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Ataxic Gait Caused by Giant Axonal Neuropathy (GAN): A Case Report

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Abstract

Giant axonal neuropathy (GAN) causes severe polyneuropathy and abnormalities of the central nervous system. There are accumulating intermediate filaments in GAN, which are typical of giant axon pathology. Neuropathy is the result of this disease and it leads to progressive impairments. A 9-year-old boy presented with gait disturbance, homozygous gigaxonin gene mutation, and abnormal brain magnetic resonance imaging (MRI), electromyogram (EMG), and nerve conduction velocity (NCV) studies.

Introduction

Giant axonal neuropathy (GAN) affects both the peripheral nervous system and the central nervous system and is a rare hereditary autosomal recessive disease. So far, several cases of GAN have been reported. The disease commonly manifests during the first decade of life, along with peripheral sensory-motor neuropathy, secondary central nervous system involvement, kinky hair types, and a wide range of prognoses.(1).

In all patients, the nerve biopsy showed an increase in giant axons filled with neurofilament, which is associated with axonal loss and demyelination. GAN is caused by mutations in the gene encoding the gigaxonin protein. In the defective protein, there is an N-terminal BTB/POZ domain and a C-terminal kelch repeat domain, which are involved in protein-protein interactions(1).

It usually appears between the ages of 2 and 3, but rarely after age 10. In addition to the distal weakness, amyotrophy, and lack of tendon reflexes in the lower limbs, it appears to be a progressive distal motor sensory neuropathy. Hair is often described as frrizzy in patients with pale, tightly curled hair. M otor milestones is generally delayed. The distal extremities gradually become weak and clumsy. Sensation is impaired, and tendon reflexes are absent. Pyramidal signs are often positive.

Eventually, dysarthria, nystagmus, facial weakness, and mental retardation appear. In the first or second decade of life, patients usually become wheelchair users and die between the ages of 10 and 30. The electrophysiologic examination often reveals severe axonal neuropathy, and the EEG is usually characterized by slow waves. (2). There may be high signal intensity patchy areas in T2-weighted MRI scans of the brain, indicating abnormal myelination (3). GAN cannot be treated. However,It can be slowed down by treating its symptoms. Symptomatic therapy aims to optimize intellectual and physical development. Therapy includes speech, physical, and occupational therapies(1).

Patients and Methods

Patients and electrophysiologic examination

We investigated a two-generation family with five members (parents, three sons, one of whom is affected). Clinical examination was performed by a neurologist. Nerve conduction velocities (NCV) were determined with a Dantec Keypoint recording unit (Medtronic, Denmark) using surface electrodes.

Molecular genetic analysis

We collected peripheral blood samples from the proband and her family. Genetic DNA was extracted. 1.0 g of genomic DNA per sample was used to prepare the DNA samples. Human whole-exome enrichment was performed using Twist Human Core Exome Kit, and CeGaT GmbH sequenced the library on an Illumina platform with a raw coverage of 350X and a mean on-target coverage of 98X. Almost all exons and 10bp flanking them were detected and analyzed. Variations detected include single point mutations and small indels (within 20bp).

Results

Clinical presentation and laboratory examination

In a 9-year-old boy, the gait was ataxic. Perinatal and prenatal development were normal. His physical & cognitive development was normal before age 4. Later, he showed motor regression with slow running, gait imbalance, and exercise intolerance. In the beginning, his school performance was normal, but in recent years, it declined. He is the product of consanguineous marriage and there was no history of neuromuscular disorders in the family.

He had kinky hair and hammertoes upon examination.The gait was ataxic. An symmetrical atrophy of distal muscles was noted in both lower limbs.

Muscle strengths were graded 4/5 distally of the upper limbs and 3/5 distally of the lower limbs. The tendon reflexes in the upper limbs were normal, but decreased in the lower limbs. The gait of her walk was wide-based with foot drop, and neither she could walk on her toes nor on her heels. Sensory loss was most apparent distally. There were no foot deformities, but the patient had lumbar scoliosis. Neurological examinations of the patient's parents, his two brothers, and his family history revealed no signs of peripheral neuropathy.

The routine blood chemistry included creatine kinase, pyruvic and lactic acid, as well as vitamins E and B.

Electrophysiological examination and brain imaging

Electrophysiological examination showed signs of a severe predominantly axonal sensory and motor neuropathy with reduced compound motor nerve action potentials. Nerve conduction velocity **(**NCV**)** studies indicated predominantly axonal sensorimotor neuropathy.

Brain MRI showed signal hyperintensity in the bilateral GP and dentate nuclei with cerebellum intra-tentorial white matter and also moderate cerebral atrophy and slight reduction in the size of the body of the corpus callosum. The cerebellar size was normal, but bilateral symmetric deep cerebellar white matter signal changes were observed. No specific abnormal spectrum was seen based on measuring citterent metabolites in MR Spectroscopy, including NAA/Cr, Choline Cr and Choline/NAA ratio.

Molecular genetic analysis

Next-generation sequencing was performed. Upon sequencing the gigaxonin gene, a homozygous nonsense mutation was found in exon 7.

Gene/ Transcript*	Variant Location	Variant	Chromosome Position **(**GRCh37**)**	Zygosity1	Related Phenotypes	OMIM number	Inheritan pattern	Variant Classification
GAN ENST00000568107.2 NM 022041	Exon 7	c.1162 1163 delCTinsA p.L388Rfs*20	Chro 81.397.474-81,397,475	Hom	Giant axonal neuropathy-I	256850	AR	Likely pathogenic
ITPRI ENST00000302640.8 NM 001168272	Exon 23	c.276IG>A p.G921S	Chr3: 4,718,324	Het	Gillespie syndrome	206700	AD/ AR	VUS
					Spinocerebellar ataxia-15	606658	AD	
					Congenital nonprogressive spinocerebellar ataxia-20 **(**SCA29**)**	117360	AD	

A table showing the data. Genome analysis. **Het: Heterozygotic, Hon: Homozygotic, Heml: Menus xoto**

The sural nerve biopsy was not possible since the parents refused, but the characteristic combination of clinical features (peripheral nervous system, central nervous system, and hair) allows a reliable diagnosis based solely on clinical observations.

Discussion

A number of neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), infantile spinal muscular atrophy (SMA), and Charcot-Marie-Tooth disease, are associated with cytoskeletal abnormalities. These changes in GAN, however, are unusually striking. Axon biopsy revealed disorganized neurofilaments and enlarged axons. Other intermediate filaments (IFs) accumulate in skin fibroblasts, Schwann cells, and muscle fibers(3, 4). The findings of Pena SD indicate that GAN is caused by disorganization of intermediate filaments in cultured fibroblasts from GAN patients.(5).

There may also be a decrease in the availability of motor proteins. There is still some uncertainty as to whether the dense accumulation of intermediate filaments (primarily neurofilaments) in GAN tissues is a compensatory response to reduced microtubule density or whether gigaxonin directly regulates intermediate filament organization and function by controlling an unidentified partner. Common molecular pathways are involved in the abnormal cytoskeletal organization and dysfunction of ubiquitin-proteasomes in many neurodegenerative conditions. Characterizing the molecular defects underlying GAN may provide insight into their pathogenesis. Gigaxonin regulates microtubule assembly and dynamics by facilitating ubiquitin-proteasome degradation of excess proteins (UPS)((5).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the parents have given their consent for the 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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