Epilepsy & Behavior 101 (2019) 106539

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

The role of PCDH19 in refractory status epilepticus

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ARTICLE INFO

Article history:
Received 27 August 2019
Accepted 3 September 2019
Available online 31 October 2019

Keywords:
Genetic epilepsy
PCDH19
Status epilepticus
Developmental and epileptic encephalopathy
Prevalence

ABSTRACT

PCDH19-Girls Clustering Epilepsy (GCE) is an epileptic syndrome with infantile onset, characterized by clustered and fever-induced seizures, often associated with intellectual disability (ID) and autistic features. Seizures clusters could progress into status epilepticus (SE) with different semiology, both convulsive and nonconvulsive SE (NCSE), and often refractory to conventional antiepileptic drugs. We reviewed literature on PCDH19-GCE, in order to define prevalence, semiology, treatments, and outcome of SE. We conducted a comprehensive review of the PCDH19-GCE literature on the public databases PubMed and EMBASE from January 2008 to July 2019. An overall number of 59 full-text articles were selected, retrieved, and assessed for eligibility.

We collected 269 cases with PCDH19-GCE, in 85 of them, a history of SE was reported. Prevalence of SE in all selected series of PCDH19-GCE series is 31.5%. Data on SE were fully exhaustive in 21 cases. There was no gender difference in SE occurrence. Median age at first SE occurrence was 12 months (6 months–11 years). Semiology of SE was reported in 17 cases: it was convulsive in 15 and nonconvulsive in 2. Status epilepticus was refractory in 15 out of 21 cases (71.4%). Benzodiazepine was the most commonly used drug for SE. Alternative treatments with steroids and ketogenic diet were reported as well. We found a high prevalence of ID and autism (19 out of 21 patients, 90%).

Despite the relatively high frequency of SE in those patients, there are few specific descriptions of the semiology, EEG pattern, and treatment approach. We strongly believe that a multicenter study looking specifically at SE characteristics might improve the knowledge and consequently the overall outcome.

This article is part of the Special Issue "Proceedings of the 7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures".

1. Introduction

PCDH19-Girls Clustering Epilepsy (GCE) is an X-linked disorder caused by *PCDH19* gene variants. Epilepsy onset is around the first year of life and is characterized mostly by clustered and fever-induced seizures. Intellectual disability (ID) and psychiatric disturbances are reported in about two-thirds of cases, and the severity of the phenotype seems to be correlated with the age of epilepsy onset [1,2]. Although *PCDH19* gene is located on Xq22, this condition has an unusual X-linked mode of inheritance sparing transmitting males who are affected only when somatic mosaicism for the *PCDH19* genetic variant occurs [3–6]. *PCDH19* gene is one of the most frequently mutated genes in epilepsy following *SCN1A* [4,7].

Focal seizures mostly recur in clusters lasting hours to days, and in several cases, they could progress into status epilepticus (SE). While clusters are described in almost all patients, prevalence of SE has been reported to be highly variable from 10% to 53% of patients [8,9]. Status epilepticus might be both convulsive or nonconvulsive, and often refractory to conventional antiepileptic drugs [10], while immunotherapies have been used with variable efficacy [11,12].

We reviewed literature on PCDH19-CGE in order to define prevalence, semiology, treatments, and outcome of SE. This might improve knowledge on ictal semiology, management of SE, reduce overtreatment, and identify predictor factors for outcome after SE.

2. Material and methods

We conducted a comprehensive review of the PCDH19-GCE related literature. A computerized search of public databases PubMed and EMBASE from January 2008 to July 2019 was performed. The search terms were as follows: PCDH19, PCDH 19, Protocadherin19, and Protocadherin 19. We collected 76 abstracts from PubMed and 106 abstracts from EMBASE. Full-text papers were then selected according to the following criteria: 1) peer-reviewed and written in English, 2) reporting the Complementary DNA (cDNA) or protein change, and 3)

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https://doi.org/10.1016/j.yebeh.2019.106539
1525-5050/

Table 1
SE characteristics of 21 cases fully described in literature.

Paper	*PCDH19* gene variant	Gender	Age at epilepsy onset (m)	Age at SE (m)	Repetitive SE	Semiology (CSE/NCSE)	Refractory SE	Treatment of SE	Effective drugs	Age at FU (y)	Outcome
Hynes et al., 2010	c.826T/C; p.S276P	F	n.a.	84	Yes	CSE	Yes	n.a.	PHT, CLB, LTG	7	Moderate ID/autism
Dibbens et al., 2011	c.74T > C (siblings)	F	n.a.	48	No	n.a.	n.a.	n.a.	n.a.	15	ID/autism
	c.74T > C (siblings)	F	n.a.	132	No	n.a.	n.a.	n.a.	n.a.	20	ID/autism
Camacho et al., 2012	c.746A > G,	F	n.a.	10	Yes (1–4 SE/year)	CSE	Yes	n.a.	MDZ	12	Severe ID/psychiatric symptoms
	c.1955T > C	F	n.a.	8	Yes (every 3–5 months)	CSE	Yes	n.a.	MDZ	22	Moderate ID/psychiatric symptoms
Higurashi et al., 2012	p.Val191Leu	F	n.a.	6	No	n.a.	n.a.	n.a.	n.a.	8	Severe ID/autistic
Bertani et al., 2015	c.2406_2419dup; p.Leu807Profs[a]6	F	n.a.	96	No	CSE	Yes	n.a.	mPSL	8	Cognitive impairment
Higurashi et al., 2015	p.L719[a]	F	13	24	Yes	CSE	Yes	MDZ, CBZ, CZP, VPA, LTG, LEV	mPSL	5	Normal
	p.K120Rfs[a]3	F	10	10	No	CSE	Yes	MDZ, PB	mPSL	3	Moderate ID
	p.D417H	F	5	23	Yes	CSE	Yes	MDZ, PHT, CLB, LEV, Kbr, DZP	mPSL	2,8	Normal
	p.D596G	F	6	12	No	CSE	Yes	CBZ, PHT, lidocaine, PB	mPSL	1,5	Hyperactive
	p.D45Gfs[a]43	F	8	132	Yes	CSE	Yes	Kbr, CZB	PSL	11	Moderate ID
Perez et al., 2017	c.2147 + 2T > C	M	11	18	n.a.	NCSE	No	LEV	LEV	8	Severe ID/autism
Trivisano et al., 2018	c.706C > T	F	10.5	12	Yes	CSE	Yes	PB, MDZ, DZP	n.a.	43	Moderate ID/autism
	c.1129G > C	F	8	8	Yes	CSE	Yes	MDZ, PB, VPA	mPSL, i.v.IG	16	Severe ID/autism
	c.2676-6A > G Intronic	F	7	13	Yes	NCSE	Yes	PB, TPM, VPA	MDZ, STP[a]	15	Severe ID/autism
	c.2617-1G > A Intornic	F	10	11	Yes	CSE	Yes	MDZ, anestethics, PB, VPA, LEV	Ketogenic Diet	12	Severe ID/autism
	c.1352C > T	M	10	24	No	CSE	Yes	PB, VPA, LEV	MDZ	8	Mild ID/ASD
	c.799T > G	F	7	12	Yes	CSE	Yes	PHT, ACTH	PB	14	Severe ID/autism
	c.1973T > G	F	5	10	Yes	CSE	Yes	PHT, LEV, PB	mPSL	23	Moderate ID
Liu a. et al., 2019	c.1804C > T; p.R602X, de novo	F	30	8	n.a.	n.a.	n.a.	n.a.	n.a.		ID/aggressive behavior/autism

Table legend: F = female; M = male; m = months; y = years; CSE = convulsive status epilepticus; NCSE = nonconvulsive status epilepticus; PHT = phenytoin; CLB = clobazam; LTG = lamotrigine; MDZ = midazolam; CBZ = carbamazepine; CZP = clonazepam; VPA = valproate; LEV = levetiracetam; PB = phenobarbital; TPM = topiramate; KBr = potassium bromide; DZP = diazepam; ACTH = adrenocorticotropic hormone; STP = stiripentol; mPSL = methylprednisolone; PSL = prednisolone; ID = intellectual disability; ASD = autism spectrum disorder; FU = follow-up.

[a] STP was effective in reduction of SE frequency, not used for the treatment of SE (Trivisano M, Specchio N, Vigevano F. Extending the use of stiripentol to other epileptic syndromes: a case of PCDH19-related epilepsy. Eur J Paediatr Neurol. 2015;19(2):248–50).

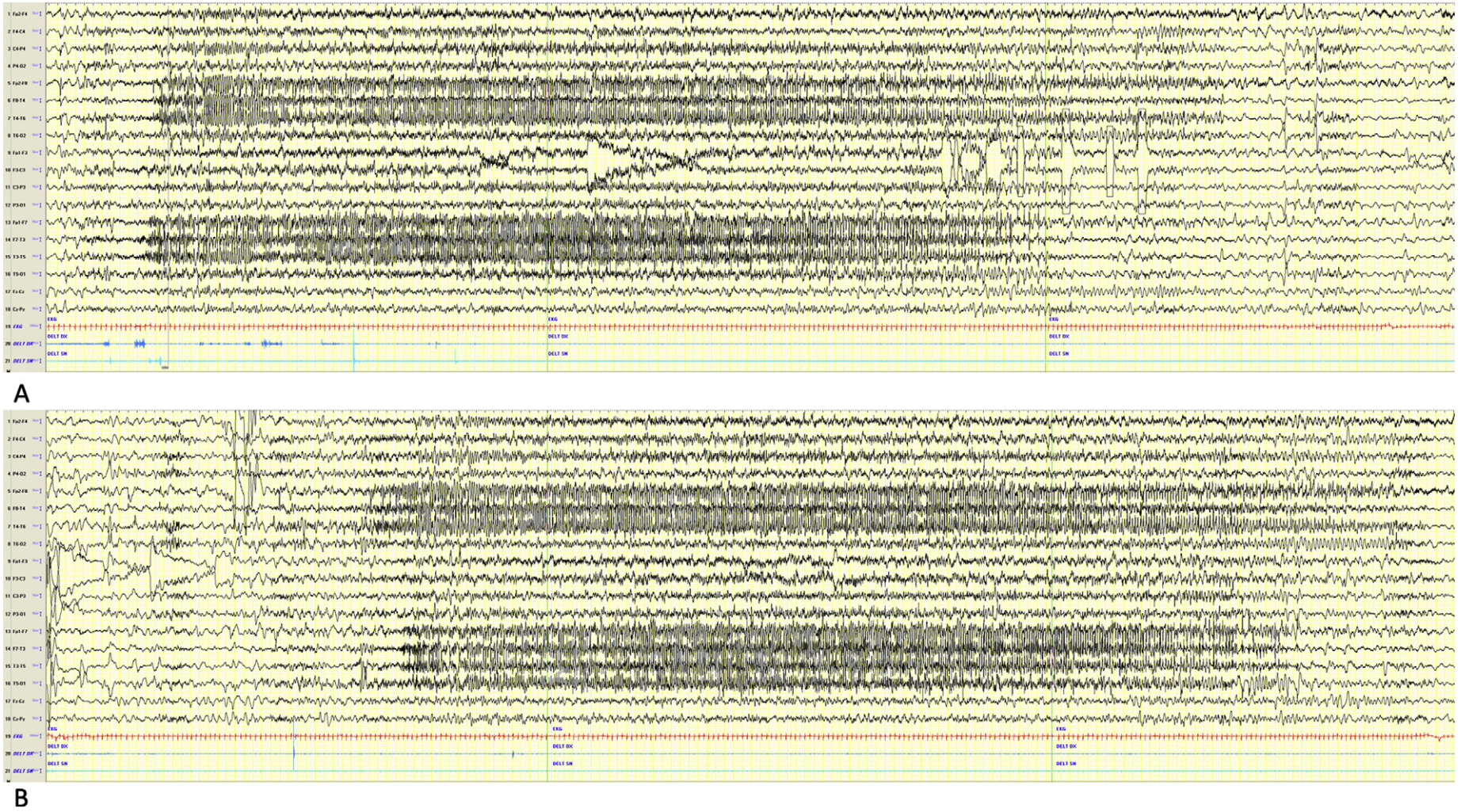

Fig. 1. Ictal EEG showing repetitive focal motor seizures, representing a convulsive status epilepticus. In both events, a diffuse paroxysmal fast activity is followed by rhythmic repetitive spikes with a higher amplitude over bilateral frontal and temporal regions. Seizures were occurring every 30–45 s.

were original cases only, 4) available information regarding SE or refractory clusters.

An overall number of 59 full-text articles were selected, retrieved, and assessed for eligibility. We collected data on epilepsy history, age at SE occurrence, semiology and duration, treatment, and outcome. To minimize the bias through reporting of the same individual from multiple publications, we used mutation (cDNA or protein change) and age at seizure onset to identify duplicates.

Status epilepticus has been classified according to the current International League Against Epilepsy criteria [13].

3. Results

We collected 269 cases with PCDH19-GCE, in 85 of them, a history of SE was reported (31.5%). Full data on SE were available for 21 patients [1,6,12,14–19] (see Table 1). For the majority of papers, it was only mentioned if the patients experienced SE or not, however, no data on ictal semiology and duration were available. There was no gender difference in SE occurrence. Median age at first SE occurrence was 12 months (6 months–11 years). Semiology of SE was reported in 17 patients: 15 patients had focal motor SE and 2 patients had nonconvulsive SE (NCSE) (Figs. 1 and 2). Status epilepticus was refractory in 15 out of 21 cases (71.4%).

4. Discussion

PCDH19-GCE is an epileptic syndrome characterized by an occurrence of seizures mostly in cluster. This feature is reported in almost all patients and, in some of them, clusters could progress into SE [1]. Given the high variability of prevalence of SE in PCDH19-GCE in reported cases, through this review, we looked at all patients reported and extrapolated the number of patients experiencing at least one SE during the disease course. The overall prevalence – based on our search – is 31.5%. The previously reported high variability of prevalence most probably is due to the small numbers of patients reported in each paper, however, considering only series of at least 10 patients ($n = 7$), we looked the prevalence of SE, and it ranged from 9,5% to 31% [1–3,9,10,18,19]. Moreover, SE seems to occur mostly during infancy and childhood [10]. After puberty, most of the patients have a spontaneous reduction of seizure frequency, and the most disabling features are ID and behavioral disturbances [1,2].

Status epilepticus in patients with PCDH19-GCE is not well described, and in the majority of papers, it is only mentioned if the patients experienced SE, but further features such as age at occurrence, ictal semiology, and treatments are not detailed. More attention is focused on cluster occurrence that often requires an aggressive treatment for SE.

About SE semiology, there are very few information in reported cases. In the majority of cases, it is reported as convulsive SE consisting of repetitive focal motor seizures [1,10]. Rarely, NCSE might occur, characterized by unresponsiveness, eye deviation, oral automatisms, and distal myoclonic jerks, and in some patients, vegetative symptoms such as tachycardia and/or abnormal breathing might also be associated [1].

In most of reported cases, there is not a clear-cut difference between clusters and SE, in terms of needs for patients (Intensive Care Unit (ICU) admission, use of intravenous medications, impact on general healthcare). Moreover, very often, clusters are quite intense and prolonged, and there is a need for aggressive treatment with intravenous benzodiazepines, mostly midazolam [10].

Other than benzodiazepine, there are no specific indications for the treatment of SE in PCDH19-GCE [20], and therapeutic approach is based mainly on personal experience rather than on scientific evidences. Alternative treatments, such as steroids and ketogenic diet, have been also reported for the treatment of refractory SE in PCHD19-GCE. Immunotherapies have been used for the treatment of refractory clusters and SE [12,18,21] during past years, mostly before the genetic diagnosis [12,21]. Later on, the use of steroids was supported by the possible involvement of neurosteroids in the pathogenesis of PCDH19-GCE [11,22]. The most frequently used immunotherapy for the treatment of SE has been intravenous methylprednisolone [12,18], and also, the use of intravenous immunoglobulin (ivIG) has been reported [21]. A dysregulation in the expression of Aldo-Keto Reductase 1C1–3 (AKR1C1–3) genes (encoding for steroid hormone metabolizing enzymes) in skin fibroblasts and reduced blood levels of allopregnanolone (a GABA-R modulator showing anticonvulsant effects) have been demonstrated in patients with PCDH19-GCE [11,22]. However, although phase III

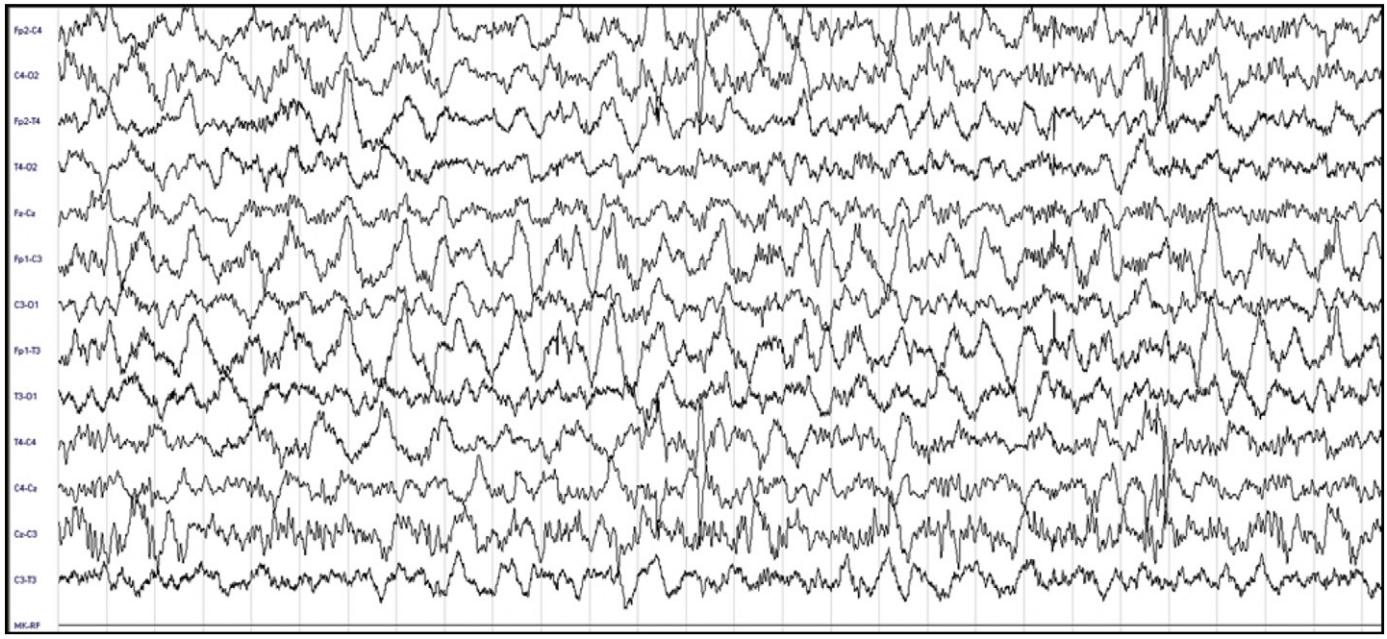

Fig. 2. The ictal EEG shows the presence of a continuous delta activity, diffuse over both hemispheres and prevalent over the frontal and temporal bilateral regions, with higher amplitude over the left hemisphere and intermingled with spikes of low voltage. Patients (at the age of 4 years and 5 months) has scarce interaction with fixe gaze, few myoclonic jerks without significant motor signs.

studies with ganaxolone – a synthetic analog of allopregnanolone, acting on synaptic and extrasynaptic $GABA_A$ receptor – have been conducted, until now, there are no cases of PCDH19-GCE SE treated with intravenous allopregnanolone.

Ketogenic diet has been reported in two cases of convulsive SE with success [1,23]. However, one of the two had a complex genetic etiology due to two different genetic variants, in *PCDH19* and *GABRG2* genes, therefore, no further conclusions about its efficacy could be find out [23].

Another important issue is the relation between the SE occurrence and the clinical outcome of PCDH19 mutated patients. PCDH19-GCE is characterized by a wide spectrum of severity ranging from patients with well-controlled epilepsy and normal cognitive development to patients with drug-resistant epilepsy, ID, and autism spectrum disorder (ASD) [1,2]. We previously analyzed in a large series of 61 patients, a possible relation between the SE occurrence and the global clinical outcome, in terms of ID, ASD, and seizure persistence at follow-up, and we failed to find any relations [1]. Overall one-third of patients with PCDH19-GCE have a normal psychomotor development [1], no clear-cut relationships have been identified between the cognitive outcome and epilepsy course. Looking at the collected data in this review – and taking into account the small number of patients – we found a high prevalence of ID and autism (19 out of 21 patients, 90%). This statement should be confirmed as far as there might be a bias in the evaluation due to the small amount of data reported.

5. Conclusions

PCDH19-GCE is a genetic condition with high prevalence of recurrence for SE: despite the relatively high frequency of SE in those patients, there are few specific descriptions of the semiology, EEG pattern, and treatment approach. There are still difficulties in the definition of what is SE in PCDH19-GCE: we feel that some overlapping between the definition of clusters and SE in those patients might exist. We strongly believe that a multicenter study looking specifically at SE characteristics might improve the knowledge and consequently the overall outcome.

Ethical publication statement

We confirm that we have read the Journal position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of competing interest

None of the authors has any conflict of interest to disclose.

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