SUPPLEMENT ARTICLE

OPEN

Optimizing the management of transthyretin familial amyloid polyneuropathy in Europe: early diagnosis and effective care

*David Adams, on behalf of the European Network for TTR-FAP (ATTReuNET)**

FOREWORD

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is an autosomal dominant disorder caused by the extracellular deposition of insoluble amyloid fibrils in the endoneurium. TTR-FAP occurs as a result of transthyretin (TTR) gene mutation, and more than 100 TTR mutation types are recognized [1]. It is a highly disabling and life-threatening disease, characterized by progressive sensorimotor and autonomic neuropathy, and is fatal within 7–12 years of disease onset [2]. For some time, it was believed that TTR-FAP was an endemic disease in Europe, affecting only north Portugal, Sweden, Cyprus, and Majorca; however, with improvements in diagnostic methods in recent years, numerous sporadic cases have been diagnosed in many other countries [1].

This supplement arose from discussions that took place during two meetings (November 2012 and March 2014) of an emerging group that is provisionally called the European Network for TTR-FAP (ATTReuNET). The group currently includes a representative panel of 15 TTR-FAP experts from 10 European countries (Bulgaria, Cyprus, France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, and Turkey), including nine National Reference Centres for familial amyloid polyneuropathy. As an emergent network, ATTReuNET is open to collaborations with other expert centres in Europe. The group members devised and completed a semistructured questionnaire on the situation of TTR-FAP in their countries prior to the 2012 meeting and updated the responses in 2014. This information was used to guide the live discussion, with a focus on five main areas: epidemiology and local structure of care; diagnosis; management and funding; follow-up care of both patients and asymptomatic carriers; and the overall patient experience. This supplement contains three articles that aim to disseminate the major findings from these meetings and to align these findings with data available from a systematic review of the published literature base. Electronic database searches (NCBI PubMed) formed the basis of the literature search within the time frame (1952 to December 2014). Key search terms included 'transthyretin familial amyloid polyneuropathy,' 'familial amyloid polyneuropathy,' 'transthyretin amyloidosis,' 'TTR-FAP,' 'TTR-FAP and Europe,' and 'TTR-FAP and Bulgaria/Cyprus/France/Germany/Italy/the Netherlands/Portugal/Spain/Sweden/Turkey.' Essentially, this supplement lays the foundations for expert recommendations on the current epidemiology, genetic basis, diagnosis, management, and follow-up of TTR-FAP, highlighting the need for genetic counselling and early detection of TTR-FAP among asymptomatic carriers.

In the first article of this supplement, Yesim Parman and coauthors recount the history of discovery and development of TTR-FAP across Europe, beginning with the first description of the disease in northern Portugal in 1952, followed by the emergence of genetic tests after 1989. The disease prevalence is highly variable, with a large genotypic and phenotypic heterogeneity across Europe. The most common mutation type is the methionine-for-valine substitution at position 30 (Val30Met) in the amyloid fibril protein. The available local treatment structures and resources in each country were identified. To improve patient management and

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care, a network approach to TTR-FAP was proposed and evaluated based on the current experience of countries with existing national rare disease plans, such as France.

Early and accurate diagnosis of TTR-FAP remains essential to ensure a better prognosis. Detection and diagnostic methods used across Europe vary according to available expertise and facilities, but delayed diagnosis remains an issue in most countries. In article two of the series, David Adams and coauthors present an expert perspective on algorithms for diagnosis, treatment, and follow-up of patients with TTR-FAP. With increased understanding of the disease, it is no longer sufficient to monitor and treat TTR-FAP based on the neurological symptoms alone. Baseline assessments and ongoing monitoring are recommended for other amyloid-related complications involving the heart, eyes, and kidney commonly found in patients with TTR-FAP. Liver transplants are no longer the only treatment option available for these patients, as new pharmacotherapies have been developed and are in use across Europe.

Despite being a severe, rare disease with an established hereditary origin, there remains little guidance surrounding early monitoring and diagnosis of asymptomatic carriers of the mutated TTR-FAP gene. This topic is discussed by Laura Obici and colleagues in article three of this series. Genetic counselling is a priority for siblings of diagnosed patients since they are at greatest risk of developing TTR-FAP; however, the current legal policies on genetic testing differ among European countries. In most countries, the majority of genetic counselling is carried out by designated expert genetic counsellors. A routine and structured monitoring plan is proposed for asymptomatic carriers to detect and confirm the diagnosis of TTR-FAP and to initiate treatment as soon as possible.

TTR-FAP is an important genetic disease with evolving therapeutic strategies. We hope that this supplement provides a useful and timely update with practical information and the resources to guide the care and management of your TTR-FAP patients and their families.

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