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Research Article

Alpha-1-Antitrypsin Deficiency in Children: Clinical Impact of the Liver Involvement

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Abstract

Introduction: Alpha-1-antitrypsin deficiency (AATD) is one of the most common genetic disorders causing pulmonary and hepatic damage. In practice, diagnosis is often too late, when pulmonary destruction or liver damage has become irreversible. There is clear evidence in the literature that affected patients present with clinical and laboratory signs in the neonatal period. We analyzed a large cohort of AATD pediatric patients in order to asses signs and symptoms leading to diagnosis. Furthermore, the hepatological follow-up examination should be evaluated with regard to analyze predictive parameters for the prognosis of liver disease.

Methods: Data from 109 children and adolescents presenting in our outpatient clinic from 1995 to 2009 were retrospectively analyzed. We also prospectively sent 85 questionnaires to families with at least one child with AATD to assess the need for follow-up examinations and testing of siblings.

Results: The genotype distribution was: PI-ZZ, n = 58; PI-MZ, n = 41; PI-MS, n = 6; PI-SZ, n = 4. 39 of 58 homozygotes had elevated liver enzymes and 17 had pathologic findings on hepatic ultrasound. Over half of the retrospectively analysed patients had neonatal signs of AATD. 50 questionnaires were returned revealing the existence of 43 siblings of the 16 heterozygotes and 34 homozygotes patients. Prior to our intervention, only 28 of these 43 siblings had been tested for AATD. We newly diagnosed 2 homozygous and 7 heterozygous siblings.

Conclusion: Results show that AATD is still highly underdiagnosed, even though it can easily be detected by pediatricians during the neonatal period. Family care and advice should be improved because an unacceptably high percentage of siblings of AATD patients do not receive AATD diagnostic testing, despite there being an index patient in the family. General awareness of AATD should be increased and a neonatal screening should be discussed more intensively.

Keywords: Alpha-1-Antitrypsin Deficiency; Liver Disease; Diagnosis; Neonatal Cholestasis

Abbreviations

AATD: Alpha-1 Anti-Trypsin Deficiency

Introduction

Alpha-1-antitrypsin deficiency (AATD) is one of the most common genetic disorders, with an estimated prevalence of 1:2000 to 1:5000 in Europe and Scandinavia, depending on the geographic location and type of epidemiologic study [9]. The alpha-1-antitrypsin gene, or SERPINA1 gene (serine proteinase inhibitor), is located on chromosome 14. Patients with the homozygous AAT deficiency PI-ZZ genotype usually have AAT serum concentrations that are no more than 0.3 g/L (usual range in individuals with the normal PI-MM genotype: 0.9–2.0 g/L) and the AAT molecules in these individuals show impaired function [12]. In subjects with milder forms of AATD (e. g, with genotypes PI-SS, PI-SZ, PI-MZ, and PI-MS), serum AAT concentrations usually range from 0.5–1.0 g/L [1,8].

In childhood, homozygous PI-ZZ AATD may be associated with acute or chronic liver disease; in adulthood, individuals are at risk of elastase-mediated chronic destructive lung disease, which may result in severe emphysema leading to decreased life expectancy [16]. AAT is mainly synthesized in hepatocytes. It belongs to the group of serine proteinase inhibitors and inhibits the activity of proteolytic enzymes such as neutrophil elastase.

The mutant "Z" form of the AAT protein molecule is characterized by the accumulation of misfolded protein within hepatocytes resulting in possible liver disease, which may already be symptomatic in infancy. Characteristically, this liver disorder presents as prolonged neonatal jaundice with conjugated hyperbilirubinemia (in about 90% of patients) and elevated liver enzymes (in about 50% of patients), with about 1% to 2% of patients developing liver cirrhosis [5,11,18]. However, most patients present with transient clinical symptoms so further diagnostic tests are not initiated; this can often result in missed diagnoses of AATD in early childhood. Usually there are no pulmonary symptoms present in children and adolescents, although AATD may aggravate other pulmonary diseases, even in childhood. When the first pulmonary symptoms occur in early or middle adulthood in homozygous AATD individuals, in most cases, a variety of other pulmonary diseases are initially considered which are not recognized as being caused by AATD, such as chronic bronchitis, asthma, or nonhereditary chronic obstructive pulmonary disease. In many patients, AATD is either never diagnosed or diagnosed too late and when severe lung destruction is already present [9]. The diversity of individual clinical courses may be explained in part by further unknown genetic cofactors and the individual's lifestyle. Smoking and even exposure to environmental tobacco smoke are important risk factors for developing early pulmonary destruction [4].

Treatment of AATD is very limited and is mostly supportive. There are studies describing the positive effect of ursodeoxycholic acid on AATD-mediated hepatopathy [10]. The intravenous substitution of AAT is recommended at a certain degree of impaired lung function and leads to the delayed progression of lung destruction [16]. The annual flu vaccination and a pneumococcal vaccine every 5 years are recommended by the World Health Organization. End-stage liver and lung disease can be treated by organ transplantation, with good overall results [5].

Although homozygous AATD is one of the most common genetic disorders, there are no official neonatal screening programs established worldwide. Just one screening program has been performed more than 30 years ago in Scandinavia, results have been published by Sveger [17]. By analyzing our cohort of pediatric AATD patients, our study aimed to document the clinical symptoms and the diagnostic and laboratory findings at the time of diagnosis, and in a long-term follow-up period. Most importantly, we wanted to assess whether patients had sufficient follow-up examinations, whether siblings were adequately diagnosed, or whether their AATD, if present, was missed altogether.

Patients and Methods

Study polulation

This retrospective study included 109 children and adolescents presenting in our outpatient clinic for Pediatric Gastroenterology and Hepatology at the University Medical Center Hamburg between the years of 1995 and 2009. The patients were referred by general practitioners or pediatricians because of unclear clinical symptoms, elevated liver enzymes, or for further diagnostic tests after having been diagnosed as a result of a low AAT level in the serum.

Study design

In the first part of the study, patients' charts were analyzed with regards to laboratory and clinical findings that led to a diagnosis, and signs and symptoms of AATD were documented in the long-term follow-up (3 to 14 years following diagnosis) investigation. In a second, prospective part of the study, a standardized questionnaire was sent to all affected families in order to obtain additional follow-up information on the patients and to determine the need for diagnostic testing in potentially affected siblings.

Results

A total of 109 children with the diagnosis of AATD were identified in our retrospective charts analysis by genotyping in addition to measurement of AAT serum concentration. PI-ZZ, PI-MZ, PI-MS, and PI-SZ genotypes were found in 58, 41, 6, and 4 patients, respectively.

Patient characteristics for the homozygous patients (PI-ZZ) are presented in Table 1; this table also provides information on the presenting signs and symptoms leading to the diagnosis of homozygous AATD, as well as retrospective information on neonatal presentation. In 17 of the patients, the diagnosis of AATD was not made in the neonatal period despite the presence of prolonged jaundice or elevated liver enzymes.

Median serum concentrations of AAT were 0.26 g/L (range, 0.1 to 0.9 g/L) in subjects with the PI-ZZ genotype, 0.4 g/L (0.2 to 0.6 g/L) in PI-SZ patients, 0.83 g/L (0.3 to1.1 g/L) in PI-MZ patients, and 1.07 g/L (1.0 to 1.1 g/L) in PI-MS patients.

Table 2 provides the long-term follow-up information (3

to 14 years) on clinical, laboratory, and ultrasound findings for the homozygous Pi-ZZ children. Of the 58 homozygous patients, 46 (79.3%) were seen routinely for clinical and laboratory follow-up examinations by either a primary care physician or a pediatric hepatologist. All 58 patients had body mass indexes (BMI) within the normal age-related range.

None of the children had pulmonary symptoms which could be related to AATD; however, 16 patients had other pulmonary symptoms, mostly due to asthma. These findings are limited to the fact that early pulmonary involvement by AATD cannot be easily distinguished from other pulmonary diseases. A total of 8 homozygous patients received a liver transplant after progression to liver cirrhosis and are still alive with very good graft function and quality of life (Table 2).

The group of heterozygous children did not show any clinical signs or symptoms of AATD. A total of 85 questionnaires were sent to affected families, of which 50 (58.8%) were returned. The remaining 35 (41.2%) families were lost to follow-up due to non-response or move to an unknown address. Altogether, 43 siblings were identified from homozygous or heterozygous patients. Of these, 21 siblings had already been tested for AATD and 22 siblings were tested by us as a result of the questionnaire; 2 patients with PI-ZZ genotype and 7 heterozygous children were newly identified. Moreover, results from AATD diagnostic tests are pending for a further 11 children, for a variety of reasons. The results are summarized in Figure 1.

Discussion

In our current study on AATD in children and adolescents reported here, we carried out a follow-up analysis of our cohort of patients and families in order to assess the individual course of the disease, detect siblings who might be affected by AATD, and optimize patient care. Additionally, we analyzed the signs and symptoms leading to a diagnosis of AATD.

Although AATD is one of the most common inherited metabolic disorders [9] there are still important questions that need answering, such as how the individual course of liver disease can lead to chronic liver disease and liver transplantation. A study published by Hinds et al demonstrated that the development of liver disease not only varies in affected patients, but there is also a variable degree of liver involvement in siblings with PI-ZZ AATD liver disease; this suggests that further environmental and/or genetic factors must be involved in determining disease severity [6]. There is no doubt that homozygous patients are at risk of developing chronic liver disease and, more frequently, severe pulmonary destruction in adulthood [7]; however, the role of heterozygous subtypes of AATD in chronic liver disease is still not fully understood [15]. Unfortunately, the risk for liver failure can not be predicted and therefore, life-long follow-up examinations are mandatory for homozygous patients.

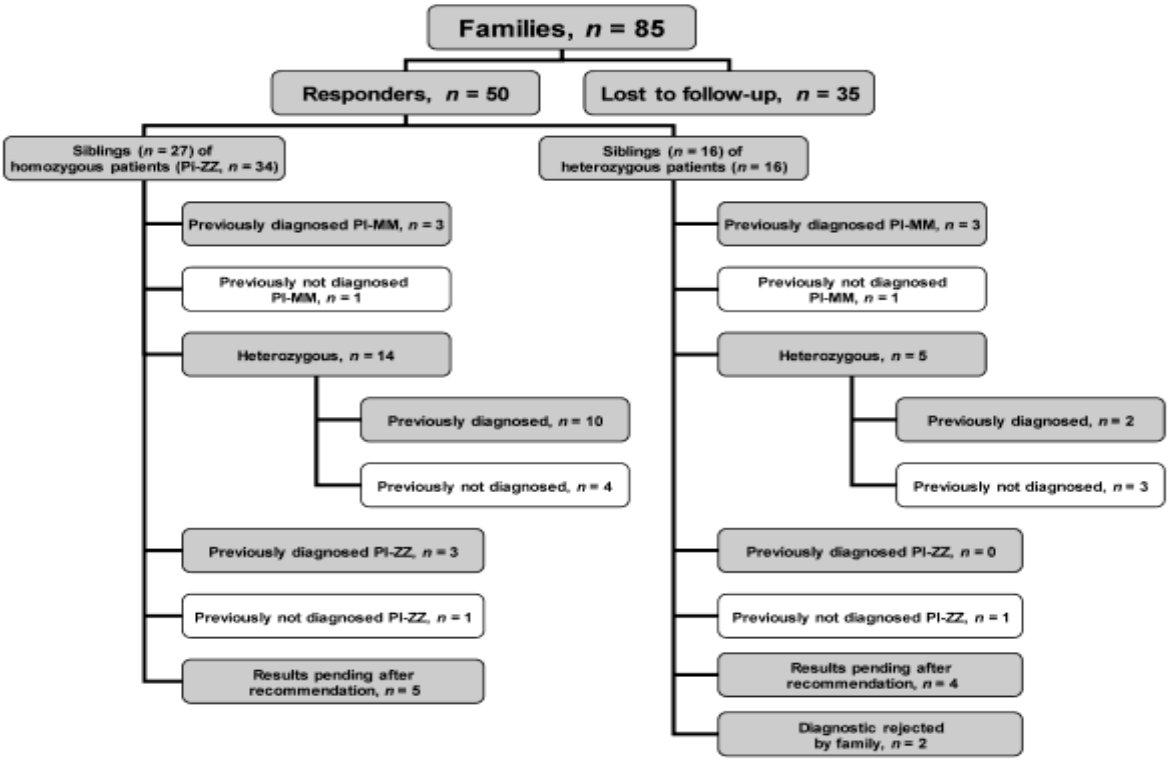

Figure 1. Results from a questionnaire sent to a total of 85 families with children suffering from AATD.

In the cohort reported here, the most common signs and symptoms leading to diagnosis of homozygous AATD were elevated liver enzymes or jaundice/cholestasis (n = 35; 60.3%). Retrospectively, 28 patients had "liver signs" and could have been diagnosed in the neonatal period. However, only 23 of these patients were diagnosed in the first weeks of life. These findings are consistent with previous reports demonstrating that the vast majority of PI-ZZ patients can be diagnosed in childhood because of the high frequency of elevated liver function tests and/or neonatal jaundice [11,14,3]. Affected children may present with neonatal cholestatic jaundice or, in some cases, during the investigation of abnormal liver function. Therefore, it should be mandatory to check for AATD in all neonates presenting with neonatal cholestasis or a pathologic liver function test. In a relevant proportion of patients in our cohort, the diagnosis of AATD was established late (n = 17) for a variety of reasons or because the existence of an affected sibling led to diagnosis (n = 6) (Table 1).

Gender	Median Age at Diagnosis (Range)	Neonatal Signs or Symptoms (in Retrospect)	Symptoms Leading to Diagnosis
Females, *n* = 28 Males, *n* = 30	2.1 y (0.1–10 y)	Hyperbilirubinemia, *n* = 20 (34.5%) Elevated liver enzymes, *n* = 8 (13.8%) No signs, *n* = 2 (3.4%) Unknown, *n* = 28 (48.3%)	Elevated liver enzymes, *n* = 23 (39.7%) Jaundice/cholestasis, *n* = 12 (20.7%) Asymptomatic siblings or patients with known AATD, *n* = 6 (10.3%) Hepatomegaly, *n* = 2 (3.4%) Failure to thrive, *n* = 1 (1.7%) Miscellaneous, *n* = 2 (3.4%) Unknown, *n* = 12 (20.7%)

Table 1. Patient characteristics of 58 homozygous (PI-ZZ) AATD children.

The individual course of homozygous AATD cannot be predicted and, in particular, the pathogenesis of liver damage is not fully understood. Some children may develop chronic liver failure with liver cirrhosis and require liver transplantation, while others do not progress to significant liver involvement [13,2]. In our series (Table 2), 39 out of 58 PI-ZZ patients (67.2%) showed pathologic liver function tests and 17 out of 58 patients (29.3%) presented with significant pathologic findings on liver ultrasound (irregular structure of the parenchyma or reduced portal vein flow). Additionally, 8 patients (13.8%) developed chronic liver failure and had a liver transplant; 16 patients had pulmonary symptoms (asthma or recurrent pulmonary infections), but none of these symptoms could be directly related to the homozygous AATD. The vast majority of patients with homozygous AATD do not develop pulmonary symptoms before the third or fourth decade of life [5]. The findings of this study suggest that improved cooperation between adult and pediatric doctors may lead to the identification of at risk parents. Once they have been identified, it is hoped that their risk of developing severe lung disease will be reduced, for example by timely treatment with augmentation therapy.

Elevated Liver Function Tests	Pathologic Findings on Liver Ultrasound	Pulmonary Symptoms	Liver Transplantation
Yes, *n* = 39 (67.2%) **No, *n* = 17 (29.3%)** Unknown, *n* = 2	**Yes, *n* = 17 (29.3%)** **No, *n* = 41 (70.7%)**	**Yes, *n* = 16 (27.6%)** (Asthma, *n* = 9; frequent pulmonary infections, *n* = 5; chronic bronchitis, *n* = 2) **No, *n* = 42 (72.4%)**	***n* = 8 (13.8%)**

Table 2. Long-term clinical follow-up in 58 homozygous children with AATD (PI-ZZ).

We sent a total of 85 questionnaires to families who were registered in our outpatient clinic as having at least 1 child with homozygous or heterozygous AATD. Out of the 50 responding families, there were 34 families (68.0%) with a homozygous child and 16 (32.0%) with a heterozygous one. In the families with a homozygous child, a total of 27 siblings were recorded. At least 11 of these siblings (40.7%) had never been checked for AATD, which is an unacceptably high rate, since all families should be aware of the consequences of homozygous AATD. This finding indicates that there are insufficient policies that recommend diagnostic testing at the reference center. As a result of our questionnaire, one PI-ZZ patient has been newly diagnosed and in 5 patients we have recommended that the appropriate testing be done by the primary care physician because the families were not able to come to our institution. The results for these children are pending. In the families with heterozygous children, 16 siblings have been identified, 11 (68.8%) of which had not been tested for AATD. In addition to the 1 homozygous patient mentioned above, 1 child has been newly diagnosed to be PI-ZZ in the families with heterozygous index patients, and as a direct consequence of our questionnaire. Given that 41.2% of our families were lost to follow-up, it can be assumed that a substantial number of siblings with heterozygous or homozygous AATD have not been diagnosed up to now. We have to admit that the high number of undiagnosed siblings serve as a sign for insufficient primary care and counseling after the disease having been diagnosed in the index patient. We assume that this phenomenon affects other centers as well since most of the patients do not have clinical symptoms and therefore predispose for lost to follow-up.

In order to diagnose children correctly, and particularly those with homozygous AATD, national registries should be established and pediatric hepatologists consequently should follow-up children and their families with regard to AATD. AATD awareness must be increased in order to prevent affected individuals from developing severe pulmonary disease. For example, these individuals should receive replacement therapy with AAT. Hepatic decompensation (development of cirrhosis) should be diagnosed at an early stage. In our center homozygous patients are treated with ursodeoxycholic acid (UDCA); However there are no data in the literature available which proof a clinical impact of UDCA. Furthermore, ethical issues should be taken into account when considering the genetic testing of relatives of a proband that has genetic disease.

It is being discussed if a general screening for AATD, as it has been done in Sweden, should be underwent or not. There are pros and cons and most countries still want to avoid the costs for screening.

Conclusion

In summary, our single-center study clearly demonstrates the need to improve awareness of one of the most common genetic disorders, which leads to hepatic and pulmonary destruction. Given the fact that most children with homozygous AATD presented in the neonatal period with jaundice and/or elevated liver enzymes, the pediatrician is in an ideal position to diagnose children with AATD. Furthermore, consequent follow-up examinations in affected families, including all siblings, should be mandatory.

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