CErebral Dysgenesis, Neuropathy, Ichthyosis, and Keratoderma (CEDNIK) Syndrome with Brain Stem Malformation

Dear Editor,

CErebral Dysgenesis, Neuropathy, Ichthyosis, and Keratoderma (CEDNIK) syndrome, a novel and rare neurocutaneous condition, was first described by Sprecher *et al.* in 2005.[1] CEDNIK syndrome is characterized by severe psychomotor retardation, failure to thrive, progressive microcephaly, facial dysmorphism, visual impairment, sensori-neural hearing loss, ichthyosis, and palmoplantar keratoderma.[1,2] The radiological abnormalities include defects in corpus callosum, cortical dysplasia, pachygyria, and polymicrogyria.[2,3] Currently there is no curative therapy available for this syndrome and the lifespan is limited.[2] The abnormal expression of synaptosomal-associated protein 29-KD (SNAP29) which belong to the t-SNARE family of proteins, functions as a negative modulator of the neurotransmitter release as it probably slows the recycling of the SNARE complex and the synaptic vesicles.[4] The resulting disruption of vesicle trafficking is the underlying molecular mechanism causing CEDNIK syndrome.[5] *SNAP29* gene is mapped to chromosome 22q11.2 by homozygosity mapping in seven patients belonging to two large families.[1] Till date, only 12 patients with CEDNIK syndrome have been reported in literature; all belonging to the Arab and Pakistani origin.[2] Here we report a child of South-Indian origin with brainstem malformation, a novel imaging finding in this syndrome.

The index patient, six-year-old female, second born of second-degree consanguineous parentage, was delivered at term without any complications. Her APGAR score was 10 and she weighed 3.3 kg at birth. She had poor sucking pattern during the initial few weeks and was managed by feeding with expressed breast milk. Dryness and scaling of palms and soles were seen from 4 months of age. She had gross developmental delay and has not achieved the ability to walk or speak words yet. Family history was not significant. Her occipito-frontal circumference was 45 cm (z score, <-3), weight was 11.5 kg (z score, < -3) and height was 110 cm (z score,-1). She had dysmorphic facial features [Figure 1a]: (depressed nasal bridge, hypertelorism, and synorphys), palmoplantar keratoderma [Figure 1b], ichthyosis, and excessive body hair. Her dentition was normal. Her auditory regard was poor; however, she was able to track objects visually. Ophthalmology assessment showed bilateral esotropia and optic atrophy. Motor system manifestations included generalized hypotonia, weakness, and areflexia.

The motor nerve conduction study showed reduced conduction velocities from bilateral median (20 and 22 m/s) and ulnar nerves (21 and 23 m/s) along with mild prolongation of distal and F wave latencies. The compound muscle action potential and F waves of the lower limb nerves were not elicited. The sensory potentials from superficial, sural, and ulnar nerves were not recordable and the peak latencies from median nerves were increased (4.2 and 4.3 ms). Thus, the electroneurographic study was confirmatory for the presence of diffuse sensorimotor demyelinating polyneuropathy. The electromyography from right tibialis anterior and rectus femoris was also suggestive of neurogenic process. Visual evoked potential showed prolonged P100 latency on the left side. Brainstem auditory evoked potential showed prolonged peak latencies of waves III, IV, V bilaterally suggestive of brainstem pathology.

Magnetic resonance imaging (MRI) of the brain [Figure 2] at age 3 years, showed dysgenesis of the corpus callosum, bilateral frontoparietal polymicrogyria with abnormal cortical folding, T2W diffuse white matter hyperintensity, and hypoplastic intraconal optic nerves. In addition, brain stem malformation in the form of elongated pons and short medulla was seen. We considered Zellweger spectrum disorders, tubilinopathies, congenital disorders of glycosylation, congenital muscular dystrophy and CEDNIK syndrome as possible causes for her condition. Her routine blood investigations including serum creatine phosphokinase (73 U/L) was normal. Clinical exome sequencing identified a homozygous single base pair insertion in exon 3 of the *SNAP29* gene [(c.486_487insA)

which was corroborated by Sanger sequencing (variant of uncertain significance). This mutation resulted in shift of the reading frame and premature termination of the protein (p.Ser163LysfsTer6) confirming the diagnosis of CEDNIK syndrome.

The homozygous mutation c. 486_487insA (p.ser163LysfsTer6) in the *SNAP29* gene identified in this patient was reported previously in 2 Pakistani children and was proved pathogenic by molecular studies. The transfection studies in HeLa cells demonstrated that the c.486insA mutation resulted in production of truncated SNAP29 protein. The loss-of-function of this particular mutation was further confirmed in organotypic cell cultures which showed abnormal differentiation of keratinocytes.[3] Skin biopsy from the affected patient revealed accumulation of clear vesicles in the spinous and granular layers of epidermis as well as in the stratum corneum.[1,5] Neonatal lethality, acanthosis, hyperkeratosis, abnormal keratinocyte differentiation, and increased proliferation were seen in both total SNAP29 knockout mice and keratinocytes specific knockout mice. The comparable phenotypic findings observed in these animal studies substantiate the pathogenic role of SNAP29 deficiency in CEDNIK syndrome.[6]

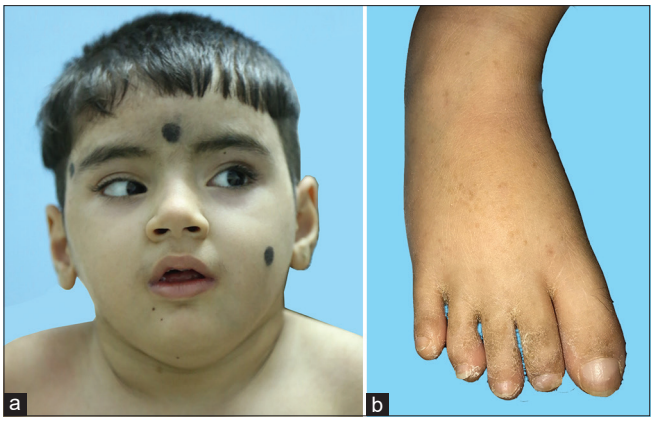

Figure 1: Photograph of the patient shows (a) hypertelorism, depressed nasal bridge, and synorphis; (b) plantar keratoderma

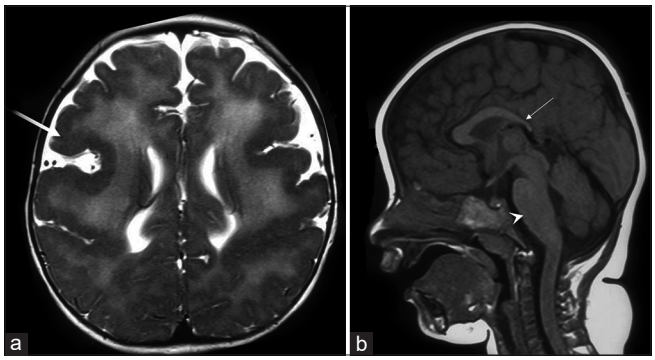

Figure 2: MRI brain (a) Axial T2W image shows bilateral perisylvian polymicrogyria (thick arrow) with confluent white matter hyperintensity; (b) Sagittal T1W image shows posterior callosal dysgenesis (thin arrow) and malformed brainstem with abnormal elongation of the pons (arrow head)

Bilateral polymicrogyria, cerebral white matter abnormalities, and dysgenesis of corpus callosum observed in this patient were seen in previously described cases as well.[1-3] But, the mechanistic process underlying these findings are obscure. The occurrence of polymicrogyria could be due to pial defects, impaired proliferation, and migration of neuroblasts or cortical organization defects that is related to post migrational maturational abnormalities. The causes include congenital cytomegalovirus infection, ischemia, syndromic (Zellweger syndrome, congenital muscular dystrophy, and congenital disorders of glycosylation) or mutations in numerous genes.[7] The genetic mutations involving *TUBB2*, *GPR56*, *SRPX2*, *TBR2*, *PAX6*, *KIAA1279,* and *RAB3GAP1* that are required for microtubules, radial glia formation, or transcription can lead to neuronal migration defects including polymicrogyria. But, with the uncovering of *SNAP29* gene as a cause of CEDNIK syndrome, the vesicular transport is recognized as a decisive component in the neuronal positioning and migration.[8] SNAP29 located on multiple intracellular membranes including golgi apparatus and synaptic vesicles is critical for neuronal morphogenesis, neuritogenesis, and axon branching.[4] The brainstem malformation in this patient has not been reported previously and it could be due to the neuronal migration defects per se. Hindbrain malformations are also associated with lissencephaly, polymicrogyria, and cerebellar hypoplasia.[9] How exactly, SNAP 29/SNARE proteins are involved in the embryogenesis of hindbrain is vaguely articulated.

In this patient, there is clinical evidence for peripheral neuropathy and through electrophysiological study, demyelination of sensory, and motor nerves was confirmed. The characterization of neuropathy as demyelinating or axonal has not been described in previously reported cases.[1-3] Mutations involving endosomal trafficking and signaling (*LITAF*), vesicular transport (*RAB7*), endocytosis (*DNM2*), endocytic recycling pathway (*SH3TC2*) etc., can result in inherited peripheral neuropathies underscoring the importance of the role of vesicular and membrane trafficking for the myelin formation and maintenance of the peripheral nervous system.[10]

We describe the first case of CEDNIK syndrome from South-India caused by a homozygous *SNAP29* mutation. The striking observation noted in this case is the brainstem malformation as an additional radiological feature broadening the imaging phenotype of CEDNIK syndrome. Another important finding is the demyelinating pattern of peripheral neuropathy, observed in this case which suggests that SNAP29 has a potential role in peripheral myelin formation and maintenance.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/

their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Sprecher E, Ishida-Yamamoto A, Mizrahi-Koren M, Rapaport D, Goldsher D, Indelman M, *et al*. A mutation in SNAP29, coding for SNARE protein involved in intracellular trafficking, causes a novel neurocutaneous syndrome characterized by cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma. Am J Hum Genet 2005;77:242-51.
2. Hsu T, Coughlin CC, Monaghan KG, Fiala E, McKinstry RC, Paciorkowski AR, *et al*. CEDNIK: Phenotypic and molecular characterization of an additional patient and review of the literature. Child Neurol Open 2017;4:1-6.
3. Fuchs-Telem D, Stewart H, Rapaport D, Nousbeck J, Gat A, Gini M, *et al*. CEDNIK syndrome results from loss-of-function mutations in SNAP29. Br J Dermatol 2011;164:610-6
4. Pan PY, Cai Q, Lin L, Lu PH, Duan S, Sheng ZH. SNAP-29-mediated modulation of synaptic transmission in cultured hippocampal neurons. J Biol Chem 2005;280:25769-79.
5. Rapaport D, Lugassy Y, Sprecher E, Horowitz M. Loss of SNAP29 impairs endocytic recycling and cell motility. PLoS One 2010;5:e9759.
6. Schiller SA, Seebode C, Wieser GL, Goebbels S, Möbius W, Horowitz M, *et al*. Establishment of two mouse models for CEDNIK syndrome. Reveals the pivotal role of SNAP29 in epidermal differentiation. J Invest Dermatol 2016;136:672-9.
7. Squier W, Jansen A. Polymicrogyria: Pathology, fetal origins and mechanisms. Acta Neuropathol Commun 2014;2:80.
8. Moffat JJ, Ka M, Jung EM, Kim WY. Genes and brain malformations associated with abnormal neuron positioning. Mol Brain 2015;8:72.
9. Barkovich AJ, Millen KJ, Dobyns WB.A developmental and genetic classification for midbrain-hindbrain malformations. Brain 2009;132:3199-230.
10. Bussmann J, Storkebaum E. Molecular pathogenesis of peripheral neuropathies: Insights from Drosophila models. Curr Opin Genet Dev 2017;44:61-73.

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