Bariatric surgery as a potential trigger for worsening hereditary spastic paraparesis: Case report

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Introduction

HSP is a heterogeneous group of genetic neurodegenerative disorders characterized by slowly progressive spasticity caused by degeneration of the long tracts of the spinal cord, particularly the corticospinal tract and dorsal columns. HSP is divided into uncomplicated and complicated forms depending on the presence of other neurologic features beyond spastic paraparesis. Uncomplicated HSP describes spastic paraparesis with possible sphincter disturbances while complicated HSP is accompanied by additional features, such as ataxia, optic atrophy, pigmentary retinopathy, intellectual disability, extrapyramidal signs, dementia, deafness, peripheral neuropathy, and epilepsy. We report a patient with c.1246C>T (p.R416C) heterozygous variant on the *ATL1* gene causing a complicated form of hereditary spastic paraparesis (HSP) who had an early age of onset but had non-progressive disease until a rapid decline at age 57 after bariatric surgery. The same mutation on the *ATL1* gene was identified in family members with HSP at a young age. Intriguingly, the mother of the proband carrying the mutation remained asymptomatic.[1] This suggests that environmental factors, modulator genes, or epigenetic factors contribute to the varied presentation of HSP. Our case report suggests that bariatric surgery could be a potential inciting event for clinical worsening in patients with HSP.

Case Report / Presentation:

The patient of interest is a Caucasian man who had symptoms starting at age 5. His weakness first manifested with clumsy walking and difficulty running. He has had poor balance since young. He believes that his weakness first started in his thighs before extending distally. At the age of 7, the patient was evaluated in several hospitals and underwent three myeloencephalograms and electrophysiological studies reported to be without concern for demyelinating disorder. He reports that his motor deficit, notably affecting only his lower extremity muscles diffusely, plateaued at age 10. He did not have any major ambulatory dysfunction until age 57. At age 57, he underwent bariatric surgery and lost approximately 130 pounds. Since then, he has noticed worsening lower extremity strength with decreased ability to ascend and descend the stairs or walk longer distances. He has had no weakness in the upper extremities, trunk, or cranial nerves. His other symptoms include difficulty hearing since age 50 for which he has hearing aids as well as dysphagia secondary to achalasia requiring myotomy. Several months after his bariatric surgery, his neurologic exam demonstrated distal arm weakness, left worse than the right, as well as distal greater than proximal leg weakness, again left worse than right. He had more muscle wasting in his distal compared to proximal leg muscles. His reflexes were 3+ throughout with positive Babinski reflexes. He had diminished pinprick, proprioception, and vibration sense in the toes with a graded reduction in the distal legs up to the shin. His gait showed feet dragging with inverted knees. No one in his family, including his four brothers and two children, had similar symptoms. Normal results were obtained for vitamin B12, folate, thyroid stimulating hormone, and creatinine, including negative serologies for ganglioside antibodies, hepatitis C, and Smith ribonucleoprotein antibodies. His hemoglobin A1C was 5.4%. At this time, electrodiagnostic testing demonstrated length-dependent motor and sensory axonal polyneuropathy. There was also evidence of active and chronic bilateral lower lumbar and upper sacral radiculopathies of mild-to-moderate severity. Magnetic resonance imaging of the spine showed moderate-to-severe central canal stenosis at C5-C6, L2-L3, L4-L5, and L5-S1. He was not deemed to be a candidate for intervention of his spinal stenosis by neurosurgery because his symptoms were thought to be out of proportion to his degree of cervical stenosis . Finally, he underwent genetic testing which demonstrated a c.1246C>T heterozygous variant on the *ATL1* gene consistent with a diagnosis of HSP. By age 61, he could only walk short distances with a walker but mainly relied on a scooter for transport.

Discussion:

More than 80 mutations have been found to cause HSP[2], with some genes discovered to be involved in the axonal transport of macromolecules, organelles, and cargoes.[3-4] Onset for HSP varies from early childhood to 70 years of age, with variability in age of onset seen even among family members with the same genetic mutation.[5] Our patient had features of HSP at a young age but appeared to reach a plateau at age 10. He retained the ability to walk until age 57 when he lost a significant amount of weight after bariatric surgery. His slowly progressive muscle atrophy and weakness, hyperreflexia, electrodiagnostic testing showing length-dependent motor and sensory axonal polyneuropathy, and genetic analysis showing a mutation in the *ATL1* gene were consistent with a diagnosis of HSP. In patients with a pathogenic *ATL1* gene mutation causing HSP, less than 25% required the use of a walking aid or wheelchair after a mean disease duration of 32 years.[6]

His clinical course was unusual because most patients with HSP reach a plateau after a period of continuous worsening. To our knowledge, there have been no other case reports documenting a rapid decline in weakness after patients have reached clinical stability for decades. Our case report suggests that bariatric surgery or its downstream effects may be a factor contributing to this unusual clinical course.

The incidence of developing peripheral neuropathy after bariatric surgery is around 16%.[7] Sural nerve biopsies in these patients showed axonal degeneration with perivascular inflammation.[7] Deficiencies in vitamin B1, vitamin B6, vitamin B12, vitamin E, copper, and niacin were considered the greatest risk factors, although nutritional deficiency was not present in all patients who developed neuropathy after bariatric surgery.[8-10] At the same time, a meta-analysis found that neuropathic symptoms improved in patients with diabetes after bariatric surgery.[11] Although no frank nutritional deficiencies were identified in our patient, micronutrient deficiencies may have contributed to his progressive axonal neuropathy. Furthermore, research into bariatric surgery has shown that obesity-related epigenome is altered after bariatric surgery via different patterns of DNA methylation.[12] The epigenetic reprogramming may have altered the phenotypic expression of this patient's genetic mutation, promoting disease progression. Our patient was likely more vulnerable to nerve injury due to his underlying HSP.

For many years, the range of phenotypic expressions among patients with HSP has puzzled clinicians. Until now, no identifiable stressors have been proposed for the initial presentation or clinical worsening in patients with HSP. Bariatric surgery may have evoked worsening symptoms of neuropathy either by itself due to micronutrient deficiencies or in combination with the genetic abnormality in this susceptible individual who carried an *ATL1* gene mutation.

In conclusion, this report summarizes our experience with an *ALT1* linked case of HSP in an adult patient who experienced an acceleration of his disease post bariatric surgery. Until specific treatments for HSP subtypes become available, careful considerations of underlying neurological condition(s) in addition to typical bariatric pre-surgical clearance evaluations seem necessary in order to mitigate disease and its impact on patient function.

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