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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Conceptual Paper

Alpha-1-Antitrypsin Deficiency: Need for a New Approach to its Diagnosis

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Received: February 28, 2019; **Published:** March 21, 2019

Our first approach to Alpha-1-antitrypsin deficiency (A1ATD) dates back to the late seventies when one of us (GF) was a postgraduate student in the Department of Pathology of the Catholic University of Rome. Vittorio Tisòn, a prestigious Italian pathologist from the University of Bologna, gave a lecture on "rare liver diseases", focusing his speech on A1ATD. Tisòn showed us his ability of performing a so complex and, in those times, fascinating diagnosis of A1ATD by recognizing the storage of A1AT in the typical PAS-positive diastase-resistant globules that characterize A1ATD-associated liver disease. Previously, our professor of Pediatrics in the Faculty of Medicine of the University of Cagliari, Antonio Cao, had told us that A1ATD was not present in the Sardinian population, probably due to a peculiar ethnic origin of Sardinians who are different from Caucasians both in physiology and in Pathology [1]. The intriguing lecture of Prof. Tisòn induced the authors to look for globules in liver biopsies and, eventually, the globules were found. But the way for diagnosing A1ATD was going to become much more complex and tortuous than expected, as indicated by Antonio Cao. A serum sample of the patient was immediately sent to the Catholic University of Rome for performing immunoelectrofocusing (IEF), the choice laboratory method for diagnosing the disease. IEF allows a differentiation of the normal (PiMM) and the most frequent pathological variants (PiZZ and PiSS), thanks to its ability to evidence the different electrophoretic speed of the three variants. The answer was sharp: normal phenotype. This result excluded our diagnosis based on the typical hepatic globules (diagnosis in the meantime confirmed by Vittorio Tison) and left us in trouble to define the entity we were dealing with [2]. After a clinico-pathological discussion with the clinician who had performed the liver biopsy, he concluded for a wrong diagnosis performed by a young pathologist (GF), fascinated by the possibility of performing a brilliant diagnosis of a rare disease instead of considering more probable less rare etiologies. The following ten years were really hard for our group involved in the search for A1ATD. The answer of IEF was always PiMM, even in cases with low A1AT serum levels and in patients with PAS-positive globules in the liver biopsy. In the early nineties, we found a tremendous number of liver globules in then liver biopsy of a woman and, even in this case, IEF evidenced a PiMM phenotype excluding the diagnosis of A1ATD. Disappointed by this result, eventually we sent the DNA of the patient to a Centre for the diagnosis of genetic diseases in Genova. The entire gene of A1AT was sequenced (in those times, several days were requested for sequencing each exon) and eventually the Sardinian paradox (frequent disease but under-diagnosed) of A1AT was explained. Whereas the fifth exon, where the mutation of the Z variant is present, was normal, a TTC deletion was detected in the second exon. The molecular analysis allowed the diagnosis of a new A1AT variant, that we called M-Cagliari, from the town of origin of the patient [3]. This variant of A1AT is now included in the list of M-like variants, which share the same phenotype at IEF with the normal PiMM variant, but are associated with lung and/or liver disease. For these reasons a specific molecular test for this variant was designed [4]. Subsequently, it was found that the M-Cagliari variant is characterized by the same mutation of a previously described M-like variant, the M-Malton [5].

A first consideration emerges from this peculiar Sardinian story of A1ATD: IEF, that is generally considered the gold standard method for the diagnosis of this genetic disease, is a very useful tool for the diagnosis of the Z and the S variants, but it is not appropriate for the

diagnosis of the so called rare M-like pathological variants. Our personal experience suggests that caution should be taken in considering a "normal" phenotype at IEF as an excluding test of the diagnosis of A1AT deficiency, when referred to a patient in whom clinical, (emphysema) laboratory (low A1AT serum levels) or liver (hepatocytic globules) are highly suggestive for this diagnosis. Coming back to the Sardinian population, all the patients of Sardinian origin diagnosed to carry A1ATD during the last twenty years, showed a M-like phenotype. The absence (or extreme rarity) of the Z variant in our island, makes IEF not useful for diagnosing A1ATD, and lays stress on the possibility that, even in other populations, A1ATD might be under-diagnosed, when only or mainly based on IEF.

According with our experience, another factor that should be considered with caution, before excluding the diagnosis of A1ATD, is represented by the interpretation of the serum levels of A1AT. Given that the two alleles of the alpha-1-antitrypsin gene are co-dominant, in heterozygous PiM/M-Cagliari subjects carrying an inflammation, serum levels ofA1AT may reach normal values. As a consequence, when high sensitivity - PCR values are in the normal range (< 1 mg/dL) the cut off for A1AT serum levels should be maintained at 100 mg/dL, but in patients in which high sensitivity - PCR levels are > 1 mg/dL, the cut off for A1AT should be elevated to 110 mg/dL. From a practical point of view, the diagnosis of A1AT deficiency should not be excluded even in the presence of serum A1AT levels within the normal range.

All these data taken together, we suggest to go back to the initial story of A1ATD, when Sten Eriksson first described the disease, mainly based on the correlation between clinical data and the electrophoretic pattern of serum proteins, characterized by the marked decrease of the alpha-1 component. In our experience, the electrophoretic values below 1,5 g/l of alpha-1 globulins represent the cut off for considering a patient for genetic analyses for A1ATdeficiency.

In conclusion, our experience regarding A1ATD confirms the previously reported complexity of this systemic disease, and lays stress on the multiple possible mistakes that every medical doctor facing with this disease may encounter in his/her clinical practice. Operating with caution, avoiding to be halted in the diagnostic process by one laboratory test, might transform A1AT from a rarely diagnosed disease [6] to a relatively frequent disease [7].

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Volume 8 Issue 4 April 2019