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Original Article

Evaluation of hair structural abnormalities in children with different neurological diseases

Süleyman Hilmi Sevinç[1], Sedat Işıkay[2]

[1]Department of Pediatrics, Gaziantep University Faculty of Medicine, Gaziantep; [2]Division of Pediatric Neurology, Department of Pediatrics, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye.

ABSTRACT

Background. Hair microscopy is a fast and effortless diagnostic method for many diseases affecting hair in daily practice. Many diseases can present with hair shaft disorders in pediatric neurology practice.

Methods. Children with pathological hair findings were included in our study. Microscopic evaluation of the hair was performed under light microscopy. The clinical findings, pathological hair shaft findings, laboratory tests, and final diagnosis of the patients were evaluated.

Results. In our study, 16 patients with rare pathological hair findings were identified. Of these 16 patients, nine were diagnosed with giant axonal neuropathy, three with Griscelli syndrome, two with Menkes disease, and two with autosomal recessive woolly hair disease. In hair inspection, curly and tangled hair in patients with giant axonal neuropathy; silvery blond hair in patients with Griscelli syndrome; sparse, coarse, and light-colored hair in patients with Menkes disease; and hypotrichosis in patients with autosomal recessive woolly hair were remarkable findings. Dystrophic hair was detected in most of the patients on light microscopy. In addition, signs of trichorrhexis nodosa, tricoptylosis, and pili torti were found. In particular, pigment deposition in the hair shaft of two patients diagnosed with Griscelli syndrome and pili torti findings in two patients with Menkes disease were the most important findings suggestingthe diagnosis.

Conclusions. Detection of hair findings in the physical examination and performing light microscopic evaluation facilitates the diagnosis of rare diseases accompanied by hair findings. A hair examination should be performed as a part of physical and neurological examinationson eachpatient regardless of thecomplaint.

Key words: hair microscopy, giant axonal neuropathy, Griscelli syndrome, Menkes disease, child.

Hair is a skin appendage that affects the appearance of the person and can be easily examined by a glance in the routine examination. The hair findings can give clues in terms of a child's healthy growth, development, and nutrition, and sometimes they can be the first sign of many congenital or acquired diseases. Examination of the hair structure with a microscope is a simple yet important method in diagnosing many hair-related diseases. There are different types of hair findings in neurogenetic diseases such as giant axonal neuropathy (GAN), Menkes disease, Cockayne syndrome, and Gricelli syndrome (GS).[1]

Anomalies of the hair shaft are divided into two; congenital and acquired. Hair shaft anomalies are also divided into two regarding the presence of hair loss. The first group is hair shaft anomalies that cause hair loss by breaching which are: monilethrix, trichorrhexis nodosa, pseudomonilethrix, trichorrhexis invaginata, pili torti, trichodystrophia, and pili bifurcate. The second group is hair shaft anomalies that do not cause hair breakage or shedding including woolly hair and pili annulati.[1-3]

The normal hair shaft consists of the outer cuticula, the cortex below it, and the innermost medulla. Normally, the hair shaft should be

✉ Sedat Işıkay
dr.sedatisikay@mynet.com

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thick at the root and slightly thin at the ends, but the hair should be of the same thickness and color throughout its length. Trichorrhexis nodosa is the most common hair shaft anomaly. It is the longitudinal separation of hair in one or more areas along the hair shaft. As the fibers close to the exterior of the hair are separated outward, the hair diameter appears to be enlarged in these areas. These areas appear to be a few nodules along the hair shaft. From this point, the hair breaks easily and the hair is short in clinical evaluations. The ends of the broken hair look like a paintbrush. White dots on the hair that can be seen even with the naked eye indicate these nodules. It is frequently detected in Netherton syndrome, Pollitt syndrome, Tay syndrome, Basex-Dupre-Christol syndrome, Tricho-hepato-enteric syndrome, argininosuccinic aciduria, Menkes disease, Kabuki syndrome, ectodermal dysplasia, and biotin deficiency diseases.[1-3] Trichopitylosis is the fringing of hair fibers at the ends of the hair shaft by separating from each other. It can be seen in healthy people at the ends of long hair. If this is observed at the ends of short hair, many hair shaft anomalies should be considered. The woolly hair has irregular serpentine folds along the hair shaft and often broken hair. This is called Woolly hair nevus, which may be autosomal dominant or autosomal recessive. Woolly hair can also be seen in many genetic diseases such as giant axonal neuropathy. Pili torti is the 180-degree rotation of the hair shaft around its axis; which may cause hair breakage and shedding. Such findings occur in Menkes disease.[1-4]

In this study, the hair findings of 16 pediatric patients who were admitted to our outpatient clinic and were found to have hair structural abnormalities on examinations were evaluated with along their clinical findings. Thus, the important contribution of hair microscopy to the diagnosis of neurological diseases was revealed.

Material and Methods

Patients who applied to Gaziantep University Faculty of Medicine, Pediatric Neurology Outpatient Clinic between August 2020 and September 2021 and who had pathological hair findings in their physical examination were included in this study. During the study period, approximately 9000 patients applied to our outpatient clinic. All of these patients underwent a detailed physical examination. In the physical examination, hair findings were detected by inspection in 46 patients. In 10 of these patients, cosmetic treatment in the form of hair dye was applied to the hair and these patients were not evaluated further. No features were found in the detailed hair examination and hair microscopy of 20 patients. The remaining 16 patients were included in the study. Detailed clinical and laboratory findings of these patients were evaluated and recorded.

Before starting the study, ethical approval was obtained from the hospital's non-interventional clinical research ethics committee (Gaziantep University Non-Interventional Clinical Studies Ethics Committee dated 30.06.2021 and decision no: 2020/430). This study was supported by Gaziantep University Scientific Research Projects Management Unit with the project numbered TF.UT.21.27.

Before the genetic analysis of all patients included in the study, an informed consent form approved by the families of the patients was obtained. Written and signed consent forms were obtained from the patients and their families for the use of photographs.

Hair samples were obtained from the top and lateral regions of patients with common hair differences. In cases with localized hair differences, hair samples were taken from those dissimilar areas. Hair samples were obtained by cutting with scissors. Microscopic evaluation of the hair was made using a light microscope.

The preparations were prepared dry between slides and coverslips. At least 40-50 hair strands were examined from each patient's hair sample. Hair strands were evaluated under the light microscope at X4, X40, and X100 magnifications. Pathological hair structural findings detected in each patient were recorded. The relations between the clinical findings, hair findings, laboratory tests, and final diagnosis of the patients were evaluated.

Results

Totally sixteen patients were included in the study; nine with giant axonal neuropathy, three with Griscelli syndrome, two with Menkes disease, and two with autosomal recessive woolly hair disease.

Patients with Giant Axonal Neuropathy

Of nine patients with giant axonal neuropathy, six (62.5%) were female and three (37.5%) were male, the mean age was 10 years (5-16). All patients had first-degree parental consanguinity.

There was no affected family member except siblings with a similar disease. Patients 1 and 2; 3 and 4; 5 and 6 were siblings. None of the patients had a history of prenatal, natal, or postnatal problems. All of these patients have lived in the South eastern Anatolia Region. In patients 2, 4, and 6, developmental delay was described by the families since infancy. The complaints of all patients started between the ages of 2-4 years. The disease started with gait disturbance in the form of unsteady gait and frequent falls in all patients and the complaints progressed rapidly within a few years. Varying degrees of cerebellar findings were present in all patients. Again, deep tendon reflexes could not be obtained in any of the patients.

Complete blood count, routine biochemical tests, serum vitamin B_{12}, and vitamin E levels, thyroid function tests, serum ammonia and lactate levels, blood-urine amino acids, urinary organic acids, and very long-chain fatty acids were found to be normal in all patients. A lumbar puncture was not performed on any patient. Ophthalmological examination of all patients was normal.

All patients had coarse, dense, curly, and woolly hair on physical examination (Fig. 1 and 2). In the hair microscopy of the patients, the hair strands were circular and compatible with the curly hair (Fig. 3 and 4). Except for patient 2, hair shaft disorders in the form of trichorrhexis nodosa and tricoptylosis were detected (Fig. 4).

The diseases of patients 2, 4, and 6 were severe with no ambulation, strabismus, scoliosis, cavus deformity, and contractures. All three patients had moderate intellectual disability.

Brain magnetic resonance imaging (MRI) was performed in all patients except patient 6. In brain MRI, hyperintense white matter lesions were present in all patients except patients 3 and 7 (Fig. 5 and 6). There was cerebral and cerebellar atrophy in three patients (Patients 2, 8 and 9) and only cerebellar atrophy in two patients (Patients 1 and 5). An asymptomatic pineal gland cyst was detected in patient 7 (Fig. 5). There was a variation of the cavum septum pellucidum in four of the patients (Fig. 5, 6, and 7). The lateral ventricles of patient 2 were found to be asymmetrically dilated (Fig. 5).

Electroencephalogram (EEG) was performed on all patients. Patient 8 was also under follow-

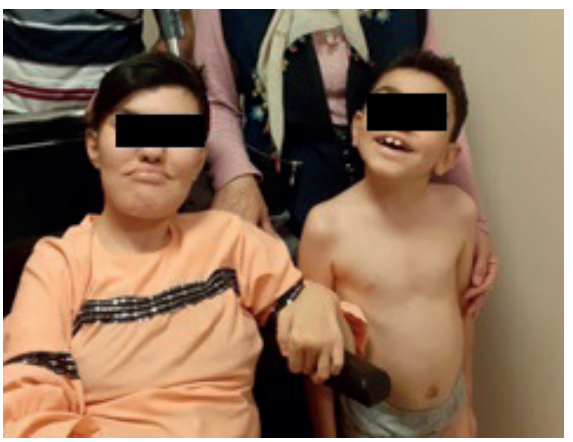

Fig. 1. The appearance of the tangled and curly hair of patients 1 (right) and 2 (left).

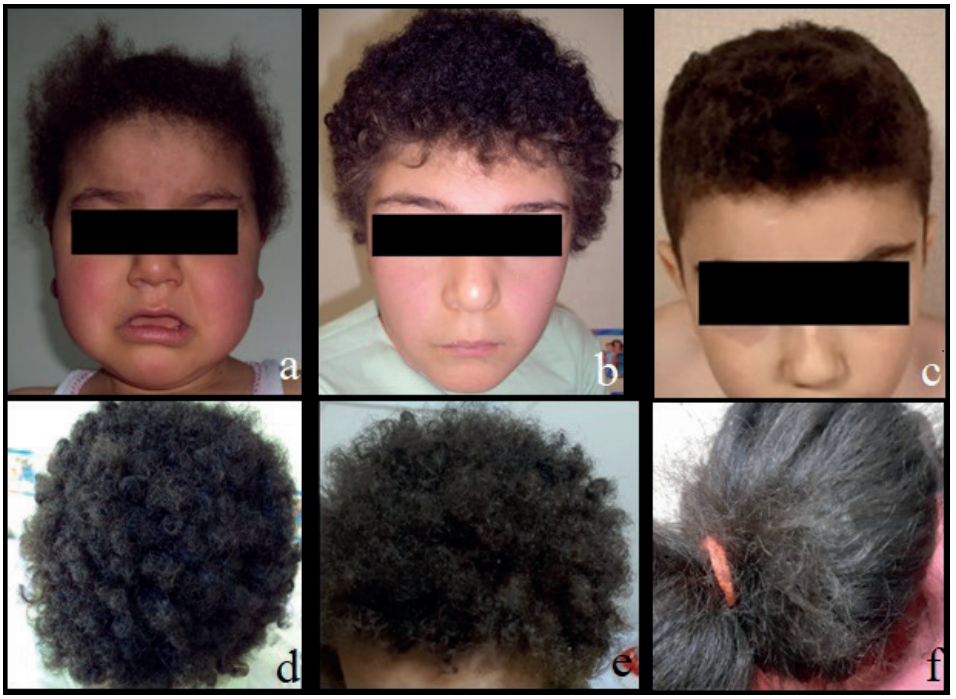

Fig. 2. The appearance of the tangled and curly hair of Patient 3 (a), Patient 4 (b), Patient 5 (c), Patient 6 (d), Patient 7 (e), and Patient 8 (f).

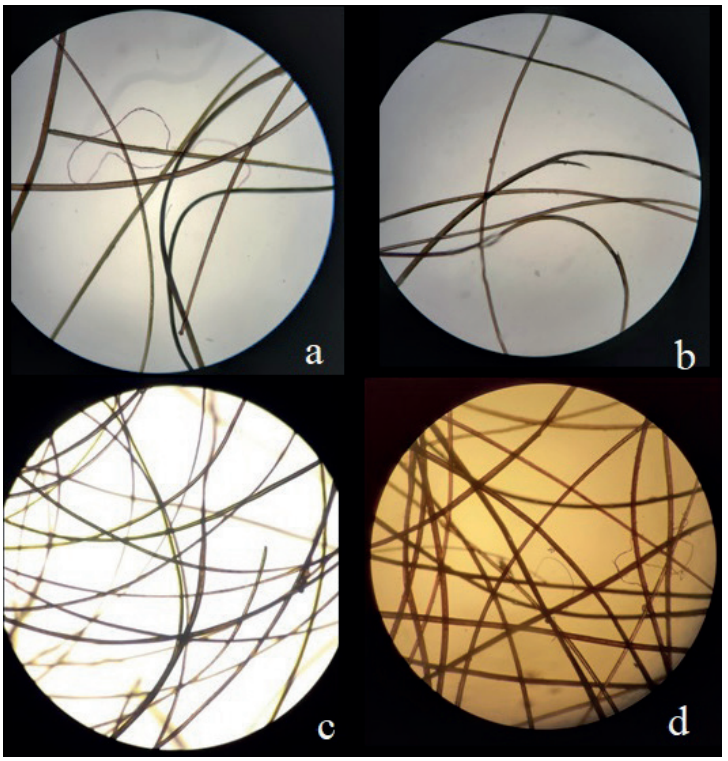

Fig. 3. Light microscopic appearance of hair strands of patient 3 at 4X magnification. The appearance of curly and dystrophic hair strands with different thicknesses (a-d). Sign of trichoptylosis (b).

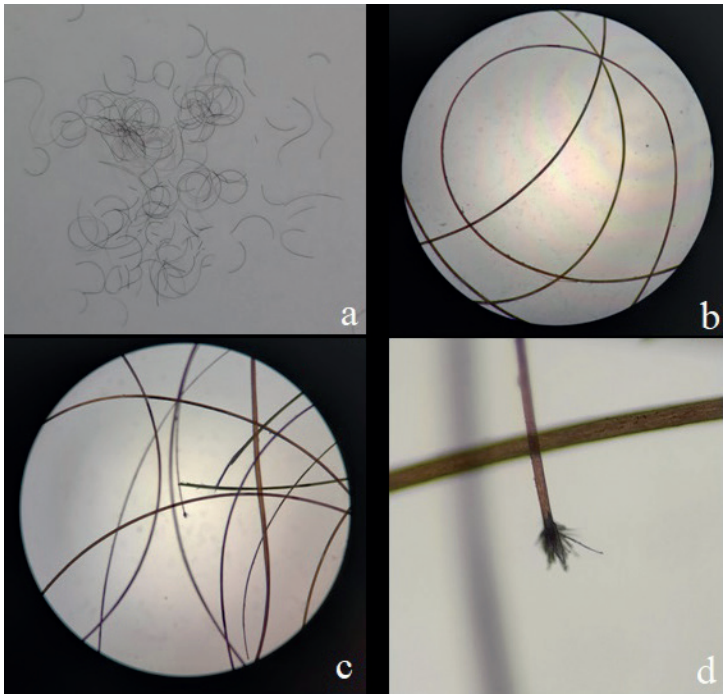

Fig. 4. Curly hair of patient 9 (a), circular hair strands at 4X magnification in microscopic examination (b, c), the appearance of trichorrhexis nodosa sign at 4X (c) and 10X (d) magnifications.

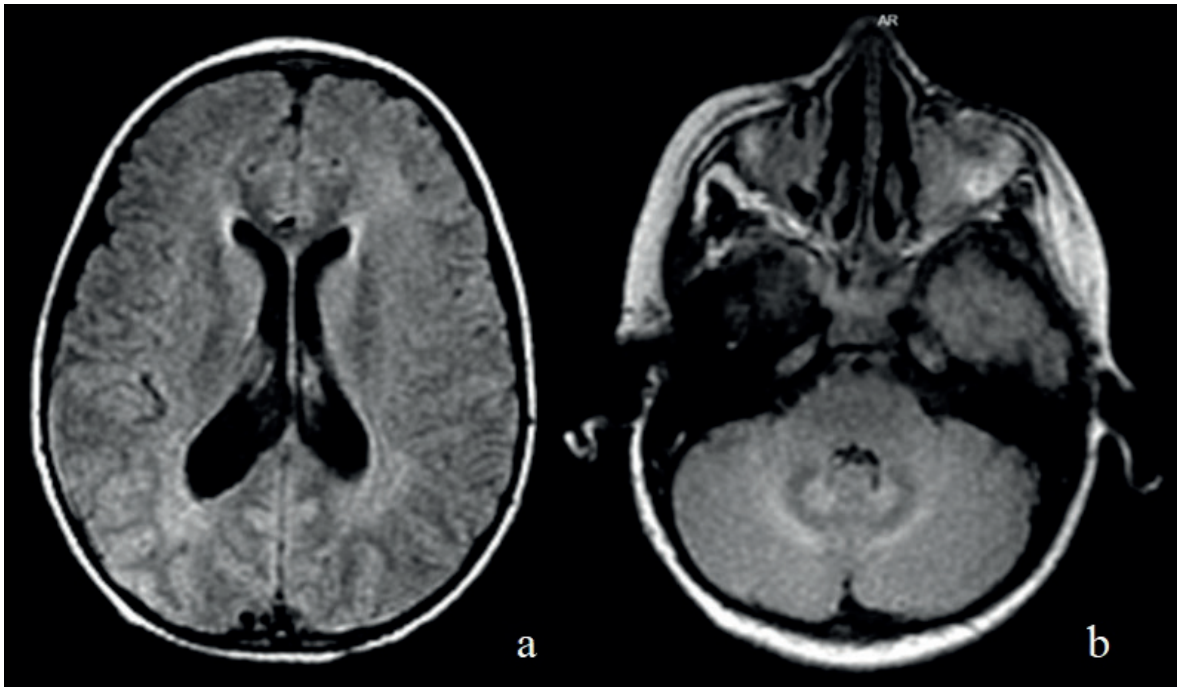

Fig. 5. Asymmetric ventricular dilatation (a) in axial T2-FLAIR sections of patient 2 (a, b), especially in posterior localization, hyperintense periventricular (a), subcortical, cerebellar deep white matter areas (b), and hypointense dentate nuclei (a, b).

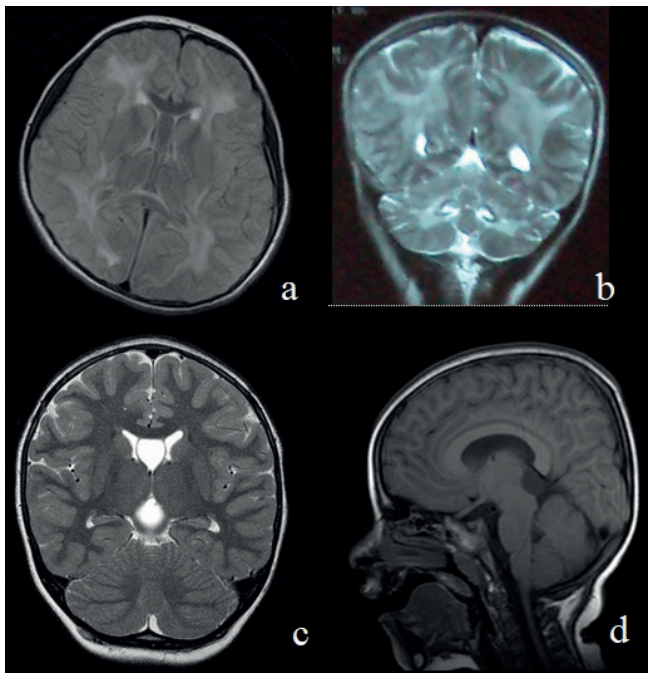

Fig. 6. Patient 3, Cranial MRI appearance of hyperintense areas in the periventricular white matter and variation of the cavum septum pellucidum on T2-FLAIR-weighted axial sections (a). The appearance of hyperintensity in the subcortical white matter areas and dentate nuclei of the cerebrum-cerebellum in the T2-weighted coronal sections of patient 4 (b). The appearance of a cavum septum pellucidum variation (c) in the T2-weighted-coronal section and pineal gland cyst in the pineal gland localization (d) in T1-weighted sagittal sections (d).

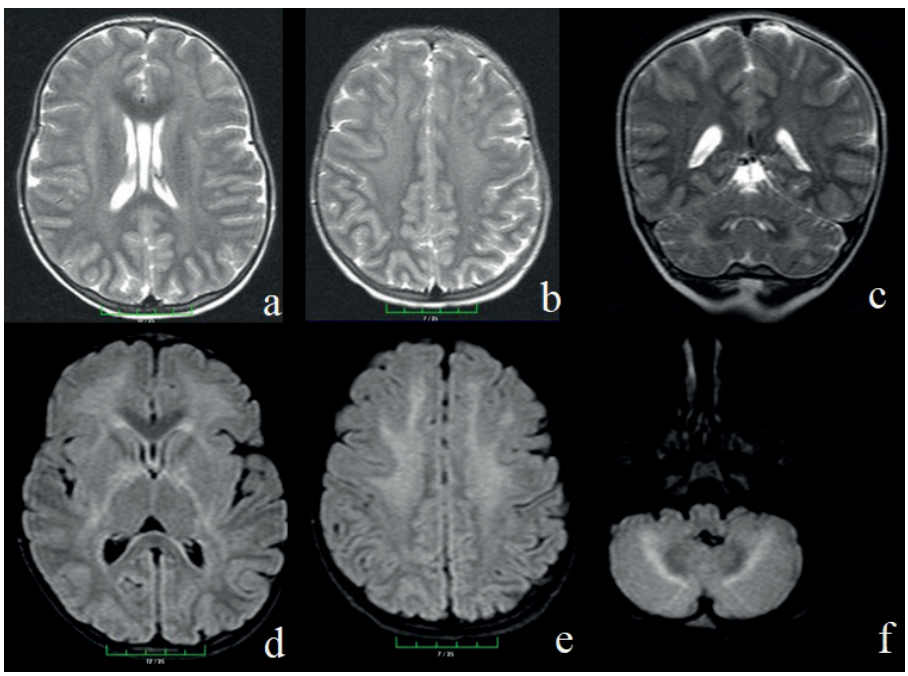

Fig. 7. T2-weighted (a-c) and T2-FLAIR (d-f) axial sections of patient 8 with hyperintense areas in periventricular-subcortical (a, b, d, e) and cerebellar white matter (c, f), internal capsule posterior leg areas and hypointense areas in and dentate nuclei. The appearance of cerebral (a-e) and cerebellar atrophic (c) areas and cavum septum pellucidum variation (a, d) with prominence in occipital and perirolandic areas.

up (for the last 3 years) with the diagnosis of epilepsy. In his EEG, there were bilateral asynchronous parietotemporooccipital sharp waves. Seizure control was achieved with levetiracetam, valproic acid, and clonazepam treatments. Electroencephalogram was unremarkable in other patients.

Electromyography (EMG) examination was performed on all patients. As a result of nerve conduction studies, all patients had sensory-motor neuropathy findings, especially in the axonal weight. Needle EMG was performed in cases 1 and 7, and chronic denervation findings showing partial reinnervation were obtained.

Gene analysis was performed in patients 1, 3, 5, 7, 8, and 9. While homozygous [IVS9 (+1G>T)] was detected in patient 9, c.1502+1 G>T homozygous mutation was detected in the mutation analysis of the other five patients. Heterozygous mutations were found in the parents of these patients.

A nerve biopsy was not performed on any of our patients. The clinical findings of the patients are summarized in Table I. Genetic counseling was given to the families of all patients.

Patients with Griscelli syndrome:

Case 1

A 2.5-year-old boy, was admitted with the complaint of intermittent high fever for about two months. Due to the high fever, he was hospitalized in another center, and treated with antibiotics, but no etiological cause was revealed. He was admitted to our clinic for further evaluation. The patient was consulted with the pediatric neurology department due to developmental delay. On physical examination, his hair, eyebrows, and eyelashes were silvery gray. The patient's skin was rough and dry. There were punctuated hypopigmented areas on the face, arm, and leg skin (Fig. 8a). Height and weight were below 3rd percentile. He had abdominal distention and hepatosplenomegaly. Routine blood tests were normal except for the findings of anemia at the time of admission. Peripheral smear showed findings consistent with hypochromic microcytic anemia. The erythrocyte sedimentation rate was 20. C-reactive protein, coagulation functions, electrolytes, ferritin, uric acid, and kidney and liver functions were within normal limits. Hepatitis A, B, and C, HIV-1, cytomegalovirus (CMV), Ebstein Barr virus (EBV), tuberculosis, salmonella, and mycoplasma serologies were normal. Antinuclear antibody (ANA) and anti-double stranded DNA were negative. The immunoglobulin panel was normal.

Hepatosplenomegaly was detected in the abdominal ultrasonography (USG). Thorax tomography was normal. Bone marrow aspiration was considered normal. Lumbar puncture showed normal cerebrospinal fluid (CSF) opening pressure. No cells were seen, CSF protein was 20 mg/dL, and glucose was 45 mg/dL. Brain MRI could not be performed owing to poor condition of the patient. The patient died on the 21st day of hospitalization due to a severe pulmonary infection. Natural killer cells (NK) activity and CD25 levels of the patient could not be evaluated.

Case 2

Case 2 was the sister of case 1. His 11-year-old sister was hospitalized simultaneously in the same ward due to weakness, fatigue, inability to walk, and poor general condition. In her physical examination, she also had silvery gray hair, eyebrows, and eyelashes (Fig. 8b). The patient's skin was rough and dry. There were punctuated hypopigmented areas on the face, arm, and leg skin. Height and weight percentiles were below the 3 percentiles. Deep tendon reflexes were absent in the lower and upper extremities. She had no organomegaly. There were thenar and hypothenar atrophy of the hands. Neurogenic findings were observed in EMG, there was severe mixed neuropathy, predominantly as sensory-motor axonal

Table I. Clinical data of the patients with giant axonal neuropathy.

Date	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age/Gender	10/M	16/F	10/F	16/F	6/F	15/F	5/M	6/F	6/M
Onset age	2	3	4	4	3	4	3	2	3
The symptoms at onset	Gait disturbance, falling	Gait disturbance	Gait disturbance	Gait disturbance	Gait disturbance, falling	Gait disturbance, falling	Gait disturbance, falling	Gait disturbance	Gait disturbance
Curly and tangled hair	+	+	+	+	+	+	+	+	+
Microscopic findings	TN	-	TN, TP	TN, TP	TN	TN	TN	TN	TN, TP
Intellectual Disability	-	+	-	+	-	+	-	-	-
Scoliosis	+	+	-	+	-	+	-	-	+
Areflexia	+	+	+	+	+	+	+	+	+
Cerebellar findings	+	+	+	+	+	+	+	+	+
Babinski sign	+	-	-	-	+	-	+	-	-
Peripheral neuropathy	+	+	+	+	+	+	+	+	+
Epilepsy	-	-	-	-	-	-	-	+	-
Extremity deformity	-	+	-	+	-	+	-	-	-
Motor function	walks	unable to walk	walks	unable to walk	walks	unable to walk	walks	walks	walks
GAN mutation	+	Not analyzed	+	Not analyzed	+	Not analyzed	+	+	-

GAN: Giant axonal neuropathy, TN: Trichorrhexis nodosa, TP: Trichoptilosis

neuropathy. The patient was followed up in another center for three years with the diagnosis of acute demyelinating encephalomyelitis (ADEM), and steroid and intravenous immune globulin treatments were administered. In the first brain MRI, diffuse involvement was present in the cerebellar and cerebral white matter areas (Fig. 9). Follow up brain MRI performed during her hospitalization which was obtained 3 years after the inital MRI, both cerebral and cerebellar involvement and diffuse atrophy were observed in the white matter areas (Fig. 10). Hair microscopy of both siblings revealed hypopigmentation and pigment deposition (Fig. 8). The case was transferred to the pediatric oncology department for with presumed diagnosis of hemophagocytic lymphohistiocytosis (HLH) with central nervous system involvement. However, the patient died without a definitive diagnosis due to pulmonary infection during follow-up. Both siblings were diagnosed as Griscelli Syndrome based on clinical and laboratory examinations. Genetic testing was not available, yet genetic counseling was provided for the family.

Case 3

A 14-year-old female patient was admitted because of poor school performance. On physical examination, she had silvery gray hair, eyebrows, and eyelashes (Fig. 8c). The patient's skin was rough and dry. There were punctuated hypopigmented areas on the face, arm, and leg skin. In the hair microscopy, clustered melanin granules were seen in the hair shaft (Fig. 8f).

Complete blood count, blood chemistry were normal. Psychometric evaluation revealed mild intellectual disability. The patient was diagnosed with Griscelli syndrome type 1 based on clinical and microscopic findings. In the gene analysis, a homozygous pathogenic variant c.5152C>T (p.Gln1718*) mutation was detected in the *MYO5A* gene, and the clinical diagnosis was confirmed.

Fig. 8. The appearance of silvery blond hair (a-c), eyebrows (a, c), and eyelashes (a) of patients 1 (a), 2 (b), and 3 (c) and punctate and circular hypopigmented lesions on the face of Patient 1. Light microscopic view of abnormal melanin pigment clusters along the hair shaft at X10 and X40 magnifications (d-f).

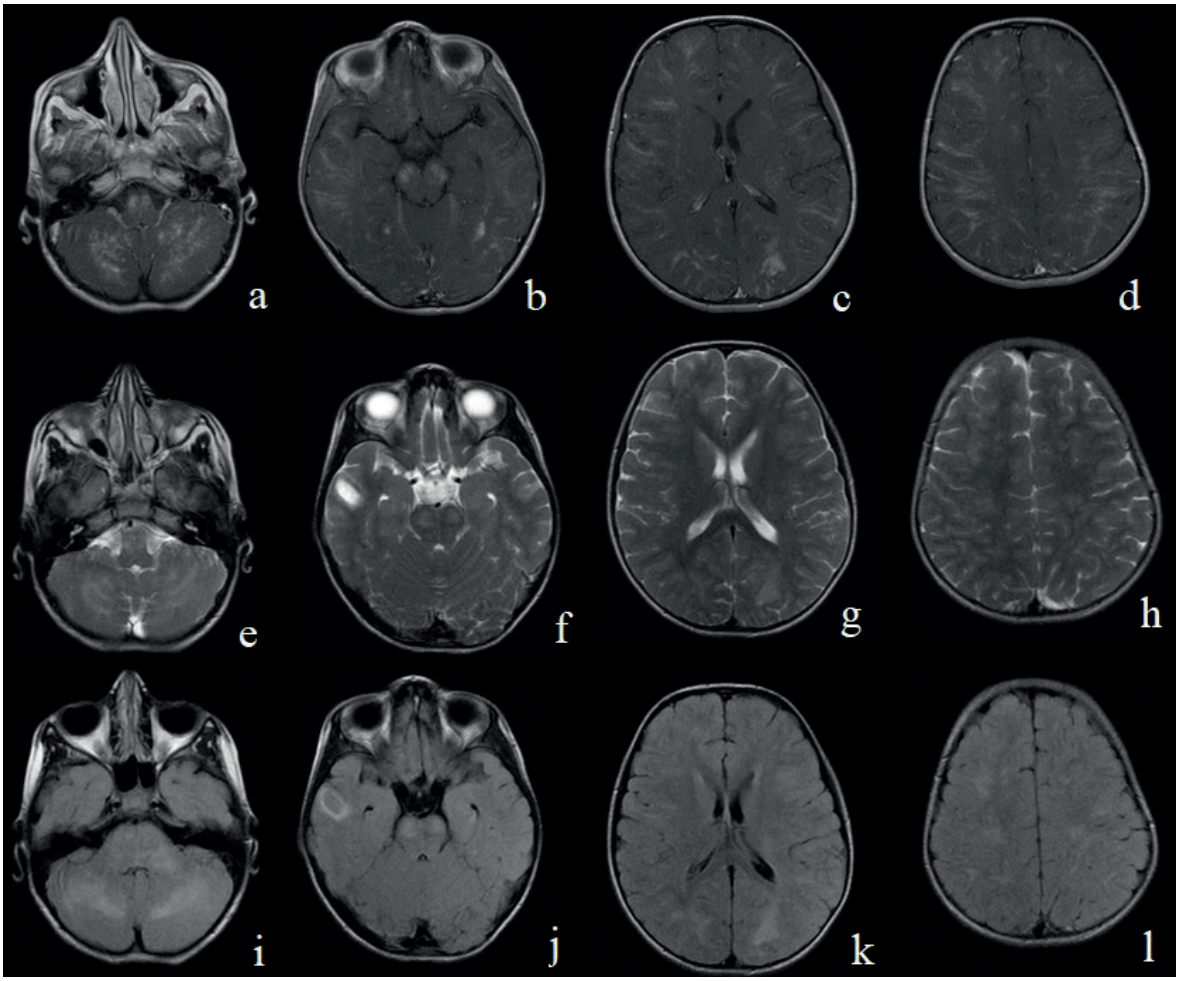

Fig. 9. The appearance of hyperintense areas on subcortical deep white matter areas in the cerebral (b-d, f-h, j-l), cerebellar (a, e, i), brain-stem (a, e), pontocerebellar (i), and mesencephalon tegmentum (b, f, j) on T1-weighted (a-d), T2-weighted (e-h), and T2FLAIR (i-l) sections of axial images of brain magnetic resonance imaging of the patient.

Patients with Menkes Disease:

Two patients were diagnosed with Menkes disease. The first patient was a 15-month-old male with complaints of laxity and developmental delay compared to his peers. His prenatal history was unremarkable. He was born in the hospital with a normal spontaneous delivery with a birth weight of 3250 grams. Family history revealed parental consanguinity. In physical examination; he was restless, and hypoactive. His body weight was 10.1 kg (50th percentile), height was 76 cm (50th percentile), and head circumference was 43 cm (10-25th percentile). He was hypotonic on examination. There was no eye tracking. In laboratory examinations, complete blood count, routine biochemical tests including renal and liver functions, serum ammonia and lactate levels, coagulation parameters, congenital metabolic screening tests, quantitative amino acid levels in the blood, serum Vitamin B12 and biotinidase levels, and urinary organic acid levels were found within normal limits. Toxoplasmosis, cytomegalovirus, rubella, and herpes simplex virus types 1 and 2 serum IgM and IgG tests were unremarkable. Serum copper was <10 μg/dL (85-190 μg/dL) and ceruloplasmin level was 0.07 g/L (0.15-0.48 g/L). Cardiac examination, echocardiography,

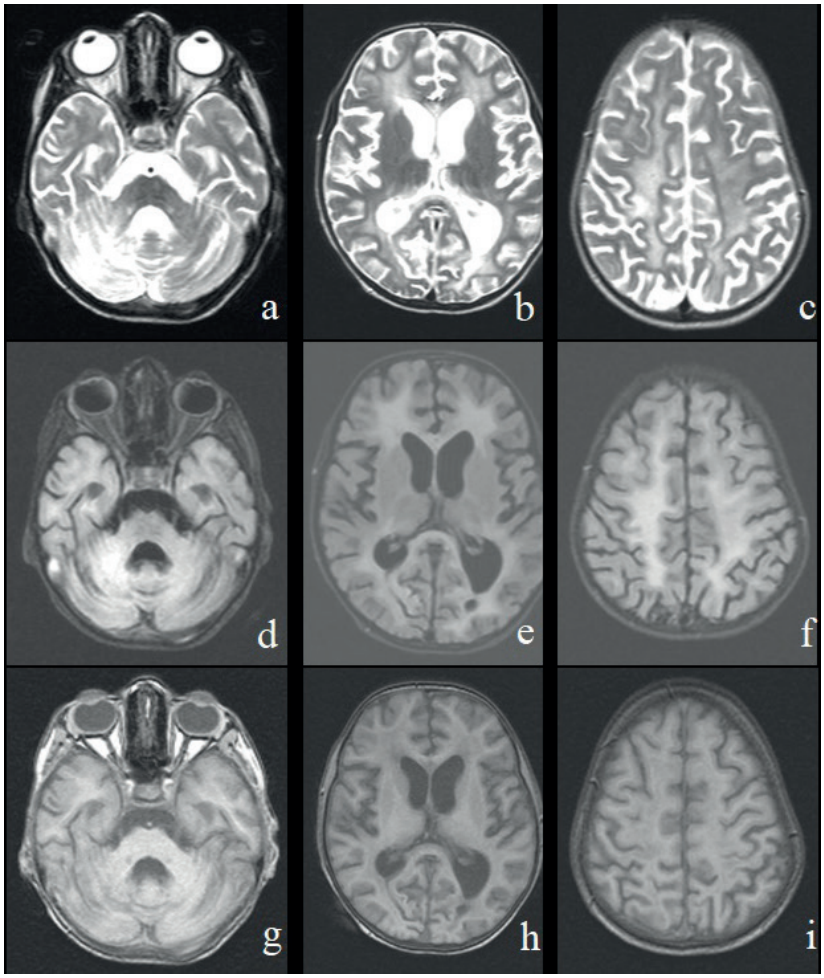

Fig. 10. The appearance of diffuse cortical atrophy in the brain (a-i) and cerebellum (a, d, g) on T2-weighted (a-c), T2-FLAIR (d-f), and T1-weighted (g-i) sections on brain magnetic resonance imaging. The appearance of asymmetric wide lateral ventricles (b, e, h) and enlarge 4th ventricle (a, d, g) secondary to diffuse atrophy. Also, the appearance of diffuse white matter atrophy and hyperintensity in all sections, especially in T2-weighted ones.

and abdominal ultrasonography were found to be normal. Brain MRI revealed atrophy in the brain parenchyma (Fig. 11). In hair examination, his hair was sparse, weak, and light-colored. In the microscopic examination of the hair, trichorrhexis nodosa and pili torti findings were detected (Fig. 11). Gene analysis revealed a homozygous mutation in the ATP7A gene.

The second patient, a 9-month old male patient, was admitted with complaints of weakness in head control and inability to sit with support. He was born after a normal spontaneous delivery at term with a birth weight of 3080 grams. His parents were relatives. His body weight was 7.5 kg (25-50th percentile), and his height was 68 cm (25-50th percentile). On neurological examination; he was restless, hypoactive and hypotonic. Fundus examination was normal. Deep tendon reflexes were hypoactive. In laboratory examinations, complete blood count, routine biochemistry tests including liver and renal function tests, coagulation tests, metabolic screening tests such as serum ammonia and lactate levels, amino acid levels in the blood, serum vitamin B12 level, and biotinidase

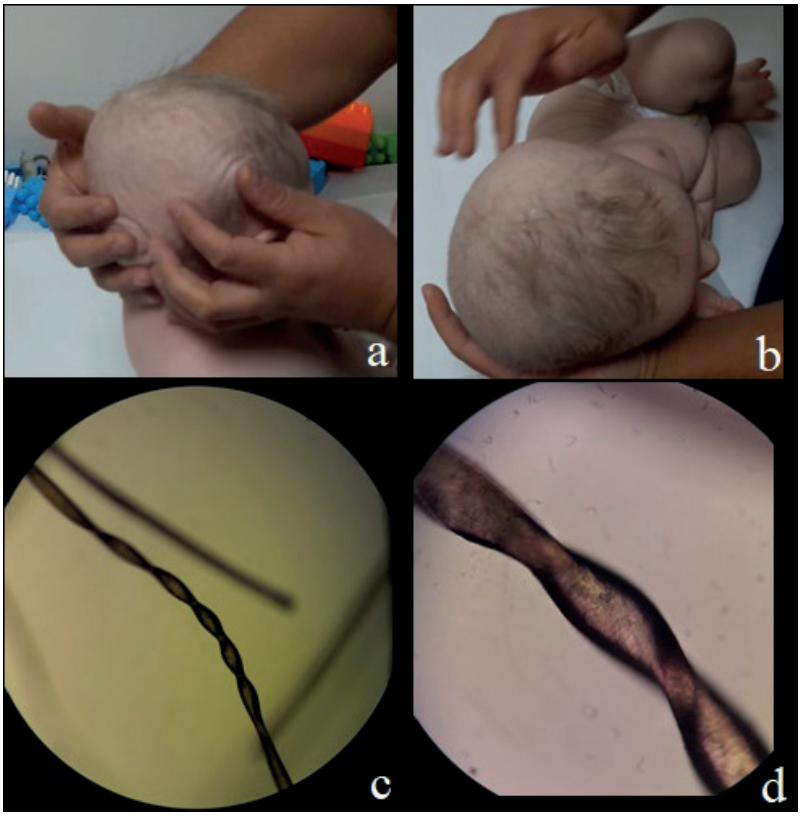

Fig. 11. The appearance of the sparse, weak, and light-colored hair of the patient with the diagnosis of Menkes disease. The appearance of the Pili torti signs at 4X (c) and 10X (d) magnifications on light microscopy (c, d).

activity, and urinary organic acid levels were found within normal limits. Toxoplasmosis, cytomegalovirus, rubella, Epstein-Barr virus, and herpes simplex virus types 1 and 2 serum Ig M and Ig G tests were negative. Serum copper was 36 μg/dL (85-190 μg/dL) and ceruloplasmin level was 0.12 g/L (0.15-0.48 g/L). Brain MRI showed atrophy in the brain parenchyma.

His hair was evaluated because it was light-colored. Pili torti and trichorrhexis nodosa were detected in the microscopic examination of the hair (Fig. 12). A homozygous mutation in the ATP7A gene was detected in the genetic examination.

Patients with autosomal recessive woolly hair:

Two patients were diagnosed with autosomal recessive woolly hair disease. The first patient was a 15-month-old male patient. He has been followed up for febrile seizures. Hair findings had been noticed by his family since he was born. There was no sweating complaint. Family history was negative for similar hair findings. On physical examination, his hair was light colored, brittle, woolly, and sparse. He had long eyelashes and light blond eyebrows (Fig. 13). His nails and teeth were normal. Physical examination was otherwise normal. Brain MRI and EEG were normal. Hair microscopy showed irregular and dysmorphic findings. Trichoptilosis and Trichorrhexis nodosa findings were present (Fig. 13). A whole exome analysis was performed on the patient, and a homozygous *LPAR6* gene mutation (c.373_374delAA) was detected. He was diagnosed with ARWH type 1.

The second patient was a 16-month-old male patient. He has been followed up for

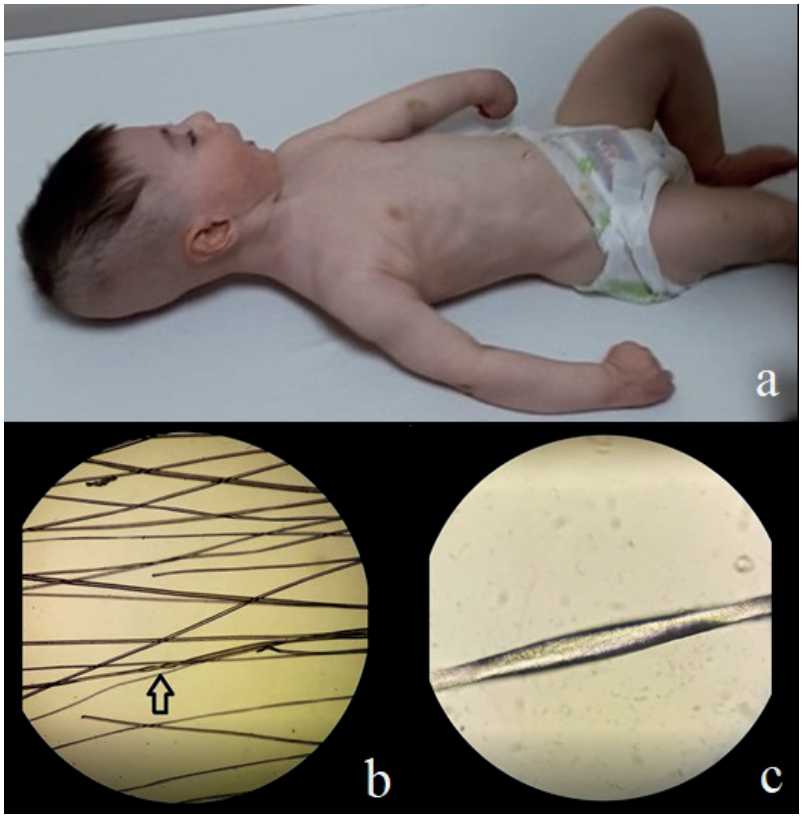

Fig. 12. The appearance of sparse hair on the occipital and parietal regions, but more frequent hair on the upper and front regions, of the patient with the diagnosis of Menkes disease (a). The appearance of hypopigmented, light-colored hair strands, and the Pili torti sign at 4X (c) and 10X (d) magnifications on light microscopy (b, c).

complicated febrile seizures. Hair findings had been noticed by his family since birth. Family history was negative for similar hair findings. On physical examination, his hair was light-colored, fragile, woolly, and sparse (Fig. 14). He had long eyelashes and light blond eyebrows. Nails and teeth were normal. Physical and neurological examinations were otherwise normal. Brain MRI and EEG were normal. Hair microscopy showed irregular and dysmorphic findings. Trichoptilosis and trichorrhexis nodosa findings were present (Fig. 14). In the *LIPH* gene analysis, homozygous missense mutation [c.501C>A, p.(Tyr167*)] was found in the 6th exon of the *LIPH* gene, which was heterozygous in both parents. The patient was diagnosed with ARWH type 2.

Discussion

Giant axonal neuropathy (GAN) is a severe, progressive, and rare autosomal recessive disease affecting the nervous system. Clinical manifestations usually begin around three years of age. Patients have a similar appearance, generally with tangled and curly hair, and neuropathy.[5,6] Life expectancy is usually between 10 and 30 years.[7] The hallmark of GAN in nerve biopsy is axonal swelling due to intermittent neurofilament deposition. Histopathologically, the presence of nodal or internodal axons with segmental enlargement in diameter is diagnostic finding.[8] It is suggested that patients with severe early-onset peripheral motor and sensory neuropathy, distinctly

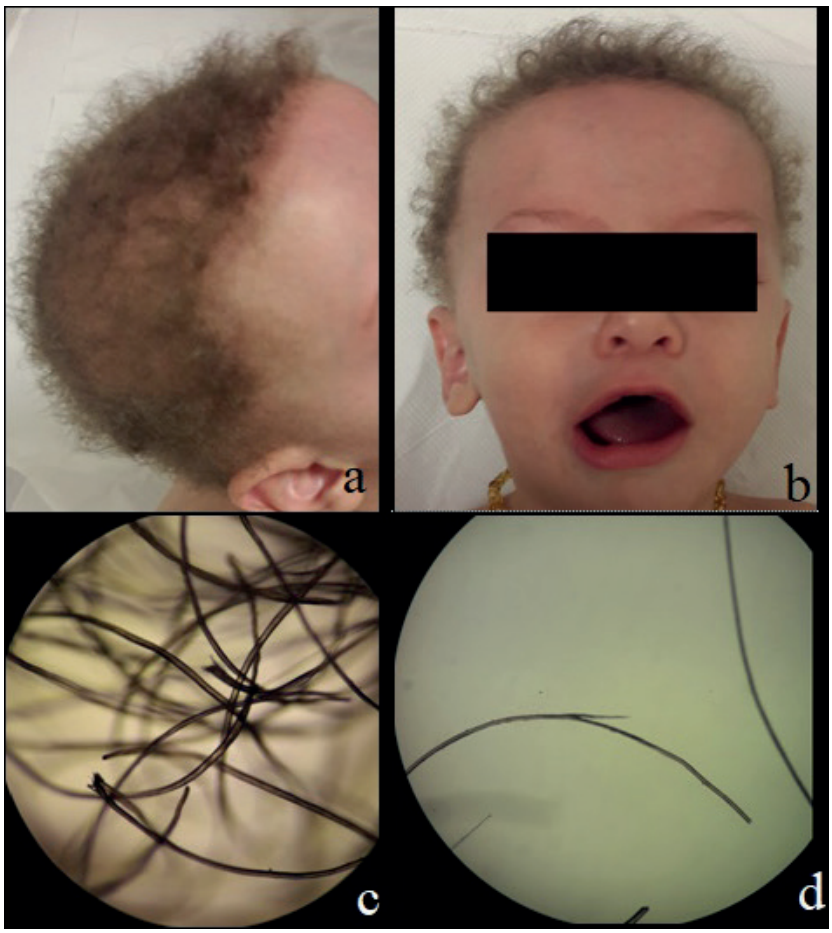

Fig. 13. The appearance of the patient's sparse, weak, fine, and woolly hair that is consistent with hypotrichosis (a, b). The appearance of dystrophic and circular hair strands (c, d), Trichorrhexis nodosa (c), and Trichoptilosis (d) findings at X4 magnification on light microscopy.

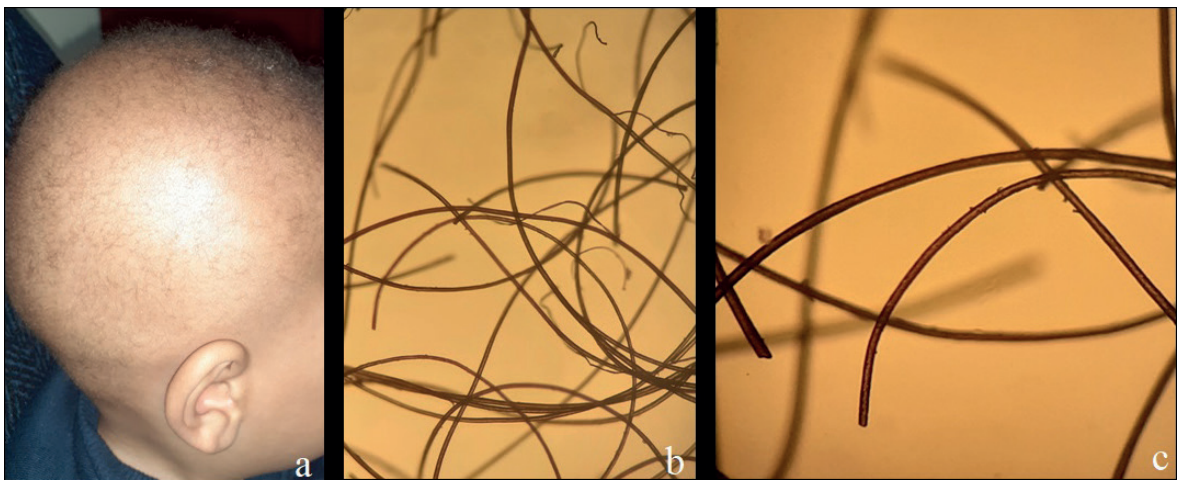

Fig. 14. The appearance of the patient's sparse and woolly hair that is consistent with hypotrichosis (a). The appearance of dystrophic, thin, and curled hair strands of different thicknesses and thickness at X4 magnification on light microscopy (b, c).

dense and curly hair different from parents, intellectual disability, cerebellar, and pyramidal findings should be considered as GAN.[9]

Typical clinical findings of GAN present with both motor and sensory involvement, including sensory dysfunction, clumsiness, weakness, absence of deep tendon reflexes, and marked gait disturbance.[5,9] Affected patients may show symptoms that progress from clumsy gait to marked difficulty with ambulation. In our study, phenotypic findings were consistent with GAN in all of our patients. Symptoms started in the age range of 2-4 years. Besides, a nerve biopsy was not performed because the definitive diagnosis was made with clinical and genetic findings.

Lesions in the CNS are the cause of intellectual disability, epileptic seizures, spasticity, dysmetria, nystagmus, and dysarthria. Scoliosis, ophthalmoplegia, and optic atrophy have been reported less frequently. Cranial nerves, especially the 3rd and 4th nerves, may also be involved.[5,10-13]

In most of the reported cases of GAN, CNS involvement was identified early in the disease.[11] In addition; diffuse demyelination with preservation of U-fibers, atrophy of the brain, brain stem, cerebellum, and corpus callosum can be seen in brain MRI. Most cases are accompanied by the cavum septum pellucidum variations.[14,15] Most of our patients had hyperintense white matter lesions, and varying degrees of brain and cerebellum atrophy, consistent with the literature. Cavum septum variation was detected in four of our patients. A cyst was detected in the pineal gland localization in one of our patients. To our knowledge, this association was not previously reported in the literature. However, Almeida et al.[16] reported the presence of a pituitary cyst in a patient with GAN. In one of our patients, asymmetrical dilatation of lateral ventricles was detecte attributed to cerebral atrophy.

Tangled or curly hair is a characteristic finding in patients with GAN. Also, patients have a characteristic facial appearance with pale skin, a wide forehead, and long eyelashes. Hair findings are usually seen at an early age.[17,18] Wavy, tangled, curly, and coarse hair has been associated with abnormal keratinization. It is thought to develop as a result of the segmental axonal expansion of peripheral nerves due to abnormal neurofilament aggregation.[19] In our study, all patients had similar hair findings. In our patients, the first and the most important finding that attracted our attention was the hair findings, leading to the diagnosis during the initial admission of the patients. Lycklama et al.[20] reported that patients with GAN may have trichorrhexis nodosa on their hair ends. In another study, it is reported that the pili torti sign, frequently seen in Menkes disease, can also be seen in patients with GAN.[21] However, hair strands in Menkes patients may be distinguished from patients with GAN by their lighter color and easy-breaking characteristics.[21] In our study, we found trichorrhexis nodosa in most of our patients, and trichopitylosis in fewer patients, in microscopic evaluation. To our knowledge, the finding of trichoptilosis has not been reported in previous studies. Almeida et al.[16] detected the finding of pili canaliculi as a longitudinal depression on the hair shaft in the electron microscopic evaluation of a pediatric patient.

Central nervous system involvement may cause epileptic seizures and intellectual disability. Intellectual disability usually begins before the age of 10.[7,14] All but three of our patients had normal intelligence.

In the literature, disorganised background activity involving spikes, and paroxysmal activities have been reported in the EEG.[14,22] In our study, only Patient 8 was diagnosed with epilepsy. In his EEG, there were parietotemporooccipital sharp-waves. Seizure control was achieved with levetiracetam, valproic acid, and clonazepam treatments. The GAN gene is localized on chromosome 16q24. This gene encodes the protein gigaxonin and mutations cause the loss of function of this protein.[13,23] In addition, it has been

reported that the disease is not associated with 16q24 in some families. These patients showed slower progression without signs of CNS involvement.[24] C.1502+1 G>T and R293X mutations have been described in previously reported Turkish patients. The geography and some clinical findings of patients with these mutations were found to be similar. The patients with c.1502+1 G>T mutation were from Southeastern Anatolia Region of our country. In addition to the classical findings in patients with this mutation, the association of cavum septum pellucidum variation in brain MRI has been reported.[13,17]

Significant periventricular hyperintense areas were not observed on T2-weighted MRI in patients 3 and 7. Patient 7 had a pineal gland cyst. This finding has never been reported before in the literature in patients with GAN. In the literature, various systemic diseases such as puberty precocs, gastrointestinal diseases such as constipation, reflux, regurgitation, and lactose intolerance, dermatological problems such as ichthyosis and keratosis pilaris, diabetes, and renal tubular acidosis have been reported in patients with GAN.[18] In our study, no other accompanying disease was detected in any of our patients.

Severe early-onset neuropathies [(Charcot-Marie-Tooth disease type (CMT) 2e, CMT4A, CMT4B, CMT4C, CMT4E), Friedreich's ataxia, distal hereditary motor neuropathy], leukodystrophies (metachromatic leukodystrophy and globoid cell leukodystrophy), spinal muscular atrophy, and some rare diseases such as infantile neuroaxonal dystrophy should be considered in the differential diagnosis. Typical giant axons can be seen in some cases of CMT. Other causes of neuropathy such as toxic neuropathy due to smelling glue, n-hexane toxicity, Acrylamide toxicity, and vitamin B_{12} deficiency should also be excluded.[9,18,25] When the CNS is affected, Alexander disease, Fazio-Londe disease, and Menkes disease should be considered in the differential diagnosis.[7] All examinations of our patients were normal and there were no findings suggestive of other genetic neuropathies. Another disease that should be considered in the differential diagnosis is chronic inflammatory polyneuropathy disease (CIPD) with similar clinical findings of neuropathy, progressive progression, and EMG findings.[26]

Griscelli syndrome is a rare autosomal recessive disease with three different subtypes.

Type 1 (*MYO5A*), Type 2 (*RAB27A*), and Type 3 (*MLPH*) develop as a result of related gene mutations. All 3 subtypes have partial albinism affecting the hair and skin. Neurological problems develop in Griscelli syndrome type 1, which is associated with type 2 immune system dysfunction and the development of HLH. Neurological problems such as seizures, and ataxia may develop secondary to CNS involvement. GS3 is presented with dermatological findings.[11,27-29]

Hemophagocytic lymphohistiocytosis is a hyper-inflammation syndrome characterized by fever, hepatosplenomegaly, cytopenia, elevated biomarkers, and sometimes CNS involvement. Primary HLH is associated with genetic defects in the familial HLH genes *UNC13D*, *PRF1*, *STXBP2*, and *STX11*, and the X-linked lymphoproliferative disease genes *SH2D1A* and *XIAP*. The genes involved in pigment transportation such as *NLRC4*, *CDC42* and *LYST*, *RAB27A*, and *AP3B1* genes are also included. All of the proteins encoded by these genes have been involved in lymphocyte cytolytic activity.[11,30,31] RAB27A, a member of the GTPase family, is required for the distribution of pigment-containing melanosomes in melanocytes and the release of cytolytic granules from T cells and natural killer cells. Thus, RAB27A controls these functions through two different cells by interacting with different effective proteins. Primary HLH is usually fatal with a rapid course and the only curative treatment is hematopoietic stem cell transplantation.[11,28-31]

The clinical and neurological findings observed in two siblings with GS were consistent with

the GS phenotype. However, the diagnosis of classical HLH could not be established at the first stage because the routine examinations and bone marrow aspiration findings were normal and the family history did not meet the criteria. However, HLH symptoms and laboratory findings (cytopenia, high CD25, low NK cell activity) appear as the disease progresses. During HLH, CNS involvement may develop at the beginning or at any time of the disease. CNS involvement can be seen as seizure, epilepsy, ataxia, seven nerve paralysis, spasticity, or coma.[32-34] In both patients, the clinical presentation probably developed as CNS HLH and not as typical systemic HLH.

Similarly, in a study, it was reported that HLH may merely affect the CNS.[34] In that study, it was reported that pathogenic mutations of *PRF1*, *RAB27A, UNC13D, LYST*, and *STXBP2* were detected in these patients; and the definitive diagnosis of HLH patients presenting with CNS involvement was established in an average of 28 months.[34] Our case 2 could be evaluated in this regard, approximately three years after the onset of complaints. Since the diagnosis could be established late, there was no chance of treatment.

Treatment regimens for patients with GS are determined depending on the subtypes. In type 1 cases, the treatment is adapted according to the patient's symptoms and clinical presentation. Because type 2 is fatal, it requires bone marrow transplantation. Type 3 does not require any treatment. In a retrospective study, the presence of neurological symptoms before bone marrow transplantation (BMT) in children diagnosed with Griscelli syndrome type 2 indicates a poor prognosis, and the 5- year survival rate was reported to be 50±12.5%.[35] Bone marrow transplantation was not performed in our two patients, who were siblings, because the diagnosis could not be made on time. Both patients died during follow-up. In a similar case with GS, cure was provided with early diagnosis and treatment.[36] Since there were isolated dermatological findings in Case 3, no specific treatment was given.

Menkes disease is a rare X-linked recessive disease that is predominantly affected by the CNS and shows GAN-like hair findings. Copper is a trace element required as a cofactor for many enzymes. The protein that ensures the release of copper from the intracellular environment to the outside of the cell and its transport in the intracellular environment is ATP7A. In the absence of this protein, copper accumulates in the cell and causes the dysfunction of copper- dependent enzymes. Clinical findings in Menkes disease result from dysfunction of copper- dependent enzymes (tyrosinase, cytochrome c oxidase, dopamine beta-hydroxylase, lysyl- oxidase). Patients with Menkes disease show normal development until the first two to three months of their life. Symptoms and signs include hypotonia, feeding difficulties, seizures, dysmorphic facial appearance, and mental and motor retardation, which usually begin in the first months of life. Since these symptoms or signs are not specific, the differential diagnosis includes many chronic neurological diseases.[37] In our study, in both patients, the present findings suggested neurometabolic diseases. Clinical and hair findings of both patients suggested Menkes disease. The diagnosis of Menkes disease is usually made with suspicion in infants with typical neurological changes and hair findings. Hair color is usually white, silvery, or gray. The hair is short, sparse, coarse, shiny, and twisted. Pili torti and monilethrix are usually seen as hair shaft abnormalities. Although rare, patients may have normal hair at birth, but this hair later evolves into light-colored, short, brittle, woolly hair.[37,38] Both patients had light-colored, brittle, woolly hair. Hair microscopy revealed pili torti and trichorrhexis nodosa findings. Light-colored hair and pili torti are not specific to Menkes disease and can also be seen in some other metabolic and hereditary diseases (such as phenylketonuria, trichorrhexis nodosa, and biotin deficiency).[37,38] These diseases were excluded with the family history, clinical, imaging, and laboratory findings of our patients. With cranial imaging, infarcts, cortical atrophy, torsion in intracranial vessels, and hypoplasia

in the cerebellum can be observed.[37] Cerebral atrophy findings were detected in both of our patients. Menkes disease is diagnosed by low serum copper and ceruloplasmin levels. Serum copper and ceruloplasmin levels were found to be low in both of our patients. The definitive diagnosis is made by genetic analysis. Both of our patients had homozygous mutations. There is no effective treatment method for Menkes disease. Symptomatic treatments and genetic counseling for the family are recommended.[37-39]

Isolated autosomal recessive woolly hair/hypotrichosis (ARWH) is a rare genetic hair disorder characterized by tightly curled sparse hair. These patients consist of a genetically heterogeneous group. ARWH type 1, type 2, and type 3 develop as a result of *LPAR6*, *LIPH*, and *KRT25* mutations. The frequency of these mutations varies according to ethnicity and country/geographic location. In the majority of ARWH cases, the *LIPH* mutation has been identified in Pakistan, Japan, and Russia. Loss of LIPH and LPAR6 function resulting from the mutation causes a decrease in the LIPH-LPA-LPAR6 signaling pathway and results in a decrease in the transactivation of EGFR signal. This causes regression of the phenotypic development of the hair. There is no definitive treatment for the disease. In prospective studies, it has been suggested that topical minoxidil application may be a promising treatment in patients due to *LIPH* mutation.[40] Interestingly, both of our patients presented with febrile seizures. To our knowledge, no cases were reported in literature presenting with a neurological complaint. Hair findings were noted in the physical examination which indicated the diagnosis. The first patient was diagnosed with ARWH type 1 with LPAR6 gene mutation, and the other patient with ARWH type 2 due to *LIPH* gene mutation. No problems were encountered in their follow-ups.

In this study, we aimed to establish the importance of light microscopic evaluation of hair, which is a simple and inexpensive examination, in the diagnosis of some rare neurogenetic diseases. Hair examination should be a part of physical examination in pediatric neurology practice. Underlying diseases should be considered in every patient with a local or general abnormality in their hair. The main limitation of this study is the low number of patients with hair findings.

In conclusion, hair shaft disorders have many etiological causes, especially genetic diseases. Since consanguineous marriages are common in the Southeastern Anatolia Region of Turkey, where we practice, autosomal recessive genetic diseases are not uncommon in our routine practice. The diagnosis of genetic diseases require detailed clinical evaluation and phenotyping and relavant genetic tests. A careful clinical evaluation including hair examination may provide hints regarding rare neurogenetic diseases and guide genetic tests.

Ethical approval

The study was carried out following the Declaration of Helsinki of the World Medical Association and approved by the Research Ethics Committee of Gaziantep University (Gaziantep University Non-Interventional Clinical Studies Ethics Committee dated 30.06.2021 and decision no: 2020/430).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SI; data collection: SI, SHS; analysis and interpretation of results: SI; draft manuscript preparation: SI, SHS. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Singh G, Miteva M. Prognosis and management of congenital hair shaft disorders with fragility-part I. Pediatr Dermatol 2016; 33: 473-480. https://doi.org/10.1111/pde.12894
2. Singh G, Miteva M. Prognosis and management of congenital hair shaft disorders without fragility-part II. Pediatr Dermatol 2016; 33: 481-487. https://doi.org/10.1111/pde.12902
3. Rogers M. Hair shaft abnormalities: part I. Australas J Dermatol 1995; 36: 179-184. https://doi.org/10.1111/j.1440-0960.1995.tb00969.x
4. Ahmed A, Almohanna H, Griggs J, Tosti A. Genetic hair disorders: a review. Dermatol Ther (Heidelb) 2019; 9: 421-448. https://doi.org/10.1007/s13555-019-0313-2
5. Igisu H, Ohta M, Tabira T, Hosokawa S, Goto I. Giant axonal neuropathy. A clinical entity affecting the central as well as the peripheral nervous system. Neurology 1975; 25: 717-721. https://doi.org/10.1212/wnl.25.8.717
6. Kuhlenbaumer G, Timmerman V, Bomont P. Giant axonal neuropathy. Gene Rev 2013 (updated 2014). In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Bean LJH, Stephens K, et al. (eds). GeneReviews®. Seattle, WA: University of Washington; 1993-2016.
7. Ouvrier RA. Giant axonal neuropathy. A review. Brain Dev 1989; 11: 207-214. https://doi.org/10.1016/s0387-7604(89)80038-5
8. Carpenter S, Karpati G, Andermann F, Gold R. Giant axonal neuropathy. A clinically and morphologically distinct neurological disease. Arch Neurol 1974; 31: 312-316. https://doi.org/10.1001/archneur.1974.00490410060005
9. Tazir M, Nouioua S, Magy L, et al. Phenotypic variability in giant axonal neuropathy. Neuromuscul Disord 2009; 19: 270-274. https://doi.org/10.1016/j.nmd.2009.01.011
10. Guazzi GC, Malandrini A, Gerli R, Federico A. Giant axonal neuropathy in 2 siblings: a generalized disorder of intermediate filaments. Eur Neurol 1991; 31: 50-56. https://doi.org/10.1159/000116646
11. Zhang Q, Zhao YZ, Ma HH, et al. Successful rescue of a lethal Griscelli syndrome type 2 presenting with neurological involvement and hemophagocytic lymphohistiocytosis: a case report. BMC Pediatr 2021; 21: 253. https://doi.org/10.1186/s12887-021-02720-1
12. Kretzschmar HA, Berg BO, Davis RL. Giant axonal neuropathy: a neuropathological study. Acta Neuropathol 1987; 73: 138-144. https://doi.org/10.1007/BF00693779
13. Bomont P, Cavalier L, Blondeau F, et al. The gene encoding gigaxonin, a new member of the cytoskeletal BTB/kelch repeat family, is mutated in giant axonal neuropathy. Nat Genet 2000; 26: 370-374. https://doi.org/10.1038/81701
14. 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. https://doi.org/10.1136/jnnp.2003.035162
15. Akagi M, Mohri I, Iwatani Y, et al. Clinicogenetical features of a Japanese patient with giant axonal neuropathy. Brain Dev 2012; 34: 156-162. https://doi.org/10.1016/j.braindev.2011.02.003
16. Almeida HL de Jr, Garcias G, Silva RME, Batista SL, Pasetto F. Pili canaliculi as manifestation of giant axonal neuropathy. An Bras Dermatol 2016; 91: 125-127. https://doi.org/10.1590/abd1806-4841.20164677
17. Sabatelli M, Bertini E, Servidei S, Fernandez E, Magi S, Tonali P. Giant axonal neuropathy: report on a case with focal fiber loss. Acta Neuropathol 1992; 83: 543-546. https://doi.org/10.1007/BF00310034
18. 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. https://doi.org/10.1002/mus.24321
19. Yang Y, Allen E, Ding J, Wang W. Giant axonal neuropathy. Cell Mol Life Sci 2007; 64: 601-609. https://doi.org/10.1007/s00018-007-6396-4
20. Lycklama à Nijeholt J, Koerten HK, de Wolff FA. Giant axonal degeneration: scanning electron microscopic and biochemical study of scalp hair. Dermatology 1994; 188: 258-262. https://doi.org/10.1159/000247162
21. Fabrizi GM, Cavallaro T, Angiari C, et al. Giant axon and neurofilament accumulation in Charcot-Marie-Tooth disease type 2E. Neurology 2004; 62: 1429-1431. https://doi.org/10.1212/01.wnl.0000120664.07186.3c

22. Lampl Y, Eshel Y, Ben-David E, Gilad R, Sarova-Pinhas I, Sandbank U. Giant axonal neuropathy with predominant central nervous system manifestations. Dev Med Child Neurol 1992; 34: 164-169. https://doi.org/10.1111/j.1469-8749.1992.tb14983.x

23. Ben Hamida C, Cavalier L, Belal S, et al. Homozygosity mapping of giant axonal neuropathy gene to chromosome 16q24.1. Neurogenetics 1997; 1: 129-133. https://doi.org/10.1007/s100480050019

24. Tazir M, Vallat JM, Bomont P, et al. Genetic heterogeneity in giant axonal neuropathy: an Algerian family not linked to chromosome 16q24.1. Neuromuscul Disord 2002; 12: 849-852. https://doi.org/10.1016/s0960-8966(02)00029-9

25. Zemmouri 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: 592-598. https://doi.org/10.1016/s0960-8966(00)00141-3

26. 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. https://doi.org/10.24953/turkjped.2019.02.019

27. Pastural E, Barrat FJ, Dufourcq-Lagelouse R, et al. Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. Nat Genet 1997; 16: 289-292. https://doi.org/10.1038/ng0797-289

28. Ménasché G, Pastural E, Feldmann J, et al. Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. Nat Genet 2000; 25: 173-176. https://doi.org/10.1038/76024

29. Ménasché G, Ho CH, Sanal O, et al. Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). J Clin Invest 2003; 112: 450-456. https://doi.org/10.1172/JCI18264

30. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. Blood 2020; 135: 1332-1343. https://doi.org/10.1182/blood.2019000936

31. Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: recommendations from the North American Consortium for Histiocytosis (NACHO). Pediatr Blood Cancer 2019; 66: e27929. https://doi.org/10.1002/pbc.27929

32. Yang S, Zhang L, Jia C, Ma H, Henter J-I, Shen K. Frequency and development of CNS involvement in Chinese children with hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2010; 54: 408-415. https://doi.org/10.1002/pbc.22239

33. Zhao Y, Shi J, Li X, et al. Salvage therapy with dose-escalating ruxolitinib as a bridge to allogeneic stem cell transplantation for refractory hemophagocytic lymphohistiocytosis. Bone Marrow Transplant 2020; 55: 824-826. https://doi.org/10.1038/s41409-019-0577-2

34. Blincoe A, Heeg M, Campbell PK, et al. Neuroinflammatory disease as an ısolated manifestation of hemophagocytic lymphohistiocytosis. J Clin Immunol 2020; 40: 901-916. https://doi.org/10.1007/s10875-020-00814-6

35. Al-Mofareh M, Ayas M, Al-Seraihy A, et al. Hematopoietic stem cell transplantation in children with Griscelli syndrome type 2: a single-center report on 35 patients. Bone Marrow Transplant 2020; 55: 2026-2034. https://doi.org/10.1038/s41409-020-0885-6

36. Zhang M, Bracaglia C, Prencipe G, et al. A Heterozygous RAB27A mutation associated with delayed cytolytic granule polarization and hemophagocytic lymphohistiocytosis. J Immunol 2016; 196: 2492-2503. https://doi.org/10.4049/jimmunol.1501284

37. Ramani PK, Parayil Sankaran B. Menkes Kinky Hair Disease. 2021 Jul 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. PMID: 32809752.

38. Moore CM, Howell RR. Ectodermal manifestations in Menkes disease. Clin Genet 1985; 28: 532-540. https://doi.org/10.1111/j.1399-0004.1985.tb00422.x

39. Vairo FPE, Chwal BC, Perini S, Ferreira MAP, de Freitas Lopes AC, Saute JAM. A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease. Mol Genet Metab 2019; 126: 6-13. https://doi.org/10.1016/j.ymgme.2018.12.005

40. Akiyama M. Isolated autosomal recessive woolly hair/hypotrichosis: genetics, pathogenesis and therapies. J Eur Acad Dermatol Venereol 2021; 35: 1788-1796. https://doi.org/10.1111/jdv.17350