A Young Boy with Microcephaly, Ichthyosis and Cerebral Dysgenesis: A Rare Case of CEDNIK Syndrome

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ABSTRACT

Cerebral dysgenesis, neuropathy, ichthyosis and keratoderma (CEDNIK syndrome) is an extremely rare condition with only 19 cases diagnosed worldwide. It is an autosomal recessive syndrome occurs as a result of homozygous deletion in 22q11.2 as well as a mutation in Synaptosomal-associated protein 29 (SNAP29) which is a protein that regulate vesicle fusion in the cells. We report a rare case of CEDNIK syndrome which is the first case reported in Bahrain and the Arabian gulf. The patient presented with skin changes, developmental delay and his brain MRI showed significant cerebral dysgenesis.

INTRODUCTION

CEDNIK syndrome is a neurocutaneous genetic syndrome caused by a genetic mutation of SNAP29 that code for a Soluble NSF N-ethylmaleimide-sensitive factor, Attachment-Protein Receptor (SNARE protein) which is responsible for programming of vesicle trafficking and fusion. Loss of SNAP29 expression thought to be associated with CEDNIK syndrome[1].

CEDNIK Syndrome is a very uncommon genetic syndrome. To date, only 19 cases of CEDNIK syndrome has been reported worldwide[2]. Our case is the only cases of CEDNIK Syndrome reported in Bahrain and the Arabian gulf region.

The aim to report this case is to increase the awareness of such rare syndrome in order for physicians to recognize it and enable families of affected members to prevent having further child with CEDNIK Syndrome. We also aim to highlight the importance of utilizing whole exome sequencing in diagnosing such rare syndrome.

THE CASE

A 5-Year-old Bahraini boy presented to our hospital with history of motor and cognitive regression which started at the age of six months as the patient lost ability to roll over and not able to maintain seated position. The patient was also unable to crawl or walk. According to the parents the patient was not able to communicate with them with poor eye contact. There was also a significant speech delay as the child was only able to say few words.

The patient seen by dermatologist at the age of four months because of generalized body eczematous rash and seborrheic dermatitis along with skin excoriation and hyperkeratosis.

At the age of five months the patient had multiple hospital admissions due to recurrent pneumonias.

The patient was born at 39 weeks of gestation by spontaneous vaginal delivery to a 25 year old Bahraini mother, with a birth weight of 3.15 kg which was on the 25th percentile a head circumference (H.C) of 35 cm which was on the 50th percentile.

The parents are third degree cousins and has one healthy 9 years old son. There is no family history of any chronic or genetic diseases, and the patient received all his schedule immunizations.

Physical examination showed a microcephalic child with poor communication. Head circumference of 48 cm which is on the third percentile with dysmorphic features in the form of short forehead with bitemporal hollowing, microphthalmia, micrognathia, short philtrum and high arch palate.

Neurological examination revealed truncal hypotonia with power 4 out of 5 in all limbs with absent reflexes. He also had horizontal nystagmus. Dermatological examination showed focal areas of ichthyosis on the dorsum of the hands, feets, scalp and the back.

The initial investigations showed negative Toxoplasmosis, rubella, cytomegalovirus, herpes simplex (TORCH) and HIV results. The patients routine karyotype result showed a normal male 46XY . His initial brain MRI showed corpus callosum dysgenesis with cerebral dysplasia and polymicrogyria (Figure 1,2). The whole exome sequencing confirmed the pathologic C.487 dup p.(Ser 163 LYsfs*6) in homozygosity in the SNAP 29 gene associated with CEDNIK Syndrome.

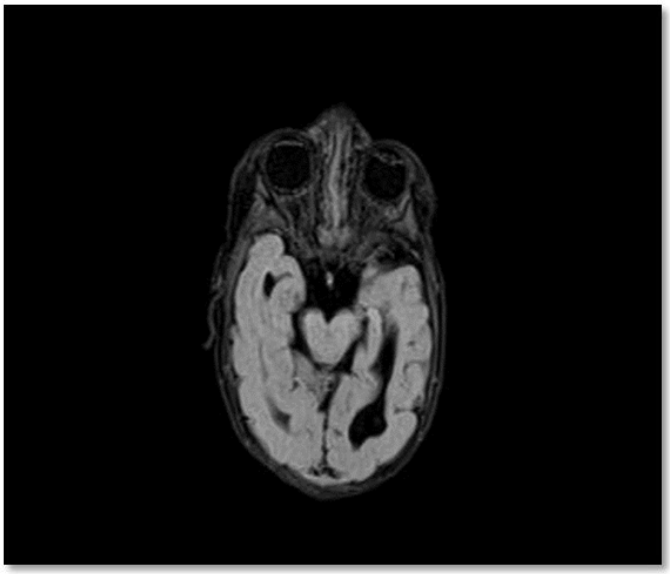

Figure 1: Brain MRI, axial view, T2 flair, image showed significant left cerebral hemisphere dysgenesis

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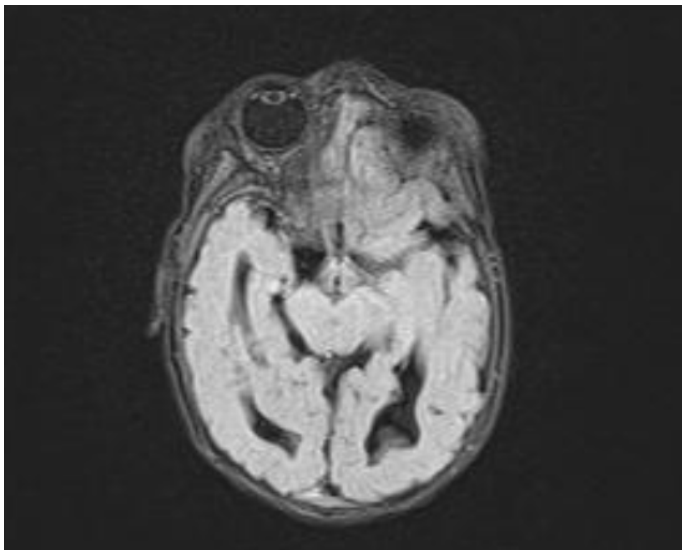

Figure 2: Brain MRI, axial view, T2 flair, image showed significant bilateral cerebral dysgenesis

DISCUSSION

CEDNIK syndrome is an autosomal recessive neurocutaneous genetic syndrome that results from homozygous deletion in the SNAP29 gene (22q11.2) on chromosome 22, which encodes a SNARE protein. This protein regulates vesicle fusion in cells and plays a major role in the pathophysiology and the clinical features seen in CEDNIK syndrome[3]. The classical presentation of CEDNIK Syndrome include significant developmental delay intellectual disability, microcephaly brain abnormalities, failure to thrive, sensorineural deafness, skin changes like ichthyosis and palmoplantar keratoderma. Upon histopathological analysis of the skin, multiple clear vesicles were seen in the stratum spinosum and granular layer of the skin. Patients with CEDNIK syndrome have a typical facial dysmorphic features as seen in our case, it includes low-set ears, small chin and pointed nasal tip. Some skeletal abnormalities like scoliosis and syndactyly have been associated with the syndrome as well[2,3].

It is often challenging to make a diagnosis for this rare syndrome. Although, the diagnosis of CEDNIK syndrome can be made based on the clinical ground and brain MRI findings. However, WES and molecular genetic testing are considered to be the gold standard for the diagnosis[4].

There are not enough data available in literature about CEDNIK syndrome however, the overall prognosis is poor and associated with short life expectancy and infection is considered to be the leading cause of death in patients with CEDNIK syndrome[5].

CONCLUSION

CEDNIK syndrome is an extremely rare condition with only 19 cases has been diagnosed worldwide. Detailed history, neurological and dermatological examination along with neuroimaging should be done in any patient with developmental delay. However, whole exome sequencing test is very helpful in diagnosing such rare syndrome. Finally, the prognosis of CEDNIK syndrome is poor; as affected individual usually die at early childhood.

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