms of tobacco consumption, the distribution of phenotypes and the inclusion of children and patients under treatment with replacement therapy. The most important challenge of the registry is to collect good quality, long-term follow-up data that will allow better understanding of the natural history of the disease in real life.

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Declaration of Interest Statement

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The authors alone are responsible for the content and writing of the paper.

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