Familial amyloid polyneuropathy (FAP) type I and the probands of "new" families: Apropos of a clinical case

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Abstract

Familial amyloid polyneuropathy (FAP) type I is a progressive autosomal dominant neurodegenerative disorder characterized by an extracellular amyloid fibrils deposit in the conjunctive tissue, except in the brain and hepatic parenchyma affecting the peripheral nervous system in particular. FAP type I existence showed to be related to valine aminoacid replacement by methionine in the position 30 of the transthyretin gene (TTR V30M). Sporadic cases of FAP TTR V30M have been described in all of the foci of this disease. Its existence raises some interesting questions especially on the hereditary form and the possibility of genetic modifiers.

The authors report a FAP TTR V30M case, whose relatives were not affected by the disease, reviewing the genetic epidemiology of such condition.

Key words: proband, sporadic case, new families, transthyretin.

CASE REPORT

A Caucasian female 40 years of age, was referred is to the Internal Medicine Clinic of Santarem District Hospital due to epigastralgia evolving for four months. She was born and resides in Santarem, a housewife, single and has always lived in Portugal. She was not having any medication. Both the paternal and maternal ascendants were born in Santarem and Pampilhosa da Serra, respectively, and there was no history of hereditary pathology in the family. Apparently healthy until October 2007, when she started having epigastralgia paroxysmal episodes of moderate intensity, grinding type, without irradiation and without relation with food. Such episodes occurred in an insidious way, 2 to 3 times a month, associated with nausea and food vomiting stopping in a few minutes.

She went often to the Emergency Service of Santarem District Hospital to clarify her complaints. She underwent several additional tests for diagnosis (haemogram, biochemistry, clotting, abdominal simple radiography and abdominal echography), having been informed that she had anaemia and renal microlithiasis. She was medicated with omeprazole 20 mg/day. As the complaints persisted, she was admitted into the hospital in March 2008. She brought with her diagnosis additional tests (haemogram and biochemistry) showing haemoglobin of 11.6 g/dL (12.5 – 15.5), amylasemia of 206 U/L (0 – 160) and ESR of 55 mm/first hour (≤ 14). A short urine test revealed pyuria, leukocyturia and protein 3+. The objective exam showed a good general condition, hydrated, colored mucosa, apyretic, blood pressure of 110/60 mmHg, regular and rhythmic pulse 60 bpm. Respiratory rate 15 cycles/minutes. Remaining observation and neurologic exam without alterations.

It was decided to implement antibiotherapy to treat the urinary infection and additional diagnostic tests were requested. The upper gastrointestinal endoscopy and abdominal echography did not show any changes. The echocardiogram, mode M and 2D, have shown a slight anterior and posterior pericardial effusion. In the short urine test type II a 4+ protein was shown and the protein dosage in the 24h urine was 1.0g . She was discharged, after clinical improvement, to the Internal Medicine Clinic.

Assessed in October 2008, she was pale, lad lost weight, was depressed, with malleoli edema and petechiae on the legs lower thirds. She was complaining of an increase on epigastralgia frequency (four – six episodes/month), adynamia and weight loss of about 7 kg. It was decided to supplement the study, started on admission, to exclude possible collagenosis. Serial proteins immunoelectrophoresis results

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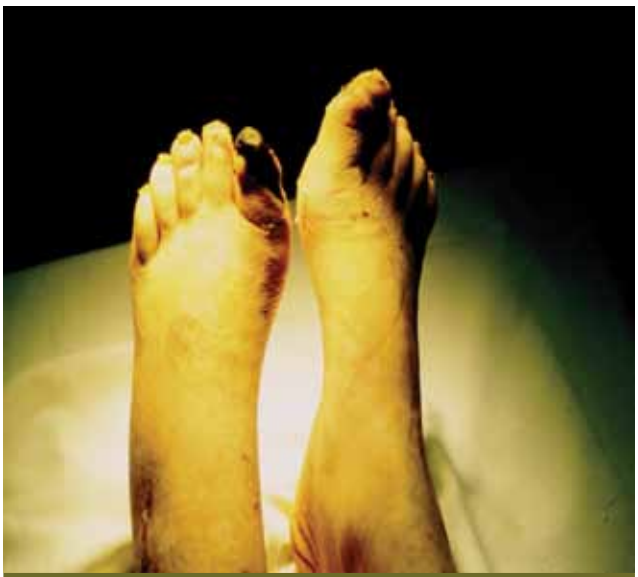
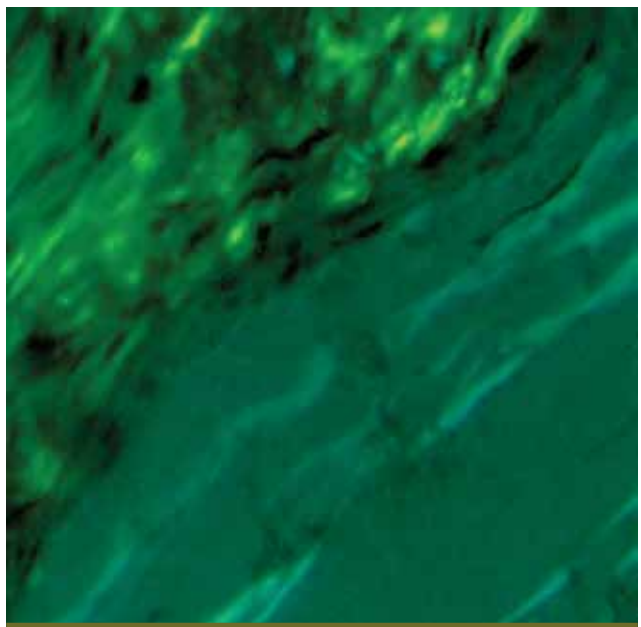


Patient with left foot hallux necrosis and *livedo reticularis* in both feet.

FIG. 1



Congo red x400: shows neuromuscular tissue and the presence of amyloid substance with emerald green birefringence under the polarized optical microscopy.

FIG. 2

of immunoglobulin and complement were normal. Urinary immunoelectrophoresis showed non selective proteinuria. Serology for the HBV, HCV, HIV 1 and 2, VDRL, Waller Rose, LE cell, ANA, Anti-DNA, A-SSA, A-SM and A-RNP were negative.

The myelogram and bone biopsy were normal. Due to proteinuria persistence it was carried out a renal biopsy which has shown widespread deposits of the amyloid substance in the glomeruli and some arteriole, positive for Congo red deserving immunohistochemical characterization.

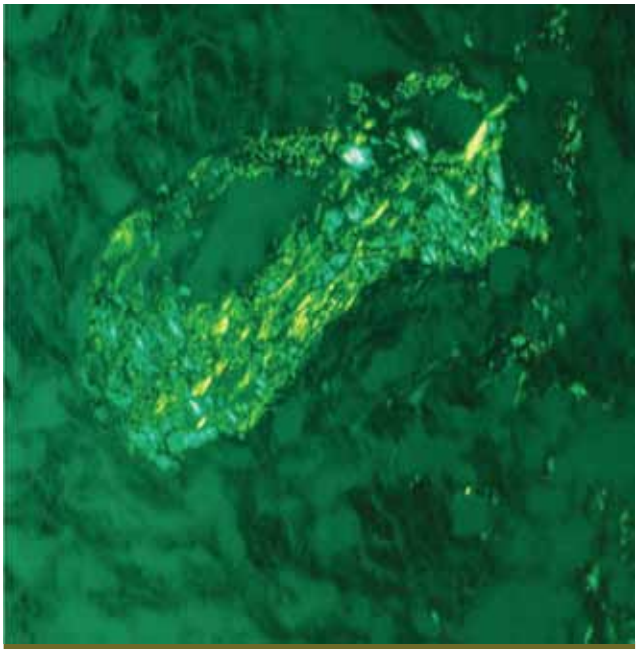
By the end of January 2009 when readmitted, due to watery diarrhea, weight-loss of 10 kg and syncope, she complained of a worsening of petechial cutaneous lesions, and paresthesia of the distal extremities of the lower limbs. Simultaneously, it had to be referred the appearance of new lesions compatible with plantar perforating disease and the necrosis of the left foot first toe, *livedo reticularis*, to above the knees (*Fig. 1*) and diastolic postural hypotension confirmed by Schellong's test. In the neurologic exam there was bilateral hyporeflexia of the lower limps with painful hypoesthesia, both tactile and thermal up to the knee. The electromyography carried out has shown a polyneuropathy predominantly sensitive of the lower limbs. The biopsy histopathological study of the left extern saphenous nerve (*Fig. 2*) as well as of the abdominal fatness (*Fig. 3*) has revealed deposits of amyloid substance. The immunohistochemical characterization of the amyloid deposits in the renal biopsy performed at Institute Abel Salazar, was compatible with renal amyloidosis, Portuguese type.

The genetic study for transthyretin Val30Met, through ELISA technique, carried out in Porto Paramyloidosis Study Center was positive what enable to come to the conclusion it was a patient with familial amyloidotic polyneuropathy, Portuguese type.

She started treatment with colchicine and wide spectrum antibiotherapy, surgical debridement of necrotic tissue with dearticulation of the first toe and distal extremity of the second toe of the left foot. After clinical stabilization and improvement of lesions of the plantar perforating disease she was referred to Porto Paramyloidosis Center.

DISCUSSION

Hereditary amyloidotic diseases include Familial Amyloidotic Polyneuropathy (FAP), which are organized in several types: FAP type I, Andrade's or the Portuguese type; FAP type II, Rukovina's or Indian



Congo red x 400: shows abdominal wall adipose tissue and nodal amyloid deposits with emerald green gloss, birefringent to polarized optical microscopy.

FIG. 3

type; FAP type III, Van Alen's or Iowa type; FAP type IV, Meretoja's or Finnish type. [1,2]

FAP type I, Andrade's or Portuguese, also called paramyloidosis or commonly "doença dos pézinhos" is a dominant autosomal hereditary disease caused by a mutation of the transthyretin gene (pre-albumin) where Valine is replaced by Methionine in the position 30 (TTR V30M). The genetic mutation produced essentially in the liver, is an amyloidogenic protein, depositing itself in several organs and tissues.[1,3]

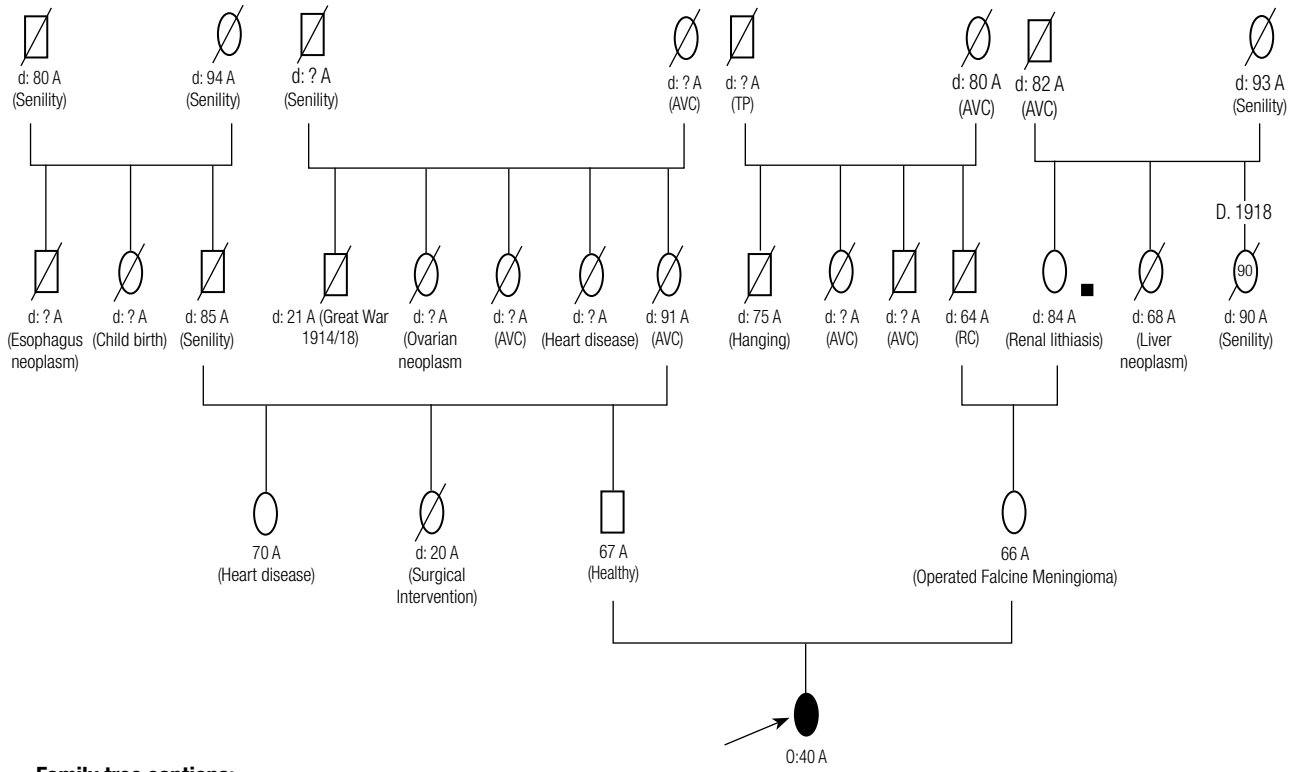
In the description published in Brain, Prof. Nário Corino da Costa Andrade, approaches in a detailed way, the aspects that can contribute to the understanding of paramyloidosis etiopathogenesis.

He detected the familial character of the disease, but the existence of 13 isolated cases, one of which was precisely one of the two *pinceps* cases, will make very hard to establish hereditary dominance. Therefore, Andrade suggests a detailed investigation both of genetic as environmental factors.[4] In the first genetic study of FAP type I in Portugal, carried out 30 years after the first description of Corino de Andrade, Becker et al., suggested that such cases, identified as sporadic, may result of new mutations and argue in favor of such mutation as being present in a silent form in one of the parents.[5] In 1978, Costa et al have demonstrated that transthyretin was the main element of amyloid fibrils in FAP. Some years later it was confirmed that in the patient's plasma it was circulating an abnormal protein, a TTR V30M as a result of a one-off mutation in the TTR gene. The discovery of this biochemical marker enabled to confirm FAP type I diagnosis in individuals without a family history of such disease. In a similar way it enables to exclude the possibility of new mutations, confirming that in these isolated cases, a healthy parent is an asymptomatic carrier of TTR V30M.[4] In the case presented, it was not possible to identify cases of PAF V30M both in the ascendants as in the other relatives (*Fig. 4*). In spite of that, the biopsy of the left external saphenous nerve (*Fig. 2*), the abdominal fatness (*Fig. 3*) and the genetic study for transthyretin V30M enabled to confirm the diagnosis of paramyloidosis.

The disease started around 40 years of age, manifesting itself by motor sensitive autonomic polyneuropathy progressing rapidly, myocardiopathy, renal insufficiency, progressive weight-loss, eye changes and gastrointestinal disorders.[3,6]

Digestive manifestations end up being seen in all patients, although at the beginning they can be absent. However they can also be an initial manifestation of what happens in 24.2% of patients.[7] In paramyloidosis sporadic cases when digestive symptoms are predominant, the clinical diagnosis can be particularly difficult if there is not a previous family history of the disease.[8] Many of FAP gastrointestinal symptoms can emerge in patients with dyspepsia and gastrointestinal functional disorders.[7] Therefore in sporadic cases all depends on the capacity of the specialist in giving value and associating the different complaints not forgetting this pathology, with the aim of making a diagnosis hypothesis and moving towards the molecular study. Conversely, it would be difficult to integrate all the complaints, being surprised eventually.[8] In the current case it is evident the difficulty of reaching an early diagnosis and it has highlighted the importance of not taking the family history and the geographic origin as a negative criteria for diagnosing FAP V30 M.

The existence of such cases raises some interesting questions, namely the hereditary mode and the hypothesis of genetic modifiers. Many of them denominated sporadic/isolate, seem to correspond to patients whose previous generation were asympto-



Family tree.

FIG. 4

matic carriers, or later onset, with a symptomatology which was confused with the usual manifestations of advanced age.[6] They seem to form a distinct group with a later onset age than the group of patients with a parent affected and there are families coming from distinct geographic areas of the regions of higher disease prevalence.[4]

In the case presented the parents were not tested however one can not rule out the hypothesis of asymptomatic FAP TTR V30ME cases in this family, i.e., we cannot state that we are before a new family where a mutation was already present in previous generations but it was clinically silent. However the identification of TTR V30M in this patient enables us to exclude it the possibility of a new mutation. It seems to exist in the Portuguese population with FAP some kind of protection, evident in families with few people affected and symptomatic patients in advanced age. Asymptomatic carriers can remain asymptomatic throughout their lives, although transmitting the gene to the following generation.[8,4] The description of cases of discordance between TTR V30M homozygotic twins and the potentiating effect of neurotoxic factors, supports the hypothesis of nongenetic factors input to trigger such disease.[9,10,11] However it is unknown what causes the progression to a symptomatic stage. [9]

The number of sporadic cases of FAP TTR V30 M with non affected parents has increased. The increment in the number of identified patients results of an improvement of health care and the discovery of the biochemical and molecular marker.

Longitudinal studies of FAP TTR V30M families already performed show that family members which are TTR V30M (-) to not develop the disease while

the family members which are TTR V30 M (+) have a higher probability of developing it. Nevertheless, some remain asymptomatic until later stages of life, including dying without developing it. Some authors advocate that these TTR V30M carriers should undergo a follow-up and electromyogram to an early identification of the subclinical changes.[6]

CONCLUSION

Sporadic cases of FAP V30 M, have been notified since the initial description by Corino de Andrade, however its clinical and genetic importance was not demonstrated until now.[8] Its emergence in areas where such entity is not known, it emphasizes the need to take FAP into account in the differential diagnosis of patients with primarily sensitive polyneuropathy and/or dysautonomia changes.

In such cases it is compulsory a search of amyloid deposits in peripheral nerves and abdominal fatness biopsies, as well as a genetic study of TTR V30 M.[6]

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