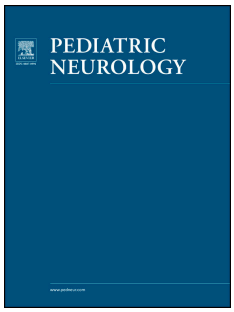

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***PCDH19*- related Epilepsy Syndrome: A comprehensive Clinical Review**

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Abstract

PCDH19 related epilepsy is a distinct childhood-onset epilepsy syndrome characterized by brief clusters of febrile and afebrile seizures with onset primarily before three years of age, cognitive impairment, autistic trait, and behavioral abnormalities. *PCDH19* gene is located in Xq22 and produces non-clustered delta protocadherin. This disorder primarily manifests in heterozygote females due to random X chromosome inactivation leading to somatic mosaicism and abnormal cellular interference between cells with and without delta-protocadherin. This author provides a narrative review of clinical features based on a comprehensive literature review (MEDLINE using PubMed and OvidSP vendors with appropriate keywords to incorporate recent evidence), personal practice and experience. Significant progress has been made in the last ten years, including identification of the gene responsible for the condition, characterization of clinical phenotypes, and development of animal models. More rigorous studies involving quality of life measures as well as standardized neuropsychiatric testing are necessary to understand the full spectrum of the disease. A recent discovery of allopregnanolone deficiency in *PCDH19* patients leads to opportunities in precision therapy. A phase 3 clinical study is currently active to evaluate the efficacy, safety, and tolerability of adjunctive ganaxolone (an allopregnanolone analog) therapy.

Keywords: *PCDH19;* epilepsy; autism, cognitive delay; allopregnanolone; protocadherin

Introduction

PCDH19 related epilepsy is a distinct childhood-onset epilepsy syndrome characterized by brief clusters of febrile and afebrile seizures with onset primarily before three years of age. Though clinical features vary significantly, standard features are summarized in table 1.

In 1971, Juberg et al. reported 15 females with EFMR (epilepsy restricted to female with mental retardation) in a large family from North America. They started to have seizures between 6-18 months of age. [1]Only females were affected, and no male in the family had epilepsy in this cohort. In 1997, Ryan et al. identified X-linked inheritance of EFMR due to the absence of transmission of the disease from one male to another. [2] However, only in 2008, *PCDH19* (located in Xq22) was detected as the specific gene responsible for this condition. [3]

Genetics

This disorder has an unusual X-linked inheritance. Usually, X-linked recessive and dominant diseases cause more severe phenotype or lethality in males, but *PCDH19* epilepsy syndrome primarily occurs in heterozygote females. *PCDH19* gene produces a non-clustered delta protocadherin, consisting of 1148 amino acids. [4] This particular subclass of protocadherins is expressed in the developing and adult nervous system and overexpressed in the limbic system. These protocadherins are essential for calcium-dependent cell-cell interaction and adhesion. Whole or partial gene deletion or alternation of the coding region (nonsense, missense, splice site, or frameshift mutations) can cause a loss of function of the gene with the production of cells with impaired cell-cell interaction. Approximately 150 mutations of PCDH19 have been discovered, with more than half affecting extracellular adhesive domains by missense mutations. [5]Alteration of protein function can subsequently occur in various ways: interference of homophilic adhesion, impairment of interaction with other cadherins, impaired folding and stability of the protein with reduced concentration at the cell surface, or alternation of calcium affinity with early degradation of the protein. Mutations affecting the intracellular segment of protein are rare and may produce disease phenotype by alteration of intracellular signaling pathways.

As females inactivate the X chromosome randomly in the cell, it produces somatic mosaicism with mixtures of two types of cells- with and without protocadherin. This somatic mosaicism produces abnormal cellular interference between these two types of cells with subsequent dysfunctional cell sorting and synaptogenesis. On the contrary, males with hemizygote mutations will produce only one type of cell with a particular deficient subclass of protocadherin but will remain asymptomatic due to the absence of cellular interference. However, males with somatic mosaicism of this gene produce similar phenotypes to heterozygote females due to cellular interference between two different types of cells. [4-9]

Other than the cellular interference hypothesis, a research group implicated blood-brain barrier (BBB) dysfunction as the probable etiology of this epilepsy. *PCDH19* is highly expressed in the endothelial cells, more in the central nervous system compared to other organs. Higurashi et al. proposed that seizures in *PCDH19* mutations are commonly originated in the limbic region, which is closer to the

periventricular regions without the BBB. [10] They also hypothesized that seizure remission during adolescence occurs due to the maturation of the BBB.

Tan et al. studied the transcriptomes of skin fibroblasts of *PCDH19* patients and identified dysregulated AKR1C1-3. [11], which converts 5 alpha-dihydroprogesterone to allopregnanolone. These researchers suggested that dysregulation of these genes leads to an allopregnanolone deficiency. In later studies, other reproductive hormones deficiency was detected, including progesterone sulfate. Trivisano et al. found a global decrease of all neuroactive steroids in 12 patients with *PCDH19* mutation, including basal cortisol and progesterone sulfate levels in postpubertal girls. [12]ACTH stimulation test further revealed decreased production of cortisol, pregnanolone sulfate, and 17 OH-progesterone in prepubertal girls. Some experts proposed that the reason for active epilepsy between late infancy to prepubertal time frame is likely due to the interval between mini puberty of infancy and true puberty during adolescence. It is important to note that allopregnanolone is the most potent positive modulator of GABAA receptors and increases both tonic and phasic inhibitory currents. However, the role of other neurosteroids, including progesterone sulfate, is not entirely clear. Though dysregulated steroidogenesis is noted in *PCDH19* epilepsy patients, further studies related to stress-induced seizure exacerbation and exogenous steroid's role in seizure control are needed.

Clinical features

Large scale studies related to clinical phenotype *PCDH19* syndrome are summarized in table 2. [13-25]

PCDH19 epilepsy has a distinct clinical phenotype. Initially, it was described in SCN1A negative Dravet syndrome patients, but except in some severely affected patients, a clear phenotypic difference exists between these two epilepsy syndromes (Table 3). Seizures usually start in late infancy, but almost always before three years of age. A biphasic course with several brief clusters of febrile seizures followed by clusters of afebrile seizures had been described, but clusters can persists days, weeks, or months at the onset. Chemaly et al. proposed that fever sensitivity may be highest after age two years rather than at the onset of seizures. [22] After reviewing the electroclinical phenotype of 13 molecularly confirmed *PCDH19* patients, three clinical stages were identified in this study: 1.seizure clusters without fever in the first two years of life in healthy girls, 2. Seizure clusters during febrile illness between 2-10 years, and 3. less frequent seizures and more behavioral disturbances after ten years of age.

Focal seizures predominate at the onset and throughout life. Hypomotor seizures with staring and behavioral arrest are frequent compared to convulsive seizures. Seizures described as generalized tonic-clonic seizures by eyewitnesses may be focal seizures with rapid bilateral propagation. Affective symptoms with fearful screaming have been described as a prominent feature by several experts. As opposed to Dravet syndrome, later development of absence, myoclonic, atonic and tonic seizures is rare, and photo- and pattern- sensitivity are only rarely reported. Incidence of status epilepticus is rare compared to Dravet syndrome, but still, approximately a third of patients may develop status. Temperature sensitivity and seizures related to fever or hot water immersion have been described in multiple reports. Lotte et al. described approximately 14% of patients with worsening of seizures after vaccination and approximately 12% related to emotional stress. [24] In this particular study, 24 patients

(in a cohort of 58 patients) remained seizure-free for more than one year after an active seizure period of average 10.7 years. Trivisano et al. performed a receiver operating characteristic analysis in 61 patients and detected with high sensitivity and specificity that seizure clusters significantly decreases after the age of 10.5 years. [25]

Electroencephalography

Due to seizure clusters during infancy, many children would undergo video EEG monitoring, and ictal EEG reports are readily available in the literature. Though generalized seizure onset has been reported, the vast majority of seizures are focal in onset. Seizures starting from the frontotemporal region are most frequent, but seizures from the posterior head region were also described. Stereotypic seizure onset from one localized brain region can occur, leading to concern about structural malformation and presurgical workup. Seizures can propagate to another hemisphere frequently, and occasionally switching between hemispheres during one cluster. Fast activity over a localized brain region was also described as an interictal finding. Interictal EEG can be normal, but focal or generalized slowing, as well as various epileptiform discharges such as focal and generalized sharp and spike-wave discharges, have been reported. In contrast to Dravet syndrome, photosensitivity has been only rarely described. It is unknown if interictal EEG during clusters of seizures detect more abnormality compared to EEG performed distant to seizures.

Brain MRI

Initial studies reported mostly normal brain MRIs associated with this condition. Lotte et al. noted normal brain MRI in 81% of 58 patients. [20]A focal cortical dysplasia was identified in 4% of patients with further suspicion of the same diagnosis in an additional 10% of cases. One patient noted to have hippocampal sclerosis, and another patient had an arachnoid cyst. However, Kurian described five children with a cortical malformation (4 of them had FCD I or IIa, but one had subependymal periventricular nodular heterotopia- a disorder of cortical migration rather than cell proliferation). [25] In two of these patients, histopathology confirmed the diagnosis. Seizure control improved in two patients after epilepsy surgery.

Treatment

Unfortunately, PCDH19 related epilepsy is usually refractory of antiepileptic treatment. No one agent is usually more effective than others. Moreover, physicians and families have difficulty assessing the effectiveness of a particular AED due to the natural fluctuation of seizures and provocation of seizure clusters by illness and fever. These patients very rarely would be on monotherapy. Polytherapy with various combinations has been explored, and none definitively has proven to be superior.

Contrary to Dravet syndrome, definite seizure exacerbation from sodium channel blockers such as lamotrigine and carbamazepine has not been proven. However, carbamazepine may not be as effective

despite predominant focal seizures seen with this condition. Polytherapy combinations, typically used for Dravet syndrome, have been used for this with various rates of success. A retrospective study confirmed most benefits from bromide and clobazam in both 3 and 12- months of treatment. Lotte et al. reported a retrospective study of antiseizure medicines in 58 patients (2-27 years old, mean age 10.6 years) with *PCDH19* mutation. [26] These researchers identified clobazam and bromide as the most effective medicines, with approximately two-thirds of patients had more than 50% seizure reductions after three months of therapy. During long-term follow up at 12 months, again, these two medicines were noted to be most effective, but the response rate was declined to 50% for bromide and 43% for clobazam. Out of 28 patients exposed to clobazam for three months, 12(43%) remained seizure-free in 3 months, and 15 patients exposed for 12 months, 4 (27%) were seizure-free. Concern regarding tolerance of clobazam was not particularly observed. Both carbamazepine and oxcarbazepine caused seizure worsening in approximately 10-12% of patients during the first three months, but approximately one fifth to one-fourth patients had a positive response from these also. Valproate and levetiracetam were the most commonly used AEDs in this cohort, and both produced around >30% responder rate in 3 months, and >50% patients had >50% seizure reduction in one year. Phenytoin was used in 14 patients, and it was particularly ineffective for 12 of these patients, and one patient had worsening of seizures after phenytoin exposure. The ketogenic diet was used in 4 patients, and two of them had a positive response, and one patient remained seizure-free for three months. One patient remained on the diet for the long-term with a 50-74% seizure reduction. Only one patient was exposed to VNS with 75-90% seizure reduction for three months, and one year follow up. Higurashi et al. observed seizure worsening secondary to topiramate and valproate, but similar worsening did not occur in the cohort reported by Lotte et al. [15]. Physicians also frequently use various combinations of clobazam, valproic acid, and stiripentol for treatment.

Higurashi et al. emphasized the use of low dose midazolam infusion as an effective treatment modality during seizure clusters. [16]However, the effect was transient with potential worsening during dose reduction. Intravenous phenytoin and phenobarbital were also used during seizure clusters to terminate clusters successfully. Though no drug was noted to particularly more effective than others, carbamazepine was again noted to be least effective in this cohort.

However, the therapeutic efficacy of the antiepileptic drugs is challenging to assess due to remarkable fluctuation in the seizure pattern, occasionally triggered by fever and infection as well as spontaneous improvement in the control after puberty. Kurian et al. described two patients with improved seizure control after epilepsy surgery of focal cortical dysplasia. [27]

Interestingly, corticosteroids have been used in this condition, particularly during seizure clusters. Though corticosteroids may suppress seizure clusters, rapid recurrence occurs with no definite long term benefit in seizure control. Higurashi et al. assessed response in seizure clusters from corticosteroid in 5 Japanese patients and observed four of these patients received 10-30 mg/kg of methylprednisolone once daily for up to 3 days. [10] Suppression of seizure clusters was observed, but the effect was transient with recurrence in a short interval. One of these patients received corticosteroid for an encephalopathic state with concurrent delta slowing in the EEG. Immediate improvement in the sensorium was observed after methylprednisolone administration. Moreover, one patient received

prophylactic oral betamethasone or prednisolone for three days during the febrile period since age three years with no recurrence of moderate/ severe episodes. Interestingly, all these patients tested positive for anti-NMDA receptor antibodies in serum and/or CSF, which is likely secondary to nonspecific sensitization after blood-brain barrier breakdown during seizure clusters rather than autoimmune pathogenesis.

Cognitive development

Usually, cognitive impairment becomes prominent after the age of 2 years. Only rarely, children can have a developmental delay before seizure onset. Cognitive impairment may not be directly correlated with seizure severity. Severe intellectual impairment is rare, and patients usually have borderline or mild to moderate cognitive impairment. A significant percentage of patients can have normal intellectual development. Camacho et al. reviewed previously published 110 patients with *PCDH19* mutation and found 75% of the patients with intellectual impairment.[28] Out of the 83 patients with intellectual disability, 39 (47%) had moderate to severe affliction. However, many of these patients did not have a standardized assessment, and only clinical observation was used for the diagnosis. Cappelletti et al. performed a detailed cognitive assessment using Griffiths Mental Developmental scales and Wechsler scales in 11 girls with *PCDH19* mutations. [29]Six of them had normal development or mild delay in the psychomotor development, and 5 of them had Global Quotient (GQ) range of 91-98(one had GQ of 71). On the other hand, 5 had a moderate disability with a range of GQ 40-50. Interestingly, even in typically developing patients, a delay in the acquisition of expressive speech was noted with gradual improvement over time.

On the contrary to Dravet syndrome, intellectual disability remained stable during the follow-up period of the study in children with moderate to severe impairment. However, patient number 10 in the study, had a normal development during the initial assessment at age 4, but follow up examination at age 8 and age 20 showed mild disability with GQ decreased from 98 at age 4 to 64 and 62 at the age of 8 and 20 years old, respectively. [29] Authors proposed that the absence of language during infancy before the seizure onset may be a negative predictor of intellectual dysfunction. Kolc et al. identified 195 previously published affected individuals with *PCDH19* and found normal intelligence in 28.2% of patients. [30] Mild, moderate, and severe/profound developmental delays were identified in 27.2%, 22.2%, and 17.4% of the patients. The authors found that seizure onset before 12 months associated with more severe intellectual disability. Approximately 15% of the patients had a preexisting developmental delay before the onset of seizures. Thus, other than seizure clusters and epileptiform activity, an independent negative consequence on development occurs from the mutation. Dysfunction in the axon outgrowth and synaptic connections is hypothesized as the potential etiology of cognitive dysfunction. Moreover, executive function deficit (deficit in planning, organization, abstract reasoning, impulse control) and adaptive behavior impairment may be particularly compromised in this population, and rather than general clinical examination, a comprehensive and standardized examination is necessary to understand the full spectrum of the deficits.

Psychiatric symptoms

Kolc et al. published a systematic review related to psychiatric comorbidities of *PCDH19* epilepsy. This study included 38 previously published original articles describing 271 patients, and out of these 213 patients had documentation of psychiatric function. [30]Approximately 60% of females and 80% of mosaic males had psychiatric diagnoses. Approximately 20% of the described patients had autism. Attention deficit hyperactive disorder was described around 6% of the cases. Other behavioral disturbances were also described, including anxiety, obsessive-compulsive disorders, and oppositional defiant disorders. Multiple psychiatric comorbidities were identified in approximately one-fifth of the patients. The authors identified a positive trend (not statistically significant) of psychiatric diagnoses in the presence of earlier seizure onset. Approximately one-quarter patients with normal cognition have psychiatric comorbidity. Interestingly, there were psychiatric issues in 9 hemizygous males, such as "rigid and controlling personalities, and obsessive interests and traits." Vlaskamp et al. reported that eight patients developed later-onset psychotic disorders, including schizophrenia, at the mean age of 21 years. [31]

Future directions

Significant progress has been made in the last ten years, including identification of the gene responsible for the condition, characterization of clinical phenotypes, and development of animal models. However, a prospective natural history study is necessary to understand the clinical progression of different symptoms. Although the emergence of more neuropsychiatric abnormalities is noted during the postpubertal phase, further biologic explanation such as developmental vs. electrophysiological abnormality is currently unavailable. Although sleep dysfunction has emerged recently as potential comorbidity, further studies are necessary for confirmation.[24] Formal guideline formulation with early referral to behavioral specialists, psychiatrists, sleep specialists, and counselors are necessary as well as close follow up with pediatric neurologists and epileptologists.

There has been a significant advancement in the understanding of the biological significance of the mutation. Pederick et al. showed in- vitro assays of a bone marrow-derived cell line that in heterozygote female mice, a significant sorting mismatch occurs between wild type and null cells and produces an altered network activity.[32,33]This mismatch did not occur in case of homozygous loss of *PCDH19* in both cell populations. Moreover, Bassani et al. showed that *PCDH19* interacts with GABAA receptors in rat brain and can influence GABAA receptor expression and inhibition of postsynaptic currents. [34] Additionally, seizure susceptibility was increased with alteration in the neuronal migration, orientation, and dendritic arborization in the in vivo study. Ganaxolone is a positive allosteric modulator of the GABAA receptor (both synaptic and extrasynaptic locations) and has anticonvulsant activity. [35]Ganaxolone has been studied in CDKL5 deficiency disorder, refractory status epilepticus, focal epilepsy, infantile spasms, catamenial epilepsy, and behavioral abnormalities associated with fragile X syndrome. [36]Sullivan et al. performed an open-label Phase 2 study of ganaxolone, an allopregnanolone analog, in 11 patients from 6 centers in the U.S. and Italy. [37] Median change in seizure (including all types) frequency over 28 days was 26%. Importantly, the patients (6 out of 11) with low allopregnanolone-sulfate had significantly more seizure reduction compared to other patients. A

double-blind, placebo-controlled, Phase 3 clinical study is currently ongoing to evaluate the efficacy, safety, and tolerability of adjunctive ganaxolone therapy. [38]

There have been several studies that specifically looked for genotype-phenotype correlation without significant progress. However, Smith et al. observed in a recent study that missense variants may be more likely associated with normal development compared to those with loss-of-function variants.[24] It has also been noted that whole gene deletion patients may have a more severe phenotype. However, in general, weak genotype-phenotype correlation so far raises the possibility of other modifiers. Further large scale studies to determine X-inactivation may be helpful in this regard.

More research is needed regarding the neuropsychiatric profile of genotype-positive heterozygote father. Though these individuals are mostly neurotypical, sporadic reports of abnormal behavioral traits and cognitive impairment are present. Systemic studies are necessary to understand the extent of neuropsychiatric dysfunction in heterozygote carrier fathers.

PCDH19 knock out mouse model has made several important discoveries possible. In one of the mouse models, Hayashi et al. noted that heterozygous female mice had a mosaic of *PCDH19*–positive and –negative cells at layer V and also had decreased fear response. [39]However, these mice did not have clinical seizures (intracranial recording showed epileptic activity) and did not closely mimic the human condition. Brain structure also found to be mostly normal. Zebrafish mutants also did not have seizures but noted to have structural abnormalities in the optic tectum.[40] But, in vitro studies using human induced pluripotent stem cells with loss of function variant showed premature neurogenesis of progenitor cells. [41] Besides, the behavioral phenotypes of homozygous female mice should be examined, and a more detailed study of dendrite pattern and spine morphology, as well as precise interaction mechanisms between the same and different types of protocadherins, should be conducted. Lastly, cellular interference should be studied in other diseases to understand if this unique pathogenesis applies to other epilepsies.

Although clinical research is significantly lacking, there has been much progress in the basic science research of *PCDH19* over the last few years. Current treatment continues to focus on seizure management with conventional seizure medicines, and precision therapies that can target underlying pathogenesis are desperately needed to not only improve seizures but for the amelioration of the prominent neuropsychiatric symptoms in these patients. Also, rigorous studies involving quality of life measures as well as standardized neuropsychiatric testing are necessary to understand the full spectrum of the disease.

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Table 1. Common clinical features of PCDH19 mutation

Childhood-onset epilepsy with clusters of febrile and afebrile seizures; generalized and focal seizures Intractable seizures during the first decade of life with the requirement of polytherapy Better control of seizures after puberty with possible remission
Cognitive impairment
Behavioral abnormalities (attention deficit, impulsiveness, executive function deficit, obsessive behaviors, depression, schizophreniform psychosis, panic attacks, aggression, self-injurious behavior)
Autism

Table 2. Clinical and EEG characteristics of PCDH19- related Epilepsy Syndrome

Reference	Number of patients	Seizure onset	Seizure types	EEG	Intellectual disability	Psychiatric abnormality
Scheffer et al.[13]	27	Mean 14 months(6-36 months)	TC(26), tonic(4), partial(11), absence(5), atonic 3) and myoclonic (4)	Generalized and focal epileptiform abnormalities	Normal (7), always delayed (4), normal followed by regression (12). 67% of females having ID or being of borderline intellect	Autistic (6), obsessive (9), and aggressive (7) features
Higurashi et al. [14]	8	Mean 11.5±7.3 months(5-25 months)	Generalized TC (4/8, 50.0%), tonic (3/8, 37.5%), and focal seizures with (2/8, 25.0%) or without secondary generalization (3/8, 37.5%)	Interictal EEG recordings often showed focal spikes and slow background activity.	5/8 with disability(4 with moderate to severe disability and IQ of 31-50)	Autism(2) and hyperactivity(1)
Higurashi et al.[15]	17	Mean age at onset, 8.6 months	Tonic seizures (13/18, probably including focal tonic seizures), tonic-clonic seizures (8/18), focal seizures often with subsequent generalization (17/18)	Ictal activities often originated in the frontal and/or temporal regions (9/13). A posterior focus involving the occipital region was observed in 4 cases, especially during infancy. Frequent abnormalities in interictal EEG included focal(poly)spike(s)/spike(s)-and-wave discharges (14/18) and slowing of the background activities (4/18)	ID (15/18)	Autistic traits (13/18)
Marini et al. [16]	35	Mean age 10 months	The predominant and more consistent ictal sign was fearful screaming, occurring in 24 patients (70.5%); it was present since epilepsy onset in 12 and appeared later on, during the course in the remaining 12 patients. Three patients (9%) had both focal and generalized seizures, the latter consisting of absences and myoclonus.	Ictal EEG during focal seizures showed a prominent involvement of the frontotemporal regions (22 patients). About 45% of patients had an alternating EEG pattern, with the ictal discharge, migrating from one hemisphere to the contralateral during the same ictal event.	Cognitive impairment occurred in 70% [mild (42%), moderate (54%) and severe (4%)]	Autistic features occurred in 28.5%.

Depienne et al.[17]	13 (including 1 male mosaic patient)	Mean age of seizures onset of 9.5 months (ranging from 7.5 to 12 months	Febrile and afebrile GTCS, absences, partial seizure, hemiclonic seizures, secondary generalized seizure		ID [mild (6), moderate (4), and severe delay (3)].	Behavioral disturbances(5) and autistic features(2)
Marini et al[18]	13	Mean age at seizure onset - 8.5 months	Afebrile TC, febrile, and afebrile SE, absences, myoclonic, and focal seizures.	Background activity normal in 11/13 patients (85%) and slow in 2. Focal seizures from the centroparietooccipital regions in 5 patients (46%) and from the frontotemporal regions in 2	ID[11 patients-mild (7; 64%), moderate (1; 9%) and severe (3; 27%)]	Autistic and ID(5 patients-38%)
Specchio et al[19]	6	Mean age at seizure onset - 15.5 ± 11 months (range 9–38)	Generalized TC, tonic, focal with or without secondary generalization	Ictal discharge from temporal lobe in five patients	ID(3 patients)	Autism in 2 patients
Harssel et al[20]	15	4-17 months	TC, hemiclonic, myoclonic, focal, tonic	Focal, multifocal or bilateral synchronous discharges, and background activity was either normal or showed slowing	All but one had delayed development	8 had aggression/hyperactivity or attention deficit and 5 had an autistic trait
Liu et al.[21]	21	5-18 months	GTCS, focal, myoclonic	Focal or multifocal seizures from the centroparieto-occipital regions or temporal region in five patients. Generalized seizures including TC seizures, tonic seizures and clonic–tonic–clonic seizures were recorded in four patients. Multiple seizure types recorded from one patient.	ID(17 patients)	Autistic trait(3)
Chemaly et al [22]	13	4-14 months	GTCS, focal, atypical absence	Early seizures in 10/13 patients, and focal seizures (n=8) with temporo-occipital and frontal onset.	All but one(IQ-85) with mild to moderate delay	Autism(9 patients)
Depiene et al. [23]	25	2-54 months	Generalized TC, tonic, focal, hemiclonic, absence, myoclonic	Normal, focal and generalized seizures	12-moderate/severe ID, 6- mild delay	7 with behavioral disturbances
Smith et al.[24]	38	11.8 months(range 4-48 months)	22 (58%) had focal seizures, 4 (11%) had generalized seizures and 8 (21%) had both focal and generalized seizures		ID in 30(most prominently in speech and language) 8/38 (22%) had an average intellect	29/38(76%) with behavioral abnormalities; Autistic features were present in 22/38 (58%), of whom 12 had a formal diagnosis of autism spectrum disorder (ASD)
Trivisano et al.[25]	61	10 months(range 1-68 months)	Seizures with motor onset (85.2%) and nonmotor onset (59.0%). Generalized (11.4%)	Epileptiform abnormalities (63.9%), focal (79.4%), diffuse (23.5%). Focal seizures from temporal (82.8%), frontal (6.2%), parieto-occipital (6.2%), and central (4.7%) regions	36 patients (59.0%) had ID and behavioral disturbances and ID was moderate to severe in 21 patients.	ASD in 31 patients

ID- Intellectual disability

Table 3. Differentiating features between PCDH19 epilepsy and Dravet syndrome

	PCDH19 epilepsy	**Dravet syndrome**
Seizure onset	Usually later; around 10-11 months	Around 6 months
Gender	Primarily females (rarely in mosaic males)	Both male and female
Photo and pattern sensitivity	Rare	Common
Status epilepticus	Less common	More common
Brief seizure clusters	More common	Relatively rare
Seizure with affective symptoms	Common	Rare
Hemiclonic seizures	Rare	Common
Absence and myoclonic seizures	Rare	Common
Intellectual impairment	Variable involvement	Commonly present
Seizure remission after puberty	Common	Rare
Polyspike wave discharges in EEG	Rare	Common
Gait abnormality	Rare	Crouch gait