

Epilepsy in Prader-Willi syndrome: clinical, diagnostic and treatment aspects

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Background: Epilepsy associated with Prader-Willi syndrome (PWS) represents an early and important complication, often not clearly reported and described in the literature. Consequently, there are controversial data about the clinical characteristics of epilepsy and electroencephalographic (EEG) abnormalities found in these patients.

Data sources: Based on recent original publications, we have reviewed the different types of seizures and EEG findings in PWS patients, the response to antiepileptic treatment, and the prognosis of epilepsy.

Results: The frequency of epilepsy in PWS patients ranges from 4% to 26%. The types of seizure include generalized tonic-clonic seizures, complex partial seizures, atypical absence, staring spells, and myoclonic, tonic and hemiclonic seizures, but the most frequent type is focal epilepsy. Status epilepticus has never been reported. EEG abnormalities are not typical but variable in different patients. However, generalized and focal discharges are the most frequently reported findings. There is no evidence of relationship between the course of epilepsy and frequency, morphology and spread of EEG discharges. However, epilepsy in PWS patients is usually responsive to antiepileptic monotherapy with rapid seizure control and a good outcome.

Conclusions: The frequency of epilepsy is higher in PWS patients than in general populations and this complication can be a challenge for the clinicians of these patients. Prospective studies are needed to confirm the good long-term prognosis.

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Key words: epilepsy;
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Introduction

Prader-Willi syndrome (PWS) is a complex, multisystem disorder, affecting about one in 10 000-15 000 births; it is clinically characterized by neonatal hypotonia, feeding difficulties in infancy, delayed psychomotor development, childhood-onset obesity, short stature, hypogonadism, emotional problems and behavioural abnormalities.^[1]

Diagnostic criteria were first proposed 32 years ago^[2] and, in 1993, clinical diagnostic criteria for PWS were developed through a consensus process.^[3] There are three categories of diagnostic criteria: major, minor and supportive. In 2001, Gunay-Aygun et al^[4] suggested revised clinical criteria to help identify the appropriate patients for DNA testing for PWS. The suggested age groupings are based on characteristic phases of the natural history of PWS. Some of the features serve to diagnose the syndrome in the first years of life, whereas others are useful during early childhood or during and after adolescence.

The genetic basis of PWS is as complex as its clinical features. It is caused by absence of expression of the paternally active genes in the PWS critical region on 15q11-q13 chromosome. In about 70% of cases, this is the result of deletion of this region from the paternal chromosome 15. In about 28%, it depends on maternal uniparental disomy (UPD, inheritance of 2 copies of a chromosome from the mother and no copies from the father, instead of the normal 1 copy from each parent) of chromosome 15, and in <2%, it is attributable to a mutation or a deletion in the imprinting center or other imprinting defect.^[5] Methylation analysis and UPD studies for standardized analysis of parent-of-origin for genes in this region, together with fluorescence *in situ* hybridization (FISH) are the gold standard for the diagnosis of PWS.^[6-8]

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Incidence of epilepsy and clinical findings

PWS is associated with an increased incidence of epilepsy and narcolepsy. Epilepsy is frequently reported in Angelman syndrome (AS, absent expression of the same region of the chromosome 15, but from the maternally inherited chromosome) and in 15q11 isodicentric duplication syndrome, but it is less common and not well characterized among PWS patients.

We reviewed all published articles and case reports on epilepsy in PWS in order to clarify the incidence of epilepsy and clinical and electroencephalographic findings.

The first review on PWS and epilepsy was published in 2010.^[9] It presented the case of a 2.5-year-old boy with PWS and a history of neonatal superior sagittal sinus thrombosis who had atonic seizures originated from the parasagittal region. The review postulated that microscarring from neonatal venous sinus thrombosis, history of febrile seizures, and PWS are predisposing factors to epilepsy and it emphasized the importance of video electroencephalography for PWS patients with drop episodes in order to differentiate cataplexy from seizures.

The reported incidence of cataplexy in PWS ranges from 16% to 28%^[10,11] and PWS patients are often evaluated for seizures because of staring spells. Benson et al^[9] reviewed the results of four different studies on PWS patients with epilepsy/febrile seizures:^[12-15]

- 1) Wang et al^[12] conducted their study on 50 patients and found one patient with atypical absence and seven patients with generalized tonic-clonic seizures; 2) Kumada et al^[13] analyzed 76 patients with PWS and reported on four patients with seizures, three of whom had multiple seizure types; 3) Fan et al^[14] described 10 of 56 patients with seizures: two complex febrile, six generalized tonic-clonic and febrile and one atypical absence. Two patients in their cohort initially presented febrile seizures and then developed epilepsy; and 4) Varela et al^[15] reported a higher incidence of febrile seizures in PWS patients with a deletion than in those with UPD and suggested that the aplinsufficiency of seizure-related genes in the deleted region of the 15q11-q13 chromosome may contribute to the increasing risk of febrile seizures. The conclusion was that approximately 26% of PWS patients have seizures compared to 89% of AS patients.

Afterwards, four studies^[16-19] evaluated the frequency of epilepsy in PWS patients; three studies^[16,18,19] focused their attention on the characteristics of epilepsy, while Sinnema et al^[17] reported only the frequency of epilepsy, that was about 11%. Comparison of these studies^[16,18,19] shows that the prevalence of seizures ranges from 13% to 32%, and the prevalence of epilepsy ranges from 4% to 26%. The lower rate of epilepsy reported by Gilboa

et al^[19] was probably partially due to the high proportion of UPD among their patients (40, 5%), compared with other cohorts.^[14-16,20,21]

These studies also tried to find a correlation between the genotype of patients and the prevalence of epilepsy and clinical seizure type; Vendrame et al^[16] concluded that the incidence of seizures in PWS patients with deletion genotype is higher comparable to patients with other genotypes, without statistical significance; Takeshita et al^[18] suggested that the frequency of seizures was not significantly related to PWS genotypes, in contrast to previous studies^[12,14,15] that reported that the frequency of seizures was more significant in the deletion group than in the UPD group.

As to seizure types, the frequency of febrile seizures ranges from 6.4%^[19] to 12%^[18] which was in consistent with previous reports.^[12,14,15] Since the prevalence of febrile seizures ranges from 3.4% to 9.3%^[22] in the general pediatric population, the frequency of febrile seizures in PWS patients is higher than in the general population.

The majority of patients with seizures presented focal epilepsy,^[16,18,19] in contrast to the results of some previous reports^[12,14,15,23,24] that generalized tonic-clonic seizures were more common. No patient had status epilepticus. Vendrame et al^[16] reported that focal epilepsy was involved in complex partial seizures, particularly staring spells as reported previously^[12,14,24] with a lower frequency. Since the prevalence of epilepsy ranges from 0.5% to 1%^[25,26] in the general pediatric population, the frequency of epilepsy in PWS patients is higher than that in the general population. The majority of individuals have the first episodes of seizures before they were 2 years old.

Electroencephalographic (EEG) findings

In 2005, Wang et al^[12] described EEG characteristics of patients with PWS. They compared the electro-clinical characteristics of seizures between PWS and AS patients in order to explore the possible mechanisms of epileptogenesis in these two syndromes. The most characteristics of EEG findings in the AS patients were: 1) Prolonged runs of rhythmic 2-3 Hz activity (200-500 microV) often more prominent bifrontally which are associated with ill-defined spikes or sharp waves; and 2) Spikes mixed with 3-4 Hz components (>200 microV), mainly posteriorly, and facilitated by eye closure.

Among the PWS patients, EEG findings were: 1) Persistent high-amplitude 4-6 Hz activities not related to drowsiness; 2) Focal paroxysmal discharges; and 3) Polyspike and wave short bursts. EEG findings of the AS patients were never seen in the PWS patients.

According to previous studies,^[27,28] a class of patients with PWS and AS (both <5%) has a mutation affecting the imprinting process, and a single gene (*Ubiquitin-protein ligase E3A, UBE3A*) that displays regional brain-specific imprinting in humans and mice is implicated in AS.^[29,30] In these cases, AS is associated with loss of maternal expression of the UBE3A gene. However, PWS is likely to be a contiguous-gene syndrome and multiple imprinted, paternally expressed genes have been identified.^[31]

Epileptic seizures occur in around 80% of patients with AS,^[32-34] and there is a genotype-phenotype correlation.^[32,34] Patients with single *UBE3A* gene mutation, UPD or methylation imprinting abnormalities present milder epilepsy than those with deletions. In the study of Wang et al,^[12] patients with no detectable cytogenetic or molecular defect at the AS locus displayed similar AS phenotype, seizure severity and EEG abnormalities compared with those with such a defect.

The gene *GABRB3* (*gamma-aminobutyric acid, a receptor, beta 3*) is mapped to the AS region; since patients with PWS have a large deletion at the same region, but only few have seizures or EEG abnormalities, and since 20%-30% AS patients with epilepsy have no detectable deletion of 15q11-q13, this deletion cannot be solely responsible for the associated EEG abnormalities and seizures in the AS patients. A study^[35] found that mice deficient in maternal *UBE3A* had EEG abnormalities; it postulated that the *UBE3A* gene has a potential role for epileptogenesis and that the interaction between *UBE3A* and *GABRB3*, located nearby, can result in the severe epilepsy seen in the patients with AS.

Subsequent studies did not find particular EEG characteristics in the PWS patients; the majority of EEG findings showed focal or generalized spikes or spike-wave complexes, with onset from different cerebral regions, and diffuse high voltage slow waves, according to the type of seizures. In 2009, Fan et al^[14] concluded that differences in EEG findings and seizure severity between the PWS and AS patients supported that the interaction between the lack of the maternally expressed *UBE3A* gene and GABA receptor subunit cluster might contribute to the more severe epilepsy phenotype in AS, defined as the higher frequency of seizure, the EEG patterns and the poor response to treatment in the AS patients.

Vendrame et al^[16] reported that staring spells were the most common seizures in their cohort, but in five patients there was no correlation between EEG and seizures. In a study^[19] EEG did not show the previously reported findings, but found a subclinical electrographic seizure pattern in five individuals, not reported in other studies.

Neuroradiological alterations

In the past years, many researchers have tried to find peculiar characteristics of the central nervous system in patients with PWS. Miller et al^[36] in 1996 described pituitary size in patients with PWS. They did not find any statistically significant difference between the PWS patients and both controls and children with isolated growth hormone deficiency; consequently, size determination of the pituitary by magnetic resonance imaging (MRI) did not help to identify PWS subjects.

In contrast, in 2006 Miller et al^[37] hypothesized that since several of the imprinted genes in the 15q11-q13 region are normally expressed in the brain and are probably necessary for neuronal growth and development, PWS patients have alterations in grey and white matters. In their study, all PWS patients had mild or moderate ventriculomegaly on MRI scan, especially in children under 2 years of age. PWS patients over 5 years old had decreased volume brain tissue in the parietal-occipital lobes, causing broadening of the local sulci. They found Sylvian fissure polymicrogyria in 12 of the 20 patients with PWS, and particularly in 8 of these patients who had deletion genotype, but no patient with UPD genotype presented this abnormality. Thirteen of the 20 patients with PWS presented lack of insula closure because of failure of the Sylvian fissure to close completely. There was no gender relationship in unilateral failure to close, but 5 of 7 patients with bilateral failure to close were females.

Iughetti et al^[38] analyzed 91 patients with PWS and found a reduction in pituitary height in 45 patients, including empty sella in 4 patients, complete absence of posterior pituitary bright spot in 6 patients, and minor neuroradiological alterations such as ventriculomegaly and thin corpus callosum in 10 patients. Further studies supported their findings.^[36,39]

None of these studies distinguished between MRI findings in both PWS patients with epilepsy and those without epilepsy. The table shows subsequent studies that described MRI findings in PWS patients with epilepsy.^[13,14,16,18,19] MRI was performed in 37 patients with PWS and epilepsy and findings were normal in 26 patients. Takeshita et al^[18] performed MRI in 9 of 31 patients with seizures and they observed alterations in one patient who had diffuse atrophy after encephalopathy. In one patient described by Benson et al,^[9] MRI performed at birth revealed a subdural hematoma along the right tentorium and a non-occlusive thrombus in the inferior and posterior superior sagittal sinus extending into the right transverse sinus. But the MRI performed after the onset of seizures did not show any new abnormality.

Vendrame et al^[16] found that MRI findings were within normal limits in 15 children: 4 children had

Table. Clinical and electroencephalographic characteristics of epilepsy in patients with Prader-Willi syndrome

Author	Patients (n)	Mutation type	Patients with seizures (n)	Patients with nonfebrile seizures (n)	Onset age of seizures (range)	Characteristics of seizures	Electroencephalographic findings	Imaging studies	Treatment	Prognosis
Wang et al. ^[12] (2005)	50	36 deletions 9 UPD	8	8	NA	7 GTC 1 AAE	High-amplitude 4-6 Hz activities not related to drowsiness, 5 Focal discharges, 4 Polyspike and wave short bursts, 1	NA	NA	NA
Kumada et al. ^[13] (2005)	4	4 deletions	4	4	1 y 2 mon- 3 y 11 mon	3 GTC 3 CPS 2 myoclonic 1 tonic 1 hemiconic	Normal, 1 Multifocal sp, diffuse HVS, sp-w, 1 Lf. PP sp, 1 Rt. CC sp, 1	Cerebral atrophy, 1 Normal, 2	NA	Good, 3 Poor, 1
Varela et al. ^[15] (2005)	75	51 deletions 24 UPD	19	NA	NA	NA	NA	NA	NA	NA
Fan et al. ^[14] (2009)	56	45 deletions 10 UPD 1 PID	10	8	6 mon-72 mon	6 GTC 1 CPS 1 AAE	Non-specific spikes, 1 Sp, 4 Normal, 3	Normal, 6 Ventricular megal and periventricular leukomalacia, 1 O, 2	V, 5 C, 2 D, 4	Good, 7 Poor, 1
Vendrame et al. ^[16] (2010)	92	41 deletions 29 UPD or PID	30	24	2 d-11 y	10 CPS 8 staring spells 3 GTC sec 2 AAE 1 myoclonic	Normal, 10 Generalized and focal discharges, 6 Multifocal discharges, 3 Generalized discharges, 2 Bifrontal discharges, 1 Rt. temporal discharges, 1	Normal, 13 Enlarged ventricles, 3 Generalized atrophy, 1	C, 5 L, 5 Lt, 5 V, 2 Polytherapy, 1	Good, 19 Poor, 1
Takeshita et al. ^[18] (2013)	142	109 deletions 31 UPD 1 PID	31	9	1 d-4 y	8 GTC 2 AAE 1 CPS	Multifocal discharges, 5 Focal discharges, 4	Normal, 4 Diffuse atrophy, 1	V, 6 C, 2 D, 2 P, 1	Good, all
Gilboa et al. ^[19] (2013)	126	73 deletions 51 UPD 2 PID	17	5	1 mon-5 y	1 GTC 1 staring 3 focal	Focal discharges, 4	Normal, 1 Abnormal, 4	V e Lt, 1 C e Vig, 1 Polytherapy, 2 P e T, 1	Good, 4 Poor, 1

GTC: generalised tonic-clonic; CPS: complex partial seizures; AAE: atypical absence epilepsy; sp: spikes; sp-w: spikes-waves; HVS: high voltage slow waves; Rt: right; Lf: left; PP: parietal; CC: central; V: valproic acid; C: carbamazepine; D: diazepam; L: levetiracetam; Lt: lamotrigine; P: phenobarbital; O: oxcarbamazepine; Vig: vigabatrin; NA: not available; UPD: uniparental disomy; PID: presumed imprinting disorder.

ventriculomegaly and 1 had diffuse cortical atrophy and suffered from coarctation of the aorta; none of the children showed brain abnormalities.

Gilboa et al.^[19] reported that brain abnormalities were present in 33% of individuals with or without epilepsy. Imaging studies were available for all subjects with PWS and epilepsy and only one was normal. Findings were different in all patients with epilepsy (Table).

In conclusion, most patients with PWS have no brain abnormality and there is no correlation between neuroradiological findings and epilepsy. Four patients with PWS and epilepsy showed ventriculomegaly, which is often reported in conditions associated with mental retardation^[40] and that could be a marker of cerebral dysgenesis. Several paternally expressed genes found in the PWS region in mice seem to be necessary for normal brain development and one of these genes, *Necdin* (*NDN*) is upregulated during neuronal differentiation. One study^[41] found that *NDN* deficiency would cause brain abnormalities in infants

with PWS and that ventriculomegaly is a manifestation of abnormal neuronal development.

Management and outcome

At present, the treatment of PWS patients is age dependent and includes addressing the consequences of the syndrome and anticipatory guidance. It is recommended a team approach. Most of the studies focused on endocrine complications, which are the main features of the syndrome.^[42-45]

Epilepsy and seizures are not considered criteria for PWS.^[3] There is still no consensus for the therapy of epilepsy in PWS patients. No study has addressed the problem of the antiepileptic therapy in these patients. Four studies^[14,16,18,19] showed that almost all the patients were treated with mono-therapy (44 of 46 patients) and 41 patients controlled seizures by using one antiepileptic drug (Table).^[14,18] The most frequently used drugs were old ones such as valproic acid (14

patients), carbamazepine (10), and diazepam (6). Among new antiepileptic drugs, the frequently used drugs were levetiracetam (5 patients) and lamotrigine (6).

Good outcome was seen in nearly all PWS patients with epilepsy, except in 3 patients.^[14] Only one patient had intractable epilepsy despite polytherapy. Vendrame et al^[16] found 22 of 23 patients obtained seizure control, ie, seizure control after mono-therapy in 13 patients, and reduction of seizure frequency without therapy in 9, which are in agreement with the results of a previous study.^[14] They reported intractable epilepsy in one patient with staring spells who generalized hypotonic seizures at age of 9 years despite a three-AED therapy. Gilboa et al^[19] reported one patient with a history of encephalitis at the age of 20 months and generalized atrophy at MRI. The patient with multiple seizures was treated with polytherapy, but he still presented seizures at 10 years of age.

It is important to remember that in children with PWS who easily gain weight, therapy with valproic acid (used in 14 patients) can contribute to developing overweight with consequent dyslipidemia and metabolic syndrome that can be associated with long-term vascular complications, such as hypertension and atherosclerosis. Moreover, an elevation in the levels of uric acid and homocysteine, together with oxidative stress, may contribute to atherosclerotic risk in patients under long-term therapy with valproic acid.^[46]

Conclusions

Patients with PWS can suffer for epilepsy (very often partial epilepsy) with a high frequency of focal EEG abnormalities. This complication must be considered for the care of these patients. There is no clear correlation between EEG abnormalities, severity of epilepsy and response to antiepileptic treatment. However, the overall prognosis of epilepsy is favourable, with good response to anticonvulsants monotherapy. In fact, data from follow-up studies confirm that the majority of patients are seizure free after few years of treatment.

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