CASE STUDY

Progressive Neuromuscular Syndrome and Loss of Muscle Control Over Thirteen Years: Genetic Analysis Provides Answers

Quick Summary

- A fit and healthy individual reported progressive loss of control over skeletal muscles from the age of 27.
- Family history revealed non-consanguinity with conspicuous absence of similar neuromusculopathies in first-degree and second-degree relatives of the patient.
- The patient was advised genetic testing at the age of 43 years. He had consulted doctors from India and US in the intervening years, but no diagnosis was arrived at.
- The patient harbors mutations in the *GNE* gene that resulted in the manifestation of muscle deterioration.
- Post-diagnosis, the patient has been provided with sialic acid supplements to overcome the physiological deficits caused by the mutations in the *GNE* gene.

Patient Profile

Vikram Reddy, a 40–year-old mechanical engineer (name and profession changed to protect patient privacy) reported experiences of sudden and severe episodes of loss of neuromuscular control, starting from the age of 27 years. A fall during a game of tennis was the first such incident, in 1999. The loss of coordination was attributed to a drop foot problem, diagnosed soon after. Gradually, the progression of loss of control over his leg spread from the ankle upwards towards the hip. He consulted doctors at a leading neurophysiology research centre and hospital in Bangalore (1999), who concluded that his gradual loss of strength and neuromuscular coordination was of neurogenic origins.

About two years prior to consulting doctors at UMass Memorial Hospital, Worcester, MA, USA (2012), Vikram noticed a similar development of neuromuscular disability in his hands. By 2012, he was able to climb stairs only if support from a sturdy handrail was available. He was able to drive and shave himself, but brushing teeth and washing his face were challenging tasks. His shoulders and biceps had lost strength. Vikram was unable to lift packages with his arms. Other sensory responses like speaking, chewing and swallowing remained normal. Likewise, Vikram had not lost control of bowel movements or over his bladder.

A complete medical assessment also highlighted the fact that Vikram was an intelligent and alert person. He showed accurate knowledge and recall of his progressive disabilities.

Although he carried his right shoulder a little below his left, he did not suffer from scoliosis or fasciculations (involuntary muscle tics). He had lordosis but the MRI of his spine was unremarkable, without prominent defects. He could close his eyes tightly and was able to smile as well. His pectoral muscles were prominent. His ability to flex his neck was also normal. He did not have a history of visual disability throughout life, either. He had suffered from neither meningitis, encephalitis, nor polio, which ruled out degeneration of his central nervous system.

His limb musculature, in both hands and legs, was slack. Muscle thinning was evident in both limbs, yet not enough to indicate wastage of muscles. Vikram was able to sense pinpricks, hot and cold stimuli, light touch and vibrations. He was also able to sense his joint positions. However, deep tendon reflexes were absent. He was able to walk but with difficulty that resulted from inadequate control over his limb muscles.

*Name changed to protect patient privacy

Differential Diagnosis

Doctors at Memorial Hospital ruled out Amyotrophic lateral sclerosis (ALS) because corticospinal neurons were not involved. In an earlier consultation, doctors from Bangalore had suggested that this neuromuscular syndrome is a result of dysfunction of nerves in the limbs, in a localized fashion. Lack of sensory neuropathy ruled out early onset Kennedy's disease (also known as Spinal and bulbar muscular atrophy, SBMA) as well. Deficiencies in amino acid synthesis and mutations in branching enzymes as well as heat-shock proteins (proteins involved in repair mechanisms) were also considered. Gene sequencing was suggested in order to confirm or rule out Spinal muscular Atrophy (SMA that results from mutations in the *SMN1* gene).

Genetic Testing In India

In 2010, Vikram was referred to a prominent clinical geneticist in Calicut in his search for answers for the progressive loss of control over his limb muscles. The doctor recommended genetic counselling as well as testing, in order to understand the basis of his curious and unsettling disability.

Family Tree Pre-Genetic Testing

A genetic counselor from Strand Life Sciences met Vikram in order to understand his family history. Vikram's father, aged 72 years and his mother, aged 65 years, had had no significant medical problems in their life. Vikram's siblings, an older brother and sister, have not reported the incidence of muscular disabilities like him. Vikram's father had two brothers, while his mother had four brothers and two sisters. Vikram's extended family members were also normal and did not show any signs of degeneration, like him.

Results of Genetic Testing

The Strand Test for Neuromuscular Disorders was prescribed for Vikram. This test covers genes involved in neuromuscular syndromes.

Two mutations were identified in the *GNE* gene, in this case.

Results

This individual harbors:

- This individual harbors two 'Variants of Unknown Significance' , p.Val696Met and p.HIs552Arg, in exons 12 and 10 respectively, in the *GNE* gene.

Key Findings

Gene	Variation	Zygosity	Clinical significance
GNE	chr9:36217445C>T c.2086G>A p.Val696Met	Heterozygous	Variant of Unknown Significance
GNE	chr9:36219996T>C c.1655A>G p.His552Arg	Heterozygous	Variant of Unknown Significance

Neuromuscular Defects Caused by *GNE* Mutations

Vikram has two variants of unknown significance (VUS) in the *GNE* gene. The *GNE* gene codes for an enzyme that attaches a sugar - sialic acid - to various other proteins. This modification is essential for cell migration, cell attachment, and communication between cells. Lack of this enzyme has been associated with myopathies such as Nonaka myopathy and inclusion body myopathy 2 (Urtizberea & Béhin 2015; Huizing et al. 2014). *GNE* myopathies are also known as hereditary inclusion body myopathy (HIBM) and distal myopathy with rimmed vacuoles (DMRV), in medical literature. Myopathies described under various names but ultimately resulting from mutations of the *GNE* gene are now collectively termed as *GNE* myopathies. Muscle weakness sets in late adolescence or early adulthood and gradually worsens over time. Several mutations in the *GNE* gene have been reported with varying effects on muscle degeneration (Celeste et al. 2014; Cai et al. 2013; No et al. 2013). Typically, the tibialis anterior and the hamstring muscles are affected by *GNE* myopathies.

GNE myopathies are inherited in an autosomal recessive manner. In Vikram's case, he seems to have inherited both mutations in a compound heterozygous manner. One VUS, each is present on one copy of the *GNE* gene and a concerted effect of both mutations is seen in a trans manner. The Val696Met mutation is very common in the Indian population (Nalini et al. 2013).

Treatment Plan

Vikram was advised to take sialic acid supplements to counter the deficiencies caused by the two *GNE* mutations. This therapy has been evaluated in animal models of *GNE* myopathies as well as in phase I clinical trials (Yonekawa et al. 2014; Nishino & Noguchi 2012; Argov & Mitrani-Rosenbaum 2008). Vikram has responded well to the therapy and is progressively regaining control over his limbs.

Conclusions

- Vikram, a 40-year-old mechanical engineer had suffered from progressive debilitating control over his skeletal muscles from the age of 27 years.
- Loss of muscle control initiated in the legs and gradually spread from the ankles to the hips and to the arms.
- Genetic testing was advised to Vikram in order to arrive at an accurate diagnosis of his neuromuscular syndrome, suspected to be of neurogenic origin.
- Vikram was diagnosed with '*GNE* myopathy' based on the identification of two VUS mutations, one each per gene copy, in his *GNE* gene, acting in a compound heterozygous manner.
- A precise diagnosis of *GNE* myopathy has led to the prescription of sialic acid supplements to Vikram, enabling him to regain better control over his limbs.

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