Screening for hereditary transthyretin amyloidosis in Bulgaria

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Abstract

Transthyretin amyloid (ATTR) amyloidosis is a rare disorder with an adult-onset defined by the accumulation of misfolded fibrils predominantly in peripheral nerves, the heart, and the digestive tract. The disease is characterized by two forms - hereditary (ATTRv) or acquired (ATTRwt). Various point mutations in the transthyretin gene induce the hereditary form of the disease. For finding new cases of ATTR amyloidosis and proper screening, the establishment of a multidisciplinary team and a Centre of Excellence (CoE) is essential. CoE provides regular education and training for better diagnosis and treatment.

In the current review, we focus on the importance of having a multidisciplinary team and CoE, the screening strategy for ATTR amyloidosis in Bulgaria, and assessments performed when a patient is first suspected of having this rare disease.

Keywords: transthyretin amyloidosis, screening, rare diseases, centre of excellence

Introduction

Transthyretin amyloid (ATTR) amyloidosis is a rare disorder with an adult-onset defined by the accumulation of misfolded fibrils predominantly in peripheral nerves, the heart, and the digestive tract [1]. The disease is characterized by two forms - hereditary (ATTRv) or acquired (ATTRwt). Various point mutations in the transthyretin (*TTR)* gene [2] induce the hereditary form of the disease.

The disease is rare; however, there are cases reported in almost every European country with some specific endemic areas – Portugal, Sweden, France, Italy, Bulgaria [3,4]. There are also enough patients in Turkey, Romania, North Macedonia [5,6].

The different mutations in those regions lead to different phenotypes of the disease. Furthermore, having in mind the low awareness of the disease among healthcare professionals, the delay in diagnosis could be up to 7 years from the onset of symptoms [7]. Treatment of ATTR amyloidosis at an early stage is associated with improved outcomes, and therefore early diagnosis is essential [4,8].

For finding new cases of ATTR amyloidosis and proper screening, the establishment of a multidisciplinary team and a Centre of Excellence (CoE) is essential. CoE provides regular education and training for better diagnosis and treatment. Established CoE, such as the one in Sofia, Bulgaria, could serve as a model for the launching of new CoEs for ATTR amyloidosis in other countries [9].

In the current review, we focus on the importance of having a multidisciplinary team and CoE, the screening strategy for ATTR amyloidosis in Bulgaria, and assessments performed when a patient is first suspected of having this rare disease.

A multidisciplinary team and Centre of Excellence

The expert ATTR Amyloidosis Centre at the University Hospital 'Alexandrovska' in Sofia, Bulgaria, was set up in early 2016. It is currently a member of the European Reference Network for Neuromuscular Disease (ERN-EURO-NMD). Our team recently published a model for CoE Support [9] that could be a useful example to underscore the various

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steps needed to establish a new CoE for ATTR amyloidosis across Europe.

A *sine qua non* in the success of a CoE is the motivated team of experts required to diagnose the patient effectively. As ATTR amyloidosis is a multisystemic disorder, our experience has shown that the following specialists are essential: neurologists, ophthalmologists, cardiologists, gastroenterologists, nephrologists, geneticists, physiotherapists, psychologists, pathologists, and nurses. The current board members invite the members of the CoE based on their experience with ATTR cases and their proficiency in the disease. The criteria for the invitation of new members are not strict and are based on a consensus decision [9].

Importantly, in times of COVID-19 pandemic, the CoE can be 'virtual' to some extent as the experts within the team may work in different centres, relying on emails, telemedicine, and phone contact in addition to regular face-to-face meetings to discuss specific patient cases. At the Bulgarian CoE, team communication is almost daily, with group meetings being held monthly. It is essential to ensure regular communication and engagement among the team to effectively manage the patient and provide an individualized course of action according to our patients' needs.

Genetic screening

Once an index patient from a family with no known history of ATTR amyloidosis has been diagnosed, genetic counselling for family members is a crucial consideration given that the disease is genetically inherited [10]. Therefore, family members of those diagnosed with ATTR amyloidosis are at risk of developing the disease as they may carry the *TTR* gene mutation [11].

A genetic screening programme is well-established at our CoE so that diagnosed patients and their adult family members have the opportunity for testing. This allows structured monitoring of individuals who carry a mutant *TTR* gene and enhances the possibility of early diagnosis of ATTR amyloidosis [12]. Genetic counselling allows family members of a person diagnosed with the disease to make an informed decision about genetic testing.

A widespread information campaign could be considered wherever clusters of families with mutant *TTR* genes are suspected.

In Bulgaria, a dedicated team from the CoE organized a widespread information campaign on the disease and visited family members of diagnosed patients wherever clusters of families with mutant *TTR* genes are suspected. These at-risk were then offered genetic testing and counselling. This approach led to identifying 11 new symptomatic patients and 60 asymptomatic genetic carriers in Bulgaria [9].

Once asymptomatic carriers of a *TTR* gene mutation have been identified, there is potential to follow them in a structured clinical approach to diagnose ATTR amyloidosis at the earliest symptomatic stage when treatment is most likely to be effective [13]. In Bulgaria, the CoE follows up not only diagnosed patients but also related family members who have been identified as carrying a mutant *TTR* gene and are at risk of developing symptomatic disease. Follow up of all identified (asymptomatic) *TTR* gene mutation carriers is carried out in a defined order according to an accepted programme of mean age of onset for every mutation: carriers between the age of 30 and 40 are followed up once every 5 years, 40-45 aged – once every 2 years, those at the age of 45-50 – once a year and above 50 years – twice a year. The asymptomatic carriers with a Gly47Glu *TTR* mutation make an exception in the follow-up strategy due to the earlier onset of the disease symptoms: carriers between the age of 20 and 25 are followed up once every 5 years, those between 25 and 30 – once in 2 years, and those above 30 – twice a year. The Bulgarian CoE follows up more than 100 asymptomatic genetic carriers [9].

Assessments performed when a patient is first suspected of having ATTR amyloidosis

Neurology

When a patient is first suspected of having ATTR amyloidosis at the Bulgarian CoE the following assessments have been done: patient clinical history, family history, neurological examination, physical examination, nerve conduction studies, autonomic tests, neuro-ophthalmological examination, blood and biochemistry examination, and sural nerve biopsy. For follow-up of the patients and their progression, we use neurological examination, modified body mass index, nerve conduction studies, autonomic tests, blood and biochemistry examinations, and urine analysis [14]. The Bulgarian Society of Neuromuscular Diseases and the Bulgarian Society of Neurology has a guideline for diagnosing and treating ATTR patients [15].

Cardiology

Updated knowledge about the clinical presentation, diagnostic algorithm, available and future therapeutic options for ATTR-cardiomyopathy (ATTR-CM) are a prerequisite for early identification, timely treatment, and better prognosis of the affected patients. The cardiologists in our team routinely perform electrocardiography, echocardiography, cardiac biomarkers (N-terminal pro b-type natriuretic peptide and troponin), bone scintigraphy, more rarely cardiac magnetic resonance imaging, and myocardial biopsy (if needed). For appropriate monitoring of ATTR patients and their progression, electrocardiography, echocardiography, and cardiac biomarkers are mainly used [16,17]. Moreover, the Bulgarian Society of Cardiology has issued a diagnostic algorithm in transthyretin amyloidosis with cardiomyopathy [18].

Gastroenterology

Gastrointestinal (GI) manifestations are common in ATTRv amyloidosis [18,19] and are associated with

reduced quality of life [4,6,19]. GI disturbances are present even before the onset of the polyneuropathy in some cases, and initial symptoms are often diarrhea, constipation, unintentional weight loss, or nausea [6]. In our CoE, gastroenterologists regularly perform a consultation, biomarkers for intestinal inflammation (faecal calprotectin), hydrogen breath test, abdominal ultrasound, and endoscopies with staging biopsies for Congo red staining [20,21]. Recently, gastroenterologists from our team initiated a European working group of 14 gastroenterologists and neurologists from 10 countries that published the first Recommendations for the diagnosis and management of transthyretin amyloidosis with gastrointestinal manifestations [6]. We believe that this document will help for the early and accurate identification of ATTR amyloidosis patients with GI manifestations and allow early-stage treatment.

Conclusion

Screening for hereditary transthyretin amyloidosis is essential for finding new cases of ATTR amyloidosis and carriers of *TTR* mutations. The early diagnosis requires a multidisciplinary team of motivated and experienced specialists. The low awareness of the disease among healthcare professionals is still a significant problem, and CoE provides regular education and training for better diagnosis and treatment. We believe that an established CoE such as the Bulgarian one could serve as a model for setting up new CoEs for ATTR amyloidosis.

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