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Review Article

Epilepsy in 47 Angelman Syndrome Patients: A Follow-Up Study

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Abstract

In Svt. Luka`s Institute of Child Neurology and Epilepsy (Svt. Luka`s ICNE), we follow 47 patients (26 male and 21 female patients) with a genetically confirmed Angelman syndrome (AS) aged 2-20 (the mean age of patients was 8.5). Angelman syndrome was diagnosed by DNA methylation analysis in 32 patients and DNA sequencing technologies in 15 patients (12 deletions and 3 nucleotide substitutions). 92 video EEG monitoring in 34 out of 47 patients were available for our analysis. The wakefulness EEG had the following characteristics: alpha rhythm (13 patients); Theta pattern (24 patients); High amplitude delta waves in the frontal regions -Delta F pattern (23 patients); lateralized or generalized Delta-theta activity in the posterior temporo-parieto-occipital areas - Delta-theta-OPT pattern (26 patients), Periodic posterior rhythm slowing (24 patients), anterior rhythm slowing (16 patients), generalized slowing (25 patients). Epileptiform activity during wakefulness was characterized by presence of low-amplitude spikes during slow waves - Notched pattern (25 patients); focal discharges without slowing (12 patients). Sleep EEG revealed 1) Hypnagogic hypersynchronous activity (9 patients), 2) Sleep spindles (18 patients); 3) the absence of sleep spindles with high delta wave activity (16 patients). Epileptiform activity during wakefulness was characterized by 1) low-amplitude spikes during delta waves (notched slow waves); 2) focal epileptiform activity without slowing; 3) benign focal epileptiform discharges of childhood (BFEDC) in 15% of children at the age of 3-7 years; 4) Hypsarrhythmia (3 patients during sleep). Of the 47 patients, 45 had epilepsy with debut of seizures up to 5 years of age. Long-term follow-up data was available for 40 of 47 patients. Drug-induced remission was observed in 36 patients. After a few years of remission, 24 of 30 had a relapse. The severity of the disease is influenced by the type of the mutation and the length of the deletion, as well as persistent epileptic seizures. the most effective anticonvulsants for AS patients in this study were valproic acid, levetiracetam, and ethosuximide as monotherapy; valproic acid in combination with levetiracetam or ethosuximide. Early genetic diagnosis of AS facilitates the selection of anticonvulsants.

Keywords: *Angelman Syndrome; UBE3A Gene; Epilepsy; Video-EEG Monitoring; Notched Delta Pattern; Delta-Theta-OPT Pattern; Benign Focal Epileptiform Discharges of Childhood (BFEDC)*

Angelman syndrome (AS) is a chromosomal syndrome, which results from a mutation of the maternal UBE3A gene. It is characterized by intellectual disability, autism spectrum features, steadiness instability when walking, atypical laughter, epilepsy, and specific EEG patterns [12].

This study aimed to investigate the neurological status, the onset, the clinical picture, the EEG patterns and the course of epilepsy in children with genetically confirmed AS, depending on the type of mutation.

The study is relevant due to lack of data from large studies with statistically significant numbers of AS patients. In Svt. Luka`s Institute of Child Neurology and Epilepsy (Svt. Luka`s ICNE), we follow 47 patients (26 male and 21 female) with a genetically confirmed Angelman syndrome (AS) aged 2 - 20 (the mean age of patients was 8.5 - see table 1) during the period from 2000 to 2020.

Age (range)	n	%
2 - 6	19	45.24
7 - 12	19	45.24
13 - 20	7	16.67%

Table 1: *Age of patients.*

Anamnesis data All AS patients were born from normal pregnancies. Other children in the families were healthy. No cases of inherited AS were observed. 72.9% of patients delivered full-term without complications. In 6 cases (15.38%) the delivery was complicated by uterine inertia with the following emergency caesarean section. Five children (11.72%) were premature. In 81.25% of newborns the body mass index was normal. In 18.75% of patients the birth weight was less than 2900 g. The APGAR scores is 5 - 8, the average score is 7 - 8 points.

The delivery was complicated in 43.2% of cases. This patients were treated in Neonate Pathology Department. The discharge diagnoses were the hypoxic ischemic encephalopathy (29.7% of cases), feeding impairment, hypotrophy, malnutrition (refusal to feed) (2.7%), premature birth (8.1%), and necrotizing enterocolitis (NEC) (2.7%) (Figure 1).

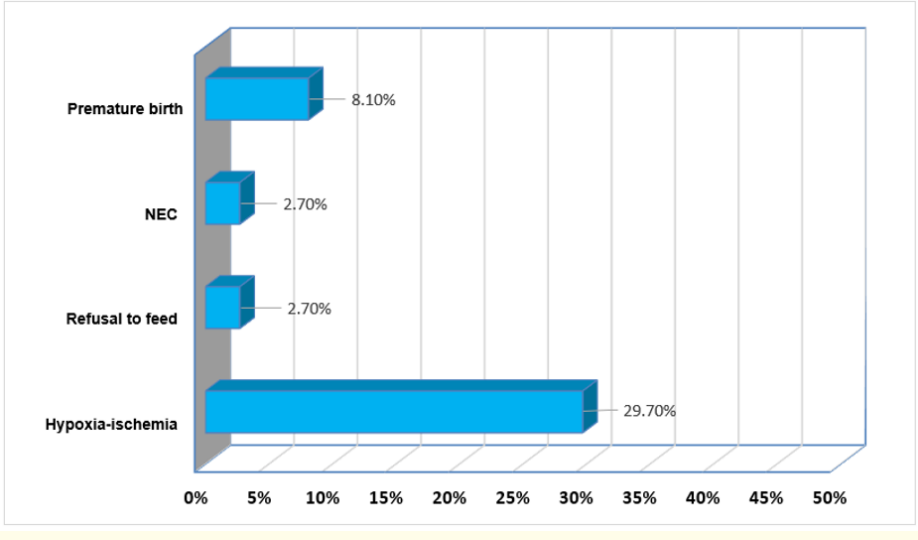

Figure 1: *Perinatal complications in patients with AS.*

Thus, almost every second child with AS has a complicated perinatal history (these factors can aggravate the AS-induced developmental delay and epilepsy).

Vaccination (Figure 2): Most children with a complicated perinatal history (hypoxia-ischemia, premature birth, etc.), had vaccinations postponed for medical reasons for up to 1 year. Of the other 22 children (46.8%), 15 children were vaccinated and had no complications

(fever, developmental delay, convulsions). 7 children developed fever (above 37.5°C). Of these, five developed the first febrile seizures, followed by aggravation of developmental delay and autistic spectrum manifestations. Thus, 5% of patients developed certain vaccination-induced complications.

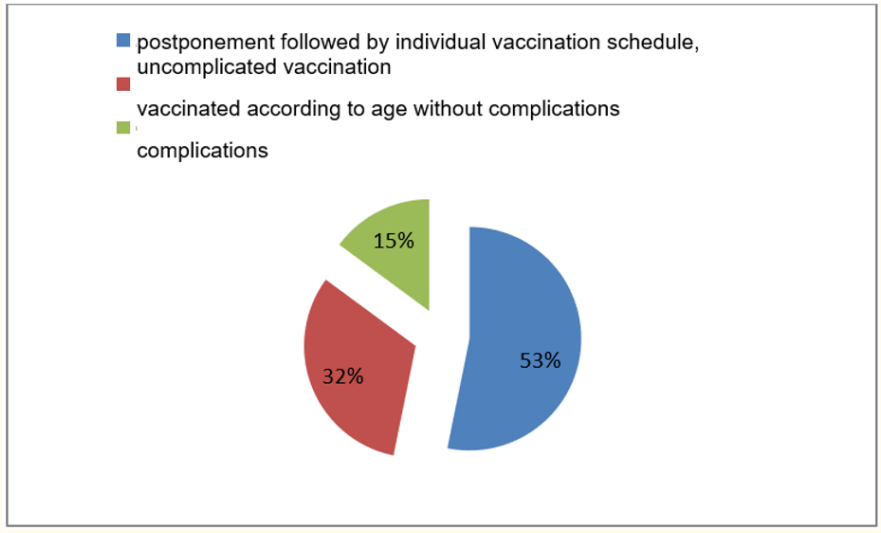

Figure 2: *Vaccination in patients with AS. See explanation in the text.*

AS was diagnosed by DNA methylation analysis in 32 patients and DNA sequencing technologies in 15 patients. Sequencing identified 12 deletions and 3 nucleotide substitutions. Of these, 45 patients have epilepsy. All patients were up to 5 years of age at the onset of epilepsy. Patients were treated with different anticonvulsants. Long-term follow-up data was available for 40 of 47 patients. Drug-induced remission was observed in 36 patients. After a few years of remission, 24 of 30 had a relapse that was quickly relieved in 23 patients. Patients did not respond to anticonvulsant therapy due to the following causes: 1) noncompliance of the parents, 2) late genetic diagnosis, and 3) carbamazepine and oxcarbazepine treatment. The severity of the disease is influenced by the type of the mutation and the length of the deletion. Children with nucleotide substitutions have the most favorable clinical manifestations. In case of deletion, larger deletions are associated with more severe developmental delay with the impossibility to walk independently and more severe epilepsy. No significant correlation was observed between the type of mutation and the course of epilepsy (type of seizures, EEG changes, effective anticonvulsants). The severity of developmental delay depends not only on the type of mutation, but also on the severity of epilepsy. The most effective anticonvulsants for treating AS patients were valproic acid, levetiracetam, and ethosuximide as monotherapy; valproic acid in combination with levetiracetam or ethosuximide. Combination therapy with levetiracetam and ethosuximide was less effective. We conclude that the severity of developmental delay depends not only on the type of mutation, but also on the severity of epilepsy. Although the developmental delay in these patients is AS-induced, uncontrolled seizures and pronounced EEG changes may also affect cognitive development and behavior. To improve the efficacy of anticonvulsant therapy, Angelman syndrome has to be diagnosed as early as possible, since the treatment of epilepsy in AS patients has certain specific features.

Mental, motor, and speech development: All patients had a delay in mental, motor and speech development, and the severity of the delay increased with age. 17% of patients are able to walk independently (Figure 3): 13% patients starting to walk at the age of 2 - 3, 18%

- at the age of 3 - 4, 26% patients - at the age of 4 - 5, and 13% - at the age of 5 - 6, respectively. Thus, the ability to walk independently can develop up to 5 years of age (it does not develop later on). The remaining 30% patients over 6 years old cannot walk; of these, 10% move by crawling or using a support, 20% cannot not move independently. All patients have atonic-astatic syndrome. The severity of movement disorders according to GMFCS corresponds: to level 1 in 70% of cases, to level 2 in 10% of cases, and to level 3 in 20% of case, respectively.

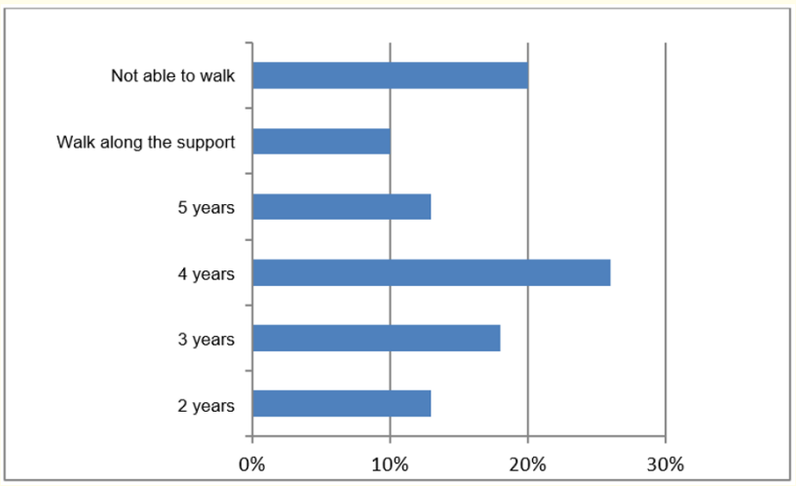

Figure 3: *The ability to walk independently.*

Speech development: The vast majority (47 of 49 patients, 95.74%) of patients do not use verbal communication. Two female patients with a nucleotide substitution in UBEA3 gene have an active vocabulary of up to 20 words and use simple two-word phrases.

All 47 patients have sleep disorders and autistic behavior of varying severity.

MRI data (Figure 4): As a rule, MRI was carried out for diagnostic purposes before AS was confirmed. In most cases, MRI reveals post-hypoxic changes (periventricular leukomalacia - PVL - in 11.9% of cases, cortical/subcortical atrophy accompanied by hypomyelination and ventriculomegaly in 19.05% of cases, parieto-occipital gliosis in 4.76% of cases). In total, post-hypoxic changes were found in 35.7% of all patients (including those who did not undergo MRI). Interestingly, almost the same proportion of patients have complicated perinatal history. Focal cortical dysplasia (FCD) was found in 7.14% of cases. The investigation was carried out to determine the feasibility of surgical treatment for epilepsy. Taking into account the main diagnosis of AS, surgery was not performed.

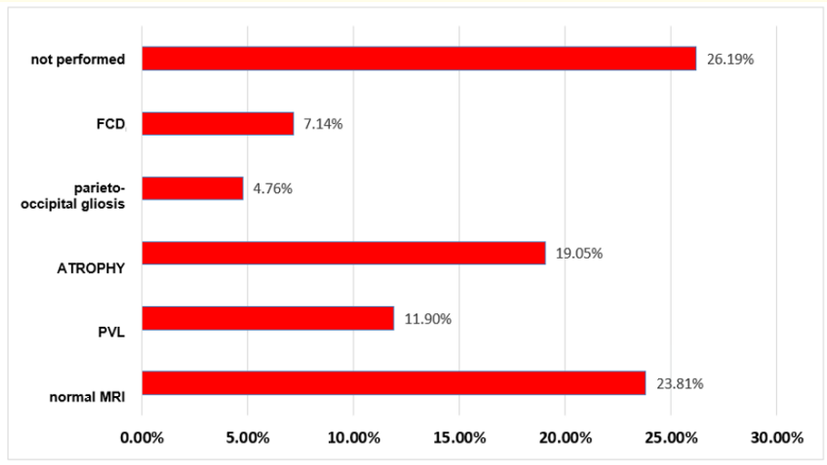

Figure 4: *MRI data in patients with AS.*

Genetic diagnosis (Table 2): In thirty-four cases (68.0%), AS was diagnosed using DNA methylation in 15q11.2-q13 region. Of these, only 2 patients underwent further genetic diagnosis. The other families refused to have the type of mutation determined, despite the fact that the importance of sequencing was explained to them.

Type of mutation	Proportion
Methylation	65.10%
Sequencing	34.90%
Deletion	76.90%
Nucleotide substitution	23.10%
UBE3 G>T	7.70%
UBE3 G>A	15.40%

Table 2: *Genetic testing data.*

Sequencing (chromosomal microarray analysis/epilepsy panel/intellectual disability and autism spectrum disorders panel) revealed 15 cases of AS. Of these, most patients had a deletion (12 patients), while 3 patients had a nucleotide substitution.

Of 12 patients with a deletion confirmed by sequencing, 7 patients had a mutation length of 5 - 6 Mb, 3 patients had a mutation length of 7 - 8 Mb, and 2 patients had a mutation length of more than 8 Mb. Patients with a longer mutation had more severe manifestations (intellectual disability, autism spectrum features, seizures).

Epilepsy: In our study, 95.7% of patients had epilepsy. Only 2 patients (a 15-year-old girl and a 14-year-old boy, both with the UBE3A gene mutation) have never had seizures. It should be noted that Svt. Luka`s ICNE specializes in paroxysmal disorders. Therefore, such a high proportion of patients with epilepsy may be due to the specific profile of our Institute.

The information on the onset of seizures in 47 patients is presented below for clarity (See table 3 and figure 5). Most patients had their first seizures at the age of 1 - 3 (75.6%). None had the onset of seizures after the age of 5 in this group.

Epilepsy onset	Proportion
< 1 yo	18.90%
1 - 2 yo	40.50%
2 - 3 yo	35.10%
4 yo	0%
5 yo	5.40%
6 yo	0%

Table 3: *The age of the onset of seizures.*

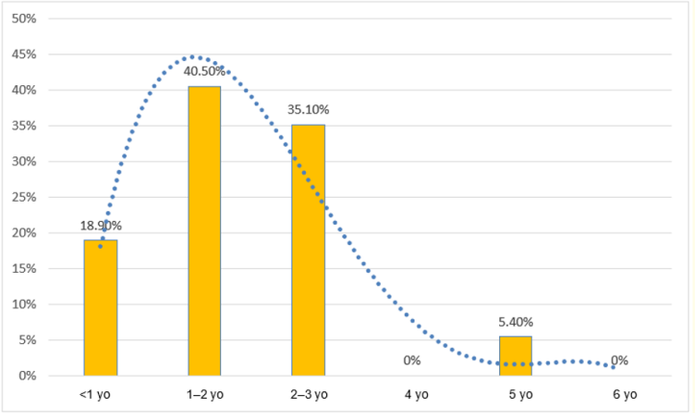

Figure 5: *The age of the onset of seizures.*

84% of patients developed their first seizures with fever. Most patients had generalized onset seizures (generalized tonic-clonic seizures, atypical absences, myoclonic seizures) (See figure 6). However, almost every third patient had focal onset seizures (35.9% had focal motor seizures with head and eye turning, while 17.9% had asymmetric tonic seizures). Infantile spasms were observed in 12.8% of patients.

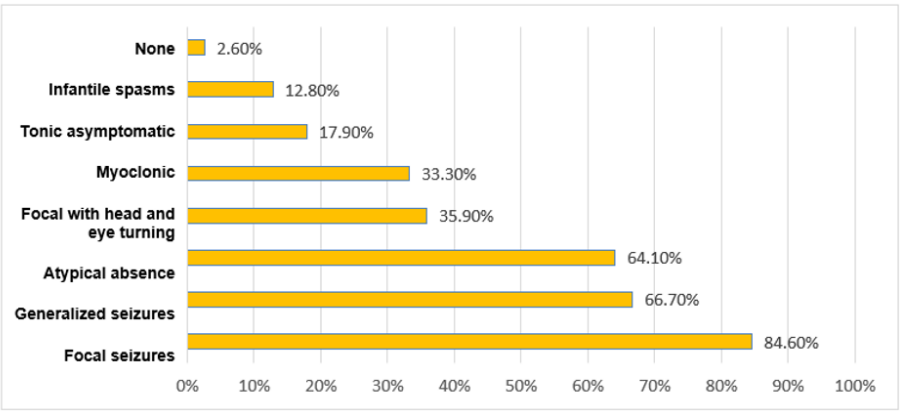

Figure 6: *Seizure types in patients with AS.*

Course of epilepsy: 40 of 47 patients were included in the follow-up. The patients received different drugs in monotherapy or in combinations, as well as a ketogenic diet (See table 4). 34 of 40 patients achieved remission. The scheme of therapy that alleviated seizures is shown in the figure 7.

Fields	n	Proportion
Valproates	36	90%
Ethosuximide	19	47.50%
Levetiracetam	23	57.50%
Pagluferal	1	2.50%
Vigabatrin	1	2.50%
Oxcarbazepine	3	7.50%
Carbamazepine	2	5%
Topiramate	7	17.50%
Lamotrigine	4	10%
Sultiam	2	5%
Zonesamide	1	2.50%
Perampanel	1	2.50%
Corticosteroids	3	7.50%
Ketogenic Diet	1	2.50%

Table 4: *Antiepileptic therapy in patients with AS.*

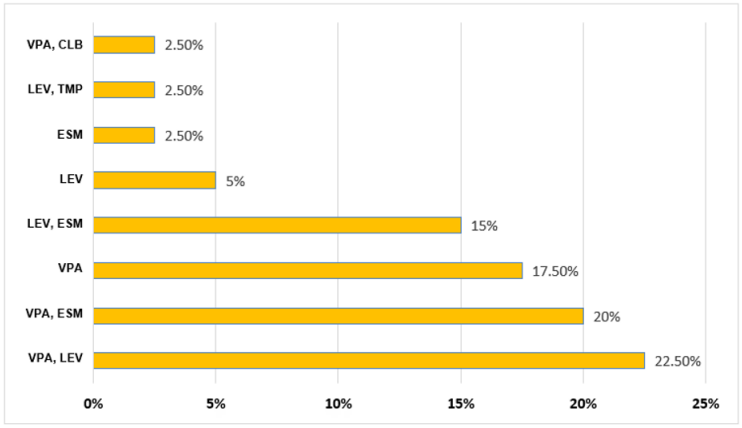

Figure 7: *AEDs that stopped seizures in patients with AS.*

Notes: VPA: Valproic Acid; CLB: Clobazam; LEV: Levetiracetam; TMP: Topiramate; ESM: Ethosuximide.

We analyzed why seizure remission was not achieved (See table 5).

Fields	n	Proportion
None	11	27.50%
West syndrome	1	2.50%
non-compliance	3	7.50%
late onset AEDs	3	7.50%
parents decrease doses	1	2.50%
Oxcarbazepine/ carbamazepine	1	2.50%
late genetic diagnosis	8	20%

Table 5: *Additional causes (other than syndromic) of continued seizures.*

Of 36 patients who achieved remission, 24 patients had a relapse, i.e. the recurrence and gradual increase of seizures. The trigger factors included (1) febrile fever and (2) a dose decrease. The first factor is associated with the genetic basis of AS and cannot be modified. However, the second factor is due to: (1) Underestimation of the severity of epilepsy by the doctor or parents when the dose of anticonvulsants was deliberately reduced (e.g. after a long period without seizures) and (2) Irregular assessments of a patient with AS by an epileptologist when the child gains weight and a therapeutic dose becomes insufficient.

Thus, although epilepsy is genetically determined, it is possible to eliminate seizures with sufficient doses of anticonvulsants and in the absence of fever. In contrast to the determination of optimal therapy at the onset of epilepsy, the treatment on relapse is prescribed faster and is more targeted. This may explain that the relapse remained untreated only in one patient of 23 (See table 6). Thus, of 40 patients with epilepsy (with available follow-up data), we were not able to eliminate seizures in 13.5% of cases at the onset and in 5% of cases on relapse, therefore, 18.5% of patients were resistant to therapy.

Fields	n	Proportion
Remission 1	36	87.50%
Relapse 1	24	60%
Remission 2	23	57.50%
Relapse 2	2	5%
Stable remission	33	82.50%

Table 6: *The course of epilepsy in SA patients.*

EEG changes (Figure 8**):** The wakefulness EEG of patients with Angelman syndrome had the following characteristics: alpha rhythm in 13 of 34 patients; Theta pattern (24 of 34 patients); High amplitude delta waves in the frontal regions -Delta F pattern (23 of 34 patients); Delta-theta activity mainly in the posterior temporo-parieto-occipital areas - Delta-theta-OPT pattern, lateralized or generalized (26 patients), Periodic posterior rhythm slowing (24 patients), anterior rhythm slowing (16 patients), generalized slowing (25 patients). Epileptiform activity during wakefulness was characterized by presence of low-amplitude spikes during slow waves - Notched pattern (25 patients); focal discharges without slowing (12 patients). Sleep EEG revealed 1) Hypnagogic hypersynchronous activity (9 patients), 2) Sleep spindles (18 patients); 3) the absence of sleep spindles with high delta wave activity (16 patients); 4) delta slowing tends to decrease with age. Pathological delta waves during sleep were not detected only in 1 patient (1.2%) without epilepsy (with UBE3A gene mutation). Epileptiform activity during wakefulness was characterized by 1) low-amplitude spikes during delta waves (notched slow waves); 2) focal epileptiform activity without slowing; 3) benign focal epileptiform discharges of childhood (BFEDC) in 15% of children at the age of 3-7 years; 4) Hypsarrhythmia (3 patients during sleep). The index of epileptiform activity during sleep (including notched slow waves) was less than 5% in 8 patients, 5 - 30% in 13 patients, 30-70% in 10 patients, and more than 70% in 2 patients.

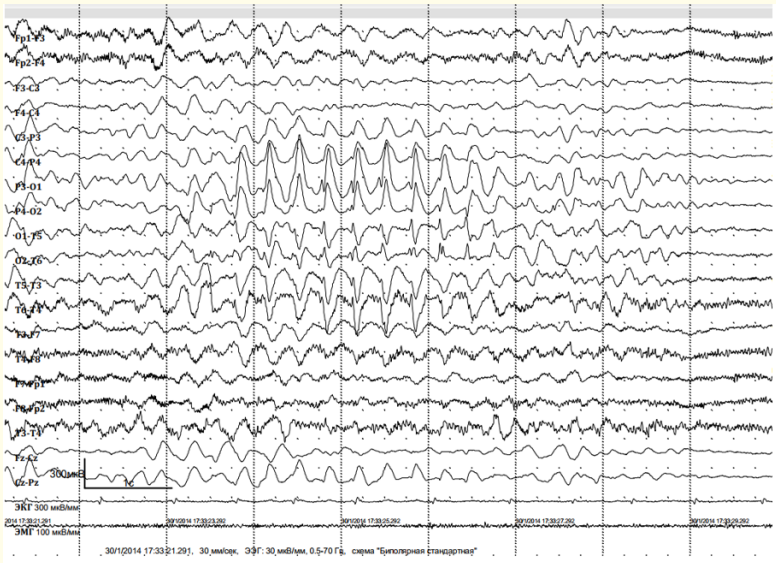

Figure 8: *Sleep EEG. Patient E., 5 years old, AS. Continued theta-delta waves in the posterior regions with the inclusion of spikes (Notch-delta); bilaterally, with alternative localization.*

Discussion

According to the Angelman Syndrome Foundation, the prevalence of Angelman syndrome is estimated to be approximately 1 in 10,000 - 20,000 people in the general population; 4.8% in patients with intellectual disability and 7% in patients with epilepsy [4,23,24]. Boys and girls are affected with equal frequency [22]. In our study, we follow 26 male and 21 female patients.

AS results from one of four types of mutation: spontaneous maternal 15q11.2-q13 deletion in 15q11.2-q13 region (70% of cases), maternal UBE3A ubiquitin gene mutation (11%), paternal uniparental disomy (3-7%), imprinting center defect (2 - 3%) [22].

DNA methylation helps to diagnose AS in approximately 80% of cases. If no abnormalities are revealed, geneticists recommend further diagnosis using DNA sequencing (chromosomal microarray analysis). The risk of having another child with AS depends on the specific chromosome abnormality [1,3,7]. In our study, 34 and 15 patients were diagnosed with AS using DNA methylation analysis and modern DNA sequencing technologies, respectively, with 12 cases of deletion and 3 cases of nucleotide substitution being identified. The severity of the disease is influenced by the type of the mutation and the length of the deletion. Children with nucleotide substitutions have the most favorable clinical manifestations. In case of deletion, larger deletions are associated with more severe developmental delay with the impossibility to walk independently and more severe epilepsy. The severity of developmental delay depends not only on the type of mutation, but also on the severity of epilepsy. According to the published data [1,3,24], AS is usually diagnosed at the age of 3 years or later. Early AS diagnosis is facilitated by the onset of epilepsy and its differential diagnosis.

The incidence of epilepsy in AS patients is estimated to be more than 80% [20,23]. In our study, 45 of 47 patients have epilepsy (95,7%). All patients were up to 5 years of age at the onset of epilepsy. According to the published data, the onset of epilepsy occurs at an age between 3 months and 20 years (most often at the age of 2 - 3 years) [19]. In the first 3 years, seizures occur in 85% of patients [21]. The onset of epilepsy is usually induced by fever. In 50% of cases, seizures continue to be febrile-induced throughout life [21]. In older children, even a slight subfebrile condition leads to more frequent attacks. In 35% of cases, patients tend to develop status epilepticus [18,21].

All types of seizures can develop in AS patients; generalized seizures (atypical absence and myoclonic seizures) develop in 100% of cases. Occipital motor seizures and hemiclonic seizures are less frequent [11,18,21]. Some studies describe infantile spasms [6,14,21], however, West syndrome (infantile spasms and hypsarrhythmia) is not associated with AS [15].

Long-term follow-up data was available for 40 of 47 patients. Drug-induced remission was observed in 36 patients. Patients were treated with different anticonvulsants. After a few years of remission, 24 of 30 had a relapse that was quickly relieved in 23 patients. Patients did not respond to anticonvulsant therapy due to the following causes: 1) noncompliance of the parents, 2) late genetic diagnosis, and 3) carbamazepine and oxcarbazepine treatment. The most effective anticonvulsants for treating AS patients were valproic acid, levetiracetam, and ethosuximide as monotherapy; valproic acid in combination with levetiracetam or ethosuximide. Combination therapy with levetiracetam and ethosuximide was less effective.

According to the published data, valproic acid, clonazepam, and ethosuximide as monotherapy or as a part of combination therapy showed the greatest efficacy in seizure control. Benzodiazepines are indicated for myoclonic seizures, as well as for atypical absence seizures [6,10,17]. Ethosuximide therapy was efficient in case of atypical absence seizures and non-convulsive status epilepticus [17]. Combination therapy with valproic acid (30 - 50 mg/kg per day) and ethosuximide (20 - 30 mg/kg per day), topiramate monotherapy (2 - 5 mg/kg per day), and combination therapy with topiramate and ethosuximide are also effective [5].

Phenytoin, carbamazepine, oxcarbazepine, and vigabatrin as monotherapy can lead to aggravation of seizures in patients with AS. At the same time, in case of focal motor seizures, it is possible to use valproic acid (30 - 50 mg/kg per day) in combination with carbamazepine

(10 - 20 mg/kg per day) or with oxcarbazepine (15 - 25 mg/kg per day) at low or medium doses [9,13,16,21].

Non-convulsive status epilepticus responds to benzodiazepines and corticosteroids [4].

In rare cases, the ketogenic diet was shown to be effective in AS patients [2,8].

Conclusion

We conclude that the severity of developmental delay depends not only on the type of mutation, but also on the severity of epilepsy. Although the developmental delay in these patients is AS-induced, uncontrolled seizures and pronounced EEG changes may also affect cognitive development and behavior. To improve the efficacy of anticonvulsant therapy, Angelman syndrome has to be diagnosed as early as possible, since the treatment of epilepsy in AS patients has certain specific features.

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