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TRANSTHYRETIN -RELATED FAMILIAL AMYLOID POLYNEUROPATHY (TTR-FAP) POLINEUROPATHY – CHALLENGE DIAGNOSIS AND CASE PRESENTATION

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ABSTRACT

Introduction Transthyretin -Related Familial Amyloid Polyneuropathy (TTR-FAP) is a rare cause of polyneuropathy, mainly in Romania, but also in other geographic area of Europe, Japan and north America.

Polyneuropathies are common in neurology practice, but prevalence and incidence are not known, usually are underreported and misdiagnosis. Almost one third of polyneuropathies remain idiopathic, in spite of extensive work-out to identify etiology. Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is a multisystemic disease neurological manifestation caused by the accumulation of amyloidogenic transthyretin (TTR) protein in tissues. It is an autosomal dominant syndrome, and there are more than 100 forms of TTr associated with FAP. The disease is characterized by progressive peripheral and autonomic neuropathy, and visceral amyloid involvement like cardiac amyloidosis.

Case presentation We present the case of a male, aged 48, who experienced from 18 month paresthesias of distal inferior limb and fatigue, with an important weight loss. The patient was diagnosed with mixed polyneuropathy, and he was extensively investigated. Etiology was not established. He began to feel dizziness and faints several times, and these new features lead to our final diagnosis.

Conclusions Etiology of a polyneuropathy case could be very challenging for general neurologist due to a numerous causes. A large variety of signs and symptoms lead the clinician to a narrow diagnostic possibilities and still this might take a long time. Polyneuropathy and cardiac involvement make a mark for life threatening disease but potentially curable

Keywords polyneuropathy, transthyretin hereditary amyloidosis, cardiac amyloids

Introduction

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Polyneuropathies are common in neurology practice, but prevalence and incidence are not known, usually are underreported and misdiagnosis. Almost one third of polyneuropathies remain idiopathic, in spite of extensive work-out to identify etiology. Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is a multisystemic disease neurological manifestation caused by the accumulation of amyloidogenic transthyretin (TTR) protein in tissues. It is an autosomal dominant syndrome, and there are more than 100 forms of TTr associated with FAP. The disease is characterized by progressive peripheral and autonomic neuropathy, and visceral amyloid involvement like cardiac amyloidosis.

Case Presentation

A 48-year-old male presented to our clinic with paresthesias of distal inferior limbs, fatigue, loss of appetite and increasing gait disturbances of 18 months duration. He reported tingling pain

in the feet and lower legs as well as an important weight loss, about 20 kg.

He was diagnosed with polyneuropathy of unknown origin 6 months after onset of symptoms. His medical history was empty. Moderate intake of alcohol was declared, about 4 units of alcohol per week.

His family's medical history was unremarkable, but he mentioned about premature death of his father.

First neurological examination - neurological clinical examination revealed a distal hyporeflexia with absence of Achilles tendon reflexes, mild distal motor impairment of inferior limb 4/5 MRC, walking on heels and toes preserved with mild difficulty, no objective signs of sensitivity impairment despite of complains of parestesias and pain.

General examination shows no abnormality except for asthenic conformation. However due to appetite decrease and loss of weight (14 kg), extensive workout was performed. Superior digestive endoscopy revealed mild chronic gastritis, resolved after 1 month of PPI and sucralfate intake. Paraneoplastic panel including alpha-fetal protein, CA 19-9, CA 72-4, carcinoembryonic antigen, PSA, NSE were negative. HIV and syphilis serology, viral hepatitis, thyroid functions, folates, B12 deficiency, were negative, as well.

Motor conduction studies of the inferior and upper extremities, including investigation of both the median and ulnar nerves established axonal chronic polyneuropathy. No other findings were highlighted. Rheumatology assessments included antinuclear antibodies negative. The patient was referred for MRI of the lumbar spine that showed minor lumbar discard of L4-L5, and L5-S1 with impingement of roots of L4 and S1. Conus medularis and cauda equina were normal.

Immunoelectrophoretic was normal.

The diagnostic was presumable idiopathic axonal polyneuropathy, after ruling out main causes of polyneuropathies. After six months, the complains of the patient worsen, with progressive motor deficit and impairment of walking, in spite of empirical treatment with alpha lipoic acid. Lumbar puncture was done and it showed minor hyperproteinorahia (59 mg/dl),10 elements, positive Pandy + and normal glucose in CSF. Electromyography was performed and shows the same abnormality, sustaining the axonal chronic polyneuropathy diagnostic. On this examination, median nerve entrapment signs were more exhibit, so further workout were required. Sural nerve biopsy shows severe neuropathy with axonal degeneration and secondary demyelination process. No amyloid deposits are found. Mild paresthesias of the superior limb extremities are declared of the patient. A subsequent treatment with corticosteroids was started, for a period of, without no response. The CIDP form was abandoned as diagnostic in this case.

A routine cardiologic examination and transthoracic echocardiography was done, due to increased fatigue syndrome of this patient. No abnormalities were found. Gabapentin was added to treatment. 8 months later, the complains of the patient includes vertigo and disequilibrium, with several falls.

Arterial hypotension was discovered at this point, (clinostatism Tas=130/80 mmHg, orthostatism Tas 80mm Hg) :Targeted anamnesis reveals erectile dysfunction for one year and so called dizziness for a few months. Constipation was also identified. Hippocratic finger or clubbing were observed for first time.

Transthoracic echocardiography shows cardiomyopathy with features of amyloid deposition, which is a very important clue for the diagnosis. Left ventricular hypertrophic changes with sparkling like aspects is shown, including thickening of the atrial wall, interatrial septum and atrioventricular valves.

A large size of left atrial ventricle is shown. Diastolic disfunction is more important than systolic one. All aspects can be observed in Figures 1, 2, 3

18 months after onset, genetic test for TTR Fap polyneuropathy was finally done and shows PE 74 Q Glu54GLP mutation. Cardiac MRI confirm amyloid deposit.

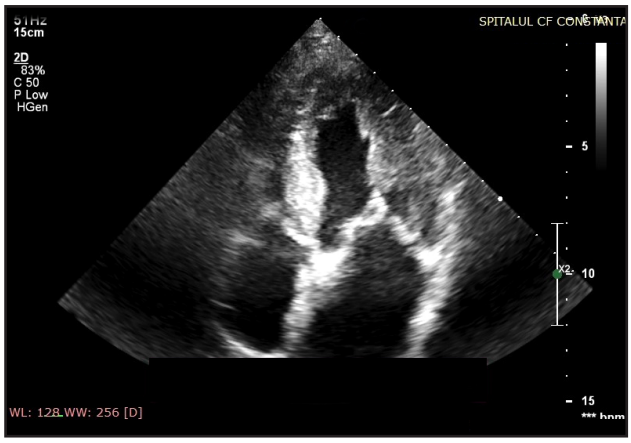

Figure 1

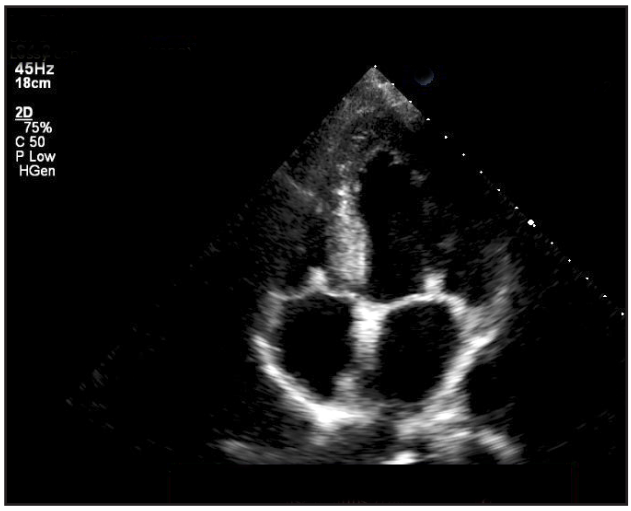

Figure 2

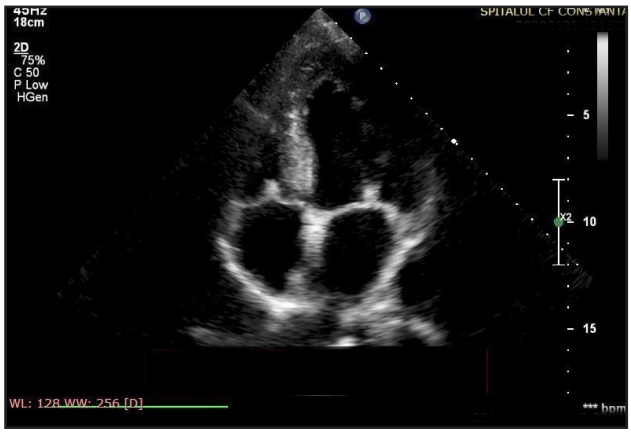

Figure 3

Neurological examination confirms the progression of tetramyelic motor deficit involving more distal than proximal all four limbs. Tafamidys (20 mg /day) treatment and symptomatic treatment of arterial hypotension (mydrodrine) were initiated at this point.

After another 3 months, due to increase sensitive symptoms of medial nerve entrapment, a surgical treatment was performed. The son of the patient was tested and found positive for same mutation at 18 years old, confirming the hereditary inheritance.

Discussions

Hereditary transthyretin (ATTR) amyloidosis is a highly autosomal dominant disease which shows broad genetic and phenotypic variability. The knowledges of this disease increased constantly in the past 5 years, and lead to new genes identifications (1).

Peripheral nerves disease could be present, even without other marks of systemic involvements, such as cardiomyopathy or dysautonomic features. General presentation as a mixed polyneuropathy could lead to misdiagnoses or delay of etiological treatment.

In our case, the complete diagnostic was finally made up after 18 months.

Differential diagnoses include a large pallet of acquired polyneuropathies such as paraneoplastic, metabolic (alcoholic or B12 deficiency), chronic demyelinated inflammatory polyneuropathy without relapses, infectiousness polyneuropathies (HIV or syphilis)

Other causes, ruled out due to extensive neurological work out, were lumbar spinal stenosis, lumbo-sacral radiculopathy, paraproteinemic polyneuropathies, vasculitis peripheral polyneuropathy, and even motor neuron disease. Lack of family history and absence of early recognized cardiac involvement led to a delay for genetic testing in this case. We also noticed the absence of amyloid deposits at sural nerve biopsy. But those biopsy results vary at various stages of the disease and negative results should not rule out genetic testing (2, 3).

Chronic inflammatory demyelinating polyneuropathy (CIDP) was suspected even in absence of recurrent pattern, sustained by electromyographic findings and cerebrospinal fluid (CSF) results. There is also no obvious explanation for presence of mild cytoalbuminological dissociation in CSF.

Genetic test was performed and identify a mutation Glu54GLN. In Romania, this mutation was first described in 2012, and since then 23

patients (18 symptomatic and 3 asymptomatic) were identified. All patients, including our patient, originated from the same geographical area, in NE of Romania, but theoretically from unrelated families (4).

Our patient showed mixed phenotype, both neurological and cardiac, of TTR-FAP. Distal paresthesia was the first symptom, and autonomic disfunction, symptomatic carpal tunnel syndrome and cardiac involvement occurred in time.

Cardiac characteristics of Glu54Gln-mutated hATTR has similar echocardiographic features to other forms of ATTRh.

Existing data suggest that weakness may not be appreciated until 50 to 80 % of fibers are lost (5), thus increasing the difficulty of the diagnosis and postponing the moment the patient present for consultation. It is rare for polyneuropathy to be purely motor or purely sensitive, most of them are mixed and this could lead to a large variety of etiology

TTR amyloid cardiopathy is a life threating condition defined as intramyocardial deposits of amyloid fibrils derived of pathogenic mutation of transthyretin, hereditary or wild type of TTR (6) Treatments options for TTR FAP are the TTR tetramer stabilizer tafamidis, patisiran and inotersen (7).

Tafamidis has been shown to stabilize the variant transthyretin tetramer, including the Glu54Gln variant, in an ex vivo study (8). Considering that a good knowledge of the different TTR mutations might help to improve the care for the patients, this precise, genetic diagnosis is of great importance (9).

Conclusions

Assessment of a polyneuropathy case could be very challenging for general neurologist due to a numerous factors.

Details regarding progression in time and new information are important, as well as targeted anamnesis about autonomic dysfunction, for example. Symptoms of early satiety, constipation, diarrhea, impotence, abnormal sweating and lightheadedness must be carefully investigated for. Autonomic symptoms could be a component of a generalized polyneuropathy or a distal small fibers neuropathy. When autonomic impairments are detected, we should consider metabolic neuropathy like in diabetes, amyloidosis, or paraneoplastic syndromes, or even hereditary neuropathy. A genetic etiology should be considered even without positive family history, in a generalized polyneuropathy presentation, with relative early age at onset.

ATTR amyloidosis should be considered and TTR gene testing performed in the differential diagnosis of idiopathic sporadic progressive axonal and mixed axonal-demyelinating polyneuropathies.

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