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# Epilepsy and sleep disorders improve in adolescents and adults with Angelman syndrome: A multicenter study on 46 patients

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ABSTRACT

*Objective:* Actual knowledge on evolution of Angelman syndrome (AS) relies on questionnaire-based cohort studies, phone interviews, or small retrospective cohort studies focused on specific clinical–genetic features. These reports provide conflicting results. The aim of this study was to assess the long-term outcome of epilepsy, sleep disorders, and EEG in a vast series of AS subjects.
*Methods:* We collected patients with genetically confirmed AS, aged ≥ 14 years, followed in three tertiary epilepsy Centers or attending the meetings of the Italian Organization for AS (OrSA). Retrospective clinical and EEG data were retrieved from hospital archives or family documents. At index evaluation (IE) (last visit at tertiary Centers or single visit during OrSA meetings), caregivers were interviewed about anamnestic data and filled questionnaires on sleep disorders and daily-living skills. Patients underwent general and neurologic evaluation, and video-EEG recordings. All available EEGs were analyzed to compare evolution of spike–wave index (SWI) over the years.
*Results:* Forty-six subjects aged 14–45 years were included: 24 from tertiary Centers, 22 from OrSA meetings. During childhood, 42/46 (91.3%) had seizures, which improved over the years in all subjects. Among patients with epilepsy, 27(64%) became seizure-free at a median age of 10 years and 4 remained seizure-free even after antiepileptic withdrawal. During childhood, 39/46 (84.8%) had sleep disorders, which improved in 27/39 (69%) over the years. At IE, daily-living skills corresponded to age ≤ 1.6 years in 29/46 (63%). Electroencephalogram showed typical AS patterns in 35/46 (76.1%). In EEGs recorded from 10 patients, SWI was not significantly different between infancy/childhood and adolescence/adulthood.
*Conclusion:* Improvement of epilepsy or sleep disorders should not disregard the clinical suspicion of AS in adolescent or adult patients with suggestive features. Drug withdrawal might be considered in the management of epilepsy despite the persistence of epileptiform abnormalities.



## 1. Introduction

Angelman syndrome (AS) is a genetic disorder clinically characterized by intellectual disability, absent speech, facial dysmorphisms, ataxia, tremors, sleep disorders, and seizures [1]. It is caused by deficient expression of the maternal copy of the ubiquitin protein ligase E3A (UBE3A) gene on 15q11-q13, due to one of four molecular etiologies: deletion, paternal uniparental disomy, imprinting defect, and mutations in the maternally inherited copy of UBE3A [2]. Clinical variability exists among the different genetic subgroups as patients with the deletion of maternal copy of 15q11.2-13 region usually show the most severe phenotype [2,3].

Epilepsy occurs in >80% patients, often beginning in infancy or early childhood. Seizures may be polymorphic and manifest as atypical absences, myoclonic, generalized tonic–clonic, unilateral clonic, or atonic attacks [1,3,4]. Cortical tremor is present in most patients [3]. Sleep disorders have been described in up to 80% of patients with AS. They mainly consist of abnormal sleep–wake cycle, multiple nocturnal awakenings, difficulties in falling asleep, and diminished need for sleep [1,3]. Electroencephalography (EEG) abnormalities are evident

*Abbreviations:* AEDs, antiepileptic drugs; AS, Angelman syndrome; EEG, electroencephalogram; ILAE, International League Against Epilepsy; IE, index evaluation; OrSA, Italian Organization for AS; SWI, spike–wave index; UBE3A, ubiquitin protein ligase E3A.

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within the first 2 years of life in more than 80% of subjects, and may not correlate with clinically evident seizures [1]. Three typical EEG patterns have been described, the most common being runs of diffuse, rhythmic, delta waves, usually with anterior predominance, sometimes with superimposed spikes [5].

Clinical and EEG features of AS have been exhaustively described only in pediatric populations [1–5]. Actual knowledge on adolescent and adult patients with AS is provided by wide cohort studies based on questionnaires to family members [4,6] or detailed phone interviews to primary caregivers [7]. A few retrospective studies on smaller cohorts focused on specific AS features [6,8], or were limited to patients with AS with deletion [8–11] or to institutionalized subjects [10]. Many of these studies included children [8,9,11]. Another study did not clearly define the modalities of data collection [12].

The aim of this study was to assess the long-term outcome of epilepsy, sleep disorders, and EEG in a vast series AS subjects, thus improving proper identification and management of adolescent and adult patients with AS.

## 2. Patients and methods

### 2.1. Included subjects

We collected data from 46 patients aged ≥14 years with genetically confirmed AS. Twenty-four patients were recruited from 3 Italian Neurologic Centers: "Bianchi-Melacrino-Morelli" Hospital of Reggio Calabria, annually attended by an average of 1200 patients with epilepsy, mainly adults coming from Calabria (1,973,000 inhabitants); "Oasi SS. Maria" Institute of Troina (Enna), annually attended by an average of 900 patients with epilepsy, mainly children with intellectual disability coming from Sicily (5,074,000 inhabitants); "E. Medea" Institute of Conegliano-Pieve di Soligo, annually attended by an average of 1000 patients with epilepsy, both children and adults, coming from all over Italy. These 24 patients were retrospectively identified from the databases of the three Centers over a 16-year-period. The remaining 22 subjects were recruited during the 2014 and 2015 Italian Organization for AS (OrSA) national meetings, which are attended every year by an average of 40–50 AS subjects of any age with their families.

### 2.2. Data collection

Retrospective clinical data and EEG/polygraphic recordings were retrieved from hospital archives or documents owned by families. All patients underwent an index evaluation (IE) corresponding to the last visit at tertiary Centers or to a single visit during the OrSA meetings. At IE, all patients underwent general and neurologic evaluation, as well as video-EEG (or video-polygraphy including EEG and surface electromyography of bilateral carpal flexors and extensors, in cooperating subjects). All caregivers were interviewed about relevant anamnestic data and were asked to fill comprehensive questionnaires on sleep disorders and daily-living skills. Clinical information about genotype, epilepsy, and sleep disorders was obtained by 5 clinicians (EF, CS, ME, PB, UA). In patients with seizure disorders, we considered the following: age at onset, past and present semiology according to the ILAE Commission on Classification and Terminology [13], frequency, AEDs used, and response to therapy. In patients with sleep disorders, we evaluated: age at onset, treatment, evolution over time, and response to therapy. All patients underwent different EEGs (19 electrodes placed according to 10/20 International System) or polygraphic studies during their life span, and one video-EEG or video-polygraphy at IE. Electroencephalogram recordings at IE were performed during wakefulness and, in 21 patients, also during sleep. Electroencephalograms performed at epilepsy onset were analyzed when available. To quantify interictal epileptiform abnormalities, we calculated percent of time occupied by spike–wave discharges (spike–wave index: SWI), separately during wakefulness and sleep, in all available EEGs. When childhood and adolescence/adulthood EEGs were available for the same patient, the highest SWI recorded in infancy or childhood was compared with the highest SWI recorded during adolescence or adulthood. This comparison was performed separately for awake and sleep recordings. Moreover, awake and sleep SWIs were compared in all available EEGs. All EEGs were independently evaluated and rated by two epileptologists (CS and EF) who came to agreement after mutual discussion of doubtful cases. At IE, neuropsychological evaluation was performed by means of the "Vineland Adaptive Behavior Scale" [14]. This scale evaluates personal autonomy and social skills in daily-living activities and allows the calculation of the corresponding mental age with a minimum detectable value of 1.6 years. At IE, caregivers were asked to fill a sleep disorder questionnaire (adapted from Bruni et al. [6]), consisting on 35 scored items exploring 11 domains: "reduced sleep duration", "prolonged sleep latency", "bedtime problems", "sleep–wake transition disorders", "poor sleep quality", "night awakenings", "abnormal movements during sleep", "sleep breathing disorders", "parasomnias", and "daytime sleepiness" (see Supplementary file 1).

### 2.3. Statistical analysis

We assessed the influence of both recruitment modality and genotype on the outcome by comparing different variables (epilepsy, sleep disorders and daily-living skills) between two recruitment groups (patients from Centers and from OrSA meetings) and among four genotypes (deletion, paternal uniparental disomy, imprinting defect, and mutations in the maternal copy of UBE3A). Statistical analysis was performed with MedCalc, version 15.11.4, using chi-square test, Wilcoxon rank sum test, Student's *t*-test and one-way ANOVA, as appropriate. A $p$ value $< 0.05$ was considered statistically significant. Categorical variables were expressed as percentages, whereas continuous variables were expressed as mean, standard deviation, median, and range. The present study was conducted according to the Declaration of Helsinki Criteria and was approved by the local Ethical Committee of the coordinating Center ("Bianchi-Melacrino-Morelli" Hospital of Reggio Calabria, Italy). All legal tutors gave their written informed consent.

## 3. Results

Forty-six AS subjects were included (27 males, 58.7%). The mean age at IE was 25 years (range: 14–45 years). The genetic defect consisted in maternal deletion (30 subjects, 65.2%), paternal uniparental disomy (7 subjects, 15.2%), UBE3A gene mutations (5 subjects, 10.9%), or imprinting defect (4 subjects, 8.7%). During life-span, 42/46 (91.3%) patients experienced seizures, and 39/46 (84.8%) had sleep disorders.

### 3.1. Epilepsy

During infancy and childhood, 8 out of 42 epilepsy subjects had myoclonic status epilepticus confirmed by video-polygraphic recordings, 17/42 tonic–clonic seizures, 6/42 focal seizures, 15/42 myoclonic seizures, and 12/42 absence seizures. From the median age of 10 years (range: 2–39), 27/42 patients with epilepsy (64.3%) became seizure-free. In particular, 23 of these 27 patients never tried drug withdrawal and were still under AEDs at IE, while the remaining 4 discontinued AEDs without seizure relapse. Seizure frequency significantly decreased from epilepsy onset to IE in all subjects (positive differences = 0, negative differences = 39, $p < 0.001$). At IE, seizure frequency distribution was significantly affected neither by recruitment group ($p = 0.20$; Fig. 2A), nor by genotype ($p = 0.05$ for comparison of all genetic subtypes separately, Fig. 2B; $p = 0.54$ for comparison of subjects carrying deletion with all other patients with different genotypes). At IE, 15/42 (35.7%) patients were still experiencing seizures (Fig. 1). In particular, myoclonic status epilepticus (confirmed by video-polygraphic recording) persisted in 2/42 subjects, tonic–clonic seizures in 3/42, focal seizures in 3/42, myoclonic seizures in 9/42, and absences in 10/42. Cortical tremor was