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Analysis of the characteristics of epilepsy in 37 patients with the molecular diagnosis of Angelman syndrome

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ABSTRACT – Angelman syndrome is a genetic disorder caused by defects in the maternally inherited imprinted domain located on chromosome 15q11-q13. Most patients with Angelman syndrome present with severe mental retardation, characteristic physical appearance, behavioral traits, and severe, early-onset epilepsy. We retrospectively reviewed the medical histories of 37 patients, all with the molecular diagnosis of Angelman syndrome and at least three years of follow-up in our neurology department, for further information about their epilepsy: age of onset, type of seizures initially and during follow-up, EEG recordings, treatments and response. The molecular studies showed 87% deletions *de novo*, 8% uniparental, paternal disomy, and 5% imprinting defects. The median age at diagnosis was 6.5 years, with 20% having begun to manifest febrile seizures at an average age of 1.9 years. Nearly all (95%) presented with epilepsy, the majority under the age of three (76%). The most frequent seizure types were myoclonic, atonic, generalized tonic-clonic and atypical absences. At onset, two patients exhibited West syndrome. EEG recordings typical of Angelman syndrome were found in 68%. Normalization of EEG appeared in 12 patients after nine years. Control of epileptic seizures improved after the age of 8.5 years. The most effective treatments were valproic acid and clonazepam. We conclude that epilepsy was present in nearly all of our cases with Angelman syndrome, and that the EEG can be a useful diagnostic tool. On comparing the severity of epilepsy with the type of genetic alteration, we did not find any statistically significant correlations.

Key words: Angelman syndrome, molecular diagnosis, epilepsy, West syndrome, EEG, treatment

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Angelman syndrome (AS) – a rare genetic disorder affecting an estimated one out of every 20,000 individuals – is characterized by developmental delay, seizures, absence of speech, motor impairment and a peculiar behavioral phenotype (Angelman 1965, Clayton-Smith and Pembrey 1992). The most common genetic defect, present in 70% of the patients, is a *de novo* deletion of maternal origin on chromosome 15q11-q13. Between 3-5% of AS patients present uniparental paternal disomy of chromosome 15, and in 8% of cases, the disorder originates in an imprinting

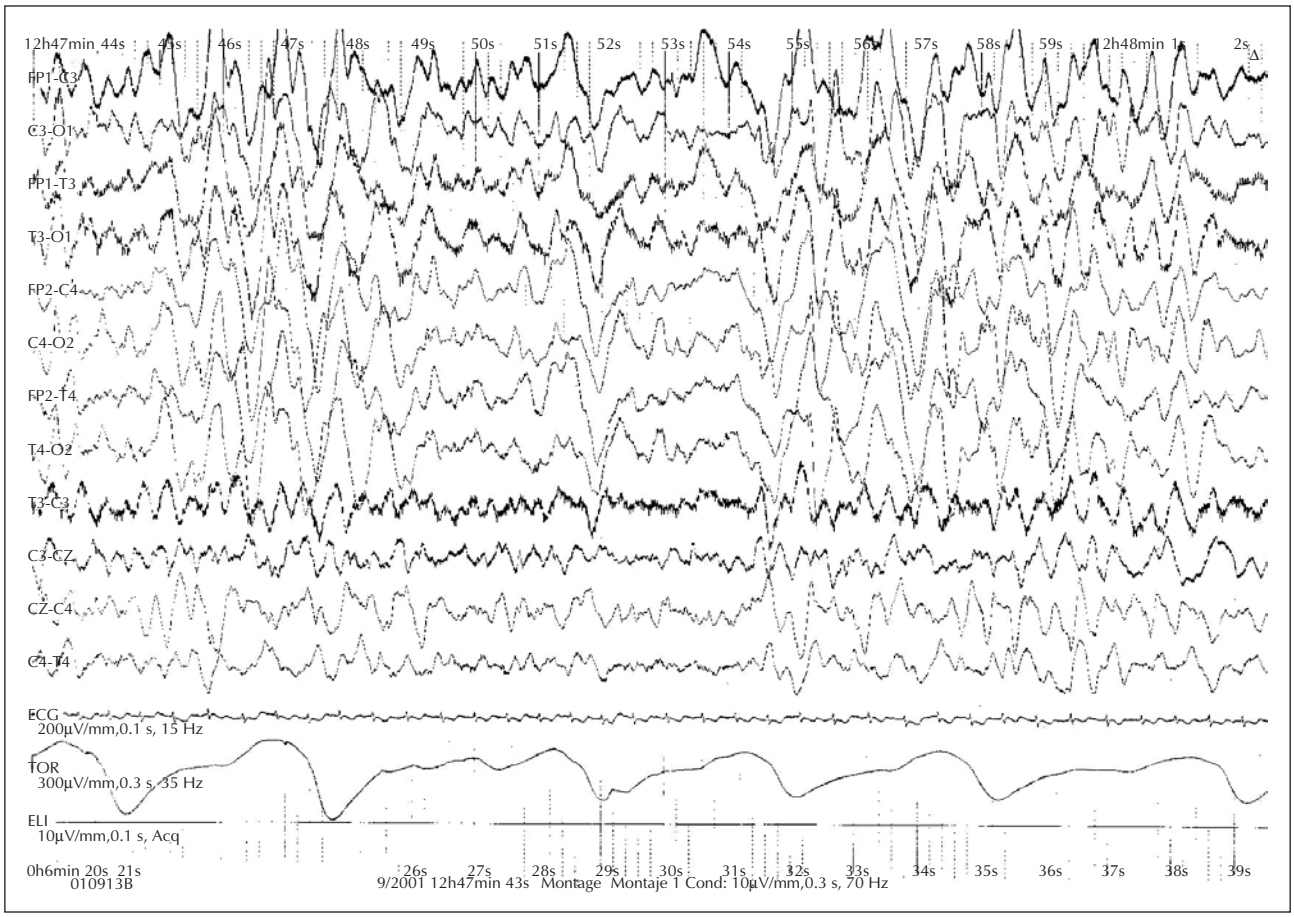


Figure 1. Typical EEG with high amplitude rhythmic 2-3/s activity in a 3-year-old boy with AS.

mutation. On the basis of molecular findings, patients can be classified into five groups: i) deletion; ii) uniparental paternal disomy (UPD); iii) imprinting defects; iv) mutation in a gene encoding a ubiquitin-protein ligase (UBE3A); and v) mechanism not identified, with biparental inheritance and a normal allelic methylation pattern (15-20% of the patients) (Magenis *et al.* 1987, Imaizumi *et al.* 1990, Malcolm *et al.* 1991, Jiang *et al.* 1999, Fridman and Koiffmann 2000, Garnacho *et al.* 2000). The majority of patients with AS present with severe mental retardation, a characteristic facial appearance, epilepsy and behavior disturbances (Magenis *et al.* 1987, Imaizumi *et al.* 1990, Malcolm *et al.* 1991, Clayton-Smith and Pembrey 1992, Smith *et al.* 1996, Jiang *et al.* 1999, Fridman and Koiffmann 2000, Garnacho *et al.* 2000, Galván-Manso *et al.* 2002). The epilepsy is severe and the seizures difficult to control, the most frequent types being atypical absences, generalized tonic-clonic, atonic and myoclonic (Laan *et al.* 1997, Minassian *et al.* 1998, Ruggieri and McShane 1998, Clayton-Smith 2001).

EEG recordings are characteristic for AS patients – high-amplitude delta activity with slow-spike waves, at 2-3 Hz of high voltage – and for this reason the EEG can be useful for diagnosing AS in patients (Boyd *et al.* 1988, Campos Tristan *et al.* 1993, Østergaard and Juhl 1997) *(figure 1)*. To date there have been few studies analyzing the natural history of epilepsy in large series of patients with AS (Smith *et al.* 1996, Laan *et al.* 1997, Garnacho *et al.* 2000).

Materials and methods

We retrospectively reviewed the medical histories of 37 patients with the molecular diagnosis of AS who had been followed for a minimum of three years by the neurology service of the Hospital San Joan de Déu in Barcelona. The genetic study was carried out using an analysis of the methylation pattern of the 15q11-q13 region as a diagnostic test, followed by familial segregation analysis of chromosome 15 markers in order to determine the type of underlying mutation. All patients exhibiting clinical features of AS but with normal methylation were excluded from the sample. We studied the characteristics of the epilepsy, age of onset, frequency and type of febrile sei-

zures both initially and during treatment, and the type of treatment received. We also analyzed the characteristics of the EEG results both initially and during follow-up.

Results

Our series consisted of 19 female (F) and 18 male (M) patients between 3.2 and 23 years of age, with an average age of 13.3 (±5.2 years). The duration of follow-up ranged from 3.4 to 20 years, with an average duration of 14.2 years.

The results of the genetic study showed 87% (32/37) *de novo* deletion, 8% UPD (3/37), and 5% imprinting defects (2/37). No patients showed any deficit of the UBE3A gene.

The average age at the molecular diagnosis of AS was 6.5 years (±4.5 years), with an age range between six months and 15 years. In the patients under three years of age presenting with epilepsy (28) (76%), the diagnosis of AS was made at an average age of 6.1 years. In the seven patients over three years of age presenting with epilepsy, the average age at diagnosis was 10.4 years.

In our series, eight patients (two F, six M), all carriers of the maternal deletion, presented with febrile seizures. The average age of onset was 1.9 years (±9 months; age range four months to three years). None of the three patients with UPD presented with febrile seizures.

The febrile seizures were of the generalized tonic-clonic type in five patients, atonic in three patients and myoclonic in one. None of our patients had a history of febrile seizures in their family. The time interval between the onset of febrile seizures and the presentation of a febrile crisis varied between four months and four years, with an average of 1.3 years.

Of the total sample, 35 patients (95%; 17 female and 18 male), had epilepsy. Of the two patients who did not present with epilepsy, one was a carrier of the maternal deletion, and the other UPD.

In our series, the average onset age of epilepsy was 2.1 years (±1.4 years), with an age range of one month to 6.7 years. The distribution by age and sex is shown in *table 1*. The average age at onset for patients with the maternal deletion was 1.9 years (±1.3 years, with an age range of four months to 6.7 years), and for the patients with UPD, 3.1 years (±2.6 years, with an age range of 1.2 years to five years); eleven patients (four female, seven male), all carriers of maternal deletions, had signs of epilepsy in the first year of life.

Among our patients, we found that myoclonic seizures were the most frequent type of initial seizure (25%; n=11), followed by atonic seizures (23%; n=10), generalized tonic-clonic seizures (21%; n=9), atypical absences (12%; n=9), spasms in extension (9%; n=4), flexor spasms (5%; n=2) and partial seizures (5%; n=2) *(table 2)*.

Table 1. Age at onset of epilepsy in Angelman syndrome (n=35).

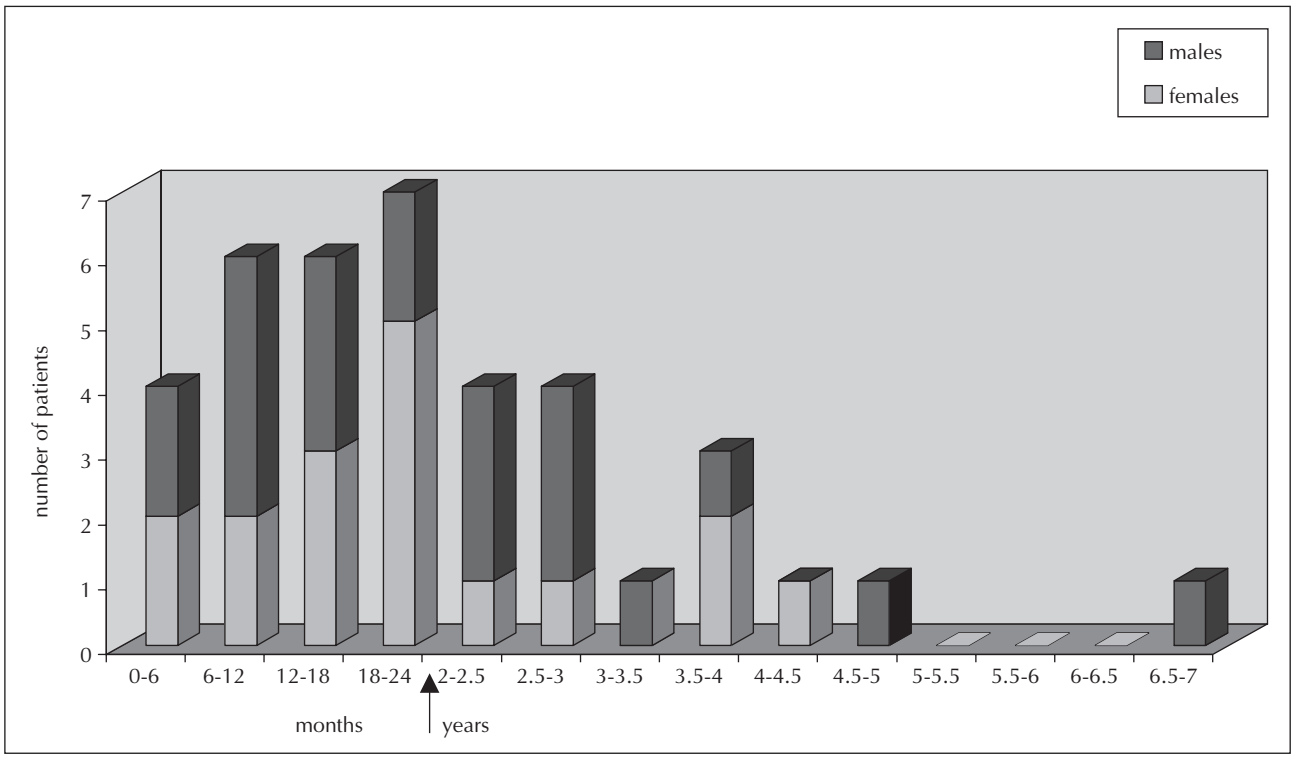
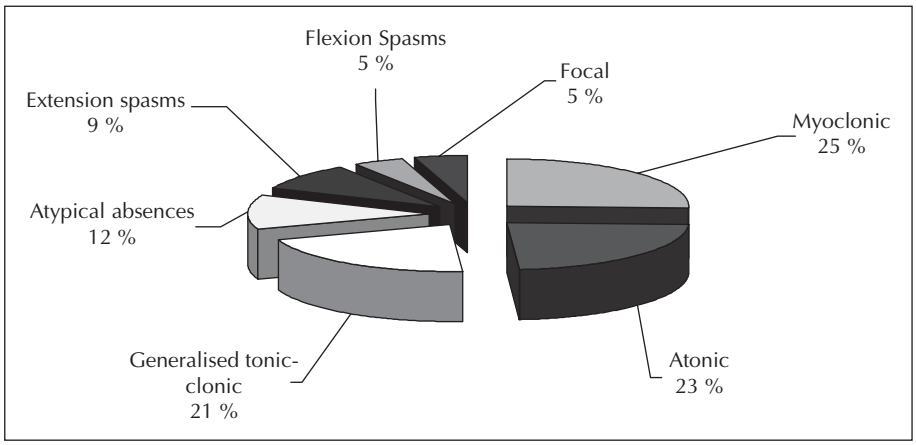


Table 2. Initial epileptic seizure type in Angelman syndrome.



The average age at onset for epilepsy varied according to the type of seizures. The most frequent seizures, myoclonic and atonic, began at 2.1 years on average, both with a range of four months to five years. The onset of atypical absences and generalized tonic-clonic seizures occurred at ages 3.14 and 3.1 years, respectively. Onset occurred even earlier in patients with partial seizures (1.4 years), tonic spasms in extension (one year), and tonic spasms in flexion (seven months).

In our series, 15 patients presented episodes of non-convulsive status epilepticus, to be discussed in a separate paper.

Two patients initially presented with West syndrome, with spasms in flexion and hypsarrythmic EEG patterns, one at eight months and the other at 10 months of age. Both were carriers of the maternal deletion. During follow-up they showed physical characteristics of AS and the diagnosis was confirmed at four and seven years of age, respectively. One of these patients, now 12 years old, developed a resistant form of epilepsy requiring multidrug treatment; partial control of seizures has been achieved with valproic acid (VPA) and clonazepam (CZP). The other patient has been off therapy since the age of 10.

In one case, the first sign of epilepsy occurred at 15 days of life: a series of flexion spasms. However, follow-up EEG never shown hypsarrhythmia. At present, the child (now 16 years old) is being treated with VPA and CZP, but the seizures have not yet been controlled.

In our series, the EEG initially showed the typical AS pattern characterized by slow waves of high voltage in 17 patients (48%). Widespread paroxysms were recorded in 12, hypsarrhythmia in two, focal paroxysms in two, and normal pattern in two. At follow-up, 24 patients (10 female and 14 male) out of the total of 37, presented EEG abnormalities suggestive of AS. Fourteen had already shown the typical pattern in the initial EEG, while seven initially presented with generalized paroxysms, two with hypsarrhythmia and one with focal alterations.

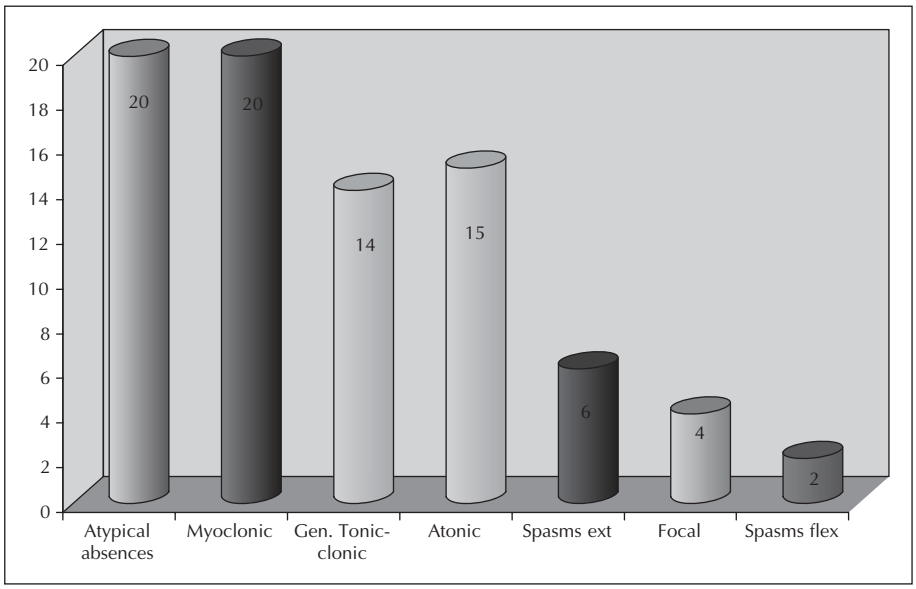
Normalization of EEG appeared in 12 patients at an average age of 9.9 years (±1.9 years, with an age range of six years to 13 years).

The distribution of EEG patterns in follow-up was high-amplitude delta waves (32 patients), bilateral paroxysms (23 patients), focal paroxysms (15 patients), and multifocal paroxysms (six patients, one of them without clinical seizures). The interictal EEG patterns were related to the type of initial seizure: in atypical absences the most frequent finding was a pattern of high-amplitude delta waves (six), while generalized paroxysms were observed in only one case. In atonic seizures, generalized paroxysms were the most frequent type (six), while in spasms in extension and in myoclonic seizures, these two EEG patterns were found in roughly equal proportions. In patients with tonic-clonic seizures, we found high-amplitude delta waves (four patients), generalized paroxysms (one), focal paroxysms (two) and normal tracing (two). In the two patients with partial seizures, we found high-amplitude delta waves. Finally, of the three cases with flexion spasms, two presented a pattern of hypsarrhythmia and one of generalized paroxysms.

During follow-up, atypical absences were recorded in 20 patients (57%), myoclonic seizures in 20 patients (57%), atonic seizures in 15 patients (43%), generalized tonic-clonic seizures in 14 patients (40%), tonic extension spasms in six patients (17%) and in flexion in two (6%), and partial seizures in four patients (11%) *(table 3)*.

Some patients always presented the same type of seizure while others experienced several types during follow-up. Among the patients with a single seizure type, four had generalized tonic-clonic seizures, three myoclonic seizures, three atonic seizures and one atypical absences. None of them presented focal seizures. Of the eight patients who presented all three of the most frequent types of

Table 3. Types of seizures during follow-up.



seizures (atypical absences, myoclonic, and atonic), two also presented tonic-clonic seizures. All of the patients in this last group were carriers of the maternal deletion, and they suffered from resistant epilepsy that required multi-drug treatment. At present, the epilepsy is under control in four of these patients (aged between 10 and 21 years), and treatment was discontinued.

The drugs most frequently used in the initial treatment were valproic acid (VPA) (42%) with control of the seizures in 80% of the patients, and phenobarbital (PB) (29%) with control of the seizures in 30% of the patients. The most effective drug was clonazepam (CZP), used as the first treatment in nine patients (26%) with a 100% positive response.

During a follow-up, the most frequently prescribed anti-epileptic drugs were VPA, CZP and PB. The most effective was CZP, with a 90% success rate in the control of seizures, followed by VPA, with a success rate of 81%. Valproate and CZP were used in combination to treat 13 of the patients (64%) with good results (>90% control of seizures).

With regard to other antiepileptic drugs, carbamazepine (CBZ) was used in seven patients, with no response in six; lamotrigine (LTG) in two patients with no response in either; and ethosuximide (ESM) and gabapentine (GBP) in one, with no response. Two patients treated with vigabatrin (VGB) have worsened in terms of the frequency and severity of seizures.

Of the 35 patients with epilepsy, at present eight (23%) are off treatment, 17 (48%) are receiving a single drug (seven CZP, seven VPA, two PB and one CLB), and 10 (29%) are receiving combined drug therapy *(table 4)*.

Complete control of seizures was achieved in 25 patients. Partial control was achieved in five, while in five cases the epilepsy was not controlled. Atonic and generalized tonic-clonic seizures were more easily controlled than myoclonic seizures and atypical absences. Control of seizures was achieved at an average age of 8.5 years for the female patients, and 9.2 years for the male patients. In eight patients (two female and six male) treatment was discontinued at an average age of 10.7 years (±3.14 years, with an age range of 6.2 years to 16 years).

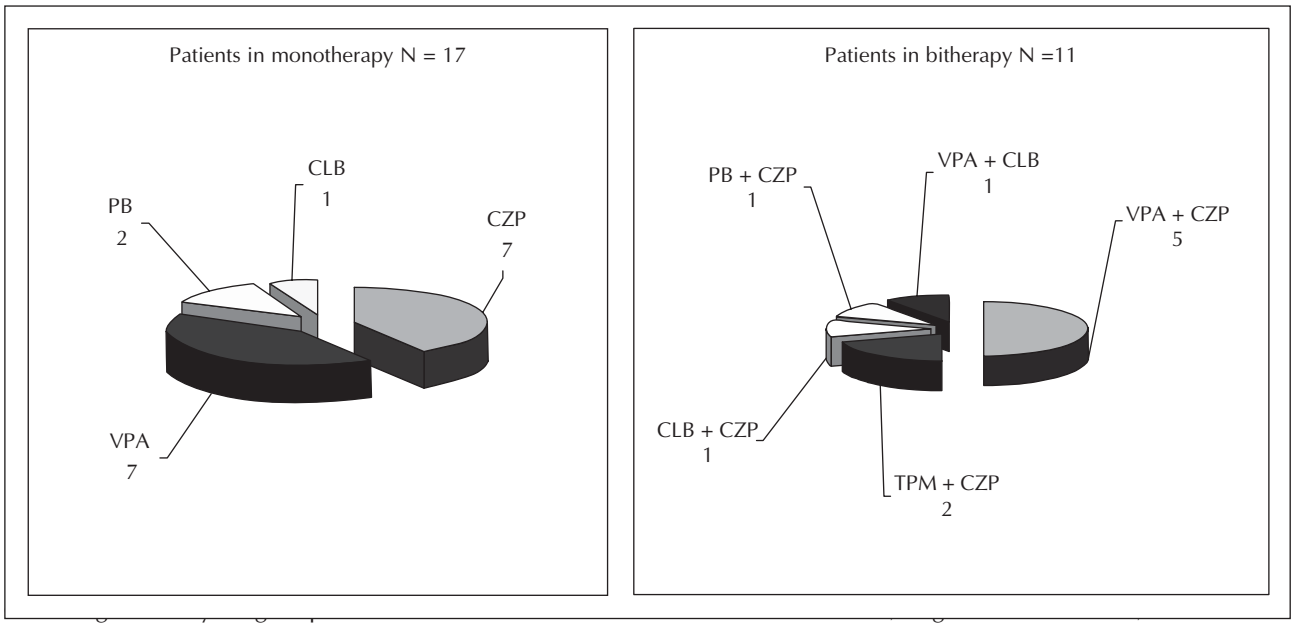
Discussion

The incidence of epilepsy in our series (95%) is similar to that found by other authors (Smith *et al.* 1996, Galvan Manso et al. 2002, Laan *et al.* 1997, Minassian *et al.* 1998, Ruggieri and McShane 1998). Epilepsy in AS is drug-resistant and of early onset in most cases, especially before the age of three years (Boyd *et al.* 1988, Rubin *et al.* 1997).

In our series, febrile seizures were more frequent (21%) than in the general population (3-5%), and of the eight patients with febrile seizures, six were male and two were female. All of them belonged to the group with the maternally inherited deletion. The age of onset of febrile seizures varied between 30 and 36 months of age, later than in the general population (18-24 months).

Comparing the type of seizure with the age at onset of seizures, we found statistically significant correlations among our patients, with atonic seizures and tonic spasms

Table 4. Treatment choices at end of follow-up.



average age at diagnosis for the patients presenting with early-onset epilepsy, probably because for patients with delayed psychomotor development, a more or less typical phenotype and EEG results can be suggestive of AS, thus facilitating early diagnosis and rendering other diagnostic procedures unnecessary.

Comparing the type of genetic alteration with the severity of epilepsy, we found no statistically significant correlations. Some, although not all, of our patients with maternal deletion presented with drug-resistant epilepsy, as did one of the patients with UPD. Some studies report statistically significant correlations between the phenotype characteristics of the patients, their genetic anomalies, the severity of their epilepsy, and their degree of retardation (Clayton-Smith 1993, Buntinx *et al.* 1995, Laan *et al.* 1997, Minassian *et al.* 1998, Buoni *et al.* 1999, Lossie *et al.* 2001, Lossie *et al.* 2001). According to these studies, the patients with a deletion would be more severely affected than the patients with UPD or with imprinting defects. In this last group, the seizures seem to be less severe (Buoni *et al.* 1999). Nevertheless, other studies, including ours, do not support this phenotype-genotype correlation (Buntinx *et al.* 1995).

The onset of epilepsy in the form of West syndrome is seldom reported in the literature for patients with AS; it is referred to only in cases with inversion-duplication of chromosome 15 (Van Lierde *et al.* 1990, Cabrera *et al.* 1998).

The typical EEG patterns, although not pathognomic, are present early in the course of the syndrome, even before the onset of epilepsy, usually in the first two years of life. They become progressively less significant, especially the slow waves, and can disappear by the age of 10 years

1995, Viani *et al.* 1995, Rubin *et al.* 1997, Kuenzle *et al.* 1998). During follow-up, we found EEG results suggestive of AS in 68% of the patients.

In agreement with other series (Ruggieri and McShane 1998), we found that the most frequent types of seizures were atypical absences and generalized tonic-clonic, atonic and myoclonic seizures. The most effective antiepileptic drugs were VPA and CZP used alone, and combination of VPA and CZP or VPA and CLB.

In patients with AS, some antiepileptic drugs have an aggravating effect; in our series this was especially true for VGB (Kuenzle *et al.* 1998).

Conclusion

Epilepsy in Angelman syndrome is an almost universal finding. Not infrequently, onset occurs initially in the form of febrile seizures, and in some cases as West syndrome. Onset is early, usually before the age of three, and presents with different types of seizures.

Concerning evolution of the epilepsy, control is difficult to achieve between three and nine years of age; it requires combination drug treatment. In preadolescence and adolescence it is easier to control, and in many patients the treatment can be discontinued.

The EEG is a valuable diagnostic tool. The most frequent types of seizures are atypical absences, generalized tonic-clonic, atonic and myoclonic seizures. The best treatment response is obtained with VPA and CZP. We have not found significant differences between the severity of epilepsy and the type of molecular alteration. □

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