Current Review of Leptomeningeal Amyloidosis Associated With Transthyretin Mutations

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**Introduction:** Leptomeningeal amyloidosis (LA) represents a rare subtype of familial transthyretin (TTR) amyloidosis, characterized by deposition of amyloid in cranial and spinal leptomeninges. Of > 120 TTR mutations identified, few have been associated with LA.

**Case Report:** A 27-year-old male presented with a 2-year history of progressive symptoms including cognitive decline and right-sided weakness and numbness. Cerebrospinal fluid (CSF) analyses demonstrated high protein level. Gadolinium-enhanced magnetic resonance imaging (MRI) revealed extensive leptomeningeal enhancement over the surface of the brain and spinal cord. Pathologic analyses revealed a TTR mutation c.113A>G (p.D38G).

**Review Summary:** Fifteen mutations and genotype-phenotype correlation of 72 LA patients have been summarized to provide an overview of LA associated with transthyretin mutations. The mean age of clinical onset was 44.9 years and the neurological symptoms primarily included cognitive impairment, headache, ataxia seizures and hearing, visual loss. CSF analysis showed elevated high CSF protein level and MRI revealed extensive leptomeningeal enhancement.

**Conclusion:** Clinicians should be aware of this rare form of familial transthyretin amyloidosis as well as its typical MRI enhancement and high CSF protein. The important role of biopsy, genetic testing and the potential early diagnosis value of contrast MRI were suggested. Early recognition of these characteristics is important to provide misdiagnosis and shorten the time before correct diagnosis. These findings expand the phenotypic spectrum of TTR gene and have implications for the diagnosis, treatment, and systematic study of LA.

**Key Words:** leptomeningeal amyloidosis, transthyretin, leptomeningeal enhancement, TTR mutations

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Familial transthyretin amyloidosis is a life-threatening and gain-of-toxic-function autosomal dominant disorder commonly caused by mutation of the transthyretin gene (TTR; OMIM 176300) located at chromosome 18q12.1. So far, > 120 mutations in the TTR gene have been found worldwide. The TTR gene product forms a plasma and cerebrospinal fluid (CSF) homotrimer, synthesized by the liver, choroid plexus and retina, and involved in the transport of retinol and thyroxine. TTR mutations render the gene product prone to dissociate into its constituent monomers leading to extracellular build-up of amyloid fibrils in major organs and neural tissues. The 3 main phenotypes of hereditary transthyretin amyloidosis are familial amyloid polyneuropathy (FAP), familial amyloid cardiomyopathy (FAC), and familial leptomeningeal amyloidosis (LA).

Familial LA is a rare manifestation of TTR amyloidosis, characterized by amyloid deposition in the meninges of the brain and spinal cord, often with ocular involvement. Patients present with a wide spectrum of central nervous system (CNS) including cognitive difficulties, ataxia, epilepsy, headache, visual, and hearing loss. The wide variety of clinical phenotypes frequently leads to misdiagnosis, a considerable time before correct diagnosis and poorer patient outcomes. While many TTR mutations could cause FAP, familial LA was extremely rare. Since first described by Goren et al in 1980, only 15 TTR mutations causing LA have been identified. Until now, these mutations have been found exclusively in European, American, and Japanese patients.

Here we described leptomeningeal involvement secondary to a TTR c.113A>G (p.D38G, formerly labeled as “D18G”) mutation in a patient of Chinese origin, corroborated by clinical, radiologic, and histopathologic findings. As the LA syndrome remains extremely rare, for a clearer delineation of the clinical evaluation and genetic presentation, the relevant literature for LA have been reviewed. The aim of this article is to demonstrate TTR mutations and phenotypic spectrum in order to have potential value in the diagnosis, treatment, and elucidation of its pathogenic mechanisms.
METHODS

The spectrum of clinical symptoms and the genetic analysis of a LA with p.D38G mutation were identified and investigated. Genetic testing was performed on DNA obtained from a peripheral blood sample. DNA isolation and high throughput sequencing Genomic DNA was extracted from peripheral blood according to the manufacturer’s instructions (QIAGEN, Hilden, Germany). DNA sequencing libraries were then prepared according to Illumina standard protocol. Fragments in the exonic regions of targeted genes were captured by a specific Amyloidosis Disease GenePanel using biotinylated oligo-probes (MyGenostics GenCap Enrichment Technologies, MyGenostics, Baltimore, MD). The capture experiment was conducted according to the manufacturer’s protocol. SIFT (http://sift.jcvi.org/) and POLYPHEN2 (http://genetics.bwh.harvard.edu/pph2/) were used to analyze the amino acid substitutions of p.D38G. Due to the syndrome remains extremely rare, we searched PubMed and MEDLINE databases to find LA cases in reports published till August 2019 using the terms: “leptomeningeal amyloidosis” or “oculoleptomeningeal amyloidosis”; all identified articles published in English and articles referenced therein were reviewed. The patient inclusion criteria consisted of transthyretin mutations and presented LA symptoms.

CASE REPORT

A 27-year-old right-handed Chinese man was admitted in our department with rapidly progressive cognitive decline over a 2-year period. He presented initially in February 2017 with headache, nausea and vomit for 1 months. He also had a fever with highest temperature 39°C. At his local hospital, a noncontrast head magnetic resonance imaging (MRI) was normal. He was diagnosed with viral encephalitis and received antiviral therapy. Three months later, he developed progressive confusion, fatigue, and weakness in limbs. In June 2017, he suffered from recurrent episodes of memory loss, slurred speech, right-sided weakness and numbness, lasting 4 to 5 hours. The episodes were initially every 3 weeks but increased in frequency over time. In October 2017, the patient was found blurred consciousness and right limb weakness. Then he was referred to our department. Cardiovascular, ophthalmic, audiometric, respiratory, and abdominal examination was unremarkable. The neurological examination revealed cognitive decline. Screening cognitive testing demonstrated short-term and long-term memory decline and impairment of attention and calculation [Mini- mental State Examination, (MMSE) = 24/30; Montreal Cognitive Assessment (MoCA) = 21/30]. Examination of the limbs revealed brisk reflexes in right lower limbs. There was no relevant past medical history. His father had suffered from coronary heart disease and renal dysfunction. He died of a myocardial infarction in his 40s. His mother died of car accident in her 50s. The blood and urine tests were normal or negative including full blood count, electrolytes, liver function, renal function, thyroid function, cardiac enzymes, B12 and folate, serum ACE and ANA, ANCA, antineuronal antibodies, and immunofixation. Lumbar puncture demonstrated CSF protein was elevated at 339 mg/dL and IgA, IgG was increased at 4.64 and 39.20 mg/dL. CSF analyses were negative for encephalitis and paraneoplastic autoimmune encephalitis. No organisms were cultured (including Mycobacterium tuberculosis) and no cellular atypia was seen. The patient had normal levels of myelin basic protein and aquaporin-4 with no neuromyelitis optica and a normal cell count without oligoclonal bands. Gadolinium-enhanced MRI of the brain and spine revealed extensive leptomeningeal enhancement over the surface of the brain and spinal cord (Figs. 1A–F). Cerebral and spinal angiography was normal. Nerve conduction studies and autonomic function testing were negative. 

FIGURE 1. Leptomeningeal enhancement over brain and spinal cord. (A–C) Gadolinium-enhanced transverse, coronal and sagittal T1-weighted magnetic resonance imaging (MRI) brain demonstrating enhancement extending along the meninges. (D–F) Gadolinium-enhanced sagittal T1-weighted MRI of the cervical thoracic and lumbar vertebra spine demonstrating thick irregular leptomeningeal enhancement (red arrow) over the spinal cord surface.
ECG, echocardiogram, and cardiac MRI demonstrated normal cardiac function. The patient was ultimately referred to neurosurgery for consideration of leptomeningeal biopsy for the purpose of providing a tissue diagnosis. He underwent a L5 to S1 laminectomy for biopsy of the intradural lesion. Intraoperatively, the arachnoid mater was markedly thickened and of a grayish, discolored appearance. These rust-colored, thickened tissues were sampled as specimen for biopsy. Pathologic analysis revealed congo red positive. In this rare form of the disease, this pattern is diagnostic (Figs. 2A, B). Proteomic analysis by mass spectrometry of congo red positive material indicated amyloid deposition of the transthyretin type.

Genetic testing performed on DNA obtained from a peripheral blood sample revealed a heterozygous adenine to guanine transversion at nucleotide 113 of the TTR gene, resulting in an asparagic acid (Asp) to glycine (Gly) substitution (p.D38G). Both SIFT (http://sift.jcvi.org/) and POLYPHEN2 (http://genetics.bwh.harvard.edu/pph2/) predicted the mutation c.113A>G to be deleterious, which means they probably damage and affect protein functions.

REVIEW OF THE LITERATURE

LA was first described by Goren et al in 1980, since then 15 TTR mutations causing LA have been identified. Until now, these have been found exclusively in European, American, and Japanese patients. In addition to the present case, a total of 72 genetically confirmed cases (including our case) were identified and summarized to provide an overview of the clinical and genetic features of LA (Table 1).

Epidemiology and Pathophysiology

All of the LA patients included in the present report had their diagnoses genetically confirmed. c.113A>G (16.7%), c.265T>C (16.7%), and C.148G>A (15.2%) are most common mutations associated with LA. Of all mutations, c.148G>A and c.217G>A only show the CNS symptoms without autonomic neuropathy, peripheral neuropathy, or cardiac involvement. These 2 genes only responded to LA but not FAP or FAC. These mutations exclusively found in European (60%), American (33.3%), and Japanese (26.7%) patients. The only mutation found in China is c.113A>G.

Recent studies on LA pathogenesis came from an electron microscopic study of sural nerve biopsy specimens from 49 Val30Met. This work has shown that the direct damage of amyloid fibers leads to the damage of Schwann cells and basal lamina. The loss of small fiber axons and vasculopathy may also contribute to the pathogenesis of neuropathy.

Clinical Phenotype

The average onset age of all LA patients is 44.9±9.1. Among these mutations, c.191T>C, c.215T>C, and c.113A>G are early-onset mutations. The prior studies suggest that the c.113A>G mutation caused LA with later onset age. However, in our study, we found that c.113A>G is an early-onset variant. The average disease duration is 9.3±7.1, which means LA is a life-threatening disease. All reported cases showed CNS symptoms. More specifically, of the 15 patients, 13 (86.7%) suffered from cognitive impairment, 10 (66.7%) exhibited ataxia, and 9 (60%) showed headache. Seizures and hydrocephalus were also evident in the patients. Stroke and subarachnoid hemorrhage (SAH) were also detected in many patients which suggest that amyloid angiopathy could also destroy dura mater, leptomeninges, and neocortical blood vessels. Autonomic neuropathy and peripheral neuropathy were also accompanied with LA in 8 (53.3%) and 11 (66.7%) patients.
| Amino Acid Change (Mature Protein) | Nucleotide Change | Cases Ref | Countries | Age of Onset (y) | Disease Duration (y) | CNS Neurological Symptoms | Autonomic Neuropathy | Peripheral Neuropathy | Hearing Loss | Visual Loss | Cardiac Dysfunction | CNS Protein | Neuroimaging |
|----------------------------------|------------------|-----------|-----------|-----------------|---------------------|--------------------------|----------------------|---------------------|-------------|------------|----------------------|------------|-------------|
| p.D38G (D18G) c.113A > T         | 13 our case6,12,15,18 | Hungary, Japan, USA, China | 35.9 ± 8.5 | 16.7 ± 10.6 | Cognitive impairment, headache, ataxia, stroke, SAH | + | − | + | + | + | High | Leptomeningeal enhancement, superficial siderosis |
| p.L32P (L12P) c.95T > C          | 428–31            | UK, Nigeria, Germany | 36.1 ± 6.0 | 15 | Cognitive impairment, headache, ataxia, stroke, seizures, SAH | + | + | + | − | + | High | Leptomeningeal enhancement |
| p.A45T (A25T) c.133G > A         | 316,21,32         | Japan, Spain | 46.0 ± 4.4 | 7.5 ± 4.9 | Cognitive impairment, ataxia, stroke, seizures, SAH | − | + | + | − | − | − | High | Leptomeningeal enhancement, superficial siderosis |
| p.V50G (V30G) c.148G > A         | 77,33,34          | USA, Germany | 46.1 ± 8.9 | 5.6 ± 3.6 | Cognitive impairment, headache, ataxia, stroke, seizures, SAH | − | − | − | + | + | − | High | Leptomeningeal enhancement |
| p.V50M (V30M) c.148G > A         | 1117,35           | Mexico, Japan | 56.5 ± 4.3 | — | Headache, seizures, hydrocephalus | + | + | − | − | − | − | High | Leptomeningeal enhancement |
| p.A56P (A36P) c.166G > C         | 336               | Italy | 38 ± 1.7 | 17.5 ± 20.5 | Cognitive impairment, ataxia, stroke | − | + | + | + | − | − | High | Leptomeningeal enhancement, Hydrocephalus |
| p.F64S F44S c.191T > C           | 137               | USA | 26 | — | Cognitive impairment, headache | + | + | + | − | − | − | — | Leptomeningeal enhancement |
| p.T69P T49P c.205A > C           | 119               | Ireland | 53 | — | Cognitive impairment, headache, seizures | − | + | − | − | − | − | − | — | Leptomeningeal enhancement |
| p.G73R G53R c.217G > A           | 238               | USA | 51.0 ± 7.1 | 17 | Cognitive impairment, ataxia, stroke, seizures, hydrocephalus, SAH | − | − | − | − | − | − | − | — | Leptomeningeal enhancement, Hydrocephalus |
| p.G73E G53E c.218G > A           | 314               | France | 38.3 ± 3.2 | 4.5 ± 3.5 | Cognitive impairment, ataxia, stroke, seizures, hydrocephalus, SAH | − | + | − | − | − | − | − | — | — | Leptomeningeal enhancement |
| p.G73A G53A c.218G > C           | 113               | UK | 40 | — | Cognitive impairment, ataxia, stroke, seizures, SAH | − | + | + | − | − | − | − | — | — | Leptomeningeal enhancement |
| p.F84S F64S c.215T > C           | 339,40            | Canada | 28 | 12 | Cognitive impairment, ataxia, stroke, seizures, hydrocephalus | + | + | + | + | + | − | — | — | — | Leptomeningeal enhancement |
| p.Y89H Y69H c.265T > C           | 139,41–43         | USA, Sweden, Canada | 50.4 ± 9.2 | 7.7 ± 3.1 | Cognitive impairment, ataxia, headache, stroke, seizures, SAH | − | + | − | − | − | − | − | — | — | Leptomeningeal enhancement |
| p.I127M I107M c.381T > C         | 144               | Canada | 51 | — | Ataxia | + | + | − | − | − | − | — | — | — | — |
| p.Y134C Y114C c.401A > G         | 66                | Japan | — | — | Cognitive impairment | + | + | − | − | − | − | — | — | — | — |

CNS indicates central nervous system; SAH, subarachnoid hemorrhage.
Clinical trials: antisense oligonucleotides and small interfering RNAs types of gene silencing therapies have been evaluated in phase 3 trials. However, after liver transplantation, neuropathy can occur in 20% of patients. A 20-year retrospective analysis of the FAP World Transplant Registry revealed 20-year survival after liver transplant was 55.3%. After liver transplantation, most patients have been reported to have stable clinical manifestations. However, the frequency and severity of adverse events have been reported to increase. In our study, 15 mutations and its genotype-phenotype correlation for LA have been summarized, while its underlying pathogenic mechanism is still somewhat unclear. A proposed mechanism which may explain CNS selectivity is that highly destabilized TTR proteins encoded by these variants were completely degraded through the endoplasmic reticulum-associated degradation mechanism in peripheral tissues. They could cause local CNS impairment, because these mutants were secreted with lower efficacy from choroid plexus due to a stabilizing effect of thyroxine chaperoning, which is highly concentrated in choroid plexus cells.

In this study, we identified a 27-year-old with c.113A>G (p.D38G, D18G) mutation which showed rapidly progressive cognitive decline over a 2-year period. Four previously discovered D38G, V30M, and D18G mutations were characterized by dementia, spasticity or hearing loss without ocular disease or polyneuropathy. Two Japanese brothers were also reported with D18G mutations. These 2 patients had recurrent SAH, presumably secondary to amyloid laden, friable vessels. The third report due to D18G mutation was a US woman. She had developmental delay, headache, and vomiting. Another Chinese group also identified the p.D38G variant in an early-onset LA family. The hydrocephalus-associated clinical symptoms and the absence of peripheral neuropathy, vitreous opacities, and cardiac impairment in that family further support the high CNS selectivity of the p.D38G variant. These findings indicate that besides genetic factors, environment factors may also modify the manifestations of LA.

Medical management of LA involves liver transplantation and pharmacological agents. However, best medical management specific for LA is lacking. Some previous studies suggest LA cannot be blocked by liver transplantation as mutant TTR protein are mainly secreted from choroid plexus but not liver. The associated imaging findings, patients with LA may be referred for consideration of neurosurgical intervention. Awareness of this rare pathology, and its consideration among the differential diagnosis, may limit unnecessary surgery in cases for which diagnosis can be made by less invasive means or through genetic testing. Neurosurgical management, as in this case, is limited to biopsy for cases in which less invasive strategies fail to yield a diagnosis.

In conclusion, thanks to a better understanding of the TTR amyloid formation, therapeutic developments which are less invasive than liver transplantation have been founded. TTR stabilizer drugs are safe and seem to delay the disease progression in some groups of patients. Indeed, gene modifying and amyloid fibrils targeting drugs open a new area in the field with the hope that we can safely bring about long-term stabilization of the disease.
several patients suffered from autonomic, peripheral neuropathy, and cardiac dysfunction. CSF analysis showed elevated high CSF protein level and MRI revealed extensive leptomeningeal enhancement. These findings suggest that clinicians should be aware of this rare form of familial transthyretin amyloidosis as well as its typical MRI enhancement and high CSF protein. The important role of biopsy, genetic testing and the potential early diagnosis value of contrast MRI were suggested. No curative treatment for LA is presently available, and thus early recognition of these characteristics is important to provide misdiagnosis and shorten the time before correct diagnosis. These findings expand the phenotypic spectrum of TTR gene and have implications for the diagnosis, treatment, and systematic study of LA.

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