

Giant Axonal Neuropathy with Unusual Neuroimaging Caused by Compound Heterozygous Mutations in *GAN* Gene

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To the Editor: Giant axonal neuropathy (GAN) is a rare neurodegenerative disease caused by recessive mutations in *GAN* gene encoding gigaxonin. Nerve pathology of GAN shows typical giant axon with accumulating intermediate filaments. The disease is progressive with impairments in both peripheral and central nervous system. Here, we reported a case presenting gait disturbance, giant axon in nerve biopsy, and abnormalities in brain magnetic resonance imaging (MRI).

A 13-year-old girl presented progressive gait disturbance for 7 years. She had a normal physical and cognitive developmental milestone before age 3. Thereafter, she showed motor retrogradation with slow running, gait imbalance, and exercise intolerance. She received Achilles tendon lengthening surgery at the age of 9. During the past 2 years, she felt numbness in distal lower limbs and difficult in doing buttons and using chopsticks. She was the first child of healthy nonconsanguineous parents with no family history of neuromuscular disorders.

On examination, she had kinky hair, bilateral pes cavus, and hammer toes. Neurological examination revealed normal mini-mental state examination score of 30, vertical and horizontal end-gaze nystagmus. Symmetrical distal muscle atrophy was observed in both lower limbs. Muscle strengths were graded 4/5 distally of the upper limbs and 3/5 distally of the lower limbs. Tendon reflexes were normal in upper limbs, but absent in lower limbs. The superficial sensation was decreased in distal upper and lower limbs, while deep sensation was decreased in distal lower limbs. The patient had impaired finger-to-nose tests, positive Holmes rebound phenomena and mildly impaired alternating movements, and heel-to-knee-to-shin tests. Romberg's test was positive. Bilateral Babinski signs were found positive. Her gait was wide-based with foot drop, and she could neither walk on her toes nor heels.

Nerve conduction velocity studies indicated predominantly axonal sensorimotor neuropathy. Full spinal X-ray showed scoliosis [Figure 1c]. Brain MRI revealed lesions around the fourth ventricle [Figure 1a and 1b]. Nerve biopsy showed moderate myelinated nerve fiber loss, several regenerative clusters, and scattered giant axons. Neurofilament accumulation in giant axons was detected by electron microscope [Figure 1d–1f].

Next-generation sequencing was performed. She had compound heterozygous mutations which were inherited from her father and mother (c.1174G>A [p.E392K] and c.1634G>A [p.R545H] mutations in *GAN* gene), respectively. Mutation of c.1174G>A was predicted to be pathogenic by SIFT, PolyPhen-2, and mutation taste. Meanwhile, the mutation was highly conserved among different species. The mutation of c.1634G>A was reported in GAN patient associated with distal limb weakness and generalized areflexia.^[1]

Giant axonal neuropathy caused by *GAN* gene mutation is a rare neurodegenerative disease. *GAN* gene encodes gigaxonin protein which plays an important role in cytoskeleton formation by stabilizing microtubule network.^[2] Till now, there are more than 80 cases of *GAN* mutant patients reported in literature.^[3] The initial symptoms of GAN include kinky hair, progressively walking disturbance or cerebella, and cognitive impairments.^[3] White matter changes on brain MRI have been reported, in many cases, diffuse or scattered, supratentorial or infratentorial. However, normal brain MRI is also commonly seen.^[4,5] Other changes include cerebral and/or cerebellar and/or brainstem atrophy.^[3] The brain MRI of reported patient with homozygous c.1634G>A mutations showed Arnold-Chiari I malformation rather than white matter changes.^[1] The presence of giant axon with accumulation of neurofilaments and axonal spheroids is the hallmarks in nerve biopsy.^[3] Our patient presented typical progressive sensorimotor neuropathy and cerebellar ataxia. Brain MRI showed abnormal signals along the bottom of the fourth ventricle which was typically seen in neuromyelitis optica (NMO) and in the cerebellum. However, this type of lesion was not commonly reported in GAN before and made it necessary to differentiate GAN from NMO or Wernicke disease on brain MRI.

Giant axonal neuropathy caused by mutations in *GAN* gene should be taken into consideration for patients with early-onset, progressive sensorimotor axonal neuropathy, and central nervous

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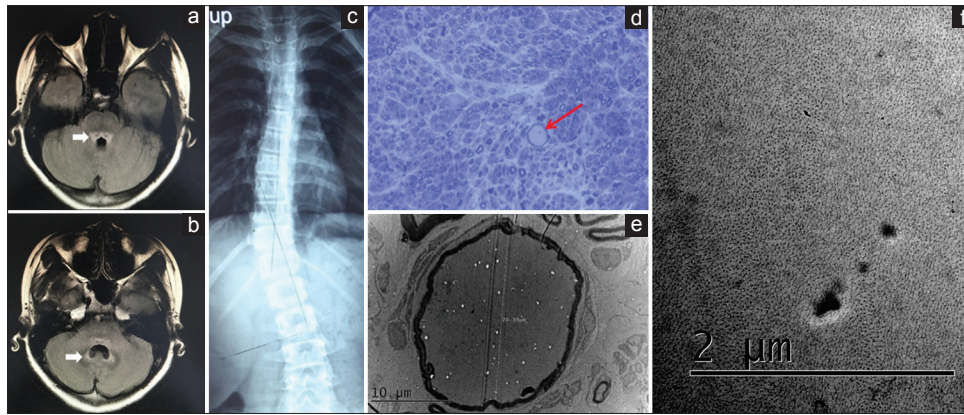


Figure 1: (a and b) Brain MRI showed signal hyperintensity in cerebellum and the bottom of the fourth ventricle on FLAIR (white arrows). (c) Spinal X-ray revealed scoliosis. (d) Giant axon in nerve biopsy by toluidine blue staining $\times 400$ (red arrow). (e) The axon diameter was $20.39 \mu\text{m}$ by electron microscope. (f) Neurofilaments were fulfilled in the giant axon. FLAIR: Fluid-attenuated inversion recovery; MRI: Magnetic resonance imaging.

system abnormality. Giant axons found in nerve biopsy, and gene test can help in making the diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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