Profiles of cases included in the Spanish registry of patients with alpha-1 antitrypsin deficiency☆

Características de los casos incluidos en el Registro Español de Pacientes con déficit de alfa-1 antitripsina

Dear Editor:

Alpha-1 antitrypsin (AAT) is a protein whose main function is the inactivation of neutrophil elastase. The gene that encodes AAT is transmitted by simple Mendelian inheritance in an autosomal codominant pattern in two alleles, one from each parent. The normal allele is known as PiM. The most frequent deficient alleles are PiS and PiZ, which encode abnormal proteins that polymerise in the liver so that 80–90% of AAT-Z and 40–50% of AAT-S molecules remain inside hepatocytes grouped into polymers. The main clinical manifestations of severe AAT deficiency (which is mainly associated with the PI*ZZ and PI*SZ phenotypes) are liver disease, which results from the toxicity of polymerised AAT, and emphysema in adulthood, especially in smokers, due to low concentrations of AAT.

The gene frequencies of 104 per 1000 individuals for the PiS mutation and 17 per 1000 individuals for the PiZ mutations suggest that in Spain there should be approximately 12,000 PiZZ individuals and 145,000 PiSZ individuals.[1] However, only a minority of less than 5% of affected individuals develop severe liver disease, and approximately 60% of adult smokers develop chronic obstructive pulmonary disease.

The Spanish registry of patients with AAT deficiency (Registro Español de Pacientes con déficit de AAT [REDAAT]) was initially established in the 1990s to collect data on adults with lung disease and individuals identified through family screening, and later children as well. The data is gathered by a network of more than 120 physicians through the website http://www.redaat.es.[2,3]

We proceed to present the first case series of paediatric patients with AAT deficiency published in Spain, which consists of the cases registered in the REDAAT.

Of the total of 511 individuals included in the REDAAT up to January 1, 2014, 42 (8.3%) were younger than 18 years. There was a predominance of males, who accounted for 25 cases (59.5%). The phenotype distribution was the following: 32 (76.2%) Pi*ZZ; 7 (16.7%) PiSZ and 3 (7%) carriers of rare variants. The mean age at diagnosis was 7.3 years (SD, 6.2). Of all these children, 33.3% were asymptomatic and 45% had some type of respiratory manifestation. The mean age at onset of symptoms was 8.7 years (SD, 7).

Liver disease was the reason for AAT deficiency testing in 47.6% of the cases, followed by family screening, which accounted for testing in 28.6% of the cases. The most frequent symptom was productive cough (16.7%), followed by acute dyspnoea (11.9%) and exertional dyspnoea (9.5%) (Table 1). The registry does not hold detailed information on liver function or gastrointestinal symptoms, but in cases first identified due to liver disease, mild hypertransaminasaemia was the principal finding. With regard to patient outcomes, only one patient required a liver transplant.

Table 1 Reason for AAT quantification and respiratory symptoms of the paediatric patients included in the REDAAT.

Reason	Main symptom
Liver disease, 20 (48.8%)	Asymptomatic 14 (33.3%)
Family screening, 12 (29.3%)	Undocumented 9 (21.4%)
Lung disease, 6 (14.6%)	Productive cough 7 (16.7%)
Other, 2 (4.9%)	Acute dyspnoea 5 (11.9%)
Other disease, 1 (2.4%)	Exertional dyspnoea 4 (9.5%)
Not documented, 1 (2.4%)	Cough 3 (9.1%)

Data expressed as *n* (%).
AAT, alpha-1 antitrypsin; REDAAT, Spanish registry of patients with alpha-1 antitrypsin deficiency.

The paediatric population represents a special subset in the registry, which was initially limited to adults. The most frequent reason for AAT quantification was liver disease, followed by family screening. There is a large number of children with respiratory symptoms that cannot be considered secondary to AAT deficiency, as they are not specific for lung involvement in this disease, and it is known that the incidence of respiratory problems in Pi*ZZ children is similar to that of the general population.[4]

The value of including these patients in the registry and especially of collecting long-term data resides in the future possibility of studying the impact of early diagnosis in the clinical outcome of affected individuals, learning the natural history of lung disease associated to this deficit from its onset, and increasing the interest of paediatricians in identifying children with severe AAT deficiency.

Its detection allows for counselling families on the risk of passing the deficient alleles to their offspring and also raising awareness on healthy lifestyle habits, as it has been demonstrated that the life expectancy of non-smokers is similar to that of the general population, while individuals exposed to tobacco smoke are at high risk of developing emphysema, which greatly impacts quality of life as well as survival. Furthermore, previous studies have evinced that smoking initiation rates in adolescents with AAT deficiency were lower compared to the general population, and that lung function remained normal at 20 years' followup.[5] Moreover, diagnosing AAT deficiency during childhood allows for making additions to the vaccination schedule (influenza vaccine) and early treatment of infections and allergies to minimise future lung damage.

References

1. Vidal R, Blanco I, Casas F, Jardi R, Miravitlles M. Diagnóstico y tratamiento del déficit de alfa-1 antitripsina. Arch Bronconeumol. 2006;42:645–59.

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2. Lara B, Blanco I, Miravitlles M, de Gracia J, Monreal M, Orriols R, et al. Registros de enfermedades respiratorias en España: fundamentos y organización. Arch Bronconeumol. 2011;47:389–96.
3. Lara B, Miravitlles M. Spanish Registry of patients with alpha-1 antitrypsin deficiency; comparison of the characteristics of PISZ and PIZZ individuals. COPD. 2015;12:S27–31.
4. Bernspang E, Wollmer P, Sveger T, Piituilainen E. Lung function in 30 year old alpha-1 antitrypsin deficient individual. Respir Med. 2009;103:861–5.
5. Wall M, Moe E, Eisenberg J, Powers M, Buist N, Buist AS. Long-term follow-up of a cohort of children with alpha-1 antitrypsin deficiency. J Pediatr. 1990;116:248–51.

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Lyme disease in paediatrics☆

Enfermedad de Lyme en edad pediátrica

Dear Editor,

Lyme disease is one of the most common tick-borne zoonoses in the northern hemisphere, and its incidence peaks in the paediatric age group.[1] It is caused by spirochetes of the *Borrelia burgdorferi* sensu lato complex, and in Europe it is transmitted by the bite of the *Ixodes ricinus* hard-bodied tick.[1,2]

Its main clinical manifestations are neurologic, cutaneous, musculoskeletal and cardiovascular, and the disease progresses through several stages over time. Stage I (early localized disease) may feature erythema migrans, stage II (early disseminated infection) meningitis, radiculitis, mononeuritis, cranial nerve palsy, carditis, arrhythmias, and acute arthritis; and stage III (late persistent disease) acrodermatitis chronica atrophicans, recurrent chronic arthritis and late neuroborreliosis.[2] Unless the patient presents with erythema migrans, which is a pathognomonic skin lesion, the diagnosis of Lyme disease requires serologic confirmation by enzyme immunoassay (ELISA) and/or western blot testing with compatible clinical manifestations.[1] With adequate antibiotic treatment, the prognosis is generally excellent.[1,2]

We conducted a descriptive, observational and retrospective study between January 2006 and December 2013 with the purpose of determining the incidence of Lyme disease and improving our understanding of its clinical manifestations in the paediatric population of our health area. After obtaining the approval of the ethics board, we reviewed the medical records of individuals aged less than 15 years with a confirmed diagnosis of Lyme disease in the service area of the Hospital Universitario Lucus Augusti of Lugo, which serves a paediatric population of 22,570. The cases included in the study also met the surveillance case definition of Lyme disease of the Centres for Disease Control and Prevention,[3] as they featured compatible manifestations and were confirmed by ELISA (VIDAS bioMérieux, St Louis, MO, USA) and western blot (EUROLINE-WB, EUROIMMUN AG, Lübeck, Germany), except in patients presenting with erythema migrans. We collected data for the age and sex of patients, history of tick bites, the month and year at diagnosis, clinical manifestations, laboratory data and received treatment (Table 1).

We identified 10 patients in the period under study, which entails a mean incidence of 5.5 cases per 100,000 inhabitants per year, higher than the one described in the general population of other areas of Spain.[4] This data could be explained by the abundance of precipitation, lowland forests and hosts in the region under study, which favour the presence of the vector.[2] Most patients were male and had been diagnosed in August, a summer month during which outdoor activities are more frequent and it is easier to come in contact with the tick, the bites of which are painless, a fact that accounts for only half of the patients remembering being bitten. The most frequent manifestations were cutaneous (40%), followed by neurologic (30%) and articular (10%); furthermore, more than 20% of the patients had both cutaneous and neurologic manifestations. The most common cutaneous manifestation was erythema migrans in the upper half of the body, as opposed to the lower limbs, a location that is more frequent in adults.[1] Meningitis with a predominance of mononuclear cells and elevated proteins in the cerebrospinal fluid is one of the main neurologic manifestations of Lyme disease in children, along with peripheral facial nerve palsy.[1] Radiculitis, which is very frequent in adults,[2] is less common in children, as observed in our study. All patients had a favourable outcome after antibiotic treatment, except for the patient that had articular manifestations, who developed recurrent chronic arthritis, an outcome that may happen in 10% of cases.[5] Polymerase chain reaction testing of the joint fluid in this patient identified *B. garinii*, one of the most prevalent genospecies in Spain.[2] Laboratory tests did not find significant leukocytosis nor elevation of acute phase reactants, and 80% of the patients did not develop fever, which is a characteristic finding in other tick-borne diseases, such as recurrent fever. Antibiotic prophylaxis following the tick bite is not routinely indicated,

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