Long-term outcome of epilepsy in patients with Prader–Willi syndrome

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Abstract Prader–Willi syndrome is a multisystemic genetic disorder that can be associated with epilepsy. Thereis insufficient information concerning the clinical and electroencephalographic characteristics of epilepsy and the long-term outcome of these patients. The aim of this study is to describe seizure types, electroencephalographic pat- terns and long-term seizure outcome in Prader–Willi syn- drome patients suffering from epilepsy. We retrospectivelystudied 38 patients with Prader–Willi syndrome and sei- zures. Results of neuroimaging studies were obtained for

35 individuals. We subdivided these patients into two groups: group A, 24 patients, without brain lesions; and group B, 11 patients, with brain abnormalities. All patients were re-evaluated after a period of at least 10 years. Twenty-one patients (55.2 %) were affected by generalizedepilepsy and 17 patients (44.8 %) presented focal epilepsy. The most common seizure type was generalized tonic–clonic seizure. The mean age at seizure onset was 4.5 years(ranged from 1 month to 14 years). In the follow-up per- iod, seizure freedom was achieved in 32 patients (84.2 %). Seizure freedom was associated with electroencephalo- graphic normalization, while the six children presenting drug-resistant epilepsy showed persistence of electroen-cephalographic abnormalities. Group B patients showed a higher prevalence of drug-resistant epilepsy. Patients with Prader–Willi syndrome were frequently affected by gen- eralized seizures. Most of the patients had a favorable evolution, although, patients with brain abnormalities pre- sented a worse outcome, suggesting that the presence of these lesions can influence the response to antiepileptic therapy.

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Introduction

Prader–Willi syndrome (PWS) is a complex, multisystemic disorder, characterized by intellectual disabilities, described for the first time in 1956, with a prevalence of about 1:45,000, according to recent findings; [1] its main clinical features include neonatal hypotonia, feeding difficulties, delayed psychomotor development, obesity, short stature, hypogonadism, emotional problems and behavioural alterations [2]. Diagnostic criteria are distinguished into three categories, major, minor and supportive, and were developed through a consensus process, in 1993, and revised in 2001 [3, 4]. This syndrome is caused by the absence of expression of the active genes in the PWS critical region on chromosome 15q11–q13; in about 70 % of the cases, it is determined by a deletion of this region on the paternal chromosome 15; in about 28 %, it is the result of maternal uniparental disomy (UPD, inheritance of both chromosome 15 copies from the mother, instead of one copy from each parent); and in ⩽2 % of cases, it is caused by a mutation or a deletion in the imprinting center or by other imprinting defects (PID) [5].

Epilepsy is not considered a diagnostic criterion of PWS, but previous studies found that the syndrome is associated with an high incidence of seizures; [6–16, 21] in particular, the prevalence of febrile seizure ranges from 13 to 32 %, and the prevalence of epilepsy varies from 4 to 26 %. The type of seizures is variable and very often not clearly described. Electroencephalographic (EEG) findings are also poorly defined. Moreover, some studies reported cerebral abnormalities in subjects with PWS, but there are no studies that evaluated the possible relations between cerebral lesions and epilepsy [16–18].

Therefore, the two main aims of this study are to describe clinical, EEG and brain abnormalities of PWSpatients with epilepsy and to compare the outcome of epilepsy between patients with and without brain malfor- mations and their long-term outcome.

Materials and methods

We retrospectively evaluated the long-term seizure outcome in patients with PWS who had been referred to 16 Epilepsy Centers in Italy. We included children who had been observed between 1993 and 2003 and clinically managed in these centers for at least 10 years. Patients with personal history of previous brain damage (e.g. intraventricular hemorrhage) or other known causes of epilepsy were excluded from the study. Clinical diagnosis of PWS was based on clinical diagnostic criteria [3, 4] and was then confirmed by genetics testing, through methylation study and FISH, or by an analysis of the parental inheritance pattern of chromosome 15, if indicated, according to the recommendations of the American Society of Human Genetics/American College of Medical Genetics [19]. Seizures were classified on the basis of the clinical and EEG findings, according to International League Against Epilepsy [20]. Electroencephalogram (EEG) was performed according to the International 10–20 system and all recordings were visually interpreted by a blinded EEG-certified neurologist. Interictal awake and sleep EEG recordings were performed in all children.

We evaluated patient age at seizure onset, history of febrile seizures, seizure type, family history of epilepsy, EEG and neuroradiological findings, history of medications, including the number of AEDs and outcome. When epilepsy was diagnosed, brain MRI (25 patients) or CT scans (10 patients) were carried out and reviewed by a medical doctor blinded for clinical information.

We analyzed clinical, EEG and brain MRI or CT characteristics and long-term outcome of 38 PWS individuals from the onset of epilepsy and after a period of at least 10 years.

Statistical analysis was performed with SPSS Version 16 for Macintosh Computers (Apple Inc, Cupertino, CA, USA). A Fisher's exact test was used for group comparison; moreover, the unpaired *t* test was used. Significance for all analysis was set up at $p \backslash 0.05$.

Results

General clinical and genetic features

Our series consisted of 38 PWS patients, 22 males (57.8 %) and 16 females (42.2 %). Age at epilepsy onset ranged from 1 month to 14 years, with a mean age of 4.5 years; in particular, seizure onset was before 2 years of age in 8 patients, between 2 and 9 years of age in 25 children, between 9 and 14 years of age in 5 subjects.

Genotypes were obtained in all patients, except two: 30 patients (83.3 %) had a deletion of chromosome 15, six (15.8 %) had UPD, no patient had PID; genetic tests performed were FISH in 12 patients and karyotype analysis in 24 patients; moreover, also methylation analysis has been carried out in eight patients. In the two subjects in whom genetic tests were not performed, the diagnosis of PWS was based on clinical diagnostic criteria [3, 4].

Family history was positive for epilepsy in eight cases (21 %). Febrile seizures were reported in 15 patients (39.4 %): 12 children (80 %) presented simple febrile seizures, while 3 children had complex febrile convulsions.

Seizure type, EEG and brain MRI findings, antiepileptic therapy

Twenty-one patients (55.2 %) presented generalized epilepsy, while 17 (44.8 %) had focal epilepsy. All patients with generalized epilepsy presented ictal impairment of consciousness; 19 individuals had generalized tonic–clonic seizures, associated in some cases with atonic and myoclonic seizures. Eight patients presented staring spells. Two subjects suffered from atypical absence epilepsy. Three children showed eyelid myoclonia associated with tonic–clonic seizures in one case, with atonic seizures in one patient and with occipital epilepsy in a child. All subjects with focal epilepsy did not present impairment of consciousness; most seizures were characterized by sensory symptoms associated with focal tonic–clonic seizures of one or two limbs and followed by secondary generalization in seven cases. No episode of status epilepticus was reported in the patients both at the onset of epilepsy and during follow-up.

Background EEG activity was normal in all patients. Interictal awake EEG recordings showed focal and multifocal isolated spikes or polyspikes in 26 children (68.4 %) and generalized spike- and polyspike-waves in 12 patients (31.6 %). In 32 patients, we obtained sleep EEG that confirmed the abnormalities found in awake EEG with normal presence of vertex sharp wave tran- sients, K complexes and spindles. No photoparoxysmal response was seen during intermittent photic stimulation in all patients.

In 10 patients, ictal EEG recordings showed generalized spike-wave paroxysms for approximately 2 min, associated with GTCS.

Reports on imaging studies were available for 35 patients: 11 studies (28.9 %) were abnormal. The most frequent lesion was ventriculomegaly, reported in five patients (45.4 %); four subjects presented cortical atrophy, one child had hypoplasia of corpus callosum and the last presented periventricular leukomalacia. Ventriculomegaly was found associated with hydrocephalus and Arnold–Chiari malformation in one patient and with hypoplasia of corpus callosum in two. The location of these lesions was associated with neither type of epilepsy (generalized or focal) nor EEG findings.

Thirty-four children received antiepileptic drugs (AEDs): the most used AEDs were sodium valproate (VPA) among the old AEDs, levetiracetam (LEV) and to- piramate (TPM) among the new AEDs. Other prescribed AEDs were carbamazepine (CBZ), clobazam (CLB), clo- nazepam (CZP) and lamotrigine (LTG). Most patients were treated with monotherapy; the subjects requiring poly- therapy presented generalized epilepsy and abnormal findings at EEG and brain MRI.

Four patients were not treated with AEDs because of a very low seizure frequency; the administration of rectal diazepam was prescribed if necessary.

We subdivided our patients in two groups: group A, 24 patients (15 males, 9 females) without brain abnormalities; group B, 11 patients (4 males, 7 females) with brain lesions. Between the two groups, there were significant differences in the mean age of epilepsy onset (4.8 years in group A, 3.6 years in group B), the gender (female subjects represented the 37.5 % of group A and the 63.6 % of group B) and antiepileptic therapy (in group A one patient received polytherapy, while in group B four patients required multiple AEDs).

Data about seizures type, EEG, brain MRI or CT findings and antiepileptic therapy are resumed in Table 1.

Table 1 Characteristics of the patients

Patient and gender	Age of onset seizures (years)	Seizure types	EEG	Brain imaging	Therapy	Epilepsy outcome	EEG outcome
1, M	11.1	GTCS	Rt and Lf Fr slow s–w	N.A.	VPA CLB	Seizure free	Normal
2, F	14.0	Deviation of the eyes with rare tonic–clonic seizures, staring spells	Generalized slow s–w	Normal	CZP LEV	Seizure free	Normal
3, M	3.2	Mnestic and sensory symptoms, visual hallucinations, followed by automatic movements of the hands and mouth	Lf Temp-Occ spikes	Normal	LEV	Seizure free	Normal
4, M	5.2	GTCS	Spikes and generalized poly-s–w	N.A.	VPA	Seizure free	Normal
5, F	5.7	GTCS	Generalized discharges	Hypoplasia corpus callosum	VPA LEV	Seizure free	Normal
6, M	4.1	Deviation of the eyes with atonic seizures	Lf Occ spikes	Normal	No therapy	Seizure free	Normal
7, F	1.8	GTCS	Rt and Lf Temp-Occ spikes	Cortical atrophy	No therapy	Seizure free	Normal
8, M	4.3	Sensory symptoms, followed by secondarily GTCS	Par-Temp spikes	Normal	No therapy	Seizure free	Normal
9, F	3.9	Myoclonic seizures with visual symptoms, staring spells	Rt and Lf Temp-Occ spikes	Normal	CLB	Seizure free	Normal
10, F	4.7	GTCS, atonic seizures	Rt and Lf Fr spikes	Cortical atrophy	LEV LTG CZP	GTCS	Generalized discharges
11, M	5.2	GTCS, atonic seizures	Rt and Lf Fr spikes	Normal	TPM	GTCS	Generalized discharges
12, F	9.7	Sensory symptoms, followed by hemiconvulsions GTCS	Lf multifocal discharges	Ventricular enlargement hypoplasia corpus callosum type 1 Arnold–Chiari disease	CBZ	Seizure free	Normal
13, M	1.3	GTCS	Generalized discharges	N.A.	PB	Seizure free	Normal
14, F	0.8	Hemiconvulsions, secondarily GTCS, staring spells	Temp s–w discharges	Ventricular enlargement	VPA LEV	Seizure free	Normal

15, M	4.6	Elementary and complex visual hallucinations, partial visual loss and deviation of the eyes with ipsilateral turning of head	Lf Occ discharges	Cortical atrophy	TPM	Seizure free	Normal
16, F	1.3	Impairment of tactile sensations and of proprioception and sensory symptoms	Par slow waves	Ventricular enlargement	No therapy	Seizure free	Normal
17, F	1.6	Sensory symptoms and unusual behaviors, followed by hemiconvulsions	Lf Temp spikes	Ventricular enlargement, hypoplasia corpus callosum	No therapy	Seizure free	Normal

Table 1 continued

Patient and gender	Age of onset seizures (years)	Seizure types	EEG	Brain imaging	Therapy	Epilepsy outcome	EEG outcome
18, M	2.3	Focal motor seizures (left arm), staring spells	Fr-Temp poli-s–w	Normal	VPA	FE	Fr-Temp poli-s–w
19, F	2.2	GTCS	Temp s–w	Normal	VPA	Seizure free	Normal
20, M	2.4	Atypical absence epilepsy	Lf Fr-Temp spikes	Normal	TPM	Seizure free	Normal
21, F	4.7	GTCS	Rt Temp discharges	Normal	VPA	Seizure free	Normal
22, M	13.1	Deviation of the mouth with inability to speak and hypersalivation, followed by GTCS	Rolandic spikes	Normal	CBZ	Seizure free	Normal
23, M	9.2	GTCS, myoclonic	Generalized s–w	Normal	LEV	Seizure free	Normal
24, M	4.1	GTCS	Generalized waves of 4–6 Hz	Ventricular enlargement, hypoplasia corpus callosum	VPA TPM	Seizure free	Normal
25, M	4.2	GTCS	Generalized poli-s–w	Normal	VPA	Seizure free	Normal
26, M	6.4	Atypical absence epilepsy	Focal discharges	Normal	VPA	Seizure free	Normal
27, M	3.6	Atonic seizures, staring spells	Generalized s–w	Normal	VPA	Seizure free	Normal
28, M	5.7	Focal motor (left arm) with secondary generalization	Rt Fr spikes	Cortical atrophy	CBZ	FE	Fr spikes
29, F	7.3	Sensations of déja vu with inability to speak, staring spells	Temp spikes	Normal	CBZ	Seizure free	Normal
30, F	3.2	GTCS	Generalized s–w	Normal	VPA	Seizure-free	Normal
31, M	4.6	GTCS, atonic	Generalized poly-s–w	Normal	VPA	Seizure-free	Normal
32, M	8.3	GTCS, myoclonic	Generalized waves of 4–6 Hz	Normal	VPA	Seizure-free	Normal
33, M	At birth	GTCS	Occ spikes of 8–10 Hz and slow waves	Periventricular leukomalacia	VPA	GTCS	Occ spikes of 8–10 Hz and slow waves
34, F	0.9	GTCS	Lf Par spikes at eyes closure	Normal	VPA	GTCS	Lf Par spikes at eyes closure
35, F	At birth	Focal motor (right limb), staring spells	Focal discharges of 7–8 Hz	Normal	VPA	GTCS	Normal

Table 1 continued

Patient and gender	Age of onset seizures (years)	Seizure types	EEG	Brain imaging	Therapy	Epilepsy outcome	EEG outcome
36, F	3.6	Focal motor (left arm) with secondary generalization	Focal slow waves	Normal	No therapy	Seizure-free	Normal
37, M	3.3	GTCS	Generalized s–w	Normal	VPA	Seizure-free	Normal
38, M	2.4	Focal motor seizures with secondary generalization, staring spells	Lf Tem s–w	Normal	LEV	Seizure-free	Normal

M male, *F* female, *GTCS* generalized tonic–clonic seizures, *Rt* right, *Lf* left, *Fr* frontal, *s–w* spike–waves, *VPA* sodium valproate, *CLB* clobazam, *N.A.* not available, *CZP* clonazepam, *LEV* levetiracetam, *Temp-Occ* temporo-occipital, *Occ* occipital, *Par-Temp* parieto-temporal, *LTG* lamotrigine, *TPM* topiramate, *CBZ* carbamazepine, *PB* phenobarbital, *Temp* temporal, *Par* parietal, *Fr-Temp* fronto-temporal

Long-term follow-up

Duration of follow-up was at least 10 years in all patients of both groups. All patients of both groups who became seizure-free stopped antiepileptic treatment after a median duration of therapy of 2.11 years (range 2–3 years and 8 months) and remained seizure-free until the end of follow-up.

Group A: 20 patients (83.3 %) were seizure-free. In these patients, we found an association between the clinical response to antiepileptic therapy and EEG pattern improvement: all patients who became seizure-free showed a complete normalization of the EEG abnormalities. Four patients (16.7 %), three with generalized epilepsy and one with focal epilepsy continued monotherapy, respectively, one child with TPM and three children with VPA, because of persistence of seizures, after a first withdrawal of therapy.

Group B: eight patients (72.7 %) were seizure-free and EEG findings normalized. At the end of follow-up, three children (27.3 %), one male with diffuse cortical atrophy, one male with periventricular leukomalacia, and one female with diffuse cortical atrophy, continued, respectively, polytherapy with LEV, LTG and CZP, and monotherapy with CBZ and VPA, because of frequent seizures.

The age of onset of epilepsy was significantly higher in group A than in group B patients (group A vs. B: 4.6 years vs. 3.8 years) ($p \nwarrow 0.05$). The percentage of seizure-free patients was significantly higher in group A patients (group A vs. B: 83.3 vs. 72.7 %; $p \backslash 0.05$).

The three patients in whom neuroimaging studies were not performed became seizure-free after 2 years from the beginning of therapy and, therefore, AEDs were stopped: all three children were still seizure-free on last evaluation.

Discussion

This is the first study that describes in detail the clinical and EEG characteristics of epilepsy in PWS patients with epilepsy and their long-term evolution, and that analyzes the differences between patients with and without brain lesions, their response to AEDs and their outcome.

According to our experience, we cannot recognize awell-defined epileptic syndrome with typical EEG abnormalities associated with PWS. On the other side, our series showed that generalized epilepsy was the most common type of epilepsy, with a high prevalence of GTCS; after GTCS, atypical absence represented the second clinical manifestation. Other common seizure types were staring spells and atonic seizures; such seizure types have been reported in previous studies [9, 13, 16, 21]. Sometimes, staring spells do not have an EEG correlation, suggesting a non-epileptic origin of these disturbances. Our findings

in contrast with prior studies [6, 10, 13, 15, 16, 21], that reported a high prevalence of focal epilepsy and in agreement with other authors [9, 11], who have reported an high frequency of generalized epilepsies.

We found 15 children with PWS who suffered from febrile seizures, representing 39.4 % of our cohort of children with seizures. Febrile seizures in PWS have been previously reported with widely varying frequencies: [9, 10, 12, 13, 21] febrile seizures accounted for 100 % of the seizures in PWS in the report by Varela et al. [12], 11 % of the seizures in the study by Wang et al. and Vendrame et al. [9, 13], and 8 % of seizures in the report by Butler et al. [21]. Moreover, the rate of febrile convulsions seems to be similar to what was found in Angelman syndrome (approximately 43 % of the patients) [22], and different from what was found in other neurodevelopmental syndromes; e.g. in Down syndrome febrile seizures occur more rarely (approximately 0.9 %) [23].

Concerning EEG findings, we found various EEG abnormalities (multifocal and focal, diffuse spikes), confirming that in PWS there is no characteristic EEG feature.

Eleven patients (28.9 %) presented cerebral lesions at brain MRI; the most frequent abnormality was ventriculomegaly found in five subjects, followed by cortical atrophy and, sometimes, associated with hypoplasia of the corpus callosum. There are very few studies that have evaluated brain abnormalities in a cohort of individuals with PWS suggesting that, in some cases, ventriculomegaly can be associated with other brain lesions [13, 16, 17]. Miller et al. [18] hypothesized that ventriculomegaly could be a marker of cerebral dysgenesis and a manifestation of abnormal neuronal development, since it is often present in conditions, such as PWS, associated with intellectual disabilities. Currently it remains unclear whether ventriculomegaly results from loss or abnormal growth of gray matter, white matter or both.

In our patients, the presence of cerebral abnormalities is not related to a peculiar seizure type; also in previous studies, no clear association between brain lesions and type of epilepsy was found [10, 11, 13, 15, 16].

Literature data provided inconsistent information concerning the long-term prognosis of epilepsy in patients with PWS. On follow-up evaluation, outcome was good in the majority of children: in fact, only 6 of 38 patients did not remain seizure-free after withdrawal of antiepileptic therapy. No study compared the long-term outcome of epilepsy in patients with and without brain abnormalities. The comparison between group A and B patients showed that subjects with brain lesions had an earlier onset of epilepsy and required more often multiple AEDs; it is possible that brain abnormalities may result in an earlier onset of epilepsy. After long-term follow-up, 72.7 % of patients with brain abnormalities were seizure-free and 83.3 % of subjects without cerebral lesions showed disappearance of epilepsy, without recurrence of seizures. These data confirm the good response to antiepileptic monotherapy but also suggest that the presence of central nervous system abnormalities should be considered by the physicians as a risk factor of persistence of epilepsy.

From the literature analysis, the optimal therapeutical choice is unclear; in our series, VPA was used in 18 patients (47.4 %) and it was efficient in the control ofseizures in 14 children (77.8 %): our experience suggests that it is quite possible that, in PWS, VPA is more effectivethan the other anti-convulsants. It is important to rememberthat this drug can contribute to develop overweight with consequent dyslipidemia and metabolic syndrome that can be associated with long-term vascular complications, such as hypertension and atherosclerosis [24]. Thus, therapy with VPA should be carefully monitored.

Some methodological limitations of our study need to be addressed: because of its retrospective nature, accurate information of seizure frequency and semiology may involve considerable methodological difficulties; there may be a selection bias because the data were acquired from several epilepsy centers.

We conclude in saying that epilepsy in PWS patients has a favorable prognosis and a good response to antiepileptic therapy, with resolution of seizures at long-term follow-up, both in patients with and without brain lesions, although the patients with brain abnormalities have a higher risk to develop drug-resistant epilepsy.

Conflicts of interest All the authors have declared no conflicts of interests.

Ethical standard Written informed consent was obtained by parents or caregivers of all recruited patients. This study was approved by the Ethical Committee at the University Hospital ‘‘Santa Maria della Misericordia’’ in Perugia, Italy.

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