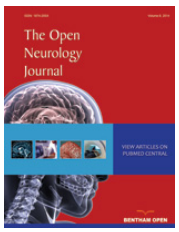

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CASE REPORT

Very Early Onset of ATTRE89Q Amyloidosis in a Homozygous Patient

Massimo Russo[1,*], Francescopaolo Cucinotta[1], Luca Gentile[1], Gian Maria Fabrizi[2], Federica Taioli[2], Giuseppe Vita[1], Antonio Toscano[1] and Anna Mazzeo[1]

[1]*Department of Clinical and Experimental Medicine, Unit of Neurology and Neuromuscular Diseases, University of Messina, Messina, Italy*
[2]*Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy*

Abstract:

Case Presentarion:

Hereditary transthyretin amyloidosis is a progressive, fatal disease that generally involves the peripheral nervous system, the autonomic nervous system, and the heart. It is autosomal dominant with different penetrance depending on the mutation and the genetic background. Many other missense mutations of the *TTR* gene may cause the disease. Being an overall rare disease is very rare to observe the condition of homozygosity. In particular, cases of homozygosity have been described in patients with ATTRV30M and ATTRV122I amyloidosis. In the former, the phenotype does not seem to be aggravated, having an age of onset and disease course that does not appear to differ from those of heterozygotes, while in the latter, the onset appears to be earlier.

Conclusion:

We report the first case of ATTRE89Q amyloidosis in a patient that was homozygous for the E89Q mutation in the TTR gene. The clinical phenotype resulted in the earlier disease onset reported in this form of amyloidosis, suggesting that the homozygous condition may be prognostically negative.

Keywords: Transthyretin, Cardiac Amyloidosis, Homozygous, E89Q, ATTRE89Q, Early-onset .

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1. INTRODUCTION

Hereditary transthyretin amyloidosis (ATTRv) is a progressive, fatal disease that generally involves the peripheral nervous system, the autonomic nervous system, and the heart [1]. Andrade made the first description in 1952; since then, for several decades, it has been considered a disease limited to Portugal. Later, it has been well documented and has also been found to be endemic in Japan and Sweden and is now considered a worldwide disease [2, 3]. It is transmitted as an autosomal dominant trait, due to missense mutations in the *TTR* gene, with V30M mutation identified in most patients in the endemic foci. However, more than one hundred and thirty other mutations have been described, with varying geographic distributions and organ involvement [4, 5]. The ATTRV30M amyloidosis originally described by Andrade is typically associated with sensory-motor axonal polyneuropathy, often involving the autonomic nervous system. Several other mutations can determine a similar phenotype [6, 7]. In recent years, many other mutations associated with a cardiac or a mixed phenotype have been identified and described [8].

The diagnostic delay, which was about 3-4 years up to 10 years ago, in recent years is often shorter, probably thanks to the attention which recently has greatly increased towards this disease [9]. Indeed, nowadays, drugs that are very effective in slowing or perhaps even stopping the disease are available; however, their effectiveness seems to be more evident in the early stages of the disease [10 - 12]. Life expectancy in untreated patients is nearly 10 years in V30M patients [13], but is much shorter in patients with mutations that cause cardiac amyloidosis. In ATTRI68L amyloidosis, in which the phenotype is predominantly cardiac, the survival is only 37% from the onset of the disease [14, 15].

Many different missense mutations of the *TTR* gene have been described within the same country or even in the same region [5, 6]. The clinical phenotype may be distinct in relation to the mutation and other genetic factors that are likely to determine a considerable clinical variability even in patients with the same amino acid substitution [5, 16, 17]. For example, it is well known that the ATTRV30M amyloidosis typically has an early onset in Portugal and a late-onset in Sweden and

* Address correspondence to this author at Department of Clinical and Experimental Medicine, Unit of Neurology and Neuromuscular Diseases, University of Messina, Messina, Italy; Tel: +390902213504;
E-mail: russom@unime.it

Japan. Polymorphism of mitochondrial DNA may be one underlying mechanism of onset variation [18].

As ATTRV30M amyloidosis is the most frequent, there are several descriptions of homozygous patients for this mutation in the literature. Despite this, the genotype-phenotype correlation of this condition is controversial: in some cases, it does not appear to differ significantly from heterozygosity; in others, it appears to cause an early onset [19 - 21]. Surprisingly, in several cases, a late onset of symptoms and a greater survival were reported [22]. Peculiarly, ATTRV30M homozygosity was associated with a higher incidence of vitreous opacity [20 - 22], and in Japan with CNS involvement [23].

As far as we know, the only other *TTR* mutation already described in the homozygous condition is V122I. ATTRV122I amyloidosis causes a predominant or exclusively cardiac involvement. ATTRV122I homozygosity was associated with an early age of onset of the disease, as observed in a cohort of 13 patients [24]. Furthermore, we have recently described a patient that surprisingly has a neuropathic rather than cardiac phenotype [25].

We describe the first case of ATTRE89Q amyloidosis in a patient that was homozygous for this mutation.

2. CASE REPORT

The patient reported that at the age of 32 years, he suffered from bilateral carpal tunnel syndrome (CTS), successfully treated with surgery. In the next 5 years, he did not present any symptoms, but when he was 37 years old, he started to complain of dyspnoea on exertion. He reported the appearance of breathlessness after climbing one floor of stairs, attributable to heart failure in the second class of New York Heart Association functional classification (NYHA). An electrocardiogram revealed sinus-rhythm and low-voltage of the QRS complexes. An echocardiogram showed diffuse left ventricular wall thickness, an interventricular septal wall thickness of 18 mm, and increased atrial septal thickness with pericardial effusion. He received a diagnosis of hypertrophic cardiomyopathy.

After symptoms worsened and dyspnoea became present even with minimal effort (NYHA class III), he underwent a heart transplant at the age of 40. Subsequently the transplant, he started taking anti-rejection therapy with cyclosporine. When he was 41 years old, he started to complain of sexual disturbances and, in the following years, he developed a progressive and severe autonomic dysfunction causing orthostatic hypotension and constipation alternating with diarrhea. Symptoms secondary to dysautonomia have been treated with symptomatic medications such as midodrine and loperamide, however, the compound autonomic dysfunction test score [26] calculated retrospectively fell from 18/20 to 10/20 over a 6-year period. Since the age of 47, he started to notice burning pain distally in lower limbs and a few months later, progressive gait disturbances attributed partly to pain and partly to lack of balance.

At the admission to our tertiary neuromuscular centre, neurological examination showed ataxic gait associated with a positive Romberg's maneuver. Mild weakness of ankle dorsiflexion and toe extension (MRC 4) and absent tendon reflexes. Pinprick was reduced distally up to the knees, while vibration sensation measured with the Rydel-Seiffer tuning fork was 0 at the ankles and 4 at the knees. Pinprick was slightly reduced in the median nerve area of distribution on both sides. Joint position sense was normal. A blood sample was taken for *TTR* analysis, and a neurophysiological evaluation was planned, but the patient died a few days later for sudden cardiac death. Unfortunately, a myocardial biopsy was not performed. However, the echocardiographic images were strongly suggestive of amyloid heart disease.

We then investigated the family history, discovering that it was suggestive of heart disease of unidentified cause. The parents were apparently unrelated, and they were born in different cities, although from the same geographical area in Syracuse. His mother and two brothers died suddenly at the age of 53, 58, and 63 years, respectively. The mother and one brother also had symptoms compatible with carpal tunnel syndrome some years before death. A genetic test for *TTR* revealed that he was homozygous for ATTRE89Q mutation (C265G).

3. DISCUSSION

Among the genetic mutations responsible for ATTRv amyloidosis, the E89Q mutation is the third most frequent worldwide, in agreement with an analysis of the THAOS register of 2013. This mutation has been associated with a mixed phenotype of the disease, characterized by neuropathic, cardiological, and autonomic involvement [27]. The geographical areas affected by this mutation are mostly Bulgaria and Italy (Sicily) [28], being in our region the variant that most often causes ATTRv cardiac amyloidosis [29].

In patients carrying this mutation in Bulgaria, the disease is characterized by differences in penetrance and age of onset also within the same family, for which a role played by regulatory and epigenetic factors in the etiopathogenesis of amyloidosis has been hypothesized. In Bulgaria, the average age of onset is 35-70 years, with a predominantly nervous involvement in half of the patients and cardiologic in the other half [30].

In Italy, instead, a recent study of forty subjects carrier of this mutation showed how the onset of the disease occurs during the 5^{th}-6^{st} decade with neuropathic disorders (paraesthesia, gait, and balance disorders), carpal tunnel syndrome and dysautonomic disorders (orthostatic hypotension and constipation/diarrhea), with subsequent appearance of heart failure. Nevertheless, instrumental evaluations such as ECG, echocardiography, and cardiac scintigraphy in asymptomatic subjects have shown that cardiac involvement precedes neurological and autonomic involvement. The main cause of death in these patients is heart failure associated with amyloidosis. The mean age at death was 63 years [5, 31].

To our knowledge, this is the first patient homozygous for this allele. This case showed the earliest onset of disease we have ever observed for ATTRE89Q amyloidosis, with an onset at 32 years of age, with bilateral CTS, followed by severe progressive cardiomyopathy five years later that made necessary heart transplantation. Severe autonomic involvement

appeared, later on, followed by sensory-motor polyneuropathy. Overall, patient survival from onset of cardiac symptoms was relatively long, not showing a more aggressive course of the disease than that observed in patients heterozygous for this mutation [6]. However, we must consider that early-onset probably favoured heart transplantation, without which the patient's survival would have been reasonably much shorter.

CONCLUSION

The medical awareness of ATTR amyloidosis has increased over the past years and the medical awareness is now higher due to the availability of new innovative drugs motivating neurologists to include the examination of the transthyretin gene in patients with axonal polyneuropathy of unknown cause, especially when associated with carpal tunnel syndrome or dysautonomia [6, 32]. However, ATTRv cardiac amyloidosis is still underdiagnosed, and the very long diagnostic delay of this clinical case is proof of this. Cardiologists should pay close attention to the characteristic echocardiographic aspects suggestive of this form of cardiac amyloidosis [29]. In case of suspicion, 99mTc-diphosphonate imaging and/or magnetic resonance imaging with late gadolinium should represent the second level exams [33]. *TTR* gene analysis must be performed to confirm the diagnosis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethics committee of the province of Messina, Italy, Report number 3/2016.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Mrs. V.G has authorized Dr. Massimo Russo to use the clinical data in his possession relating to her husband for descriptive scientific purposes.

STANDARDS OF REPORTING

CARE guidelines and methodology were followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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