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IM - CASE RECORD

Syncope and autonomic failure in a middle-aged man

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Colombo, Solbiati (internal medicine)

An Albanian 54-year-old man presented to the Emergency Department (ED) after a transient loss of consciousness that occurred while walking in the street. The episode was preceded by dizziness, vertigo and palpitations, and was followed by fatigue and paraesthesia in the right arm and leg. A long-standing history (1–2 years) of lower limb fatigue with progressive walking problems, slow speech rate, confusion and severe weight loss (about 70 kg) was reported. The patient also described previous syncopal episodes similar to the present one. A patient's friend, who had not seen him in years, noticed that the patient was more confused and slow in moving and speaking than what he recalled.

His past medical history was positive for type-2 diabetes, visual impairment in the left eye and a previous vitreous haemorrhage. The family medical history was unremarkable.

On admission to the Internal Medicine Unit, the patient was alert, attentive and partially oriented, with no sign of dehydration, hypo-perfusion or congestive heart failure. Chest and abdomen physical examinations were normal. Blood pressure was 95/50 mmHg in the supine position, and the systolic blood pressure dropped to 65 mmHg while standing. Heart rate was 78 beats/min and regular, peripheral oxygen saturation was 96% in room air and body temperature was 36 °C. Neurological examination showed slurred speech, severe loss of muscle mass with diffuse limb fasciculations, diffuse absence of tendon reflexes, no response to plantar cutaneous stimulation, distal anaesthesia, postural tremor along with lower limb weakness, ataxic gait, bilateral foot drop and postural instability, distal anaesthesia for epicritic and proprioceptive sensibility without any impairment in the cranial nerves.

Routine blood tests and chest X-ray study were normal. The ECG showed low voltages in both precordial and limb leads. The brain computed tomography was normal.

Preliminary investigations

Colombo, Solbiati, Ceriani (internal medicine)

The transient loss of consciousness was interpreted as syncope due to orthostatic hypotension. Considering the patient history of recurrent syncopal episodes and the abnormal ECG, 72-h ECG telemetry and a trans-thoracic echocardiography were performed. The monitoring was negative for significant dysrhythmic events, and the echocardiography showed left ventricular diastolic dysfunction and hypertrophy, especially at the interventricular septum (14 mm), which had a sparkling appearance.

Orthostatic hypotension along with muscular hypotrophy, widespread absence of tendon reflexes and loss of sensitivity suggested a problem of the peripheral nervous system. In agreement with our consultant neurologists, we obtained an electromyography: it showed a severe chronic and active axonal polyneuropathy. To deepen the differential diagnosis of the polyneuropathy that was the leading condition at that moment, we asked our neurologist for a consultation.

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Further investigations

Frattini, Di Fonzo (neurology)

The presenting syndrome was compatible with a chronic axonal polyneuropathy possibly due to vitamin deficiency, infection or a paraneoplastic cause (see Table 1).

The patient underwent brain and spine MRI and lumbar puncture. The MRI was normal, while the cerebrospinal fluid analysis showed normal glucose and cell counts and an increase in proteins (195 mg/dl). The cytological examination, search for oligoclonal bands, PCR for herpes simplex virus, Epstein–Barr virus, varicella–zoster virus, human herpesvirus 6, Enterovirus, Treponema, Toxoplasma and Cytomegalovirus, *B. burgdorferi* IgG and IgM, and Gram stain and culture for bacteria and mycobacteria were all negative. Blood tests for QuantiFERON-TB, B- and C-hepatitis, search for oligoclonal bands, *B. burgdorferi* IgG and IgM, screening for celiac disease, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies and HIV were all negative. Vitamin B12, folate, serum protein electrophoresis, erythrocyte sedimentation rate, kidney function and urine test were normal. To note, a TSH-suppression test showed normal fT3 and fT4 and negative anti-thyroid antibodies, normal kappa- and lambda-light-chain values with a slight increase in their ratio. To exclude possible paraneoplastic aetiology of the neuropathy, we obtained neck, chest and abdomen contrast-enhancement computed tomography, PET scan, testicular ultrasound, upper endoscopy (with biopsies) and tumour biomarkers, all negatives. Anti-Hu-Yo-Ri-MA1-MA2-CV2-amphiphysin antibodies were negative in both serum and cerebrospinal fluid.

Colombo, Solbiati, Ceriani (internal medicine)

All the tests suggested by our consultant neurologists were negative. Because of the presence of peripheral neuropathy, left ventricle hypertrophy and evidence of low-voltage at ECG, we suspected that systemic amyloidosis might be the cause of the patient's symptoms. Accordingly, the patient underwent abdominal fat pad biopsy, bone marrow aspiration with biopsy and cardiac MRI for possible cardiac and neuropathic amyloidosis.

Zilocchi (radiology)

Contrast-enhanced cardiac MRI showed bi-ventricular hypertrophy, diffuse sub-endocardial delayed enhancement and little pericardial effusion; these findings are strongly suggestive for cardiac amyloidosis (see Figs. 1, 2).

Diagnosis and brief discussion

Frattini, Di Fonzo (neurology); Del Bo (genetics)

Abdominal fat pad biopsy and bone marrow aspiration and biopsy were negative. Since the screening for AL amyloidosis was negative, we obtained a gene sequencing of the transthyretin (ATTR) gene coding regions looking for hereditary amyloidosis, which showed a heterozygous mutation c.160 A > G, p.Arg34Gly. This mutation is known to be pathogenic, as demonstrated in one male patient from Kosovo [1].

Table 1 Causes of axonal neuropathies

Metabolic	Diabetes mellitus, chronic renal failure
Paraproteinemia	Multiple myeloma, Waldenstrom's disease, MGUS, POEMS
Vitamin deficiency	B1, B12, B7, nicotinic acid
Toxic-iatrogenic	Chemotherapeutic drugs, phenytoin, isoniazid, alcohol
Vasculitis	Wegener's granulomatosis, Churg–Strauss syndrome, Sjogren's syndrome, rheumatoid arthritis, lupus erythematosus
Paraneoplastic syndromes	Especially associated to small-cell carcinoma of the lung, B-cell lymphoma, ovarian cancer (anti-Hu, CRMP-5, LGI1)
Infections	Leprosy, HIV, lyme, hepatitis
Hereditary axonal polyneuropathies	CMT2, CMTX, familial amyloidosis, porphyria
Others	Sarcoidosis, traumatic

MGUS Monoclonal gammopathy of uncertain significance, *POEMS* polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy skin change syndrome, *CRMP-5* collapsing response mediator protein 5, *LG1* leucine rich. Glioma inactivated 1, *CMT2* Charcot–Marie–Tooth type-2 disease, *CMTX* Charcot–Marie–Tooth X-linked disease.

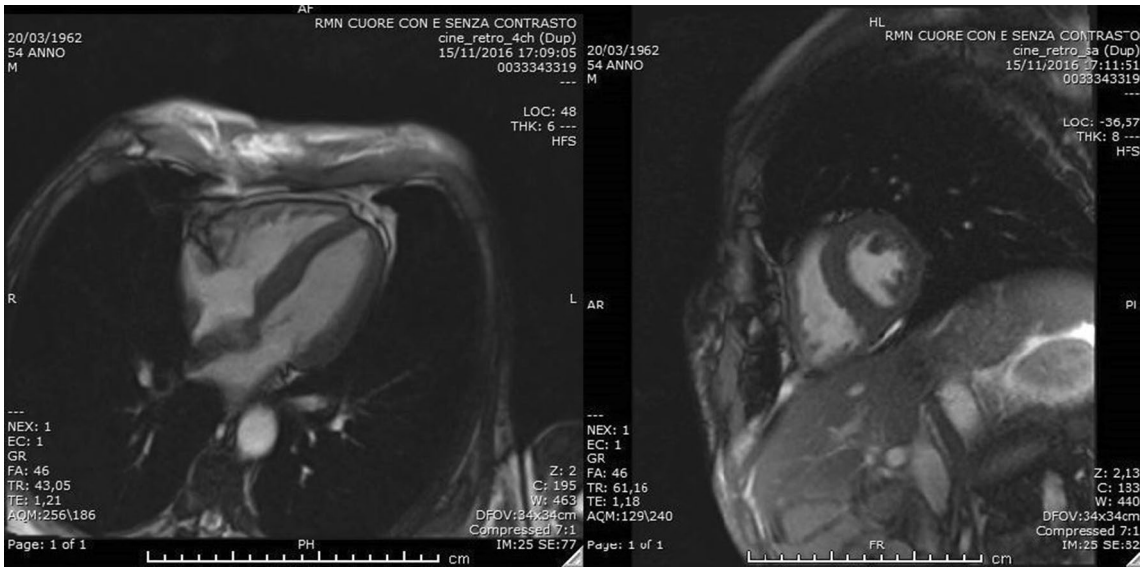

Fig. 1 Cardiac MRI four chambers and short-axis two chambers in cine-TrueFISP sequences. Note the important bi-ventricular hypertrophy and little pericardial effusion typical of cardiac amyloidosis

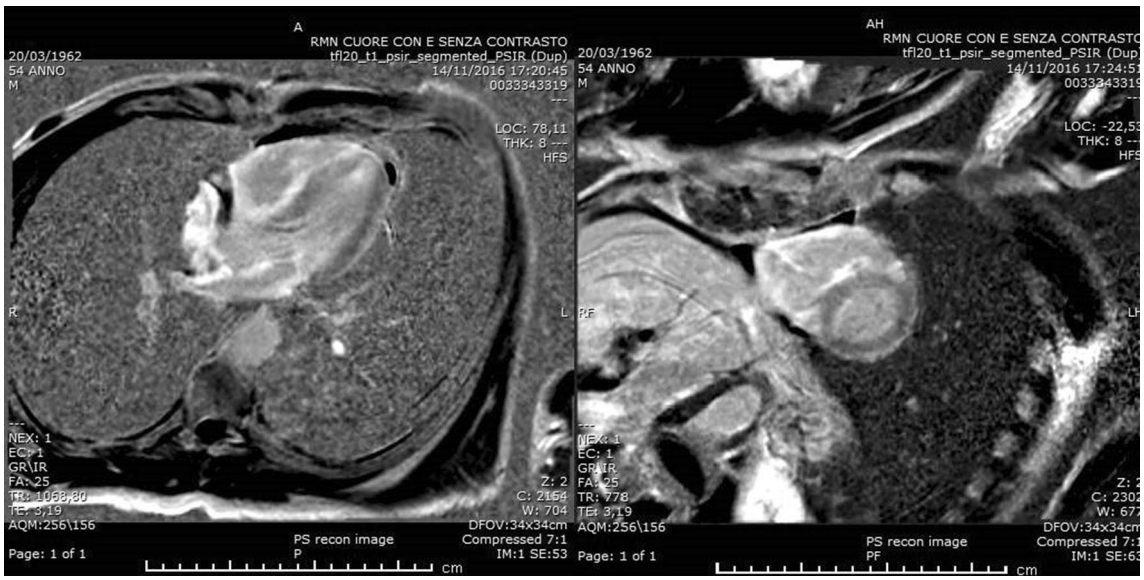

Fig. 2 Cardiac MRI four chambers and short-axis two chambers view in T1 PSIR sequences. Note the subendocardial delayed enhancement typical of amyloidosis

Colombo, Solbiati (internal medicine)

Cardiac amyloidosis and amyloid neuropathy are caused by a deposition of amyloid protein in the heart or in nerves. In primary (or AL) amyloidosis, the amyloid protein is made of misfolded immunoglobulin light chains. The most common non-AL amyloidosis is ATTR amyloidosis that is due to a deposition of a wild type (in the elderly) or mutated transthyretin (i.e. hereditary amyloidosis). Amyloid cardiomyopathy is common in both AL and ATTR amyloidosis; vice versa nerve involvement is more common in hereditary ATTR amyloidosis.

To make a diagnosis of systemic amyloidosis, both a suggestive clinical picture and a demonstration of amyloid deposition in the organism are required [2, 3]. Minimally invasive site biopsies may demonstrate tissue amyloid deposition with little harm for the patient, but they have only a moderate sensitivity. For example, fat pad aspiration biopsy

has an estimated sensitivity and specificity of 60–85% and 92–100%, respectively, depending on the site of involvement and type of amyloidosis [4, 5]. Bone marrow biopsy has even a lower diagnostic accuracy, with a sensitivity of 50–80% [6].

Even if we could not demonstrate a pathological accumulation of amyloid protein in the patient, we deemed our findings sufficient for the diagnosis. First, the clinical picture was typical; second, the causal role for the particular mutation we found was already described [1]; and third, cardiac magnetic resonance results were highly specific for cardiac amyloidosis. Cardiac MRI has a very good diagnostic accuracy, with a specificity reaching 92% in a recent meta-analysis [7]: a positive high-specificity test to rule-in the diagnosis if the clinical presentation is typical [8]. For these reasons, we judged further invasive assays (such as myocardial biopsy) unnecessary and unsafe [9].

Management

Colombo, Solbiati (internal medicine); Frattini, Di Fonzo (neurology)

The management of hereditary ATTR amyloidosis depends on the disease stage. In young patients with few co-morbidities and little neurological involvement, liver transplantation is the treatment of choice. In older patients with more severe neurological involvement or multi-organ dysfunction, the target is to slow disease progression [3]. Two drugs are available for disease control in hereditary ATTR; they both act on protein misfolding. Diflunisal is a low-cost non-steroidal anti-inflammatory drug that slows neurologic impairment [10]. Tafamidis is a novel high-cost drug, specifically designed for ATTR amyloidosis that slows the neurologic progression of the disease [11].

In our case, due to the patient's lack of healthcare reimbursement at the time of hospital discharge, we started diflunisal to reduce the neurological impairment rate of progression. Furthermore, we advised the patient and his family to have genetic counselling performed, and we found that the patient's daughter was affected by the same mutation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in the present study involving human being were in accordance with the ethical standards of the institutional and national research committee and with 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

References

1. Levy J, Hawkins PN, Rowczenio D, Godfrey T, Stawell R, Zamir E (2012) Familial amyloid polyneuropathy associated with the novel transthyretin variant Arg34Gly. Amyloid 19:201–203
2. Patel KS, Hawkins PN (2015) Cardiac amyloidosis, where are we today? J Intern Med 278:126–144
3. Adams D, Suhr OB, Hund E et al (2016) First European Consensus For Diagnosis, management and treatment of transthyretin familial amyloid polyneuropathy. Curr Opin Neurol 29:S14–S26
4. Van Gamaren II, Hazenberg BP, Bijzet J, van Rijswijk MH (2006) Diagnostic accuracy of subcutaneous aspiration for detecting systemic amyloidosis and its utility in clinical practice. Arthritis Rheum 54:2015–2021
5. Perfetto F, Cappelli F, Bergesio F et al (2013) Cardiac amyloidosis: the heart of the matter. Intern Emerg Med 8:191–203
6. Kyle RA, Greipp PR (1983) Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 58:665
7. Zhao L, Tian Z, Fang Q (2016) Diagnostic accuracy of cardiovascular magnetic resonance for patient with suspected cardiac amyloidosis, a systematic review and meta-analysis. BMC cardiovasc Disord. 16:129
8. Costantino G, Montano N, Casazza G (2016) When should we change our clinical practice based on the results of a clinical study? Diagnostic accuracy studies II: the diagnostic accuracy. Intern Emerg Med 11:755–757
9. Rahman JE, Helou EF, Gelzer-Bell R et al (2004) Noninvasive diagnosis of biopsy-proven cardiac amyloidosis. J Am Coll Cardiol 43:410
10. Berk JL, Suhr OB, Obici L et al (2013) Repurposing diflunisal for amyloid polyneuropathy: a randomized clinical trial. JAMA 310:2658–2667
11. Waddington Cruz M, Amass L, Keohane D, Schwartz J, Li H, Gundapaneni B (2016) Early intervention with tafamidis provide long term delay of neurologic progression in transthyretin hereditary amyloid polyneuropathy. Amyloid 23:178–183