

## Infantile convulsions and choreoathetosis syndrome with PRRT2 mutation – A case report

Velusamy S<sup>1</sup>, Sathish Kumar M<sup>2</sup>, Dhivya K<sup>3</sup>

From <sup>1</sup>Professor of Neurology, <sup>2</sup>Senior Resident, <sup>3</sup>Paediatric Postgraduate, Department of Neurology, Government Stanley Medical College and Hospital, Chennai, Tamil Nadu, India

### ABSTRACT

Infantile convulsions and choreoathetosis (ICCA) syndrome is a rare autosomal dominant disorder characterized by convulsions during infancy with paroxysmal choreoathetosis at a later age. Mutations in the proline-rich transmembrane protein 2 (PRRT2) gene were identified as a cause for ICCA syndrome. Carbamazepine or phenytoin prevents seizure recurrence and controls dyskinesias. Here, we report a child with ICCA syndrome with a homozygous mutation in the PRRT2 gene.

**Key words:** Infantile convulsions, Paroxysmal dyskinesia, PRRT2

Infantile convulsions and choreoathetosis (ICCA syndrome) is a rare autosomal dominant disorder characterized by infantile seizures during the 1<sup>st</sup> year of life and paroxysmal dyskinesias (PDs) during childhood or adolescence [1]. The exact prevalence of ICCA syndrome is still unknown [1]. Mutations in the gene proline-rich transmembrane protein 2 (PRRT2) at 16p11.2 have been identified as the cause for ICCA syndrome [2,3]. Children with ICCA syndrome who exhibited a severe clinical phenotype including intellectual disability are reported to have a homozygous mutation [4].

### CASE REPORT

A 1-year, 6-month-old girl child born to non-consanguineous parents had recurrent attacks of paroxysmal choreoathetotic movements for 3 weeks. The choreoathetotic movements involved the head, neck, upper, and lower extremities. The movements occurred even at rest and subsided spontaneously. The movements usually lasted 30–60 s and there was no associated loss of consciousness. The child used to get about 15–20 episodes everyday. The episodes were so severe that it limited the child's ability to stand during the episode. The child was completely normal in between the episodes. These attacks did not occur during sleep.

Her past history revealed an episode of generalized tonic-clonic seizure following a day of fever for which she was hospitalized at the age of 1½ months. Subsequently, during the hospital stay, the

child developed multiple episodes of afebrile generalized seizures which were managed by IV anti-seizure medications. On starting oral phenytoin, the child developed a generalized maculopapular rash and hence phenytoin was withdrawn. The child was started on oral levetiracetam and she became seizure free.

There were no significant perinatal events. Her motor and social milestones were normal. Her language milestones were slightly delayed. She was able to speak four meaningful words. There was no family history of epilepsy, movement disorder, migraine, or any other neurological illness.

General examination was normal. Neurological examination failed to detect any significant abnormality other than the brief episodic choreoathetotic movements in both extremities, lasting for 30–60 s.

Routine laboratory investigations were within normal limits. Serum calcium was normal. MRI Brain and EEG were normal. Tandem mass spectrometry for metabolic disorders yielded negative results. Genetic workup was done. Clinical exome sequencing revealed a homozygous mutation in the PRRT2 gene involving c640\_641 insC (p.Arg217ProfsTer8) of exon 2 on chromosome 16.


Carbamazepine 10 mg/kg/day was started and levetiracetam was stopped. She is seizure free for the past year and there is no recurrence of dyskinetic episodes.

### DISCUSSION

ICCA syndrome is a rare neurological disorder characterized by familial infantile seizures during the 1<sup>st</sup> year of life and PD during childhood or adolescence [1]. Szepetowski *et al.* first reported ICCA syndrome in 1997 in four French families [2]

**Correspondence to:** Dr. S. Velusamy, 115, Dhinesh Street, Panneer nagar part2, Mugappair east, Chennai-600037, Tamil Nadu, India. E-mail: drvelsneuro@yahoo.co.in

© 2022 Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC-ND 4.0).

Access this article online	
Received - 07 February 2022 Initial Review - 10 February 2022 Accepted - 26 February 2022	Quick Response code 
DOI: 10.32677/ijch.v9i2.3311	

and the gene has been mapped to the pericentromeric region of chromosome 16 [3]. Homozygous PRRT2 mutations promote familial infantile seizures (BFIS) and familial paroxysmal kinesigenic dystonia [4]. More than 50 families with ICCA syndrome have been described in the literature [1,5]. More than 200 ICCA cases with PRRT2 mutation have been reported [6].

Infantile seizures begin at 3–12 months of age with a family history of similar types of seizures. Seizures are afebrile, focal, or generalized and usually disappear after the 1<sup>st</sup> year of life [7,8]. PDs are characterized by sudden involuntary movements comprising dystonia, chorea, and athetosis or a combination of these. PD can occur spontaneously or may be precipitated by sudden movements [9]. ICCA syndrome shares overlapping features of infantile seizures and PDs [2,10].

Molecular analysis provides a definitive diagnosis for patients with suspected ICCA. Identification of pathogenic mutation helps in accurate treatment. Mutations in PRRT2 at 16p11.2 and SCN8A are the cause for ICCA syndrome [2,3,11]. PRRT2 gene encodes a transmembrane protein involved in regulating the synaptic vesicular release of neurotransmitters and hence PRRT2-associated disorders may be classified as synaptopathy. PRRT2 is mainly expressed in glutaminergic neurons in the brain with a high level in the hippocampus, basal ganglia, cerebral cortex, and cerebellum [12]. Mutations in the PRRT2 gene cause paroxysmal disorders such as paroxysmal kinesigenic dyskinesia, benign familial infantile epilepsy, ICCA, hemiplegic migraine, and episodic ataxia [13].

Apart from mutations in the PRRT2 gene, mutations in SCN8A encoding for voltage-gated sodium channels can also cause the association of PD and epilepsy. Patients with SCN8A gene mutation in ICCA syndrome present with various seizure types including focal, tonic, clonic, myoclonic, and absence seizures and they are refractory to antiepileptic medications [14]. Even if the early developmental stage was normal, patients with SCN8A mutation develop moderate-to-severe intellectual disability [11].

ICCA syndrome has a good prognosis [2] and it responds well to antiepileptics such as phenytoin or carbamazepine [15]. Carbamazepine was effective in controlling dyskinesia and seizures in this child.

## CONCLUSION

This case is reported for its rarity. When a child presents with infantile onset seizures and choreoathetosis at a later age, one should consider the possibility of ICCA syndrome and order for genetic testing. Genetic study helps in confirmation of clinical

diagnosis, precision treatment, and in counseling parents.

## REFERENCES

1. Rochette J, Roll P, Fu HY, Lemoing AG, Royer B, Roubertie A, *et al.* Novel familial cases of ICCA (infantile convulsion with choreoathetosis) syndrome. *Epileptic Disord* 2010;12:199-204.
2. Szepletowski P, Rochette J, Berquin P, Piussan C, Lathrop GM, Monaco AP. Familial infantile convulsions and paroxysmal choreoathetosis: A new neurological syndrome linked to the pericentromeric region of human chromosome 16. *Am J Hum Genet* 1997;61:889-98.
3. Lee WL, Tay A, Ong HT, Goh L, Monaco AP, Szepletowski P. Association of infantile convulsions with paroxysmal dyskinesias (ICCA syndrome): Confirmation of linkage to human chromosome 16p12-q12 in a Chinese family. *Hum Genet* 1998;103:608-12.
4. Labate A, Tarantino P, Viri M, Mumoli L, Gagliardi M, Romeo A, *et al.* Homozygous c.649dupC mutation in PRRT2 worsens the BFIS/PKD phenotype with mental retardation, episodic ataxia, and absences. *Epilepsia* 2012;53:196-9.
5. Espeche A, Cercosimo R, Caraballo RH. Benign familial seizures and paroxysmal dyskinesia: A well-defined familial syndrome. *Seizure* 2011;20:686-91.
6. Fakhari DE, Saffari A, Westenberger A, Klein C. The evolving spectrum of PRRT2-associated paroxysmal diseases. *Brain* 2015;138:3476-95.
7. Caraballo RH, Cersasimo RO, Amartino H, Szepletowski P, Fejerman N. Benign familial infantile seizures: Further delineation of the syndrome. *J Child Neurol* 2002;17:696-9.
8. Watanabe K, Yamamoto N, Negoro T, Takaesu E, Aso K, Furune S, *et al.* Benign complex partial epilepsies in infancy. *Pediatr Neurol* 1987;3:208-11.
9. Bruno MK, Hallett M, Gwinn-Hardy K, Sorensen B, Considine E, Tucker S, *et al.* Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: New diagnostic criteria. *Neurology* 2004;63:2280-7.
10. Caraballo R, Pavsek S, Lemainque A, Gastaldi M, Echenne B, Motte J, *et al.* Linkage of benign familial infantile convulsions to chromosome 16p12-q12 suggests allelism to the infantile convulsions and choreoathetosis syndrome. *Am J Hum Genet* 2001;68:788-94.
11. Gardella E, Becker F, Moller RS, Schubert J, Lemke JR, Larsen LH, *et al.* Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation. *Ann Neurol* 2015;79:428-36.
12. Vilet RV, Anel JR, Brilstra E, Verbeek N, Verschuuren-Bemelmans C, Boon M, *et al.* PRRT2 phenotypes and penetrance of paroxysmal kinesigenic dyskinesia and infantile convulsions. *Neurology* 2012;79:777-84.
13. Gardiner AR, Bhatia KP, Stamelou M, Dale RC, Kurian MA, Schneider SA, *et al.* PRRT2 gene mutations: Paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. *Neurology* 2012;79:2115-21.
14. Larsen J, Carvill GL, Gardella E, Kluger G, Schmiedel G, Barisic N, *et al.* The phenotypic spectrum of SCN8A encephalopathy. *Neurology* 2015;84:480-9.
15. Li H, Wu Z. PRRT2 mutations and PRRT2 disorders. *Hum Genet Embryol* 2013;3:1.

*Funding: None; Conflicts of Interest: None Stated.*

**How to cite this article:** Velusamy S, Kumar MS, Dhivya K. Infantile convulsions and choreoathetosis syndrome with PRRT2 mutation – A case report. *Indian J Child Health*. 2022; 9(2):25-26.