

Giant axonal neuropathy: A differential diagnosis of consideration

Pınar Edem¹, Mert Karakaya², Brunhilde Wirth², Tuncay Derya Okur¹, Uluç Yiş¹

¹Division of Child Neurology, Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey;

²Institute of Human Genetics, Center for Molecular Medicine Cologne, and Institute of Genetics, University of Cologne, Cologne, Germany. E-mail: pinaredem@gmail.com

Received: 17th January 2018, Revised: 20th April 2018, Accepted: 2nd May 2018

SUMMARY: Edem P, Karakaya M, Wirth B, Okur TD, Yiş U. Giant axonal neuropathy: A differential diagnosis of consideration. Turk J Pediatr 2019; 61: 275-278.

Giant axonal neuropathy (GAN) is a rare neurodegenerative disorder affecting both the central and peripheral nervous systems progressively. The recessive mutations of the *GAN* gene are responsible for the disease. Although some clinical aspects, like coarse and kinky hair, are suggestive, other diseases may interfere with diagnosis. We describe a case who previously had been diagnosed with and treated for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP); after re-evaluation, genetic testing was received, and the patient was diagnosed with GAN.

Key words: giant axonal neuropathy, polyneuropathies, neurodegenerative diseases.

Giant axonal neuropathy (GAN) is an autosomal recessive neurodegenerative disease affecting both the peripheral and central nervous systems.¹⁻³ Mutations in the *GAN* gene, located on chromosome 16q24.1, causes the disease. Symptoms begin in early childhood, usually by age four, progressing to ambulatory loss during the twenties and death in the second or third decade. Neurological abnormalities due to sensorimotor polyneuropathy are weakness and atrophy prominent in distal muscles, sensorial defects, loss of deep-tendon reflexes, and gait and posture disturbances. Oculomotor and facial cranial nerve impairment may also coexist.^{1,4} Involvement of cerebral cortex, cerebellum, brain stem, and pyramidal tract can develop over time, causing symptoms like cerebellar dysfunction, intellectual disability, seizures, nystagmus, and dysarthria.⁵ Brain magnetic resonance imaging (MRI) especially shows findings of white matter abnormalities, resembling leukodystrophies.⁶ Coarse and kinky hair is one of the diagnostic features of the disease, though this can be absent in some cases. Diseases like Charcot-Marie-Tooth hereditary neuropathy type 4 (CMT4), classic infantile neuroaxonal dystrophy (INAD), and leukodystrophies, like arylsulfatase-A deficiency,

can be considered in the differential diagnosis. Here we report the case of a patient with giant axonal neuropathy who had a former diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) which, to our knowledge, has not been reported as a previous diagnosis before.

Case Report

A 10-year-old boy presented with progressive gait disturbance and frequent falls. He was the first child of healthy parents who were first cousins. He was born at term without any complications. His motor and mental development during infancy was normal. He experienced frequent falls beginning when he first started walking at 14 months of age. His difficulty in walking had become more evident over time, and he had been diagnosed with polyneuropathy at three years of age. He was considered to have CIDP and received corticosteroid and monthly intravenous immunoglobulin treatments. Recently, speech disturbance, especially abnormalities in pronunciation, had become evident. Although his motor and mental development was normal during infancy, his academic success had decreased in the last three years. He had no



Fig. 1. This image shows the symmetrical wasting and color change of the distal lower limbs of the patient (A). This image shows hypothenar and thenar atrophy and impossibility of assessing the hair change since the patient had a short hair cut (B).

history of seizures. He had had intermittent symptoms, like abdominal pain, dyspepsia, constipation, and dysuria, since three years of age.

His physical examination revealed oculomotor apraxia, symmetrical muscle weakness and atrophy prominent in lower and distal extremities, hypothenar and thenar atrophy, areflexia, dysidiadochokinesia, wide-based and ataxic gait, pes planus, and dry and mottled appearing skin on distal lower extremities (Fig. 1A and B). Characteristics of his hair could not be assessed because he had a very

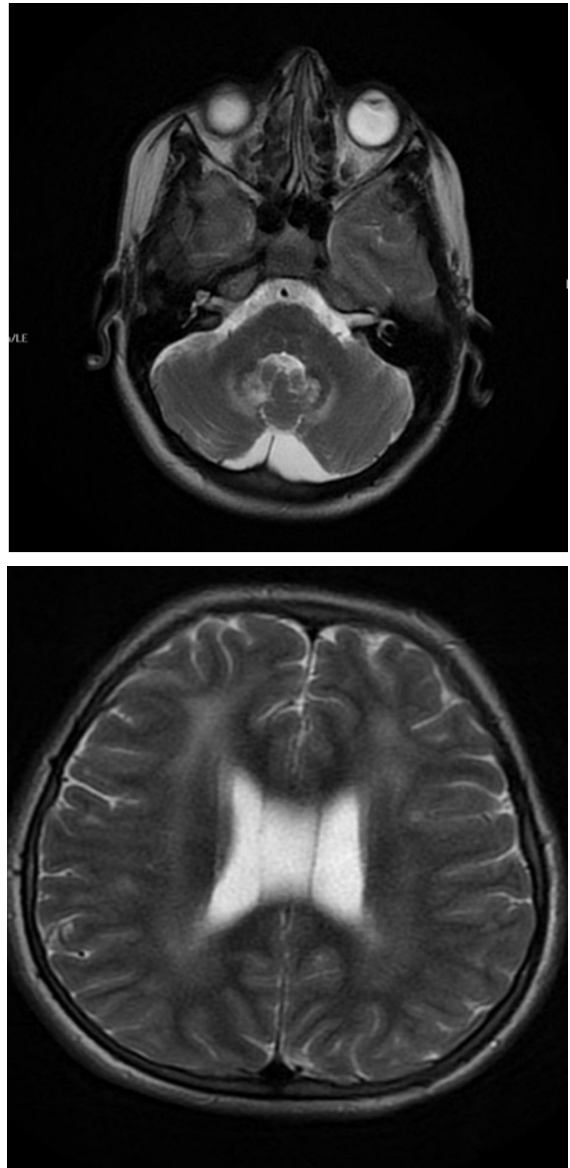


Fig. 2. T2 hyperintensity in the dentate nuclei, cerebellar peduncles, periventricular and subcortical white matter (A and B).

short haircut (Fig. 1B). Ocular examination and audiogram were normal. Complete blood count; biochemistry, including blood glucose, lactate, ammonia, hepatic, and renal function tests; vitamin B12; and thyroid hormones were also normal.

Brain MRI at age four had been reported as normal. Brain MRI at the age of 10 showed T2 hyperintensity in the dentate nuclei, cerebellar peduncles, and periventricular and subcortical white matter (Fig. 2A and B). Electromyoneurography was consistent with

axonal sensorimotor polyneuropathy prominent in lower extremities. We received a written informed consent from the parents of the patient for genetic testing. A neuromuscular next-generation panel identified c.1502+1 G>T mutation in the *GAN* gene. The patient was diagnosed with giant axonal neuropathy, and all immunomodulatory treatments for CIDP were stopped. We present the case after having obtained informed consent from the family.

Discussion

Giant axonal neuropathy is one of the rare diseases presenting with both central and peripheral nervous system involvement, like CMT4, INAD, Menkes Disease, thiamine deficiency, porphyria, mitochondrial diseases, and leukodystrophies.

Clinical diagnosis of CIDP was probably based on the progressive nature of the disease and the reduction in conduction velocity, prolonged distal latency, and prolonged F-wave minimal latency which all indeed pointed to a possible CIDP diagnosis.⁷ Also, the appearance of central nervous system findings over time may have been challenging since peripheral neuropathy is more prominent at the beginning of the disease; in our case, neuropathy revealed itself as gait disturbance and frequent falls. When we evaluated the patient, he had not benefited from the treatment, and axonal sensorimotor polyneuropathy was prominent. This case is important for calling attention to the disease, as our patient was being treated with the diagnosis of CIDP which, to our knowledge, has not been described in a patient previously.

The *GAN* gene on chromosome 16q24.1 encodes a protein called gigaxonin. Gigaxonin is responsible for maintenance of cytoskeletal stability by binding to the light chain of microtubule-associated protein 1B (MAP1B-LC), tubulin-folding cofactor B (TBCB), and a novel microtubule-associated protein, MAP8.⁴ When the *GAN* gene is defective, the cytoskeletal stability is deteriorated as a result of accumulation of cytoplasmic intermediate filaments (IF) in various cells. This is considered to be the cause of axonal transport dysfunction and axonal loss. Frizzy, coarse hair may also be associated with abnormal keratinization⁴. Pathologically, abnormal neurofilament aggregation results in

segmental axonal enlargements of peripheral nerves. Involvement of the central nervous system is more prominent in the corticospinal tracts, the middle cerebellar peduncles, dorsal columns, and oligocerebellar connections⁴. Brain MRI presents diffuse, demyelination sparing U-fibres and atrophy of cerebellum, brain stem, and corpus callosum.^{1,2} Cavum septi pellucidi et vergae variation may accompany these symptoms.¹

Gigaxonin protein is a member of BTB (Bric-à-brac, Tramtrack, and Broad-complex) kelch superfamily. Nonsense mutations and mutations in the BTB region might be associated with early onset and rapid progression.² Genotype-phenotype correlations could not have been defined in previously described mutations.^{1,2}

The c.1502+1 G>T mutation has previously been reported in Turkish patients.^{1,2} Those patients were also from the same south-eastern region of the country, which suggests that this mutation may have a founder effect. The typical clinical and MRI findings, such as mental retardation; axonal neuropathy; cerebellar and pyramidal tract signs; cranial nerve abnormalities; frizzly hair; white matter abnormality; involvement of brain stem, basal ganglia, and thalami; and cavum septi pellucidi et vergae were described in patients having this mutation. Some of these findings also exist in our patient. Furthermore, gastrointestinal, and urinary symptoms may also be associated with c.1502+1 G>T mutation. Although less-investigated, cases with autonomic nervous system involvement are described in the literature. Symptoms like constipation, lactose intolerance, reflux and regurgitation⁸, and perikaryal IF arrangements in the myenteric plexus⁹ have been mentioned. Both gastrointestinal and urinary symptoms in our case may be due to autonomic nervous system involvement, which are documented in animal models.¹⁰ Although correlation between clinical and genetic findings needs further investigation, clinical and radiological features mentioned may be investigated initially in patients from south-eastern Turkey.

The diagnosis of *GAN* may be confused with CIDP, and patients may receive unnecessary immunotherapy due to this misdiagnosis. Hair findings may not always be so typical and apparent. In Turkey, since consanguineous

marriage is common, giant axonal neuropathy should be considered as a diagnosis in patients with gait and posture disturbances, muscle weakness and atrophy, cerebellar dysfunction, intellectual disability, dysarthria, and seizures.

REFERENCES

1. Demir E, Bomont P, Erdem S, et al. Giant axonal neuropathy: clinical and genetic study in six cases. *J Neurol Neurosurg Psychiatry* 2005; 76: 825-832.
2. Akagi M, Mohri I, Iwatani Y, et al. Clinicogenetical features of a Japanese patient with giant axonal neuropathy. *Brain Dev* 2012; 34: 156-162.
3. Koichihara R, Saito T, Ishiyama A, et al. A mild case of giant axonal neuropathy without central nervous system manifestation. *Brain Dev* 2016; 38: 350-353.
4. Yang Y, Allen E, Ding J, Wang W. Giant axonal neuropathy. *Cell Mol Life Sci* 2007; 64: 601-609.
5. Incecik F, Herguner OM, Ceylaner S, Zorludemir S, Altunbasak S. Giant axonal disease: Report of eight cases. *Brain Dev* 2015; 37: 803-807.
6. Erol I, Alehan F, Alkan O, Bruno C. Involvement of the globus pallidus in giant axonal neuropathy. *Pediatr Neurol* 2012; 47: 382-384.
7. Haliloğlu G, Yüksel D, Temoçin CM, Topaloğlu H. Challenges in pediatric chronic inflammatory demyelinating polyneuropathy. *Neuromuscul Disord* 2016; 26: 817-824.
8. Johnson-Kerner BL, Roth L, Greene JP, Wichterle H, Sproule DM. Giant axonal neuropathy: An updated perspective on its pathology and pathogenesis. *Muscle Nerve* 2014; 50: 467-476.
9. Gambarelli D, Hassoun J, Pellissier JF, Livet MO, Pinsard N, Toga M. Giant axonal neuropathy. Involvement of peripheral nerve, myenteric plexus and extra-neuronal area. *Acta Neuropathol* 1977; 39: 261-269.
10. Armao D, Bailey RM, Bouldin TW, Kim Y, Gray SJ. Autonomic nervous system involvement in the giant axonal neuropathy (GAN) KO mouse: implications for human disease. *Clin Auton Res* 2016; 26: 307-313.