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INTRODUCING STANDARDS OF THE BEST MEDICAL PRACTICE FOR PATIENTS WITH INHERITED ALPHA-1-ANTITRYPSIN DEFICIENCY IN CENTRAL EASTERN EUROPE

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Abstract

The Leonardo da Vinci project "Introducing standards of the best medical practice for patients with inherited alpha-1-antitrypsin Deficiency in Central Eastern Europe" belongs to a sub-programme of the European Commission's Lifelong Learning Programme. It started in November 2011 and is conducted in cooperation with eight European partners. The project's main goal is to support development of a Central-Eastern European Network (CEE) for alpha-1-antitrypsin Deficiency (AATD) early diagnostics and treatment. Alpha-1-antitrypsin (AAT) is one of the major serine protease inhibitors in the human circulation, and is an acute phase protein produced predominantly by hepatocytes. Severe inherited AATD deficiency occurs in about 1 in 2.500 individuals; most commonly in those of European ancestry. AATD considerably increases the risk of liver disorder in infants, children and adults, while respiratory complications are observed mainly in adults. The average concentration of AAT in plasma in healthy individuals is 1.3 mg/ml. The concentration of AAT during acute phase processes rises 3- to 4-fold above normal. Alpha1-Antitrypsin deficiency (AATD) is a disorder inherited in an autosomal co-dominant fashion. The mutant Z AAT protein differs from the normal M variant by a single amino acid substitution (Glu 342 Lys). Severe ZZ AAT deficiency was first recognized as a hereditary condition predisposing to disease on the basis of 90% lower plasma levels of the protein arising not from the lack of AAT synthesis, but from a defect in its secretion. Most Caucasians of North European descent are homozygous for the normal M variant of AAT, but some carry the Z allele, which is associated with an increased risk of early-onset emphysema and liver disease. The great advantage and main focus of the project is to create a long-lasting European network of cooperation between medical institutions involved in AATD medical care. The network is a response to the needs of CEE countries and at the same time it will help them to participate in the broader frame of the European network of medical centres specializing in AATD.

Key words: rare diseases, alpha-1-antitrypsin Deficiency, Central-Eastern Europe, European Commission's Lifelong Learning Programme, clinical manifestation, diagnostics, networking.

The project "Introducing standards of the best medical practice for patients with inherited alpha-1-antitrypsin Deficiency in Central Eastern Europe" (Alfa-1-Qual) belongs to a group of

medical initiatives funded by the Leonardo da Vinci programme. It is a sub-programme of the European Commission's Lifelong Learning Programme which was established in 2007. It is concentrated on the teaching and training needs of European workers who can acquire new skills, knowledge and qualifications. Our project funded by the Leonardo da Vinci programme started in November 2011 and is conducted in a cooperation between eight European partners: Vilnius University Faculty of Medicine, Lithuania, The National Institute of Tuberculosis and Lung Diseases (project coordinator), Poland, Hannover Medical School, Germany, Marius Nasta Institute of Pneumophysiology, Romania, Leiden Univeristy Medical Centre h/o Academisch Ziekenhuis Leiden, the Netherlands, PJ Safarik Univeristy, Faculty of Medicine, Slovakia, Dr.Georgi Stranski UMHAT Pleven EAD, Bulgaria, Università degli Studi di Pavia, Italy. The project's main goal is to support the development of a Central Eastern European Network (CEE) for alpha-1-antitrypsin Deficiency (AATD) early diagnostics and treatment and to serve as a model of control of single rare disease in the CEE region.

Discovery of Alpha1-antitrypsin deficiency and its link to emphysema and liver cirrhosis

In 1952, C-B Laurell at Malmö University Hospital, Sweden, made outstanding contributions to protein research by introducing plasma protein electrophoresis as a tool for clinical investigations. Medical investigators in Malmö began to use this technique, and in 1961 clinicians in respiratory medicine introduced the use of plasma electrophoresis for all patients. C-B Laurell personally checked every electrophoretic result and, unexpectedly, noted the absence of the alpha1 band in two samples, both of which were from a hospital specialized in respiratory medicine [1, 2]. At this point C-B Laurell and his co-workers verified that the two sera had a very low AAT activity, and therefore the two patients had an apparent deficiency of AAT. Both suffered from severe respiratory insufficiency caused by emphysema.

This finding led to a retrospective analysis of hundreds of stored paper electrophoretic patterns in the laboratory archives of the Malmö and Lund hospitals. Investigators found several more AAT deficiency patterns, which had earlier been overlooked. C-B Laurell and Sten Eriksson evaluated these patients thoroughly including spirometry, chest X-ray and plasma samples. It then became evident, as published in 1963 by Laurell and Eriksson [3], that AAT deficiency is an inherited condition and relates to emphysema.

Since AAT is an acute phase protein produced mainly in the liver, investigators in Malmö expected to find abnormal liver function in AAT deficient patients. However, they were disappointed to find normal results for liver function tests in a number of cases. Eriksson wrote that in 1962 they had seen a patient with cryptogenic, decompensated cirrhosis who also lacked the AAT band in the electrophoresis strip. Unfortunately, the finding was misinterpreted in the belief that the patient had developed an acquired AAT deficiency secondary to a severely impaired liver function. The association between liver diseases and inherited AAT deficiency, therefore, was documentted for the first time not in Malmö, but in the USA by Sharp and colleagues, in 1969 [4].

Thus, the clinical importance of AAT was highlighted in individuals with inherited AAT deficiency who exhibit an increased susceptibility to developing chronic inflammatory conditions including chronic obstructive pulmonary disease, and liver diseases (Figure 1).

Figure 1 – Aschematic diagram depicting the role of polymers of alpha-1-antitrypsin in the development of liver and lung diseases (Alam et al. J Respir Cell Mol Biol, 2010)

Genetic variants of Alpha1-antitrypsin and diagnosis

Alpha1-Antitrypsin (AAT), also referred to as alpha$_1$-proteinase inhibitor or SERPINA1, is an acute phase protein mainly synthesised (70–80%) by the liver cells and secreted into the circulation. The average plasma concentration of AAT is normally about 1.3–1.7 mg/mL, with a half-life of 3 to 5 days. Caucasians of northern Europe and North America have the highest allele frequencies for AAT deficiency [5]. The alleles of AAT are inherited in an autosomal codominant manner (Figure 2), and the most common allele is M, its frequency being at least 0.87. The Pi-system was developed, based on the migration of the AAT variants in an electric field. The position of the migrated proteins is identified by a letter, where M is normal, while the positions of the slower-moving proteins are marked by letters before M in the alphabet and those of the faster-moving proteins are denoted by letters after M. At least 60 deficient mutations have been described [6]. They comprise single point mutations, truncated (nonsense, frameshift and splicing) mutations, deletions of single codons and larger deletions. Most of them are located in the four coding exons of the gene. The most common deficient variants are named Z (G/A, Glu342Lys, in exon V) and S (A/T, Glu264Val, in exon III) (Table 1).

Table 1

Main genetic variants of AAT

Variant	Mutation	Genotype	Plasma levels (mg/dL)	Allele frequency in European Caucasians	Effect of mutation
M		MM	150–350	93/100	Normal function and plasma levels
Z	Glu 342-Lys 342	MZ ZZ ZS	90–210 2.5–7 75–120	4.6 or 10/100 1/1600 1/750	Plasma levels lower; increased risk of developing disease
S	Val264-Glu264	MS SS SZ	80–136 100–140 75–120	5 or 10/100 1/1600 1/750	Plasma levels lower; associations with diseases increased or not clear
Null (Q0)	Various		≤ 2.5	Rare	No detectable AAT levels; increased risk of developing disease
Dysfunctional	Various		Variable	Rare	Reduced levels or lost function; increased risk of developing disease

When both parents are heterozygotes, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier (see Figure 2). In the rare instance in which one parent is homozygous (ZZ) and one parent is heterozygous, the risk to each sibling of being affected is 50%. Unless an individual with AATD has children with a reproductive partner who is affected or a carrier, his/her offspring will be obligate heterozygotes (carriers) for the disease-causing mutation.

The current approach to laboratory diagnosis of AAT deficiency uses a combination of serum AAT measurement and identification of the AAT phenotype by the isoelectric focussing (IEF) pattern. More recently, genotyping for S and Z variants is performed by PCR-RFLP (Polymerase Chain Reaction-restriction fragment length polymorphism) or melting probes. Sequencing is the final procedure carried out to determine the actual variant(s) when genotyping is unable to provide a complete identification of both AAT deficient alleles.

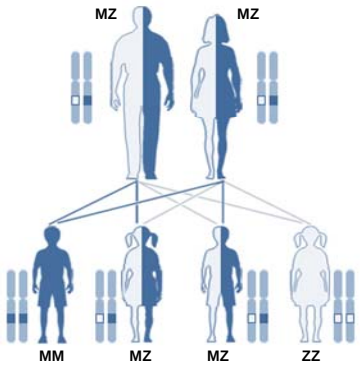

Figure 2 – Alpha-1-antitrypsin is inherited in an autosomal codominant pattern

Liver diseases with AAT deficiency

Histological examination of the liver of individuals who are homozygous (ZZ) or heterozygous (MZ or SZ) for the Z allele typically shows that the hepatocytes contain globules of an amorphous material which are resistant to diastase and positive for periodic-acid-Schiff (PAS), and immunologically stained for AAT [7]. Today it is well established that Z, but also Siiyama (Ser53Phe) and Mmalton (52Phe del) variants of AAT, form polymers and are retained as PAS-positive inclusion bodies in the liver. This accumulation of polymerized AAT within the endoplasmic reticulum (ER) of hepatocytes is thought to be associated with increased risk of ing liver diseases. Research from several laboratories has identified a possible role for the ER stress in Z AAT-induced heaptocyte injury, however, the causative role of ER stress in human liver diseases has yet to be proven [8, 9].

Specific symptoms of an AAT deficiency child can be such as abdominal (belly) swelling or pain that does not go away, bruising easily, dark urine, or light coloured stools. Moreover, there can be seen itching all over body, not gaining weight or growing as fast as other children of the same age; vomiting (throwing up) blood, or passing bloody or black stools, yellowing of the skin or the whites of the eyes.

In infants liver disease associated with ZZ AATD typically presents as neonatal cholestatic jaundice which often subsides spontaneously after a few months. However, the outcome in later childhood and adolescence varies a lot, ranging from normalization of liver test results to early cirrhosis requiring liver transplantation [10]. As a matter of fact, even in children with an apparently favourable outcome, a significant degree of liver fibrosis may be present [11]. Why only some Z subjects develop liver disease is not known, and currently no medical treatment is recommended for liver disease associated with AATD.

In the follow-up study of 44 children with AATD-associated liver disease initially manifest as cirrhosis or portal hypertension, outcomes ranged from liver transplantation in two, to relatively healthy lives up to 23 years after diagnosis in seven [12]. The overall risk to an individual with ZZ of developing severe liver disease in childhood is generally low (~2%); the risk is higher among siblings of a child with the ZZ type and liver disease. When liver abnormalities in the proband are mild and resolve, the risk of liver disease in siblings with the PI ZZ type is about 13%. When liver disease in the proband is severe, the risk of severe liver disease in siblings with the ZZ type may be about 40% [13].

Identification of pre-symptomatic biomarkers is, therefore, the prerequisite for further pathophysiological studies of the liver disease processes in ZZ AATD.

In a prospective screening study of 200,000 newborns in Sweden, between November 1972

and September 1974, 120 children were identified as being ZZ and 48 SZ AATD [14]. Out of these 168 children with AAT deficiency, 1 SZ and 5 ZZ children died in early childhood, 14 ZZ infants had prolonged obstructive jaundice, 9 had severe clinical and laboratory evidence of liver disease, 5 had only laboratory evidence of liver disease, and 8 had minimal abnormalities in serum bilirubin and hepatic enzyme activity and variable hepatosplenomegaly. 52% of ZZ and 24% of SZ infants gave abnormal results from the liver-function tests at 3 months. From this study the conclusion is that most of the PiZZ and PiSZ cases are associated with hepatic dysfunction during the first three months of life.

In this cohort the natural history of liver diseases and routine liver test abnormalities have been surveyed from infancy up to 40 years of age in AATD individuals identified. A subset of 14 patients presented with neonatal cholestasis, and 3 of them developed severe liver disease [14]. Other ZZ AATD individuals from adolescence onwards presented no clinical symptoms of liver disease, and less than 10% had marginally abnormal liver test results [15–17]. Unfortunately, from retrospective studies we know that up to 25% of those with ZZ AATD may suffer from liver cirrhosis and from liver cancer in late adulthood [18–20].

Respiratory disorders with AAT deficiency

The first signs and symptoms of lung disease caused by AAT deficiency usually appear between ages 20 and 50. The earliest symptoms can be shortness of breath following mild activity, wheezing, persistent cough, recurrent lung infections, persistent sputum (or phlegm) production. In addition, a history of suspected allergies and/or asthma, and sinus infections can be related to inherited AAT deficiency.

If a child has been diagnosed with AAT deficiency, it is important to protect him/her from exposure to environmental pollutants that can be inhaled, including pollen, dust, organic fumes, and second-hand tobacco smoke. These substances can irritate airways, and cause or worsen lung problems. Chemicals can also be absorbed through the skin and thus damage the liver.

This protection is necessary because environmental pollutants, specifically second-hand smoking, can destroy functional activities of AAT protein which is already at much lower concentrations in AAT deficiency subjects if compared to those with a normal genetic variant.

The statements above are clearly supported by the results from the study investigating the effects of second-hand tobacco smoke on children with reduced levels of AAT [21]. Random samples of school children (aged 9–11 yrs) (n = 3,526) were studied according to the International Study of Asthma and Allergies in Childhood (ISAAC) phase II protocol, including parental questionnaires, pulmonary function and allergy testing. Children with low levels of AAT showed significant, albeit small, decreements in baseline lung function. When exposed to second-hand tobacco smoke pronounced decrements of pulmonary function, particularly in measures of mid- to end-expiratory flow rates, were seen in these children as compared to exposed children with normal levels of AAT.

Thus parents of children with AAT deficiency should be advised to prevent their children from being exposed to environmental tobacco smoke and dissuade them from taking up smoking.

Whether AAT deficiency increases the risk of developing early childhood asthma is not clear. For example, in a random sample of children (aged 9–11 years; n = 5629) AAT genotypes MS or MZ, or low AAT plasma levels, were found not to be associated with an increased risk of developing asthma. However, asthmatics with low levels of AAT were particularly prone to develop airway hyperresponsiveness and reduced lung function [22].

In another study 1992 [23] ten children and adolescents (aged four to 21 years) with the ZZ AAT deficiency were investigated with regard to obstructive airway disease, and tests of lung function and allergy tests were performed. It was shown that bronchial asthma occurred in three out of ten patients and was no indication of emphysema in any of the nine patients. No statistically significant increased incidence of bronchial asthma was found among unselected ZZ-patients compared to the overall population.

However, in a study performed by Colp et al, 1993, a survey of 393 Puerto Rican and 354 non-Hispanic paediatric patients at Beth

Israel Hospital, New York, revealed a significantly larger percentage of asthmatic subjects among Puerto Ricans [24]. Next, AAT concentration and phenotypes in 61 Puerto Rican asthmatic children revealed a significantly larger number with a deficient S or Z variant of AAT. A family history of asthma was more common among asthmatic than control subjects and was most common for AAT deficiency AAT carriers in either asthmatic or control subjects.

The development of childhood asthma or other airways disorders may occur in separate cases with AAT deficiency. Whether asthma is more common or not among AAT deficiency subjects remains to be proven.

Other diseases associated with AAT deficiency

Although AAT deficiency is perhaps best known as a cause of early, severe, and rapidly progressive emphysema in adults, and liver cirrhosis in children and adults, multiple organ systems may be affected resulting in a broad spectrum of clinical disease such as hepatitis, haemorrhagic diathesis, Ehlers-Danlos-like syndrome, pancreatic disease, and panniculitis. Specifically, several case reports show an association between AAT deficiency and allergic dermatitis, eczema, panniculitis and other disease in childhood [25].

AAT deficiency was recently found to be associated with joint dislocation and scoliosis in Williams syndrome (WS). Elastin deficiency is the proximal cause for the connective tissue abnormalities in WS and elastase is the primary enzyme that causes elastin degradation. Low levels of AAT result in decreased elastase inhibition and therefore uncontrolled elastase may promote increased elastin degradation during inflammation.

Inguinal hernias are typically diagnosed in infancy in WS and occur in ~40% as compared with ~5% incidence in the general paediatric population [26]. Because decreased elastic fibres in the abdominal wall as a consequence of aging are associated with inguinal hernias in the general population, it was speculated that AAT deficiency might be associated with hernia occurrence in WS. Authors [27] examined a cohort of 205 individuals (age at the time of examination ranged from 9 months to 45 years) with WS for mutations in the AAT gene, and found that individuals with classic WS deletions and AAT genotypes MS or MZ were more likely than those with a normal MM genotype to have joint dislocation or scoliosis. However, carrier status for AAT deficiency was not correlated with the presence of inguinal hernia or with presence or severity. These findings suggest that genes important in elastin metabolism are candidates for variability in the connective tissue abnormalities in WS.

Conclusion

AAT deficiency is a genetic disease characterized by low levels and/or function of AAT protein. AAT deficiency can result in the development of COPD, liver disease, and certain skin conditions [28]. The disease can be diagnosed by demonstrating a low level of AAT protein and genotype screening for S and Z mutations, which are the most common. However, there are many genetic variants in A1AT deficiency, and this screening may miss rarer cases, such as those caused by dysfunctional protein but not the deficiency in protein levels. The wide variation in possible mutations, limitations in diagnostics, points to the importance of combining clinical suspicion with measurement of protein levels, phenotypic analysis, and in appropriate cases expanded genetic analysis. So far, the main facts suggesting when to suspect deficiency of AAT are:

- Asthma, chronic bronchitis, emphysema in a young individual (less than 45 years old).
- Emphysema in a non-smoker.
- Family history of emphysema and/or liver disease (unexplained cirrhosis or hepatoma).
- Clinical findings or history of unexplained chronic liver disease.
- Clinical findings or history of panniculitis.

The great advantage and main focus of the Alfa-1-Qual project is to create a long-lasting European network of cooperation between medical institutions involved in AATD medical care and strengthen efforts in favour of innovative pulmonology. The network is a response to the needs of CEE countries and at the same time it will help them to participate in the broader frame of the European network of medical centres specializing in AATD [29].

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Р е з и м е

ВОВЕДУВАЊЕ СТАНДАРДИ ЗА НАЈДОБРА МЕДИЦИНСКА ПРАКТИКА ЗА ПАЦИЕНТИ СО НАСЛЕДНА АЛФА-1-АНТИТРИПСИН ДЕФИЦИЕНЦИЈА ВО ЦЕНТРАЛНА И ВО ИСТОЧНА ЕВРОПА

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[5] Работна група за ретки болести на Европската академија за педијатрија, Брисел, Белгија

Проектот Леонардо да Винчи „Воведување најдобра медицинска практика за пациенти со наследна алфа-1-антитрипсин дефициенција во Централна и во Источна Европа“ припаѓа на потпрограмата на Доживотна програма за учење на Европската комисија. Тој започна во ноември 2011 година и се спроведува во кооперација со осум европски партнери. Главна цел на Програмата е да го поддржи развојот на Централноисточна европска мрежа (ЦИЕ) за алфа-1-антитрипсин дефициенција (ААТД), рана дијагностика и третман. Алфа-1-антитрипсин (ААТ) е еден од главните инхибитори на серинската протеиназа во човечката циркулација и е реактант на акутната фаза кој предоминантно се продуцира од хепатоцитите. Просечна концентрација на ААТ кај здрави лица е 1.3 мг/мл. Концентрацијата на ААТ во текот на акутната фаза расте 3–4 пати над нормалата. ААТД е заболување кое се наследува на автозомен кодоминантен начин. Мутантниот Z ААТ протеин се разликува од нормалната М-варијанта по поединечната аминокиселинска супституција (Glu 342 Lys). Прва тешка ZZ ААТ дефициенција е препознаена како хередитарна кондиција, која предиспонира за болеста врз база на 90% пониски плазма-вредности на протеинот што не произлегуваат од недостатокот во синтезата на протеинот, туку поради дефицитот во неговата секреција. Повеќето припадници на кавкаските и на северноевропските народи се хомозиготи за нормална ММ-варијанта на ААТ, но некои го носат Z-алелот, кој е асоциран со наголемен ризик за ран почеток на емфизем и хепатална болест. Голем напредок и главен фокус на проектот е да се креира долготрајна Европска мрежа за кооперација помеѓу медицинските институции инволвирани во грижата за ААТД и да се засилат напорите во однос на иновативната пулмонологија. Мрежата е одговор на потребите на ЦИЕ-земјите и истовремено ќе им овозможи да партиципираат во поширокаата рамка на медицински центри специјализирани за ААТД.

Клучни зборови: ретки болести, Алфа-1-антитрипсин дефициенција, Централноисточна Европа, Програма на Европската комисија за долготрајно учење, клинички манифестации, вмрежување.