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Research Article

Epidemiological and Clinical Characteristics of Transthyretin Familial Amyloid Polyneuropathy in the Republic of North Macedonia

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Abstract

Introduction: Familial amyloid polyneuropathy (FAP) associated with genetic variants of the transthyretin (TTR) is the most prevalent type of hereditary systemic amyloidosis, and more than 100 amyloidogenic point mutations in the TTR gene have been described.

Materials and Methods: We present the epidemiological and clinical features of patients already diagnosed with TTR-FAP, with confirmed pathogen mutation in the TTR gene in the Republic of North Macedonia.

Results: So far in the Republic of North Macedonia, fourteen patients with TTR-FAP have been diagnosed. Additionally, nine of the patients are in the first stage, three in the second stage and two patients in the third stage. Four of the fourteen patients are treated with Tafamidis, 20 mg. Moreover, pathogenic mutations in the TTR gene were confirmed in all fourteen patients. Thirteen patients have confirmed Glu89Gln genetic pathogenic mutation (all are from Macedonian origin). These patients are from the eastern part of North Macedonia. One Muslim patient has a confirmed genetic pathogenic mutation Phe53Val. Only this patient comes from the western part of North Macedonia. On the other hand, it is interesting fact that the largest number of TTR-FAP patients from the neighboring Republic of Bulgaria, is from the southwestern part of the country, that is, around the border with the Republic of North Macedonia. This is an indication of an endemic area for the TTR-FAP on the Balkan. In ten of TTR-FAP patients, the symptoms of the nervous system are predominant and in four patients of the cardiovascular system.

Conclusion: The epidemiological features of this disease are of great importance in order to detect endemic regions. In the future, screening for this rare disease may be contemplated, especially in endemic areas.

Keywords: FAP; Epidemiology; Amyloid; TTR-Mutation

Introduction

Hereditary transthyretin amyloidosis is a rare, autosomal-dominant disease identified by extracellular deposition of amyloid fibrils consisted of the transthyretin (TTR). TTR is a homotetrameric plasma protein transporting thyroxine and retinol binding-protein-vitamin A complex [1]. Until now, more than 120 amyloidogenic mutations in the TTR gene have been recognized. Among the most common clinical phenotypes resulting from these mutations are hereditary amyloid polyneuropathy and cardiomyopathy [2]. The prevalence of this disease (including secondary amyloidosis) in Europe is estimated to be at 47/100 000 in 2014 [10]. In endemic zones in Portugal and Sweden, the prevalence may reach up to 1 in 1000 citizens [3]. Recently, an increased number of TTR-FAP cases have been registered in Germany, Bulgaria and Turkey [4]. Endemic regions for FAP have been also reported in Mallorca and Cyprus [14].

Materials and Methods We present the epidemiological and clinical features of patients already diagnosed with TTR-FAP, with confirmed pathogen mutation in the TTR gene in the Republic of North Macedonia.

Results So far in the Republic of North Macedonia, fourteen patients with TTR-FAP have been diagnosed. Additionally, nine of the patients are in the first stage, three in the second stage and two in the third stage. Four of the fourteen patients are treated with Tafamidis, 20 mg. Moreover, pathogenic mutations in the TTR gene were confirmed in all fourteen patients. Thirteen patients have confirmed Glu89Gln genetic pathogenic mutation (all are from Macedonian origin). These patients are from the eastern part of North Macedonia. One Muslim patient has a confirmed genetic pathogenic mutation Phe53Val. Only this patient comes from the western part of North Macedonia. On the other hand, it is an interesting fact that the largest number of TTR-FAP patients from the neighboring Republic of Bulgaria is from the southwestern part of the country, that is, around the border with the Republic of North Macedonia. This is an indication of an endemic area for the TTR-FAP on the Balkan. Also, Congo red staining of samples from subcutaneous fat tissue aspiration biopsy was positive in all fourteen patients, which is in favor of amyloid deposits. In ten of TTR-FAP patients, the symptoms of the nervous system are predominant and in four patients of the cardiovascular system. Patients with Glu89Gln mutation show mixed phenotype - peripheral polyneuropathy and cardiomyopa-

thy, with or without the presence of carpal tunnel syndrome. In the patients who have predominant nervous system symptoms, electromyography with the neurography provides data for a generalized, symmetrical, chronic, partial, sensor-motor, neurogenic lesions with features predominantly of axonal neuropathy and signs of segmental demyelination. Musculoskeletal reflexes are weakened also. Contrary, to patients with predominant cardiovascular system symptoms, echocardiography shows moderate diastolic dysfunction of the left ventricle with reduced stroke volume. Also, there is dilatation of the left atrium and concentric hypertrophy of the left ventricle. Clearly, this finding is in favor of the pressure load on the left ventricle. Last, but not least nine patients with TTR-FAP have sustained diseases such as Diabetes mellitus type 2, Pericardial effusion, Hypertension arterial, Hypotension arterial, Struma multinodulare, Atherosclerosis.

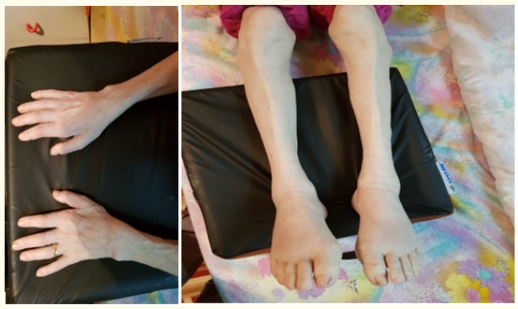

Figure 1: Hypotrophy of the upper and lower limbs at TTR-FAP patient.

tered in Sicily and Sardinia (Italy) and the European part of Turkey [10]. It is important to expect geographical aggregation near the coast of the Mediterranean Sea in Asia and North Africa [11]. Certain studies have shown inter or intrapopulation common origin for Val30Met mutation carriers from Portuguese, Brazilian, Swedish, Italian and Japanese population [12]. Another well-known TTR mutation is Val122Ile, characteristic for the African population and heart involvement [13]. Hopefully, in the future, additional population data will be obtained for the geographical distribution and phenotypic variations of the Glu89Gln TTR mutation in order to obtain a clearer picture of the prevalence of this mutation. This kind of mutation has also been reported in many FAP patients in the South-West part of the Republic of Bulgaria.

Figure 2: Map of the TTR gene mutations distribution in North Macedonia.

Discussion

TTR-FAP is clinically manifested as progressive and irreversible sensory-motor and autonomic neuropathy. It usually begins with sensory disturbances in the toes, extending upward to the proximal part of the legs. Usually, when these disorders reach the knees, hands are also affected [5]. The clinical presentation of TTR-FAP is regulated by the interaction of a number of factors, including genotype, patient geographic origin, regional variation, gene mutation penetration and age at onset of symptoms. As a result, a wide range of phenotypes associated with TTR-FAP occurs [6]. This rare disease is transmitted in an autosomal dominant manner [4]. TTR-FAP has heterogeneity in genotype and phenotype, with more than 100 known mutations [7]. The type of mutation has a profound effect on the outcome, clinical presentation pattern, and the progressive nature of the disease. The most common and also the first mutation identified in the TTR gene is a Val 30 Met in the amyloid fibril protein [8]. The TTR-FAP phenotype depends on gender and age at the onset of symptoms. Male patients with late-onset of symptoms (age > 50 years) have an increased risk of developing cardiomyopathy and heart failure [9]. Our results for the geographical distribution of Glu89Gln positive patients in the Republic of Northern Macedonia has shown to be concentrated in the southeastern part of the country. Some historical evidence suggests that large numbers of migrations have focused on the coastline of the Mediterranean Sea. Interestingly, the Glu89Gln mutation is regis-

Conclusion

TTR-FAP is an autosomal-dominantly inherited fatal multisystem disease leading to death approximately 10 years after the onset of symptoms. The epidemiological features of this disease are of great importance in order to detect endemic regions. In this way, patients would be diagnosed with the gene pathogenic mutation earlier and at the same time preventing the progression of the disease. In the future, screening for this rare disease may be contemplated, especially in endemic areas.

Conflict of Interest

There is not a conflict of interest.

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Volume 3 Issue 12 December 2019