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Epileptic Disorders

ORIGINAL ARTICLE

Functional (dissociative) seizures in PCDH19-clustering epilepsy: Clinical characteristics and diagnostic challenges

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Abstract

Objective: Functional (dissociative) seizures (FDS) are increasingly recognized among individuals with epilepsy, intellectual disability (ID), and psychiatric disorders, but their occurrence in PCDH19-clustering epilepsy (CE) has not been systematically described. We aimed to characterize the clinical features, diagnostic pathways, and management of FDS in individuals with genetically confirmed PCDH19-CE.

Methods: We conducted a multicenter retrospective study across six tertiary European Epilepsy Centers. Individuals with genetically confirmed PCDH19-CE and a diagnosis of FDS according to the International League Against Epilepsy (ILAE) criteria were included. Demographic, clinical, neuropsychiatric,

neurophysiological, neuroimaging, and treatment-related data were collected from medical records.

Results: Among 27 individuals with genetically confirmed PCDH19-CE, eight (29.6%) experienced FDS. The median age at FDS onset was 16 years. Most affected individuals had some degree of ID, and nearly all exhibited psychiatric comorbidities, particularly behavioral dysregulation and autism spectrum disorder. Six patients were initially misdiagnosed with epileptic seizures, resulting in unnecessary antiseizure medication (ASM) escalation and hospitalizations. Following FDS diagnosis, ASM reduction or modification was undertaken in three patients. Multidisciplinary management involving psychiatry, psychology, and occupational therapy was implemented in most cases, and all treated individuals demonstrated clinical improvement.

Significance: FDS may constitute an important comorbidity in individuals with PCDH19-CE, particularly during adolescence and adulthood. Early recognition of FDS may prevent unnecessary diagnostic and therapeutic interventions, reduce inappropriate ASM escalation, and improve patient outcomes through timely multidisciplinary care.

KEYWORDS

functional seizures, neuropsychiatric comorbidities, PCDH19-clustering epilepsy

1 | INTRODUCTION

Pathogenic variants in *PCDH19*, encoding protocadherin-19, cause a rare and distinctive X-linked developmental and epileptic encephalopathy. It is classically characterized by infantile-onset, treatment-resistant seizures often presenting with febrile seizure clusters and variably associated with intellectual disability (ID) and a range of psychiatric/behavioral disorders including autism spectrum disorder (ASD).[1–3]

Functional (dissociative, non-epileptic) seizures (FDS) are commonly encountered in individuals with epilepsy and, when misdiagnosed, represent a major source of diagnostic error. Such misdiagnosis often leads to unnecessary escalation of antiseizure medications (ASM), diagnostic/therapeutic procedures, repeated emergency department visits, and a marked reduction in quality of life for both patients and their families. Early and accurate identification—through careful history taking, semiological analysis, opportunistic bystander home video, and video-EEG monitoring—together with clear communication, are essential to prevent overtreatment and to guide patients toward appropriate multidisciplinary management.[4–7]

Patients with *PCDH19*-clustering epilepsy (*PCDH19-CE*) accumulate multiple recognized risk factors for FDS, including early-onset epileptic seizures, high-burden epilepsy with frequent emergency encounters during clusters, female predominance, co-occurring ASD and ID, emotional dysregulation, and exposure to intensive ASM polytherapy. However, the clinical features and diagnostic challenges associated with FDS in PCDH19-CE remain poorly characterized, creating a diagnostic blind spot that may foster misclassification of events as epileptic, unnecessary drug treatment escalation, missed opportunities to implement multidisciplinary approaches for FDS, and avoidable loss of quality of life.

2 | MATERIALS AND METHODS

This was a multicenter, retrospective, descriptive study conducted across six tertiary European Epilepsy Centers with expertise in the diagnosis and management of genetic epilepsies.

Inclusion criteria were (a) a confirmed diagnosis of *PCDH19-CE*, established according to the International League Against Epilepsy (ILAE) classification[1] and supported by genetic confirmation of a pathogenic or likely pathogenic variant in the *PCDH19* gene according to the American College of Medical Genetics and Genomics (ACMG); (b) FDS "documented" or "clinically established" diagnosis according to ILAE criteria.[8] "Documented" FDS

was defined as confirmation based on the clinical history together with video-EEG recording of a typical event without concomitant epileptiform activity. "Clinically established" FDS was defined as the diagnosis made by an experienced epileptologist based on the clinical history, direct observation of habitual events, and a routine EEG showing no epileptiform activity in the absence of video-EEG confirmation.

Demographic, clinical, genetic, neurophysiological, and neuroimaging data were collected from patient records at each participating center and entered into a pseudonymized database. Participant recruitment occurred between March and October 2025, and written informed consent was obtained from all individuals or their legal guardians, and all procedures were performed in accordance with the principles of the Declaration of Helsinki.

Key points

- Functional (dissociative) seizures (FDS) were identified in individuals with PCDH19-clustering epilepsy (PCDH19-CE), with onset predominantly during adolescence and adulthood, suggesting that FDS may represent an underrecognized comorbidity.
- FDS showed marked clinical and semiological heterogeneity and were frequently initially misdiagnosed as epileptic seizures, highlighting diagnostic challenges in this population.
- The observed occurrence of FDS may reflect the accumulation of established risk factors, including intellectual disability, psychiatric comorbidities, psychosocial adversity, and chronic epilepsy, rather than a syndrome-specific feature of PCDH19-CE.
- Recognition of FDS may help avoid unnecessary antiseizure medication escalation and facilitate appropriate multidisciplinary management.
- Prospective studies with systematic FDS assessment are needed to determine the frequency of FDS in PCDH19-CE and whether their occurrence differs from that expected in other genetic epilepsies.

3 | RESULTS

Twenty-seven patients with genetically confirmed *PCDH19-CE* were identified across six tertiary epilepsy centers, of whom eight females fulfilled the inclusion criteria (29.6%), with a median age of 20 years (IQR 18.5). Of these, five were adults (median age 33 years, range 18–45 years) and three were younger than 18 years (median 8 years, range 6–17 years). Four of the eight individuals carried a de novo *PCDH19* variant, while three harbored inherited variants. Inheritance status was unknown in one. Information regarding maternal versus paternal inheritance was not collected. The clinical and genetic features, along with EEG and neuroimaging findings, are identified in Table 1 for each patient.

3.1 | Neuropsychological and psychiatric comorbidities

Most patients ($n = 7$) had some degree of ID, ranging from borderline to severe and four had ASD. Psychiatric diagnoses were categorized in accordance with DSM-5-TR,[9] comprising impulse control disorders ($n = 3$), disruptive behavior disorders ($n = 3$), anxiety or fear-related disorders ($n = 2$), and obsessive-compulsive or related disorders ($n = 1$). A history of adversity was verified in four patients, which included neglect, physical abuse, and bullying.

3.2 | Epileptic and functional seizures

All eight patients had epilepsy, with a median age at seizure onset of 10 months (IQR 1.5). Bilateral tonic-clonic seizures (BTC) were the most common seizure type, and patients presented with drug-resistant epilepsy from seizure onset.

Table 2 represents clinical data regarding FDS. Median age at onset of FDS was 16 years (IQR 9). At FDS onset, six patients had drug-resistant epilepsy and only two had drug-responsive epilepsy.

FDS were predominantly motor in four patients, non-motor in one, and three patients exhibited both motor and non-motor phenotypes. Clinical descriptions of FDS were variable, including within the same individual, with different episodes showing distinct semiological features rather than a stereotyped pattern, which are detailed in Table 2. The overall median duration of FDS was 30 min (IQR 28.5), 6 min for non-motor events (IQR 17.5), and 30 min for motor events (IQR 60). Motor FDS showed marked semiological heterogeneity and were accompanied by crying in three patients. The most common motor manifestation was bilateral asynchronous jerking, whereas the most common non-motor manifestation was an absent verbal response with a controlled fall.

Figure S1 illustrates age of onset for both epilepsy and FDS for each patient. The median time since FDS onset until diagnosis was 4.5 months (IQR 44.5). Six patients were initially misdiagnosed with epileptic seizures,

TABLE 1 Demographics, clinical, genetic, MRI, and EEG findings in the included PCDH19-CE patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Current age (years)	6	17	22	34	33	8	45	18
Sex	Female	Female	Female	Female	Female	Female	Female	Female
Disability (mRankin scale)	3	3	1	1	4	0	2	1
Living context	Lives with relatives	Lives with relatives	Lives with relatives	Lives with relatives	Institution	Lives with relatives	Institution	Lives with relatives
History of adversity	No	Yes	No	Yes	No	Yes	Yes	No
Intellectual disability	Mild	Moderate	Borderline	Mild	Severe	Borderline	Normal	Mild
Comorbidities	ADHD, impulse control disorder	Psychotic symptoms, ADHD, disruptive behavior disorders, impulse control disorder	ASD, obsessive-compulsive disorder	ASD, ADHD, disruptive behavior disorder, anxiety	Disruptive behavior disorder	Anxiety	ASD, impulse control disorder	ASD
Variant (DNA level)	c.1649_1650insCA	c.371A>G	c.1639G>C	c.1091dup	c.2302_2303delTC	c.1471C>T	c.918C>A	c.2452C>T
Variant (Protein level)	p.(p.Val551Argfs*19)	p.Asp124Gly	p.Ala547Pro	p.Tyr366Leufs*10	p.Ser768Leufs*15	p.(Gln491*)	p.Tyr306*	p.(Gln818*)
Inheritance	De novo	De novo	De novo	Inherited	Unknown	Inherited	Inherited	De novo
Age at epilepsy onset (months)	8	10	60	7	11	10	10	9
Seizure type (all)	BTC; focal	BTC	Focal	BTC	BTC	Focal	BTC; focal	Absence; Focal; BTC; myoclonic
Current main seizure type	BTC	BTC	Focal	BTC	BTC	Focal	BTC	BTC
Epileptic seizure frequency at onset	Every 3 months	Every 3 months	Multiple daily	Monthly	Multiple daily	Monthly	Less than annually	Monthly
Current epileptic seizure frequency	Every 6 months	Less than annually	Every 6 months	Every 3 months	Multiple daily	Monthly	Less than annually	Every 6 months
Maximum seizure-free period (months)	12	144	96	71	0	24	36	18
EEG findings	Slow background	Normal	Normal	Normal background and focal EA	Slow background generalized EA, multifocal discharges	Normal	Normal background and generalized EA	Normal
Brain MRI findings	Normal	Right MTS	Normal	Normal	Normal	Unknown	Normal	Normal
Number of previously used ASM	8	3	3	8	16	2	2	7

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; ASM, antiseizure medication; BTC, bilateral tonic–clonic; EA, epileptiform activity; EEG, electroencephalogram; MRI, magnetic resonance imaging; MTS, Mesial Temporal Sclerosis.

TABLE 2 Clinical characteristics of functional (dissociative) seizures (FDS).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age at FDS onset (years)	6	15	21	17	20	8	20	12
Epilepsy at FDS onset	Drug Resistant	Drug Resistant	Drug-responsive	Drug Resistant	Drug Resistant	Drug Resistant	Drug-responsive	Drug Resistant
ASM at FDS onset	VPA; LEV; FFA	None	LEV	CLB; TPM; CBZ	OXC; CLB	VPA; LEV; CLB	ESL; CLB	LEV; CLB; ZNS
FDS type	Motor and non-motor	Motor	Motor and non-motor	Motor	Motor	Motor	Motor and non-motor	Non-motor
FDS description	No verbal response, controlled fall, right hand tremor	Bilateral asynchronous limb jerking; isolated bilateral eye blinking	Prodromal dizziness and headache which could be followed by clusters of eye blinking; subjective sensation of "being in a movie" accompanied by blurred vision	Bilateral asynchronous limb jerking	Bilateral asynchronous upper-limb jerking	Hypermotor behaviors, characterized by pelvic thrusting and active resistance to eye opening	Hypermotor behaviors characterized by pelvic thrusting and active resistance to eye opening; No verbal response, controlled fall	"Lost" gaze, and no verbal response
Current FDS frequency	Weekly	Weekly	Monthly	Monthly	Multiple daily	Weekly	Less than annually	Weekly
ILAE FDS diagnostic criteria (8)	Documented	Documented	Documented	Documented	Documented	Documented	Clinically established	Documented
FDS diagnosis	Anamnesis; Home video recordings; Video-EEG with recorded FDS	Anamnesis; Home video recordings; Video-EEG with recorded FDS	Anamnesis; Video-EEG with recorded FDS	Video-EEG with recorded FDS	Video-EEG with recorded FDS	Anamnesis; Witnessed FS at clinical appointment; Video-EEG with recorded FS	Anamnesis; Home video recordings; Routine EEG (<1 h)	Anamnesis; Video-EEG with recorded FS
Misdiagnosis of FDS	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Time since FDS onset until diagnosis (months)	2	12	7	149	Unknown	2	Unknown	1
FDS mistakenly treated with ASM	No	Yes	Yes	Yes	Yes	Yes	No	Yes
FDS diagnosis led to treatment change	No	No	Yes	Yes	No	Yes	No	No
Multidisciplinary approach for FDS treatment	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Improvement after multidisciplinary approach	Yes	Yes	Yes	Yes	N/A	Yes	N/A	Yes

Abbreviations: ASM, antiseizure medication; CBZ, carbamazepine; CLB, clobazam; EEG, electroencephalogram; ESL, eslicarbazepine; FDS, functional seizures; FFA, fenfluramine; LEV, levetiracetam; OXC, oxcarbazepine; TPM, topiramate; VEEG, Video-electroencephalogram; VPA, valproic acid; ZNS, zonisamide.

leading to overtreatment with ASM and unnecessary hospitalizations.

Following correct FDS diagnosis, drug treatment modifications were implemented in three patients, which included a change or decrease of ASM. A multidisciplinary management approach was adopted in six cases, involving psychology, psychiatry, and in one case, occupational therapy. All patients treated with a multidisciplinary approach showed clinical improvement, determined by a reduction >50% in FDS frequency and a reduction >50% in emergency department visits.

4 | DISCUSSION

In this multicenter series, a subgroup of children and adults, approximately 30% were identified as having FDS. Although this proportion may not represent the broader *PCDH19-CE* population due to referral and selection biases inherent to tertiary centers, it suggests that FDS may represent a frequent clinical manifestation in this group. This observation is clinically relevant, as individuals with *PCDH19*-CE frequently present with drug-resistant epilepsy and represent a particularly vulnerable population at risk of overtreatment and iatrogenic complications. The estimated prevalence of functional seizures among individuals with epilepsy and ID likely ranges between 5% and 20%, with higher rates reported in tertiary care settings and in adolescents and adults, which could explain the observed frequency of FDS in our cohort of patients with PCDH19-CE.[10–12]

Aligned with previous data in epilepsy and ID, individuals with *PCDH19-CE* have several characteristics that have previously been associated with FDS, due to a combination of neurobiological and psychosocial factors. A recent study was the first to look at the contribution of common genetic variants to the presentation of FDS; however, with limitations regarding X chromosome data analysis[13] In our cohort, most patients (seven) had ID and all had psychiatric comorbidities, supporting the view that the coexistence of these established risk factors may contribute to FDS susceptibility in this population.[4,5,14]

Neuroimaging studies have demonstrated abnormalities involving limbic and related brain networks in PCDH19-CE,[3,4,13] while alterations in similar networks have also been described in FDS[15–21] Although these observations raise the possibility of partially overlapping neurobiological mechanisms, our data do not address pathophysiology directly, and any shared limbic-network substrate remains speculative. Further mechanistic studies are required to determine whether these findings are biologically relevant to FDS susceptibility in PCDH19-CE. Four patients in our cohort were treated with levetiracetam; although this ASM is associated with psychiatric adverse effects, current evidence does not support a causal relationship between levetiracetam use and FDS.[22–24]

In our cohort, the median age at FDS onset was 16 years, with most cases occurring during adolescence or early adulthood. These results could suggest that adolescence and early adulthood may constitute a period of increased vulnerability for the emergence of FDS in individuals with *PCDH19-CE*, many years after the epilepsy onset. Notably, in the general population, adolescence is recognized as a particularly vulnerable neurodevelopmental stage for the onset of psychiatric and functional neurological disorders, reinforcing the concept of a critical window of increased susceptibility for FDS emergence in individuals with PCDH19-CE.[25,26]

Following the diagnosis of FDS, treatment adjustments were implemented in three patients, including modification or reduction of ASM[24,25] These findings emphasize the clinical value of recognizing FDS, allowing optimization of antiseizure therapy and avoidance of unnecessary diagnostic and therapeutic interventions.[27,28]

In this condition, several clinical features should raise suspicion for FDS. A key discriminator is the atypically prolonged duration of events, as seen in our cohort. Furthermore, specific semiological signs, such as pelvic thrusting, active resistance to eye opening, and ictal crying, should be carefully noted. The lack of stereotypy is a critical red flag: FDS episodes were characterized by marked semiological heterogeneity and generally occurred outside the context of typical epileptic seizure clusters. These findings, combined with a high event frequency, paradoxical worsening after ASM dose escalations, and normal video-EEG during the episodes, mandate a thorough evaluation for FDS. Table S1 represents the practical differences observed both in FDS and epileptic seizures in *PCDH19*-CE.

A multidisciplinary approach involving psychology, psychiatry, and occupational therapy was adopted in most patients, and all showed clinical improvement. These findings reinforce the importance of coordinated multidisciplinary care following recognition of FDS.[7,29,30]

Whether FDS are disproportionately frequent in PCDH19-CE because of the accumulation of established risk factors or reflect a syndrome-specific susceptibility remains unknown. Comparative studies across genetic epilepsies are needed to clarify this question. Beyond neurodevelopmental vulnerability, childhood psychosocial adversity is disproportionately prevalent among individuals with ID and may amplify risk for FDS. In our series, four patients were reported to present significant adversity in addition to other risk factors. This aligns with the evidence that individuals with ID are significantly more likely than the general population to experience adverse life events.[11,12]

This study has several limitations. Its retrospective, descriptive design is vulnerable to selection and information biases and limits causal inference, and the small sample constrains generalizability. Patients come from epilepsy centers representing an inherent referral bias and, although participating centers and epileptologists have substantial expertise, identification of FDS was not uniformly confirmed with video-EEG. Finally, variability in clinical management and follow-up across centers may have influenced observed outcomes. Given the retrospective design, referral patterns, and absence of systematic screening for FDS across the broader PCDH19-CE population, the frequency of FDS in this condition cannot be determined from our data.

Despite these limitations, the study offers novel insight into a relevant and potentially under-recognized manifestation within the *PCDH19-CE* spectrum and underscores the need for multicenter, prospective investigations using standardized diagnostic criteria, protocolized video-EEG confirmation, and harmonized therapeutic and outcome assessments.

5 | CONCLUSION

This multicenter series describes FDS in individuals with genetically confirmed PCDH19-CE and highlights the clinical and diagnostic challenges associated with their recognition. FDS occurred predominantly during adolescence and adulthood and were frequently initially misdiagnosed as epileptic seizures. This association could reflect a multifactorial interplay between intrinsic neurobiological vulnerability, potentially involving limbic network dysfunction, and co-occurring psychosocial factors. These findings support the need for awareness of FDS in individuals with PCDH19-CE and careful diagnostic assessment to avoid unnecessary treatment escalation and facilitate appropriate multidisciplinary management.

AUTHOR CONTRIBUTIONS

Rita Cagigal, Victor Gomez-Mayordomo, Andrea Garcia-Ortega, Kette Valente, Rikke S. Møller, and Ángel Aledo-Serrano contributed to the conception and design of the study. Javier Peña-Ceballos, Patrick B. Moloney, Elena González-Alguacil, Nuria Lamagrande, Ethan Tennant, Maria Jesus Martínez-González, Radu-Ștefan Perjoc, Oana-Aurelia Vladâcenco, Rhys H. Thomas, Victor Soto-Insuga, Norman Delanty, and Ángel Aledo-Serrano contributed to data collection. Rita Cagigal and Ángel Aledo-Serrano contributed to the analysis and interpretation of the results and drafting of the manuscript. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Javier Peña-Ceballos has received speaker fees and travel support from Angelini Pharma, Jazz Pharmaceuticals, and LivaNova. Patrick B. Moloney has received speaker fees and/or travel support from Angelini Pharma, UCB Pharma, and Jazz Pharmaceuticals. Norman Delanty has received consultancy and speaker fees from Actio Biosciences, Angelini Pharma, Eisai, LivaNova, Neuraxpharm, UNEEG Medical, and Jazz Pharmaceuticals. Victor Soto-Insuga has received honoraria for advisory, educational, and research activities from Angelini Pharma, UCB Pharma, Jazz Pharmaceuticals, Eisai, and Rubio. Ángel Aledo-Serrano has received speaker and advisory fees from Jazz Pharmaceuticals, Praxis Medicines, UCB Pharma, Angelini Pharma, Biocodex, and Lundbeck. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PATIENT CONSENT

Written informed consent was obtained from the patients for publication of the clinical information included in this manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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