Title:

Early-onset leptomeningeal manifestation of G47R hereditary transthyretin amyloidosis

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Case

A 21-year-old British woman experienced recurrent, self-limited episodes of encephalopathy, motor weakness, speech disturbance and seizures lasting hours to days, over a four-year period. On first presentation in 2016, aged 17, lumbar puncture revealed acellular cerebrospinal fluid with raised protein, prompting a diagnosis of viral encephalitis despite negative viral PCR. Non-contrast brain MRI was normal. She was treated with acyclovir and recovered fully after two weeks. Similar self-limited episodes recurred over the years, all with full recovery without

treatment. In January 2019, in the context of one further episode, she was diagnosed with temporal lobe epilepsy and started on levetiracetam. In May 2019, she had another episode. Plain brain CT was suspicious for subarachnoid haemorrhage *(figure 1A)*. Subsequent CT arteriography was negative and MR imaging did not confirm a bleed, but revealed diffuse leptomeningeal enhancement of the brain, cranial nerves and spinal cord after gadolinium injection *(figure1B)*. CSF testing was unremarkable, except for persistently raised protein (1.6g/L). Infectious, vasculitic, paraneoplastic and inflammatory/autoimmune causes were excluded. In December 2019, she developed status epilepticus, necessitating intubation and admission to critical care unit. A subarachnoid haemorrhage was diagnosed. Although her generalised seizures improved, she remained dysphasic and continued to have right-sided focal seizures for several weeks. A previously unavailable family history revealed a diagnosis of hereditary transthyretin amyloidosis (hATTR G47R*; figure 2)* in a paternal uncle and grandmother, who was of Italian heritage, and testing confirmed our patient carried this mutation (her own father had died of an aneurysmal subarachnoid haemorrhage aged 45). On full systems review, her only other symptoms were cyclical vomiting syndrome associated to menstruation, which started in her twenties, and a tendency towards constipation, which in hindsight might relate to an incipient autonomic neuropathy. She also had a mild postural tremor since her early teens. There were no other sensory or motor symptoms suggesting peripheral neuropathy, but recently she developed paresthesia in her hands. She never presented with postural symptoms, arrhythmias or ocular manifestations. Characteristic findings on cardiac magnetic resonance and echocardiogram, Perugini grade 2 cardiac uptake on ^{99m}Tc-DPD scintigraphy, and exclusion of a clonal dyscrasia (by serum free light chain assay and serum/urine electrophoresis) fulfilled non-biopsy criteria for cardiac amyloidosis[1]. Nerve conduction studies were normal. A presumptive diagnosis of hATTR with leptomeningeal disease was made and a trial of Patisiran (Onpattro®, Alnylam Pharmaceuticals, Cambridge, Massachusetts, USA) and Tafamidis (Vyndaqel®, Pfizer, New York, USA) commenced. Two months after discharge the patient remains stable, but with marked language difficulties and low nonverbal cognitive abilities.

Discussion

A rare disease, hATTR is characterized by multiorgan extracellular deposition of amyloid fibril. These are composed of mutant TTR, a transport protein for thyroxine and vitamin A synthesized in the liver, and to a lesser extent in the choroid plexus and retina[2].

Inherited in an autosomal dominant manner, hATTR is caused by point mutations in the TTR gene, leading to protein misfolding and aggregation. The V30M point mutation, endemic to Portugal, Sweden and Japan, is the most common and typically presents with polyneuropathy. Besides polyneuropathy (formerly familial amyloid polyneuropathy), patients can present with cardiomyopathy (formerly called familial amyloid cardiomyopathy if the cardiomyopathy was predominant)[2]. A rare form of hATTR involving the central nervous system has been described (formerly called oculoleptomeningeal amyloidosis)[2].

The patient's country of origin and genotype can influence the phenotype. While Portuguese patients with the TTR V30M have an early age of disease onset (3rd-4th decades), patients from

Sweden and non-endemic regions with the same mutation present much later (7th decade). Other mutations have heterogeneous presentations, even within the same family[2].

Leptomeningeal disease is caused by amyloid deposits in pial and arachnoid membranes, as well as in subarachnoid vessels[3], resulting in transient focal deficits, headaches, seizures, ataxia, visual impairment and intracranial hemorrhage. This phenotype is predominant in TTR mutations such as D18G, A25T, Y114C, but can also occur in late-stage patients with V30M mutations, who usually present with peripheral or cardiac disease[2]. Tissue specificity in familial amyloidogenesis is influenced by intracellular folding, secretion and degradation pathways[4]. While the unstable CNS-specific TTR mutants are degraded by the endoplasmic reticulum in the liver, T4 binding to TTR synthesised in the choroid plexus stabilizes the mutant TTR, preventing endoplasmic reticulum degradation. Once the mutant TTR dissociates from T4 in the CSF, TTR aggregation and deposition occurs.

Several aspects delayed our patient's diagnosis. She is from a non-endemic region, had an extremely young disease onset and a relapsing-remitting illness for several years. The latter is an intriguing aspect of this patient's presentation. Although transient focal neurological symptoms are well known to occur in hATTR with leptomeningeal disease, these usually occur against a backdrop of progressive neurological deficits. It is possible that these events occur due to leakage of blood products from the frail leptomeningeal vessels, either causing transient focal neurological deficits or cortical irritation and seizures. We can only hypothesise that amyloid accumulation in leptomeningeal and subarachnoid vessels is a dynamic process and can initially be partially compensated. Furthermore, she is also the only individual in her family with documented leptomeningeal disease (uncle peripheral and autonomic neuropathy; grandmother asymptomatic). Codon 47 mutations have been associated with early-onset hATTR in two families[5, 6], but ours is the first leptomeningeal presentation.

Traditionally, hATTR was treated with orthotopic liver transplantation[7]. Recently, disease-modifying medications that either stabilize the TTR tetramer (e.g. Tafamidis) or inhibit TTR synthesis (e.g. Patisiran) have been developed. Given our patient's disease severity, treatment with Patisiran was started to prevent the progression of cardiac and neuropathic manifestations. Patisiran, a small interfering RNA, was shown to reduce by 80% circulating TTR[7]. Tafamidis is approved for the treatment of hATTR with early-stage symptomatic polyneuropathy. It is well-tolerated and was shown to decrease all-cause mortality, cardiovascular-related hospital admissions and neurological deterioration[7]. Like Patisiran, it is unknown whether Tafamidis is beneficial in patients with leptomeningeal disease, and its use in this context is off-label. However, evidence suggests that Tafamidis crosses the blood-brain barrier[8], and its use was requested on a compassionate basis.

In conclusion, we described the neurological manifestations of young-onset leptomeningeal disease secondary to a TTR G47R mutation. A careful family history, appropriate imaging and timely genetic testing form the cornerstones of diagnosis.

Abbreviations: FDG-PET, fluorodeoxyglucose (FDG)-positron emission tomography; hATTR, hereditary transthyretin amyloidosis; TTR, transthyretin; ^{99m}Tc-DPD, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid.

Figure legends:

Figure 1. Brain imaging abnormalities. A Plain CT scan demonstrating hyperdensity of the left sylvian fissure and left tentorium, suspicious for subarachnoid hemorrhage. **B** MR imaging after gadolinium injection showing diffuse intense leptomeningeal enhancement (including cranial nerve enhancement [not seen in this image]).

Figure 2. Family pedigree. Our index case and two family members carried pathogenic variants of the transthyretin gene, consistent with hereditary transthyretin amyloidosis. Ages (where known) are displayed. SAH, subarachnoid hemorrhage.

Practical Implications Statement:

- Hereditary transthyretin amyloidosis in both endemic and non-endemic areas can have heterogeneous clinical presentations within the same family and may be difficult to diagnose.

- Although rare, hATTR leptomeningeal amyloidosis can affect young patients and present with neurological manifestations with no or minimal peripheral nerve or systemic symptoms

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