

Alpha-1-antitripsin deficiency: the need of a new diagnostic algorithm for improving the diagnostic ability of perinatologists and pediatricians

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*“(...) there is nothing either good or bad
but thinking makes it so.
To me it is a prison.”
William Shakespeare, Hamlet, II, 2*

Keywords

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The beginning of my approach to the diagnosis of alpha-1-antitrypsin (A1AT) deficiency goes back to about forty years ago, when my professor of Pediatrics at the Faculty of Medicine at the University of Cagliari, Antonio Cao, told me as a student that A1AT deficiency was not present in the population of Sardinia, the Italian island where I was born. In those years, the diagnosis of the disease was mainly based on immunoelectrofocusing (IEF), an analytical method able to evaluate the normal (PiMM) or the pathological (PiZZ and PiSS) phenotypes, the most frequent deficient variants, allowing a “certain” diagnosis of A1AT deficiency. My professor had seen, during his clinical experience, some children affected by liver and/or pulmonary disease of unknown origin in which A1AT deficiency was considered in the differential diagnosis but, in all cases, IEF had excluded this diagnosis, showing a “normal” PiMM phenotype. Some years later, during my postgraduate course in Pathology at the Catholic University of Rome, I attended a seminar held by Vittorio Tison, then the best Italian pathologist dedicated to the diagnosis of liver diseases. This seminar left a permanent sign. Thanks to the exceptional teaching ability of Tison, I learned how to diagnose A1AT overload in liver biopsies, by the detection of the typical PAS-positive diastase-resistant globules, the diagnostic marker of this congenital metabolic disease. Coming back to my Lab, few months later I was able to diagnose the first case of chronic hepatitis with A1AT overload, by detecting the typical globules inside the cytoplasm of the hepatocytes in a liver biopsy. Unfortunately, even in this case, IEF performed by the Italian reference center for the diagnosis of A1AT deficiency did not allow the diagnosis of the disease, due to the “normal” phenotype observed. There followed a strong debate on this rare diagnosis between the young pathologist (myself) and the experienced hepatologist who performed the liver biopsy and, more in general, on the possibility of a “peculiar” presentation of A1AT deficiency in our Sardinian population. Eventually, the conclusions of the clinician were in favor of a wrong diagnosis by a young pathologist (myself), who was following improbable hypotheses of rare diseases instead of considering more probable and less rare etiologic factors of liver diseases, including alcohol [1].

The following years were frustrating, regarding the ability of my group to reach the diagnosis of the disease. I decided to perform IEF myself, but we didn't find any carrier of the pathological

“Z” A1AT variant, even in cases with low serum values of the glycoprotein. The finding of multiple and large PAS-positive globules in a liver biopsy from a woman affected by a chronic liver disease of unknown origin, one more time contrasting with the “normal” PiMM phenotype detected in our Lab at IEF, forced us to ask the cooperation of a center of Genetics in order to characterize the A1AT of our patient at gene level. The results were striking: the fifth exon, carrying the mutation site of the Z variant, was normal in our Sardinian patient, whereas a TTC deletion in position 53 was found in the second exon. On the basis of these results, our new variant was included among the pathological “M-like” A1AT variants, thanks to its phenotype similar to the normal PiMM variant, and it was defined M-Cagliari, from the town of origin of the patient in whom it was diagnosed [2]. Later on, it was found that our variant shared the same mutation with another rare M-like variant, previously defined M-Malton [3]. The intriguing aspects concerning the genetic and phenotypic aspects of our Sardinian variant induced us to abandon completely IEF, given its inability to differentiate the M-like variants from normal subjects, introducing sequencing of the A1AT gene in all cases with clinical or histological suspicion of the disease. During the last 20 years, 23 liver biopsies from Sardinian patients showing PAS-positive globules immunoreactive for a polyclonal anti-A1AT antibody were diagnosed in our Lab and, in all cases, gene sequencing revealed the presence of the M-Cagliari mutation.

All these data taken together, some considerations should be made on the past and on the future of the diagnosis of A1AT deficiency. Regarding the beginning of this Sardinian story of A1AT deficiency, I must admit that Antonio Cao was not wrong. In times in which the disease was strictly associated with the Z variant, he told me that the typical variant was not present in the Sardinian population. The most important consideration regarding our experience is that caution should be taken in considering IEF as the best method for the diagnosis of A1AT deficiency, particularly in some population, including Sardinians, in which a M-like variant represents the most frequent pathological A1AT variant. Regarding the future, my opinion is that the algorithm generally suggested for reaching a proper diagnosis of this disease should be completely changed. The cut-off of the A1AT serum values should be reconsidered, not to avoid the diagnosis of a number of heterozygous subjects

who may be affected by liver and/or lung disease. Given that the two A1AT alleles are co-dominant, and since A1AT is a phase acute protein, in all heterozygous PiMZ or PiM/M-Cagliari subjects carrying an inflammation, the M allele is induced to produce high quantities of A1AT, whose serum levels may reach normal values. In these cases, PCR serum levels should be evaluated and, when increased, the diagnosis of A1AT deficiency should not be excluded even in the presence of serum A1AT levels within the normal range. Gene sequencing should be included, on the basis of our experience, in all neonates and pediatric patients with liver or lung disease of unknown origin, including asthma, avoiding IEF. Finally, for a screening in the perinatal period, I suggest the accurate examination of the electrophoresis of serum proteins: values below 1.3 mg/dl of alpha-1 globulins might represent the cut off for considering a newborn under suspicion and for submitting her/him to genetic analyses. With a similar new approach, I think that we will transform A1AT deficiency from a rare disease into a previously rarely diagnosed disease [4], changing completely the epidemiology of this complex and fascinating metabolic disease.

If, according with Shakespeare “there is nothing good or bad, but thinking makes it so”, I could say

that A1AT deficiency has never been absent in the Sardinian population, but our thinking made it so. The main message for the future of A1AT deficiency, coming from Shakespeare and confirmed by our story, is that we should never let that the general thinking might represent a prison for our mind. In this case, eventually we didn't let it.

Declaration of interest

The Author declares that there is no conflict of interest.

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