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Poster Presentations

(P-01 — P-17)

[P-01]

A Rare *SLC6A1* Gene Variant in a Family with Intellectual Disability: A Case Report from Çanakkale, Türkiye

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Abstract

Introduction: SLC6A1-related neurodevelopmental disorder (SLC6A1-NDD) is autosomal dominant, featured by developmental delay, epilepsy, autism spectrum disorder, and attention-deficit/hyperactivity disorder. Language skills, particularly expressive language, are often more significantly affected than motor development. In this poster, we present the family's clinical findings and genetic analysis results with the SLC6A1 pathogenic variant.

Methods: Our patient, a 6-year-old girl, was referred to us because of trigonocephaly, speech retardation, autism spectrum disorder, and dysmorphic facial features. The patient's mother is 31 years old with epilepsy and intellectual disability. Her father is 41 years old with intellectual disability. There is no consanguinity between the patient's parents. We performed chromosome, microarray, and WES analysis for the proband and its family.

Results: Chromosome analysis was wild, no pathogenic or likely pathogenic variant that could explain the clinic was found in microarray analysis. Trio WES analysis detected a pathogenic heterozygous variant of SLC6A1 c.223G>A p.G75R in the proband and her mother.

Conclusion: The *SLC6A1* gene encodes a neuronal gamma-aminobutyric acid transporter protein that plays a crucial role in inhibitory neurotransmission in the brain. SLC6A1-NDD is a rare disease. Less than 500 have been reported worldwide. This case highlights the importance of comprehensive genetic analysis, such as WES, in identifying pathogenic variants associated with rare neurodevelopmental disorders.

[P-02]

A Delayed Diagnosis Case of a Patient with Treacher Collins syndrome

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Introduction

Treacher Collins syndrome [(TCS), OMIM #154500, ORPHA:861] is a genetic disorder affecting the craniofacial development. It is a rare mandibulofacial dysostosis characterized by a variety of facial abnormalities and is caused by mutations in the *TCOF1*, *POLR1D*, *POLR1C*, or *POLR1B* genes.

Case Report

Hereby, we are reporting a case of TCS with delayed diagnosis. A 16-year-old boy was consulted to our department by pediatrician due to dysmorphic features, including down-slanting palpebral fissures, eyelid coloboma, partial absence of lower eyelashes, bulbous nose, malar hypoplasia, dysmorphic ears, and oral cavity deformity. Additionally, he had bilateral hearing loss with normal intelligence. After preforming *TCOF1* gene sequence analysis, by next generation sequencing method, due to the patient's typical presentation, a likely pathogenic novel heterozygous frameshift variant [NM_000356.4: c.372dupA p.(Ala125fs)] was detected in the *TCOF1* gene.

Discussion

Despite clinical variability is common in TCS, this syndrome is usually diagnosed based on clinical examination and may be confirmed through molecular genetic testing. Our patient was an example of a delayed diagnosis, empathizing the importance of detailed physical examination and knowledge of dysmorphology in diagnosing rare diseases.

[P-03]

A Rare Case Report of Dysferlinopathy with Dominant Behaviour

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Abstract

A 39-year-old male patient presented with progressive muscle weakness. Gradual onset of fatigue started by age of six. Progressive difficulties in walking have been observed from the age of 10, and dysphagia toward solid foods manifested at 27 years of age. Subsequent to dysphagia bilateral upper extremity weakness transformed the patient's myopathic presentation into a global proximal extremity muscle weakness pattern. The dynamic and evolving nature of the patient's clinical presentation resulted in diverse diagnostic considerations over the course of follow-up, encompassing entities such as polymyositis, mitochondrial myopathy, and lipid storage myopathy. Notable magnetic resonance imaging findings were lipid atrophy, increased muscle signal, and enchondroma. EMG assessments indicated myogenic etiology and serum CK level was increasing. Biopsy showed increased lipid deposition. Clinical exome sequencing revealed a heterozygous pathogenic missense variant in DYSF:c.3172C>T(p.Arg1058Trp). Segregation analysis discloses the *de novo* occurrence of this mutation. *DYSF* gene dosage analysis with SNP-microarray was normal. Detected mutation is linked to the miyoshi muscular dystrophy type 1 (MMD1) and limb-girdle muscular dystrophy recessive type 2 (LGMDR2). It is noteworthy that dominant inheritance patterns within the realm of dysferlinopathy are exceedingly rare, with only a handful of documented cases globally. Our case represents a remarkable manifestation within this subset. Although recent research advocates against dichotomizing MMD1 and LGMDR2 into distinct cohorts for clinical assessment, the presence of dominant inheritance within one subgroup may potentially offer genetic differentiation between these two. Nevertheless, further in-depth investigations are requisite to establish the veracity of this phenomenon.

[P-04]

A Rare and Potentially Treatable Cause of Neurodegeneration: Cerebral Folate Deficiency

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Introduction

Cerebral folate deficiency is a progressive neurodegenerative disorder caused by biallelic pathogenic mutations in the *FOLR1* gene, which encodes the alpha subunit of the folate receptor in the choroid plexus. The disease manifests in late infancy with neurodevelopmental regression, hypomyelinating leukodystrophy, ataxia and epilepsy. Treatment with folinic acid has been reported to improve symptoms, and in some patients, even complete recovery has been reported.

Case Report

A 14-year-old male patient was referred to our clinic with epilepsy, neuromuscular regression and cerebellar atrophy. It was noted that he had no previous illness until the age of 7 years and his neurodevelopmental milestones were normal. He developed tremor and ataxia at the age of 7 and generalized tonic-clonic seizures at the age of 11. The seizures were partially controlled with dual antiepileptic treatment. At the age of 12, strabismus and walking difficulties were added to the patient's symptoms.

Electroencephalography revealed generalized periodic epileptic discharges, which were considered in favor of neurodegenerative processes. Cranial magnetic resonance imaging (MRI) showed hyperintense signal changes in the lentiform nuclei, cerebellar atrophy, and areas of no signal in the bilateral frontoparietal and basal ganglia on the SWI sequence, consistent with Wilson's disease (Figure 1). ATP7B sequence analysis performed for Wilson disease was normal. Then, clinical exome sequencing [SOPHiA Genetics Clinical Exome Solution v3 kit (CES; SOPHiA Genetics, Boston, MA) and sequenced on a NextSeq500 instrument (Illumina, San Diego, CA)] was performed for other possible etiology.

Clinical exome sequencing analysis revealed a homozygous non-sense variant, c.591C>A (p.Tyr197Ter), in the *FOLR1* (NM_016729.3) gene, which was classified as likely pathogenic (Figure 2). Following genetic diagnosis, low 5-methyltetrahydrofolate level in the cerebrospinal fluid supported the diagnosis. Oral folinic acid treatment was started.

Discussion

Cerebral folate deficiency due to FOLR1 mutations is a very rare disorder, with 33 patients described in the literature to date. This gene encodes the folate receptor-alpha (FOLRα), which is densely expressed in the choroid plexus and is responsible for the transport of 5-methyltetrahydrofolate across the blood-brain barrier. Loss of function variants in this gene disrupt folate transport to the brain and cause progressive neurodegeneration.

The homozygous variant of FOLR1 (NM_016729.3) c.591C>A (p.Tyr197Ter) has not been previously reported in the literature. Since this variant is located in the last exon of the protein, non-sense-mediated decay of the transcript is not clear. Although it has been suggested that this presumed truncated protein may be responsible for the late onset of symptoms in our patient, even in patients who have variant may cause a longer truncated protein is compatible with the typical course of the disease (1, 2). The late onset of symptoms in our patient may be related with diet, unknown modifier genes or obscure initial findings.

Cerebellar atrophy, found in 84% (28/33) of patients, is the most common MRI finding and may be important in the differential diagnosis. In addition, subcortical and periventricular white matter lesions, demyelination, hypomyelination, cerebral subcortical calcifications, basal ganglia calcifications, encephalomalacia, laminar necrosis, thin corpus callosum can be considered in the differential diagnosis of many diseases (3).

Conclusion

Early treatment with folinic acid has been shown to stabilize and even reverse neurodegenerative processes in some patients (3). For this reason, early diagnosis and treatment of this rare disease are of the utmost importance.

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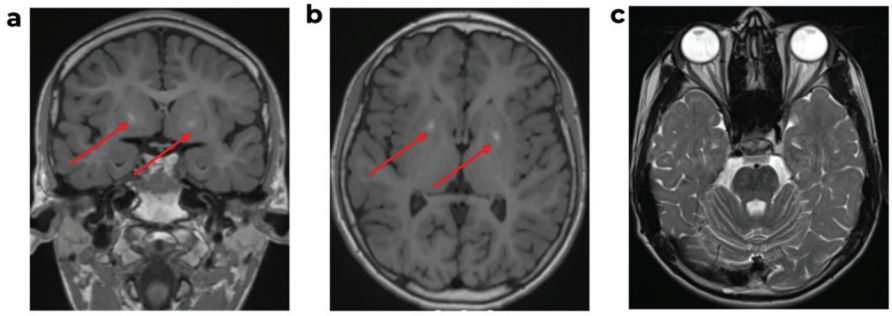

Figure 1. Cranial MRI results of the patient (a), (b) hyperintense areas in the lentiform nuclei on T1-weighted imaging (c) Prominence of cerebellar foliation

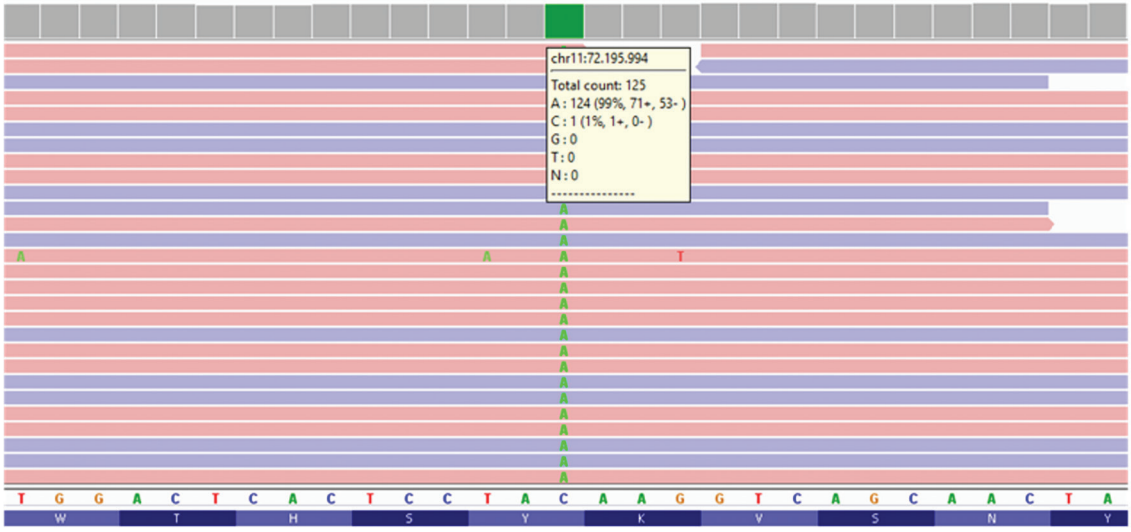

Figure 2. Integrative genomics viewer visualization of the homozygous FOLR1 (NM_016729.3) c.591C>A (p.Tyr197Ter) variant

[P-05]

A Rare Syndrome from Physical Examination to Diagnosis: Oculodentodigital Dysplasia

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Introduction

Oculodentodigital dysplasia (ODDD) is a rare disease caused by mutations in the *gap junction protein alpha-1 (GJA1)* gene located in the q22 region of chromosome 6, with high penetrance and variable expressivity (1). The *GJA1* gene, which has a coding exon, encodes the connexin 43 protein, weighing 43 kd and containing 382 amino acids. Although ODDD is mostly inherited in autosomal dominant (OD), autosomal recessive (OR) inheritance has also been described in recent clinical reports (2).

ODDD is characterized by symptoms such as craniofacial, neurological and ocular anomalies, type III syndactyly of the hands, phalanx abnormalities, diffuse skeletal dysplasia, enamel dysplasia and hypotrichosis (3).

Case Report

A 16-year-old male patient was referred to us from the department of dermatology due to keratoderma on both hands and soles of the feet, syndactyly and a dysmorphic appearance on the face. The patient had learning disabilities and early tooth loss. In the family history of the patient

who has a history of surgery due to undescended testicle; it was learned that his mother, his uncle and his uncle's son, and his maternal grandfather had a history of F4-5 (phalax) syndactyly in bilateral hands. On physical examination, high nasal root, retrognathia, blepherophymosis, short palpebral fissure, ala nasi hypoplasia, prominent columella, sawtooth appearance, F4-5 brachydactyly in bilateral hands, F4-5 cutaneous syndactyly in bilateral hands (operated), F4-5 camptodactyly in bilateral hands, F3-5 ulnar deviation in bilateral hands, bilateral plantar hyperkeratosis, and bilateral 2-3 partial cutaneous syndactyly in the feet were observed.

When the patient was consulted to the relevant departments for findings that may accompany the syndromic appearance, a slight increase in left ventricular wall thickness and left ventricular concentric hypertrophy (mild, not causing stenosis) were detected on ECHO.

At the same time, he was examined at an external center with a complaint of headache. In his brain CT examination, calcifications were randomly observed in both putamen.

When the patient's physical examination findings were scanned from databases, ODDD, oculodentodigital dysplasia (OR) and type 3 syndactyly were considered among the preliminary diagnoses. All preliminary diagnoses were due to GJA1 mutations.

OD inheritance was considered due to the vertical inheritance pattern in the family tree. With these preliminary diagnoses, DNA sequence analysis was performed on the patient with primers designed for the *GJA1* gene.

Discussion

GJA1 gene mutations can cause 6-allelic diseases inherited as OD and OR. With this case example, it can be seen that a pinpoint diagnosis can be reached in rare single-gene diseases by detailed anamnesis, system interrogation, determination of the inheritance pattern from the family tree, and physical examination findings in databases. Genotype-phenotype correlation can be made in allelic diseases with clinical evaluation.

Conclusion

A c.413G>A(p.Gly138Asp) heterozygous pathogenic variant in the *GJA1* (NM_000165.5) gene was detected in the patient.

Keywords: Oculodentodigital dysplasia, GJA1, type 3 syndactyly

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[P-06]

Diagnosis of Mandibuloacral Dysplasia in Clinical Heterogeneity of Scleroderma with Restrictive Dermopathy

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Abstract

Mandibuloacral dysplasia (MAD) is one of rare autosomal recessive syndromes characterized by postnatal onset growth retardation, craniofacial anomalies with mandibular hypoplasia, cutaneous pigmentation, lipodystrophy, rapid aging, and bone abnormalities with progressive osteolysis in the distal phalanges and clavicles. Typical feature of disease is that cases are completely normal at birth but symptoms develop as age progresses. Subtypes of MAD are defined as type A (MADA, OMIM#248370) and type B (MADB, OMIM#608612) which develops from *LMNA* and *ZMPSTE24* mutations respectively. Homozygous or compound heterozygous *LMNA* mutations create cellular stress through chromatin dynamics, and may represent a single disorder of varying degrees of severity. Detailed characteristics of MADA syndrome have not yet been clearly determined due to its rarity and limited number of announced cases. In this report, we present a case of 26-year-old female with unique MADA phenotype which shows high clinical heterogeneity. Whole exome sequencing (WES) analysis revealed a homozygous c.1580G>A (p.Arg527His) mutation in exon9 of *LMNA*. Additionally, a homozygous c.581T>C (p.Val194Ala) mutation was detected in exon6 of *SERPINB8*. *LMNA* mutation is associated with 11 different phenotypes in the literature and shows a high degree of clinical heterogeneity. For this reason, we diagnosed MADA with differential diagnosis method using genotype-phenotype data of human gene mutation database (HGMD). To evaluate phenotypic variability in the case, we evaluated our observations with MADA cases in the literature. This report aims to increase the number of reported MADA cases and strengthen genotype-phenotype correlations in cases.

Introduction

Mandibuloacral dysplasia (MAD) is a segmental form of progeria (1). MAD is a rare autosomal recessive syndrome characterized by dysmorphic findings, craniofacial anomalies, skeletal malformations, growth retardation, cutaneous pigmentation and metabolic disorders. Cases are completely normal at birth but growth retardation and dysmorphism develop as age progresses (2). Clinical signs of MADA(OMIM#248370) appear in early childhood while MADB(OMIM#608612) is defined by a more severe phenotype (3). MADA frequently arises from mutations in exons 8-10 (4). Laminopathy phenotypes of variants are quite heterogeneous. Currently, 3 autosomal recessive and 7 autosomal dominant primary laminopathies have been reported. In our clinic, we diagnosed a case with features of MAD. We performed WES analysis to determine genetic cause of clinical phenotype.

Case Report

Case was referred by dermatology with suspicion of progerioid syndrome. Complaints started in fingers at age of 2.5. growth retardation, mobility difficulties and skin atrophies became evident at age of 6. She was diagnosed with scleroderma and her complaints increased. There was a consanguineous marriage. Prenatal and postnatal were normal. Body height was 155 cm, head circumference was 52 cm and neuromotor abilities were normal. Sclerodactyly of fingers, dystrophy of fingernails and toenails were observed. There was bilateral pes planus, calluses on plantar surface, skin atrophy, superficial veins, calcinosis cutis in lumbar region and limited joint movements. It was remarkable that there was an excessive fat tissue in abdomen and submandibular region contrary to extremities. Mitral anterior leaflet prolapsed into left atrium in systole. Also, there were minimal tricuspid regurgitation, restrictive breathing, minimal thickening in pericardium, increased nodular density in fatty tissue thymus chamber in anterior mediastinum, mild mitral and aortic regurgitation (Figure 1). We determined early diagnosis as Scleroderma-Werner syndrome and/or an autosomal recessive syndrome.

Discussion

Mutations were detected in *LMNA* and *SERPINB8*. *LMNA* mutation was distinctively associated with mandibuloacral dysplasia in HGMD. *SERPINB8* mutations were associated with peeling skin syndrome 5(OMIM#617115) in OMIM.

LMNA mutations cause anomalies in nuclear structures (5). 8% of restrictive dermopathy cases are caused by mutation in *LMNA* (6). Similar to our case, clinical findings were reported as low birth weight, fragile-tight skin, joint contractures, pointed nose, micrognathia superficial erosions and vascular structuring. There were also secondary prominent superficial veins in atrophic skin of extremities and calcinosis cutis in lumbar region (1). Same mutation was reported in two children (7). MADA phenotype was observed tenuously in infancy, increased over time, and ocular proptosis developed in the boy. These are compatible with the initial period and characteristics of complaints in our case.

LMNA c.1579C>T mutation were reported with subtotal alopecia, absence of clavicle and ribs due to severe osteolysis and muscle damage (8). There was no muscle damage while alopecia and osteolysis were observed limitedly in our case. Therefore our case is a good example of allelic and clinic heterogeneity. An interesting MADA case that resemble limb-girdle myopathy were described in the literature (9). Clavicular hypoplasia and metabolic imbalance were not observed. Clinical features were reported as hypoplastic mandible, acroosteolysis, pointed nose, partial loss of subcutaneous fat tissue and progeric appearance. Case was evaluated as atypical laminopathy phenotype due to normal metabolic profile associated with general hypotonia.

SERPINB8 variant is also likely to affect phenotype. Family members, who had 2 different exons mutations, were examined with exfoliative ichthyosis (10). Hyperkeratotic plaques on palmar skin, superficial flaking on forearms and lower extremities without erythema and superficial peeling on dorsal skin of hands and feet were observed. There were calluses on plantar surface and calcinosis cutis in lumbar region in our case. However, the missense mutation in exon6 of our case has not been reported yet.

Conclusion

MADA necessitates a multidisciplinary basis. Mandibular hypoplasia, clavicular resorption, acral osteolysis, alopecia and lipodystrophy should be investigated carefully in clinic. We suggest comprehensive evaluation of progeroid syndrome outlook in pediatric patients with scleroderma-like disease. It would be possible to take measures to prevent osteolysis with early diagnosis.

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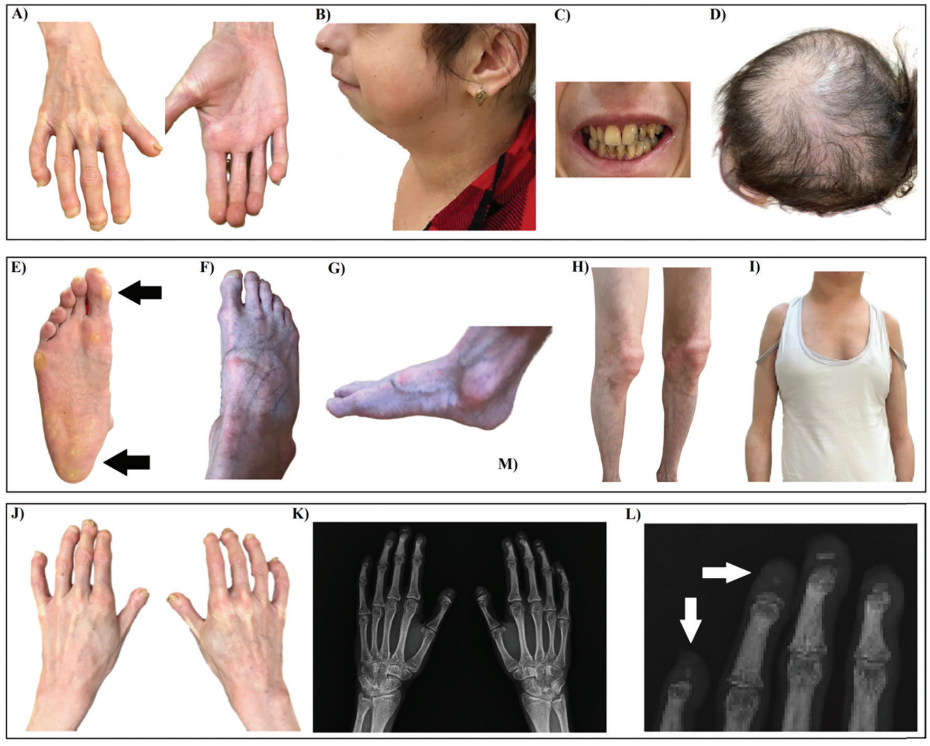

Figure 1. (A) Skin atrophy and hypoplasia of fingers, (B) mandibular hypoplasia, pinched nose and retromicrognathia, (C) crooked teeth, (D) subtotal alopecia, (E) plantar callus, (F) prominent superficial veins with dermal atrophy, (G) bilateral pes planus, (H) lipodystrophy, (I) sloping shoulders, (J) dystrophy of short distal phalanges and nails, (K) osteolysis of distal phalanges, (L) acroosteolysis

[P-07]

Legius Syndrome with a Preliminary Diagnosis of NF1-Like Syndrome: Case Report

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Introduction

Neurofibromatosis 1 (NF1) or Von Recklinghausen disease is a common autosomal dominant disorder that occures in 1 in 3,000 live births. Multiple caf´e-au-lait spots, freckling in skin fold areas, Lisch nodules, optic glioma and neurofibromas are the most common clinical findings of NF1. Other findings are short stature, macrocephaly, scoliosis, specific bone abnormalities, and increased risk of certain tumors. NF1 syndrome occurs as a result of an inactivating mutation in the *NF1* gene, located on chromosome 17q11.2 and encoding the neurofibromin protein. Neurofibromin protein is one of the main regulators affecting the complex RAS-MAP kinase signaling pathway. İnactivating mutations in the *NF1* gene results in activation of RAS-MAPK pathway, and leads to uncontrolled proliferation and an increase in the risk of malignancy. Later, many genes other than the *NF1* gene, which are associated with the RAS-MAPK signaling pathway, were found. Many of these genes cause syndromes called RASopathies, which have distinctive features as well as overlapping clinical findings. In 2007, a new RASopathy with a mild NF1-like clinic was discovered. In this new syndrome, a loss-of-function variant was detected in the *SPRED1* (OMIM# 609291) gene, which is a negative regulator of the RAS-MAPK signaling pathway. Firstly this syndrome was called NF1-like syndrome and it is now called Legius syndrome (OMIM # 611431). Findings are typically multiple

caf´e-au-lait spots and axillary freckling. Other findings include attention deficit, learning problems, and macrocephaly. Besides phenotypes of the patients are milder compared to NF1, the tumors typically observed in NF1 do not occur in these patients.

Case Report

A 29-year-old female patient, who was referred to us from the dermatology department with a preliminary diagnosis of NF, had many polymorphic brown skin spots on her body. The patient, who visited to the dermatology clinic with the complaint of hyperpigmented plaque on the lateral edge of the tongue, underwent a detailed physical examination in our clinic.

The patient, who had many caf'e-au-lait spots and axillary freckles on her body, did not have any tumors. whose eye examination of patient was evaluated as normal, the same skin findings were found in his mother, aunt and grandmother. There was no history of tumor in these people. A NF panel was taken from the patient and in this panel, there were *NF1, NF2, SPRED1* and *SMARCB1* genes.

Results

Genes within the panel were evaluated. As a result of NGS analysis, heterozygous c.C70T pathogenic variant was detected in the patient's *SPRED1* gene. This variant has also been evaluated as pathogenic by prediction programs such as Varsome and Franklin and is among the variants previously reported in the ClinVar database. After evaluation of the pathogenic variant obtained and the patient's clinic, our patient was diagnosed with Legius syndrome (OMIM# 611431). Genetic counseling was given to the patient in our genetics outpatient clinic, and it was recommended that the same variant be screened in people with similar clinical symptoms in the family.

Discussion

Legius syndrome is an autosomal dominant syndrome and occurs as a result of inactivating germline mutations in the *SPRED1* gene. In this syndrome, which can be seen in inherited or sporadic form, cafe' au-lait spots are typically observed, similar to the NF clinic, while there is no increase in the risk of developing tumors such as neurofibroma or optic glioma. The *SPRED1* gene, consisting of 8 exons, is located on the long arm of chromosome 15 and encodes the SPRED1 protein from the SPROUTY/SPRED family. SPRED1 protein plays a role as a negative regulator in the RAS-MAPK signaling pathway. In other words, loss-of-function variants in the *SPRED1* gene cause overactivation of the RAS-MAPK pathway.

In patients with a preliminary diagnosis of NF1, a detailed physical examination should be performed for differential diagnosis with NF-like syndromes. In addition, in patients with a preliminary diagnosis of NF1 and in whom no pathogenic or possible pathogenic variant can be detected in the *NF1* gene, NF-like syndromes should be considered and other genes affecting the RAS-MAPK pathway should be examined.

[P-08]

The Importance of Genetic Analysis in the Diagnosis of Complex Clinical Manifestations: A Case Report of Metabolic Rare Disease

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Abstract

Introduction: Hereditary coproporphyria (HCP) is a metabolic rare disease caused by heterozygous variants in the *CPOX* gene, with a prevalence of 1-9/1,000,000. A 54-year-old male patient was referred to our clinic due to dermatological, gastrointestinal, and cardiovascular symptoms triggered by certain medications and foods. The patient reported experiencing dermatological symptoms after using lansoprazole and rabeprazole, diarrhea following the consumption of acetylsalicylic acid, piracetam, and ginkgo biloba, and tachycardia after using pancreatic enzymes (pancreatin), N-acetylcysteine, and ursodeoxycholic acid. Additionally, he exhibited dermatological symptoms after consuming mushrooms, pepper, and peanuts. The patient's medical history includes hypothyroidism, vertigo, and a history of non-invasive papillary urothelial bladder tumor. In this study, we aim to present a patient with a detected pathogenic variant in the *CPOX* gene.

Methods: Clinical exome sequencing was performed performed from blood sample, and a heterozygous missense variant, c.1339C>T;p.R447C (NM_000097.7), was identified in the *CPOX* gene.

Discussion: HCP is a metabolic disorder characterized by gastrointestinal, cardiovascular, and neurological symptoms triggered by specific medications and foods. The patient's gastrointestinal, cardiovascular, and dermatological symptoms consistent with coproporphyria, as well as autoimmune and neurological manifestations like hypothyroidism and vertigo, may be associated with this genetic variant. However, it is possible that other genetic and environmental factors may contribute to these findings. This case emphasizes the significance of genetic testing in diagnosing rare and complex clinical manifestations.

[P-09]

A Rare Case: Smith-Magenis Syndrome

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Abstract

Smith-Magenis syndrome (OMIM #182290) is a complex neurodevelopmental disorder, with an incidence of 1/15,000-1/25,000, involving multiple organs and systems and usually occurs sporadically. This syndrome is characterized by typical dysmorphic features, speech delay, mental retardation, behavioral problems, sleep disturbance, renal and cardiac defects in some patients. The majority of cases are caused by interstitial micro-deletions in the 17p11.2 chromosome region containing the *retinoic acid induced 1* gene. We present a 2.5-year-old girl who stands out with her dysmorphic findings and delay in neuromotor steps. In the physical examination of the patient, brachycephaly, prominent forehead, square shaped coarse facial appearance, uplifted ear lobes, upslanting palpebral fissures, characteristic downturned tented upper lip vermilion, and brachydactyly were detected. In microarray analysis, a 3.6 Mbp deletion was detected in the 17p11.2 chromosome region. This case has once again demonstrated the importance of physical examination and molecular genetic methods in the diagnosis of genetic diseases.

Keywords: Smith-Magenis syndrome, 17p11.2 deletion syndrome, *RAI1* gene, microarray

[P-10]

Hereditary Hyperekplexia: Three Patients from Kayseri, Middle Anatolia and Three Different Genetic Findings by Different Methodology

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Abstract

Hereditary hyperekplexia (HPX), a neuronal disorder caused by genetic defects leading to dysfunction of glycinergic inhibitory transmission, is mainly characterized by startle responses to unexpected sensory stimuli and stiffness. HPX, a rare and underdiagnosed disorder, is manifest after birth and commonly improves with age. Establishing the correct diagnosis early is essential so that proper management may be initiated to reduce the risk of complications, such as potentially life-threatening apnea during episodes of stiffness. Defects in GLRA1 are the most common cause of HPX, inherited both in an autosomal dominant and autosomal recessive manner. Sequence analysis (95%) is the main method for detection of pathogenic variants of probands. Also copy number variations (CNVs) (5%) plays role in etiology. We here report independent three Turkish patients with hyperekplexia which stems from GLRA1 related phenotypes and we confirm mostly known genetic background of HPX by different methods in our outpatient clinic. Whole exome sequencing-CNV, microarray analysis revealed that previously reported homozygous deletion of exons 1-7 of the *GLRA1* gene in patient 1. This genetic changes thought to be probably the founder mutation in Turkish-Kurdish populations. In patient 2, homozygous c.277C>T p.Arg93Trp variant in the *GLRA1* gene was found. In patient 3, microarray analysis revealed a 299 kb deletion at the q33.1 region of the chromosome 5 which is *GLRA1* gene located in. The fact that the results of three unrelated patients in one center can be considered in terms of planning the examination for deletion/duplication analyzes first in patients with GLRA1-related phenotypes in the Turkish population.

[P-11]

Case Report: Patient with Merosin-Deficient Congenital Muscular Dystrophy with Occipital Lissencephaly

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Abstract

Merosin-deficient congenital muscular dystrophy type 1A (MDC1A) (OMIM 607855) is an autosomal recessive disorder characterized by severe muscular dystrophy, which is typically associated with abnormal white matter. MDC1A is caused by loss of function mutations in the *LAMA2* gene located at chromosome 6q22. Laminin is a major component of the basement membrane. It is thought to mediate the attachment, migration,

and organization of cells into tissues during embryonic development. Here, we described one Turkish female patient who has intellectual disablity, contractures, muscle weakness and magnetic resonance imaging (MRI) result compaible with merosine deficient dystrophies. Molecular analysis of the patient's *LAMA2* gene revealed homozygous frameshift pathogenic mutation c.3630del p. (Ile1210Metfs*14) in exon 25. A 9-year-old female patient was consultated to our department with mentioned for evaluation. Brain MRI revealed diffuse symmetrical involvement of subcortical and deep white matter pathological signal change, diffuse thinning of the brain stem and bilateral occipital lissencephaly. The patient's clinical and radiographic features were compatible with MDC1A, which was confirmed by gene studies identifying the laminin gene mutation. It is expected to result in protein dysfunction. Loss-of-function variants in LAMA2 are known to be pathogenic. So the definitive diagnosis is estabilshed as MDC1A.

[P-12]

Duplication of 1q21.3q25.3 in a Newborn with Multiple Congenital Anomalies

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Introduction

Trisomy 1q is a rare chromosomal anomaly syndrome, resulting from the partial duplication of the long arm of chromosome 1, with a highly variable phenotype principally. The major semptoms include short stature, intellectual disability, craniofacial dysmorphism (macro/microcephaly, prominent forehead, posteriorly rotated, low-set ears, abnormal palpebral fissures, microphthalmia, broad, flat nasal bridge, high-arched palate, micro/retrognathia), cardiac defects and urogenital anomalies. Patients may also present cerebral (e.g. ventriculomegaly) and gastrointestinal malformations, as well as dystonic tremor and recurrent respiratory tract infections. There is a wide spectrum of clinical manifestations due to the great variability in the extent of the duplication size. In this presentation, we aimed to present a case with 1q21.3q25.3 duplication.

Case Report

Our genetic department was consulted by the pediatrics neonatal intensive care unit for a 7-day-old newborn who had respiratory difficulties, a syndromic facial appearance, and ambiguous genitalia. On clinical examination, length was 53 cm (90-97p), weight was 3290 g (50p) and head circumference was 36 cm (75-90p). The patient's physical examination revealed microphthalmia, blepharophimosis, telecanthus, epicanthus inversus, hypertelorism, broad, flat nasal bridge, micro/retrognathia, anteverted nares, brachycephaly, short-broad neck with redundant nuchal skin, glossoptosis, bilateral incomplete cleft lip, posteriorly rotated, low-set ears, macrotia, auricular skin tag in the left ear, bilateral clenched hands, overlapping fingers on left toes, talipes calcaneovalgus, ambiguous genitalia. Cranial MRI displayed the patient had a ventriculomegaly. Echocardiography showed left ventricular hypertrophy, minimal tricuspid regurgitation and secundum ASD.

Results

Karyotype analysis was performed from the patient's peripheral blood sample and was determined as 46,XX,dup(1)(q21q25). Microarray analysis showed duplication in the 1q21.3q25.3 region with a size of 28,76 Mb. The karyotype analysis from the parent's peripheral blood sample was performed for the explanation of this duplication. The mother's karyotype analysis was normal and the father's karyotype analysis showed 46,XY,inv(1)(q21q31).

Conclusion

In most cases, the duplication is the result of an unbalanced translocation with a possible imbalance of the other participating chromosome. It is difficult to evaluate the contribution of the 1q trisomy to the phenotype in cases involving another chromosome. Cases with pure partial trisomy 1q provide an opportunity to better define the partial trisomy 1q syndrome. The extent of the partial 1q trisomy syndrome, which is a rare condition, can be assessed using array-CGH methods. In trisomy 1q syndrome, no duplication involving just this area has ever been documented. This case will add to the body of knowledge regarding how to diagnose people with comparable phenotypic features or regional duplications.

Keywords: 1q21.3q25.3, 1q duplication, array-CGH

[P-13]

The Case with the Novel NALCN Variant

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Abstract

In this study, we present a case with a milder phenotype associated with a novel variant of the *NALCN* gene. A 5-month-old male patient was referred to our department by pediatric neurology due to hypotonia, developmental delay, and hypospadias. The patient, reported to have been born to a 30-year-old mother at 38+3 weeks of gestation, with a birth weight of 2950 grams and a length of 50 cm, had parents from a neighboring village, with no known consanguinity. The patient started holding his head at 8 months and began sitting without support at 14 months. The patient's body weight was -2.48 SDS, and head circumference was -1.99 SDS. Marked hypotonia, microcephaly, ptosis and amblyopia in the left eye, a widow's peak hairline, restricted right gaze, brachycephaly, prominent philtrum, overriding toes, and contractures in the hands and feet were observed. EEG and echocardiography did not reveal any abnormalities. The karyotype result from the patient was 46, XY, and Prader-Willi FISH tests yielded normal results. Subsequently, SMA-MLPA analysis was performed and resulted in 2 copies. A clinical exome panel was performed due to hypotonia, revealing a homozygous likely pathogenic novel variant c.1495dupA (p.Ile499AsnfsTer26) in the 13th exon of the *NALCN* gene. The variant in the patient was confirmed as homozygous by Sanger sequencing. The parents and the elder male sibling were found to be heterozygous carriers of the variant. Common clinical features observed in patients with biallelic NALCN mutations include severe hypotonia, intellectual disability, speech delay, epilepsy, and optic atrophy. In the literature, significant hypotonia is reported in the infantile period in most cases. However, our patient had head control at 8 months and was able to sit without support at 14 months. It was learned that supported steps were present after physical therapy during follow-up. Seizures are typically reported in patients after the age of 3-4 years. Our patient, who is currently 30 months old, has no history of seizures, which is presumed due to his age. Some cases require gastrostomy due to feeding problems, and our patient experienced feeding difficulties with solid foods, leading to cachexia. During the patient's follow-up, muscle atrophy and dystonia were observed. While atrophy was an expected finding, dystonia had not been previously reported. Therefore, a new phenotype is considered possible in this regard.

[P-14]

A Case of Cardiophaciocutaneous Syndrome without Cardiac Manifestations

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Abstract

Cardiophaciocutaneous syndrome [(CFC); OMIM: 615279] is a developmental disorder resulting from heterozygous mutations in the *MAP2K1* gene located on chromosome 15. It is characterized by distinctive craniofacial features, cardiac anomalies, hair and skin abnormalities, postnatal growth retardation, and hypotonia. Developmental and epileptic encephalopathy-36 (OMIM: 300884) is a neurodevelopmental disorder caused by heterozygous/hemizygous mutations in the *ALG13* gene on the X chromosome, resulting in severe delays in psychomotor development. A 6-year-old male patient was referred to our department from the neurology department with complaints of epilepsy, developmental delay, inability to speak, and walk. The patient, who had third-degree consanguineous parents, had no specific family history. Physical examination revealed strabismus, downward-slanting palpebral fissures, a broad nasal bridge, fragile hair, and relative macrocephaly. Clinical exome sequencing analysis of the patient detected a pathogenic missense heterozygous variant (c.389A>G, p.Tyr130Cys) in the *MAP2K1* gene, a missense hemizygous variant of unknown significance (c.49A>G, p.Ile17Val) in the *ALG13* gene, and a missense homozygous variant of unknown significance (c.650A>G, p.Glu217Gly) in the *PEX1* gene. Metabolic tests ruled out peroxisomal diseases in our patient. Considering the prominent features of neurodevelopmental delay and dysmorphic appearance, it is important to recognize the potential phenotypic contribution of the *ALG13* gene alongside the suspicion of CFC syndrome attributed to the *MAP2K1* gene. Notably, our patient did not exhibit any of the major cardiac anomalies typically seen in CFC syndrome, which makes this case noteworthy from that perspective.

[P-15]

Familial Hyperkalemic Periodic Paralysis: The Utility of History Taking and Pedigree Drawing in the Diagnostic Odyssey of a Treatable Disease

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Introduction

Hyperkalemic periodic paralysis (HPP) is a rare, autosomal dominant condition leading to episodes of muscle weakness or paralysis.

Case Report

A fourteen-year-old boy suffering from paroxysmal generalized muscle weakness was admitted. He was born to non-consanguineus parents and his past medical history was unremarkable. His family history revealed multiple effected relatives including his sister, father, uncle, cousin, grand mom and her siblings. The detailed questioning revealed that the episodes were triggered by hunger, excessive physical exercise and food intake such as melon, banana and grapes and resolved after drinking sugary water. During hospitalization, a thirty-minute attack was observed. The serum potassium level was found 5.7 mEq/L (normal: 3.5-5.0 mEq/L) during the attack, while his baseline serum potassium level was 4.1 mEq/L. The clinical history raised the pre-diagnosis of familial HPP which is an autosomal dominant disease compatible with his pedigree. Acetazolamide therapy was initiated and he had no further attacks after treatment. The single gene analysis of *SCN4A* gene revealed a heterozygous c.2111C>T mutation and confirmed the preliminary diagnosis. *SCN4A* gene mutation alters the function of sodium channels in skeletal muscle cells with an influx of sodium ions and increases the release of potassium from muscle cells causing an inability for skeletal muscles to contract and eventually developing into muscle weakness or paralysis.

Conclusion

Familial HPP is a rare but treatable autosomal dominant neurological condition. Careful history taking and pedigree drawing enables the establishment of a preliminary diagnosis and the selection of the appropriate genetic testing, thus shortening the diagnostic odyssey.

[P-16]

Kabuki Syndrome; Clinical and Genetic Diagnosis

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Introduction

Kabuki syndrome is characterized by long palpebral fissures, eversion of lateral third of lower eyelids, thick eyelashes, ptosis, broad, arched eyebrows, sparse eyebrows, depressed nasal tip, short nasal columella, large, cupped ears, cleft lip and/or palate. It is a rare, multisystemic, genetic disease characterized by a peculiar facial appearance, postnatal growth retardation, mild-moderate mental retardation, hypotonia, skeletal anomalies and the persistence of fetal fingertip pads. Heterozygous mutations in the *KMT2D* gene on chromosome 12q13 are the most common cause of KS and are inherited in an autosomal dominant manner. Mutations in the *KDM6A* gene are inherited X-linked. In this study, we presented 4 isolated cases with dysmorphic facial appearance, microcephaly and developmental delay.

Case Reports

Case 1: A 1-year-old girl presented with dysmorphic findings, hydrocephalus and elevated LFT. The patient, whose prenatal follow-up was unremarkable, was admitted to intensive care for 1 month due to respiratory distress and seizures. On examination, his weight was 6 kg (-3.51 SDS), height: 66 cm (-3.19 SDS), head circumference: 39 cm (-5.3 SDS). Characteristic facial dysmorphic findings such as microcephaly, sparse lateral eyebrows, long eyelids, flattened nose tip, and high palate were detected (Figure 1A). Her cardiovascular, respiratory, abdominal and neurological examinations were unremarkable. ECHO revealed peripheral pulmonary stenosis and minimal pleural effusion. In the genetic analysis of the patient who was considered to have Kabuki syndrome, c.4521C>A heterozygous mutation was detected in the 16th exon of the *KMT2D* gene.

Case 2: An 18-month-old female patient applied to us due to cleft palate-lip anomaly and dysmorphic appearance. On examination, weight: 5.1 kg (-5.6 SDS), height: 66 cm (-4.7 SDS), head circumference: 38 cm (-6.9 SDS), microcephaly, cleft lip and palate anomaly, long eyelids, long eyelashes, dysplastic, large protruding ears, fetal fingertip pads, brachydactyly, nail dystrophy and hypotonicity were present (Figure 1B). Echocardiography showed large VSD, pulmonary hypertension and hypoplastic right ventricle, and cranial magnetic resonance imaging (MRI) showed corpus callosum

hypoplasia and septum pellucidum agenesis. The patient, who had left renal agenesis on renal ultrasonography, left hip dislocation on Hip Ultrasound, hypsarrhythmia and mixed epileptic spasms on electroencephalography, was receiving antiepileptic treatment due to West syndrome and levothyroxine treatment due to central hypothyroidism. Karyotype analysis found 46,XX. No mutations were found in *KMT2D* and *KDM6A* gene Sanger sequence analysis.

Case 3: A 27-month-old female patient was referred to us due to dysmorphic appearance, developmental delay and hearing loss. The patient's prenatal history was unremarkable and her family history was unremarkable. On examination, the patient weighed: 12 kg (34 kg), height: 86 cm (16 cm), head circumference: 45 cm (-2.2 SDS). scoop-shaped, nasal root prominent, eyelids long, eyelashes long, microcephaly and hypodontia were observed (Figure 1C). There were bilateral gynecomastia, fetal pads on the fingertips, brachydactyly and nail dystrophy in the hands and feet. The patient's other system examinations were normal. Left hip subluxation and hemangioma on the left arm were detected. There was bilateral mild conductive hearing loss. Dural ectasia was detected in lumbar MRI. Chromosome analysis 46,XX. In CES analysis, the frameshift c.2091dup variant was detected as heterozygous in the *KMT2D* gene.

Case 4: A 13-year-old male patient applied to us with epilepsy, developmental delay, blue sclera and dysmorphic findings. He had a history of surgery for gastric hernia when he was 4 months old, undescended testicle at 6 months, and aortic coarctation when he was 20 months old. In the physical examination of our patient, his weight was 23.5 kg (-3.2 SDS), height: 119 cm (-5.2 SDS), head circumference: 48 cm (-4.99 SDS). Face is thin, long, bitemporal stenosis, eyebrows are sparse in the distal part, scleras are blue, eyes are large, eyelids are long, ptosis, nasal root is wide, palate is narrow and high, tooth alignment and shape are distorted, ear large folds are reduced, ear lobe is very large, kyphosis, mild pectus excavatum, fingertip fetal pads, brachydactyly, and nail dystrophy were detected (Figure 1D and 2). ECO revealed operated VSD, aortic coarctation, aortic insufficiency and mitral insufficiency. As a result of CES analysis, in the *KMT2D* gene; The intronic c.14515+5G>T variant was detected as heterozygous.

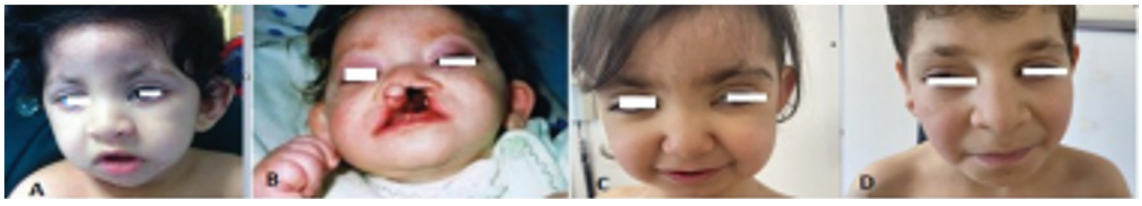

Figure 1. (A) Facial features of our 1-year-old patient, (B) 18-month-old patient with cleft palate-lip anomaly, (C) 27-month-old female patient, (D) 13-year-old patient with dysmorphic features on examination

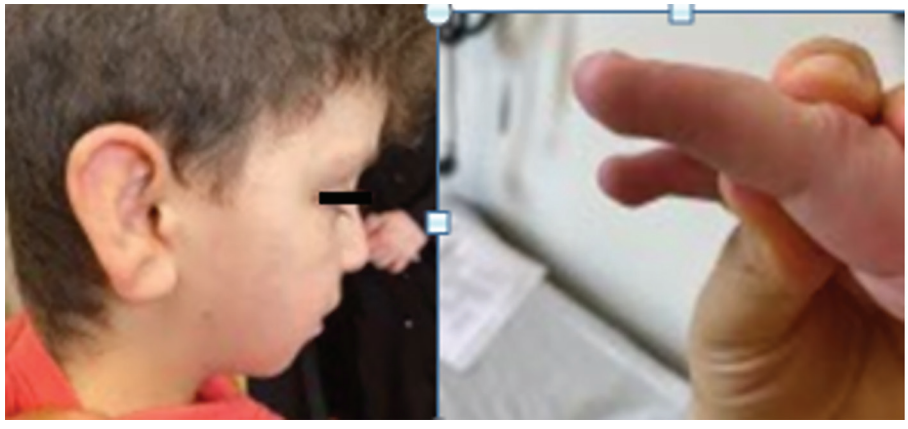

Figure 2. Presence of persistent fetal pads and large ears and ear lobe seen in our 4th case

[P-17]

A Rare Cause of Nephrolithiasis: Primary Hyperoxaluria Type 1

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Introduction

Primary hyperoxaluria is a rare autosomal recessive (OR) disease that occurs due to an increase in endogenous oxalate production. Its prevalence is 1 in a million. It occurs due to defects in glyoxalate metabolism. Three types have been described so far. Primary hyperoxaluria type 1, the most common type, occurs due to alanine glyoxalate aminotransferase (AGT) deficiency. This enzyme is encoded by the *AGXT* gene. The function of this enzyme is to catalyze the transamination of glyoxalate to glycine while converting pyruvate to alanine (1). When this enzyme does not function, the amount of endogenous glyoxalate increases. The amount of calcium oxalate excreted in urine also increases, causing clinical conditions ranging from recurrent urinary tract infections to nephrocalcinosis, nephrolithiasis, chronic renal failure and end-stage renal disease. When calcium oxalate load exceeds the urinary excretion capacity, it accumulates in various organ systems, causing systemic oxalosis (2). Diagnosis is made based on clinical history, urinary ultrasonography, urine oxalate amount and genetic examination. In necessary cases, it may be necessary to perform a liver biopsy and measure the AGT enzyme level (3). Whole exome sequencing has an important place in understanding the role of genes associated with different diseases in the etiopathogenesis of the disease (4-8). We would like to contribute to the literature by presenting a case about this very rare disease.

Case Report

A 10-year-old male patient was brought to the hospital with complaints of difficulty urinating and side pain for approximately 2 months. Abdominal pain is usually in the form of right-side pain. He stated that he had nausea, vomiting, enuresis, dribbling and intermittent urination. There was no dysuria, constipation or encopresis. He had no history of drug use and no known disease. He had a nephrolithotomy operation 1 year ago. In the family; it was learned that the grandfather, father, and cousins had a history of kidney stones, and the aunt had a history of chronic kidney failure. There was a 3rd degree consanguinity between the parents. The patient's FM scan revealed blood pressure: 100/50 mmHg, weight: 43.5 kg (74 p), height: 152.5 cm (91 p). Neurological examination, head and neck examination, circulatory system and respiratory system examination were normal. There was no rebound, guarding or tenderness on abdominal examination. Urinary system examination was normal. In the patient's examinations, creatinine: 0.56 mg/dL, Ca: 10.2 mg/dL, P: 4.46 mg/dL, ALP: 301 iu/L, PTH: 34.9 pg/mL, uric acid in spot urine/creatine ratio: 0.55; calcium/creatine: 0.44, 110 erythrocytes were detected in each area in the complete urinalysis. There was no growth in urine culture. In the urinary system USG, multiple calculi were observed in the right kidney, the largest of which was 12 mm in size in the pelvis, the calyces were dilated and the cortex was thinned in the upper pole. It was reported as follows: "The left kidney is normal and 12 mm of calculus was observed in the bladder lumen." In the stone analysis performed on the patient, it was learned that he had calcium oxalate stones. The patient's chromosome analysis was normal. Considering family history and stone analysis, *AGTX* gene was scanned with Next Generation Sequencing (NGS) with the preliminary diagnosis of primary hyperoxaluria. In NGS analysis, c.557C>T(p.Ala186Val) (rs117195882) and c.590G>A (p.R197Q) (rs346641134) compound heterozygous mutations were detected in exon 5 of the *AGXT* gene and the patient was diagnosed with primary hyperoxaluria type 1. The patient was started on ibuprofen and pyridoxine and was followed up.

Discussion

Primary hyperoxaluria type 1 is a hyperoxaluria condition that occurs as a result of the malfunction of the AGT enzyme due to the mutation in the *AGXT* gene. The clinical picture is wide ranging from recurrent urinary tract infection to end-stage renal failure. When the amount of oxalates exceeds the excretion capacity of the kidneys, it accumulates in other organs and oxalosis occurs. It most commonly affects bones, joints, skin, soft tissues, retina, heart, vessels, peripheral and central nervous systems. Oxalosis is a very important condition that affects mortality and morbidity (9). Symptoms usually begin around age 10. It was reported that 90% of the patients had nephrolithiasis and 48% had nephrocalcinosis at the time of diagnosis (10). Unfortunately, 30% of patients have been reported to have end-stage renal disease at the time of diagnosis. Definitive diagnosis is made by detecting the *AGXT* gene mutation and measuring the AGT enzyme level in liver biopsy. After diagnosis, patients' renal functions can be protected by high fluid intake, calcium oxalate crystallization inhibitor, and pyridoxine treatment. Liver and kidney transplantation is recommended together in patients who progress to end-stage renal failure (9). We diagnosed our patient with primary hyperoxaluria type 1 by detecting *AGXT* gene mutation at the age of 10. Our patient had nephrolithiasis at the time of diagnosis. We started treatment for nephrolithiasis and are following it with pyridoxine and ibuprofen treatment.

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