Angelman syndrome: Uniparental paternal disomy 15 determines mild epilepsy, but has no influence on EEG patterns

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Abstract

The authors describe the electroclinical phenotype of four patients with Angelman syndrome (AS) determined by its rarest genetic mechanism—uniparental disomy (UPD). The analysis of ours and published patients showed that in UPD, when epilepsy occurred, it was milder compared to patients with deletion, although a suggestive EEG was observed in most patients. We found that UPD patients do not completely fit the scenario delineated for AS, suggesting that patients determined by different mechanisms should be distinctly addressed, for a better understanding of this syndrome.

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Angelman syndrome (AS) is determined by different genetic mechanisms, affecting the maternal chromosome 15: deletion (DEL), uniparental disomy (UPD), imprinting center abnormalities and UBE3A mutations. One of these, paternal UPD, occurs in 1–3% of all AS patients. Although rare, there is strong evidence of a milder phenotype in the few patients described, constituting a putative subgroup representing a challenge for clinical diagnosis (Bottani et al., 1994; Fridman et al., 2000; Gillessen-Kaesbach et al., 1995).
To date, electroclinical data in UPD have been neglected, being part of reports that aim to describe clinical profiles. For this reason, it is unknown whether the binomial epilepsy-EEG is similar to that reported in patients with DEL (Laan et al., 1997). Herein, we describe the electroclinical phenotype of four children with UPD and compare these findings to DEL patients from our series of AS.

1. Methods

We evaluated 53 patients according to the Consensus for Diagnostic Criteria of AS (Williams et al., 1995). Because of their suggestive profile, they were referred for genetic evaluation.

1.1. DNA analysis

All patients were diagnosed by using the methylation test, and genetic mechanisms were characterized by microsatellite analysis (Mutirangura et al., 1993). Patients who presented normal results for both tests were screened for UBE3A mutations in the 7–16 exons, representing the coding region of the gene (Matsuura et al., 1997). No mutations were found in the UBE3A gene. Patients were not submitted to ICA mutation screening, since the combination of methylation and microsatellite analyses was not suggestive. The association of the methylation pattern of AS and normal inheritance of 15q11-13 alleles (maternal and paternal), showed by microsatellites, was the parameter used to detect cases of ICA mutation.

We included 28 genetically confirmed patients – 24 with DEL and 4 with UPD – in a prospective protocol.

1.2. Electroclinical protocol

We characterized epilepsy by history obtained from parents and caretakers with a pre-standard questionnaire, including: (1) occurrence of epilepsy; (2) age of onset; (3) seizure type; (4) febrile seizures and/or epilepsy aggravated by fever; (5) severity of epilepsy determined by history of—(i) daily seizures, (ii) disabling/injurious seizures, (iii) more than three different seizure types, (iv) status epilepticus (SE) and (iv) history of refractory epilepsy. These data were corroborated, in 21 patients, by medical records, personal contact with previous physicians and video-EEG monitoring (6–48 h; mean 8 h).

Patients underwent 1–13 EEGs (mean 2.6). A total of 91 EEGs, obtained at ages ranging from 4 months to 22 years (mean 5 years and 3 months), were analyzed. We have formerly described the methodology applied for EEG analysis (Valente et al., 2003). Suggestive EEG patterns of AS were studied regarding morphology, burst duration, occurrence, frequency, amplitude and distribution. These patterns were classified, when possible, according to those described by Boyd et al. (1988). Therefore, the following patterns were considered for this study:

1. Delta pattern: Runs of generalized, rhythmic delta activity, usually with frontal emphasis, and of high amplitude, sometimes associated with epileptiform discharges (often above 300μV).
2. Theta pattern: High amplitude (about 200μV), 4–6 Hz activity, generalized or over posterior regions, occupying most of the tracing.
3. Posterior discharges: Spike and sharp waves mixed with high amplitude 3–4 Hz activity, over posterior regions. These discharges were sometimes asymmetrical and typically triggered by passive eye closure.

We compared prevalence and severity of epilepsy, plus the EEG features mentioned above, between our UPD and DEL patients.

2. Results

2.1. Epilepsy findings

Out of our 28 patients, 25 (89.3%) had epilepsy (24 with DEL and 1 with UPD). Mean age of onset was 1.3 years (ranging from 0.3 to 5 years), preceding clinical diagnosis in 0.4–12.1 years (mean 3.3 years). All patients with epilepsy had generalized seizures and 11 also had partial seizures (39.3%). Electroclinical features of patients with DEL and UPD are detailed in Table 1.

2.1.1. DEL patients (n = 24)

All DEL patients had epilepsy with an age of onset ranging from 4 months to 2 years and 11 months (mean 1.1 years; median 0.8 years). All patients pre-
<table>
<thead>
<tr>
<th>Patient/age</th>
<th>Age of onset</th>
<th>Seizure type(s)</th>
<th>SE</th>
<th>Age of the last seizure</th>
<th>Current seizures</th>
<th>AEDs</th>
<th>Suggestive EEG patterns</th>
<th>Normal background</th>
<th>Epileptiform changes</th>
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<tr>
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<td>2y</td>
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<td>DP/PD</td>
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<tr>
<td>UPD 2/9y</td>
<td>–</td>
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<td>DP/PD</td>
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<tr>
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<td>DP/PD</td>
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<tr>
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<td>AA, 1 isolated GTC event</td>
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<td>5y</td>
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<td>DP/PD</td>
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<tr>
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<td>1y</td>
<td>PM/AA/Mcl</td>
<td>PM</td>
<td>PM/AA</td>
<td>PM/GTC</td>
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<tr>
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<td>DP/PD</td>
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<td>AA/GTC</td>
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y, years; mo, months; AA, atypical absences; CBZ, Carbamazepine; CLB, Clobazam; CLZ, Clonazepam; CP, complex partial seizures; DP, delta pattern; GT, generalized tonic seizures; GTC, generalized tonic–clonic seizures; Ml, myoclonic seizures; Nitrazepam; OLS, occipital lobe seizure; PB, phenobarbital; PD, posterior discharges; PM, partial motor seizures; PDR, posterior dominant rhythm; SE, status epilepticus; SSWC, slow spike-wave complex; TP, theta pattern; VPA, valproate; VGB, vigabatrin.

a Seizures occasionally aggravated by fever.
b Death.
presented generalized seizures and 10 had partial seizures. Febrile seizures occurred in 11 (52.4%) and SE in 17 (80.9%). Twenty-one patients (87.5%) had daily seizures, which in 16 (66.7%) were disabling. Thirteen patients (54.2%) had more than three different seizure types. Epilepsy was refractory to multiple drug trials in 79.2%. Eight (33.3%) patients achieved total seizure control and all remain under AED treatment.

2.1.2. UPD patients (n = 4)
One patient with UPD had epilepsy characterized by sporadic atypical absences from the age of 1.5 years, easily controlled at the age of 5 years, when seizures were recognized, and VPA introduced. One patient (9 years) had an isolated and afebrile episode (GTC) at the age of 6 years. The remaining two patients (8 and 9 years old) did not present seizures, even during febrile events. All patients in this group underwent prolonged V-EEG monitoring and two had polygraphic studies.

2.2. Electroencephalographic features
Patients were submitted from 1 to 13 EEGs (mean 2.6). A total of 91 EEGs were analyzed, performed between the ages of 4 months and 22 years (mean 5 years and 3 months; median 3 years and 11 months).

Suggestive EEG patterns were documented in 27 patients (96.4%). Delta pattern was found in 24 patients (85.7%), theta pattern in 9 (32.1%) and posterior discharges in 19 (67.9%). Posterior discharges were elicited by eye closure in only two patients. Morphology, distribution and occurrence of these patterns were not related to sleep/wake cycle. These patterns were present in association in 21 patients (75%). Morphologic variations of these patterns, especially delta, were observed, and their description is part of another study (Valente et al., 2003).

Fifteen patients (53.6%) had normal sleep patterns, but in only four of these (14.3%) adequate posterior dominant rhythms were obtained. Eleven patients (39.3%) presented interictal epileptiform discharges, not suggestive of AS. Six patients (21.4%) presented electrographic seizures.

2.2.1. DEL patients (n = 24 patients/56 EEGs)
All patients in this group presented suggestive EEG patterns for AS: delta pattern occurred in 21 (87.5%), theta in 9 (37.5%) and posterior discharges in 19 (67.9%). Delta pattern was almost continuous in one patient with deletion (5.3 years) and short burst (5 s) in one patient with UPD (5 years).
charges in 17 patients (70.8%). Prolonged bursts of delta pattern and posterior discharges were observed in 11 (45.8%) and 6 (25%) patients, respectively. Four DEL patients presented continuous or quasi-continuous bursts of delta pattern. Normal background was present in 1 patient (3%), interictal epileptiform discharges in 12 (50%) and electrographic seizures in 7 (29.2%), with concomitant clinical events in 6 (25%).

2.2.2. UPD patients (n = 4 patients/21 EEGs)

Three patients (75%) presented suggestive EEG for AS. Delta pattern was observed in three and posterior discharges in two, occurring in infrequent and short runs (ranging from 1 to 7 s). Seizures and interictal epileptiform discharges were not recorded in this group. All patients presented normal sleep patterns and three showed adequate posterior dominant rhythms.

2.3. Electroclinical phenotype and genotype correlation

Our data show that only 1 UPD had easy-to-control epilepsy compared to 19 patients with DEL and history of refractoriness. In relation to EEG, three UPD displayed normal age-related background activity, whereas only one DEL patient (4.8%) showed this feature. Suggestive EEG patterns of AS occurred in all patients with DEL and in three UPD. Delta pattern and posterior discharges were seen in all groups, the latter being more frequent in DEL. Theta pattern had a lower occurrence and was seen only in patients with DEL. Prolonged, quasi-continuous and continuous patterns (Fig. 1), as well as electrographic seizures, and unspecific interictal epileptiform discharges, were predominantly observed in DEL patients, whereas UPD patients did not present these characteristics.

3. Discussion

Knowledge on features of epilepsy in AS is based predominantly on the study of patients determined by deletion, since this subgroup makes up approximately 70–80% of all patients. Epilepsy in AS is described as generalized, with atypical absences and myoclonic seizures, early onset and age-related refractoriness (Laan et al., 1997; Williams et al., 1995; Valente et al., 2003). Analysis of our patients shows that only one UPD in opposition to all DEL patients had epilepsy. Accordingly, approximately 50% of reported UPD present epilepsy (Fridman et al., 2000). Therefore, although epilepsy is strongly associated with AS, it is a less useful criterion for diagnosis of AS, when determined by UPD. Moreover, when epilepsy occurs in AS caused by UPD, seizures have a later onset (Fridman et al., 2000). Because peculiar facial traits appear around 3 years of age, epilepsy findings could help to anticipate genetic counseling in DEL patients (Williams et al., 1995). However, epilepsy does not corroborate or suggest this diagnosis in patients with UPD, already challenging, because of their milder phenotype (Bottani et al., 1994; Gillessen-Kaesbach et al., 1995).

Other common features such as susceptibility to high temperature and frequent SE are rare in UPD, and only one patient with febrile seizures has been reported (Poyatos et al., 2002).

In our study, the UPD patient with epilepsy was easily controlled, compared to 79.2% DEL patients with refractory epilepsy. Data on severity of epilepsy in UPD are hard to obtain due to the inaccuracy of most descriptions, suggesting that epilepsy in UPD is mild, based only on seizure frequency, and presenting a good response to AEDs. Severe epilepsy is described in three patients (Poyatos et al., 2002; Prasad and Wagstaff, 1997), but data analysis shows that in two patients (Poyatos et al., 2002), seizures were easily controlled. Therefore, UPD seems to represent a subgroup of AS patients with milder epilepsy, especially when compared to DEL.

This is the first work that studies and delineates EEG in UPD patients and therefore, any comparison with previous vague descriptions is unfeasible. On the other hand, UPD and DEL patients did not show significant differences regarding frequency of suggestive EEGs, which was high in all groups. Thus, a suggestive EEG of AS was observed, whichever the underlying genetic mechanism or occurrence of epilepsy. However, suggestive EEG patterns are shorter and less frequent in UPD. For this reason, we believe that in this group, prolonged and serial EEGs are a contributing factor for identification of suggestive patterns. Likewise, analysis of isolated moments, as in routine EEGs, may lead to lower diagnostic rates and false-negative
results in patients with milder phenotypes. To date, a meticulous analysis of the three EEG patterns in UPD has not yet been done. In both groups, the most frequent patterns were delta followed by PD. However, in UPD, TP was not observed and although infrequent in AS, most patients had normal background activity.

In conclusion, AS patients determined by UPD do not completely fit the electroclinical scenario delineated for AS, and may represent the milder end within the spectrum of epilepsy severity in this syndrome. The occurrence of EEG patterns in both groups has additional importance to corroborate or raise clinical diagnosis of AS. From a practical point of view, this indicates that studies on epilepsy in AS should address genetic groups distinctly, as already performed with phenotypes, and suggests that the Consensus for the Diagnostic Criteria of AS should be reviewed in order to encompass the different phenotypes of this syndrome.

Findings of a milder phenotype in UPD patients could be partially correlated to the preservation of a larger genetic contingent in non-DEL patients. A cluster of GABA-A genes, especially the subunit β3, located in chromosome 15, has been correlated with the genesis of epilepsy in AS (DeLorey et al., 1998). According to Minassian et al. (1998), involvement of GABRB3 in chromosome 15q11-q13 deletion may explain severe epilepsy in AS. Indeed, GABAergic genes are not imprinting genes such as UBE3A, and therefore, inheritance of the paternal allele partially spares these genes and may explain milder features in UPD patients.

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