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Giant axonal neuropathy: A rare disease hidden in polyneuropathy

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Abstract

Background& Objective: Giant axonal neuropathy (GAN) is a serious progressive neurodegenerative disease. The aim of this study is to evaluate the frequency and phenotypic-genotypic characteristics of GAN patients, which, like many rare diseases, is disguised under the name of polyneuropathy, and to present our experience. *Methods:* In this retrospective observational study, 105 pediatric patients with polyneuropathy were screened. Demographic characteristics and clinical diagnoses were reviewed. The mean age of the patients was 10.9 years (2-18), 59 were boys (56%) and 46 were girls (44%). GAN patients who were genetically diagnosed by single gene analysis were clinically evaluated in detail. *Results:* Regarding the etiology of polyneuropathy, 43% of patients had acquired and 57% had hereditary causes. Among hereditary cases, 29% had an unknown diagnosis, and 5% were diagnosed with GAN, presenting first with gait disturbance. These patients exhibited axonal sensorimotor polyneuropathy and diverse hair types (20% straight, 20% kinky, 40% curly, 20% slightly curly). Findings included carious teeth (40%), hyperplexia (20%), and apnea (20%). Disease progression included worsening scoliosis and limb deformities (pes cavus), with pathological cranial MRI findings. Literature identified 5 GAN patients with a homozygous deletion of GAN gene exon 2-5, classified as likely pathogenic (Class 4). *Conclusion:* This study highlights the frequency of GAN among undiagnosed polyneuropathies in childhood. Although the phenotype-genotype correlation for giant axonal neuropathy has not yet been determined, we hope that further studies in the field of molecular biology will increase the chances of a better quality of life.

Keywords: GAN, rare disease, polyneuropathy

INTRODUCTION

Peripheral polyneuropathy (PNP), also known as peripheral neuropathy, refers to damage to multiple peripheral nerves with motor, sensory, or autonomic properties.[1] Although the prevalence of PNP is estimated to be 2-3% in the general population, no prevalence has been reported in children.[2] PNPs are etiologically divided into two groups: acquired and hereditary neuropathies. Acquired PNPs (metabolic/endocrinologic causes) are more common in adults, whereas inherited PNPs are more common in children.[1,2] An appropriate definition for PNPs is the Pandora's Box definition of rare genetic diseases by Angural A. *et al*. Many rare diseases will be encountered in the study of PNPs in children.[3] There is no clear definition of rare diseases. However, according to the United States of America, a disease is considered rare if it affects no more than 5 in 10,000 people.[2] Half of the patients diagnosed with rare diseases are children and 80% are inherited.[4]

Giant axonal neuropathy (GAN), known as one of these orphan diseases, is an autosomal recessive peripheral and central nervous system (CNS) disorder characterized by the presence of giant axons in peripheral nerves.[5,6] The GAN gene is located on chromosome 16q24.1 and encodes a protein called gigaxonin, which protects the cytoskeletal structure and regulates intermediate filaments. Although the abnormal gigaxonin encoded by the mutated GAN gene is thought to be responsible, the cause of the disease is not fully understood.[6] The onset of GAN disease usually occurs in early childhood, from early infancy to the 10th year of life. While death from

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respiratory failure occurs in the third decade, the disease progresses brutally in the first and second decades, requiring the use of a wheelchair.[6,7] A diffuse cerebral and cerebellar leukodystrophy can be seen on the magnetic resonance imaging (MRI) scan of the patient's brain. This finding is associated with giant axons with abnormal neurofilament accumulation.[8]

New studies indicate that the clinical spectrum of GAN is increasing.[9] It is stated that as data on the disease increases, treatment intervention studies also gain momentum.[10] With this study, we share the clinical and genetic features of our GAN cases, which, like many rare diseases, remain hidden under the general name of PNP.

METHODS

This observational study was conducted between 2015 and 2018. It was retrospective. A total of 145 patients with ICD code (G63, G63.6, G63.8, G60.8) with the diagnosis of polyneuropathy who were registered at the Department of Pediatric Neurology, Meram Medical Faculty were identified. The study was approved by the local ethics committee of Necmettin Erbakan University, Meram Medical Faculty (approval number: 2019/1693). Patients were called by phone and 105 patients who accepted the study were included in the study. These patients were invited to the hospital and re-evaluated. Demographic and clinical characteristics of patients with polyneuropathy were determined. Etiologic classification of PNP was performed. Patients diagnosed with GAN within hereditary PNP were evaluated separately. Among these patients, 5 patients (1 female and 4 males) were identified. The age, sex, birth history, family consanguinity, onset and clinical symptoms, clinical course, hair characteristics, mental status, electromyographic (EMG) nerve conduction studies, electroencephalogram (EEG) examination results, brain magnetic resonance imaging (MRI), mutation analysis, and nerve biopsy characteristics of these patients were collected.

Approval for participation was obtained from all patients (and/or parents) included in the study. The study was approved by the local ethics committee of the Necmettin Erbakan University, Meram Medical Faculty (approval number: 2019/1693).

Statistical methods

The statistical analysis was performed with the SPSS statistical package (version 25 for Windows). Data were expressed either as the mean ± SD or as the percentage.

RESULTS

A total of 105 (105) patients with a clinical diagnosis of childhood PNP were evaluated. 59 of these patients were male and 46 were female, with a mean age of 10.7 years. The etiology of PNP was examined; 43% of the patients had acquired PNP and 57% had hereditary PNP. The most common etiology in patients with acquired PNP was diabetes. The most common etiology in patients with hereditary PNP was Charcot-Marie-Tooth disease (CMT). The rate of those without a diagnosis of hereditary PNP was 29%. Demographic characteristics and clinical classification of patients with PNP are shown in Table 1. The characteristics of the variants of the patients diagnosed with GAN (5%) in our study are shown in Table 2, and the clinical characteristics are shown in Table 3. The gender distribution of the five patients whose diagnosis of GAN was confirmed by genetic mutation was as follows: one (20%) female and four (90%) male patients. It was determined that all but two patients had a family history of consanguinity.The first complaint of the families was difficulty in walking. The mean age of onset of gait difficulty was 4 years. All patients had facial thinness and bizarre hair (straight, kinky, curly). Hand deformity was observed in all patients (except Patient 5), especially in the index finger. All patients had foot deformities (pes cavus, pes planus, hammer toe, talipes equinovarus) and scoliosis. The scoliosis was the most severe in Patient 1.While the scoliosis was mild in patients 2, 3, and 5, it became more pronounced within 2 to 3 years after they began to experience difficulty in walking. Peripheral nervous system signs were present in all patients from baseline. These included distal muscle weakness and loss of deep tendon reflexes. Cerebellar (nystagmus, dysmetria, dysdiadokinesis, ataxic gait) and cerebral (dysarthria, spastic paraplegia, intellectual disability) symptoms were also observed. Table 3 and Figure 1 show the clinical characteristics of the patients. None of the patients had seizures and electroencephalography examination was normal. In 2 patients (patient 1 and 3), impaired myelinization in the cerebral cerebellar white matter was observed on brain MRI (Figure 2).Nerve conduction studies revealed motor and sensory axonal neuropathy (NCS) in all patients except Patient 1. Needle electrode electromyography (EMG) was performed only in

Table 1: Demographic and clinical characteristics of patients with polyneuropathy

Age in years, mean (range)	10.7 (2-18)
Sex,	**n (%)**
Male	59 (56)
Female	46 (44)
Etiology of Polyneuropathy	**n: 105**
Acquired polyneuropathies	**n: 45 (43%)**
Endocrinological dis.(Diabetes)	20 (19%)
Chemotherapy-related	11 (10%)
Vitamin deficiency (Vit.B12, B6.)	14 (13%)
Critical illness polyneuropathy	2 (2%)
Gullian barre syndrome (GBS)	8 (8%)
Hereditary polyneuropathies	**n: 60 (57%)**
CMT type 2E, 4C, 4E	15 (14%)
HMSN,HS(A)N/HSN	10 (10%)
Undetectable Hereditary PNP	30 (29%)
Giant axonal neuropathy	5 (5%)

CMT: Charcot-marie-tooth disease, HMSN: Hereditary motor and sensory neuropathies, HSAN: Hereditary sensory and autonomic neuropathy, HSN: hereditary sensory neuropathy (HSN), PNP: Polyneuropathy

Patients 1 and 3. No significant abnormalities were found. Sural nerve biopsy was performed only in Patient 4. The biopsy showed a neurofilament appearance compatible with GAN. In the other families, the biopsy was not accepted. Patients with clinical suspicion of GAN were evaluated by single-gene studies. The Human Gene Mutation Database (HGMD) was used for evaluation. Variant analysis was performed according to the American College of Medical Genetics (ACMG). It was observed that the exon 2-5 deletion was not defined in the GAN gene. Since it was clinically compatible, it was considered as a novel deletion with a possible pathogen.The patients had the genetic tests carried out with their own financial means. Genetic testing could not be performed for the patient's parents due to financial constraints. Additional tests performed: Routine blood tests creatine kinase, alpha-feto-protein levels, metabolic tests (lactate ammonia, tandem mass spectrometry, urine and blood organic acids, long chain fatty acids), Arylsulfatase enzyme, Charcot-Marie-Tooth (CMT) panel (ARS, AIFM1, ARHGEF10, ATP1A1, BAG3, BSCL2, C12orf65, CHN1, COX6A1, CTDP1, DHTKD1, DNM2, DYNC1H1, EGR2, FGD4, FIG4, GAN, GARS, GDAP1, GJB1, GNB4, HARS, HK1, HSPB1, HSPB8, IGHMBP2, INF2, KARS, KIF1B, LITAF, LMNA, LRSAM1, MARS, MED25, MFN2, MME, MPZ, MTMR2, NAGLU, NDRG1, NEFH, NEFL, PDK3, PLEKHG5, PMP22, PRPS1, PRX, RAB7A, SBF1, SBF2, SEPT9, SH3TC2,

Table 2: Genetic mutations and variant analysis identified in this study

ACMG Variant analysis	**Genetic analysis**	**Mutation**	**Amino acid change**	**Exon**	**n**
No information (New) likely pathogenic Giant Axonal Neuropathy	Single gene (GAN gene)	Exon 2-5 Homozygote deletion	NA	2-5	1
Class 4 likely pathogenic Giant Axonal Neuropathy	Single gene (GAN gene)	c.1709G>A Homozygote Mutation	p.C570Y	11	3
Class 4 likely pathogenic Giant Axonal Neuropathy	Single gene (GAN gene)	c.1709G>A Homozygote Mutation	p.Cys570Tyr	11	1

ACMG: The American College of Medical genetics, HGMD: The Human Gene Mutation Database; NA : No information and new Homozygote deletion

Table 3: Detailed clinical and genetic characteristics of patients with GAN

Data	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age / sex	14/Male	12/Female	11/Male	14/Male	10/Male
Age of onset	4 year	2 year	5year	4year	4 Monthly
First symptoms	Gait Disturbance	Gait Disturbance	Gait Disturbance	Gait Disturbance	Hyperekplexia, Apnea
Family kinship	Yes	Yes	Yes	No	No
Age at loss of ambulation	7 age	6 age	10 age	7 age	6 age
Hair	Straight	Kinky	Curly	Curly	Slightly Curly
Facial weakness	Yes	Yes	Yes	Yes	Yes
Absent tendon reflexes	Yes	Yes	Yes	Yes	Yes
Distal weakness	Yes	Yes	Yes	Yes	Yes
Scoliosis	Yes	Yes	Yes	Yes	Yes
Extremity deformities	Pes Cavus. Hammertoe.	Pes Cavus. Hammertoe	Pes Planus Hammertoe	Pes Cavus. Hammertoe.	Pes Planus Talipes echinovarus
Cerebral ataxia	Yes	Yes	Yes	Yes	Yes
Dysarthria	Yes	Yes	Yes	Yes	Yes
Dysphagia	Yes	Yes	No	Yes	Yes
Cognitive impairment	Yes	Yes	Yes	Yes	Yes
Echo abnormality	No	No	No	No	No
Motor and sensory axonal neuropathy (NCS)	Yes	Yes	Yes	Yes	Yes
Brain white matter abnormalities	Yes	No	Yes	No	No
GAN exon/ mutations	11.exon Homozygous	11.exon Homozygous	Exon 2-5 Homozygous	11.exon Homozygous	11.exon Homozygous
Other features			Rotten Teeth Cavum septi pellucidi etvergae		Rotten Teeth Hyperekplexia, Apnea
Biopsy abnormality	No	N.A	N.A	Yes	N.A

SLC12A6, SMAD1, SPG11, SURF1, TRIM2, TRPV4, VCP, YARS) and the FTX (frataxin) and TMYP (thymidine phosphorylase) genes.

DISCUSSION

Childhood PNPs and rare PNPs are more likely to be inherited.[1-3] Among the childhood PNP patients we studied, the median age was 10.7 years and 57% were inherited. It is clear that there is a group

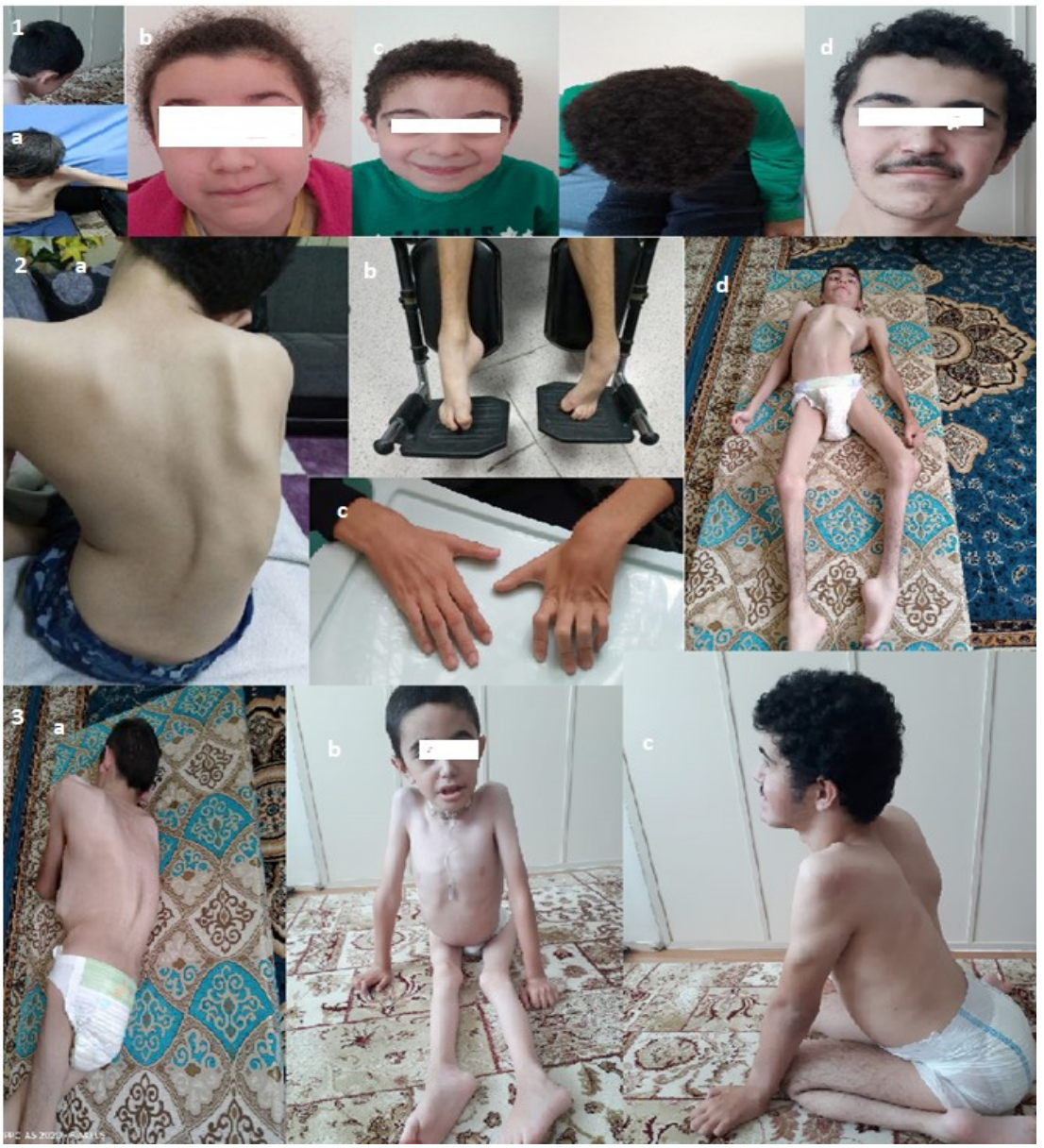

Figure 1. Clinical characteristics of patients with GAN mutation; Figure 1(a,b,c,d) (a) straight hair (b) typical curly (c and d) curly and slightly curly hair features, 2(a,b,c,d) (a) progressive and severe scoliosis (b) extremity deformities such as pes cavus, hammer toe (c)severe hand contracture, finger flexor contractures (d) scoliosis, lower extremity atrophy and contractures, 3(a,b,c) (a) severe scoliosis and distal weakness (b,c) indicates severe distal weakness and hence sitting positions. (The patient's family has given written informed consent for the publication of any potentially identifiable images or data included in this article).

of PNPs that we believe are inherited but the exact genetic disorder have not yet been identified. The prevalence of childhood PNPs and rare PNPs is unknown.[2] The identification rate of many rare diseases, including PNPs, increases when whole exome sequencing and single gene genetic studies can be performed in developing countries with high clinical experience in the world.[11-13] In our study, during the re-evaluation of childhood PNP patients, 5 of our patients diagnosed with GAN, among the very rare diseases we call the other group, were identified by a single gene study. The importance of single gene mutations in identifying rare diseases has also been emphasized in the literature.[14,15] GAN is a very rare, progressive neurodegenerative disorder. Since the mutation in

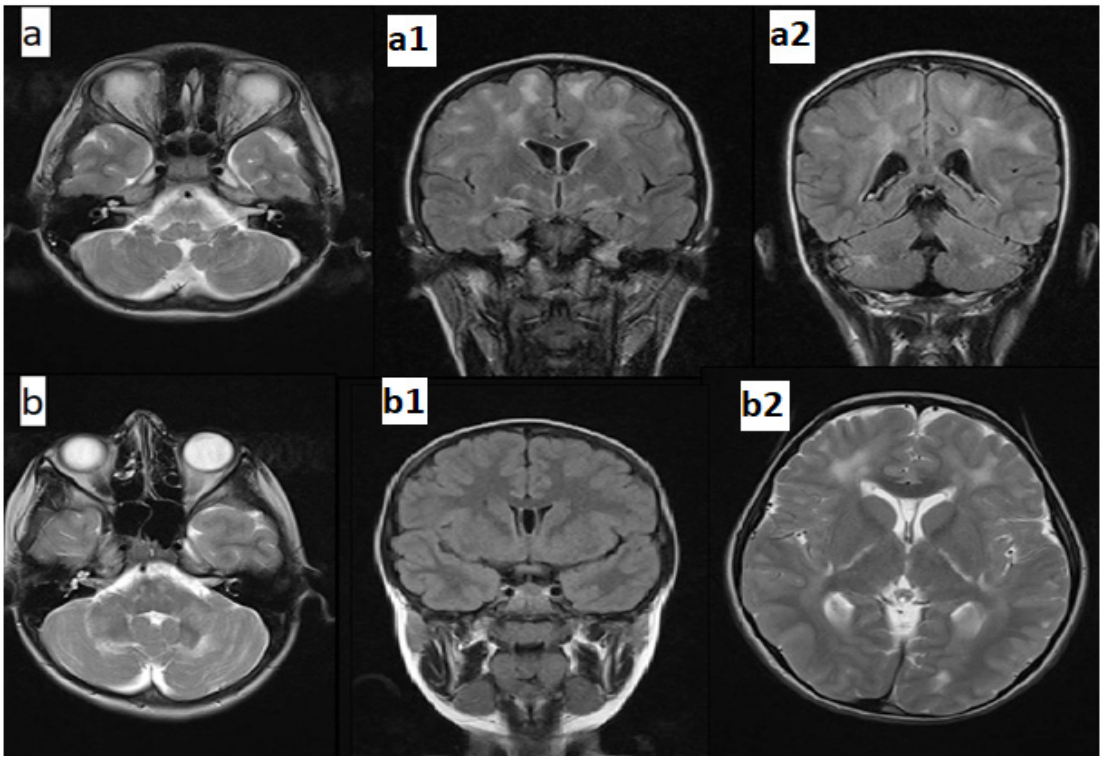

Figure 2. Brain MRI of patients with GAN mutations: Brain MRI of two patients with GAN mutation, cerebellar and cerebral abnormalities observed abnormal hyperintense signal in t2-axial and coronal/ flair sequences. MRI includes (case 1 (14 age). a-a2) abnormal bilateral dentate nuclei and hyperintense signal of the corticospinal system, globus pallidus, capsule interna posterior, and periventricular white matter, (case 3(11 age). b-b2) Variation of cavum septum pellicidum et vergae as well as hyperintense lesions in cerebellar and cerebral white matter.

the gene encoding gigaxonin disrupts the ability to break down intermediate filaments, neurofilaments and glial filaments, giant axons with accumulated neurofilaments are formed and this causes disease symptoms.[5] In patients diagnosed with GAN, involvement of the central nervous system as well as the peripheral nervous system would classically be expected, but a heterogeneous clinical spectrum of disease with different clinical and radiological findings is noted in each case.[16] Although thinness in the face and odd hair characteristics were present in the GAN patients included in the study from the beginning, as the families did not see this as a problem, the first complaint of the family was generally determined to be problems with walking.[9] Hyporeflexia, distal motor weakness, and axonal sensorimotor polyneuropathy on electrodiagnostic study were observed in all patients.[5,16-18] It is known that genotypic-phenotypic characteristics differ in GAN patients, but in our study, hyperekplexia and apnea attacks, whose relationship with GAN has not been reported before, were observed in Patient 5. For this reason, a tracheostomy was performed in our patients. In contrast to the literature, significant dental caries was observed in two of our patients (Patient 3 and Patient 5). Despite a mild disease manifestation of GAN in the literature for patients with phenotypically straight hair[5,16], in our study, Patient 1, who had straight hair, had a severe clinical course due to rapidly progressing scoliosis and the curling of the rib cage that strained the patient over time. In the literature, many symptoms such as ataxia, dysmetria, oculomotor apraxia and nystagmus, spasticity and optic atrophy, seizures, and cognitive impairment due to central nervous system involvement are mentioned in GAN patients.[20-22] Although nystagmus was observed earlier in one of our patients (patient 1), it started to appear 1-2 years after the central nervous system symptoms of cognitive impairment, hand and foot deformities, muscle atrophy and scoliosis. No patient had seizures.[17,18] As stated in the literature, during the course of GAN disease, patients need care due to limb deformities (pes

cavus), spasticity and inability to walk, but especially as scoliosis progresses, they become unable to even sit in a wheelchair. Experiencing this severe form of scoliosis negatively affects both the patient and their relatives because their cognitive state is the last thing to deteriorate. It is stated that patients usually die in the third decade due to respiratory failure.[9] In our study, no respiratory distress was observed in any patient except Patient 5. Brain MRI can demonstrate normal or diffuse cerebral and cerebellar white matter involvement in GAN.[5,9,22,23] In our study, 2 patients had cerebral and cerebellar white matter involvement (Patient 1 –Patient 3). Cavum septum pellicidum malformation, which is reported to be associated with GAN in the literature, was detected include one patient (Patient 1).

The differential diagnosis of GAN includes patients with PNP who were not diagnosed in childhood. These include diseases with central nervous system and peripheral nervous system involvement such as CMT types 2E, 4A, 4B, 4C, 4E, infantile neuroaxonal dystrophy, metachromatic leukodystrophy, Menkes syndrome, mitochondrial neurogastrointestinal encephalomyopathy and spinocerebellar ataxias.[24-28]

Genetic diagnosis is very important to avoid unnecessary testing. The mode of inheritance in GAN disease is autosomal recessive. In this disorder, mutations in the gigaxonin (GAN) gene located on chromosome 16q24.1 are frequently encountered. In our study, a single gene was studied in patients who were clinically thought to have GAN. The evaluation was made according to the Human Gene Mutation Database (HGMD). In these patients, c.1709g>a p.cys570tyr homozygous deletion in exon 11 (Patient 1), c.1709g>a p.c570y homozygous deletion in exon 11 (Patients 2, 4, 5), and homozygous deletion of exons 2-5 (Patient 3) were detected. Variant analyses were performed according to The American College of Medical Genetics (ACMG), and it was observed that exon 2-5 deletions were not detected in the GAN gene. Since it was clinically compatible, it was evaluated as a possible pathogenic new deletion. Similar studies have been found in the literature.[9] Patient 3 is the first GAN patient with a large intragenic deletion seen in the Turkish population.[17-19] Because of the economic situation of these patients, family screening could not be performed.

In our study, not entering the correct diagnosis code in the outpatient clinic setting, not spending enough time with the patient, and not being able to perform genetic testing due to economic conditions in developing countries were seen as reasons for difficulty in determining the actual disease. In the literature, it has been reported that the prevalence of rare hereditary PNPs in childhood may increase, especially with the study of single gene mutations and clarification of clinical features.[10-12]

This study provides the genotypic and phenotypic correlation in Turkish children diagnosed with GAN in PNP in childhood. The clinical follow-up of GAN shows that it is an important neurodegenerative disease that deserves further studies.

DISCLOSURE

Ethics: The study was approved by the local ethics committee of Necmettin Erbakan University Meram Medical Faculty (approval number: 2019/1693). Written informed consent was obtained from all patients (and/or their parents) included in the study.

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Conflict of interest: None

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