

## Case study

### GIANT AXONAL NEUROPATHY: CLINICAL AND PATHOLOGICAL STUDY OF A RARE CASE

#### ABSTRACT

Giant axonal neuropathy (GAN) is a rare, relatively rapidly progressive hereditary neuropathy culminating into death by second or third decade. Simple clinical clues in general physical examination can aid in diagnosis of this rare disease. We report an 11-year-old Hindu male, born out of non-consanguineous marriage, full term, with delayed motor milestones who presented with progressive sensorimotor lower motor neuron type quadriparesis (distal more than proximal) with atrophy, skeletal deformities, cranial nerve and cerebellar dysfunction, macrocephaly and dysmorphic features without any history of similar illness in his family. He had tightly curled hair while none of his parents had such hair. The patient had been wheelchair bound for past 2 years. His tightly curled hair clinched the diagnosis of giant axonal neuropathy which was confirmed by sural nerve biopsy. We are reporting this case because of rarity. So far only 54 cases have been reported worldwide.

**Keywords :** Giant axonal neuropathy (GAN), gigaxonin gene, autosomal recessive neurodegenerative disorder, mitochondria, neurofilaments

#### Introduction

Giant axonal neuropathy is an autosomal recessive neurodegenerative disorder which causes dysfunction of multiple systems in addition to central and peripheral nervous system, thus creating diagnostic dilemma [1]. GAN is caused by mutation in gigaxonin gene. The term GAN finds its origin in the observation of giant axons in nerve biopsies of affected individual. It was first reported by Berg and coworkers and Asbury [1]. The giant axons also have accumulation of neurofilaments with mitochondria and microtubules often pushed to the side [2].

#### CASE PRESENTATION

An 11-year-old Hindu male born out of non-consanguineous marriage, full term, with delayed motor milestones, presented with progressive gait difficulty leading to wheelchair bound state at

the age of 9 years. He started sitting at the age of around 1 year, standing with support around the age of 2 years and walking with support around the age of 2.5 years. He had difficulty in maintaining balance while walking and swaying on either side during walking at around 3 years of age. Gradually he developed muscle weakness and atrophy, distal followed by proximal muscles and lower limbs followed by upper limbs. He sustained painless burns over his lower limbs. For past 2 years he had become wheelchair bound due to severe weakness. There was no history suggestive of visual or auditory complaints, seizures, cognitive decline and bowel bladder involvement. Family history was negative for any similar illness in any of the family members. General physical examination revealed head circumference of 52 cm suggestive of macrocephaly, tightly curled hair, long eyelashes, lower facial weakness with weak eye closure, bilateral grade I nystagmus, high palatal arch, kyphoscoliosis, pectus excavatum, clawing of hands, hammer toes and pes planus. Motor system examination revealed symmetrical atrophy (distal more than proximal), generalized hypotonia with areflexia with muscle weakness (distal more than proximal, lower limbs more than upper limbs). Sensory examination showed impaired exteroceptive as well as proprioceptive sensations in glove and stocking distribution. Cerebellar signs and gait could not be assessed due to severe weakness and deformity. His parents were also examined in detail but no neurological deficit could be ascertained. Patient's MRI brain revealed symmetrical T2 hyperintensities in white matter, brainstem and cerebellum. Neurophysiology revealed severe sensorimotor predominantly axonal plus secondary demyelination of peripheral nerves in nerve conduction studies and prolonged peak P 100 wave latency bilaterally in Visual evoked potential studies. His EEG was normal. His other routine investigations including hemogram and biochemistry, CPK, thyroid profile, Vitamin B12 levels and CSF analysis were within normal limits. Patient underwent right sural nerve biopsy confirming giant axonal neuropathy.

## DISCUSSION-

Hereditary neuropathies constitute nearly 40% of chronic polyneuropathies (3). The clinical clues suggestive of inherited nature of polyneuropathy include history of long standing neuromuscular symptoms; skeletal anomalies like high arches, scoliosis, pes cavus, hammer toes; history of similar illness in family members and paucity of positive sensory symptoms. Even in cases without family history of similar illness, possibility of hereditary neuropathy cannot be

ruled out completely. Such scenario arises in cases of autosomal recessive disease, early demise of one or both parents or spontaneous mutation

GAN is rare neurodegenerative disorder of intermediate filaments. It is inherited in autosomal recessive manner and afflicts multiple systems. GAN can be diagnosed clinically in patients with history of longstanding neuromuscular symptoms, dysmorphic features, multisystem involvement and tightly curled hair.

Typical clinical presentation is of a child with delayed milestones and various dysmorphic features like high forehead, long eyelashes and tightly curled hair. The patient develops progressive gait ataxia suggestive of cerebellar dysfunction, muscle weakness and atrophy; skeletal deformities like hammer toes, pes planus, kyphoscoliosis; areflexia; cranial nerve involvement in the form of facial weakness and ptosis, dysarthria and intellectual decline [3] [4] [5]

Other systems that may be involved are gastrointestinal, endocrine, dermatological and renal with variable clinical manifestations.

The gene for gigaxonin is located on 16q 24.1. The exact function of this gene is debatable but probably it plays a role in maintaining neurofilament architecture by acting as a cytoskeletal component. In GAN, mutation occurs in gigaxonin gene which include frameshift, missense or nonsense mutations and results in accumulation of disorganized cytoskeletal filaments in different types of tissues. The various types of cytoskeletal filaments that may be affected include- keratin (hair), glial fibrillary acidic protein (astrocytes) and neurofilaments (peripheral nerves). The neurofilaments are most severely affected thus causing maximum degeneration and functional impairment in peripheral nervous system. The characteristic tightly curled hair is due to disorganized intermediate filaments in keratin [6]

Diagnosis of GAN can be confirmed by demonstrating giant axons in peripheral nerve biopsy although gold standard of diagnosis molecular genetic testing of the region of the gigaxonin gene. Electron micrograph of peripheral nerve biopsy reveals giant axons filled with neurofilaments. In molecular genetic testing sequence analysis of gigaxonin gene followed by mutation analysis is done. Another method is quantitative immunodetection of gigaxonin in immortalized lymphoblast cells which is significantly reduced as compared to normal population. Other diagnostic studies include nerve conduction studies, MRI brain, EEG and VEP. Nerve conduction studies reveal sensorimotor predominantly axonal with secondary axonal

changes in peripheral nerves (lower limbs more than upper limbs). MRI brain may show diffuse white matter abnormalities in periventricular regions as well as cerebellum. EEG findings vary from generalized slowing to epileptiform discharges.

GAN is an extremely rare disease. Of the 54 families with patients of GAN reported worldwide so far, most have history of consanguineous marriage. The patient reported here was born out of non-consanguineous marriage without any history of similar illness in any of his family members. His parents' examination and neurophysiology did not reveal any abnormality. Moreover, the presence of demyelinating features in neurophysiology created further diagnostic dilemma. The presence of tightly curled hair and CNS dysfunction in addition to peripheral nervous system involvement prompted us to strongly suspect GAN which was further confirmed by sural nerve biopsy.

## CONCLUSION

The multiaxial nature of the disease, extreme rarity and lack of family history of similar illness in any of the family members were the confounding factors in our case but bedside astute observation of characteristic hair phenotype clinched the diagnosis. Giant axonal neuropathy should be suspected in a child with tightly curled hair and progressive multisystem disease with more severe affection of peripheral nervous system.

### **Ethical Approval:**

As per international standard or university standards written ethical approval has been collected and preserved by the author(s).

### **Consent**

As per international standards, parental written consent has been collected and preserved by the author(s).

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