Editorial

Amyloidosis: the current situation

This issue of the journal of the Portuguese Society of Internal Medicine brings four interesting articles on amyloidosis, by Professor Políbio Serra and Silva et alteri of the Medicine Service II of the Hospitals of the Universidade de Coimbra. Written in clear, concise language, with notable scientific rigor, the articles make an important contribution, giving an opportune and updated revision, and covering themes ranging from patient cases seen by the Service over the period of a decade, to amyloidosis in haemodialysis patients, the treatment and prognosis of primary amyloidosis, and finally, his experience in the use of abdominal wall fat pad biopsy as a diagnostic method.

Since its discovery by Rokitanski, in 1832, and subsequent anatomopathological description given by Virchow, amyloidosis – the name that became consecrated due to a mistake as the substance would stain as starch – has presented a challenge for physicians and researchers. Therefore, on a par with the work of the pathologists, it became the tasks of the clinical doctors, in the decades that followed, to describe the proteiform manifestations of the disease, to perceive the possibility that in certain cases, there might be a relationship with the presence of chronic infections, and later, with chronic inflammatory diseases and with some neoplasms; to know the existence of systemic and localized forms; to describe the hereditary forms and identify the signs and symptoms that manifest the impairment of one or other organ. In other words, amyloidosis, in its different forms, became configured as an anatomoclinical entity. The amyloid substance was, then, a protein with its own tinctorial properties, which is deposited in the extracellular space, that has weak or zero antigenicity and resists, in vivo, enzyme digestion.

However, it was only after 1968 that it became possible to extract the amyloid from the deposits in the tissues, enabling the study of its composition. It was with unexpected surprise that scientists observed, in the subsequent years, that there was not just one, but several amyloid proteins today perfectly identified and linked to the various types of the disease, thereby amyloidosis became part of molecular pathology. Thus, the protein AL (light-chain immunoglobulins) of the idiopathic or primary amyloidosis, multiple myeloma, and localized ("tumoral) forms, the protein AA of reactive or secondary amyloidosis, and of familial Mediterranean fever, the transthyretin mutations of hereditary amyloidosis, the b2–microglobulin of amyloidosis in patients under haemodialysis, the precursor of amyloid protein of the nervous central system, the proteins of endocrinal amyloidosis and systemic senile amyloidosis, among others. It is known, today that the amyloid substance is comprised of the amyloid protein, which varies according to the form of the diseases, and various other components that they all have in common, like S.A.P. (amyloid P component), glycosaminoglycans, apolipoprotein E and A.E.F. (Amyloid-Enhancing Factor). It is also known that the relationship between the different amyloid proteins, and the tissues where the deposits mainly occur, is very variable, therefore it follows that in idiopathic amyloidosis (AL), it is mainly the heart and kidney that are involved, followed by the digestive tract, the peripheral nerves, the osteoarti-

cular apparatus, the liver and the spleen; in reactive amyloidosis (AA) the main sites are the kidney, heart, liver and spleen, the digestive tract an the endocrine glands, and there are never deposits in the nerves or locomotor apparatus; as for hereditary amyloidosis, the main sites are the peripheral nerves, heart, eyes (only the vitreous), the digestive tract and the kidney; in amyloidosis of haemodialysed patients (b2-microglobulin) the main sites are the locomotor apparatus and carpal tunnel. I therefore proceed, in this context, to the biochemical-clinical classifications of amyloidosis.

Various questions are raised, some of which I mention here by way of example: All the amyloid proteins circulate in the plasma, and have equal access to the different tissues. The reasons why the deposit of this protein occurs electively, in certain tissues, while sparing others, remains a mystery; in amyloidosis that is reactive to chronic infections, such as tuberculosis, syphilis or leprosy, or chronic inflammatory diseases, like rheumatoid arthritis, Betchrew or Still diseases in adults, or albeit rarely, in neoplastic diseases, such as lymphomas or carcinomas of the bronchus or kidney, it is questioned why this form of amyloidosis is not present in patients with acquired immunodeficiency syndrome, and cases of amyloidosis in patients with systemic erythematous lupus are rare; what is the role of amyloidosis in the pathogen of the Alzheimer's disease or prions disease; or the role of proteins in the acute phase such as S.A.A. (serum A amyloid), interleukins 1 and 6 or T.N.F. (tumour necrosis factor) in the pathogen of reactive amyloidosis.

With the evolution of scientific knowledge, the definition of amyloidosis was established in Oslo, in 1990 as the deposit of fibril proteins, which when stained with Congo Red and observed under a microscope under polarized light, exhibit green birefringence, and these deposits, when analyzed by X-ray diffraction, have a b-pleated structure, and when viewed under an electronic microscope, a typical fibril structure.

It is appropriate to highlight the important role of a Portuguese physician in the discovery of the first form of hereditary amyloidosis, familial amyloidotic polyneuropathy (F.A.P.), thanks to the Portuguese neurologist Corino de Andrade, whose work princeps was published in the renowned journal Brain, in 1952; and the notable research work of Pinho and Costa et alteri that led to the identification of a mutation of transthyretin (or pre-albumin) in these patients.

A consequence of the improved knowledge of the disease was the development of more sophisticated means of diagnosis, such as histochemical methods of identifying amyloid proteins; techniques in molecular biology that enabled pre-natal diagnosis of the disease; the use of imaging methods like Magnetic Resonance and Computed Tomography and Echography; and radioisotope methods to study the kinetics and evaluate the location and extension of deposits and response to therapy. It has also enabled new therapeutic medication approaches, such as the use of hepatic transplants (in certain forms of hereditary amyloidosis) and renal transplants. An interesting chapter in geographical pathology can be explored with research works that enable the traces left in the coastal populations to be followed through the genetic mutations of transthyretin brought over the years, by sailors who carried the disease with them.

As always follows, the notable scientific progress that we have seen, which kept pace, in an exemplary way, with the evolution of Science, has illuminated many interesting aspects of this disease, and raised new and important lines of enquiry. While it is true that we have advanced in our knowledge of amyloid proteins and their relationship with the different clinical forms, how far the mechanisms of fibrillogenesis and the formation of amyloid deposits, or how far or why some of these proteins become pathogenic, can be said to be still in the realm of the hypothetical. In effect, many questions have yet to be understood, notably in relation to the pathogenic mechanisms. We hope that the most effective treatment for this disease will be discovered, and that new studies will provide more clarification on this unique substance that has so intrigued and interested physicians and scientists. ■

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