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α_1 -Antitrypsin deficiency

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J K Stoller

A new series focusing on this important and under-recognised illness

Alpha₁-antitrypsin (AAT) deficiency is a common but under-recognised clinical entity.^{1–3} The editors of *Thorax* have therefore commissioned a series of papers by internationally recognised experts on the key clinical and investigative concepts in this important disease, which will offer the reader an up to date summary of AAT deficiency. Topics to be addressed include:

- the epidemiology of AAT deficiency;
- genetic aspects of AAT deficiency: phenotypes and genetic modifiers of emphysema;
- clinical manifestations and natural history of AAT deficiency;
- molecular pathophysiology of AAT deficiency;
- pathogenesis of lung disease in AAT deficiency;
- intravenous augmentation therapy for AAT deficiency: current understanding;
- new and emerging therapies for AAT deficiency; and
- CT imaging in AAT deficiency.

Why this attention to AAT deficiency now? As mentioned above, despite the fact that it affects up to one in 1600 newborn infants,² AAT deficiency is both under-recognised and “under-understood”.³ As evidence of this under-recognition, in a survey of 300 PI*ZZ individuals the mean interval between the appearance of the first

attributable symptom (almost invariably dyspnoea due to fixed airflow obstruction) and the diagnosis of AAT deficiency in a group of mean age 49 years was 7.2 years.³ Furthermore, 44% of the respondents reported seeing at least three physicians before the diagnosis of AAT deficiency was made. In the United States, of the expected 80 000–100 000 with severe AAT deficiency (PI*ZZ), fewer than 10% have been clinically recognised.⁴

Since establishing the diagnosis is both easy (a simple blood test for a serum level and, if low, a phenotype to secure the diagnosis) and relatively inexpensive (less than \$US200 for a serum level or a phenotype in most commercial laboratories and widespread availability of free testing services), there are ample opportunities to increase recognition of the condition by enhancing clinicians’ diagnostic suspicion of AAT deficiency.

What clinical features should clinicians look for? As discussed in this series⁵ and in a recently published evidence-based standards document on the diagnosis and management of individuals with AAT deficiency,⁶ AAT deficiency should be suspected in patients with fixed airflow obstruction (especially in the absence of cigarette smoking or predisposing occupational exposures), in individuals whose family history suggests emphysema and/or liver disease, and in those with suggestive clinical characteristics—for example, basilar hyperlucency on the chest

radiograph, bronchiectasis that is otherwise unexplained, panniculitis, or cirrhosis for which a known aetiology such as viral hepatitis, haemochromatosis, or Wilson’s disease is not evident.

Why make the diagnosis of AAT deficiency? As with all diseases, the impetus to diagnose is the desire to ameliorate the adverse effects of the illness, to prolong life, to improve the quality of life of affected individuals and, in the case of a genetic disease like AAT deficiency, to counsel at risk family members in order to encourage health attentive behaviour and treatment that will lessen the likelihood of disease and/or forestall its progression. Indeed, it is important to establish the diagnosis of AAT deficiency as a number of interventions are available that can produce a beneficial outcome.^{7–11} For example, population screening studies suggest that individuals identified as having PI*ZZ AAT deficiency at birth are less likely to start smoking or to continue smoking than age matched adolescent peers.^{12–13} Furthermore, although no definitive randomised clinical trial has established the clinical efficacy of augmentation therapy¹⁴—currently the intravenous infusion of purified pooled human plasma α_1 -antitrypsin—the results of many observational studies strongly suggest its clinical efficacy.^{9–10–15} Indeed, a recent standards document from the Canadian Thoracic Society¹⁶ and the aforementioned evidence-based standards document which is supported and endorsed by the European Respiratory Society, the American Thoracic Society, the American College of Chest Physicians, the American Respiratory Care Foundation, and the Alpha-1 Foundation⁶ both conclude that augmentation therapy has clinical efficacy.¹⁷ As reviewed in this series of articles, new and emerging therapies offer the prospect of even more effective treatments that can be made available to individuals known to have severe AAT deficiency.¹⁸

It is hoped that this comprehensive review will enhance the recognition of

individuals with AAT deficiency by clinicians and foster optimal medical management.

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