CEDNIK Syndrome, a Rare Neuro-Cutaneous Disorder in an Iranian Patient: Case Report and Review of Specific Neuro-Ichthyotic Syndromes

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Abstract- Cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma (CEDNIK) syndrome is an autosomal recessive neuro-cutaneous disorder characterized by a collection of clinical manifestations, including microcephaly, cerebral dysgenesis, palmoplantar keratoderma, facial dysmorphism, and ichthyosis. The etiology of this condition has been proved to be a homozygous mutation in the SNAP29 gene, which has an essential role in dermatological and neurological manifestations of this syndrome. In this report, we present the first documented Iranian patient with CEDNIK syndrome. So far, only 14 cases of this condition have been reported globally.

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Keywords: Ichthyosis; Cerebral dysgenesis; Keratoderma; Neurology; Pediatrics

Introduction

Cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma (CEDNIK) is a rare autosomal recessive neurocutaneous syndrome caused by a mutation in the SNAP29 gene that has an important role in membrane trafficking and several physiologic processes in skin, nervous and visual systems (1-4).

Patients with CEDNIK syndrome present with Global developmental delay, microcephaly, absent/thin corpus callosum, cortical abnormality, seizures, hypotonia, and sensorineural deafness. CEDNIK syndrome has been described in 14 cases previously (5-10).

Here we describe the first documented Iranian patient with CEDNIK syndrome. An 8-year-old girl presented with global developmental delay, dysmorphic features, and generalized ichthyosis. Our patient shares many features with the previously reported patients, including neuro cutaneous defects.

Case Report

Our patient was born at 36 weeks gestation and hospitalized at birth due to severe hypotonia and mild respiratory distress. Her birth weight was 2 kg, and her head circumference was 32 cm. Pregnancy was uncomplicated. Parents are first cousins, and she is the single child of this family. She didn't present with ichthyosis until 6-months of age that slowly progressed from mild to severe generalized ichthyosis at 3 years old. (Figure 1).

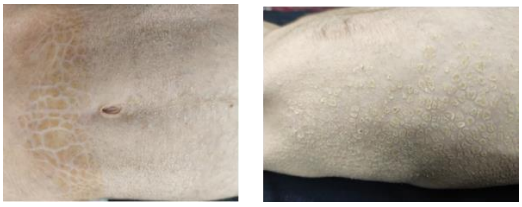

Figure 1. Severe generalized ichthyosis

By the age of 4, she was hospitalized 5 times as a result of gastroenteritis and aspiration pneumonia.

At 4 years old, she started rolling over, and one year later, she could merely crawl on her back and was unable

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to sit. She was only capable of bubbling and crying with no expression of any identified word. By the age of 5 head circumference was 47 cm, and her weight was 10 kg. Muscle bulk was atrophic, and DTR was absent. An ophthalmologic examination revealed mild optic atrophy and strabismus. ABR has not been done, but her mother expresses that her hearing is intact.

Brain MRI at 6 months old showed bilateral polymicrogyria in Sylvian fissures and agenesis of the corpus callosum and colpocephaly (Figure 2).

A genetic study revealed a mutation in the SNAP29 gene that confirmed the diagnosis of this syndrome in our patient. Exome sequencing identified a homozygous pathogenic duplication (c.487dupA:p.A162fs) in exon 3 of the SNAP29 gene.

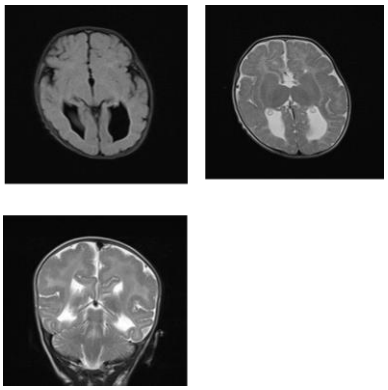

Figure 2. Bilateral polymicrogyria in Sylvian fissures and agenesis of the corpus callosum and colpocephaly

Discussion

CEDNIK syndrome (OMIM 609528) is a rare neuro-ichthyotic condition caused by a mutation in the SNAP29 gene on chromosome 22q11.2. Neurological and Dermatological manifestations are prominent features of this syndrome that will be comprehensively discussed.

Neurological manifestations of this syndrome include global developmental delay, hypotonia, microcephaly, deafness, and seizure. We have not detected any attack of seizure in our patient so far.

SNAP29 is proved to be a negative modulator of neurotransmitter release (2), which has an important role in brain development, synaptogenesis, axonal growth, and neurotransmission. These may explain the neurological manifestations of CEDNIK syndrome.

Also, SNAP29 has been proved to have an essential role in the recycling ligands of fibroblasts; thus, a decline in SNAP29 gene expression may lead to a reduction in the recycling rate of vesicle fusion proteins (3).

Dermatological manifestations in this syndrome include generalized ichthyosis, keratoderma, and collodion phenotype. Ichthyosis was not present at birth. However, it appeared at 6 months old and became more obvious 2 years later. Palmar keratoderma is evident (Figure 3).

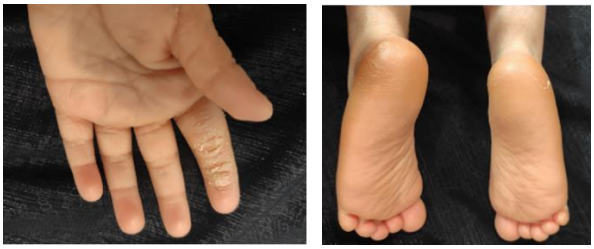

Figure 3. Palmar keratoderma

The components of a normal epidermal barrier include a cornified cell layer, keratin filaments, and an extracellular matrix. Lamellar bodies are secretory organelles that are generated in the Golgi apparatus of keratinocytes in the granular layer, which release glucosylceramide and kallikrein into the extracellular space and fortify the epidermal barrier by creating a lipid membrane.

SNAP29 has a crucial role in the secretion of lamellar bodies' contents into the extracellular space, which demonstrates its essential role in epidermal differentiation and barrier formation.

The retention of lamellar granules in the cornified layer prevents their secretion into the extracellular space, which results in inhibition of cells separating from each other and thus a considerable thickness in the epidermal layers, causing ichthyosis (5).

Corpus callosum dysgenesis, cortical dysplasia, polymicrogyria, and pachygyria are some of the MRI demonstrations in previous CEDNIK syndrome cases (5-8,11).

SNARE proteins play an important role in the development of the retina (4). The notable ophthalmologic findings in patients with CEDNIK, syndrome-including roving eye movements, hypoplastic or atrophic optic disc, and reduced peripheral retinal conductance-demonstrate the essential function of SNAP29 in the development of the visual system. Ophthalmologic findings in this syndrome are hypoplastic optic disc, optic atrophy, and strabismus. A recent evaluation of this child showed mild optic atrophy.

Some skeletal abnormalities have also been detected in patients with CEDNIK syndrome, neuromuscular scoliosis, digit clinodactyly, and toe syndactyly are some instances. Coxa valga, dislocated hips, talipes equinovarus, prominent toe pads, and bilateral broad first

toe have been reported but shortening of the second toe compared with the third one is unique in our patient.

Prominent specifications in our patient are microcephaly, Down-slanting palpebral fissures, flat nasal bridge, Synophrys, bushy eyebrows, slight hypertelorism, elongated face, and broad first toes. Additional findings in this patient that have not been previously reported are abnormal hair whorl, brittle, coarse hair (Figure 4), a tuft of hair on the low back (Figure 5), widely spaced nipples (Figure 6), and second toe shorter than the third one (Figure 7).

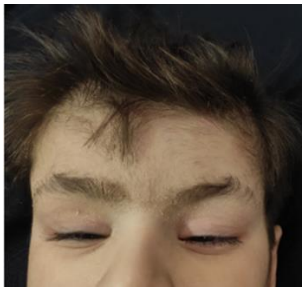

Figure 4. Abnormal hair whorl, brittle, coarse hair

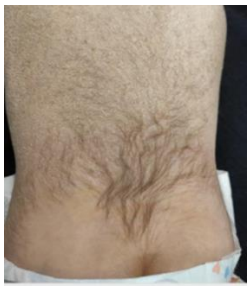

Figure 5. A tuft of hair on the low back

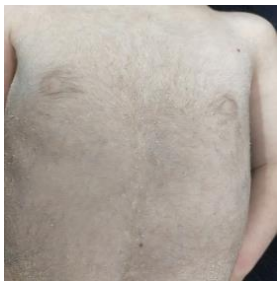

Figure 6. Widely spaced nipples

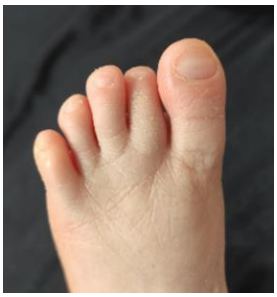

Figure 7. Second toe shorter than the third one

Dysmorphic features and MRI abnormalities of this syndrome can help clinicians narrow the diagnosis in neuro-ichthyotic syndromes. Dysmorphic features of this syndrome that have been reported previously are summarized in table 1.

To evaluate a child with ichthyosis and neurodevelopmental delay or any other neurologic symptoms, a brain MRI can limit the possible diagnoses. (12) (Table 2).

Table 1. Dysmorphic features and MRI abnormalities of CEDNIK syndrome

Dysmorphic features	MRI abnormalities
Down-slanting, short palpebral fissures, flat nasal bridge	Brain atrophy
synophrys /low frontal hairline /hirsutism	Fronto-parietal polymicrogyria
bushy eyebrows /long eyelashes	Perisylvian polymicrogyria
deep-set eye / slight hypertelorism	Agenesis of the corpus callosum
elongated face /triangular face	Pachygyria,
flat maxilla	Cortical dysplasia
small chin/small mouth	Hypoplastic corpus callosum
low set ears	Abnormal cortical folding
large ears / small ear with over folded helix	colpocephaly
bifid uvula /high arched palate	diffuse white matter T2 hyperintensity
clinodactyly	
broad first toes	
inverted nipple	
microcephaly/ brachycephaly	

Table 2. Differential Diagnosis of Neuro-Ichthyotic Disorders with Prominent Brain MRI Abnormality

Disorder	Brain MRI	Additional Features	Gene
CEDNIK syndrome	Cerebral dysgenesis, hypoplasia, or agenesis of the corpus callosum	Failure to thrive, Cerebral dysgenesis, neuropathy, palmoplantar keratoderma	SNAP29
Arthrogryposis-renal dysfunction-cholestasis (ARC)syndrome	Cerebral dysgenesis	Nephron calcinosis or small dysplastic kidneys, Cholestasis with elevated transaminases, and hyperbilirubinemia	VPS33B
Multiple sulfatase deficiency	White matter disorder	mental retardation, hepatosplenomegaly, coarse facies, and corneal clouding regression	SUMF1
Sjögren-Larsson's syndrome	White matter disorder lipid peaks on MRS	cognitive delay, seizures, Spastic diplegia, tetraplegia, pruritus	ALDH3A2
Trichothiodystrophy with Ichthyosis (Tay's syndrome)	White matter disorder Cerebellar hypoplasia	developmental delay, microcephaly, Brittle ataxia hair, short stature, photosensitivity	XPD, XPB, P8/TTDA orTTDN1
Steroid 5α-reductase type-3 deficiency	Cerebellar hypoplasia	seizures, microcephaly, nystagmus, alopecia, Elevated serum transaminases, congenital heart defects	SRD5A3
ELOVL4 deficiency	Brain atrophy, hypomyelination	intellectual disability, seizures, spastic quadriparesis, inguinal hernias, abnormal VEP	ELOVL4

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