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Familial amyloid polyneuropathy: When does it stop to be asymptomatic and need a treatment?

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INFO ARTICLE

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ABSTRACT

Transthyretin familial amyloid polyneuropathy (FAP) is a rare disease with autosomal transmission due to point mutation of the transthyretin (TTR) gene. It is the most disabling hereditary neuropathy affecting sensory, motor and autonomic nerves, and is irreversible and fatal within 7 to 12 years of onset in the absence of therapy. Diagnosis is usually delayed for 1–5 years because the onset is usually insidious, and a positive family history is lacking in 50% of late-onset cases. Penetrance is variable, and depends of the age of the carrier and age of onset in family members. Two treatments are available: liver transplantation, to suppress the main source of systemic production of mutant TTR; and TTR tetramer stabilizer drugs, to avoid the release of highly amyloidogenic monomers and oligomers. These therapies are able to stop or slow the progression of the disease in its early stages. Genetic counseling is crucial to detect carriers at risk of developing the disease. The European network for TTR-FAP recommends careful baseline assessment by questionnaire, clinical examination and neurophysiological tests, and periodic consultations to detect the onset of disease in time to start anti-amyloid therapy after biopsy findings of amyloid deposition. A therapeutic educational program is important for improving patients' awareness. Patients are considered symptomatic and ill when they themselves perceive symptoms or changes, including changes from baseline measurements on neurophysiological tests, followed by findings of amyloid deposition on biopsy. The most sensitive biopsies are from the labial salivary gland and skin.

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Abbreviations: FAP, familial amyloid polyneuropathy; TTR, transthyretin; SFN-SIQ, small-fiber neuropathy Symptom Inventory Questionnaire; NIS, Neuropathy Impairment Score.

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1. Introduction

Hereditary transthyretin familial amyloid polyneuropathy (TTR-FAP) is rare, but is the most disabling hereditary neuropathy of adults, and is fatal within 7 to 12 years of onset without therapy. TTR-FAP is due to endoneurial accumulation of amyloid deposits. FAP was first reported to be endemic in the North of Portugal [1], in Japan and in Sweden, and is now considered ubiquitous in those areas [2,3]. FAP has an autosomal transmission and is due to mutation of the transthyretin (TTR) gene, usually Val30Met, although hundreds of other mutations of the gene have been reported [4]. Age of onset is variable, ranging from early in the third decade in Northern Portugal and Japan, to usually later (after 60 years) in Sweden and in most other countries of the world [5,6], where its presentation is sporadic in half of cases. Diagnostic delay ranges from 1 to 5 years and depends on the presence, or not, of a positive family history [2]. It is a progressive, irreversible, systemic disease with an insidious onset that affects the sensory, motor and autonomic nerves, as well as the heart and eyes. The clinical presentation is also variable, usually mimicking length-dependent small-fiber polyneuropathy with autonomic involvement [1,7], but different in late-onset Val30Met cases, with predominantly large-fiber polyneuropathy [8] and sometimes mimicking chronic inflammatory demyelinating polyneuropathy (CIDP) [9].

TTR-FAP is usually assessed by a sensorimotor Neuropathy Impairment Score (NIS) [9], and staged according to walking ability in three stages for FAP [7] or five stages for polyneuropathy disability (PND) [10]. Both NIS and PND scores correlate with each other [11]. The key tools are biopsy to identify amyloid deposits [3,12–14] and genetic testing [4]. The course of disease is more rapid and the survival shorter in late-onset [9,15] than in early-onset TTR-FAP [7]. FAP is a peripheral neuropathy that, in early-onset Val30Met cases, causes predominantly axonal damage, which affects, first, the distal segments of sensory fibers and then motor fibers [16], and is more conspicuous in late-onset Val30Met FAP [17]. Some aspects of demyelinating neuropathy are found in 26–57% of cases, according to the TTR variant, in non-endemic areas in France [9].

The available anti-amyloid therapy includes liver transplantation [18] to suppress the main source of mutant TTR and, more recently, TTR tetramer stabilizer drugs [19,20]. Tafamidis meglumine obtained marketing authorization in Europe for stage-1 disease, whereas diflunisal is prescribed 'off label' [21]. Other drugs are currently under assessment in clinical trials [21]. Penetrance (the proportion of individuals with the mutation who exhibit clinical symptoms) of the disease-causing mutation is high, except in Sweden [2], and depends on the age of onset within family members and age of the carrier. The age of onset of Val30Met FAP is much lower in Portuguese than in French index cases, whereas its penetrance at 50 years is estimated to be higher in Portuguese Val30Met carriers (0.80) compared with all French samples and all mutations (0.18). In France, its penetrance at 80 years is estimated to be around 0.86 in cases of TTR-FAP, ranging from 0.73 in late-onset Val30Met cases to 0.95 with other mutations [22]. There is a 10-year risk of anticipation in cases of maternal inheritance with Val30Met TTR-FAP [23]. Early diagnosis in carriers is crucial to initiate therapy as soon as possible, and remains a major challenge for teams that follow carriers.

2. Who can answer the question: When does TTR-FAP stop being asymptomatic and need treatment?

Four main players are required for success: the carrier of the TTR gene-mutation; the neurologist specializing in peripheral neuropathy; the neurophysiologist; and the pathologist (Fig. 1). The carrier is the primary actor and the first to feel symptoms of the disease, and should consult a physician about them as soon as possible. To avoid a delay that is too long, the carrier needs to be made aware of the first possible disease symptoms by genetic screening. Specialized and

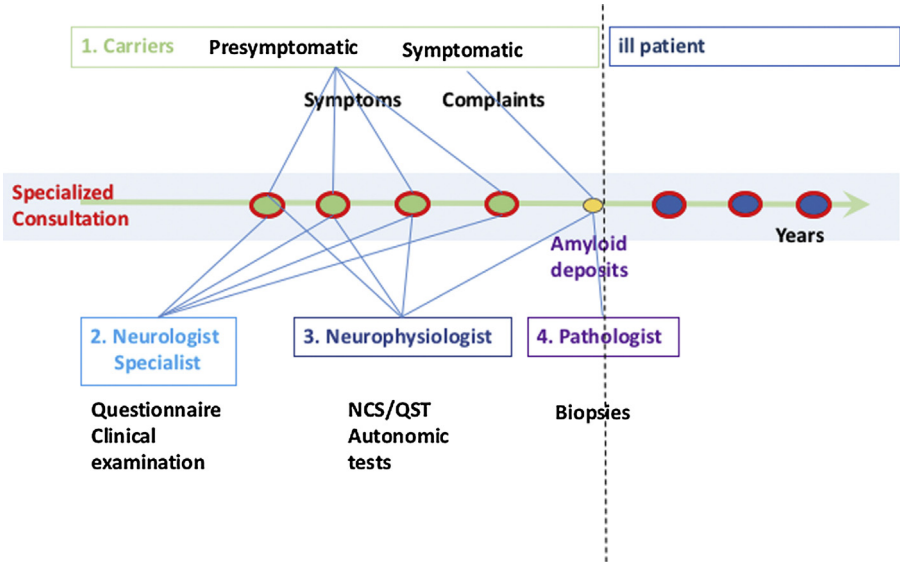

Fig. 1 – The four main players essential for deciding that a TTR (transthyretin) gene-mutation carrier is an ill FAP (familial amyloid polyneuropathy) patient.