ARTICLE

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REPORT OF NEUROLOGICAL MANIFESTATIONS IN FAMILY MEMBERS AFFECTED BY HEREDITARY TRANSTHYRETIN AMYLOID POLYNEUROPATHY

ABSTRACT

Backgrounds:
Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is an autosomal dominant disorder caused by mutations of the transthyretin (TTR) gene.
Clinical symptoms such as polyneuropathy are predominant in patients with the Glu109Gln (p.Glu89Gln) mutation.
The aim of this work is to present the neurological manifestations in family members affected by hereditary transthyretin amyloid polyneuropathy.

Materials and methods:
We report a Macedonian family (three brothers) from North Macedonia, affected by transthyretin familial amyloid polyneuropathy.

Results:
Three brothers with TTR-FAP from North Macedonia were hospitalised at the Clinic of Neurology in Skopje. In addition, there was a positive finding from the genetic analysis, with a present pathogen mutation in the TTP gene, Glu109Gln (p.Glu89Gln). The clinical presentation was with progressive length-dependent sensory-motor polyneuropathy, which started with loss of thermal and pain sensation in the feet and slowly ascends up the limbs with affected musculoskeletal reflexes. This clinical appearance is associated with variable autonomic disturbances. We used the Neuropathy Impairment Score (NIS) to determine the association between the severity of neuropathy and disease stage as well as estimate the rate of neuropathy progression. In all three brothers, an increase in the NIS scale was observed within consecutive measurements.

Conclusions:
TTR-FAP is an uncommon illness that can be life-threatening. The illness can manifest in a variety of ways with varying indications and symptoms, so it is critical to increase clinician awareness. Early initiation of anti-amyloid treatment is essential for a better outcome.

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INTRODUCTION

In more than 65 years, Andrade described the first case of a Portuguese woman, 37 years old, with transthyretin-related familial amyloid polyneuropathy (TTR-FAP), which he called "mal dos pesinhos," a peculiar neuropathy [(1)].

It is an autosomal dominant disorder caused by mutations of the transthyretin (TTR) gene. The mutant TTR protein accumulates in various tissues and organs, becomes toxic, and separates from its original tetramer form. The illness may be lethal if treatment is not received because of infections, cardiac issues, or cachexia [(2)]. TTR, which is encoded by chromosome 18, acts as a transport protein for thyroxin and vitamin A. TTR primarily originates in the liver, though small amounts are produced as well in the intestines, retinal epithelium, and choroid plexus. The TTR gene has so far been found to have more than 150 mutations [(3)]. The first one that was described, Val30Met, remains the most prevalent mutation. Regional variations lead to genotypic and phenotypic heterogeneity and have an impact on the mutation's frequency [(3)]. Thirty years ago, Portugal, Sweden, and Japan were known as endemic regions, and thus were believed to be the only places where the disease was present. But thanks to easier access to genetic testing, we now know that TTR-FAP has been identified across the world. The disease's prevalence varies significantly between endemic and non-endemic nations. In certain parts of Portugal where the illness is very common, the prevalence rate may reach 1/1000 to 1/10,000 [(4)] [(5)].

Amyloid expands up around endoneurial capillaries in peripheral nerves. Unmyelinated fibre damage happens early. Amyloid frequently invades and destroys blood vessels as the disease progresses, reducing the density of small and eventually larger myelinated fibres. Endoneurial amyloid deposits in ganglia and nerves cause damage both mechanically and toxically, which may also be triggered by Schwann cells. Endoneurial oedema, nerve ischaemia, oxidative stress, inflammation, and apoptosis are among the pathogenic mechanisms that have been proposed; these could all be targets for therapeutic intervention [(6)].

Clinical symptoms such as polyneuropathy and carpal tunnel syndrome are predominant in patients with Glu109Gln (p.Glu89Gln) mutation [(7)].

Variations in the natural history of mutations within and between them may have a variety of significant implications for creating strategies to get around obstacles in diagnosis and treatment management. With the development of new therapies, it has become increasingly important to fully understand the natural history of the disease, evaluating for multiple mutations.

The aim of this work is to present the neurological manifestations in family members affected by hereditary transthyretin amyloid polyneuropathy.

MATERIAL AND METHODS

We report a Macedonian family from Strumica (three brothers), Republic of North Macedonia, affected by transthyretin familial amyloid polyneuropathy.

RESULTS

Three brothers with TTR-FAP from North Macedonia were hospitalised at the Clinic of Neurology in Skopje. In addition, there was a positive finding from the genetic analysis. It showed a present pathogen mutation in the TTP gene, Glu109Gln (p.Glu89Gln).

The clinical presentation was with progressive length-dependent sensory-motor polyneuropathy, which started with loss of thermal and pain sensation in the feet and slowly ascends up the limbs with affected musculoskeletal reflexes. This clinical appearance is associated with variable autonomic disturbances. Deposits of Congo red-positive amyloid were found.

Electromyography (EMG) as a relevant diagnostic tool confirmed generalised, symmetrical, sensor-motor lesions with characteristics of predominantly axonal neuropathy and signs of segmental demyelination. Furthermore, they gave information that there were deceased members of the same disease in the family (father and uncle). diagnosis is based on family history, neurological evidence of a prevalent axonal polyneuropathy, identification of amyloid deposits in the tissues, and detection of TTR mutation.

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Deterioration of neurological findings was observed in the two older brothers (ages 64 and 59).
Severe cardiomyopathy is also found. They are currently receiving therapy with 20 mg of tafamidis; a proposal has been made to switch to 61 mg of the same drug. Stable neuropathy is found in the youngest brother, who is 57 years old and currently on treatment with 20 mg of tafamidis.
We used the Neuropathy Impairment Score (NIS) to determine the association between the severity of neuropathy and disease stage as well as estimate the rate of neuropathy progression.

In all three brothers, an increase in the NIS scale was observed within consecutive measurements. This score was seen to increase and progress in the oldest brother, going from 45 to 120 on the last measurement. The youngest brother experienced an increase from 41 to 82 , while the second oldest brother saw a rise from 30 to 72. Currently, the eldest brother walks with the support.

DISCUSSION

Our understanding of the clinical characteristics of TTR amyloidosis has grown considerably over the past 20 years. Nowadays, there is increased knowledge in terms of great variations in the presenting symptom, age at onset, type of neuropathy, and additional systemic involvement due to the identification of new mutation types. Compared to early-onset cases, late-onset cases have a more severe disease course and less autonomic involvement. At a ratio of 1/10, late-onset cases are predominantly male [(4)].
Other notable characteristics of the disease in non-endemic areas include low penetration rates and the absence of a family history.

The disease's distinctive characteristic is length-dependent sensory-motor neuropathy with autonomic involvement. Small fibres are usually affected in the early stages of the disease, and neuropathic pain may be the initial symptom. Neurologic symptoms and indicators worsen at stage 2, with proximal and distal weakness appearing in the lower extremities and sensory loss extending up to these regions. Patients eventually begin to walk with support [(8)]. The sensory deficit progressively expands to the anterior trunk and the proximal and distal parts of the upper extremities.
Moreover, patients are bed-ridden or in a wheelchair at stage 3. On rare occasions, the illness may begin with symptoms in the upper extremities that resemble motor neurone disease [(9)].
A significant scoring system based on a patient's ability to walk is the Polyneuropathy Disability Score (PND). It consists of four stages: stage 1 (sensory disturbances without a deficiency in walking capacity); stage 2 (impaired walking without a need for a support); stage 3 (preserved walking with the help of one adhere (3A) or two adheres (3B)); and stage 4 (wheelchair bound or bed-ridden) [(9)].
Another important quantitative scoring system that is mainly used in drug development studies is the Neuropathy Impairment Score (NIS). Furthermore, this is a summed score of polyneuropathy signs and neurophysiologic tests to quantify the overall kind and severity of polyneuropathy impairment in the frame of this disease. The score broadly characterized and quantified muscle weakness, muscle stretch reflex decrease, sensation loss of feet and hands, and neurophysiologic test abnormalities [(10)].

During the course of the illness, autonomic involvement results in major issues. Patients may report experiencing impotence, orthostatism, or diarrhoea.
Particularly, clinicians should question about erectile dysfunction, which may appear before sensory symptoms. In late stages, autonomic symptoms become more evident and may be life-threatening.
Also, clinicians should take into consideration the potential for TTR-FAP in patients who have carpal tunnel syndrome along with an unidentified polyneuropathy, particularly in men [(11)].
Additionally, amyloid deposits may accumulate at cranial nerves, nerve trunks, or nerve plexuses, leading to a variety of focal neurologic presentations. The accumulation of amyloidogenic TTR in the meninges and perivascular areas results in involvement of the central nervous system (CNS). "Amyloid spells," or stroke-like, focal neurologic deficits, are the most typical signs of central nervous system involvement [(12)].

Diagnostic challenges include the failure to detect amyloid during a biopsy, concomitant diabetes mellitus, monoclonal gammopathy, decreased nerve conduction velocity, and increased protein

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content in the cerebrospinal fluid, which can lead to an incorrect diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) [13].
Two distinct groups should be used to compare TTR-FAP assessments. Patients in the first group have a known family history, while patients in the second group present sporadically. If the patient in the first group manifests the classic symptoms of TTR amyloidosis, the diagnosis is easier to make.
On the other hand, the second group typically experiences a delayed diagnosis as a result of a variety of diagnostic obstacles and inconsistent initial symptoms.

In order to identify patients in the early stages of the disease, it is crucial to scan for carriers who fail to demonstrate any symptoms.
The frequency of follow-up for asymptomatic carriers should be determined by the type of mutation, the patient's age, and the age at which other affected family members first developed symptoms.

Pathogenic mutations have variable penetration and disease expression in patients. Genetic counselling for cascading testing of family members is also recommended. So far, in the Republic of North Macedonia, 24 people have been diagnosed with TTP-FAP [14]. The fact that nearly all of them are from the Republic of North Macedonia's southeast region is very particular.
On the other hand, it is an interesting fact that the largest number of TTR-FAP patients from the neighbouring Republic of Bulgaria is from the southwestern part of the country, that is, around the border with the Republic of North Macedonia [14].
This is an indication of an endemic area for the TTR-FAP on the Balkan.

CONCLUSIONS

TTR-FAP is an uncommon illness that can be life-threatening. The illness can manifest in a variety of ways with varying indications and symptoms, so it is critical to increase clinician awareness.

Early initiation of anti-amyloid treatment is essential for a better outcome. The prognosis appears to be improving with new treatment options. Based on the NIS findings in the members of this family, it is assumed that the treatment with 20 mg of the tafamidis drug is not effective enough in patients with the presence of a pathogen mutation in the TTP gene, Glu109Gln (p.Glu89Gln).

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