Angelman Syndrome: Difficulties in EEG Pattern Recognition and Possible Misinterpretations

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Summary: Purpose: This study aimed to evaluate the sensitivity of the EEG in Angelman syndrome (AS), to verify the age at onset of suggestive EEGs and to study EEG patterns, analyzing variations and comparing our findings with nomenclature previously used.

Methods: Seventy EEG and 15 V-EEGs of 26 patients were analyzed. Suggestive EEG patterns of AS were classified in delta pattern (DP), theta pattern (TP), and posterior discharges (PDs). Generic terms were used to simplify the analysis.

Results: Suggestive EEGs were observed in 25 (96.2%) patients. DP occurred in 22 patients with four variants—hypsarrhythmic-like: irregular, high-amplitude, generalized delta activity (DA) with multifocal epileptiform discharges (EDs); slow variant: regular, high-amplitude, generalized DA with rare EDs; ill-defined slow spike-and-wave: regular, high-amplitude, generalized DA with superimposed EDs characterizing a slow wave, with notched appearance; triphasic-like: rhythmic, moderate-amplitude DA over anterior regions with superimposed EDs. TP was observed in eight patients, as generalized or over the posterior regions. PDs were seen in 19 patients as runs of sharp waves or runs of high-amplitude slow waves with superimposed EDs. TP was the only age-related pattern (younger than 8 years) and observed only in patients with deletion. In 15 patients who had an EEG before the clinical diagnosis, 60% had a suggestive tracing.

Conclusions: Although some EEG descriptions are not very detailed, and every author describes findings in a slightly different manner, obviously a common denominator must exist. In this context, EEG seems to be a very sensitive method for the diagnosis of AS, offering an opportunity to corroborate this etiologic diagnosis. Conversely, we do not believe that these patterns may be accounted as specific, except for the delta pattern, which seems to be extremely unusual in other syndromes. Other EEG patterns observed in AS, such as theta activity and PDs, occur in a wide variety of disorders. Nonetheless, their importance for the EEG diagnosis of AS is supported by the fact that they are associated with other features and may be helpful in a proper clinical setting. Key Words: Angelman syndrome—EEG—Variants—Epilepsy—Genetic mechanisms.

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Angelman syndrome (AS) was originally described in 1965 by a British pediatrician named Harry Angelman, who reported three children with peculiar traits and introduced the term puppet children to name them (1). AS did not attract much attention in medical literature until the 1980s, when advances in the field of genetics led to renewed interest in this syndrome. According to the Consensus for Diagnostic Criteria (2), AS demonstrates, in all cases, impairment of neurologic development, poor or no language acquisition, a peculiar behavioral profile (unprovoked laughter, happy demeanor, hand flapping, hyperactivity, and attention-deficit disorder), and a wide-based gait with jerky movements. Epilepsy, suggestive EEG abnormalities, and microcephaly occur in ~80% of cases (2). Peculiar facial traits, brachycephaly, hypopigmentation, type II albinism, wide-spaced teeth, and sleep disorders have a more variable occurrence (20–80%) (2).

AS is caused by multiple genetic mechanisms, all of which affect the maternal chromosome 15q11-q13, a known imprinted region. The known genetic mechanisms for AS are deletion (DEL) (3–5), paternal uniparental disomy (UPD) (6), imprinting center abnormalities (ICAs) (7), and UBE3A mutations (8,9). They have different prevalences and risks of recurrence; therefore their recognition is important for proper genetic counseling. Maternal DEL occurs in 75–80% (10), UPDs in 2–3% (11), ICA is detected in 2–5% (12), and ~8% of all AS patients have a UBE3A mutation. The remaining 12–15% of AS patients do not have a detectable genetic mechanism, and diagnosis is performed on clinical and EEG grounds.
EEG abnormalities were reported in the original description (1); however, only two decades later, Boyd et al. (13) described three EEG patterns suggestive of AS. These patterns are not observed in newborns, but they may appear early in life, from ~4 to 9 months, and may also be helpful for diagnosis in infants, when one considers that the classic phenotype becomes evident only at the ages of 3 to 4 years (14–17).

Although recent reports have agreed with the presence of suggestive or even specific EEG patterns in this syndrome and have stressed how important they are for diagnosis, many discrepancies occur in their descriptions (14–18).

The present study aimed to analyze EEG patterns in a large number of patients with clinical and/or genetic diagnosis of AS to

1. evaluate the sensitivity of this noninvasive diagnostic method to support clinical diagnosis;
2. verify the age at onset of suggestive EEG abnormalities and to correlate this to the age at diagnosis on clinical grounds to determine whether this datum could have been used for early diagnosis; and
3. study EEG patterns, analyzing possible variations and comparing our findings with the descriptions and nomenclature used in other reports, in an attempt to organize and compile the distinct descriptive terms previously used.

PATIENTS AND METHODS

Patient demographics

Forty-five consecutive patients (72.7% female and 27.3% male, with ages from 6 months to 22 years) with a presumptive clinical diagnosis of AS were referred to the Epilepsy Center at the University of São Paulo, a tertiary institution, during a 4-year period (March 1997 through March 2001). These patients were referred for etiologic investigation from secondary and primary hospitals and were previously classified as patients with nonprogressive encephalopathy or with autistic features without a detectable cause. Seven of these patients had an associated diagnosis of cryptogenic Lennox–Gastaut syndrome (LGS) and also were referred for epilepsy management. Two infants, referred at the ages of 6 and 8 months, had as major clinical complaints impaired development with global hypotonia, epilepsy, and severe hypopigmentation.

First a child neurologist examined all patients by using criteria determined by the Consensus for Diagnostic Criteria of AS (1995) (2). Then patients were referred to the Center of Study of Human Genome, Department of Biology, where two geneticists, partially masked to previous opinions, evaluated these patients clinically and collected blood samples to perform genetic analysis, which will be detailed.

The inclusion criteria were (a) patients with genetic confirmation for chromosome 15 abnormalities (DEL, UPD, ICA, and UBE3A mutations) or (b) patients without genetic confirmation who had confirmed and congruent clinical diagnoses of AS, determined by two examiners. Therefore, lack of genetic confirmation was not considered sufficient to exclude a patient.

Although the presence of epilepsy and EEG features of AS is part of the set of abnormalities that form the consensus, they were not used as criteria of inclusion, because this would introduce a selective bias.

The exclusion criteria were (a) noncongruent clinical examinations in patients with negative genetic studies or (b) patients whose parents did not consent to genetic studies.

Twenty-two (84.6%) patients obtained a genetic confirmation: 19 with Chr15q11-13 DEL and three with UPD. None of our patients had ICA or UBE3A mutations. Four patients with congruent clinical examinations according to all examiners were included, although lacking a detectable genetic abnormality. The inclusion of these patients, who had all the consistent criteria for AS according to Williams et al. (2), was based on the strict congruency of diagnosis of AS on clinical grounds for all investigators.

According to the criteria mentioned, 19 of the 45 patients were excluded, because three refused genetic evaluation and 16 did not have any detectable genetic anomaly associated with discrepancies and doubts regarding their clinical diagnosis, in the opinion of at least one of the examiners. The divergences in these cases resulted from the fact that they had milder phenotype, not encompassing the fundamental characteristics for the diagnosis solely on clinical grounds.

Patients had 70 EEGs, which were analyzed for the study. These examinations were obtained at distinctive ages, ranging from 4 months to 22 years (mean, 5.2 years; median, 3.9 years). Most patients had from two to six EEGs (mean, 2.6) at different times and at different ages, except for four patients who had only one study. The period between these studies ranged from 6 months to 7 years. Forty-one EEGs were performed during wakefulness, drowsiness, and sleep; 21 only during sleep; and six only during wakefulness.

METHODS

DNA analysis

All patients were analyzed with the methylation test, which was performed by using the probe containing exon 1 of SNRPN-SNURF gene and by microsatellite analyses, which were performed according to Mutirangura et al. (19). After that, patients who had normal results for both tests were screened for UBE3A mutations in the 7-16 exons, representing the coding region of the gene (20). No mutations were found in the UBE3A gene. Patients
were not tested for the ICA mutation because 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 an ICA mutation case.

Neurophysiologic evaluation

All patients underwent prospective EEG and/or video-EEG (V-EEG) evaluations, with a minimum duration of 4 h. EEGs performed previously were considered if the recording was obtained with the same technical parameters as those used in our study (HFF, 70 Hz; TC, 0.3 s; PS, 30 mm/s). Analysis of previous EEGs with a minimum interval of 6 months was considered to allow evaluation of EEG patterns at early ages.

Performance of the EEGs in these patients was time consuming because of severe mental retardation associated with behavioral disorder (hyperactivity). Therefore nonroutine procedures and staff were used because patients had to be restrained and/or sedated with cloral hydrate 10% (0.5 mg/kg/dose). Scalp electrodes (10-20 or 10-10 system, if necessary) were attached with collodium, and passive eye closure was carried out in 29 EEGs under careful physical restriction when the sedation effect was over.

Analysis of EEG tracings was done simultaneously by two certified neurophysiologists. In case of disagreement, the same tracings were analyzed again at a different time. When necessary, a third staff member, closely involved in the process of performing and analyzing these examinations, was entitled to give her opinion.

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. (13). 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 >300 µV);
2. Theta pattern: High-amplitude (∼200 µV), 4- to 6-Hz activity, generalized or over posterior regions, occupying most of the tracing; and
3. Posterior discharges: Spikes and sharp waves mixed with high-amplitude 3- to 4-Hz activity, over posterior regions. These discharges were sometimes asymmetric and typically triggered by passive eye closure.

For the purpose of this study, we used generic terms to name different patterns: delta pattern, theta pattern, and posterior discharges. These terms were preferred instead of lengthy descriptions to simplify the analysis of possible variations presented by these patterns.

Other interictal abnormalities, which could not be classified in the groups mentioned earlier, also were analyzed considering the same criteria (morphology, localization, occurrence, distribution, and amplitude) and were then grouped according to their similarities. This analysis was performed to verify whether any abnormality appeared that was consistent and constant enough to be considered a distinct and novel pattern suggestive of AS.

Electrographic seizures were analyzed considering morphology, localization, and occurrence, and were quantified as rare, frequent, very frequent, or continuous.

Background activity was analyzed regarding frequency, amplitude, spatial distribution, interhemispheric symmetry, and synchrony during wakefulness, drowsiness, and sleep.

Results are presented as numbers of patients and not as numbers of EEGs. Although the number of EEGs is given for better illustration of our sample, it is not used to compare differences among patients.

RESULTS

Clinical and genetic characterization of some of these patients was previously addressed by Fridman et al. (21).

EEG patterns suggestive of AS

EEG patterns suggestive of AS were observed in 47 EEGs of 25 (96.2%) of 26 patients. Only one patient had repeatedly normal EEGs [five examinations from the ages of 1 to 5 years (one examination/year)]. This patient had a uniparental disomy and so far has not had seizures.

To analyze the frequency with which these patterns occurred, we took into account only those patients who had the suggestive EEG patterns. Therefore the number of patients considered was 25.

The delta pattern occurred in 41 EEGs [ages from 0.4 to 21.2 years (mean, 5.7 years)] of 22 (88%) of 25 patients who had an EEG suggestive of AS. Some inter- and intra-individual variations, regarding mainly morphology and distribution, were observed. We were able to classify them in four variants:

1. Hypsarrhythmic-like variant: Runs of high-amplitude, generalized, irregular delta waves, without spatial organization, associated with multifocal epileptiform discharges, characterized by spikes or sharp waves of moderate amplitude. This variant, although resembling a hypsarrhythmic pattern, had a predominance of slow waves over the epileptiform discharges. No correlation with sleep/wake cycle was noticed. This variant was seen in three EEGs [obtained at the ages of 0.4, 1.2, and 1.3 years (mean, 0.9 years)] of two (9.1%) of 22 patients (Fig. 1A);
2. Ill-defined slow spike and wave variant: Runs of regular, quasi-rhythmic, high-amplitude delta activity, with generalized distribution, usually with predominance over anterior regions, and with superimposed epileptiform discharges (spikes or sharp waves), ranging from moderate to low amplitude, occurring either on the descending or on the ascending phase of the slow wave. As observed in other variants of the delta pattern, a clear predominance of the slow-wave component is seen over the epileptiform activity, forming a complex with a peculiar morphology, characterized by a slow wave, with notched appearance (Fig. 1B). These features were registered in 32 EEGs [1.2–16.7 years (mean, 5.2 years)] of 16 (72.7%) of 22 patients;

3. Triphasic-like variant: Runs of monomorphic, rhythmic, and regular delta waves, with moderate amplitude, over anterior regions, or generalized with an evident predominance over these regions, with low-amplitude sharp waves (Fig. 1C), on the descending phase of the slow wave in nine EEGs [1–16.7 years (mean, 6 years)] of five (22.7%) of 22 patients; and
4. Slow variant: Runs of regular, high-amplitude, delta activity, with generalized distribution, usually with anterior predominance, and with none or rare epileptiform discharges (Fig. 2). This variant occurred in 24 EEGs [1–21.2 years (mean, 4.9 years)] of 15 (68.2%) of 22 patients.

These variants of delta pattern did not change during sleep (phases I and II).

Delta pattern bursts varied in duration from continuous or almost continuous. They occurred in prolonged bursts (>10 s) in 14 patients, as continuous or quasi-continuous, in five of these.

The theta pattern was observed in 14 EEGs [1.2–7 years (mean, 3.8 years)] of eight (32%) of 25 patients and was characterized by 4- to 7-Hz activity, of high amplitude (>150 μV), and with a regular, rhythmic, sinusoidal, and monotonous morphology. This pattern had a variable distribution, being observed as generalized in four EEGs of three patients, and over the posterior regions (Fig. 3A), in 14 EEGs of eight patients, of which three were asymmetric. This pattern occurred in bursts that lasted from 2 to 10 s (mean, 7 s) and was continuous in one EEG, during wakefulness and sleep. Morphology, distribution, frequency, and occurrence of this pattern were not related to the sleep/wake cycle (Fig. 3B)
and were not blocked by eye-opening during awake periods.

Posterior discharges were seen in 31 EEGs [1–16.7 years (mean, 5.3 years)] of 19 (76%) of 25 patients and were observed as:

1. Runs of rhythmic 4- to 6-Hz sharp waves in 14 EEGs of 13 (68.4%) of 19 patients; and
2. Runs of high-amplitude slow waves (theta/delta), with superimposed low-amplitude sharp waves, forming rhythmic complexes (Fig. 4), in 25 EEGs of 16 (84.2%) of 19 patients.

These posterior discharges were usually seen in short runs, except for five patients, who had bursts > 10 s.

Passive eye closure was carried out in 29 EEGs, but posterior discharges, elicited by this procedure, were observed in only one patient.

Association of more than one EEG pattern suggestive of AS was obtained in 31 EEGs of 20 (80%) of 25 patients. The most frequent associations were: delta and posterior discharges in 11 (42.3%) of 25 patients; delta and theta in two (7.7%); and theta and posterior discharges in one (3.8%) of 25 patients. Association of the three patterns in the same tracing or in serial EEGs was present in four (15.4%) patients.

The delta pattern and posterior discharges were observed in all ages (from 4 months to 22 years), and in all groups (DEL, UPD, and NEG), despite the milder phenotype in some patients. The theta pattern was the only one
that was age related, being observed in those younger than 8 years, and only in patients with DEL. The correlation of these abnormalities with distinctive genetic mechanisms is part of another study.

In the 22 patients with genetic confirmation, suggestive EEG patterns preceded the genetic diagnosis in 16 (72.7%). Moreover, in all patients without genetic confirmation, the EEG was able to corroborate the clinical diagnosis.

The age at clinical diagnosis ranged from 2 to 17 years 2 months (mean, 4.9 years; median, 3.8 years). Analysis of EEG tracings of 15 patients who had EEGs performed before the clinical diagnosis of AS revealed that nine (60%) had suggestive EEG patterns. Their ages when the EEG was obtained ranged from 5 months to 15 years 11 months (mean, 4.4 years; median, 2.4 years). In the EEGs of six patients, we could observe an early age at onset (before age 3 years) for suggestive EEG features of AS: one before the first year, three after the first but before the second year, and two patients younger than 3 years. The interval between the presence of suggestive EEG and the clinical diagnosis ranged from 3 months to 4 years 9 months (mean, 1.6 years; median, 1.2 years).

**Other EEG abnormalities**

Interictal epileptiform discharges occurred in 21 EEGs of 12 (46.2%) of 26 patients. They were characterized by spike/sharp waves over frontal regions in five (41.7%), frontocentral in four (33.3%), temporal in three (25%), posterior quadrant in six (50%), and multifocal in five (41.7%) of 12 patients. These discharges were nonspecific and did not constitute a novel EEG feature for the diagnosis of AS.

Seizures were recorded in eight (30.8%) of 26 patients during prolonged V-EEG studies and were characterized by slow spike-and-wave complexes in five patients, with concomitant atypical absence status. In one patient, we observed sharp theta activity over the right occipital region during a complex partial seizure, with sustained head and eye deviation to the left, and in other two patients, a generalized tonic-clonic event, with EEG correlate.

**Background activity**

Adequate posterior dominant rhythm (PDR) was observed in only nine EEGs of six (23.1%) of 26 patients. Normal sleep patterns, mainly sleep spindles, were seen in 26 EEGs of 19 (73.1%). The following abnormalities were observed in 42 EEGs of 22 (84.6%) of 26 patients: diffuse slowing (18 patients), slow PDR for the patient’s age (six patients), asymmetry (one patient), absence of sleep patterns (three patients), and ill-defined sleep patterns (one patient).

**DISCUSSION**

EEG is considered an important asset for syndromic diagnosis in patients with epilepsy. Its relevance may be exemplified by the occurrence of the hypsarrhythmic pattern in West syndrome (22), yielding a possible diagnosis,
as well as guiding to an early therapeutic approach. Likewise, EEG may help to support an etiologic diagnosis of AS(13) by the presence of three suggestive EEG patterns (delta, theta, and posterior discharges).

Suggestive EEG patterns of AS

In our series, EEG patterns suggestive of AS occurred in 96.2% of patients. Serial and prolonged EEGs were important to detect these patterns by increasing the sensitivity of this method. This high prevalence also is found in other series (16–18). Boyd et al. (17), in 1997, reported that of 150 cases of their personal series, 98% had EEG patterns suggestive of AS.

Although several authors (14–16,23) agreed with the existence of suggestive EEG patterns in AS, different descriptive terms have been used to name them, raising confusion and possible misinterpretations. Different names are applied to make reference to the same pattern, which becomes even more apparent when comparing published EEG tracings directly. In part, this may be explained by the wide range of morphologic variations observed in these patterns, especially when we study the delta pattern.

Delta pattern

This pattern is the most frequently mentioned in medical literature since the original description of the syndrome by
Angelman (1), reporting high-amplitude delta waves. In our study, these delta waves occurred in 41 (60.3%) of 68 EEGs, and 22 (88%) of 25 patients, in concordance with previous studies (13–16, 23–28).

As previously reported by Matsumoto et al. (15), we noticed that delta waves, called the delta pattern for this study, may have an irregular morphology, associated with moderate- to high-amplitude epileptiform discharges, with multifocal distribution. This irregularity, as well as the lack of topographic organization, led these authors to emphasize its similarity to hypsarrhythmia. Although the excessive contingent of slow waves could be used as a differential feature, the presence of a slow variant of hypsarrhythmia, as described by Hrachovy et al. (29) resembling this pattern, may lead to a misdiagnosis. The most remarkable difference between hypsarrhythmia and the delta pattern is the change with sleep in the former, characterized by fragmentation of that pattern during this state (30). This phenomenon was not observed in our series, although the restricted number of patients with this variant does not allow us to draw any further conclusions. Even though our EEG study was not evolutionary, it seems worthwhile to mention that this variant was present in EEGs performed at very early ages, in agreement with data published by Matsumoto et al. (15).
In 72.7% of our patients, we noted a gradual organization of the recordings during childhood, leading to the appearance of a more regular and synchronous delta pattern variant, with generalized distribution, usually with anterior predominance, and with superimposed epileptiform activity of variable amplitude. Because of the regular morphology and frequency of these features, ranging from 2 to 2.5 Hz, it may resemble the slow spike-and-wave complexes observed in the LGS, as previously mentioned by other authors (15,23), or otherwise named by Boyd et al. (13) as “ill-spike and wave complex.” However, in our patients, this delta variant did not have a sufficiently well-delineated epileptiform discharge to configure a slow spike-and-wave complex. Instead, the epileptiform discharge was superimposed on the slow wave, which assumed a notched appearance, with a discharge that maintained a temporal relation closer to the subsequent than to the preceding slow wave. Moreover, a clinical differential diagnosis between AS and LGS is not always evident, because seizure semiology, at a certain age, may be very similar; notably, in our study, eight patients had a previous diagnosis of cryptogenic LGS. We believe that the distinction between LGS and AS may be performed by considering the morphologic differences between the complexes, as mentioned earlier (31–34), associated with a lack of recruiting rhythm during sleep in AS (31,33,35), because these were not observed in our patients with AS, as well as in those reported by others (13–18,23).
We also observed (in 10.3% EEGs of 22.7% of patients) yet another variant, characterized by monomorphic, regular and rhythmic delta waves of moderate amplitude, with superimposed low-amplitude sharp waves, usually over the anterior regions. Such features led Laan et al. (16) to name them “triphasic complex or pattern.” We believe this variant may be differentiated from the classic triphasic complex, as described by Foley et al. (36), and a posteriori named by Bickford and Butt (37), by the absence of changes with sleep, because this delta variant does not disappear during sleep, as usually observed with classic triphasic waves.

Independent of any variation presented by the delta pattern, it did not change during sleep, except for an increase in the contingent of slow waves.

**Theta pattern**

Bowers and Jeavons (24) were the first authors to report an excessive theta activity in one AS patient at age 7 years. In this study, the theta activity was the less frequently observed pattern, occurring in 32% of our patients. This activity is monotonous and of high amplitude, varying only in distribution, occurring either more posteriorly or generalized. The lower prevalence of this pattern is probably related to the paucity of publications addressing it, although some authors report an unusual hypnagogic hypersynchrony in older AS patients (28). The occurrence of this pattern, as well as its morphology and duration, was not related to drowsiness or eye closure, in concordance with Boyd et al. (13), who reported the presence of this activity in patients during the awake and sleep states.

However, the theta pattern is not necessarily specific for AS. This theta activity is equally observed in another entity, Doose syndrome (myoclonic–astatic epilepsy), where it is called Doose rhythm (DR). Some features that may be used to differentiate DR from the theta pattern of AS are the fact that DR is blocked by eye opening, and that is usually associated with polyspike-and-wave discharges during the course of the disorder (38). These characteristics have not been observed in AS in our study or in others.

**Posterior discharges**

The presence of posterior discharges elicited by passive eye closure was emphasized by Pampiglione and Martinez (27) and Boyd et al. (13). As stated by Laan et al. (16), the lack of these discharges in their series could be correlated to difficulties in carrying out these tests on hyperactive children with severe developmental delay.

However, in our series, posterior discharges were observed in 76% of patients and, in disagreement with previous reports (13–17), were not related to passive eye closure, except in one child, despite adequate testing.

Posterior discharges were characterized by high-amplitude slow waves (delta/theta), with superimposed sharp waves, in most patients, as described by Boyd et al. (13) and Casara et al. (14). In 68.4% of the patients in our group, we observed, previously unreported, prolonged runs of sharp theta waves. It seems important to describe the latter, because in many patients, they have been interpreted as electrographic seizures originating from the occipital lobe (18).

In agreement with formerly reported series (13,16,18), association of these suggestive EEG patterns occurred in 80% of our cases, in the same EEG, or in serial EEGs from the same patient, and therefore this association assists the diagnosis.

**Other interictal and ictal abnormalities**

Other interictal epileptiform discharges were analyzed by using the same parameters as those used to evaluate the suggestive EEG patterns for AS, but they did not show sufficient evidence of specificity to configure the existence of any other characteristic pattern of this syndrome.

As reported by Matsumoto et al. (15), we also observed a high prevalence of atypical absence seizures with slow spike-and-wave complexes, sometimes unnoticed by parents and caregivers.

It remains controversial whether the EEG patterns suggestive of AS are related to ictal events (16,18,39,40). In the present study, occurrence of suggestive patterns was not correlated to clinical events. However, we must consider that polygraphic or back-averaging studies were not performed; therefore myoclonic seizures could not be completely ruled out.

**Age and genotype correlation**

The detailed analysis of electroclinical differences in distinct genetic groups is part of another study. However, in our series, EEG could have been helpful to support clinical diagnosis in the majority of the patients, especially in patients without genetic confirmation (20%). Besides, EEG could have anticipated the diagnosis in most patients; however, the unawareness of these patterns postponed proper genetic counseling. Based on this, we believe that prolonged EEG studies seem to be advisable for infants with development delay, independent of the presence of epilepsy.

Genetic confirmation is possible in 75–80% of patients (41), and diagnosis of AS is reached by a triad constituted of clinical, EEG, and genetic studies. Besides allowing diagnosis in patients without genetic confirmation, clinical–EEG correlation brings to mind the diagnostic hypothesis of AS. This may guide toward a genetic study for AS, in infants with undetermined encephalopathies (15), and thereby, make possible an early therapeutic approach (42). In this setting, genetic counseling is mandatory, because different recurrence risks exist for each distinct genetic mechanism.

One must consider that the delta pattern is not pathognomonic for AS, because it has been observed in other chromosomal disorders, such as 4p deletion (43) and more
recently, Rett syndrome (44); therefore EEG is an excellent tool for AS diagnosis taking into account the clinical scenario. It is also important to emphasize that although the phenotype may be extremely helpful to distinguish certain syndromes, such as the clear distinction between AS and 4p deletion (Wolf–Hirschhorn and Pitt–Rogers–Danks syndrome), the same does not apply to Rett syndrome. A clinical overlap between these conditions (AS and Rett syndrome), recently addressed by Watson et al. (45), may represent an additional difficulty even when considering the clinical profiles.

Although a detailed description of epilepsy was not the main purpose of this study, it is worthwhile mentioning that some AS patients had atypical absences recognized only during V-EEG. Patients with some chromosomal disorders have a higher risk for nonconvulsive status, not easily detected because of their preexisting condition and poor contact (15,23), indicating that this group may have additional benefits from this procedure. In this sense, prompt recognition of these events was essential for proper management. Although in most cases with absence status, a prolonged EEG could have established diagnosis, the ictal slow spike-and-wave complex may be confused with the interictal delta activity in AS patients, defined by Boyd et al. (13) as an “ill-defined slow spike-and-wave complex.” In these AS patients, correlation between the event and electrographic activity was important, as reported by others (15). Conversely, the similarities between some of the delta variants with hypsarrhythmic pattern and slow spike-and-wave complexes represented a pitfall for the diagnosis, with unnecessary exposure of these patients to high doses of AEDs, as illustrated by our eight patients with a previous diagnosis of LGS.

In conclusion, although some descriptions of the EEG are not very detailed, and every author describes EEG findings in a slightly different manner, obviously a common denominator must exist among these descriptions. In this context, EEG seems to be a very sensitive method for the diagnosis of AS, offering an almost unique opportunity to corroborate this etiologic diagnosis. Moreover, it has an early onset compared with the phenotype, which may anticipate the diagnosis. Although the delta pattern seems to be extremely unusual in other syndromes, we do not believe that these patterns may be counted as specific, because they may represent a common denominator to chromosomal disorders. Other EEG patterns observed in AS, such as theta activity and posterior discharges, occur in a wide variety of disorders. Nonetheless, their importance for the EEG diagnosis of AS is supported by the fact that they are associated with other features and may be helpful, when used in a proper clinical setting.

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