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Introduction

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AATD is an inherited condition that primarily affects the lung and liver. This *ERS Monograph* provides a comprehensive guide to AATD, ranging from basic biology, diagnostics and clinical presentation to reports from affected patients. http://bit.ly/2OeVD6H

AAT is the most abundant serum antiprotease [1]. It is produced predominantly by liver hepatocytes that release it into the bloodstream and subsequently into other body compartments, where it exerts its function. The AAT gene has a number of mutations and as a consequence, one in 10 Caucasians carries an AAT variant giving rise to AATD [2]. To date, >120 AAT variants have been described and among them, Pi*Z is the most clinically relevant. Consequently, a homozygous carriage of the Pi*Z variant (Pi*ZZ genotype) is the characteristic cause of severe AATD. As Pi*Z mutation leads to the retention of AAT in hepatocytes, it is characterised by strongly diminished serum AAT levels [3, 4]. While severe AATD is a rare condition (with a frequency of 1:3000 in Caucasians), some AATD genotypes are more common, have modest reduction serum AAT levels and/or even AAT levels within a normal range [2, 3].

The resulting imbalance of antiprotease activity predisposes AATD individuals to proteolytic tissue damage and thereby to premature emphysema and COPD [5, 6]. In contrast, the accumulation of misfolded/polymerised AAT may lead to neonatal hepatitis and/or development of chronic liver disease, liver cirrhosis and HCC in adults [4, 7, 8]. While lung and the liver disease constitute the major causes of mortality in AATD, AAT is also a potent immunomodulatory protein and because of that, AATD subjects are predisposed to immune disorders such as panniculitis and granulomatous vasculitis [9].

More than 50 years after its initial description and despite the fact that it is fairly common, AATD remains a highly challenging condition. Although severe AATD can be easily recognised due to a five-fold reduction in serum AAT levels, only 10–15% of individuals are detected and it often takes many years and several physicians before the correct diagnosis is established [10]. To make things more difficult, many patients report symptoms that overlap with common respiratory diseases, such as asthma and bronchitis [6]. While the

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efficacy of AAT augmentation therapy in patients with a rapid decline in lung function has been supported by several randomised clinical trials, it is not reimbursed in many countries and an uncertainty prevails as to which AATD patient needs treatment and when the treatment should start [11]. The multiplicity of genotypes and the variable clinical presentation makes the counselling of AATD individuals challenging [12] and may result in both under- and overtreatment. Compared to lung involvement, liver affection has been studied even less and the burden of liver disease in AATD is only recently being appreciated [7, 8]. On the bright side, strong multinational registries have emerged and are likely to become particularly useful in uncovering the relevance of rare AATD genotypes as well as rare disease manifestations [13].

While liver transplantation still constitutes the only curative treatment option in end-stage liver disease related to AATD, multiple clinical studies are underway and use either RNA silencing or small molecules to counteract proteotoxic liver injury [8]. Moreover, the usefulness of AAT as an immunomodulatory protein is receiving more and more attention, and AAT augmentation therapy shows promise in the treatment of various immune-mediated disorders such as graft-*versus*-host disease [14].

Whether associated with severe deficiency alleles as a homozygous or heterozygous combination, AATD can be viewed both as a frequent condition and a rare disease. As a result, physicians of multiple disciplines, who systematically test for the presence of AATD, are confronted with many different genotypes as well as a highly variable clinical presentation. In addition, patients are often waiting for a correct diagnosis and are in need of evidence-based counselling explaining both the typical disease manifestations and the disease course [10, 12]. The knowledge and the standards of treatment also vary substantially between countries. With all this in mind, the goal of this *Monograph* is to provide a comprehensive and up-to-date overview, that covers most aspects of AATD. We have tailored the information to the physician taking care of lung and liver patients in daily practice, but have also included useful information for general practitioners who are responsible for the medical guidance of these patients. The book covers basic biology [1, 4, 5], genetics [2, 12], laboratory diagnostics [3] and the major organ manifestations. It describes the clinical presentation of AATD in both adults and children [6–9, 11], and includes chapters on genetic counselling, patient views and future therapies [10, 12, 14].

The authors of the individual chapters have produced a practice-guideline publication that comprises information on scientific background as well as application at the patient's bedside. We would like to thank all authors for their hard work and involvement in the writing of this publication. We hope that this book will raise awareness about this underdiagnosed condition and improve the everyday life of individuals with AATD.

References

1. Lomas DA, Irving JA, Gooptu B. Serpinopathies. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 6–26.
2. Hobbs BD, Silverman EK, Cho MH. Genetics and epidemiology. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 27–38.
3. Ferrarotti I, Ottaviani S. Laboratory diagnosis. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 39–51.
4. Piccolo P, Attanasio S, Brunetti-Pierri N. Mechanisms of liver disease. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 93–104.

 https://doi.org/10.1183/2312508X.10026219

5. Saltini C, Krotova K. Mechanisms of lung disease. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 52–63.
6. Barrecheguren M, Bals R, Miravittles M. Clinical approach to diagnosis and assessment. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 64–77.
7. Teckman JH, Patel D. Clinical approach to paediatric liver disease. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 105–113.
8. Strnad P, Schneider CV, Clark V. Clinical approach to liver disease in adults. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 114–126.
9. Franciosi AN, Carroll TP, McElvaney NG. Rare manifestations. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 127–142.
10. Wilkens M, Hannah T. Patient view. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 1–5.
11. Ellis P, Dirksen A, Turner AM. Treatment of lung disease. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 78–92.
12. Chorostowska-Wynimko J, Jezela-Stanek A. Genetic counselling. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 143–149.
13. Schouten IGM, Stolk J, Fuge J, *et al.* Registries: roles, objectives and registry data study outcomes. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 150–158.
14. Janciauskiene S, Welte T. Future directions: diagnostic approaches and therapy with AAT. *In*: Strnad P, Brantly ML, Bals R, eds. α_1-Antitrypsin Deficiency (ERS Monograph). Sheffield, European Respiratory Society, 2019; pp. 159–178.

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