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EDITORIAL - ARTICLE IN ENGLISH AND FRENCH

Inherited alpha1-antitrypsin deficiency: Is the level the key message?

Déficit en alpha-1 antitrypsine : le taux est-il le message essentiel ?

English version

Fifty-one years ago, two scientists from the Malmö University, Carl Bertil Laurell and Sten Eriksson, first reported five individuals affected by inherited alpha1-antitrypsin (α_1-AT) deficiency [1]. Of particular interest, this original nucleus of described patients, already included the spectrum of clinical phenotypic variability associated with this genetic disorder: absence of any respiratory disease, juvenile or late pulmonary emphysema, disseminated bronchiectasis. Since then, knowledge on the related epidemiology, pathophysiology, pathogenesis, clinical course, and treatment has dramatically improved, as evidenced by the authoritative published review articles [2,3]. Still, there are a number of open questions awaiting on answer. In particular, we currently have relatively solid information on the worldwide epidemiology of α_1-AT; this information has led to the consensus that α_1-AT is likely the most common rare respiratory disorder [4]. Nevertheless, the diagnostic rate for α_1-AT is still dramatically low, with no more than 5—10% of expected individuals actually being recognized. This is true in all developed countries, irrespective of the local prevalence of the disorder and the quality of the diagnostic programs in place. Therefore, it has never been more evident that ''... inherited α_1-AT is not a rare condition, but a condition rarely diagnosed'' [5].

We are thus heartened by the fact that the opening article in a thematic series of the *Revue de Maladies Respiratoires* was devoted to the laboratory diagnosis for inherited α_1-AT deficiency. In this paper, Balduyck et al. provide an exhaustive review of the methodologies used to perform a complete diagnosis of inherited α_1-AT deficiency [6]. In fact, we are convinced that the first step in improving knowledge of inherited α_1-AT deficiency epidemiology is that a good diagnostic program, of any design [7], must contain a complete and exhaustive laboratory diagnosis flow chart. In our opinion, it is relevant that the individual/patient is provided with a complete diagnosis, especially if he/she is submitted to genetic testing for inherited α_1-AT deficiency. We are obliged to diagnose and disclose also a carriage of any deficiency allele, such as PI*MZ. According to this framework, we disagree with the diagnostic programs that disregard submitted samples if the level of α_1-AT is not in the severe deficiency zone (below 0.49 g/L or 11 μM) [8]. In fact, diagnosis of a carriage status is an obligation for genetic testing, and plays a relevant role in genetic counseling. In addition, when genetic testing is performed in a young and asymptomatic cigarette smoker, one positive result is the additional information in the hands of the physician to convince the patient to permanently quit smoking [9]. We therefore suggest applying a diagnostic flow chart, such as the one described in figure 2 of the paper by Dr Balduyck [6]. One should fix a confident blood level of α_1-AT, as in our experience is 1.13 g/L [10], and simultaneously checks the possible presence of systemic inflammatory status, by C-reactive protein measurement, thus further elevating the upper limit of detection [11].

Undoubtedly, the application of the dried blood spot (DBS) matrix to inherited α_1-AT deficiency has facilitated some aspects of the diagnostic procedure, especially shipping and handling, thus contributing to its diffusion and popularity. However, from a technical point of view, while

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DNA-based assays have shown great robustness, protein-based assays, such as quantitative dosage and isoelectric focusing (IEF), have presented a number of problems related to reproducibility. These are linked to the extremely low protein concentration in the artificially reconstituted DBS fluid [10,12]. This aspect coupled with the fact that some equipment for nephelometry determination of α_1-AT dosage are more complicated to use than others; in other words, the management software is quite rigid and not adaptable to changing conditions required by the DBS fluid. For the above reasons, in some instances, the linearity of the relationship in α_1-AT dosage between serum/plasma and DBS is not perfect. As far as IEF is concerned, it was well known that this method, usually referred to as ''phenotyping'', and considered for many decades the diagnostic gold standard for inherited α_1-AT deficiency [13], has progressively been replaced by rapid genotyping for Z and S alleles, and used as a reflex assay in many diagnostic flow charts [14]. It lost popularity due to its lack of standardization, labour-intensity, and the great skill required for the interpretation of the bands. In addition, these peculiarities precluded the application of IEF to DBS specimens in the majority of diagnostic centers. However, as pointed out in Dr Balduyck's paper, the availability of semi-automated equipment may currently lead to the application of IEF with DBS. We also confirm that, in our hands, the resolution of the bands obtained from DBS filter papers are very similar to those obtained from serum. As evidenced in the literature, there is a general consensus on the main steps of the inherited α_1-AT deficiency laboratory diagnostic flow chart, however, slight differences exist among specialized centers [14]. Diagnostic flow charts should be considered as flexible documents, ready to be updated as the technology progresses. According to this view, it is possible that IEF could be considered in the near future as more convenient than rapid genotyping, especially for mass screening.

The starting point for evaluating risk in inherited α_1-AT deficiency is the level of the serum/plasma inhibitor, with the few exceptions of the rare variants in which the risk for liver disease is provided by the genetic characterization [15]. It is now widely accepted that the risk for lung disease, i.e. the risk for developing COPD, is inversely related to the plasma level of α_1-AT [16]. According to this theory, several lines of evidence suggest that the relative risk for COPD is higher in PI*SZ individuals than in PI*MZ ones, and that in turn, risk is higher in PI*ZZ than in PI*SZ, as the PI*NullNull genotypes are those at highest risk among subjects affected by inherited α_1-AT deficiency. Some studies also suggest that the same phenotypic expression could be found in the severity of lung function impairment [17]. Accordingly, one statement made in the Balduyck paper is questionable. In our opinion, during the initial phases of replacement therapy, when checking of the trough plasma level (i.e., the levels of α_1-AT obtained at nadir, just prior to the weekly infusion), it is useful to determine when the steady-state levels are reached (usually 4—8 infusions are required). This value may help in decision making; for example, whether it is advisable to increase the weekly dosage of α_1-AT, when a protective level is not reached. In particular, the baseline levels in PI*NullNull individuals are clearly much lower than those of PI*SZ individuals requiring replacement therapy. In addition, it has been postulated that the level of α_1-AT obtained by replacement therapy could be somewhat related to the long-term clinical efficacy obtained. The recently launched SPARK trial, aimed at comparing two different doses of α_1-AT for replacement therapy, is evaluating this theory [18].

An important question raised by Dr Balduyck is whether or not it would be useful to add a functional assay, such as the anti-neutrophil elastase activity, in the diagnostic flow chart for inherited α_1-AT deficiency. Among the 150 and more α_1-AT variants so far identified, only a few are categorized as dysfunctional: two variants (Z and $M_{\text{mineral springs}}$) showed reduced neutrophil elastase capacity coupled with a reduced plasma level, one (Pittsburgh) showed a total loss of anti-neutrophil elastase activity, replaced by an anti-thrombin activity, the only known variant with normal plasma levels of α_1-AT and reduced anti-neutrophil elastase activity is the F variant [19]. This leads to an important and so far overlooked question: how many patients with juvenile emphysema and normal plasma levels of α_1-AT are actually a carrier of a dysfunctional α_1-AT variant? Besides known mutations, complete exon sequencing of *SERPINA1* (the gene encoding α_1-AT) has resulted in the detection of 15 additional variants previously unreported, whose impact on anti-neutrophil elastase activity is unknown [20], not to mention all the possible intronic, epigenetic, and post-translational protein modifications. Therefore, the inclusion of a functional assessment for α_1-AT in the diagnostic flow chart would be very useful. There is also a need for an unambiguous, standardized, reproducible, simple to use and semi-automated method. This would represent, if cost-effective, an important step forward in the laboratory diagnosis of α_1-AT deficiency/dysfunction.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Version française

Il y a 51 ans, deux scientifiques de l'Université de Malmö, Carl Bertil Laurell et Sten Eriksson, ont été les premiers à rapporter les observations de cinq individus atteints de déficit en alpha-1 antitrypsine (α_1-AT) [1]. Il est intéressant de noter que la description initiale de ces premiers patients faisait déjà état d'une variabilité de l'expression clinique de cette anomalie génétique : absence de toute atteinte respiratoire, emphysème pulmonaire juvénile ou tardif, bronchiectasies diffuses. Depuis lors, les connaissances sur l'épidémiologie, la physiopathologie, la pathogénie, l'évolution clinique et le traitement du déficit en α_1-AT se sont considérablement améliorées comme en témoignent les revues publiées faisant autorité sur le sujet [2,3]. Pourtant, un certain nombre de questions sur ce thème restent encore sans réponse. Par exemple, nous disposons actuellement de données relativement solides à propos de l'épidémiologie du déficit en α_1-AT dans le monde ; ces informations ont conduit à l'idée désormais acceptée par tous que le déficit en α_1-AT est probablement la pathologie respiratoire rare « la plus fréquente » [4]. Toutefois, l'efficacité du dépistage du déficit en α_1-AT demeure extrêmement faible avec, au