Polskie Towarzystwo Gastroenterologii, Hepatologii i Żywienia Dzieci

Standards for diagnosis and care of patients with inherited alpha-1 antitrypsin deficiency

Recommendations of the Polish Respiratory Society, Polish Society of Pediatric Pulmonology and Polish Society of Pediatric Gastroenterology

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Table of contents

1. Introduction
   1.1. Biological significance of alpha-1 antitrypsin
   1.2. Molecular basis of alpha-1 antitrypsin deficiency
2. Epidemiology and clinical significance of inherited alpha-1 antitrypsin deficiency
   2.1. Global data
   2.2. Polish data
3. Diagnosis of inherited alpha-1 antitrypsin deficiency
   3.1. Diagnostic methods — advantages and disadvantages
   3.2. Proposed diagnostic scheme
4. Treatment and care of patients with inherited alpha-1 antitrypsin deficiency
   4.1. Hepatological problems in children
   4.2. Pulmonary problems in children
   4.3. Pulmonary problems in adults
5. Summary
   5.1. Main indications for diagnosing alpha-1 antitrypsin deficiency
   5.2. Normal levels of alpha-1 antitrypsin
   5.3. Diagnostic laboratories in Poland
6. References

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1. Introduction

Alpha-1 antitrypsin (AAT) deficiency is the most common genetic disorder in the adult population of European descent. However, it is usually diagnosed late, in the fifth decade of life, typically due to advanced changes in the respiratory system or in the liver. In a large number of patients the deficiency remains undiagnosed.

Initial diagnosis towards inherited AAT deficiency should be a part of standard medical procedure for all patients with chronic respiratory tract diseases marked by persistent airway obstruction, especially for patients with diagnosed COPD, bronchial asthma with non-fully reversible airway obstruction and bronchiectasis, as well as for children with symptoms of cholestatic jaundice, cirrhosis and adults with non-alcoholic liver cirrhosis. The range of indications for diagnostic procedure for other extrapulmonary diseases of adulthood and in pediatrics as well as knowledge of optimal diagnostic algorithm, including genotyping and phenotyping methods, also require urgent dissemination in the medical community. Awareness of means of active prevention of acute and chronic respiratory diseases (strict prevention of active and passive tobacco smoking, air pollution in the workplace and at home, preemptive vaccination) as well as an evaluation of effectiveness of and indications for intravenous augmentation therapy remain important issues in care of patients with AAT deficiency (Table 1).

This document is an update to the "Standards for diagnosis and care of patients with inherited alpha-1 antitrypsin deficiency" prepared in 2010 by a working group then established by the Polish Respiratory Society.

1.1. Biological significance of alpha-1 antitrypsin

Alpha-1 antitrypsin is a glycoprotein with a molecular weight of 55 kDa composed of a single polypeptide chain (394 amino acids) which is subject to a complex process of glycosylation. This protein is synthesized mainly in the liver and subsequently secreted into the bloodstream. AAT belongs to the serpin family and is one of the most important plasma and tissue serine protease inhibitors in the human body, effectively inhibiting the action of multiple enzymes (neutrophil elastase, proteinase 3, cathepsin G, trypsin).

AAT plays a significant role in maintaining the protease-antiprotease balance under in vivo conditions. This inhibitor is an important element of the anti-elastase shield in the lungs, protecting that organ's tissue from uncontrolled, destructive influence of proteolytic enzymes. Low levels of AAT in the respiratory system lead to gradual and irreversible decline in the elasticity of the lungs. Overactivity of neutrophil elastase causes degradation of elastin (a primary component of elastic fibers) as well as of other components of the extracellular matrix in the lower respiratory tract. Exposure to inhaled irritants, particularly tobacco smoke, stimulates the development of a local inflammatory process in the respiratory tract, including release of proteases and free oxygen radicals. Their interaction with AAT promotes formation of inactive and/or polymerized forms of this protein which are characterized by pro-inflammatory activity.

Table 1. Indications for intravenous augmentation therapy with alpha-1 antitrypsin (all listed)

Severe inherited AAT deficiency emphysema
Alpha-1 antitrypsin concentration in the serum $\leq$ 11 μmol/L,
FEV_1 after bronchodilator administration = 30–65% predicted or annual decline in FEV_1 value $\geq$ 50 mL/year
Never-smokers and ex-smokers only

1.2. Molecular basis of alpha-1 antitrypsin deficiency

AAT deficiency is a genetically determined disorder caused by a mutation of the *SERPINA1* gene (previously designated *PI*, protease inhibitor), located on the long arm of chromosome 14. So far, over 130 genetic variants (alleles) of this gene have been identified, which encode AAT protein variants with different quantitative (concentration in the serum) or qualitative (biological activity) characteristics. Phenotypic AAT protein variants have been classified in a system referred to as the PI (protease inhibitor) system. This classification was created using the isoelectric focusing technique, which involves separating protein in polyacrylamide gels with an appropriate pH gradient. As a consequence of the *SERPINA1* gene mutation there are differences in amino acid composition of each protein variant, which result in changes in isoelectric point and electrophoretic mobility in the gel. This phenomenon is used to identify AAT phenotype. AAT variants marked with the initial letters of the alphabet are characterized by lower pH of the isoelectric point (a change to a more acidic amino

acid) and a greater migration distance in the gel; variants with a more alkaline isoelectric point, less mobile - are marked with the final letters of the alphabet. Ordinarily, several AAT protein bands become visible during electrophoretic separation, which is due to varying degree of its glycosylation. The most common normal variants are characterized by intermediate electrophoretic mobility and are marked with the letter M, M1A and M1V respectively ($Ala^{213}Val$) as well as clinically insignificant M2 ($Arg^{101}His$), M3 ($Glu^{376}Asp$) and M4 ($Asp^{256}Val$).

For clinical and practical purposes AAT variants have been divided into 4 classes, depending on concentration and function of a given type in the plasma. The family of normal AAT variants is designated PI*M. These are the most common alleles of the AAT gene in the European population (present in approximately 95% of people) which ensure normal levels and functioning of this inhibitor in the plasma. Deficiency variants constitute another class, whose protein products are subject to intracellular accumulation or degradation in the liver, which leads to a significant decrease in AAT levels in the bloodstream. Two most common deficiency alleles, PI*Z and PI*S, which condition severe AAT deficiency, can be found within this group. Alleles devoid of expression (so-called "null" alleles) constitute another class. These are rare genetic variants of AAT, whose protein products are not detected in the bloodstream. Genetic variants of AAT which encode dysfunctional protein form the final class.

The Z variant of the *SERPINA1* gene (very slow migration) is determined by a single point mutation leading to substitution of glutamic acid with lysine at position 342 ($Glu^{342}>Lys$) and as a result to loss of stability of the spatial structure of the protein (Z-AAT), which polymerizes while still within hepatocytes. The Z-AAT protein is characterized by low ability to inhibit proteases in the bloodstream and in tissues. In patients with the PI*ZZ genotype, that is, with two PI*Z deficiency alleles, the concentration of alpha-1 antitrypsin in the serum is 10-15% of normal.

The protein product of the S allele (slow migration) is characterized by a substitution of glutamic acid with valine at position 264 ($Glu^{264}>Val$), which causes the newly formed S-AAT protein to be degraded while still within liver cells. The AAT concentration in the serum of PI*SS homozygotes is approximately 40% lower than in individuals with normal PI*MM genotype.

2. Epidemiology and clinical significance of inherited alpha-1 antitrypsin deficiency

2.1. Global data

AAT deficiency is one of the most common inherited diseases in Europe. The severe form of AAT deficiency (PI*ZZ) has an estimated prevalence of 1 in 1500 to 1 in 3500 live births in most populations; a decreasing gradient of prevalence of PI*Z variant is observed north to south, and of PI*S variant west to east of Europe.

According to data from 58 countries, published in 2002, the total number of patients with AAT deficiency (taking PI phenotype: ZZ, SZ and SS into account) was estimated at 3.4 million in countries in northern and western Europe. Prevalence of PI*Z allele is higher, at 14 in 1000 on average, while PI*ZZ homozygotes have a prevalence of 1 in 5000. A review of 68 selected epidemiological studies conducted in 21 European countries on a group of 75,390 individuals in total estimates the average prevalence of severe AAT deficiency phenotype (PI*ZZ) in the European population at 1:4727.

Published results are inconsistent and the differences within the same populations stem from non-random sampling. High prevalence of PI*Z allele was observed in northern and western Sweden (2.3–3.2%), Estonia and Lithuania, as well as among the Danes. The PI*Z allele is somewhat rarer (2–2.25%) in northern France (Normandy and Brittany), Ireland and southern England. The rest of Europe is characterized by a prevalence of the Z variant of less than 2%. The lowest prevalence of the Z variant was observed in southern Italy and in Russia. Prevalence of PI*ZZ homozygotes is theoretically equal to the square of prevalence of the Z allele. Distribution of PI*ZZ homozygotes decreases from the north-east (1:500–5,000) in the south-western direction (1:1000–90,000).

2.2. Polish data

Polish data concerning prevalence of AAT deficiency is scarce. Most analyses concern adults and were conducted in relatively small groups, encompassing 2653 individuals in total. Based on the analysis of available data, prevalence of the PI*S and PI*Z allele is 14.5/1,000 and 10.9/1,000, respectively. This allows to estimate the prevalence of the PI*ZZ phenotype at 1/9110. 4,189 individuals with the described phenotype could therefore be expected in the Polish population of 38 million.

Recently, a study of prevalence of the main deficiency alleles has been conducted via a

screening of a population of 5,000 neonates from Warsaw and the Mazovia region. Initial results, derived from genotyping in a group of 658 children, indicate a much higher prevalence of the main deficiency genotype PI*ZZ of 1/5345, which would correspond to estimated 7000 individuals with severe deficiency (PI*ZZ) in Poland.

3. Diagnosis of inherited alpha-1 antitrypsin deficiency

3.1. Diagnostic methods — advantages and disadvantages

A complete diagnosis of AAT deficiency is based on a combination of quantitative (measurement of AAT concentration in the serum) and qualitative methods which allow to identify the variant of the AAT protein (phenotyping) or the *SERPINA1* gene (genotyping, DNA sequence analysis). Certain diagnosis of inherited AAT deficiency always requires confirming it on a molecular level. A clear identification of the protein phenotype or the genotype is therefore necessary. It is recommended that a diagnosis of AAT deficiency be confirmed by at least two diagnostic methods:

1) measurement of AAT concentration in the serum + AAT protein phenotyping,
2) measurement of AAT concentration in the serum + genotyping,
3) AAT protein phenotyping + genotyping.

The above rule allows for certain diagnosis of the most common deficiency variants. If a rare or atypical variant of AAT gene mutation is suspected, DNA sequence analysis should be performed.

3.1.1. Measurement of AAT concentration

An initial test performed for individuals with suspected deficiency of this protease inhibitor is a measurement of concentration of alpha-1 antitrypsin in the blood serum/plasma using colorimetric or immunological methods. Immunonephelometry is the method of choice due to high sensitivity of measurement. AAT concentration is typically expressed in milligrams per deciliter (mg/dL) or millimoles per liter (μmol/L or μM). Normal levels of AAT concentration in the serum in healthy individuals are between 20–39 μM which, when using a modern immunonephelometric method, corresponds to levels between 83–220 mg/dL, and when using an older rocket immunoelectrophoresis method — 150–330 mg/dL.

Observing a decreased AAT level in the tested individual (≤ 100 mg/dL) is an absolute indication to continue diagnosis and perform further qualitative tests. They should also be considered for an individual with a low normal AAT concentration (90–130 mg/dL or 12–35 μM), especially in case of concomitant pathology of the respiratory system or the liver.

AAT belongs to the acute-phase protein group, hence its concentration can be elevated in the course of multiple disease processes, even in case of concomitant deficiency. In order to increase diagnostic accuracy and reduce the risk of false negative results, it is recommended to simultaneously determine the concentration of AAT and the acute-phase protein (CRP).

3.1.2. Phenotyping

The method of identifying the AAT protein variant through isoelectric focusing (IEF) in a polyacrylamide gel (pH gradient 4.2–4.9) is a "gold standard" in diagnosing the deficiency. Small changes in the electrolytic dissociation constant of the protein allow to differentiate every AAT variant except the "null" variants.

This method is technically fairly difficult, time-consuming and, due to complex microheterogeneity stemming from glycosylation as well as the considerable number of AAT variants, requires substantial experience and the ability to analyze results. It should be remembered that phenotyping does not allow to identify mutations of the AAT gene which are not expressed. There are also rare variants of the serine protease inhibitor with identical or only slightly different values of the isoelectric point. Correct interpretation of results of electrophoresis of these phenotypes presents considerable difficulty. A result indicating the presence of a deficiency variant of the protein requires confirmation by another diagnostic method, quantitative or qualitative (as noted above).

3.1.3. Genotyping

Genotyping allows to directly identify irregularities within the *AAT* gene, that is, mutations in the *SERPINA1* gene locus responsible for the emergence of the deficiency. The most commonly used diagnostic methods allow to identify only two most frequently occurring deficiency mutations — PI*Z and PI*S.

The basis for most methods of identifying mutations is the analysis of appropriate DNA region replicated in a polymerase chain reaction (PCR). The primary material obtained from the patient in order to perform a genetic analysis is DNA isolated from peripheral blood leukocytes or, alternatively, from other tissue cells (oral mu-

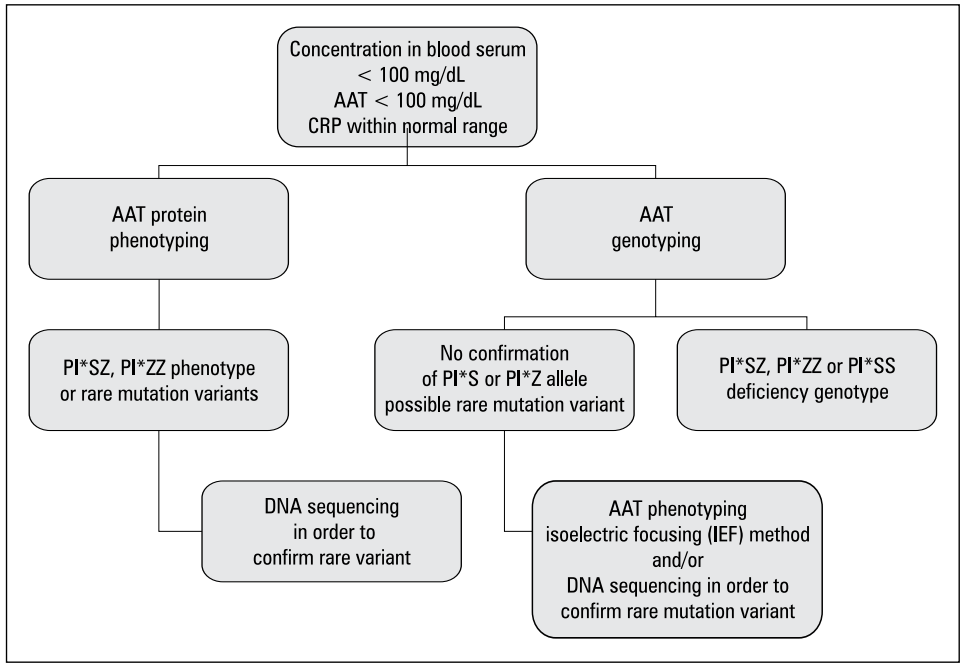

Figure 1. Proposed diagnostic algorithm for suspected severe alpha-1 antitrypsin deficiency or other mutations causing quantitative deficiency, including: AAT protein phenotyping (see section 3.1.2), AAT genotyping (see section 3.1.3) and DNA sequencing (see section 3.1.4)

cosal epithelial cells), as well as a blood sample on filter paper.

3.1.4. DNA sequence analysis

DNA sequence analysis allows to discover nucleotide mutations, that is to determine the genetic variants in the analyzed DNA fragment. It is an expensive and time-consuming method, requiring replication of *SERPINA1* gene exons using PCR technique and their sequencing. This method is not routinely used in diagnosing AAT deficiency; it is only used in case a rare or new variant of alpha-1 antitrypsin is suspected (atypical IEF pattern, low AAT concentration with no PI*Z or PI*S mutations).

3.2. Recommended diagnostic scheme for inherited alpha-1 antitrypsin deficiency

Measurement of AAT concentration in peripheral blood serum is the initial diagnostic test.

It is recommended to simultaneously estimate CRP concentration in order to exclude an active acute-phase response and avoid false negative results. It should be remembered that during an inflammatory response with activation of acute-phase protein, including CRP, AAT concentration will also be elevated and obtained result will be non-diagnostic.

AAT concentration below 100 mg/dL is an indication to continue diagnosis and perform a qualitative analysis of the AAT protein (phenotyping) or the *SERPINA1* gene (genotyping). This procedure allows for correct diagnosis in nearly 96% of patients with severe AAT deficiency and patients with rare mutations implying quantitative AAT deficiency. It should be remembered that analysis using the genotyping method typically allows to identify only two main deficiency alleles (PI*Z and PI*S) and does not preclude other mutations. Phenotyping allows to identify most deficiency variants of the AAT protein.

If definite diagnosis at this point is impossible, if rare or new AAT variants are suspected, sequence analysis of the *SERPINA1* gene, that is sequencing of the AAT gene, is necessary.

This usually allows for definite diagnosis and ends diagnostic procedure for severe AAT deficiency.

Proposed diagnostic algorithm for suspected severe alpha-1 antitrypsin deficiency or other mutations causing quantitative deficiency, including: AAT protein phenotyping (see section 3.1.2), AAT genotyping (see section 3.1.3) and DNA sequencing (see section 3.1.4), is presented in Figure 1.

In some clinically appropriate cases, especially when rarer forms of alpha-1 antitrypsin deficiency caused by a qualitative mutation implying low or no biological activity of the AAT protein are suspected, phenotyping and/or sequencing of the *SERPINA1* gene is necessary. Normal result of measurement of AAT concentration in the serum does not preclude AAT deficiency in these cases.

4. Treatment and care of patients with inherited alpha-1 antitrypsin deficiency

4.1. Hepatological problems in children

Accumulation of AAT in hepatocytes and liver damage is possible from the moment the liver begins to synthesize the protein. It is characteristic for the PI*ZZ phenotype. The argument of AAT deficiency as disease of the fetus is supported by early emergence of its symptoms in the first days or weeks of life, low birth weight of most neonates with liver damage and described cases of concomitant AAT deficiency and biliary atresia.

In most cases cholestatic jaundice prolonged beyond 4th-8th week of life and acholic stools are the first symptoms of the disease. Physical examination typically reveals increased liver span, while laboratory tests show increased transaminase activity and bilirubin concentration with predominance of bound fraction. Occasionally, diagnosis is prompted by bleeding from the neonate's umbilicus or gastrointestinal tract. AAT deficiency is often not diagnosed until the child is older, whereupon hepatomegaly, increased transaminase activity or jaundice are the first alarming symptoms, which complicate the course of the, often infective, underlying disease. The disease may first manifest itself at any age through portal hypertension complications: splenomegaly, hypersplenism, ascites, bleeding esophageal varices and encephalopathy. Singular cases of hepatocellular carcinoma occurring in children have also been described.

The course of the disease in children is unpredictable. Adverse prognostic factors are constantly being sought in order to identify the group of patients with increased risk of liver cirrhosis. It is thought that if increased transaminase levels and conjugated hyperbilirubinemia in neonates are not accompanied by neither jaundice nor hepatomegaly, prognosis is better. Conversely, the following are considered adverse prognostic factors in infancy: jaundice prolonged beyond 6 weeks, increased transaminase activity compared to the group with good prognosis and severe changes in diagnostic liver biopsy. In patients with portal hypertension and liver cirrhosis in some cases clinical condition remains stable long-term.

Oher than liver transplantation, there are currently no causal treatment options for AAT deficiency. Preventive methods applicable to children include breastfeeding or soy formula feeding, no exposure to tobacco smoke, plasma infusions before planned surgical procedures. Ursodeoxycholic acid (UDCA) preparations and fat-soluble vitamins are used in treatment of cholestasis. There are reports of vitamin E being effective in early infancy. In case of portal hypertension in the course of liver cirrhosis, endoscopic treatment of esophageal varices is effective, and in patients with increasing liver dysfunction - its transplantation is effective. Indications for liver transplantation do not differ from those in liver damage due to other causes: coagulation disorders, hypoalbuminemia, bleeding esophageal varices. AAT deficiency is the second most frequent, after biliary atresia, cause of liver transplantations in children. One of the parents is usually the donor, and the prognosis is good. AAT phenotype following transplantation is consistent with phenotype of the organ's donor. Moreover, emphysema does not develop.

4.2. Respiratory problems in children

There are usually no clinical symptoms of the disease in individuals with AAT deficiency during childhood and adolescence. Factors which may accelerate the development of the disease and cause symptoms to emerge before 20 years of age include exposure to tobacco smoke, frequent and severe lower respiratory tract infections, low socioeconomic status, malnutrition and air pollution.

Exposure to passive smoking is a serious problem negatively affecting pulmonary function in pediatric patients with AAT deficiency. It is considered one of the factors which may accelerate the onset of emphysema in children. Nicotine addiction has a proven detrimental effect on life expectancy of patients with severe AAT deficiency, shortening the life of smoking patients with this deficiency by approximately 20 years. Therefore, educational programs whose purpose is to eliminate exposure to tobacco smoke play an important role in care of patients with AAT deficiency.

Airway obstruction is often observed in patients with AAT deficiency. In a group of 127 PI*ZZ patients who have been observed for 22 consecutive years since infancy, 15% have been diagnosed with asthma, and recurrent wheezing occurred in 29%. However, the relationship between AAT deficiency and obstruction of the bronchial tree is inconstant and a relation of deficiency phenotype and reduced AAT levels to increased frequency of asthma and pollinosis in children has not been successfully shown. At the same time, increased airway hyperreactivity and worse parameters of pulmonary function in spirometry are noted in patients with asthma and

AAT deficiency. Furthermore, increased frequency of lower respiratory tract infections in infant carriers of PI*Z and PI*S alleles compared to children with normal variants has been observed.

Prevention of respiratory tract infections and reduction of air pollution are important elements in care of children with AAT deficiency. Pneumococcal vaccination and annual influenza vaccination are recommended for these patients. In case of an airway obstruction component, bronchodilators (beta-2- adrenomimetics, anticholinergic) and anti-inflammatory drugs, both nonsteroidal as well as inhaled corticosteroids, may be beneficial to the patients. Antibiotics, especially macrolides which are also anti-inflammatory, are recommended for individuals with AAT deficiency in bronchitis and upper respiratory tract infections. So far, a single case of effective augmentation therapy in a child has been described. This therapy is not currently recommended for children.

4.3. Pulmonary problems in adults

4.3.1. Risk factors

It is estimated that in 1−5% of patients with emphysema, it is conditioned by inherited AAT deficiency. The nature of relation between clinical consequences of deficiency and its genetic determinants has not been explained. The character of the mutation does not determine the clinical picture of the pulmonary disease and individuals with identical deficiency genotype may develop highly varied complications within respiratory system. Tobacco smoking is the most important environmental factor determining dynamics of pulmonary damage and development of symptoms, particularly COPD. It is a key, strong risk factor of COPD in not only individuals with severe inherited AAT deficiency (PI*ZZ, PI*SZ, PI*PI*Null/Null), but also carriers of one deficiency allele (PI*MZ). However, symptomatic form of deficiency is not always related to exposure to tobacco smoke or occupational factors.

4.3.2. Clinical picture

Emphysema, especially with early onset (before 45 years of age) and a symptomatic form of chronic obstructive pulmonary disease are the most common complications of severe AAT deficiency. Asthma marked by persistent airway obstruction (atopic and non-atopic) and bronchiectasis of unclear etiology are less common. Occasionally severe AAT deficiency is accompanied by minimal clinical symptoms, also with concomitant obstructive characteristics in pulmonary function tests. AAT deficiency may promote recurrent pneumothorax.

Symptomatology of AAT deficiency also includes vasculitis, mostly in the form of granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis) with the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) and panniculitis.

It is recommended that the pulmonary disease developing in the course of severe AAT deficiency be treated according to currently accepted therapeutic procedure for a particular disease entity. However, the necessity of particularly careful optimization and selection of drugs, strict treatment of exacerbations and careful observation of patients due to high risk of rapid disease progression should be taken into consideration.

4.3.3. Treatment of exacerbations of the pulmonary disease

Infective exacerbations of COPD are a particularly important clinical problem in patients with severe AAT deficiency. Much like in the classic form of COPD, their frequency is related to overall health and the degree to which pulmonary ventilatory reserve is limited. However, in patients with AAT deficiency episodes of exacerbation last significantly longer, which is due to impairment of the so-called acute-phase response, that is mechanisms of innate immunity whose main component is AAT. Exacerbations accelerate the processes of destruction of lung parenchyma.

4.3.4. Symptomatic treatment of the pulmonary disease during the stable period

The basic methods of symptomatic treatment of chronic diseases marked by persistent airway obstruction, in particular COPD in the course of inherited AAT deficiency, include:

— strict observance of refraining from active and passive tobacco smoking,
— strict avoidance of exposure to inhaled irritants (in the workplace and at home.,
— prevention and vigorous treatment of respiratory tract infections; annual influenza vaccination and periodic pneumococcal vaccination are recommended,
— early start of bronchodilator therapy in case symptoms of airway obstruction occur,
— general and pulmonary rehabilitation, preparing a written exercise program is recommended,
— dietary recommendations, maintaining optimal body weight is indicated,
— home oxygen therapy, in accordance with generally accepted indications,

— lung transplantation, in accordance with generally accepted indications.

Augmentation therapy with human AAT

The only specific treatment method for severe AAT deficiency is intravenous AAT substitution using protein obtained from the serum of healthy individuals.

Augmentation therapy has been accepted by relevant European and American institutions on three grounds:

— proven biochemical effectiveness of intravenous AAT preparations, which allow to achieve a stable increase in AAT concentration in the serum above the level considered protective for the lungs (> 11 μM or > 50 mg/dL determined using a nephelometric method);
— safety: serious adverse effects during the period of administration occur with a frequency close to that observed in the placebo group (27% vs. 31%), provided generally accepted procedure for intravenous infusions is followed and contraindications for augmentation therapy are observed;
— there are no other specific treatment methods for AAT deficiency.

Augmentation therapy at a dose of 60 mg/kg of body weight/week is recommended for patients with severe inherited AAT deficiency, emphysema, AAT concentration in the serum ≤ 11 μmol/L, who fulfill the following spirometric criteria: FEV_1 after bronchodilator administration = 30–65% predicted or annual decline in FEV_1 value ≥ 50 mL/year. Therapy is lifelong. Smoking is a factor precluding the patient from augmentation therapy.

There is limited clinical evidence for AAT augmentation therapy. However, significant limitations of conducting clinical trials in this group of patients due to its relatively small size have to be taken into consideration. Likewise, a lack of sufficiently sensitive biomarkers which would allow to reliably monitor the dynamics of progression of emphysema and COPD and which could constitute an adequate endpoint for these trials.

Observational studies indicate that in patients with moderate to very severe obstructive changes (FEV_1 = 31–65% predicted) intravenous AAT substitution slows the pulmonary function decline assessed using spirometry. There is no evidence that the therapy significantly affects mortality rate or life expectancy of patients with AAT deficiency.

In a recently published randomized, placebo-controlled trial, a positive influence on the dynamics of decline in FEV_1 value has not been observed; however, significant modifying influence of substitution therapy on the progression of emphysema in patients with severe AAT deficiency has been confirmed. Considerable slowdown in the loss of lung parenchyma density assessed using computed tomographic lung densitometry has been shown. The positive effect was stronger the earlier AAT augmentation was started.

The optimal form of medical procedure is therefore striving for the earliest possible diagnosis of inherited AAT deficiency and early start of optimal treatment, including substitution therapy.

A significant effect of AAT augmentation on clinical improvement in patients with mild and extremely severe airway obstruction (FEV_1 < 30% predicted) has not been shown. AAT augmentation has also not been confirmed to be an effective prevention against emphysema development in healthy adults carrying the genotype which conditions severe AAT deficiency.

High cost and the need for weekly intravenous infusions are significant limiting factors for long-term administration of intravenous AAT substitution therapy.

The effectiveness of other forms of AAT substitution (administration of AAT preparations via inhalation, pharmacologically supporting AAT secretion from the liver, administration of other neutrophil elastase inhibitors) has not been confirmed so far.

5. Summary

5.1. Main indications for diagnosing alpha-1 antitrypsin deficiency (Table 2)

Diagnosing inherited alpha-1 antitrypsin deficiency is recommended in adult patients of either gender with the following disorders diagnosed:

— emphysema, especially with early onset (before 45 years of age),
— symptomatic form of chronic obstructive pulmonary disease, regardless of exposure to tobacco smoke,
— bronchial asthma marked by persistent airway obstruction,
— persistent airway obstruction confirmed by function tests and exposure to occupational factors or tobacco smoke, regardless of whether symptoms occur,
— bronchiectasis of unclear etiology,
— vasculitis with the presence of c-ANCAs,
— liver disease of unclear etiology,
— necrotizing panniculitis.

Testing for alpha-1 antitrypsin deficiency should also be performed:

Table 2. Main indications for diagnosing alpha-1 antitrypsin deficiency

Emphysema, especially with early onset (before 45 years of age),
Symptomatic form of chronic obstructive pulmonary disease, regardless of exposure to tobacco smoke,
Bronchial asthma marked by persistent airway obstruction
Persistent airway obstruction confirmed by function tests and exposure to occupational factors or tobacco smoke, regardless of whether symptoms occur
Bronchiectasis of unclear etiology
Vasculitis with the presence of c-ANCAs
Liver disease of unclear etiology
Necrotizing panniculitis
Family members of confirmed alpha-1 antitrypsin deficiency patients
Individuals with family history of one of the aforementioned disorders

— in family members of confirmed alpha-1 antitrypsin deficiency patients,
— in individuals with family history of one of the aforementioned disorders.

5.2. Laboratory normal levels

Measurement of AAT concentration in blood serum/plasma is an initial test performed for individuals with suspected deficiency of this inhibitor.

AAT concentration can be expressed in milligrams per deciliter (mg/dL) or millimoles per liter (μmol/L or μM).

Normal levels of AAT concentration in the serum of healthy individuals are:
— when using an immunonephelometric method — 103–200 mg/dL (20–39 μM),
— when using rocket immunoelectrophoresis — 150–330 mg/dL.

AAT level < 100 mg/dL should be an indication for further qualitative tests.

Threshold (protective) concentration of AAT is 11 μmol/L, which corresponds to:
— 50 mg/dL for immunonephelometric method,
— 80 mg/dL for rocket immunoelectrophoresis.

5.3. Addresses of diagnostic laboratories

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