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Diagnosis of alpha-1 antitrypsin deficiency: a population-based study

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Introduction: Alpha-1 antitrypsin deficiency (AATD) remains an underdiagnosed condition despite initiatives developed to increase awareness. The objective was to describe the current situation of the diagnosis of AATD in primary care (PC) in Catalonia, Spain.

Methods: We performed a population-based study with data from the Information System for Development in Research in Primary Care, a population database that contains information of 5.8 million inhabitants (80% of the population of Catalonia). We collected the number of alpha-1 antitrypsin (AAT) determinations performed in the PC in two periods (2007–2008 and 2010–2011) and described the characteristics of the individuals tested.

Results: A total of 12,409 AAT determinations were performed (5,559 in 2007–2008 and 6,850 in 2010–2011), with 10.7% of them in children. As a possible indication for AAT determination, 28.9% adults and 29.4% children had a previous diagnosis of a disease related to AATD; transaminase levels were above normal in 17.7% of children and 47.1% of adults. In total, 663 (5.3%) individuals had intermediate AATD (50–100 mg/dL), 24 (0.2%) individuals had a severe deficiency (<50 mg/dL), with a prevalence of 0.19 cases of severe deficiency per 100 determinations. Nine (41%) of the adults with severe deficiency had a previous diagnosis of COPD/emphysema, and four (16.7%) were diagnosed with COPD within 6 months.

Conclusion: The number of AAT determinations in the PC is low in relation to the prevalence of COPD but increased slightly along the study period. The indication to perform the test is not always clear, and patients detected with deficiency are not always referred to a specialist.

Keywords: alpha-1 antitrypsin deficiency, population based, diagnosis, screening, COPD

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a congenital autosomical codominant condition characterized by low plasma levels of alpha-1 antitrypsin (AAT) in the blood and tissues. More than 120 genetic variants of the AAT gene have been identified and classified into three major categories: normal, with genotype M, characterized by AAT within normal ranges; deficient, characterized by reduced but detectable AAT plasma levels with genotypes Z, S, and M-like; and null, currently designated as Q0, with no detectable plasma levels.[1] AATD is one of the most common congenital disorders with an estimated prevalence between one in 2,857 and one in 5,097 in USA[1] and between one in 2,175 and one in 5,164 in Spain.[2] AATD predisposes the development of certain diseases, especially COPD in adults and liver disease, which is more frequent in children. Other less frequent conditions associated with AATD are panniculitis, vasculitis, and fibromyalgia.[1]

The World Health Organization recommends the testing of all COPD patients,[3] and the European Respiratory Society and American Thoracic Society guidelines recommend the testing of all symptomatic adults with persistent airway obstruction,

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such as COPD, emphysema, and asthma with incompletely reversible airflow obstruction, individuals with unexplained liver disease, and adults with necrotizing panniculitis or multisystemic vasculitis.[1] Similarly, the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) recommends that all COPD patients should be tested at least once in their lives.[4] Despite these recommendations, AATD is significantly underdiagnosed, and most of the patients are detected long after the onset of pulmonary or liver disease. Another implication of this late diagnosis is the delay in the detection of affected relatives, which hinders the implementation of measures, such as abstaining from tobacco exposure.[5,6]

Underdiagnosis of AATD is a challenge, particularly, for primary care (PC) physicians who attend most of the COPD patients, and this is usually the first point of contact of patients with health care providers. Computerized databases of medical records are increasingly used in clinical research to enhance the knowledge about the management and progression of this disease based on real-life data.[7] Database studies help to understand real clinical practice and to design public health strategies to improve the quality of care. The objective of this study was to describe the patterns of diagnosis of AATD in PC in Catalonia, Spain.

Methods

This was an epidemiological, population-based, observational study aimed to quantify and compare the number of AAT determinations performed in the PC in Catalonia during two 2-year periods (2007–2008 and 2010–2011) and to describe the characteristics of the individuals tested and the management of those with deficient values. Data for this study were obtained from the System for the Development of Research in Primary Care (SIDIAP) database, a computerized database containing anonymized patient records for the 5.8 million people registered in the 279 PC centers of the Catalan Health Institute (>80% of Catalonia's population). All general practitioners in the Catalan Health Institute use the same specific software called eCAP to record the clinical information of their patients. Health professionals gather this information using codes of International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, and structured forms designed for the collection of variables. SIDIAP combines information from the electronic medical records with data from other databases and registers, such as laboratory test results (from the laboratory databases), the pharmacy register, and the National Mortality Register.[8,9] For the purpose of the study, we checked the quality of the SIDIAP database. High-quality data were obtained from 2007 onward; however, data from 2012 were not available at the time of the initiation of the study. Therefore, to compare two periods of the same length, we used data from 2007 to 2008 and 2010 to 2011. The study was approved by IDIAP Jordi Gol Ethics Committee (Barcelona, Spain). This was a retrospective study with data from an anonymized database, so it was not necessary to request patient consent.

Population

All the individuals with an AAT determination during the study period were included. Based on the levels obtained in the determination, individuals were classified as follows: no deficiency: AAT >100 mg/dL; intermediate deficiency: AAT between 50 mg/dL and 100 mg/dL; and severe deficiency: AAT <50 mg/dL.[10] Since indications for AAT testing differ by age group, we classified individuals younger than 15 years as children and analyzed them separately. Demographic and clinical characteristics were recorded for all the study populations. For individuals with intermediate and severe deficiencies, we collected data on referrals to a specialist, complementary tests (spirometry and computerized tomography scans), pharmacologic treatment, and number of respiratory infections during the 6 months following the determination.

Statistical analysis

A descriptive analysis of each period (2007–2008 and 2010–2011) and of the totality of the sample was performed separately for children and adults. For qualitative variables, absolute frequencies and corresponding percentages were calculated. Quantitative variables following a normal distribution were described by mean and standard deviation, while those not following a normal distribution were described using the median and 25–75 percentiles. Differences between groups were performed using the chi-square test for categorical variables, while continuous variables were tested using the Student's *t*-test (or the Mann–Whitney *U*-test, if the variables were not normally distributed). All tests were two-tailed, and significance was set at 5%. All statistical analyses were performed using a statistical software package (SPSS Version 20.0; IBM Corporation, Armonk, NY, USA).

Results

Frequency of AAT determinations

In total, 12,409 determinations of serum AAT were performed during the 4 years of the study, of which 1,335 (10.7%) were children. The number of determinations was higher in the second period (5,559 determinations in 2007–2008 and 6,850 determinations in 2011–2011) due to the low number of individuals tested in 2007. Nonetheless, the rate of individuals tested per year did not increase

Table 1 Number of AAT determinations performed by year

Period	Children	Adults	Total	n/10,000 inhabitants
2007	331	1,998	2,329	4.33
2008	382	2,848	3,230	6.85
2007–2008	713	4,846	5,559	
2010	325	3,351	3,676	6.77
2011	297	3,676	3,174	5.82
2010–2011	622	6,228	6,850	

Abbreviation: AAT, alpha-1 antitrypsin.

significantly after 2008 (Table 1). Figure 1 shows the number of determinations performed by age groups.

Characteristics of the individuals tested

The mean age of the individuals tested was 52.6 (SD 16.3) years in adults and 4.6 (SD 4.1) years in children, with an equal distribution between sexes. Among adults, 37.1% were smokers or former smokers. The most frequent comorbidities in adults were dyslipidemia (27.6%), hypertension (27.4%), diabetes mellitus (11.7%), depression (10.1%), and ischemic heart disease (4%). Up to 41% of children and 18.5% of adults were receiving treatment for a respiratory disease at the time of the determination. The majority of the determinations were performed in urban areas. Demographic characteristics are shown in Tables 2 and 3.

Indications for AAT determinations, AAT concentrations, and follow-up

As a possible indication for AAT determination, 3,195 (28.9%) adults and 393 (29.4%) children had a previous diagnosis of a disease related to AATD. Up to 17.7% of children and 47.1% of adults had transaminase levels above normal (Tables 2 and 3). Nine percent of children were between the age 0 year and 1 year, suggesting neonatal jaundice as the most likely indication. During the previous year, 31.3% of individuals had had at least one respiratory infection and 1.3% had had pneumonia.

The mean AAT plasma level was 147.2 (36.7) mg/dL in adults and 154.1 (37.2) mg/dL in children. In total, 663 (5.3%) individuals (56 children) had an intermediate AAT deficiency, while 24 (0.2%) individuals (two children) had a severe deficiency, with a prevalence of 0.19 cases of severe deficiency per 100 determinations. Patients with severe deficiency were younger than individuals with normal AAT levels (42.5 years vs 52.9 years, P=0.003) and were more likely to have a previous diagnosis of COPD or emphysema (45.5% vs 10.8%, $P<0.05$) (Table 3).

During the 6-month follow-up, four of the patients with severe deficiency (18.1%) were newly diagnosed with COPD or emphysema, two (9.1%) following diagnostic spirometry and one (4.2%) after a computerized tomography scan. Only three patients (13.6%) were referred to a pneumologist and another patient was referred to internal medicine (Table 4).

Discussion

The results of this study show that the number of AAT determinations performed in the PC in Catalonia, Spain, is low and has not increased after 2008. In addition, in most cases, we could not identify the reason for requesting the test, and after detection of a severe deficiency, some individuals were not tested further or referred to a specialist.

AATD is one of the most common congenital disorders but remains significantly underdiagnosed despite the

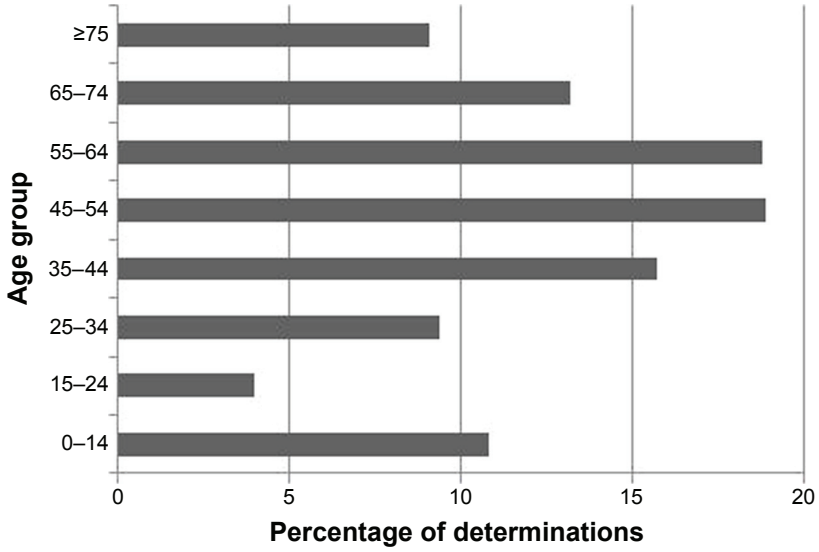

Figure 1 Distribution of percentage of AAT determinations performed by age group.
Abbreviation: AAT, alpha-1 antitrypsin.

Table 2 Demographic characteristics and diseases related to AATD of children tested for AAT during the study period

Variables	Children (n=1,335)
Mean age (SD)	4.61 (4.1)
Sex (males)	769 (57.6)
Urban setting	868 (65)
Smokers	12 (0.9)
Former smokers	2 (0.1)
Bronchiectasis	2 (0.1)
Asthma	298 (22.3)
Hepatitis	7 (0.5)
Cirrhosis	0
Hepatocarcinoma	0
High transaminase levels	236 (17.7)

Note: Data are shown as n (%) unless specified otherwise.
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency.

recommendations of national and international guidelines.[1,2] Moreover, there is still a large delay between the onset of symptoms and diagnosis,[11] with no significant improvement in this delay during the last decades.[12] In Spain, it is estimated that 12,026 patients have a severe deficiency,[13] with ~1,700 of these cases corresponding to Catalonia alone.[14] Nonetheless, only 511 cases from all over the country are diagnosed and included in the Spanish registry for AATD.[15]

Possible explanations for the underdiagnosis of AATD have been addressed in previous studies. Knowledge of AATD is generally poor even for trainees who declared a special interest in respiratory medicine.[16] Among nonpulmonologists, awareness of AATD is low in comparison with other respiratory diseases,[17] with the consequent low rate of testing for AATD.[11,12,18] A survey carried out in Spain and Portugal showed that the main reasons for not testing for AATD are the referral of patients to other specialists for testing or the erroneous perception of the high cost of the test.[19]

Despite the current recommendations of testing symptomatic adults with persistent airway obstruction and individuals with unexplained liver disease,[1,2] the rate of AAT determinations observed in our study along the years varied from 4.33 determinations per 10,000 inhabitants in 2007 to 6.85 determinations per 10,000 inhabitants in 2008, with intermediate values for 2010 and 2011. Data from a recent study performed with data from SIDIAP indicated that a mean of 6,932 new patients were diagnosed with COPD per year between 2007 and 2012, a figure well above the 375 mean number of COPD patients tested yearly for AATD during the 4 years of our study.[9] Although underdiagnosis of the deficiency has been reported in many countries, to our knowledge, this low rate of AAT determinations in the general population and in COPD patients has not been previously reported, thereby not allowing comparison of our findings with data from other countries or geographical areas.

Regarding the reasons for requesting AAT determination, we observed that only 13% of the adults tested had COPD,

Table 3 Comparison of the characteristics of adult patients tested for AAT during the study period according to AAT levels

Variable	Normal AAT levels (n=10,445)	Intermediate deficiency (n=607)	Severe deficiency (n=22)	Total (n=11,074)
Age, mean (SD)	52.9 (16.3)	48.0 (14.4)**	42.5 (15.7)**	52.6 (16.3)
Sex (males)	5,756 (55.1)	377 (62.1)**	14 (63.6)	6,147 (55.5)
Smoker	2,219 (21.2)	113 (18.6)	7 (31.8)	2,339 (21.1)
Former smoker	1,668 (16)	101 (16.6)	3 (13.6)	1,772 (16)
AAT (mg/dL), mean (SD)	150.9 (34.2)	87.6 (10.8)	27.6 (11.6)	147.2 (36.7)
Previous diseases related to AATD				
COPD	937 (9)	34 (5.6)*	6 (27.3)*	977 (8.8)
Emphysema	193 (1.8)	14 (2.3)	4 (18.2)**	211 (1.9)
Chronic bronchitis	293 (2.8)	14 (2.3)	0	307 (2.8)
Bronchiectasis	284 (2.7)	11 (1.8)	0	295 (2.7)
Asthma	794 (7.6)	45 (7.4)	3 (13.6)	842 (7.6)
Hepatitis	768 (7.4)	32 (5.3)	1 (4.5)	801 (7.2)
Cirrhosis	127 (1.2)	3 (0.5)	0	130 (1.2)
Hepatocarcinoma	4 (0)	0	0	4 (0)
High transaminase levels	5,430 (52)	313 (51.6)	8 (36.4)	5,751 (51.9)
Previous respiratory infections	3,486 (33.8)	162 (26.6)*	9 (40.9)	3,657 (33.02)
Previous pneumonia	136 (1.6)	5 (0.8)	1 (4.5)	142 (1.3)
Hypertension	2,908 (27.8)	126 (20.8)**	2 (9.1)*	3,036 (27.4)
Dyslipidemia	2,901 (27.8)	158 (26)	2 (9.1)*	3,061 (27.6)
DM	1,247 (11.9)	44 (7.2)**	1 (4.5)	1,292 (11.7)
Depression	1,070 (10.2)	51 (8.4)	2 (9.1)	1,123 (10.1)
Ischemic heart disease	428 (4.1)	13 (2.1)**	0	441 (4)

Notes: *$P<0.05$ and **$P<0.01$ compared to individuals with normal AAT levels. Data are expressed as n (%) unless specified otherwise.
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; DM, diabetes mellitus.

Table 4 Six-month follow-up of adults tested for AATD according to AAT levels

Diagnosis after AAT determination	Normal AAT levels (n=10,445)	Intermediate deficiency (n=607)	Severe deficiency (n=22)
COPD	106 (1)	5 (0.8)	2 (9.1)*
Emphysema	36 (0.3)	1 (0.2)	2 (9.1)**
Chronic bronchitis	18 (0.2)	2 (0.3)	0
Respiratory infections	3,090 (29.5)	148 (24.4)**	10 (45.5)*
Pneumonia	58 (0.6)	3 (0.5)	0
Spirometry	407 (2.9)	24 (4)	2 (9.1)
Referrals			
Pneumology	229 (2.2)	22 (3.6)*	3 (13.6)*
Gastroenterology	489 (4.7)	42 (6.9)*	0
Internal medicine	73 (0.7)	2 (0.3)	1 (4.5)

Notes: *$P<0.05$ and **$P<0.01$ compared to individuals with normal levels of AAT. Data are expressed as n (%).
Abbreviations: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency.

chronic bronchitis, or emphysema and half had high transaminase levels, which could justify the request for AAT determination. These results concur with the observation that >70% of PC physicians in Spain were aware of liver complications of AATD, but very few decided to test all COPD patients.[19] Similarly, only 0.5% of children had a codified liver disease at the time of AAT determination, and interestingly, the number of children tested for transaminitis and asthma was similar, although AATD is not a recognized cause of respiratory diseases in childhood.[20]

In an attempt to improve the rate of diagnosis of AATD in COPD, several screening initiatives or case findings have been developed,[21–25] some being carried out in the PC.[22,23] In the IDDEA project of case finding of AATD in COPD patients, volunteer PC physicians were provided with filter paper to collect dried blood spots, together with information about AATD and a Web tool. The ratio of recruitment only reached 6.6 patients per participant over the 9-month collection period, being somewhat low considering that the estimated prevalence of COPD in Spain is 10.2% of adults older than 40 years.[26] However, among the individuals tested, 4% were carriers of the severe deficient allele Z, and 0.34% were diagnosed with severe homozygous PiZZ deficiency.[23] Jain et al[24] implemented an electronic alert to encourage guideline-based testing for AATD. This alert was displayed for patients with obstructive spirometry results, and this tool was associated with an increase in the frequency of testing.

Other strategies, such as programs to educate respiratory physicians[27] and the combination of an awareness program with the offer of free diagnostic testing,[28] resulted in high rates of detection of individuals with severe AATD. Population screening programs in areas of high prevalence or protocols to measure and phenotype AAT in selected patients were found to be effective at detecting AATD patients.[29–31]

Our study has some limitations. First, the reason to request a complementary test is not recorded in the SIDIAP database, and we cannot be completely certain of the indication leading to the AAT determination. We can only assume the reason based on the codified diagnosis or the results of liver function tests. Second, databases are also subject to possible diagnostic and miscoding biases.[32] However, considering that our main objective was to quantify the number of AAT determinations performed, we believe that this possible bias had little impact, if any, on the main objective of the study. On the other hand, the SIDIAP database includes data from >80% of the population of our area, thereby ensuring the representativeness of the results for the whole population of Catalonia.

Conclusion

Our study shows that the rate of testing for AAT in PC is still low, and the reasons for requesting the determination often remain unclear. These results should help to design interventions to increase the awareness and the diagnosis of AAT in selected individuals or populations according to the current guidelines for the diagnosis and management of AATD.

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