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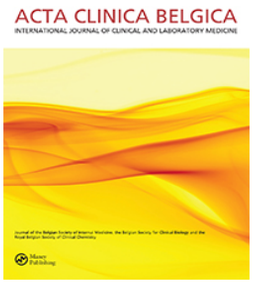

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Case Report

NEUROARTHROPATHY SECONDARY TO TRANSTHYRETIN AMYLOIDOSIS (ATTR V30M)

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ABSTRACT

In this article we report the case of a 46-years-old Portuguese woman admitted in our orthopaedic ward with right knee pain. Radiological findings were consistent with neuroarthropathy. After exclusion of the most common causes of polyneuropathy, Familial amyloid polyneuropathy (FAP) was diagnosed by the discovery of a mutation V30M on chromosome 18 by polymerase chain reaction on a fibroblast culture of her skin biopsy.

FAP is one of many aetiologies of polyneuropathy. Although a rare disease, genetic screening in selected populations makes early diagnosis and prompt treatment of asymptomatic family members readily available.

Key words: Neuroarthropathy, Transthyretin amyloidosis, Portuguese amyloidosis, Familial amyloid polyneuropathy type I

INTRODUCTION

Familial amyloid polyneuropathy (FAP) type I, also known as Transthyretin (TTR) amyloidosis, is the most common form of systemic hereditary amyloidosis. It is transmitted in an autosomal dominant way and was first described in 1952 by Andrade *et* al, in a group of Portuguese patients suffering from peripheral polyneuropathy and autonomic dysfunction (1).

The mutation causes a substitution of methionine by valine at position 30 (Val30Met) of the TTR protein, located on chromosome 18, which is synthesised by the liver. This results in a misconfiguration of the protein, which becomes insoluble and precipitates into multiple tissues (2). These amyloid deposits can cause a wide range of symptoms appearing in adulthood.

This type of amyloidosis was predominantly reported in Portugal, Scandinavian countries, Japan and the USA. In Portugal the prevalence of FAP (Val30Met) is estimated to be 1/538 with a penetrance of 80%. The mean age of onset of symptoms is 33 years (3). Nevertheless, the diagnosis is often delayed because of nonspecific symptoms and slow progression.

In this report, we describe a rare case of a neuroarthropathy leading to the diagnosis of Portuguese familial amyloidosis after one year of investigation.

CASE REPORT

On December 2007, a 46-years-old Portuguese woman was admitted to our orthopaedic ward for evaluation of arthropathy of her left distal femur. She was previously diagnosed with secondary osteomyelitis and had undergone multiple surgeries following an open fracture of her left femur in 1995.

Her past medical history was significant for bilateral carpal tunnel syndrome and subclinical hypothyroidism. Review of systems was positive for moderate alcohol consumption, urinary incontinence, frequent nausea and alternating bouts of diarrhoea and constipation.

A magnetic resonance imaging (MRI) performed on admission revealed a fracture of the proximal tibia as well as severe destruction of the joint without any signs of infection. A white cell nuclear scan by Indium 111 was negative for active infection as well.

In April 2008, a left knee arthroplasty with transplantation of allogeneic bone was performed. The histopathology of the perioperative specimen showed nonspecific inflammatory tissue, with no evidence of neoplasia or infection despite an antibiotic-free period of two months. Joint and bone destruction were therefore attributed to sequelae of her osteomyelitis. There were no peri-operative complications and the patient was discharged after 10 days of hospitalisation.

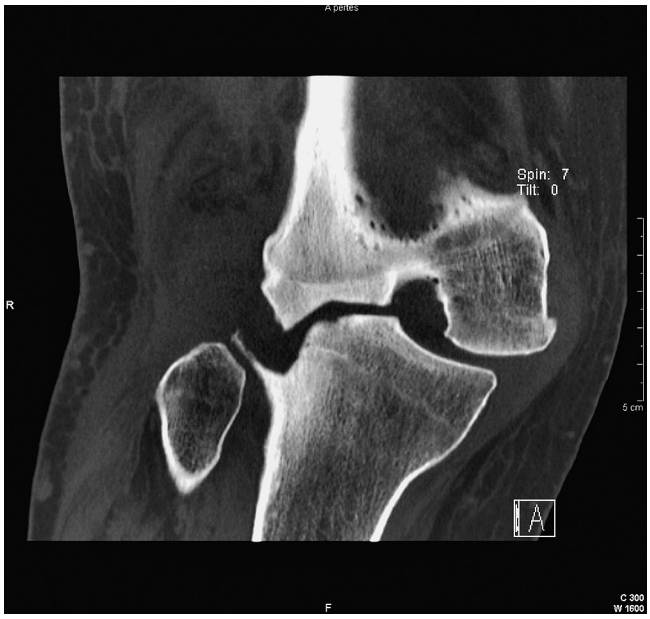

Figure 1: *CT-scan. Mirror lesion of the medial femoral condyle with osteoarthritic changes. Presence of numerous bone fragments in the joint without signs of densification.*

Three months later she was readmitted in the internal medicine ward with chronic pain of the right knee, and bilateral paresthaesia/hypoesthaesia of her lower extremities.

A computed tomography of the right knee (Figure 1) showed osteolysis of the external femoral condylum and a fracture of the proximal tibia. The hypothesis of a neurological origin of this arthropathy was elicited.

Clinical examination revealed orthostatic hypotension. Neurological examination of the upper extremities was unremarkable. Reflexes were absent in the lower extremities and she developed a trophic lesion on the right foot during hospitalisation.

The laboratory findings (CRP, FBC, fasting glucose, LFTs, U&Es, B12, HIV, and Syphilis tests)were within normal limits. TFTs showed subclinical hypothyroidism. Hypergammaglobulinaemia was noted on the electrophoresis, with no monoclonal peak and a negative Bence Jones proteinuria. Kidney function was normal, and no proteinuria was found.

Electromyographic study (EMG) showed a motor-sensory polyneuropathy in all four limbs. Somesthaesic-evoked potential test showed central motor conduction anomalies in the lower limbs and dysfunction of the peripheral motor conduction of the right upper limb. A peripheral neuropathy of both the right popliteal and median nerve was also found. MRI of the head and spinal cord were normal. No lumbar puncture was performed. Ophthalmological examination did not show any abnormalities.

Bone density assessment (DXA scan) was normal (for age and sex).

Transthoracic echocardiography of the heart was normal.

A knee arthroplasty was performed, during which synovial, bone, skin, and vastus medialis muscle biopsies were done. The histopathology test revealed no amyloid deposits and the red congo stain was negative.

The diagnosis of polyneuropathy combined with a secondary arthropathy was confirmed. The ethnic origin of our patient led us to suspect FAP type I, which was eventually confirmed by the discovery on fibroblast culture of a heterozygous *p.*Val30Met substitution of the TTR protein, located on chromosome 18.

Later, upper gastro-intestinal endoscopy with biopsies done in another hospital revealed a positive red congo stain of the muscular mucosa.

Genetic screening of family members performed after our patient was diagnosed, revealed that one of her daughters was an asymptomatic carrier, and that one of her brothers with a history of difficulty walking had the mutation (Figure 2). He eventually developed the disease. Unfortunately her parents' medical history was not available.

DISCUSSION

The main manifestations of FAP-type I are sensory-motor peripheral neuropathy and autonomic dysfunctions. Amyloid deposits can cause a wide range of organ dysfunction such as proteinuria, renal impairment, vitreous opacity, cardiomyopathy and carpal tunnel syndrome.

Neuroarthropathy, also called Charcot arthropathy, is a progressive destruction of the joints, mainly of the lower limbs. The aetiology is a sensory neuropathy, which occurs mostly in patients with a history of diabetes mellitus, syphilis, chronic alcohol abuse, syringomyelia or spinal injuries (5).

Neuroarthropathy is mainly diagnosed by imaging.

Neuroarthropathy of the knee displays specific radiological features: destruction of the medial joint compartment and, in particular, depression of the medial tibia plateau in an early stage of the disease. This subsequently leads to an unstable joint (6).

Diagnosis of neuroarthropathy secondary to FAP is very difficult.

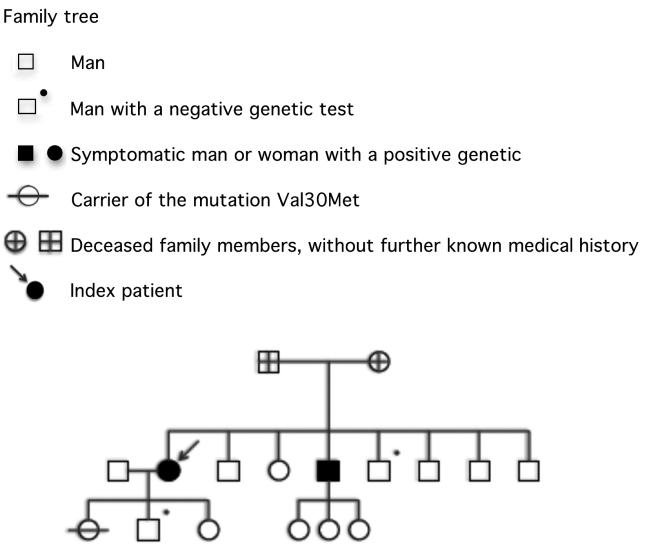

Figure 2: *Family tree.*

A negative patient or family history does not exclude the diagnosis. It is also important to rule out the most other common causes of a sensory neuropathy.

Confirmation of diagnosis in a patient with strong suspicion of neuroarthropathy secondary to FAP-type I requires genetic testing of the mutation V30M on chromosome 18 by PCR on a fibroblast culture.

In our patient, clinical features (i.e. polyneuropathy, carpal tunnel syndrome with no obvious explanation), presence of amyloid deposits in duodenal mucosa; in association with the above-mentioned mutation are strong arguments in favour of this diagnosis.

Treatment of the neuroarthropathy is challenging. Although some proposed conservative approaches including immobilisation and bisphosphonate treatment are effective, further treatments, particularly in the context of FAP, need to be studied.

Reconstructive surgery in this setting is technically difficult and complications are common. For these reasons, it is typically reserved for unstable joints or fractures (mostly associated with severe deformities). Arthrodesis is the recommended surgery in this case. However, it has been suggested that arthroplasty could be more effective for neuroarthropathy in non-diabetic patients (7).

At present, liver transplantation is the only available treatment able to stop the progression of the disease. In fact, the transplanted liver synthesises "wild type" TTR replacing the amyloidogenic TTR (ATTR) formerly produced by the liver. And yet, complications of the amyloid deposits, like neuroarthropathy, can still occur after transplantation (8).

In conclusion, neuroarthropathy of the knee is rare, but should always be considered in patients with peripheral neuropathy and a swollen knee. Early recognition of the typical radiological findings and prompt treatment may be effective in preventing development of serious deformities and disability.

FAP is also a rare cause of polyneuropathy with secondary arthropathy, and should be considered after exclusion of the most common causes, especially in patients of Portuguese, Japanese or Swedish origin.

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CONFLICT OF INTEREST: None:

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