Alpha-1-Antitrypsin Deficiency in Children: Clinical Characteristics and Diagnosis

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SUMMARY

Introduction Alpha-1-antitrypsin deficiency (AATD) is a relatively rare and clinically very heterogeneous autosomal recessive disorder.

Objective Presentation of clinical characteristics of AATD in the first months after birth, as well as the significance of testing brothers and sisters for its presence.

Methods Objectives of the study were analyzed on a sample of eight children (four male and four female, aged 63 months (mean14.81±23.96 months; range 1-63 months) with AATD confirmed based on its low serum value and pathological phenotype.

Results Of the total of eight patients, six manifested cholestasis syndrome (three male and three female, mean age 2.25±1.37 months; range 1-4.5 months), while two patients, a 3.5-year-old girl and a 5.25-year-old boy, were without symptoms and clinical-laboratory signs of the disease, disclosed during family testing. Serum alpha-1-antitrypsin level rated 0.30-0.66 g/L (0.37±0.12), among which seven were with ZZ phenotype 0.30-0.39 (0.33±0.04), and in a boy with FZ the phenotype was disclosed on family screening, 0.66 g/L. In the group of patients with cholestasis syndrome (serum GTT 444.80±203.15 U/L; range 201-676 U/L), three had mild to moderate hepatomegaly, one had longitudinal growth delay (<P3; -10.50%) and two had icterus with conjugated hyperbilirubinemia (92 and 109 μmol/L) and prolonged prothrombin time (PT 14.8 and 17 sec). All children with cholestasis syndrome also had hypertransaminasemia (ALT 80.83±33 U/L; range 37-124 U/L and AST 116.67±62.82 U/L; range 58-230 U/L).

Conclusion Cholestasis syndrome represents a basic manifestation of AATD in the first months after birth, while early testing of brothers and sisters enables early disclosure and adequate treatment of the subclinical forms of the disease.

Keywords: alpha-1-antitrypsin deficiency (AATD); infant; clinical manifestations

INTRODUCTION

Alpha-1-antitrypsin deficiency (AATD) represents a relatively rare and clinically a rather heterogeneous autosomal recessive disorder of serpinopathy group [1, 2, 3]. It is present in all regions worldwide, but most often in the population derived from the European ancestry (1:2000-6700), particularly those from Northern Europe (1:1600) [1-5]. The basis of the disease forms a defect in the hepatocyte expression of alpha-1-antitrypsin followed by damage of the liver and/or lungs, and rarely of other body structures [1, 2, 3]. Liver changes develop due to intra-hepatocytic retention and alpha-1-antitrypsin polymerization, while pulmonary and other are the result of the lack of its protective effect, as well as its regulatory participation in the process of inflammation and tissue repair [1, 6, 7, 8].

Viewed from the clinical aspect, AATD can be asymptomatic or long-lastingly and even permanently symptomatic [1, 2, 3, 9]. The type of its expression depends on the genotype, but also of numerous exogenous factors, such as various infective, toxic and other damages of the liver and/or lungs [1, 2, 3, 9]. Symptomatic liver damage can be seen in all ages, also including in first weeks after birth, while pulmonary damage occurs in persons aged over 40-50 years, but very rarely in puberty [2, 3]. Other manifestations of the disease, such as membranoproliferative glomerulitis, necrotizing panniculitis, recurrent vasculitis, vascular aneurysms and other are much rarer or exceptionally rare 1, 2, 3, 6, 7].

OBJECTIVE

The objective of the study was to present clinical characteristics of AATD in the first months after birth, as well as the significance of testing brothers and sisters for its presence.

METHODS

The studied sample was composed of eight children (four male and four female) aged 1-63 (14.81±23.96) months. Six patients had a symptomatic form of the disease, while two were disclosed during family testing. The diagnosis of AATD is based on the determination

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of its low serum level (<0.8 g/L, below 50% of normal) and phenotypic analysis [1, 10]. With the aim of adequate interpretation of alpha-1-antitrypsin concentration in serum of all patients, based on relevant clinical-laboratory parameters, also including normal values of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), we excluded possible infective and other inflammatory processes. To identify Pi alleles (alfa-1-antitripsin phenotypisation), isoelectric focusing was carried out (pH range 4.2-4.9) according to the method by Kishimoto et al. [11].

Beside a detailed anamnesis and clinical examination, also including comparison of body length (BL) and weight (BW) with referent values, serum levels of total and conjugated bilirubin, γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), prothrombin time (PT), partial thromboplastin time (PTT), total cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, glucose, calcium and phosphorus were determined. All laboratory values were compared with referent values for the matched age [10]. Also, all patients were screened by ultrasound examination of the abdomen and complete urine analysis testing. A 2.5-months old patient underwent intra-operative choliangiography with liver biopsy, as his illness history from the previous hospital already contained information on normal alpha-1-antitrypsin in serum but without data on a parallel intercurrent bacterial infection about which we were informed later. Having in mind a wide differential diagnosis of cholestasis syndrome at such an early phase of life as well as due to a possible comorbidity in all patients with the clinically manifest form of AATD, in the initial phase of the study metabolic screening of urine and serological test for *Toxoplasma gondii*, rubella, cytomegalovirus and herpes simplex virus were done in two and sweat test in three patients. Having in mind the fact that all mothers were HBs negative and that all children had been vaccinated against hepatitis B, studies were not done in this direction.

RESULTS

Of the total of eight patients with AATD, six manifested cholestasis syndrome (three male and three female, mean age 2.25±1,37 months; range 1-4.5 months), while two, a 3.5-year-old girl and a 5.25-year-old boy, were without symptoms and clinical-laboratory signs of the disease disclosed during family testing. Serum alpha-1-antitrypsin level rated 0.30-0.66 g/L (0.37±0.12), among which seven were with ZZ phenotype 0.30-0.39 (0.33±0.04), and in the boy with FZ phenotype disclosed on family screening 0.66 g/L. In the group of patients with cholestasis syndrome (serum GTT 444.80±203.15 U/L; range 201-676 U/L), three had mild to moderate hepatomegaly; one longitudinal growth delay (<P3; -10.50%) and two had icterus with conjugated hyperbilirubinemia (92 and 109 μmol/L) with prolonged PT (14.8 and 17 sec). All children with cholestasis syndrome also had hypertransaminasemia (ALT 80.83±33 U/L; range 37-124 U/L and AST 116.67±62.82 U/L; range 58-230 U/L). Liver tissue histological findings in a 2.5 months old infant with the PiZZ fenotype and serum concentration of alpha-1-antitrypsin of 0.35 g/L corresponded to neonatal hepatitis, but without evident intracellular PAS-positive globules. Either pulmonary manifestations of the disease or any other comorbid conditions with similar clinical-laboratory presentations were not registered in any of the patients.

In further course, i.e. in the children aged 1.25-6.75 years (3,52±1.88), all patients were of good general condition, normal nutritional, growth and developmental status, as well as with absence of any disorders that would point at the presence of AATD. In five of six children, cholestasis was followed by normalization; in two under treatment with ursodeoxycholic acid and in three spontaneously. Only in the oldest patient, the 7-year-old boy, we registered persistent cholestasis syndrome (serum GGT 212 U/L; normal <55 U/L) with hypercholesterolemia (6.48 mmol/L; normal <6.22 mmol/L), hypertransaminasemia (ALT 138 U/L; normal <49 U/L and AST 108 U/L; normal <36 U/L) and ultrasonographic signs of mild non-homogenous hepatomegaly. Other laboratory analyses and spleen size were within normal limits.

DISCUSSION

Alpha-1-antitrypsin is a glycoprotein, with 52 kDa molecular weight, from the superfamily of serine protease inhibitors (serpin), with a special affinity to granulocytic elastases [1, 2]. It is primarily produced in hepatocytes (~80%), and to a lesser part in macrophages, monocytes, broncho-alveolar epithelium, colonocytes and endocrine pancreas cells from where it is secreted, under the influence of proinflammatory cytokines, into the blood circulation where it forms 80% of α1-globulins fraction [3, 12, 13, 14]. It belongs to the first phase reactants of inflammation with the circulation half-life of 4-5 days and the basic role to suppress autodestructive, i.e. additional tissue damage, by neutralizing granulocytic elastase, primarily of the lungs during various infective and non-infective inflammatory processes [2, 3, 13, 14]. Beside protective-immunomodulatory effect, alfa-1-antitrypsin is significant as the tissue reparation inductor [2, 3, 15].

Alfa-1-antitripsyn encodes SERPINA 1 gene located on the long arm of chromosome 14 (14q31–32.3) [1, 2, 3]. Up-to-now over 120 variations of this gene have been discovered, among which one third is in homozygous condition or inter-individual variant combination followed by a deficit or dysfunction of alpha-1-antitrypsin [1, 9]. The most frequent normal allele present in 95% of the European population is M, while defect S and Z alleles, which are in homozygous condition (PiZZ) are responsible for 95% of clinically manifest forms of the disease [1, 15, 16]. F, Null, Siiyama, Mmalton, Mprocida, Mheerlen, Mmineral springs, Psalt-like, Mnichinan, Pduarte, Wbethesda Zaugsberg, Zbristol, Pittsburgh and other pathological mutations are much rarer or exceptionally rare [14, 15, 17-22].

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Pathogenetic basis of the most frequent form of the defect creates a defect in the expression of alpfa-1-antitrypsin followed by destructive damage of the liver and/or lungs [1, 2, 3, 14]. Liver lesion develops due to intrahepatocytic retention and polymerization of the defective alpha-1-antitrypsin, and of the lungs as the result of lack, not only of its protective effect, but also of regulatory participation in the process of inflammation and tissue reparation [1, 6, 7, 8]. The accumulation of defective alpha-1-antitripsin in the liver, most expressed in periportal and paraseptal hepatocytes, is characteristic of ZZ as well as the homozygous and heterozygous combination of Mmalton, Pduarte and Siiyama genotypes [1, 2, 14]. This pathological process, mediated by proinflammatory cytokines, induces all inflammatory diseases, either intra- or extrahepatic, particularly if followed by high fever [2, 14, 17]. In all other mutations, such as S, F, Psalt like, Null and Pitsburgh, hepatocytic retention alpha-1-antitrypsin is absent, so that only extrahepatic manifestations of the disease are expressed; in the first case due to its short half-life, in the second and third due to poor activity, in the fourth due to a complete blockage of synthesis, and in the fifth due to antithrombotic effect [1, 3, 14, 20-23]. Besides, there is also the presence of various combinations of pathological alleles, such as SZ, SF and others, and therefore, in accordance with their defectiveness, most variable clinical manifestations [1, 2, 9, 14, 18].

Clinical and phenotypic characteristics of AATD in our patients were characteristic of childhood period [12, 14]. Six of eight patients with AATD, all six with the PiZZ phynotype, manifested cholestasis syndrome, while two, without clinical-laboratory indicators of the disease, and PiZZ and PiZF phenotype, were disclosed during family testing [2, 24]. All patients with cholestasis syndrome were in early infancy (mean age 2.25±1.37 months; range 1-4.5 months) and with the PiZZ phenotype, while the remaining two were aged 3.5 and 5.25 years, and with the PiZZ and PiZF phenotype. Except for cholestasis syndrome, other manifestations of the disease were not registered. Pathohistological analysis of liver tissue in a 2.5 month old infant, with the PiZZ phenotype and serum concentration of alpha-1-antitrypsin of 0.35 g/L, did not show the presence of PAS-positive globules, which confirms the fact that such a finding, due to the short duration of the disease within the first three months, is not expected anyway [25, 26]. Although liver damage can be exceptionally severe in 1-2% of patients, most often it has a slowly progressive character so that juvenile cirrhosis develops only in 15% of cases [2, 14, 25]. Our patients, who have been under follow-up from 1.25-6.75 (3.52±1.88) years, for the time being have not either disorder of growth and development or symptoms that would point at the presence of AATD. Only one of them, a boy now aged seven years, manifests persistent cholestasis syndrome with mild hepatomegaly and ultrasound signs of initial liver cirrhosis.

CONCLUSION

AATD represents a highly heterogeneous clinical entity dependent of the type of genotype, age, as well as numerous exogenous factors. Genetic basis of the disease with early expressions forms of ZZ genotype, and clinical cholestasis syndrome. Besides, the essential characteristic of the disease is that clinical-laboratory indicators of cholestasis, present in the first weeks after birth, most often get lost at later age. Having in mind the mode of inheritance, as well as the progressive character of the disease, testing the first degree relatives for AATD enables disclosure of subclinical forms of the disease, and therefore enable the implementation of adequate measures aimed at slowing-down its progression.

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Недостатак алфа-1 антитрипсина код деце: клиничке одлике и дијагностика

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КРАТАК САДРЖАЈ

Увод Недостатак алфа-1 антитрипсина (*AATD*) је релативно редак и клинички веома хетероген аутозомно рецесивни поремећај.

Циљ рада Циљ рада је био да се прикажу клиничке одлике *AATD* у првим месецима по рођењу, као и значај тестирања браће и сестара на овај поремећај.

Методе рада Испитано је осморо деце (четири дечака и четири девојчице) узраста од месец дана до 63 месеца (просечно 14,81±23,96 месеци) са *AATD*, који је доказан на основу ниске вредности алфа-1 антитрипсина у серуму и патолошког фенотипа.

Резултати Код шесторо деце (три дечака и три девојчице) узраста од месец дана до четири и по месеца (просечно 2,25±1,37 месеци) испољио се холестазни синдром, док су два детета (троипогодишња девојчица и дечак узраста од 5,25 година) била без симптома и клиничко-лабораторијских знакова *AATD*, али је болест откривена у склопу породичног тестирања. Ниво алфа-1 антитрипсина у серуму био је 0,30–0,66 *g/l* (просечно 0,37±0,12 *g/l*), при чему код седморо деце са *ZZ* фенотипом 0,30–0,39 *g/l* (просечно 0,33±0,04 *g/l*), а код дечака са *FZ* фенотипом, откривеног породичним скринингом, 0,66 *g/l*. У групи болесника са холестазним синдромом (ниво *GGT* у серуму био је у просеку 444,80±203,15 *IU/l*; распон 201–676 *IU/l*), код три детета је утврђена блага до умерена хепатомегалија, код једног детета је уочен застој у лонгитудиналном расту (<П3; -10,50%), док је код двоје деце забележен иктерус са конјугованом хипербилирубинемијом (92 и 109 *μmol/l*) и продуженим парцијалним временом (14,8 и 17 *s*). Код све деце с холестазним синдромом утврђена је и хипертрансаминаземија с вредностима *ALT* 80,83±33 *IU/l* (распон 37–124 *IU/l*) и *AST* 116,67±62,82 *IU/l* (распон 58–230 *IU/l*).

Закључак Холестазни синдром је основна манифестација *AATD* у првим месецима по рођењу детета, док тестирање браће и сестара оболелих омогућава рано откривање и одговарајуће лечење супклиничких облика болести.

Кључне речи: дефицит алфа-1 антитрипсина; одојче; клиничке манифестације

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