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Leptomeningeal amyloidosis due to A25T TTR mutation: A case report^{☆,☆☆}

Amiloidosis leptomeníngea debida a la mutación A25T TTR. A propósito de un caso

Dear Editor:

Leptomeningeal amyloidosis is a rare form of amyloidosis caused by a limited spectrum of mutations in the transthyretin gene (TTR), including the mutation in which threonine replaces alanine at codon 25. We describe the case of a patient with the A25T TTR variant. Only one report of such a case exists in published literature.^{1,2}

The patient was a 53-year-old woman with a 4-year history of progressive symptoms of vertigo, paraparesis, and ataxic gait. One month before, she had experienced sudden neurosensory hearing loss. A neurological examination revealed normal higher functions and right-sided hypoacusia. Deep tendon reflexes were present and generalised, with intact bilateral extensor plantar reflexes. We found moderate paresis of the right leg with tactile hypoesthesia and hypopalaesthesia in both legs. Ataxic gait was also present. The CSF study revealed hyperproteinaemia (177 mg/dL) and xanthochromia. The electromyography study ruled out peripheral neuropathy. Cranial and spinal cord magnetic resonance imaging revealed superficial siderosis in the left sylvian fissure and signs of chronic bleed in CSF (Fig. 1). Both studies found thickened meninges with gadolinium uptake (see Fig. 1). The meningeal biopsy revealed abundant interstitial and perivascular amyloid deposits that were positive for TTR (see Fig. 1). A genetic study confirmed presence of the A25T TTR mutation. The patient had two healthy children who declined to undergo a genetic study. The patient's mother had died of an undiagnosed disease with similar symptoms at the age of 60. The

patient did not undergo studies to rule out the diagnosis of amyloidosis.

Leptomeningeal amyloidosis associated with TTR mutations is a rare but fatal form of amyloidosis. The A25T TTR mutation found in our patient was previously reported in a Japanese patient who also developed superficial siderosis and died due to multiple intracranial haemorrhages. The autopsy confirmed selective amyloid deposition in the leptomeninges.^{1,2}

Our patient presented both clinical signs and radiological findings compatible with superficial siderosis. Superficial siderosis of the central nervous system is caused by haemosiderin deposition in the leptomeninges and the surface of the brain. These deposits are the result of continuous or recurrent bleeding in the subarachnoid space which are due to multiple causes.³ This presentation was described in the published case of A25T TTR mutation, as well as in other cases of familial amyloidosis in which deposition predominantly affects the meninges.^{4,5} As a whole, these data stress the importance of considering leptomeningeal amyloidosis as an infrequent cause of superficial siderosis.

At present, there are no specific treatments for leptomeningeal amyloidosis. Liver transplantation, the treatment of choice for preventing the progression of neuropathy associated with most TTR mutations, is not effective in these cases; cells of the choroid plexus are the main producers of TTR in the brain.⁶ Tafamidis is an inhibitor that selectively binds to TTR in plasma and stabilises the tetrameric structure of amyloid, thereby preventing deposition.^{7,8} Unfortunately, there are no data suggesting that tafamidis would be able to cross the blood-brain barrier, and it is therefore not regarded as a means of slowing the course of the disease in cases of leptomeningeal amyloidosis (personal communication with Dr. Said). Intraventricular administration of a specific anti-sense oligonucleotide for TTR in the brains of transgenic mice with a mutated human TTR gene results in dose-dependent decreases in TTR expression in the choroid plexus. This is a compelling treatment strategy for these patients.⁶

[☆] Please cite this article as: Llull L, Berenguer J, Yagüe J, Graus F. Amiloidosis leptomeníngea debida a la mutación A25T TTR. A propósito de un caso. *Neurología*. 2014;29:382–384.

^{☆☆} This study was presented in poster format at the 64th Annual Meeting of the SEN.

Acknowledgements

We thank Dr. Solé for the images of the meningeal biopsy.

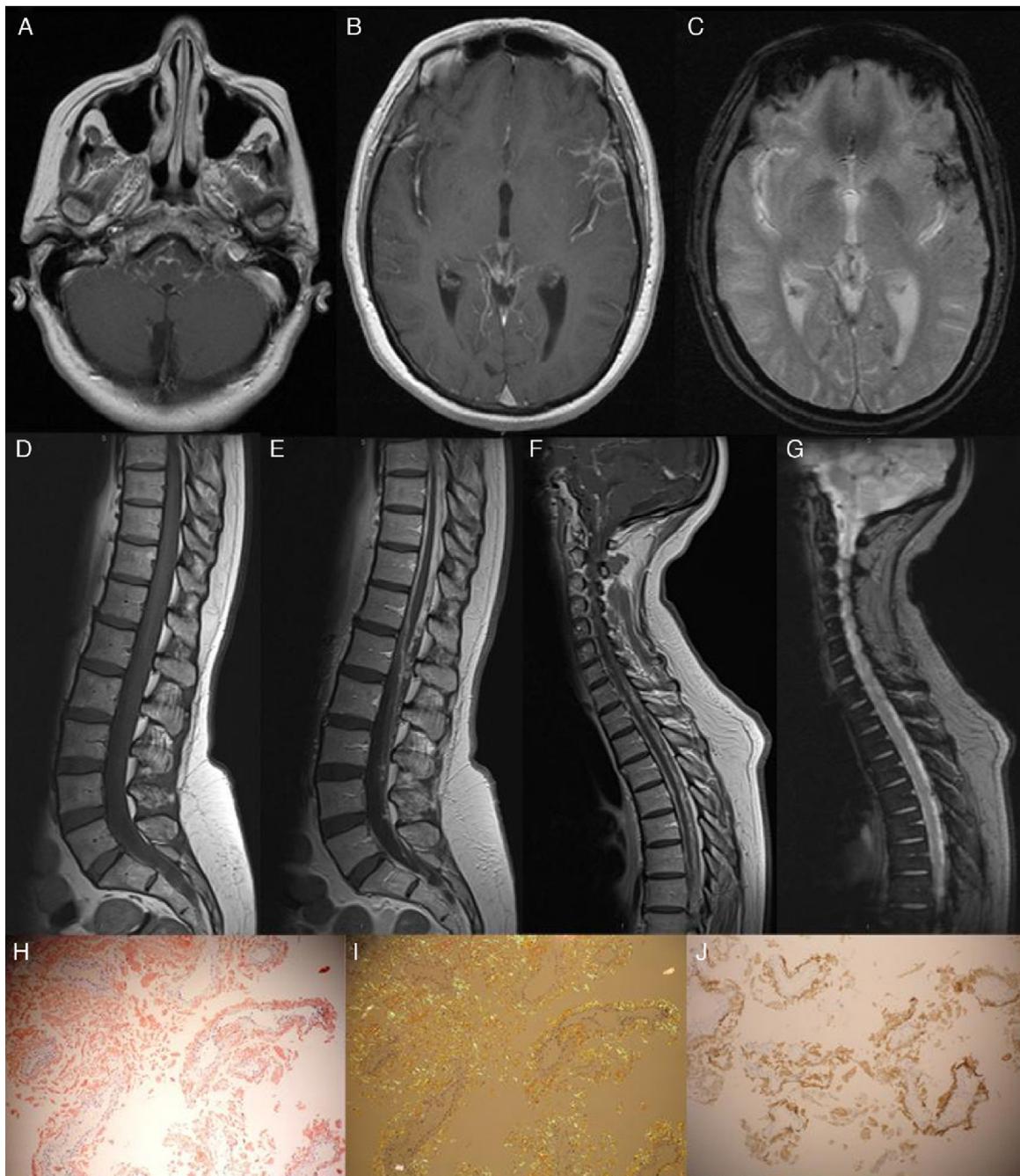


Figure 1 Gadolinium-enhanced axial T1-weighted MRI. Note the leptomeningeal contrast uptake on the surface of the brainstem and the left sylvian fissure (A and B). The T2*-weighted axial MRI shows superficial siderosis, principally in the sylvian fissure and occipital sulcus, as well as haemosiderin deposits in the left occipital horn (C). The sagittal T2*-weighted study revealed signs of chronic bleeding (G); the contrast-enhanced T1-weighted MRI showed meningeal thickening and contrast uptake (E and F). Meningeal biopsy: Under polarised light, the Congo red stain revealed abundant interstitial and perivascular amyloid deposits (H and I). Amyloid fibrils were revealed with the anti-TTR antibody (J).

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12 November 2012 15 December 2012

The clinical spectrum of frontotemporal dementia: A case of rapidly progressive dementia[☆]

El espectro clínico de las demencias frontotemporales: un caso de demencia rápidamente progresiva

Dear Editor:

Frontotemporal lobar dementias (FTLD) are a group of neurodegenerative disorders that are heterogeneous in their clinical expression, histopathological features, and genetic component. They affect frontal and temporal lobes and are associated with neuronal loss and gliosis. They are considered the third most common cause of dementia after Alzheimer disease (AD) and dementia with Lewy bodies. In patients younger than 65, they represent the second most common cause.¹ We have no incidence data but some autopsy series show that FTLD cases represent 10% to 15% of all neurodegenerative dementias.² The typical age of onset is usually younger than in AD, which manifests in patients older than 75 years. FTLD distribution is similar for men and women and we find a family history in 30% to 45% of cases, including cases with autosomal dominant inheritance.¹ Mean survival is 6 to 8 years, with a range of 2 to 15 years.³

Several groups have published consensus criteria on the clinical and histological changes that occur in FTLD.^{4,5} The histopathology of FTLD cases is characterised by linear spongiosis in layers II and III of the cortex, with predominant neuronal loss and gliosis.⁶ Furthermore, presence of aggregates or deposits in neurons or glial cells lets us classify these dementias into 4 groups: tauopathies, ubiquitinopathies, neuronal intermediate filament inclusion disease, and those with no data specifically pertaining to any of the above types.

We present the case of an 80-year-old man with a history of high blood pressure who drinks one glass of wine a day and does not smoke. He requested a medical consultation due to having fallen several times in the preceding 6 months. The first neurological examination only revealed slow walking speed with a tendency to flex the trunk forward. At 5 months after the first visit, we observed rapidly progressive exacerbation of his gait disorder. Recent memory lapses and poor sphincter control were also observed. The patient was being treated with indapamide, piracetam, allopurinol, paracetamol, and mirtazapine. Examination showed that the patient was disoriented in space and time, with generalised muscular rigidity and unstable gait. He required help from 2 people in order to walk. The patient later presented rapid neurological exacerbation and became unable to walk, eat, or control sphincters. His level of consciousness was impaired, with excessive daytime drowsiness, disorientation, and poverty of speech which evolved to no speech. He also showed intense axial hypertonia at all levels, as well as generalised muscular rigidity, predominantly in the upper limbs which exhibited cogwheel rigidity. We observed a few intermittent and subtle myoclonic jerks when the patient held up his arms. We decided to admit him to the hospital to complete the study, after which he underwent the following complementary tests: full blood count, coagulation test, baseline arterial blood gas analysis, general and liver blood tests, ammonia test, creatinine kinase level, metal ion levels, PSA blood test, and electrophysiological study. All results were normal. Negative results were obtained in the screening for vasculitis, analysis of protein 14-3-3 in cerebrospinal fluid, and syphilis serology test. Levels of vitamin B₁₂, folic acid, and thyroid hormones were normal, as were results from the CSF study. The electroencephalogram showed slower background cerebral activity with frequent bilateral paroxysmal bursts (frontal regions) of slow waves. Brain MRI showed only significant cortical and subcortical atrophy, predominantly located in the temporal lobes and with ventricular dilation secondary to atrophy. The patient's condition progressively worsened and he died one week after.

Anatomical pathology study: external examination revealed global atrophy with a moderate dilation of the ventricular system. In the histological study, we observed mild-to-severe gliosis in the cortical grey matter, especially in the lower layers, and patchy areas of microvacuolation

[☆] Please cite this article as: Castrillo Sanz A, Guerrero Becerra P, Duarte García Luis J. El espectro clínico de las demencias frontotemporales: un caso de demencia rápidamente progresiva. *Neurología*. 2014;29:384–385.