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Infantile epileptic spasm syndrome as a new NR2F1 gene phenotype

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Abstract

Introduction: NR2F1 pathogenetic variants are associated with the Bosch–Boonstra–Schaaf optic atrophy syndrome (BBSOAS). Recent studies indicate that BBSOAS patients not only have visual impairments but may also have developmental delays, hypotonia, thin corpus callosum and epileptic seizures. However, reports of BBSOAS occurrence along with infantile epileptic spasm syndrome (IESS) are rare.

Methods: Here, we report three cases involving children with IESS and BBSOAS caused by de novo NR2F1 pathogenetic variants and summarize the genotype, clinical characteristics, diagnosis and treatment of them.

Results: All three children experienced epileptic spasms and global developmental delays, with brain Magnetic Resonance Imaging (MRI) suggesting abnormalities (thinning of the corpus callosum or widened extracerebral spaces) and two of the children exhibiting abnormal visual evoked potentials.

Conclusions: Our findings indicate that new missense NR2F1 pathogenetic variants may lead to IESS with abnormal visual evoked potentials. Thus, clinicians should be aware of the Bosch–Boonstra–Schaaf optic atrophy syndrome and regular monitoring of the fundus, and the optic nerve is necessary during follow-up.

KEYWORDS
BBSOAS, infantile epileptic spasm syndrome, NR2F1

1 | INTRODUCTION

Infantile epileptic spasm syndrome (IESS), which includes West syndrome (Zuberi et al., 2022), affects about 20 out of 100,000 live births. IESS is characterized by epileptic spasms between the age of 1 month and 2 years (Demarest et al., 2022; Dimassi et al., 2016). Infants with IESS often have developmental delays and developmental stagnation or regression at the onset of epileptic spasms. Without prompt effective treatment, these effects can worsen, severely worsening the prognosis and the quality of life of the affected children. IESS

List of abbreviations: ACMG, American College of Medical Genetics and Genomics; ACTH, adrenocorticotropic hormone; BBSOAS, Bosch–Boonstra–Schaaf optic atrophy syndrome; brain MRI, brain Magnetic Resonance Imaging; DBD, DNA-binding domain; EEG, electroencephalogram; IESS, infantile epileptic spasm syndrome; LBD, ligand-binding domain; VEP, visual evoked potential.

often evolves into other types of epilepsy or syndromes, especially the Lennox–Gastaut syndrome and drug-resistant focal epilepsy (Calvo et al., 2020).

Between half and two thirds of IESS cases have structural brain abnormalities, and up to 41% of the cases are attributable to genetic factors, including trisomy 21 and pathogenetic variants in *ARX*, *CDKL5*, *STXBP1*, *IQSEC2*, *TSC1* and *TSC2* (Olson et al., 2019; Liu et al., 2018; Xian et al., 2022;Bernardo et al., 2019; Takeshita et al., 2020). Although metabolic and infectious factors rarely cause IESS, they are important contributors to its occurrence. Additionally, about a third of affected children have no identifiable causes, and genetic pathogenetic variants are thought to underlie such cases (Demarest et al., 2022).

NR2F1 is an orphan receptor belonging to the steroid/thyroid hormone receptor superfamily. It consists of a DNA-binding domain (DBD) formed by two zinc finger domains and a ligand-binding domain (LBD) with two highly conserved regions (Mehanovic et al., 2021). *NR2F1* encodes a transcription factor that plays a crucial role in neurogenesis, myelination, neural crest cell differentiation, and neocortical formation.

Recent studies have found an association between the *NR2F1* gene and Bosch–Boonstra–Schaaf optic atrophy syndrome (BBSOAS) (OMIM: 615722). Children with BBSOAS may also have epilepsy and may present with IESS (Gazdagh et al., 2022). Here, we summarize clinical data on three infants with *NR2F1* gene pathogenetic variants, who were treated at our hospital, and review previously published IESS cases resulting from *NR2F1* pathogenetic variants. We also discuss the clinical phenotypes of IESS, its treatment approaches, and the features of *NR2F1*-associated IESS and its potential treatments.

2 | METHODS

Three patients with confirmed *NR2F1* pathogenetic variants accompanied by developmental delay and epilepsy were enrolled from the First Medical Center of PLA General Hospital. Detailed clinical information was collected, including clinical manifestations, history of epilepsy, physical examination, treatment, EEG, and brain magnetic resonance imaging (MRI). Genomic DNA was extracted from the peripheral blood of the patients and their parents for trio whole-exome sequencing (Trio-WES), and each variant was interpreted according to the American College of Medical Genetics and Genomics (ACMG) guidelines. In accordance with the requirements of Research Ethics Board at First Medical Center of PLA General Hospital, informed consent was obtained from the patients' parents for participation in Trio-WES and subsequent Sanger sequencing.

3 | RESULTS

3.1 | Case presentation

3.1.1 | Case 1

A male child started to have epileptic spasms without any obvious cause at the age of 4 months, which were characterized by staring, clenching both fists and raising both upper limbs. The child was the firstborn and was delivered naturally at full term. The child's mother did not experience complications during pregnancy, but the child had a history of hypoxia during the perinatal period. The developmental delay was evident in the affected children prior to the onset of epileptic spasms and could roll over but not sit and with unstable head control at 7 months. The child's family did not have concerning medical history. The child did not have unique facial features, and their head circumference was 45 cm, and they exhibited normal muscle tone.

Blood lactate level was 2.37 mmol/L. EEG examination suggested severe arrhythmia, and one serial epileptic spasm was detected during the wake period. Brain MRI indicated a slightly thin corpus callosum (Figure 1a,b). Fundus examination revealed small optic discs. Visual evoked potential (VEP) examination revealed that the P100 wave latency was normal for both eyes. Blood and urine metabolic screening did not reveal any abnormalities. For genetic testing, the proband's peripheral blood was sequenced for two generations, and the proband's parents' peripheral blood was subjected to Sanger sequencing for verification. Trio whole exome sequencing showed that the child had a de novo *NR2F1* gene pathogenetic variant (c.257-258delinsTT, p.Cys86Phe) (NM_005654.6) but both parents had the wild type gene. Based on the ACMG guidelines, the variant was classified as likely pathogenic (PS2 + PM2 + PP3), related to BBSOAS.

The child was diagnosed with epilepsy at another hospital and was treated with oral prednisolone, which slightly relieved the epileptic spasms. Based on the child's medical history and examination results, we diagnosed the child with 'BBSOAS/IESS'. After ruling out medical contraindications, the child was treated with adrenocorticotropic hormone (ACTH) and magnesium sulphate, which relieved the epileptic spasms.

3.1.2 | Case 2

A male child presented with global development delay. At 4 months old, the child exhibited slightly poor visual tracking and did not respond to name calling but could

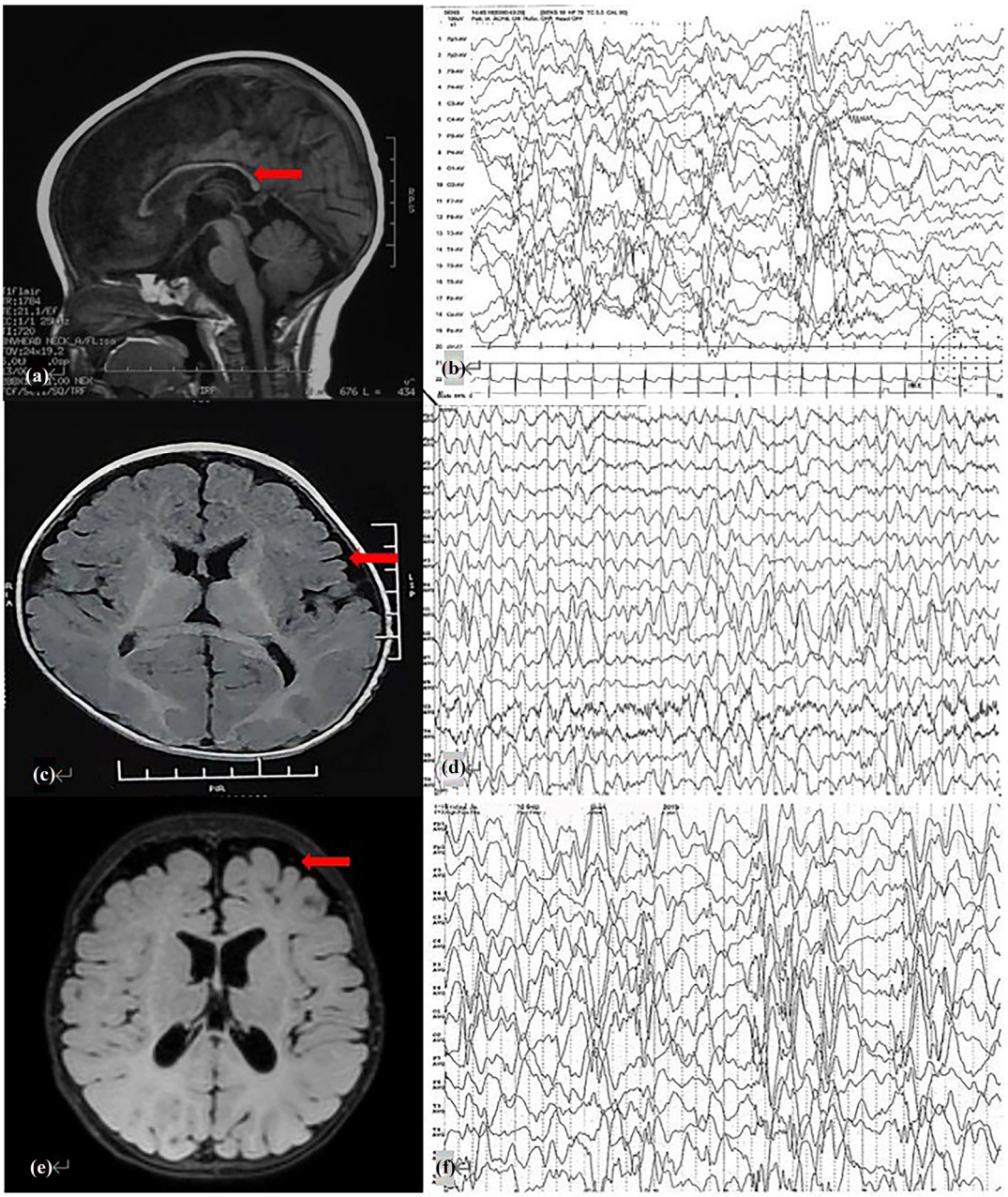

FIGURE 1 (a) Brain MRI examination of Case 1 shows thinning of the corpus callosum. (b) EEG examination during the seizure period in Case 1 shows high-amplitude disorganization. (c) Brain MRI examination of Case 2 shows widened extracerebral spaces. (d) EEG examination during the seizure period in Case 2 shows high-amplitude disorganization. (e) Brain MRI examination of Case 3 shows widened extracerebral spaces. (f) EEG examination during the seizure period in Case 3 shows high-amplitude disorganization.

track sounds and roll over. At 7 months old, the child started experiencing nodding and embracing-like epileptic spasms, mostly during wake–sleep transitions. The child was the firstborn and was born naturally at full term. In early pregnancy, the mother had taken medication to control the risk of miscarriage. The child had no history of perinatal hypoxia. At 9 months, the child could lift the head, roll over and track light and objects but could not grasp objects, say 'baba' or 'mama' or sit or stand independently. The child's maternal uncle had epilepsy. The child had no unique facial features but had a 3 × 2 cm café-au-lait spot on the left side of the chest. The child's anterior fontanelle was not closed, and his head circumference was 44.5 cm at 9 months. The muscle tone had increased.

SEEG examination suggested the following abnormal infantile patterns: (1) slow background activity, with highly arrhythmic patterns during sleep, and (2) serial epileptic spasms, mainly affecting the left parietal region. Interictal periods showed widespread slow spike–wave

complexes, predominantly in the posterior head region. Brain MRI suggested widened extra-axial spaces (Figure 1c,d). VEPs were bilaterally abnormal. Blood and urine metabolic screening did not identify abnormalities. Trio whole exome sequencing revealed a de novo *NR2F1* gene pathogenetic variant (c.403C > G p.R135G) (NM_005654.6). Based on the ACMG guidelines, the variant was classified as pathogenic (PS2 + PM1 + PM2 +PM5 +PP3), related to BBSOAS.

At a different hospital where the child had been treated earlier, the administration of oral levetiracetam, ACTH and intravenous immunoglobulin did not achieve satisfactory outcomes. The child was then treated with sodium valproate, and ACTH was replaced with oral prednisolone acetate, which reduced epileptic spasm intensity. After admission to our hospital, the child was diagnosed with 'BBSOAS/IESS' based on the medical history and examination results. After admission, the child developed a gastrointestinal infection and fever and was put on symptomatic treatment. The epileptic spasms improved after the fever had subsided.

3.1.3 | Case 3

A male child started having seizures at around 2 weeks old, which were characterized by raising the upper limbs, head shaking and staring, for about 2 s before resolving on their own. The seizures occurred once every 2 weeks and were not given much attention. At 3 months old, the child exhibited unstable head control and could not track light or objects. At 4 months old, the child started experiencing nodding and embracing-like serial seizures, mostly during drowsiness and wakefulness, which worsened gradually. The infant was the first child of unrelated, healthy parents with no family history of neurological disorders. He was born at term via spontaneous delivery. There were no significant complications during pregnancy or in the perinatal period. The child could track sounds but had poor visual tracking and could not lift the head. The child's family did not have a concerning medical history. The child did not have distinctive facial features, had a 2.5 cm × 2.5 cm lump in the left inguinal region and exhibited normal muscle tone.

The child's VEP examination results were abnormal, although brainstem auditory evoked potentials were normal. Brain MRI indicated widened extra-axial spaces, especially on the right temporal lobe. Video EEG examination revealed highly arrhythmic patterns and one serial seizure (Figure 1e,f). Blood and urine metabolic screening results were normal. Ultrasound examination indicated hydrocele in the left spermatic cord. Trio whole exome sequencing results revealed a de novo *NR2F1* gene pathogenetic variant (c.383G > A, p.Cys128Tyr) (NM_005654.6). Based on the ACMG guidelines, the variant was classified as likely pathogenic (PS2 + PM2 + PP3), related to BBSOAS.

The child was diagnosed with 'BBSOAS/IESS' and treatment with topiramate capsules, and an ACTH + magnesium sulphate intravenous drip did not significantly reduce the seizures. Follow-up video EEG examination revealed persistent atypically high arrhythmic patterns. Treatment with oral valproic acid and topiramate for 2 months did not control the epileptic spasms. Addition of a ketogenic diet did not achieve satisfactory outcomes and was discontinued after a month. Upon adding perampanel to existing oral medications (valproic acid and topiramate), the child developed fever after 2 weeks, and seizure episodes did not recur after the fever had subsided. After gradually withdrawing valproic acid and topiramate, perampanel was continued alone without any seizures.

3.2 | Literature review

A literature search done on the China National Knowledge Infrastructure (CNKI), Wanfang and PubMed databases using 'NR2F1' as the search term retrieved 16, 21 and 351 articles, respectively. After excluding irrelevant articles based on titles and content, 11 articles, which involved 13 cases of IESS associated with NR2F1, remained (Table 1) (Bertacchi et al., 2020; Chen et al., 2016; Demarest et al., 2022; Dimassi et al., 2016; Engels et al., 2009; Hino-Fukuyo, 2015, p. 1; Hino-Fukuyo, 2017; Kaiwar et al., 2017; Michaud et al., 2014; Rech et al., 2020).

All 13 cases involved pathogenetic variants within the NR2F1 DNA-binding domain (Figure 2). Two cases had insertion-deletions, one case had an unspecified pathogenetic variant and 10 had missense pathogenetic variants. Two cases described distinctive facial features. Eight cases revealed abnormalities upon brain MRI examination. Of these, one case had an unspecified description, five had thinning of the corpus callosum, one had optic nerve hypoplasia and one had asymmetry of the lateral ventricles. Visual examination of all 10 cases indicated varying degrees of impairment.

4 | DISCUSSION

Changes in NMDA and GABA receptors, as well as an increase in calcium conductance, are some of the possible pathophysiological mechanisms. However, new

TABLE 1 Genetic and clinical data of previously reported cases of Bosch–Boonstra–Schaaf optic atrophy syndrome (BBSOAS) combined with infantile epileptic encephalopathy with suppression-burst pattern (IESS), as well as the three cases reported in this article

No.	Sex	Age (y)	Facial features	Brain MRI	EEG	Ophthalmologic exam	Metabolic screening
1	NA	0.58	NA	Mild optic nerve hypoplasia	NA	NA	–
2	M	22.6	Dolichocephaly, midface hypoplasia, palpebral fissures, large protruding helix ears, bilateral skin tags on the posterior aspect of the ear lobes and retrognathia, large teeth	–	Left occipital onset seizure, hypsarrhythmia, generalized and multifocal spikes and sharp waves	+	–
3	NA	NA	NA	NA	NA	NA	NA
4	M	7	NA	Mild asymmetry of the lateral ventricles	Hypsarrhythmia and electroclinical spams	–	NA
5	F	23	Bilateral epicanthal folds, thin upper lip, smooth philtrum, micrognathia, enlarged naris	–	Hypsarrhythmia	+	–
6	F	2.961	NA	Thin corpus callosum	NA	+	NA
7	F	3.95	NA	–	NA	+	NA
8	F	4.67	NA	+	NA	+	NA
9	F	2.658	NA	–	NA	+	NA
10	F	1.4	NA	Thin corpus callosum;	NA	+	NA
11	F	7.31	NA	Thin corpus callosum	NA	+	NA
12	F	6.79	NA	Thin corpus callosum	NA	+	NA
13	F	6	NA	Thin corpus callosum	NA	+	NA
14	M	0.58	–	Thin corpus callosum	Hypsarrhythmia	+	–
15	M	0.75	–	Extracerebral widening	Hypsarrhythmia	+	–
16	M	0.58	–	–	Hypsarrhythmia	+	–

No.	DNA change	Protein change	Inheritance	Domain	Medication	Reference
1	c.329 T > G	p.F110C	De novo	Missense in DBD	ACTH	35830182
2	c.257G > T	p.C86F	De novo	Missense in DBD	ACTH	28963436
3	c403C > A	p.R135S	De novo	NA	NA	24781210
4	c.328_330delTTC	p.F110del	De novo	In-frame indel in DBD	NA	26138355
5	c.403C > T	p.R135C	De novo	Missense in DBD	ACTH VPA CZP	25877686

(Continues)

TABLE 1 (Continued)

No.	DNA change	Protein change	Inheritance	Domain	Medication	Reference
6	c.256 T > C	p.C86R	De novo	Missense in DBD	NA	32275123
7	c.262G > A	p.V88M	De novo	Missense in DBD	NA	32275123
8	c.284G > T	p.G95V	NA	Missense in DBD	NA	32275123
9	c.365G > C	p.C122S	NA	Missense in DBD	NA	32275123
10	c.425G > A	p.R142H	De novo	Missense in DBD	NA	32484994
11	c.403C > A	p.R135S	De novo	Missense in DBD	NA	26986877
12	c.425G > T	p.R142L	De novo	Missense in DBD	NA	26986877
13	c.328_330delTTC	p.F110del	De novo	In-frame indel in DBD	NA	26986877
14	c.257-258delinsTT	p.C86F	De novo	In-frame indel in DBD	ACTH, VGB	This report
15	c.403C > G	p.R135G	De novo	Missense in DBD	ACTH, VPA + LEV	This report
16	c.383G > A	p.C128Y	De novo	Missense in DBD	ACTH, TPM + VGB, Perampanel	This report

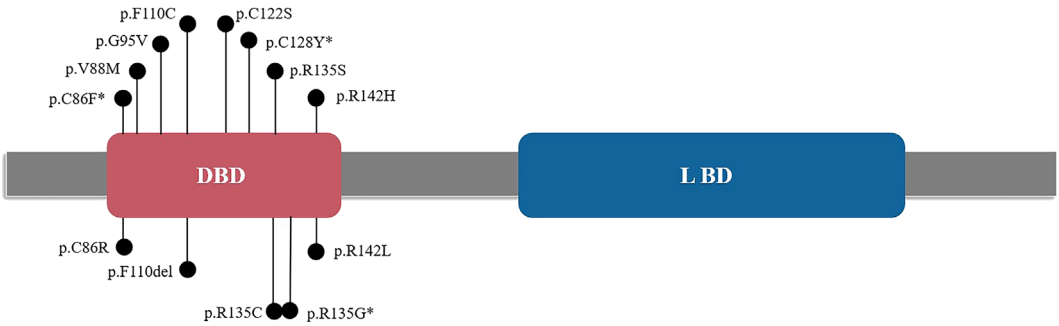

FIGURE 2 Schematic representation of the NR2F1 gene mutations reported in the Bosch–Boonstra–Schaaf optic atrophy syndrome (BBSOAS) with infantile epileptic encephalopathy with suppression-burst pattern (IESS). *Mutation sites reported in this article

therapeutic approaches that can modify the underlying neurobiological processes have not yet been identified (Specchio, Pietrafuse, Ferretti, et al., 2020). NR2F1, also known as COUP-TFI, is a member of the chicken ovalbumin upstream promoter transcription factors family, which encode a conserved nuclear receptor protein involved in transcriptional regulation (del Pino et al., 2020). This gene was first discovered by Qiu et al. (1995) and located on human chromosome 5q14. NR2F1 contains a DBD made of 76 amino acids (18% of the protein), and an LBD made of 227 amino acids (58% of the protein). The remaining 120 amino acids (28%) encode nonspecific regions (Billiet et al., 2022). Although the LBD is the longest, most pathogenic pathogenetic variants affect the DBD.

Studies in *NR2F1* knockout mice indicate that NR2F1 is important for axon, myelin sheath and cortical development. Recent findings have revealed that in addition to visual impairments, BBSOAS patients also have developmental disorders, hypotonia, thinning of the corpus callosum, autism spectrum disorders, epileptic seizures and hearing impairments (Bertacchi et al., 2022; Billiet et al., 2022; Chen et al., 2016; Kocaaga et al., 2022).

Previous findings indicated that epileptic seizures are common in BBSOAS patients and that most (25 out of 40 cases) are associated with *NR2F1* gene pathogenetic variants (Ge et al., 2020). IESS is a type of seizure that appears to be more common in BBSOAS cases. Here, we describe three patients with *NR2F1* gene pathogenetic variants, who presented with developmental delay, optic nerve atrophy and seizures. Because EEG examination showed that the three patients had varying degrees of high-amplitude dysrhythmia, they were diagnosed as having BBSOAS with IESS. Brain MRI examination found that one patient had thinning of the corpus callosum, one had widened extracerebral spaces and the other had a normal brain MRI. In previously reported cases of BBSOAS with IESS, brain MRI examination showed that

out of 13 patients, 5 had thinning of the corpus callosum, 1 had optic nerve hypoplasia, 1 had asymmetry of the lateral ventricles and 1 had unspecified abnormalities. These findings suggest that cases of BBSOAS with IESS often present with structural abnormalities. Based on brain MRI examination, previous findings have indicated that 53% of BBSOAS patients have corpus callosum abnormalities or hypoplasia. Animal experiments have confirmed that NR2F1 is involved in the development of the corpus callosum, hippocampal commissure and thalamic cortical projections, indicating the possibility of abnormal neuronal guidance and fibre bundle formation in BBSOAS patients (Chen et al., 2016; Tocco et al., 2021).

Research has found that insertions–deletions and missense pathogenetic variants in the DBD are more likely to result in severe phenotypes, such as epileptic seizures, loss of language function and impaired independent walking (Riikonen, 2020). Previous studies and the cases presented in this report indicate that amino acid changes caused by gene pathogenetic variants in patients with IESS and BBSOAS predominantly occur within the DBD. Most patients with BBSOAS and IESS also show optic atrophy and/or optic nerve hypoplasia (13 out of 16 cases), which is consistent with the previous conclusion that pathogenic variants mainly affect the DBD.

Currently, the first-line drugs for the treatment of IESS include three medications: Vigabatrin, ACTH and oral steroids. However, the treatment outcomes for IESS have been unsatisfactory thus far (Specchio, Pietrafuse, Ferretti, et al., 2020). The average short-term treatment efficacy of first-line therapy ranges from 36% to 61% (Chourasia et al., 2022). When combination therapy is used, the efficacy may be higher (around 72%), but ultimately only about one third of patients achieve long-term seizure freedom (Chourasia et al., 2022; Riikonen, 2020).

IESS is diagnosed based on age of onset, clinical presentation and electroencephalographic features. It has over 200 etiologies, but overall, the effectiveness of medication treatment is poorer for genetically related IESS. In this study, two out of three patients did not achieve seizure freedom after ACTH administration, which is consistent with previous literature. However, what has not been previously reported is that these two patients experienced a dramatic cessation of epileptic spasms and no recurrence after a febrile episode. Previous research has indicated the association of NR2F1 with immunological processes (Liang et al., 2022). We speculate that the immune regulatory changes in the body following an infection and fever may indirectly contribute to the control of spasms in these two patients.

5 | CONCLUSIONS

In conclusion, the three cases reported in this study and our literature review highlight the need to consider the possibility of *NR2F1* gene pathogenetic variants in infants with IESS. When optic nerve atrophy presents with IESS, the possibility of BBSOAS should be considered. During follow-up, regular electroencephalogram monitoring, as well as fundus and optic nerve examinations, is necessary.

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We thank the child and his family for cooperation.

DATA AVAILABILITY STATEMENT

To safeguard patient privacy, the Ethics Committee of the First Medical Center of the PLA General Hospital has restricted access to the original sequencing data used to support the conclusions of this study. Researchers who meet the criteria for access to confidential data may obtain data from the corresponding author, Guang Yang (e-mail: yangg301@126.com).

ETHICS STATEMENT

Informed consent for clinical studies and molecular genetic analysis was obtained from their parents. Ethical approval for the study was granted by the Ethics Committee of the First Medical Center of the PLA General Hospital. The written-informed consent for publication of clinical details and/or clinical images was obtained from the proband's parents.

CONFLICT OF INTEREST

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. We confirm that we have read the journal's stance on ethical publication issues and affirm that this report adheres to those guidelines.

AUTHORSHIP STATEMENT

Yan Liang wrote the first draft. Guang Yang performed the data acquisition. Lin Wan performed data analysis. Yan Liang and Yang Guang contributed to the conception and design of the study. All authors helped to revise the manuscript regarding crucial intellectual content and approved the final version for publication.

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