Epilepsy in Patients With Angelman Syndrome Caused by Deletion of the Chromosome 15q11-13

Kette D. Valente, MD, PhD; Célia P. Koiffmann, PhD; Cintia Fridman, PhD; Mônica Varella, PhD; Fernando Kok, MD, PhD; Joaquima Queiroz Andrade, MD, PhD; Rosi M. Grossmann, MD, PhD; Maria Joaquina Marques-Dias, MD, PhD

Background: Angelman syndrome (AS) is a neurogenetic disorder characterized by severe mental retardation, speech disorder, stereotyped jerky movements, and a peculiar behavioral profile, with a happy disposition and outbursts of laughter. Most patients with AS present with epilepsy and suggestive electroencephalographic patterns, which may be used as diagnostic criteria.

Objective: To study epilepsy and response to treatment in a series of patients with AS determined by deletion.

Design: Parent and caregiver interview and medical record review.

Setting: Epilepsy Center at the University of São Paulo.


Main Outcome Measures: Epilepsy severity, epilepsy evolution, and response to antiepileptic drug treatment.

Results: All patients with AS in this group had generalized epilepsy, and 10 (53%) also had partial epilepsy. Main seizure types were atypical absences and myoclonic and tonic-clonic seizures. Mean age at onset was 1 year 1 month. Epilepsy aggravated by fever occurred in 10 patients (53%) and status epilepticus in 16 (84%).

Conclusions: Patients with AS with deletion have epilepsy with early onset and stereotyped electroclinical profile regarding seizure type, severity, and response to antiepileptic drug treatment. Another feature of AS is the age-related improvement, even in refractory cases, during late childhood and puberty. These characteristics are not specific to this syndrome but, when inserted in the proper clinical context, may anticipate diagnosis. We believe that AS should be considered a differential diagnosis in developmentally delayed infants with severe, generalized, cryptogenic epilepsy; however, a proper electroclinical delineation of each genetic group is mandatory.

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to a mutation in the imprinting center. Approximately 8% of all patients with AS have a UBE3A mutation that determines loss of function of the gene encoding a ubiquitin protein ligase. The remaining 12% to 15%, despite the absence of a detectable genetic mechanism, are considered to have AS, and diagnosis is performed on clinical and electroencephalographic (EEG) grounds. Recurrence risk is distinct for each group. Therefore, identification of patients with AS is mandatory because of implications in genetic counseling.

Singh et al emphasized the scarcity of articles that provide a meticulous classification of epilepsy and epileptic syndromes, according to International League Against Epilepsy classification systems. The importance of such detailed electroclinical descriptions lies in identifying specific epileptic syndromes associated with particular chromosomal aberrations as well as providing regions of interest for genetic research.

The first studies designed to study epilepsy in AS were published in the 1990s, usually encompassing a small number of patients. Consequently, many controversies exist regarding seizure type and its evolution, as well as the best therapeutic approaches. Additionally, characterization of epilepsy in AS has been determined by studies with small sample sizes that combine patients determined by distinct genetic mechanisms into 1 group for analysis. We studied and followed up 19 patients with AS caused by 15q11-13 deletion, aiming to evaluate whether epilepsy in AS is stereotyped enough to represent a specific profile that could be of practical importance for diagnosis of AS in this group.

METHODS

Forty-five consecutive patients (73% female and 27% male, aged 6 months to 22 years) with a presumptive clinical diagnosis of AS were referred to the Epilepsy Center at the University of São Paulo during a 4-year period for clinical and electroencephalographic evaluations. A geneticist (C.P.K.) and a child neurologist (K.D.V.) separately examined all patients, using criteria determined by the Consensus for Diagnostic Criteria of AS. The inclusion criterion for this study was genetic confirmation of chromosome 15 deletion.

Of all patients referred and tested, we confirmed 26 (69% female) as having AS. Nineteen patients (73%) were determined by maternal deletion of chromosome 15q11-13, 3 (12%) had a paternal uniparental disomy, and 4 (13%) did not have a detectable genetic mechanism, but their clinical phenotype was supportive of diagnosis according to evaluations performed by both a geneticist and a child neurologist involved in this project.

EPILEPSY CHARACTERIZATION

We obtained a detailed history of epilepsy from parents and caregivers and corroborated this information by checking medical records and previous examination results (EEGs and video EEGs) and by personal contact with referring physicians. The following information was collected: (1) presence of epilepsy, (2) age at epilepsy onset, (3) seizure type at onset and during follow-up, (4) history of severe epilepsy, (5) status epilepticus (SE), (6) history of refractory epilepsy, and (7) occurrence of isolated seizures and/or febrile seizures. Video EEG monitoring (6-48 hours; mean, 8 hours) was performed in 18 patients, 15 (58%) with deletion, to detect subtle seizures that went either unnoticed or unreported by parents and/or caregivers. Seizure types were determined by history corroborated by past medical records and video EEG and were classified according to guidelines of the Commission on Classification and Terminology of the International League Against Epilepsy.

DNA ANALYSIS

All patients had their conditions diagnosed with a methylation test, and genetic mechanisms were characterized by microsatellite analysis. Patients with normal results on both tests were screened for UBE3A mutations in exons 7 through 16, representing the coding region of the gene. No mutations were found in the UBE3A gene. Patients did not undergo imprinting center abnormality mutation screening, since the combination of methylation and microsatellite analyses was not suggestive. Association of methylation pattern of AS and normal inheritance of 15q11-13 alleles (maternal and paternal), shown by microsatellite analysis, was the parameter used to detect an imprinting center abnormality mutation case.

PREVALENCE AND SEIZURE TYPE

Epilepsy occurred in 22 patients (85%) (19 with deletion and 3 with negative genetic study results). In 1 patient with uniparental disomy, epilepsy occurred as an isolated generalized tonic-clonic episode (no recurrence). All patients with deletion had epilepsy.

All 19 patients with deletion and epilepsy had generalized seizures, and 10 (53%) had partial seizures (Table 1 and Table 2). All patients had more than 1
seizure type, classified as atypical absences in 16 patients (84%), myoclonic in 13 (68%), generalized tonic-clonic or tonic in 12 (63%), simple partial with motor phenomena in 6 (32%), complex partial in 5 (26%), and myoclonic-astatic in 2 (11%).

We registered seizures in 13 (87%) of the 15 patients who underwent video EEGs (1-4 per patient). Atypical absences occurred in 7, myoclonic seizures in 3, tonic-clonic seizures in 2, atonic seizures in 1, and unnoticed occipital lobe seizures with head deviation in 1. These events were unnoticed by parents or reported as periods of decreased contact with environment in 9 patients. Six patients had SE, which was characterized as atypical absence status in 5 and myoclonic status in 1.

**Table 2. Characteristics of Epilepsy in Patients With Angelman Syndrome Determined by Deletion During Follow-up**

<table>
<thead>
<tr>
<th>Patient/Age</th>
<th>Seizure Types During Follow-up</th>
<th>Age at the Last Seizure</th>
<th>Current Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/6 y 11 mo</td>
<td>Occipital lobe evolving to CP, GTC</td>
<td>4 y 11 mo</td>
<td>Partial motor with fever, AA</td>
</tr>
<tr>
<td>2/7 y 4 mo</td>
<td>Hemiclonic aggravated by fever, AA, Mcl, SE with SP (hemiclonic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/3 y 8 mo</td>
<td>AA, GTC aggravated by fever, GTC and AA occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/13 y 7 mo</td>
<td>GTC aggravated by fever, AA, GTC occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/12 y 3 mo</td>
<td>Mcl, GT aggravated by fever, GT occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/12 y 5 mo</td>
<td>AA, Mcl, GTC, CP, Mcl occurring as SE</td>
<td>8 y 3 mo</td>
<td></td>
</tr>
<tr>
<td>7/12 y 8 mo</td>
<td>GTC, AA, Mcl, Mcl and GT occurring as SE</td>
<td>10 y</td>
<td></td>
</tr>
<tr>
<td>8/3 y 9 mo</td>
<td>Mcl, AA, GTC aggravated by fever, SP (hemiclonic) occurring as SE and MTI occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/4 y 11 mo</td>
<td>CP, AA occurring as SE</td>
<td>3 y 2 mo</td>
<td></td>
</tr>
<tr>
<td>10/6 y 2 mo</td>
<td>SP with motor phenomenon, AA, SP with motor phenomenon occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/6 y*</td>
<td>Mcl, AA, GTC, AA occurring as SE</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>12/8 y 11 mo</td>
<td>Mcl occasionally aggravated by fever, SP with motor phenomenon, AA, AA occurring as SE</td>
<td>3 y 9 mo</td>
<td></td>
</tr>
<tr>
<td>13/7 y 5 mo</td>
<td>Mcl, AA, AA occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/3 y 6 mo</td>
<td>Mcl, AA, AA occurring as SE</td>
<td>AA</td>
<td></td>
</tr>
<tr>
<td>15/7 y 3 mo</td>
<td>AA, Mcl, SP with motor phenomenon with secondary generalization, AA and Mcl occasionally aggravated by fever occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/6 y 8 mo</td>
<td>CP, Mcl, SP with motor phenomenon aggravated by fever, SP with motor phenomenon and Mcl occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17/5 y 1 mo</td>
<td>AA, Mcl, GTC aggravated by fever, AA occurring as SE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18/6 y 1 mo</td>
<td>Mcl, AA, CP with secondary generalization</td>
<td>5 y 2 mo</td>
<td>AA occurring as SE during fever, GTC, Mcl</td>
</tr>
<tr>
<td>19/8 y</td>
<td>AA, GTC aggravated by fever</td>
<td>5 y 4 mo</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AA, atypical absences; CP, complex partial seizures; GT, generalized tonic seizures; GTC, generalized tonic-clonic seizures; Mcl, myoclonic seizures; NA, not applicable; SE, status epilepticus; SP, simple partial seizures.

*Death during follow-up.

**EPILEPSY AGGRAVATED BY FEVER**

Five patients (26%) had their first seizure during a febrile episode. During follow-up, 10 (53%) had epilepsy aggravated by fever. In 8 patients (36%), seizure worsening by high or even moderate temperatures was recurrent, which led to SE in 7 patients.

**AGE AT ONSET**

Mean age at onset was 1 year 1 month (range, 4 months to 2 years 11 months). First seizures were atypical absences and myoclonic seizures in 5 (26%) each and simple partial, complex partial, and generalized tonic-clonic or tonic seizures in 3 (14%) each (Table 1). In 18 patients, epilepsy onset preceded diagnosis of AS, based on clinical phenotype, from 5 months to 5 years 9 months (mean, 2 years 8 months; median, 2 years 2 months).

**STATUS EPILEPTICUS**

Sixteen patients (84%) had SE, of which 7 cases were recurrent. Atypical absence SE (8 patients) and myo-
clonic SE (3 patients) were characterized by long-lasting periods of impaired contact accompanied by frequent head dropping or excessive trembling. These episodes were recognized as periods of cognitive decline and in 7 patients led to a misguided metabolic investigation. Introduction of carbamazepine, oxcarbazepine, and vigabatrin apparently caused (time-related) seizure worsening, leading to SE in 5 patients. Hyperthermia was associated with SE (especially with its recurrence) in 7 children.

SEVERITY AND EVOLUTIONARY ASPECTS

Eighteen patients (95%) had previous or current history of daily seizures from 4 months (median, 1 year 2 months) to 10 years (median, 4 years), of which 14 (64%) had disabling seizures, which occurred from 4 months (median, 8 months) to 7 years (median, 2 years 7 months). Multiple seizure types (more than 3 different types) were observed in 13 patients (53%) up to the age of 7 years (median, 5 years 1 month).

The analysis of previous and current seizures shows a tendency to present a decrease in the diversity of seizure type with age. There is a predominance of generalized seizures, especially atypical absences and myoclonic seizures, at older ages. During follow-up, we observed that patients who had spontaneous seizures have a tendency to exhibit or maintain seizures restricted to or predominantly seen during periods of fever or infection.

History of refractory epilepsy was reported in 16 patients (84%). Parents reported improvement, characterized by decrease in seizure frequency or seizure control, at the mean age of 5.3 years (range, 2.0-11.5 years). However, epilepsy was totally controlled only in 7 patients (37%) at the mean age of 8 years 7 months (range, 4 years to 12 years 8 months), all of which remain under antiepileptic drug treatment. Seizure type or number of seizures was not predictive of remission or better response to antiepileptic drug treatment.

ANTIEPILEPTIC DRUG TREATMENT

Valproic acid improved seizure control in 18 patients undergoing either monotherapy or polytherapy, especially when associated with clonazepam (5 patients) or phenobarbital (5 patients). Phenobarbital was effective only when coadministered with valproic acid, but not in monotherapy or with other drugs. Association of valproic acid and lamotrigine was effective in 2 cases. Carbamazepine was effective only in 1 patient, and topiramate, used in 2 patients, did not improve seizure control. Additionally, ketogenic diet, used in 4 refractory cases, was effective in all. Of the 8 patients who used carbamazepine, 5 had seizure aggravation, 1 of whom had atypical absence status. In the only patient from this series who used oxcarbazepine, a prolonged and repetitive generalized tonic-clonic seizure led to hospitalization. The introduction of vigabatrin in 1 patient had a temporal relationship with the onset of myoclonic SE (Table 3).

The estimated prevalence of AS (1 in 10 000 to 12 000)18-20 is similar to that of Rett syndrome (1 in 12 000),21 suggesting that AS remains underdiagnosed. Better understanding of epilepsy features in AS might be helpful in changing this scenario.

PREVALENCE AND SEIZURE TYPE

In agreement with previous series, our work showed that epilepsy in AS ranges from 80% to 90%.22 Analysis of such a high prevalence must consider that both our study and previous studies encompass patients determined by distinct genotypes. However, there is evidence that different genetic groups may present different profiles, with distinct degrees of severity, and that a more severe form of epilepsy occurs in patients with deletion.23 In our series, all patients with deletion had epilepsy, indicating a higher prevalence in this group, as previously demonstrated.23,24 This finding suggests that future studies on epilepsy in AS should address these groups individually.

Although seizures in AS were extensively described, the delineation of epilepsy in AS is still controversial in many aspects. All seizure types have been reported in AS, with predominance of generalized seizures, especially atypical absences15,16,24 and myoclonic seizures.25-27 In agreement with this, atypical absences and subtle myoclonic seizures were the most frequently observed and registered by us with video EEG but not the most frequently reported by parents, who tend to note mostly those accompanied by evident motor phenomena.

Because of the high frequency of atypical absences and myoclonic seizures in these patients, we observed that video EEG was crucial to recording of nonconvulsive status, which occurs as a prolonged event that lasts weeks or months and is reported as a period of decreased contact with environment, as previously reported by Matsumoto et al.15

Viani et al26 reported complex partial seizures of occipital lobe origin as a frequent event, an observation not yet corroborated by others.24,27,28 Only 1 of our patients presented with this seizure type during monitoring, and no parent reported similar events when specifically questioned.

Infantile spasms are described in some chromosomal disorders, such as Down syndrome19,22 or inv dup(15)13,37, however, they were not observed in our patients, even at younger ages, and are rarely reported in AS.15,26 Other less frequently reported seizure types are atonic, myoclonic-absence, hemigeneralized, and partial.16,22,38 It is possible that the frequency of myoclonic seizures or even pure atomic seizures may be higher in our patients. However, one of the most challenging aspects in the study of epilepsy in children, especially those with severe cognitive impairment, is the difficulty of differentiating certain seizure types by history alone. This is a limitation of our study and of all previous work that addresses this issue. Although we analyzed seizure semiology by video EEG to avoid
misdiagnoses, this was a partial solution, since we could record only patients’ current seizures.

AGE AT ONSET

One of the most important aspects of AS is the late onset of clinical phenotype, especially the diagnostic facial traits. However, in these developmentally delayed infants, epilepsy has an early onset, preceding clinical diagnosis in most patients.

The atypical absences and myoclonic seizures were the most frequent seizures at onset, as reported by Matsumoto et al.15 Laan et al24 reported epilepsy with an occasional later onset (5 years old). In our experience, prospective family interviews instead of medical record reviews may result in identification of unreported or unnoticed subtle seizures, such as myoclonic and atypical absences, occurring earlier than surmised.

EPILEPSY AGGRAVATED BY FEVER

Seizure worsening during fever occurred in 53%, a high rate if compared with overall age-matched population, and similar to the rates reported by Viani et al26 and Laan et al. As in the series of Viani et al,26 in some cases fever triggered the first seizure. Buoni et al28 reported these events in AS related to moderate temperatures. In our patients, there was a predominance of generalized seizures during these episodes. Although febrile seizures are extensively reported as a frequent event in AS, descriptions of the seizure type aggravated by fever are scant.

STATUS EPILEPTICUS

Although frequently documented and reported, variations exist regarding prevalence and seizure type. Laan et al24 reported SE in 36.1% of their patients, and Sugi-
moto et al\textsuperscript{10} reported SE in 75\% of patients. In our series, SE occurred in 84\%, and the main seizure types were atypical absence, myoclonic seizure, and generalized tonic-clonic seizure, similar to that reported by Laan et al.\textsuperscript{24} Our high prevalence may be related to video EEG monitoring when nonconvulsive status was observed, although this was mostly not noticed by relatives or otherwise reported as a reduction in motor activity and/or cognitive impairment. Our incidence of myoclonic status was below that reported by others,\textsuperscript{25-27} probably because some of these investigators performed polygraphic recordings and back-averaging techniques.\textsuperscript{25,27}

**AGE-RELATED IMPROVEMENT**

Severity of epilepsy was measured by high seizure frequency, presence of injurious seizures that impaired daily activities, occurrence of multiple seizure types, and SE. Presence of disabling seizures and multiple seizure types has already been respectively reported by Laan et al\textsuperscript{24} and Matsumoto et al.\textsuperscript{15} We also observed frequent occurrence of daily seizures and a tendency of milder epilepsy at later ages or, less commonly, with total control. Buonì et al\textsuperscript{28} and Laan et al\textsuperscript{24} indicated that seizures were age dependent, as observed in our study. However, there has been some discussion as to whether seizure improvement occurs during late childhood and puberty\textsuperscript{6,20,60} or during adulthood.\textsuperscript{25,40,41} Epilepsy in our patients was considered severe or at least as having a period of severity, mainly during early childhood and infancy, with a decrease in seizure frequency predominantly in late childhood. In a retrospective study, Laan et al\textsuperscript{24} reported that atypical absences and myoclonic seizures persist in adulthood but are milder, as observed in our patients. In our series, relatives often reported a period of refractoriness, followed by improvement during childhood and early puberty. Nonetheless, complete seizure control was obtained in only 37\% of our patients.

Minassian et al\textsuperscript{21} stressed the importance of video EEG monitoring in detecting seizures in adults because of their sporadic nature. To date, information on adults with AS, especially focusing on epilepsy, is scarce, and larger series with adults are necessary to elucidate the evolution of epilepsy in AS.

**RESPONSE TO TREATMENT**

Nakatsu et al,\textsuperscript{42} who studied an AS homologue region deleted in a mutant mouse (the pink-eyed cleft palate [p(cp)] mouse) reported that the genes encoding \(\gamma\)-aminobutyric acid type A (GABA\(_A\)) receptor subunits \(\alpha_5, \beta_3\), and \(\gamma_3\) were disrupted. This deletion led to alterations of binding properties of the GABA\(_A\) receptors in the brain, providing an in vivo model system for studying GABA\(_A\) receptor function in AS. Although UBE3A dysfunction is seen as the cause of AS, GABA genes may have a contributory role in the phenotype,\textsuperscript{43,44} especially in epilepsy. It may be postulated that the good therapeutic response to valproic acid, phenobarbital, and clonazepam, regardless of seizure type, observed in our series and in parents’ questionnaires\textsuperscript{45} may be determined by this GABA\(_A\)ergic receptor deletion. Along the same lines, benzodiazepines seem to be effective, which may be related to the decrease in benzodiazepine receptor density in 60\% to 80\% of cases, as demonstrated by Odano et al.\textsuperscript{46} However, vigabatrin, which is also a GABA\(_A\)ergic drug, was not effective in these patients. The ability of vigabatrin in increasing GABA without enhancing GABA\(_A\)ergic receptor function may be a possible explanation for its failure in AS. As with vigabatrin, we observed seizure aggravation with carbamazepine and oxcarbazepine. On the other hand, a ketogenic diet was effective in all 4 patients who tried it. Topiramate\textsuperscript{47} and ethosuximide\textsuperscript{48} improved epilepsy in a small series of patients who had AS with refractory epilepsy. To date, we cannot corroborate these findings because of our limited experience with these drugs in AS.

**SIMILARITIES WITH OTHER CHROMOSOMAL DISORDERS**

The occurrence of age-related refractory epilepsy with atypical absences and myoclonic seizures, worsened by fever and frequently occurring as SE, has suggested a clinical profile that may be helpful in identifying patients with AS, especially infants. However, a similar profile has been described in other chromosomal disorders,\textsuperscript{49-51} indicating that the electroclinical picture of AS is useful only when inserted into its proper clinical context. The origin of these similarities is unknown, and theories that try to implicate GABA\(_A\)ergic genes as a common denominator do not contemplate all syndromes involved.

In conclusion, patients with AS determined by deletion present with a high prevalence of early-onset epilepsy, often severe and refractory. Seizure onset usually precedes clinical diagnosis based on phenotype and could be used as an element for earlier diagnosis. Proper characterization of epilepsy in AS may be an important diagnostic tool, since epilepsy is stereotyped with the presence of atypical absences, myoclonic seizures, epilepsy aggravated by fever, and SE during infancy and early childhood. We believe that AS should be considered as a differential diagnosis in developmentally delayed infants with severe, generalized cryptogenic epilepsy. The delineation of the electroclinical behavior in each group is important to determine possible differences among groups.

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Correspondence: Kette D. Valente, MD, PhD, Department of Psychiatry, University of São Paulo, R. Jesuíno Arruda, 901/51, 04532-082 São Paulo, SP Brazil (kettevalente@msn.com).

Author Contributions: Study concept and design: Valente. Acquisition of data: Valente, Koifffmann, Fridman, Varella, Kok, Andrade, and Grossmann. Analysis and interpretation of data: Valente, Koifffmann, Varella, Kok, Andrade, Grossmann, and Marques-Dias. Drafting of the manuscript: Valente. Critical revision of the manuscript for important intellectual content: Valente, Koifffmann, Fridman, Varella, Kok, Andrade, Grossmann, and Marques-Dias. Obtained funding: Valente, Koifffmann, and Marques-Dias. Administrative, technical, and material support: Valente, Fridman, Andrade, and Grossmann. Study supervision: Valente, Andrade, Grossmann, and Marques-Dias.