Rare Cause of West syndrome secondary to Tubulinopathy due to Congenital Symmetric Circumferential Skin Creases (CSCSC) Kunze Type due to a Novel Variant in *MAPRE2* Gene

Congenital symmetric circumferential skin creases (CSCSC) is characterized by the ringed creases of limbs and neck with intellectual disability, speech delay, short stature, facial dysmorphism, and various abnormality of fingers and toes.[1] Kunze J *et al*.[2] described CSCSC in two families and Isrie M *et al*.[3] identified underlying genetic abnormality due to *MAPRE2 or TUBB*.[3] The prevalence is not known, and less than 50 cases have been reported. This is the first report of *MAPRE2* mutation from Indian subcontinent. West syndrome (WS) was first reported by William James West in 1841.[4] The predominant cause of WS from Indian sub-continent reported was structural.[5,6] Mutations in *MAPRE2* gene cause features of tubulinopathy leading to structural changes in the brain. However, no association has been reported between WS and CSCSC. Hence, we are reporting this case.

A 1-year-old boy born to a non-consanguineous marriage with normal birth history presented with developmental delay, excess skin folds in all four limbs, and epileptic spasms from 7 months of age. He attained partial head control, palmar grasp, social smile, stranger anxiety, cooing, and babbling. He developed epileptic spasms in clusters after awakening from sleep at 7 months of age. Following development of epileptic spasms there was loss of social smile and partial head control. On examination, normal anthropometry, dysmorphism in the form of hypertelorism, microophthalmia, epicanthal folds, depressed nasal bridge, low set, and small ears [Figure 1] were noted. There were multiple folds of symmetrical circumferential skin creases noted in all limbs [Figure 1]. On neurological examination, he was dull looking, not following light and sound consistently, tone was decreased, complete head lag on pull to sit, power was 3/5(medical research council grading), and brisk deep tendon reflexes. On investigations, MRI of the brain showed enlargement of ventricles and irregular ventricular margins, bilateral heterotropia of frontal horns and dysmoprhic basal ganglia, hypoplastic corpus callosum, and dysplastic brainstem [Figure 2]. EEG was suggestive of hypsarrhythmia. A novel homozygous missense pathogenic variant c. 458G > T (p.W153L) noted in exon 4 of the *MAPRE2* gene. Treatment with oral prednisolone and rehabilitation, spasms have decreased, and development of the child improved. We advised for antenatal diagnosis for next child to prevent recurrence.

The CSCSC includes two different types, CSCSC1 caused by *TUBB* gene (OMIM# 156610) and CSCSC2 by *MAPRE2* gene (OMIM# 605789), due to different molecular basis. Based on global developmental delay, characteristic skin lesions, and MRI findings, we considered possibility of CSCSC. We also considered following differential diagnosis and excluded; Ehlers-Danlos syndrome (EDS), cutis laxa, Bethlem, and Ullrich congenital muscular dystrophies. The EDS has joint laxity, predominantly motor delay with involvement of eye and heart; however, all these features were absent in the current case. The classical features of cutis laxa are lax skin, isolated motor delay, developmental dysplasia of hip joint, and abnormal skin involvement over limbs and trunk but epileptic spasms and cognitive delay are uncommon that present in the current child. The Bethlem and Ullrich congenital muscular dystrophies usually have distal laxity and proximal muscle contractures with muscle weakness, these features were not present in this child. Hence, finally we diagnosed as CSCSC

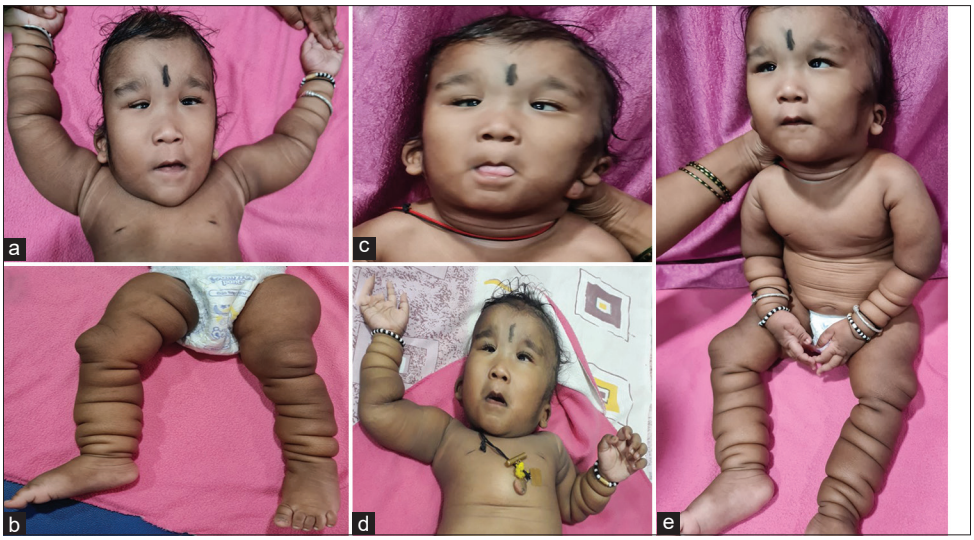

Figure 1: showing narrow eye openings -blepharophimosis, small eyes- microphthalmia, wide spaced eyes -hypertelorism, skin of the upper eyelid covering the inner corner of the eye-epicanthal folds, strabismus, broad nasal bridge, low-set ears, a small mouth (a, b, d), multiple rings of folded excess skin on the arms and legs (b, e)

based on classical skin folds and MRI findings and confirmed by pathogenic variant in *MAPRE2* gene.

Isrie M *et al*.[3] in their report showed that the two individuals with a homozygous *MAPRE2* mutation (M2 and M8) had a more severe neurological involvement having severe intellectual disability and seizures, absent in the two individuals with a heterozygous *MAPRE2* mutation (M1 and M9). However, the authors were reluctant to conclude the phenotype-genotype correlation and insisted on study of larger allelic series to do so. Feng J *et al*.[7] reported a 2-year-old boy with absent expressive speech, normal to mild overgrowth, facial dysmorphic features, remarkable circumferential skin creases on both forearms and ankles, and had a de novo missense *MAPRE2* variant, c. 518G > A (p.Arg173Gln. Berkun L *et al*.[8] reported an infant with developmental delay, severe growth delay, dysmorphic features, and multiple congenital anomalies including retinal coloboma, congenital pyloric stenosis, and circumferential skin creases due to homozygous mutations in *MAPRE2* and circumferential skin lesions.

A novel homozygous missense variant c. 458G > T (p.W153L) was noted in exon 4 of the *MAPRE2* gene. The variant is disease causing by MutationTaster. The variant is damaging by SIFT and probably damaging by Polyphen-2. The variant is not reported in 1000 exome gnomAD or ExAC databases. The mutation is in a mutational hot spot and/or critical and well-established functional domain without benign variation. There is no report of WS reported in association with *MAPRE2* gene mutations.

To conclude, any child presenting with WS, global developmental delay, excessive characteristic symmetrical skin creases, dysmorphism, and tubulopathy, CSCSC type 2 to be considered and look for changes in the MRI of the brain and confirmed by genetic testing for *MAPRE2* gene variants. Genetic counseling to be done to prevent recurrence.

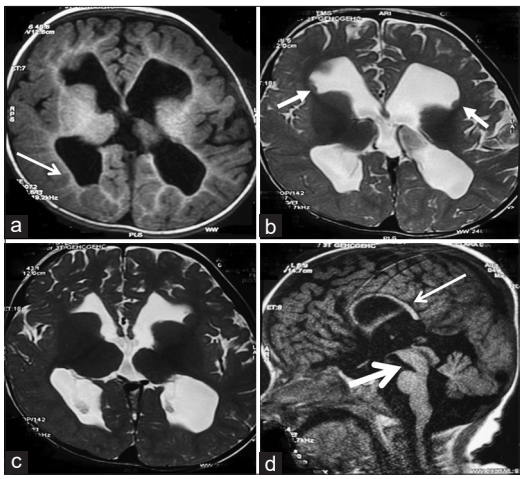

Figure 2: Axial T1 MPRAGE (a) and T2WI (b) showing enlargement of ventricles with irregular margins and polymicrogyria in the right temporal lobe (arrow in a). Also noted is bilateral subependymal heterotropia (arrows in b).Axial T2WI (c) demonstrating dysmorphic basal ganglia and (d) sagittal T1W image showing hypoplastic corpus callosum (long arrow) and dysplastic brainstem (short arrow)

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Vykuntaraju K. Gowda, Varunvenkat M. Srinivasan[1], Varsha Reddy[1], Maya Bhat[2]

Departments of Pediatric Neurology and [1]Pedaitrics, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, [2]Department of Neuroradiology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India

Address for correspondence: Dr. Vykuntaraju K. Gowda, Professor and HOD, Department of Pediatric Neurology, Indira Gandhi Institute of Child Health, Near NIMHANS, Bengaluru - 560 029, Karnataka, India.
E-mail: drknvraju08@gmail.com

References

1. Ross, CM. Generalized folded skin with an underlying lipomatous nevus. "The Michelin Tire baby". Arch Dermatol 1969;100:320-3.
2. Kunze J, Riehm H. A new genetic disorder: Autosomal-dominant multiple benign ring-shaped skin creases. Eur J Pediatr 1982;138:301-3.
3. Isrie M, Breuss M, Tian G, Hansen AH, Cristofoli F, Morandell J, *et al*. Mutations in either TUBB or MAPRE2 cause circumferential skin creases Kunze type. Am J Hum Genet 2015;97:790-800.
4. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, *et al*. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512-21.
5. Kaushik JS, Patra B, Sharma S, Yadav J, Aneja S. Clinical spectrum, and outcome of West syndrome in children from Northern India. Seizure 2013;22:617-21.
6. Singhi P, Ray M. Profile of West syndrome in North Indian children. Brain Dev 2005;27:135-40.
7. Feng J, Lan X, Shen J, Song X, Tang X, Xu W, *et al*. A de novo MAPRE2 variant in a patient with congenital symmetric circumferential skin creases type 2. Mol Genet Genomic Med 2020;8:e1096.
8. Berkun L, Slae M, Mor-Shaked H, Koplewitz B, Eventov-Friedman S, Harel T. Homozygous variants in MAPRE2 and CDON in individual with skin folds, growth delay, retinal coloboma, and pyloric stenosis. Am J Med Genet A 2019;179:2454-8.

Submitted: 14-May-2021 **Revised:** 12-Jun-2021 **Accepted:** 14-Jun-2021
Published: 22-Oct-2021

DOI: 10.4103/aian.AIAN_420_21