CASE REPORT

Giant axonal neuropathy: a rare inherited neuropathy with simple clinical clues

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SUMMARY

Giant axonal neuropathy (GAN) is a rare hereditary neurodegenerative disorder characterised by accumulation of excess neurofilaments in the axons of peripheral and central nervous systems, which hampers signal transmission. It usually manifests in infancy and early childhood and is slowly progressive. Those affected with GAN have characteristic curly kinky hair, everted feet and a crouched gait, which suggest the diagnosis in most cases. We describe twin children who presented with difficulty in walking and an abnormal gait since they began walking; clinical clues such as hair changes led us to the final diagnosis.

BACKGROUND

Giant axonal neuropathy (GAN) is a rare hereditary neurodegenerative disorder.¹ It is a severe childhood disorder, affecting peripheral nerves as well as central nervous system (CNS), due to mutation in the GAN gene encoding gigaxonin, a protein implicated in cytoskeletal functions and dynamics.² GAN is characterised by accumulation of excess neurofilaments (NFs) in the axons of peripheral nerves and CNS, which hampers signal transmission.^{3–5} It usually manifests in infancy and early childhood and is slowly progressive.⁵ The confirmative diagnosis requires advanced diagnostic aids such as MRI, electroneuromyography and peripheral nerve biopsy, which are available in few hospitals. It is a rare condition, characterised by curly kinky hair, everted feet and a crouched gait, with early onset CNS involvement including pyramidal and cerebellar signs that almost clinch the diagnosis. But recently, clinical heterogeneity has been demonstrated with GAN cases presenting with a mild Charcot-Marie-Tooth (CMT)-like phenotype.⁶ We describe twin children who presented with difficulty in walking and an abnormal gait since they started walking. A rare finding of retinitis pigmentosa was present in the first twin; this association has not been reported so far.⁷

CASE PRESENTATION

Case 1 (first twin): An 8-year-old boy born to a second degree consanguineously married couple presented with difficulty in walking and delayed attainment of milestones. He started walking at 2 years and since then had an abnormal gait and dragged his feet while walking. For the past 2 years his gait had worsened and he had frequent falls while walking. He sat at 9 months and attained speech at 24 months. He had poor school performance. He was toilet trained and self-fed but needed

help while dressing. His vision and hearing were normal and he had no history of seizures. Physical examination disclosed curled and rough hair (figure 1) and head circumference within normal limits. Neurological examination showed a crouched gait with everted feet, spastic diplegia and areflexia with positive cerebellar signs. Fundoscopic examination revealed bilateral optic atrophy with atypical bilateral retinitis pigmentosa.

Laboratory examination (blood count, biochemistry including lactate, ammonia, hepatic and renal function test) were normal. Cranial MRI revealed hyper intensities in bilateral cerebellar dentate nuclei and internal capsule on T2/fluid-attenuated inversion recovery sequences (figure 2A1–D1 series). The abnormal hair and neuroimaging findings made us suspect giant axonal neuropathy, hence a nerve biopsy was performed. The nerve biopsy showed scattered onion bulbs with concentric lamellae of Schwann cells surrounding atrophic axons (figure 3). There was severe loss of myelinated fibres, especially those with a large diameter, suggesting axonal neuropathy (figure 3C). Vessels in the endoneurium and epineurium were thickened (reflecting chronicity), with some epineural vessels showing polymorphs marginating along the wall (procedural). On immunohistochemistry, the giant axons were noted to contain increased phosphorylated NFs distending the axon (figure 3B). A portion of the nerve biopsy submitted for electron microscopy showed occasional fibroblasts and Schwann cells filled with intermediate filaments reflecting generalised disorder of intermediate filament accumulation. Because of lack of facilities, genetic studies could not be undertaken.

Case 2 (second twin): An 8-year-old girl, presented with similar symptoms, but in contrast to her brother her illness was less severe; clinical as well as neuroimaging findings were the same (figures 1 and 2A2–D2). Laboratory investigations were within normal range.

An elder sibling had died at 16 years of age with a similar illness, and a third sibling died at 2.5 years of age due to asthma. One child (the second sibling) is normal.

Supportive treatment was offered for both the cases in the form of physiotherapy to improve the locomotive capacity of the children and maintain a normal range of movement of joints.

OUTCOME AND FOLLOW-UP

With physiotherapy the children have been able to maintain independent ambulation but with abnormal gait for the past 2 years.

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Figure 1 Clinical photograph showing the rough, curly hair of the twins, which provided the clue to the diagnosis.

DISCUSSION

GAN is a rare autosomal recessive disorder affecting the CNS as well as peripheral nervous system. Signs of GAN initially begin in the peripheral nervous system with difficulty in walking, loss of sensation, coordination and areflexia; it later involves the CNS resulting in decline in mental function and loss of control of body movements. Seizures and visual problems are also seen in some patients.⁵ Very rarely is retinitis pigmentosa encountered, as in our first case. Kinky hair is a characteristic feature of GAN.⁷

MRI of GAN-reported cases shows hyperintensity signals of both the globus pallidus on T1-weighted images, which indicate accumulation of NFs and involvement of the bilateral thalamus. Sural nerve biopsies reveal giant axons in all funicles, enclosed by thinned out myelin sheaths and, occasionally, loose 'onion cell' Schwann cell hyperplasia.⁴ Similar findings were observed in our case. Although these are hallmarks of GAN, it is important to note that they can also be found in other hereditary conditions such as CMT2E and CMT4C.⁸ The association of this axonal neuropathy and CNS clinical, including cranial MRI, findings with or without kinky hair is highly suggestive of GAN. This association should prompt genetic testing, if available, of the GAN gene.

GAN is due to mutation of the 'GAN' gene located on the chromosome 16q24.1. This gene encodes for protein gigaxonin, which is involved in cellular function that destroys excess or damaged proteins using an 'ubiquitin proteasome pathway'.^{5 9 10} Neurons without functional gigaxonin accumulate excess NFs in axons to become distended; these giant axons do not transmit signals properly, eventually resulting in problem in movement. Intermediate filament (IF) disorganisation in GAN not only involves NFs, but also all IF types in neuronal and non-neuronal cells. These alterations extend to GFAP, keratin, desmin and vimentin in humans and suggest a role for gigaxonin in maintaining IF architecture.⁹

GAN is associated with a characteristic abnormality of 'thick and tightly curled lacklustre hair'; this is of interest because hair is also composed of epithelial IF.¹⁰ Diagnosis of GAN is established by clinical findings correlated with brain MRI, peripheral nerve biopsy and electroneuromyography findings. Our cases demonstrated the typical signs of GAN with thick, tightly curled lacklustre hair and had characteristic brain MRI changes.

Mutation of the BTB-Kelch protein-gigaxonin responsible for GAN, interestingly the p.R138H mutation in gigaxonin, is at the same position in the BACK domain as in KLHL-7 in retinitis pigmentosa, an autosomal dominant disorder. KLHL-7 involved in retinitis pigmentosa and gigaxonin in GAN both function in an ubiquitin proteasome pathway. Mutation in its BACK domain affects the ability of KLHL-7 to act as a chaperon between Cullin-E3 ligase and its substrate. Failure to efficiently ubiquitinate the target substrate could therefore result in accumulation of substrate leading to cellular toxicity within the highly metabolically active photoreceptor and neurons.¹¹ This explains the basis of retinitis pigmentosa in GAN.

Treatment is mainly supportive, involving a team consisting of a paediatric neurologist, physiotherapist, orthopaedic surgeon, psychologist, and speech and occupational therapists.⁸ GAN generally progresses slowly as neurons degenerate and die. Gradually the brain and spinal cord get involved causing gradual decline in mental function, loss of control of body movements and seizures. Most children become wheelchair dependent in the second decade of life. Some children may survive into early adulthood.⁹ Genetic counselling is very important as GAN is an autosomal recessive disorder with 25% chance of recurrence. If GAN gene testing was performed in the

Figure 2 MRI of the brain of twin-1 (A1–D1) and twin-2 (A2–D2). (A and B) T1 and T2 axial images of cerebellum and brain stem showing signal changes in the dentate nucleus. (C) The dentate nucleus signal changes seen in the T2 coronal sections of the brain. (D) The signal changes in the posterior limb of internal capsules in the T axial sections at the level of the basal ganglia.

Figure 3 Nerve biopsy: several giant axons of varying sizes (arrows) dispersed within the fascicles (20–200 μm) (A). These contain abundant phosphorylated neurofilaments distending the axoplasm to giant proportions (B). *Electron microscopy*: closely packed aggregates of neurofilaments distending and displacing normal organelles within the axoplasm (B, inset). *Myelin stains*: thinned out attenuated myelin sheaths surrounding the giant axons (C). ((A) H&E $\times 20$, (B) Immunostain neurofilament $\times 40$, (B, inset) uranyl acetate—lead citrate $\times 28665$, (C) Kulchitsky Pal $\times 40$).

first case such that a prenatal diagnosis could be performed in the second case, the birth of the index cases could be avoided.

Patient's perspective

Our family had three children with Giant Axonal Neuropathy. Failure of recognition and diagnosis of the condition in the first affected child resulted in lack of genetic counselling resulting in the birth of the index cases.

Learning points

- Among the various inherited neuropathies in childhood, giant axonal neuropathy (GAN) has important clinical clues and neuroimaging clues, which should suggest the diagnosis and prompt appropriate confirmatory tests.
- Early diagnosis and patient or parental education about the condition is most important.
- As GAN is an autosomal recessive disorder with 25% chance of recurrence, genetic counselling is very important.

Contributors MK conceived and designed the study and was involved in management of the patients. He is the guarantor. SR and SK were involved in the work up of the case and reviewed the literature. AM analysed the nerve biopsy tissue and interpreted the findings. The final manuscript was approved by all authors.

Competing interests None.

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REFERENCES

- 1 Sharma A, Gokulchandran N, Chopra G, *et al*. Administration of autologous bone marrow-derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life. *Cell Transplant* 2012;21 (Suppl 1):S79–90.
- 2 Tazir M, Nouioua S, Magy L, *et al*. Phenotypic variability in giant axonal neuropathy. *Neuromuscul Disord* 2009;19:270–4.
- 3 Tandan R, Little BW, Emery ES, *et al*. Childhood giant axonal neuropathy. Case report and review of the literature. *J Neurol Sci* 1987;82:205–28.
- 4 Ravishankar S, Goel G, Rautenstrauss CP, *et al*. Spectrum of magnetic resonance imaging findings in a family with giant axonal neuropathy confirmed by genetic studies. *Neurol India* 2009;57:181–4.
- 5 Bruno C, Bertini E, Federico A, *et al*. Clinical and molecular findings in patients with giant axonal neuropathy (GAN). *Neurology* 2004;62:13–16.
- 6 Zemouri R, Azzedine H, Assami S, *et al*. Charcot-Marie-Tooth 2-like presentation of an Algerian family with giant axonal neuropathy. *Neuromuscul Disord* 2000;10:592–8.
- 7 Friedman JS, Ray JW, Waseem N, *et al*. Mutations in a BTB-Kelch protein, KLHL7, cause autosomal-dominant retinitis pigmentosa. *Am J Hum Genet* 2009;84:792–800.
- 8 Kuhlensäumer G, Timmerman V, Bomont P. Giant axonal neuropathy. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, eds. *GeneReviews™ [Internet]*. Seattle, WA: University of Washington, 1993–2003 Jan 09 [updated 21 Jun 2012].
- 9 Flanigan KM, Crawford TO, Griffin JW, *et al*. Localization of the giant axonal neuropathy gene to chromosome 16q24. *Ann Neurol* 1998;43:143–8.
- 10 Klymkowsky MW, Plummer DJ. Giant axonal neuropathy: a conditional mutation affecting cytoskeletal organization. *J Cell Biol* 1985;100:245–50.
- 11 Mahammad S, Murthy SNP, Didonna A, *et al*. Giant axonal neuropathy-associated gigaxonin mutations impair intermediate filament protein degradation. *J Clin Invest* 2013;123:1964–75.

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