

Clinical, Pathological and Imaging findings of Giant Axonal Neuropathy (GAN): report from India with review of literature and differential diagnosis

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Abstract

Giant axonal neuropathy is a rare autosomal recessive neuro-degenerative disease with simple clinical clues. We describe an 11 year old boy with progressive difficulty in walking with recurrent falls. On examination he had characteristic frizzy curly hair with axonal motor sensory peripheral neuropathy, proximal myopathy, pyramidal and cerebellar signs. Imaging of brain revealed bilateral symmetrical cerebral and cerebellar white matter changes including brainstem and spinal cord. Sural nerve biopsy revealed giant axons of 50-100 microns with tightly packed neurofilaments.

Key words: frizzy hair, giant axons, neurodegeneration

Introduction

Giant axonal Neuropathy (GAN) is a rare childhood onset neurodegenerative disorder caused by accumulation of neurofilaments within the swollen axons [1]. Both peripheral and central nervous system are affected [1-3], the commonest clinical manifestations are peripheral neuropathy, cerebellar ataxia, intellectual disability and pyramidal tract

dysfunction. The pathology is that of a distal axonopathy most severely affecting peripheral nerves, pyramidal tracts, posterior spinal columns, and the cerebellum. The abnormal curly hair is usual and represent abnormal organisation of intermediate filaments in many cell types apart from neurons [1].

Case Presentation

11 year old boy, first in birth order, born of consanguineous union, full term, normal delivery, cried immediately after birth with normal birth weight with delay in attainment of motor milestones of development. Parents noted to have progressive difficulty in walking since 3 yrs of age. The time he started walking, he was noted sway to either side requiring support. There was history of difficulty in getting up from squatting requiring support, however no history of Grower's sign. There was history of slipping of slippers out of the feet while walking with his knowledge, later he could not even grip the slippers. No history of sensory symptoms.

History of Jaundice was present at 3 yr of age which was resolved with treatment. No history of blindness, deafness, seizures. On clinical examination (Fig 1a-1c), had characteristic facial dysmorphism with high forehead, frizzy curly hair, long philtrum, flat feet with clawing of fingers of the hands. The hair texture was different from that of the parents and the sibling. He had proximo-distal weakness of the limbs (distal > proximal) with stance ataxia and gait ataxia requiring support to stand. He had global hyporeflexia in all four limbs with upgoing plantars on both sides. He also had gaze evoked cerebellar nystagmus with normal vision and hearing.

Manuscript received: 11th December 2016

Reviewed: 20th December 2016

Author Corrected: 28th December 2016

Accepted for Publication: 5th January 2017



Fig 1a-1b: Clinical photograph of the patient showing high forehead, frizzy and curled hair

Fig 1c- clawing of fingers of left hand with flat feet

Magnetic Resonance Imaging of the Brain and spine (Fig 2a-2d) revealed T1 iso, T2 hyper intensities along the corticospinal tracts from internal capsule, midbrain, pons, medulla and peri-trigonal white matter of Brain and deep white matter of cerebellum including symmetrical dentate nuclear hyperintensity. Spine imaging revealed hyper intensity of cervical spinal cord with atrophy. Electrophysiology of peripheral nervous system revealed severe symmetrical axonal motor more than sensory, lower limb predominant peripheral neuropathy. Visual evoked potentials (VEP) of both eyes revealed normal optic nerve function. EEG showed slowing of background activity however no epileptiform discharges. CSF analysis was within normal limits.

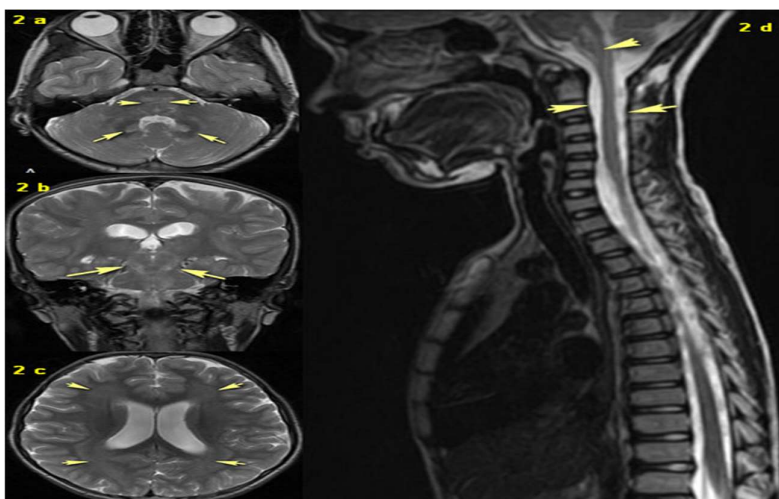


Fig 2a-2d: T2 weighted MRI sequences of brain and spine showing hyperintensities of pons (pontocerebellar fibers), medulla (2a-2d, arrow), symmetrical dentate nuclear hyperintensities of cerebellum (2a axial MRI, arrow), pyramidal tract hyperintensities (2b coronal MRI, arrow), and periventricular whitematter hyperintensities with sparing of subcortical U fibers, minimal ventriculomegaly (2c axial MRI, arrow) and cervical cord signal changes and atrophy(2d sagittal MRI spine,arrow)

Sural nerve biopsy was done which (Fig 3a-3d) revealed expanded fascicles with several fascicles showing “giant sized distended axons” (ranging from 50-100 micron) that were surrounded by thinned out/absent myelin sheaths. The axonal dilatations were segmental and were filled with phosphorylated neurofilament. Vessels included were normal. Ubiquitin immunostaining highlights the giant axons (Fig 3b). Electron microscopic examination of nerve biopsy tissue (Fig 3d) confirmed the dense accumulation of neurofilaments forming tight fascicles and “Giant axons,” the characteristic hallmark of the disease.

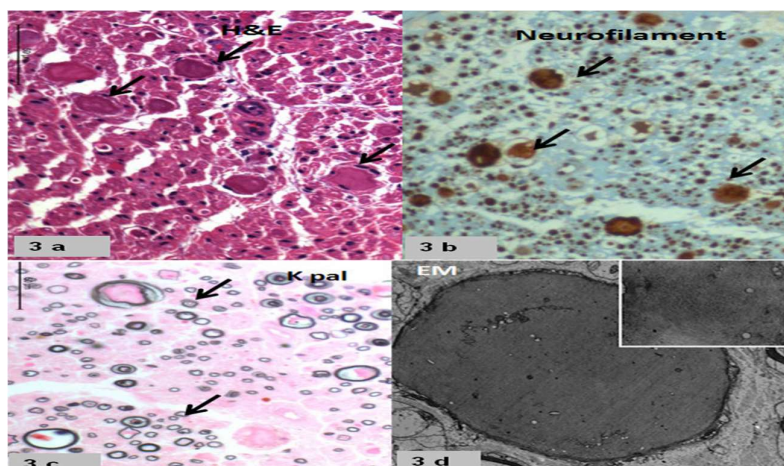


Fig 3a-3d: Sural nerve biopsy shows several distended axons (3a, arrows) that are filled with phosphorylated neurofilament (3b, arrow) and enclosed by thin attenuated myelin sheaths (3c) (3d) Electron micrograph reveals dense accumulation of neurofilaments forming tight fascicles. Inset shows close up view of neurofilaments. [3a: H&E staining, 3b: Neurofilament ubiquitin immunostain (Scale bar=100 microns, 3c: Kulchitsky Pal 9 scale bar=50 microns, 3d: Uranyl acetate-lead citrate x14,000. D, Inset x 36,000]

Discussion

Our patient was labelled with a diagnosis of ‘Giant axonal neuropathy’ (GAN) in view of its multi-axial nature of involvement based on classical clinical phenotype, imaging and pathological distinct features. Inheritance pattern of autosomal recessive nature was sought from consanguineous parentage. Clinically he had frizzy curly hair with cerebellar dysfunction at presentation with later progressed to involve peripheral nerves, muscular atrophy, pyramidal system with moderate intellectual disability. Imaging had demonstrated symmetrical whitematter changes of brain (sparing subcortical U fibers), brainstem, cerebellum and cervical spinal cord. Sural nerve biopsy revealed characteristic Focal Giant axons of 50-100 microns. Curly hair is usual however straight hair was associated with milder phenotype.

E Demir et al [4], reported 6 patients of GAN with age at onset of 3.5-4.5 years and all of them had Frizzy hair, peripheral neuropathy, cerebellar signs and Babinski’s sign, mental retardation was seen in five, scoliosis and ptosis was observed in four, precocious puberty was seen in two patients. Our patient also had similar findings except ptosis. E Demir et al [4], also described imaging features of brain in 4 patients showing predominant white matter abnormality (anterior to posterior gradient and cerebellar) with cavum septum pellucidum with sparing of basal ganglia and corpus callosum. Our patient had White matter abnormality of cerebrum and cerebellum predominantly in the posterior region with changes of midbrain, pons, medulla and cervical cord. Similar case studies were presented by Vijayakumar et al [5], Kamate et al [6] and Ravishankar et al [7]. As against to published literature of sparing of basal ganglia in GAN, Erol I et al [8] described globus pallidus changes in GAN.

Review of Literature- Giant axonal Neuropathy is a rare autosomal recessive neurodegenerative disease caused by mutations in GAN gene located on chromosome 16q24.1, encoding a protein ‘gigaxonin’, playing an important role in the regulation of turnover of Intermediate filaments. The first case of GAN was described by Asbury and Berg [1] in 1972, in a 6-year-old girl with kinky hair, progressive clumsiness, muscle weakness and atrophy, areflexia, and sensory loss. The GAN had its onset in childhood around 3 years of age with progressive multi-systemic degenerative disease process involving gastrointestinal, renal, and endocrinal but the major burden would be on the peripheral nervous system and central nervous system with characteristic facial dysmorphism, skin and hair abnormalities.

Typical presentation would be a child of 3 years of age with facial dysmorphism of high foreheads, pale complexions, and long eyelashes, tightly curled frizzy hair along with progressive sensory motor neuropathy affecting both peripheral and central nervous system manifesting as initial gait disturbance with frequent falls, distal weakness with progressive areflexia, ataxia, dysarthria, dysphagia and wheel chair bound by first decade and death due to respiratory failure by third decade [9].

The peripheral neuropathy of GAN is different from certain inherited neuropathies in which there would be a prominent proximal muscle weakness presenting as waddling gait and positive Grower's sign and winging of scapulae and wasting of pectoral muscles. The gastrointestinal manifestations are constipation [10], reflux, regurgitation [11] and lactose intolerance [12]. Endocrinal symptoms are diabetes [13] and precocious puberty [14] and that of renal are renal tubular acidosis [15]. The dermatological symptoms are ichthyosis and keratosis pilaris [15]. Not all patients of GAN do have described curly frizzy hair; the straight hair is correlated with milder neuromuscular phenotype [12].

The diagnostic requisite of GAN is the characteristic clinical phenotype with demonstration of 'Giant Axons' in the peripheral nerve biopsy. However the gold standard diagnostic testing is to detect the mutations in causative gene of GAN [9]. The mutational analysis in our patient could not be done due to logistic reasons. The term 'Giant axonal Neurodegeneration' is more suitable than neuropathy itself because of its multi-axial nature of the disease. Till now there is no effective pharmacological remedy for this disease. Genetic counseling to the parents is of utmost important in the management.

Differential diagnosis and when to consider GAN: The clinical differential diagnosis of GAN is based on its characteristic hair phenotype and axonal pathology. Table 1 illustrates the differentiating features of GAN with similar presenting disease phenotypes [9].

Table-1: Differential diagnosis of Giant Axonal Neuropathy based on clinical, laboratory and imaging findings [9]

Disease category	Inheritance	Gene	Clinical features	Giant Axons in Peripheral nerve biopsy	MRI Brain/Spine findings
Giant axonal neuropathy	AR	GAN	Distal and proximal weakness, ataxia, nystagmus, Kinky frizzy hair	Present	White matter changes of brain, brainstem and spinal cord
CMT2E	AD	Heterogeneous	Distal weakness and wasting, loss of sensation. Initial symptoms include foot drop and claw toes	present	Normal
Infantile Neuroaxonal dystrophy	AR	PLA2G6	Delay in motor milestones, muscle weakness and stiffness, seizure, deafness, blindness	Axonal spheroides	Brain atrophy, white matter changes, dentate nuclei hyperintensities, eye of tiger sign
Distal hereditary motor neuropathy	X-linked recessive: allelic with Menkes disease	ATP7A	General weakness, Patients have kinky/brittle hair	absent	Normal
Fredriechs ataxia	AR	FXN	Distal weakness, ataxia, dysarthria, scoliosis, pescavus, diabetes, cardiac disease	absent	Normal cerebellum with spinal cord atrophy
Metachromatic leucodystrophy	AR	ARSA	Muscle wasting, weakness, developmental delay, progressive loss of vision, Dysphagia, seizures, dementia	absent	Symmetrical confluent whitematter hyperintensity in tigroid pattern, sparing of subcortical U fibers
Krabbe's disease	AR	GALC	Muscle weakness and stiffness, slowing of mental and motor milestones, seizures	Absent	T2hyperintensities of bilateral thalami, periventricular white matter sparing of U fibers
Spinomuscular atrophy	AR	SMN	Proximal weakness, areflexia, delayed motor development, Tongue fasciculations	Absent	Not required, if done showed T2 hyperintensity of cervical cord

CMT2E- Charcot Marie tooth disease type 2E,

Conclusion

Even inherited diseases can easily be diagnosed through simple clinical clues if looked carefully. A child presenting with characteristic tightly curled kinked hair, with progressive sensory motor weakness of limbs, pyramidal, cerebellar signs and mental retardation, think of giant axonal neuropathy.

Funding: Nil, **Conflict of interest:** None initiated,
Perission from IRB: Yes

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How to cite this article?

Pasha SA, Rao DA, Padmaja A, B Anil, A. Mahadevan. Clinical, Pathological and Imaging findings of Giant Axonal Neuropathy (GAN): report from India with review of literature and differential diagnosis. *J PediatrRes.*2017;4(01): 42-46.doi:10.17511/ijpr.2017.i01.09