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CLINICAL REPORT

PRICKLE1-related early onset epileptic encephalopathy

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The PRICKLE1 (Prickle Planar Cell Polarity Protein 1-MIM 608500) gene is involved in different phases of human development. The related diseases include autosomal recessive progressive myoclonus epilepsy - ataxia syndrome, neural tube defects associated with heterozygous mutations, agenesis of corpus callosum, polymicrogyria, and autistic spectrum disorder. Reported here is a young boy with a new variant (NM_153026.2:c.820G>A, p.Ala274Thr) presenting with an early infantile epileptic encephalopathy with developmental arrest.

KEYWORDS

epileptic encephalopathy, genetic epilepsy, intellectual disability, progressive myoclonus epilepsy

1 | INTRODUCTION

The Prickle Planar Cell Polarity Protein 1 (*PRICKLE1*-MIM 608500) gene is involved in a calcium mediated regulation of planar neuronal polarity signaling during embryonic development as well as in neuronal morphogenesis, migration, and networking (Bassuk et al., 2008).

PRICKLE1-related phenotypes not only include autosomal recessive progressive myoclonus epilepsy (PME)-ataxia syndrome (MIM 612437) and neural tube defects associated with heterozygous mutations but also agenesis of corpus callosum, polymicrogyria, and autistic spectrum disorder (Bassuk et al., 2008; Bassuk & Sherr, 2015; Bosoi et al., 2011; Tao et al., 2011; Todd & Bassuk, 2018). The broad heterogeneity of the phenotypic spectrum could be explained by a dosage effect involving the encoded protein for patients carrying heterozygous variants and by the variable degrees of impairment that may occur in the cascade of signals modulated by *PRICKLE1* in the other cases (Bassuk et al., 2008; Bassuk & Sherr, 2015; Bosoi et al., 2011; Tao et al., 2011; Todd & Bassuk, 2018).

Early clinical characterization of these rare disorders is limited. We report on a young boy with a new *PRICKLE1* mutation presenting with early infantile epileptic encephalopathy and reviewed the cases so far reported in the literature.

2 | CLINICAL REPORT

This 25-month-old boy was born from nonconsanguineous Indian parents after an uneventful pregnancy and labor. Family history evidenced a single relative in the maternal line with drug-responsive tonic seizures during childhood. The child's psychomotor development before the epilepsy onset was normal.

At the age of 10 months, he manifested prolonged daily clusters of head-nodding attacks and myoclonic jerks. After the age of 13 months, tonic and focal motor seizures also appeared and progressive developmental delay became apparent (at the age of 14 months Griffith's Mental Developmental Scales DQ was less than 50) with reduced alertness, poor social interactions, and feeding. Despite ataxia, the child could still walk unsupported at 18 months of age. No notable dismorphic features or other non-neurological signs and symptoms were observed. Ictal electroencephalogram (EEG) revealed generalized delta activity associated with diffuse epileptiform discharges. Interictal EEGs showed multifocal spikes and sharp waves. Brain magnetic resonance imaging and an extensive neurometabolic work-up were unremarkable.

Seizures were partially responsive to a combination of adrenocorticotropic hormone (ACTH) (two cycles), valproate, and clonazepam while other drugs (including phenobarbital, clobazam, pyridoxine, and vigabatrin) were ineffective.

On the last examination, at 23 months of age, the boy showed mild ataxia, immature language, hyperactive behavior, and poor eye contact.

A next generation sequencing panel including 95 genes causing early infantile epilepsies revealed a novel homozygous missense mutation in the *PRICKLE1* gene (NM_153026.2:c.820G>A, p.Ala274Thr). Both parents were heterozygous carriers of the mutation.

TABLE 1 Clinical, EEG, and neuroimaging findings of all patients from the literature carrying pathogenic variants in *PRICKLE1* gene

Patient sex	Variant	Age at the evaluation	Clinical features (age at onset/diagnosis)	Seizure types	Developmental delay	Intellectual disability	EEG	Brain MRI	Outcome	Response to antiepileptic treatment
1 (Bassuk et al., 2008) F	c.311G>A p.Arg104Gln (HOM)	18 yr	Ataxia (15 mo) Action tremor (4 yr) Coarse jerky hand movement (10 yr) Dysarthria (10 yr) Seizures (10 yr)	Atonic; progressive myoclonus epilepsy	No (not tested)	No (not tested)	Generalized or paroxysmal sharp/slow-wave activity	Normal	NR	Responsive to valproate
2 (Bassuk et al., 2008) F	c.311G>A p.Arg104Gln (HOM)	15 yr	Ataxia (15 mo) Action hand tremor (4 yr) Dysarthria (NR) Seizures (9 yr)	Atonic; progressive myoclonusepilepsy	No (not tested)	No (not tested)	Generalized or paroxysmal sharp/slow-wave activity	Normal	NR	Responsive to valproate
3 (Bassuk et al., 2008) F	c.311G>A p.Arg104Gln (HOM)	12 yr	Ataxia (15 mo) Action hand tremor (4 yr) Dysarthria (NR) Seizures (9 yr)	Atonic; progressive myoclonusepilepsy	No (not tested)	No (not tested)	Generalized or paroxysmal sharp/slow-wave activity	Normal	NR	Responsive to valproate
4 (Bassuk et al., 2008) M	c.311G>A p.Arg104Gln (HOM)	8 yr	Ataxia (15 mo) Hand tremor (3 yr) Dysarthria (NR) Seizures (8 yr)	Atonic; progressive myoclonusepilepsy	No (not tested)	No (not tested)	Generalized or paroxysmal sharp/slow-wave activity	Normal	NR	Partially responsive to valproate
5–12 (Bassuk et al., 2008) (5 M and 3F)	c.311G>A p.Arg104Gln (HOM)	NR	Ataxia (4–5 yr) Progressive myoclonus epilepsy (mean age: 7 yr)	Progressive myoclonusepilepsy	No (not tested)	No (not tested)	Not reported	Normal	NR	NR
13–20 (Bassuk et al., 2008) (4 M and 4F)	c.311G>A p.Arg104Gln (HOM)	17–37 yr	Ataxia (NR) Action and rest myoclonus (NR) Seizures (5–10 yr)	Myoclonic (5 pt) or tonic–clonic (1 pt) or both (2 pt); tonic–clonic (7 pt) and progressive myoclonus epilepsy	Yes (4 pt)	No or mild (not reported if tested)	Mild diffuse background slowing with generalized spike–wave or polyspike-wave discharges and photosensitivity	Normal	Wheelchair-bound (3 pt)	Responsive to valproate or topiramate
21 (Bassuk et al., 2008) M	c.311G>A p.Arg104Gln (HOM)	11 yr	Ataxia (4 yr) Dysarthria (4 yr) Seizures (9 yr) Upward gaze paresis, axonal neuropathy, decreased limb reflexes (NR)	Generalized tonic clonic; progressive myoclonic epilepsy	No (not tested)	Mild (not tested)	Slightly slow background with epileptiform discharges	Normal	Death	Partially responsive to valproate
22 (Bassuk et al., 2008) F	c.311G>A p.Arg104Gln (HOM)	9 yr	Ataxia (4 yr) Dysarthria (4 yr) Seizures (9 yr) Upward gaze paresis, axonal neuropathy, absent limb reflexes (NR)	Generalized tonic clonic; progressive myoclonic epilepsy	No (not tested)	No (not tested)	Bilateral, synchronous spike and wave or polyspike wave over the posterior regions	Normal	NR	Partially responsive to valproate
23 (Bassuk et al., 2008) F	c.311G>A p.Arg104Gln (HOM)	4 yr	Ataxia (3 yr) Dysarthria (4 yr) Seizures (9 yr) Upward gaze paresis, axonal neuropathy, absent limb reflexes (NR)	Progressive myoclonic epilepsy	No (not tested)	No (not tested)	Normal	NR	NR	NR

TABLE 1 (Continued)

Patient sex	Variant	Age at the evaluation	Clinical features (age at onset/diagnosis)	Seizure types	Developmental delay	Intellectual disability	EEG	Brain MRI	Outcome	Response to antiepileptic treatment
24 (Tao et al., 2011) M	C431G>A p.Arg144His (het)	NR	Seizures (NR)	Myoclonicseizures	NR	Mild (not tested)	Generalizedepileptic discharges	NR	NR	NR
25 (Tao et al., 2011) F	C1414T>C p.Tyr472His (het)	NR	Seizures (NR)	Juvenilemyoclonicepilepsy	NR	NR	NR	NR	NR	NR
26 (Bosoi et al., 2011) F	c.206 T>C p.Ile69Thr (het)	22 yr	Diastematomyeliatype II (NR)	NR	NR	NR	NR	NR	NR	NR
27 (Bosoi et al., 2011) M	c.241A>C p.Asn81His (het)	NR	Lumbosacralmyelomeningocele (NR)	NR	NR	NR	NR	NR	NR	NR
28 (Bosoi et al., 2011) NR	c.824C>T p.Thr275Met (het)	22 yr	Lumbosacral myelomeningocele, hydrocephalus, Chiari Type II malformation, and tethered cord (NR)	NR	NR	NR	NR	NR	NR	NR
29 (Bosoi et al., 2011) M	c.1648G>A p.Val550Met (het)	NR	Myelomeningocele (NR)	NR	NR	NR	NR	NR	NR	NR
30 (Bosoi et al., 2011) M	c.2044C>T p.Arg682Cys (het)	NR	Myelomeningocele (NR)	NR	NR	NR	NR	NR	NR	NR
31 (Bosoi et al., 2011) M	c.2216C>T p.Ser739Phe (het)	NR	Myelomeningocele (NR)	NR	NR	NR	NR	NR	NR	NR
32 (Bosoi et al., 2011) M	c. 2311G>A p.Asp771Asn (het)	NR	Caudalagenesis (NR)	NR	NR	NR	NR	NR	NR	NR
33 (Bassuk & Sherr, 2015) NR	c.427 T>G p.Ser143Ala (het)	Fetus of 19 weeks	Prenatal diagnosis	NR	NR	NR	NR	Agenesis of the corpus callosum, mild ventriculomegaly, polymicrogyria	NR	NR
34 (Todd & Bassuk, 2018) M	c0.1444G>A de novo	7 yr	Seizures (7 mo) Developmental delay (18 mo) Mild intellectual disability (6 yr) Autism spectrum disorder (6 yr)	Myoclonic seizures	Yes (not reported if tested)	Yes (not reported if tested)	Generalized spike and waves discharges	Normal	NR	NR
35 M Our case	c.820G>A p.Ala274Thr (HOM)	10 M	Epileptic encephalopathy (10 mo) Mild ataxia (18 mo)	Atonic, myoclonic, tonic, and focal motor seizures	No	Yes	Generalized delta activity associated with spikes/multiple spikes and sharp waves or generalized spike and waves discharges	Normal	NR	Partially responsive to ACTH, valproate, and clonazepam)

Note. F = female; M = male; HOM = homozygous; HET = heterozygous; NR = not reported; yr = years; mo = months; DQ = developmental quotient.

3 | DISCUSSION

Table 1 summarizes mutational data and clinical characteristics of the patients with *PRICKLE1*-related encephalopathy so far reported (Bassuk et al., 2008; Bassuk & Sherr, 2015; Bosoi et al., 2011; Tao et al., 2011; Todd & Bassuk, 2018). PME has been reported in 23 subjects with homozygous variants and in two patients with heterozygous variants (Table 1; Ehaideb et al., 2014; Paemka et al., 2015; Tao et al., 2011).

A positive neurocognitive outcome and a complete or partial responsiveness to valproate were reported in almost all cases (Table 1; Bassuk et al., 2008; Bassuk & Sherr, 2015; Bosoi et al., 2011; Tao et al., 2011; Todd & Bassuk, 2018). In some patients (patients 4, 7, and 8 in Table 1 and the case reported here) a minor efficacy of antiepileptic treatment was observed even if no specific phenotypic feature was highlighted as a reliable predictor for an optimal responsiveness (Bassuk et al., 2008; Bassuk & Sherr, 2015; Bosoi et al., 2011; Tao et al., 2011; Todd & Bassuk, 2018).

The patients so far reported presented a later onset of seizures (mean age higher than 4 years with the significant exception of patient 34 in Table 1 who was a 7-month-old male carrying a de novo mutation and presenting with myoclonic seizures) and a less severe epilepsy than our patient (Bassuk et al., 2008; Bassuk & Sherr, 2015; Bosoi et al., 2011; Tao et al., 2011; Todd & Bassuk, 2018).

Epilepsy with pleomorphic seizures and concomitant developmental arrest suggested the diagnosis of epileptic encephalopathy in our patient. Seizures-related developmental and cognitive impairment have not been mentioned as part of the *PRICKLE1*-related phenotypes even though a systematic neurodevelopmental evaluation has not been performed in the previously reported patients (Table 1; Bassuk et al., 2008; Bassuk & Sherr, 2015; Bosoi et al., 2011; Tao et al., 2011; Todd & Bassuk, 2018). Variants of *PRICKLE1* might contribute to epileptogenesis via various mechanisms such as: (a) impairment of calcium mediated signaling in different brain regions, especially the cortex, thalamus, and hippocampus; (b) impairment of microtubule-associated vesicle transport of neurotransmitters; and (c) dysregulation of neurites' outgrowth and neuronal connectivity (Bassuk et al., 2008; Ehaideb et al., 2014; Todd & Bassuk, 2018).The mutation c.820G>A was indicated as pathogenic by different in silico prediction softwares (Mutation Taster, Polyphen 2, and SIFT) and the Combined Annotation Dependent Depletion (CADD) score was of 31. Three individuals heterozygous for this mutation, none homozygous, were present in the GnomAD database (http://gnomad.broadinstitute.org/). Mutation Taster and Interpro analysis predicted loss of the third Lin11-Isi1-Mec3 (LIM) zinc binding domain of the protein. As a consequence of the p.Ala274Thr transition, the substitution of an alanine residue with threonine changes the polarized protein distribution that is required for planar cell polarity signaling. A similar effect was demonstrated in zebrafish for a mutation involving an adjacent residue (p.Thr275Met), which had been detected in a patient with neural tube defect and hydrocephalus but no epilepsy (Bosoi et al., 2011).

The role of *PRICKLE1* in different aspects of embryo neurodevelopment would suggest that cognitive and neurological functions can be impaired as a direct consequence of the defective protein, although severe epilepsy might have worsened the clinical picture (Bassuk et al., 2008; Bassuk & Sherr, 2015; Bosoi et al., 2011; Tao et al., 2011). Moreover, the alterations of neuronal signaling and networking cascades in which *PRICKLE1* is involved may result in dysfunctions of RE-1 silencing transcription factor or ubiquitin-specific peptidase 9 X-linked, which may as such contribute to the worsening of cognitive status (Bassuk et al., 2008; Paemka et al., 2015; Todd & Bassuk, 2018).

4 | CONCLUSIONS

This clinical report highlights the fact that in the context of an epileptic encephalopathy with developmental arrest, early onset severe PME-ataxia syndrome can be a *PRICKLE1*-associated phenotype.

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CONFLICT OF INTEREST

None.

AUTHORS CONTRIBUTION

Mario Mastrangelo coordinated the clinical follow-up of the reported patient, planned the realization of the article, wrote the first draft, and revised the manuscript; Manuela Tolve analyzed genetic data and revised the manuscript; Martina Martinelli and Sofia Pia di Noia contributed to the clinical follow-up of the patient, to the collection of data from the literature and to the revision of the manuscript; Elena Parrini performed and interpreted the molecular studies and reviewed the manuscript for clinical and genetic content; Vincenzo Leuzzi contributed to the clinical follow-up of the reported patient and edited the manuscript as senior author.

FINANCIAL DISCLOSURES

None of the authors have any disclosure to declare.

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