LETTER TO THE EDITOR

To the Editor

Gelsolin Familial Amyloidosis Peripheral Neuropathy in Canada: A Case Report

Keywords: Neuromuscular Disorders, Peripheral Neuropathy

Hereditary gelsolin amyloidosis (AGel amyloidosis) is a rare multisystemic disorder caused by a mutation on the gelsolin gene (G654A or G654T). The clinical presentation is typically characterized by a triad of ophthalmic, neurologic, and dermatologic findings. AGel amyloidosis has been reported in several countries, primarily in Japan and Finland. We report a genetically confirmed case of gelsolin familial amyloidosis in Canada.

A 55-year-old male presented with a 15-year history of progressive bilateral facial muscle weakness. The symptoms started during a trip to India, where he developed twitching in his left upper lip. There was no known exposure to tuberculosis or leprosy. The twitching resolved, but he noted progressive flattening of the left nasolabial fold, with spilling of liquids from the angle of his mouth and lip biting while eating. Talking for prolonged periods caused spasms in other facial muscles. Later, he noticed altered sensation over the right forehead and tingling in his fingers. There was no double vision, visual disturbance, dysphagia, autonomic symptoms, or hearing impairment. The patient developed a transient painless right foot drop with no sensory complaints that resolved completely within 3 months, but otherwise he had no limb weakness. The patient had a history of lattice corneal dystrophy diagnosed at age 54 and atrial fibrillation. There was no history of diabetes or other conditions.

His parents were born in Scotland and then immigrated to Canada. The patient also has Finnish background, which he confirmed with commercial genetic ancestry testing. His father has corneal dystrophy but has never been tested for AGel amyloidosis. On the father's side, he has one second-degree and two first-degree cousins with bilateral facial paralysis.

The patient had bifacial paresis, worse on the left, and reduced sensation over the right forehead. Examination of other cranial nerves was normal. Muscle bulk, power, and tone were normal. Reflexes were brisk and symmetrical, and plantar responses were flexor. Sensation was normal to light touch, proprioception, pinprick, and temperature, but vibration was slightly reduced in the toes. The neurologic examination was otherwise normal. Figure 1 shows the patient's facial weakness.

Electrodiagnostic testing demonstrated bilateral facial neuropathies, with prolonged distal latencies and a reduced compound muscle action potential amplitude on the left facial nerve. The blink reflex test was abnormal, with prolonged R1 latencies bilaterally that was worse on the left, and borderline ipsilateral R2 latencies. This demonstrates dysfunction of the efferent pathway although compromise of the afferent pathway cannot be ruled out. Figure 2 depicts the blink reflex testing. Additional nerve conduction studies demonstrated a mild, length-dependent, primarily axonal polyneuropathy. Sensory responses were reduced in amplitude at the feet, with mild slowing. There were some elements of demyelination, including absent F waves and mild slowing (~37 m/s) in nerves with normal compound muscle action potentials, but no conduction blocks. There was also evidence of bilateral median neuropathies at the wrists.

Extensive laboratory investigations including serum immunoelectrophoresis, rheumatologic screen, Lyme antibodies, and angiotensin-converting enzyme level were negative. Given the foot drop, a hereditary neuropathy such as hereditary neuropathy with liability to pressure palsy was considered, but genetic testing for this and CMT1A was negative. Genetic testing showed a mutation on one allele of the gelsolin gene in the first base of codon 187 (Asn-187). Brain MRI and thoracic CT were normal. A skin punch biopsy showed normal intraepidermal nerve fiber density and absence of amyloid deposits.

Gelsolin familial amyloidosis is a rare autosomal dominant disorder that was first described in 1969 by the Finnish ophthalmologist Jouko Meretoja.[1] It is also known as amyloid polyneuropathy type IV, and has been mostly reported in Finland or in patients of Finnish descent,[2] but has also been described in Japanese families. AGel is caused by a point mutation in the gelsolin gene, located on chromosome 9q34. The most common mutation results in substitution of asparagine for aspartic acid at codon 187 (gelsolin-Asn187),[3] as detected in our patient. A mutation on the same codon, but with replacement by tyrosine (gelsolin-Tyr187) has also been reported.[4]

AGel amyloidosis is characterized by multisystem involvement secondary to amyloid deposition. The most common manifestations include cranial neuropathies, mild peripheral neuropathy, carpal tunnel syndrome, lattice corneal dystrophy type II (LCD-2), glaucoma/cataract, and cutis laxa. LCD-2 was first described by Meretoja in 1969 and is one of the cardinal signs of AGel caused by deposition of amyloid in the cornea. It usually manifests in the third decade of life, preceding other symptoms, and can present earlier in homozygotes. Patients with LCD-2 complain of dry eyes, visual impairment, and photosensitivity.[2]

Regarding the cranial neuropathies, the facial nerves are preferentially involved with progressive bilateral weakness. However, other cranial nerves can also be affected, and the facial sensory symptoms and blink reflex pattern found in our patient suggest trigeminal involvement. The differential diagnosis for bilateral facial neuropathy includes: Bell palsy, sarcoidosis, Lyme disease, Guillain-Barre syndrome, Tangier disease, leprosy, vasculitis, and Melkersson-Rosenthal and Mobius syndromes, amongst others.[1]

The peripheral neuropathy in AGel amyloidosis affects primarily the large nerve fibers,[5] which is in contrast to other amyloid polyneuropathies. The development of transient unilateral foot drop has not been described before because the peripheral neuropathy is usually described as mild and primarily axonal, although there are few reports on demyelination.[1] We cannot rule out an incidental peroneal compressive neuropathy, and amyloid deposition can increase the risk of compressive neuropathies such as in the median nerve. Mild autonomic dysfunction has been described, usually occurring in the third decade of life.[2] Our patient has not developed autonomic symptoms, which is in keeping with the normal intraepidermal nerve fiber density. Amyloid deposition was not observed on the skin biopsy sample, but this is not surprising because amyloid deposits tend to be patchy and the sample size of a skin punch biopsy is small.

AGel amyloidosis is often associated with a benign course with normal lifespan, except for homozygotes, who tend to have

https://doi.org/10.1017/cjn.2015.56 Published online by Cambridge University Press

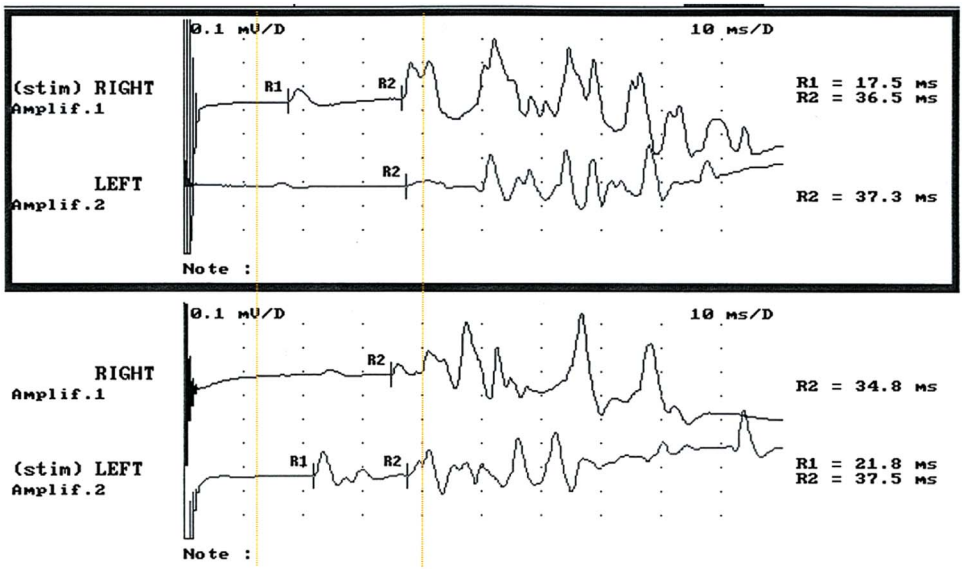

Figure 1: *Bifacial weakness. (A and C) The patient is attempting to wrinkle his forehead, which proves impossible. (B) The patient is attempting to smile, showing severe weakness on the left. (D) The patient is unable to seal his lips.*

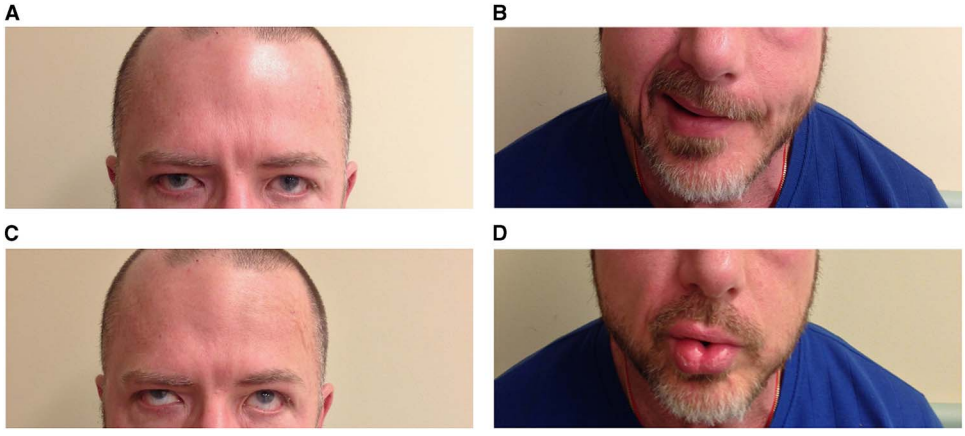

Figure 2: *Blink reflex. The yellow lines show the normal limit for latencies of the R1 responses (13 ms, left line) and R2 responses (40 ms, right line). This test was abnormal, with prolonged R1 latencies bilaterally, more on the left, and borderline R2 latencies. This pattern suggests that both the afferent (trigeminal nerve) and efferent (facial nerve) pathways are involved, which can be seen in demyelinating neuropathies.*

more severe disease and can have renal failure.[4] There are no specific treatments; however, ophthalmological follow-up is essential to prevent and/or treat corneal dryness and ulcers. Surgical treatment can include carpal tunnel surgery in symptomatic patients, and plastic surgery to improve facial asymmetry and function, for instance when skin lagging affects vision or mouth closure.[1] Repeated procedures are often needed.

To our knowledge, this is the first reported case of AGel amyloidosis in Canada; this may reflect underdiagnosis. AGel amyloidosis should be considered in the differential diagnosis of progressive bilateral facial neuropathies. A high degree of suspicion is needed to make the diagnosis promptly. Despite the lack of specific treatment, the diagnosis allows patients to understand their disease and the physician to avoid unnecessary interventions.

Disclosures

MA, CB, AA, and DAL have no disclosures to report. VB has acted as consultant for Grifols, CSL, Bionevia, Lilly, Pfizer, Dainippon Sumitomo, and Eisai and has received research grant support from all of these companies.

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https://doi.org/10.1017/cjn.2015.56 Published online by Cambridge University Press

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https://doi.org/10.1017/cjn.2015.56 Published online by Cambridge University Press