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THEMATIC SERIES ''ALPHA-1 ANTITRYPSIN DEFICIENCY'' - ARTICLE IN ENGLISH AND FRENCH
Coordinated by J.-F. Mornex and A. Cuvelier

Diagnosis of alpha-1 antitrypsin deficiency: Modalities, indications and diagnosis strategy

Diagnostic du déficit en alpha-1 antitrypsine : les moyens, les indications et la stratégie diagnostique

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KEYWORDS
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PI phenotype;
Genotyping;
Decision tree

Summary Alpha-1 antitrypsin (α_1-AT) deficiency is an autosomal recessive genetic disorder, which predisposes affected patients to development of pulmonary emphysema or liver cirrhosis. Despite the guidelines from the American Thoracic Society and the European Respiratory Society about α_1-AT deficiency screening, it remains significantly under recognized. So, it seems necessary to propose an efficient and suitable biological approach to improve diagnosis and management of α_1-AT deficiency. α_1-AT is a 52 kDa glycoprotein predominantly produced in the liver and its physiological serum concentration for adults ranges from 0.9 to 2.0 g/L (17—39 μmol/L). It is encoded by the *SERPINA1* gene, which is highly pleomorphic, and to date, more than 100 alleles have been identified. α_1-AT testing would initially involve

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quantification of serum α_1-AT concentration with possible complementary measurement of the elastase inhibitory capacity of serum. If the serum α_1-AT concentration is reduced below the reference value, two strategies for laboratory testing can be used: (i) serum α_1-AT phenotyping by isoelectric focusing which allows identification of the most common variant designated as the PI M variant but also of various deficient variants besides the predominant PI S and PI Z ones; (ii) genotyping by allele-specific PCR methods which allows only identification of the deficient PI S and PI Z alleles. Identification of the null alleles or of other rare deficient alleles can be performed by direct sequencing of the whole *SERPINA1* gene as a reflex test.

MOTS CLÉS
Déficit en alpha-1 antitrypsine ;
SERPINA1 ;
Phénotype PI ;
Génotypage ;
Arbre de décision

Résumé Le déficit en alpha-1 antitrypsine (α_1-AT) est une maladie génétique autosomique récessive dont les manifestations cliniques majeures sont principalement l'emphysème pulmonaire et la cirrhose hépatique. Malgré les recommandations de l'American Thoracic Society et de l'European Respiratory Society, le déficit en α_1-AT reste encore sous-diagnostiqué. Enrayer ce sous-diagnostic passe par la mise en place d'une démarche diagnostique adaptée et efficace. L'α_1-AT, glycoprotéine de masse moléculaire 52 kDa, de synthèse essentiellement hépatique, est présente dans le plasma humain à une concentration de 0,9 à 2 g/L (17 à 39 µmol/L). Il existe, pour cette antiprotéase, un polymorphisme génétique important : plus de 100 allèles sont caractérisés à ce jour. L'exploration des déficits en α_1-AT fait appel, en première intention, au dosage pondéral de l'α_1-AT circulante, éventuellement complété par la mesure de l'activité antiélastasique sérique. Si un déficit pondéral ou fonctionnel est détecté, deux démarches complémentaires peuvent être envisagées : la détermination du phénotype d'α_1-AT par isoélectrofocalisation qui permet d'identifier les variants normaux PI M mais aussi un certain nombre de variants déficitaires, dont les plus fréquents, PI S et PI Z, ou le génotypage par PCR allèle-spécifique qui permet de caractériser les allèles déficitaires PI S et PI Z. Le recours au séquençage complet des exons codants du gène *SERPINA1* se justifie pour l'identification précise des allèles déficitaires rares et des allèles qualifiés de *null*.

English version

Introduction

Alpha-1 antitrypsin (α_1-AT) deficiency is an autosomal recessive genetic disorder, which predisposes patients to develop progressive and irreversible pulmonary emphysema or liver cirrhosis [1,2]. α_1-AT deficiency is one of the most common hereditary diseases with a frequency as high as that of cystic fibrosis [3]. However, the diagnosis is often delayed [4—6].

α_1-AT belongs to the serine protease inhibitor serpin superfamily, which plays a major role in the regulation of physiological processes such as inflammation and coagulation [7]. Serpins share a high polypeptide sequence homology and a three-dimensional architecture with 3 ß sheets with folding motif and 9 α helices [1]. All serpins have an active site, which constitutes a mobile reactive loop. Their structural integrity is necessary for their functional activity and any conformational change may impair it. Thus, congenital α_1-AT deficiency is considered a conformational disease associated with an impaired α_1-AT folding [8].

Alpha-1 antitrypsin

Physiological role

In humans, α_1-AT is the main circulating protease inhibitor, protecting the lung parenchyma against more than 90% of proteolytic attacks. It plays also a role in the inflammatory response by positively regulating the acute phase of inflammation. Its anti-inflammatory activity relies on its leukocyte anti-elastase and anti-proteinase 3 activity but also on the regulation of the expression of pro-inflammatory cytokines, including interleukin 6 (IL6), interleukin 8 (IL8) and tumour necrosis factor alpha (TNFα) [9,10]. Finally, it also controls apoptosis [11] and inhibits angiogenesis and tumour growth [12].

Structural features

α_1-AT is a 52 kDa glycoprotein circulating in the human plasma at concentrations ranging between 0.9 and 2 g/L. It is mainly produced by the liver but also by alveolar macrophages and bronchial and intestinal epithelial cells. It has a half-life of 4—5 days. Because of its relatively small size, this antiprotease can easily diffuse through tissues.

The mature form consists of a single 394-amino acid polypeptide chain containing 10—15% of sugars organized into three lateral N-glycan chains. The glycosylation is heterogeneous and leads to eight circulating isoglycoforms of which five are predominant and can be identified by isoelectric focusing (IEF).

SERPINA1 gene and genetic variability

The 12.2 Kb α_1-AT gene (*SERPINA1*) is located on the long arm of chromosome 14 (14q31-32.3; OMIM# 107400.NM_000295

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