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Epilepsy and interictal epileptiform activity in patients with autism spectrum disorders☆

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ABSTRACT

Purpose: The purpose of this study was to determine the prevalence of epilepsy and subclinical epileptiform abnormalities in children with autism spectrum disorder (ASD), and to investigate its effects on core autistic symptoms and adaptive behavior skills.
Methods: Patients with diagnosis of ASD who met full criteria on Autism Diagnostic Interview-Revised (ADI-R) were included in the study. Adaptive behavior skills were assessed by Vineland Adaptive Behavior Scale-II (VABS-II). Clinical assessment for epilepsy and video electroencephalography (EEG) (v-EEG) examinations during wakefulness and/or sleep were prospectively performed in all patients.
Results: A total of 112 patients with diagnosis of ASD of mean age 6.58 ± 3.72 were included in the study. Based on clinical and v-EEG assessments, three groups of patients were defined: 1) patients with epilepsy (n = 17; 15.2%); 2) patients with epileptiform discharges in absence of clinical seizures (n = 14; 12.5%); 3) patients without epilepsy and without epileptiform discharges (n = 81; 72.3%). There were no significant differences between three groups of patients on ADI-R subscores. Speech development was also not significantly related to epilepsy. There was a slight tendency of the VABS-II motor skills score to be higher in the group of patients with autism without clinical diagnosis of epilepsy and without subclinical epileptiform discharges ($p < 0.05$) in comparison with the two other groups. According to this tendency, we might claim that patients with higher scores on motor skills could have 0.88 times lower odds for having epileptiform EEG activity.
Conclusions: According to our results, we were not able to detect differences in the ADI-R between the three populations with ASD, all with unknown etiology. Epilepsy, as well as subclinical epileptic discharges, showed small effects on Motor Skills in patients with autism, and had no effect on adaptive behavior Communication/Socialization/Daily Living Skills.

1. Introduction

Autism spectrum disorders (ASD) are a group of disorders that have increased recognition worldwide with a prevalence of 1–1.5% of children and adults. The Center for Disease Control and Prevention released data on the prevalence of autism in the United States in 2017. This surveillance study identified 1 in 59 children (1 in 42 boys and 1 in 189 girls) as having ASD [1,2]. The main clinical manifestations of this group of disorders are persistent deficits in social communication and interaction, and restricted, repetitive patterns of behavior, interests, and activities. The etiology of this group of disorders is still unknown, although a large number of studies were oriented towards discovering its causes. The studies are multidimensional and explore different aspects of autism — genetic factors, brain morphology, somatic disorders in children with autism, and the influence of pre- and perinatal factors on the risk of ASD [3].

The cooccurrence of ASD and epilepsy is now well-established [4], and literature presents a wide range of estimates from 5% [5] to 46% [6] that is significantly higher than the prevalence of epilepsy in the general population, which ranges from 0.5% to 0.7% [7]. Wide range of estimated prevalence of epilepsy in patients with autism stems from the fact that data are drawn from a number of different types of samples that might employ different definitions used from either one of the diagnoses and include differences in terms of population ascertainment method, sample age range, and inclusion or exclusion of other cooccurring medical conditions or intellectual disability [4,8,9]. A

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meta-analysis of the 23 studies found that the prevalence of epilepsy in people with autism and intellectual disability was 21.5% (2150/10000) and 8% (800/10000) [10] for people with autism without intellectual disability. Recently, there have also been reports of high rates of epileptiform electroencephalographic abnormalities in children with autism, without a history of seizures or epilepsy [11,12]. The frequency of epileptiform abnormalities on electroencephalography (EEG) in patients with autism has been described by various researchers to be as high as 23.6% [13], 42.5–43% [14,15], to 60.8% [16].

Clinicians need solid evidence to support advice given to parents and children with autism in relation to comorbidities associated with their condition, especially epilepsy. Both, ASD and epilepsy by themselves have significant impact on the child's quality of life and increase the stress and burden for the families. The clinical appearance of children with epilepsy or ASD only is different from the clinical appearance of children with ASD and epilepsy. Only few published studies have compared the clinical profiles of individuals who have both ASD and epilepsy with individuals who have ASD only [17–20].

The aim of our prospective study was to determine the prevalence of epileptic seizures, epilepsy, and subclinical epileptiform EEG abnormalities in children with ASD. Also, this study aimed to investigate if the cooccurrence of epilepsy or subclinical epileptiform discharges affects core autistic symptoms and adaptive behavior skills of patients with ASD. From a practical standpoint clinician needs to be aware of these risk factors in order to provide appropriate work-up and counseling to family.

2. Material and methods

2.1. Subjects

Consecutive patients of the Clinic for Children and Adolescents, Institute of Mental Health in the period 2010–2015, with diagnosis of the ASD according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) Criteria [21] were recruited for the study. Our clinic is referral center for patients with autism to which the patients from all over the country are admitted as inpatients or outpatients for assessment, diagnostic work-ups, and therapeutic interventions. The children were referred for neuropsychiatric evaluation by child psychiatrist from regional centers, pediatricians, allied health professionals, and parents. Diagnosis was established or confirmed by experienced child psychiatrists and met full criteria for ASD on Autism Diagnostic Interview-Revised (ADI-R) [22].

The internal protocol of the Clinic assumed detailed neurological evaluation and EEG procedure at the Department for epilepsy and clinical neurophysiology for all patients with ASD, and they were consecutively selected during 2010–2015 period. Patients with single-gene defect disease, notably tuberous sclerosis, Rett syndrome, Angelman's syndrome, fragile X-syndrome, cytogenetic abnormalities such as Down syndrome, as well as congenital brain malformations, or a prior history of known childhood epileptic syndromes (Landau–Kleffner, Lennox–Gastaut, and infantile spasms) were excluded from the study.

The research was approved by local Ethic Committee. The process of informed consent for participation in the study was performed before testing, including the consent of parents or guardians. Obtained data are kept confidential.

2.2. Study procedures

2.2.1. Autistic spectrum disorder assessment

All parents were asked to provide basic demographic questions about patients through a demographic questionnaire that was created for the purposes of this study.

In this prospective research, clinical diagnosis of the ASD was confirmed by ADI-R [22], a standardized semistructured interview for parents designed to evaluate signs related to autism and ASDs consisting of 93 items. Quantified domains are obtained by sum of specific items related to Social Reciprocity, Communication, Restrictive, and Repetitive Behavior. Communication domain is separately accounted for verbal and nonverbal children. The diagnostic algorithm provides information on whether the child meets the diagnostic criteria for autism. Higher scores on ADI-R account for greater impairment, meaning worse symptoms of ASD.

If the criteria for ASD were met, the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) [23] was performed for assessment of social adaptive skills of patients — individual and social skills of the person from birth to adulthood. The VABS-II questions were answered by parents or caregivers and were related to description of patients' adaptive behavior. The instrument assesses adaptive behavior in domains of Communication (receptive, expressive, and written communication skills), Daily Living Skills (personal behavior as well as domestic and community interaction skills), Socialization (play and leisure time, interpersonal relationships, and various coping skills), and Motor Skills (gross and fine), providing the composite score (VABS-II score), which summarizes the patients' skills in all four domains. It was administered by certified child psychologists. Scores are calculated by transforming the subtests raw scores to age standardized score using the population norms, subtest transformed scores, and transform to composite scores. At the end, we have a scores for each domains and Adaptive Behavior Composite score ($M = 100$, $SD = 15$). Lower scores indicate greater impairment in adaptive functioning. Duration, depending on the ability of the respondents, is up to 60 min.

2.2.2. Clinical assessment of epilepsy

Two neurologists–epileptologists (MM,VR) performed neurological examination and semistructured interview with parents/guardians and/or patients about clinical history of seizures or epilepsy, and they were blinded to others' clinical epilepsy assessment findings. Special care was taken to obtain a detailed description of seizures from persons who had witnessed the seizures and who also had a good knowledge of the individual and his or her behavior. The diagnosis of epileptic seizures or epilepsy was defined as clinical manifestations that should arise from pathological and excessive discharges of neurons in the brain (International League against Epilepsy, ILAE) [24]. Epilepsy is defined as two or more epileptic seizures unprovoked by a directly identified cause [25]. The following characteristics of epilepsy were assessed: type and severity of seizures, age at the onset of epilepsy and antiepileptic treatment. According to the seizure types patients are grouped into the following: 1) partial seizure group (simple partial, complex partial with or without secondarily generalized seizures), 2) generalized seizure group (myoclonic, clonic, tonic, atonic, tonic–clonic without partial onset), and 3) patients with unclassified seizures. Seizure severity groups were defined according to a composite measure that includes both type and frequency of seizures [26].

2.2.3. Electroencephalographic recordings

The video-EEGs (v-EEGs) were performed during wakefulness and sleep in dedicated EEG laboratory on digital EEG (NicoletOne with the Tornado V44 amplifier, Viasys Healthcare Inc., USA,), with qualified and experienced technicians. Electro-caps were used with International 10–20 position of electrodes with impedance less than 5 kΩ. Recordings were performed for 20 min with 5 min of hyperventilation and photo stimulation, performed according to the Guidelines for Photic Stimulation of the ILAE [27]. Some of the recordings were unusable for interpretation due to excessive amount of movement or muscle artifacts due to patient noncompliance, and those recordings were not used for the study. Melatonin was administered to induce sleep in patients that could not achieve spontaneous sleep, based on evidence that it shows a very good efficacy in sleep induction for EEG recording, even in children with severe behavior problems [28], without changing EEG recordings [29–31].

The v-EEG studies were coded and independently interpreted by two epileptologists–neurologists who do not know the identity of the respondents, and was blinded to the others' interpretation of EEG recordings. The v-EEG records, in parallel with the above-mentioned clinical evaluation, were repeated once after 6 months, and in case of the first epileptic seizure occurrence. The analysis was focused on paroxysmal epileptiform and nonepileptiform abnormality of background activity. Epileptiform discharges including focal spikes, multifocal spikes, generalized spikes, and the spike-waves complexes were encoded separately. Abnormal sleep EEG architecture is considered if sleep spindles were not formed, or were not bilateral and synchronous, since by age 12 to 18 months most sleep spindles should be expressed in a bilaterally synchronous and symmetric fashion, with maximal expression over the central regions [32]. The EEG interpretation was compared to determine the agreement between the electroencephalographers. Two epileptologists agreed completely on presence of epileptiform discharges on every EEG for all patients.

Finally, in each case, the seizure semiology and EEG findings were thoroughly discussed by two epileptologists. Only cases with complete agreement were coded as patients with epilepsy diagnosis or patients with epileptic discharges in absence of seizures. There were two disputable cases, both with epileptic discharges and severe autism symptoms, in which one epileptologist thought a subject may have epilepsy, whereas the other did not. The first one had staring episodes with lack of awareness of the existence of others and the other had repetitive motor activity. Both patients were classified as epileptic discharges in absence of epilepsy.

2.3. Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 18.0). Various descriptive statistics (means, standard deviations, frequencies, and percentages) are used to present data. We used Chi square test to examine relations between categorical variables, such as groups of patients (with and without epilepsy and/or epileptic discharges) and gender. Further on, multivariate analysis of variance (MANOVA) was used to determine differences between various groups of patients (with and without epilepsy and/or epileptic discharges) on test scores (ADI-R and VABS-II). By binary logistic regression, we tested prediction of epileptiform activity appearance based on ADI-R and VABS-II scores.

3. Results

The group of 112 children with autism (boys 90, girls 22) was examined, and the characteristics of sample are summarized in Table 1. The mean age at study entry was 6.58 ± 3.72 years (range 2–18, 77.2% of patients were 3–8 years old); male to female ratio was 4.1:1 (Table 1). (See Fig. 1.)

3.1. Epilepsy

Of the 112 included patients, diagnosis of epilepsy was clinically confirmed in 17 patients (15.2%). According to the above-mentioned criteria, 10 patients had focal onset seizures; 6 patients had generalized onset seizures, and in 1 patient, seizure type remained unclassified. Frequency and severity of seizures were low in 35.3% and moderate in 59.2%. All patients (n = 17) were treated with antiepileptic drugs, around 60% with monotherapy (Table 1).

3.2. EEG recordings

The v-EEG recordings were obtained in 112 patients, including 98 EEGs performed during wakefulness and 46 sleep EEGs. In fourteen patients, awake EEG could not be recorded because of their noncompliance, but sleep EEG was performed. In 32 patients, both awake and sleep EEGs was available. Sleep EEGs had significantly higher sensitivity to detect the epileptiform abnormalities than awake EEGs (41.3% versus 20.4%, $\chi^2 = 6.92$; df = 1; $p < 0.05$). Abnormal, slow background activity was registered in 14.3% of recordings during wakefulness. Abnormal sleep architecture during stage II sleep was found in 8.7% of all sleep EEG recordings. By repeated v-EEG examinations during wakefulness and/or sleep, epileptiform discharges in absence of clinical seizures were recorded in 14 patients (12.5%).

According to clinical and v-EEG assessments three groups of patients with ASD were defined: 1) patients with epilepsy (n = 17; 15.2%); 2) patients with epileptiform discharges in absence of clinical seizures (n = 14; 12.5%); 3) patients without epilepsy and without epileptiform discharges (n = 81; 72.3%).

We did not find significantly different male to female ratio ($\chi^2 = 1.34$; df = 2; $p > 0.05$) in all three groups of patients: in group with epilepsy (2.4:1), group of patients without epilepsy and without epileptic discharges (4.79:1), and patients with epileptic discharges in absence of clinical seizures (3.67:1).

3.3. Autistic spectrum disorder symptoms and adaptive behavior skills

The ADI-R assessments were performed in all patients (n = 112), but two cases were excluded from the analysis because of missing data on the Social reciprocity scale (Table 2). Multivariate analysis of variance did not reveal significant multivariate effect of the patient group on ADI-R scores ($F = 1.06$, df = 5;110, $p > 0.05$). Also, none of the univariate effects were significant, meaning that there were no statistically significant differences on ADI-R subscores between three groups of patients: with epilepsy, with epileptiform discharges in absence of clinical seizures, and without epilepsy and without epileptiform discharges (Table 2).

We also did not find significant relation between speech development and epilepsy ($\chi^2 = 2.43$; df = 1; $p > 0.05$). Epilepsy was diagnosed in 21.1% (12/57) of the nonverbal patients and in 11.3% (6/53) of verbal ones (Table 2).

Verbal subjects' ADI-R Communication score was similar in the three groups defined according to EEG findings: in patients with abnormal background EEG activity (n = 6, 16.0 ± 8.51), in patients with subclinical epileptiform discharges (n = 4, 15.0 ± 4.32), and in patients with normal EEG recordings (n = 43; 16.3 ± 6.07) ($F = 0.81$, df = 2;50, $p > 0.05$).

Nonverbal subjects' ADI-R Communication score was also similar in three groups defined according to EEG findings: in patients with abnormal background EEG activity (n = 12, 12.17 ± 2.55), in patients with subclinical epileptiform discharges (n = 9, 12.0 ± 1.41), and in patients with normal EEG recordings (n = 36; 11.08 ± 2.31) ($F = 1.35$, df = 2;61, $p > 0.05$).

Because of missing data, VABS-II subscores and Adaptive Behavior Composite score were completed in 85 of 112 patients (Table 2). On VABS-II scores, multivariate analysis of variance (MANOVA) did reveal significant multivariate effect of the patient group ($F = 2.40$, df = 5; 85, $p < 0.05$, $\eta^2 = 0.10$). Further on, univariate tests revealed significant differences between three clinical groups (with epilepsy, with epileptiform discharges in absence of clinical seizures, and without epilepsy and without epileptiform discharges) on motor skills score ($F = 3.41$, df = 2; 85, $p < 0.05$; $\eta^2 = 0.07$) (Table 2). If we would apply Bonferroni significance correction for univariate effects, none of the effects would pass new significance level (0.05/5 = 0.01). On the other hand, since multivariate test revealed significant differences between groups, with middle effect size ($\eta^2 = 0.10$), we believe that those effects are probably due to some of the individual variables, that is, they can be related to some of the univariate effects more than to others. Further on, since motor skills scale shows highest effect size for group differences ($\eta^2 = 0.07$), and it is the only scale passing original significance level, we decided to investigate this effect in more details. The least significant difference (LSD) posthoc tests showed that this score was significantly

Table 1
Clinical characteristics of the study groups.

			n	Percent
Age at study entry (Mean, range)	6.58 ± 3.72 (2–18 years)			
Age at seizure onset (Mean, range)	3.67 ± 4.23 (1–14 years)			
Gender	Male		90	80.4
	Female		22	19.6
	Male/female ratio	4.1		
Clinical groups of the patients				
Patients without epilepsy, without epileptiform discharges in EEG	Total		81	72.3
	Male		67	
	Female		14	
	Male/female ratio	4.79		
Patients without epilepsy, with epileptiform discharges in EEG	Total		14	12.5
	Male		11	
	Female		3	
	Male/female ratio	3.67		
Patients with epilepsy	Total		17	15.2
	Male		12	
	Female		5	
	Male/female ratio	2.4		
	Seizure type	Partial seizure group (SPS, CPS with or without secondarily GTCS)	10	58.8
		Generalized seizure group (myoclonic, absences, clonic, tonic, atonic, tonic–clonic without partial onset)	6	35.3
		Unclassified seizures	1	5.9
	Seizure severity	Low (1 GTCS/1–4 CPS/1–20 SPS per year)	6	35.3
		Moderate (2–4 GTCS/5–12 CPS/21–100 SPS per year)	9	52.9
		High (>5 GTCS/>13 CPS/>101 SPS per year)	2	11.8
Video-EEG recordings				
Wakefullness[a]	Total number of recordings		98	100
	Normal EEG		63	64.3
	Abnormal background activity		14	14.3
	Focal slow activity		1	1.0
	Focal epileptiform discharges		18	18.4
	Generalized epileptiform discharges		2	2.0
Sleep[b]	Total number of recordings		46	100
	Normal sleep EEG		27	58.7
	Abnormal sleep architecture		4	8.7
	Focal epileptiform discharges		10	21.7
	Generalized epileptiform discharges		9	19.6

Antiepileptic drugs	n	Percent
Total	17	100
Monotherapy	10	58.8
VPA	4	
LTG	5	
CBZ	1	
Polytherapy	7	41.2
VPA + LTG	4	
LEV + LTG	2	
LTG + TPM	1	

GTCS — generalized tonic–clonic seizure; CPS — complex partial seizure; SPS — simplex partial seizure; VPA — valproic acid; LTG — lamotrigine; CBZ — carbamazepine; LEV — levetiracetam; TPM — topiramate.
[a] In fourteen patients, awake EEG could not be recorded because of their noncompliance, but sleep EEG was performed.
[b] Thirty-two patients had EEG during wakefulness and sleep (both) from the total of 46.

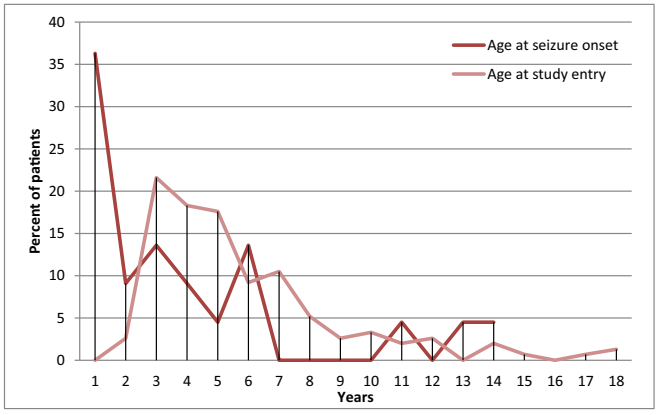

Fig. 1. Age of patient's seizure onset.

higher in the group of patients with autism without clinical diagnosis of epilepsy and without subclinical epileptic discharges (n = 59; 72.33 ± 13.83), compared with patients with epilepsy (n = 12; 66.27 ± 7.89) and also compared with patients without clinical diagnosis of epilepsy but with epileptic discharges (n = 14; 66.77 ± 16.51). Posthoc test did not show significant differences between groups of patients with epilepsy and patients without clinical diagnosis of epilepsy but with epileptic discharges. According to that, we can conclude that there was at least a tendency for motor skills score to be higher in the group of patients with autism without clinical diagnosis of epilepsy and without subclinical epileptiform discharges in comparison with two other groups.

Binary logistic regression model with epileptiform abnormalities in EEG as criterion variable, and ADI-R and VABS-II subscores as predictors, showed only marginally significant prediction ($\chi^2 = 16.155$, df = 10, p = 0.09). We did consider it since motor skills on VABS-II appeared

Table 2
Autistic spectrum disorder symptoms and adaptive behavior skills in study groups.

Instruments	All patients[a]		Patients without epilepsy and without epileptiform EEG discharges		Patients without epilepsy, with epileptic activity		Patients with epilepsy			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F[b]	Sign.
ADI-R	n = 110		n = 80		n = 13		n = 17			
Social reciprocity	21.26	6.22	20.89	6.19	20.92	6.45	23.29	6.16	1.08	0.342
Communication – (verbal subjects)	n = 53		n = 43		n = 4		n = 6			
	16.17	6.16	16.30	6.07	15.00	4.32	16.00	8.51	0.03	0.971
Communication – (nonverbal subjects)	n = 57		n = 36		n = 9		n = 12			
	11.46	2.27	11.08	2.31	12.00	1.41	12.17	2.55	0.88	0.417
Restrictive and Repetitive Behavior	6.25	2.65	6.35	2.71	5.69	2.21	6.24	2.70	0.32	0.723
Early developmental disorder (before 36 months)	4.17	1.13	4.15	1.11	3.85	1.52	4.47	0.87	1.12	0.331
VABS-II	n = 85		n = 59		n = 14		n = 12			
Communication	59.64	13.41	61.15	14.09	59.07	9.59	52.83	12.42	1.86	0.163
Daily Living Skills	70.72	14.94	71.25	14.89	73.36	12.82	65.00	17.19	1.25	0.289
Socialization	61.48	9.91	61.98	10.37	63.21	6.78	57.00	10.10	1.57	0.212
Motor Skills	72.33	13.83	75.42	13.37	66.77	16.51	66.27	7.89	3.41	0.037
Adaptive Behavior	63.21	11.02	64.25	11.52	63.64	7.71	57.58	10.82	1.77	0.174

ADI-R — Autism Diagnostic Interview-Revised; VABS-II — Vineland Adaptive Behavior Scale-II.
[a] Number of participants is less than 112 since we had missing data (ADI-R was completed in 110 patients; VABS-II was completed in 85 patients).
[b] F = Multivariate analysis of variance (MANOVA).

also as marginally significant predictor in the model (B = −0,124; Exp (B) = 0.884, 95% C.I. 0.773–1.01; p = 0.069). Results indicate that patients with higher scores on motor skills show slight tendency to have lower odds for having epileptiform activity. More precisely, each increase of motor skills for 1 point might lower odds for having epileptiform activity 0.88 times, but once again, this effect is only marginally significant, and it can be considered as questionable.

Lastly, since for 66 participants, we did not obtain sleep EEG, one might be concerned that some of those patients could be "false negatives". We might ask whether if they had sleep captured on EEG, would it show epileptiform activity? We decided to test if this possibility could change our results, and we repeated MANOVA only on patients who did have sleep EEG recordings (n = 46). Results were quite similar to previously mentioned. On ADI-R scores, multivariate analysis of variance did not reveal significant multivariate effect of the patient group ($F = 0.97$, df = 5; 46, $p > 0.05$), neither any of the univariate effects were significant. On VABS-II scores, we could obtain only marginally significant multivariate effect of the patient group ($F = 2.06$, df = 5; 46, $p = 0.09$, $\eta^2 = 0.20$), which can be acceptable taking sample size reduction into account (n = 46). Also, univariate tests again revealed significant differences between three clinical groups on motor skills score ($F = 3.58$, df = 2; 46, $p < 0.05$; $\eta^2 = 0.14$). These additional analyses of only participants who had sleep on EEGs were in line with our primary findings.

4. Discussion

The prevalence of epilepsy in our group of patients with ASD with unexplained cause was 15.2%. We found epileptiform discharges in 20.4% of awake and 41.3% of sleep recordings, and also in 12.5% of patients with absence of seizures or epilepsy. According to our results, there was a correlation between motor ability, as measured by the VABS-II motor scores, and the presence of interictal epileptic discharges (IEDs) and/or epilepsy.

4.1. Epilepsy

The frequency of epilepsy (15.2%) in our sample was near the median rate for epilepsy of 16.7% (range 4.8–26.4%) summarized from eight studies by Volkmar [33]. Our estimated prevalence (15.2%) is slightly lower than 19% that was found in a large hospital-based cohort of almost 25,000 patients under the age of 35 years evaluated for ASD comorbidities [34]. However, in a Japanese study, in a sample of 1000 clinic patients with ASD, 37% were found to have epilepsy [35], whereas in Italian clinical sample, it was 28.2% [36]. On the other hand, our estimated prevalence is slightly higher than 12.5% as in the largest existing research database study included almost 6000 patients with ASD under the age of 17 years [37].

The focus of our study was on ASD with unexplained cause, and as such, it differs a bit from other studies that have include all-comers (including patients with single –gene disorders, congenital brain malformations, as well as with epileptic encephalopathies), or which have focused on people with a particular etiology such as tuberous sclerosis. This may explain any differences in the prevalence of epilepsy in this particular survey versus others. The incidence and prevalence of epilepsy in studies depends on selection of patients, factors such as coexisting intellectual deficits, family history, serious slowing down speech, associated genetic disorders/syndromes, age and sex in the study, and the expression of autistic characteristics, as well as on sampling and diagnostic methods used [38]. It is noted that higher rates are often reported from clinical-based samples, because cases seen in clinics tend to be more severe, with regression, and in greater need of clinical attention. Compared to ADI-R distribution in the large population-based study among 5555 Spanish school-aged children (mean ADI-R scores of 13.3 and 14.9 for 2–5 years old children and 10–12 years old children respectively in social reciprocity domain, 9.6 and 12.7 in the communication domain, and 4.0–4.8 in the restricted, repetitive and stereotyped behaviors domain used [39]), our patients (age range 2–18 years, mean 6.6 ± 3.72) had more severe autism symptoms (mean ADI-R social reciprocity domain 21.2; communication domain — verbal subjects 16.1, nonverbal subjects 11.4; restrictive and repetitive behavior 6.25) (Table 2).

We found that prevalence of epilepsy in nonverbal group of patients was 21.1% and almost two times lower in verbal group of patients (11.3%). Given that 51% of our cohort with ASD has difficulties in language comprehension, compliance, or cooperation, and these difficulties may interfere with measuring the cognitive abilities with an intelligence quotient (IQ) test; we did not estimate their cognitive functioning. That could be one of the study limitations, because strong association between intellectual development and epilepsy in people with ASD is widely known. Independent associations were found between epilepsy and lower cognitive ability. For a one standard deviation increase in IQ, the odds of having epilepsy decreased by 47% [37]. Studies also indicate that there are groups of genes associated with either

intellectual disability or autism spectrum disorder that are involved in many of the same molecular and biological functions. This indicates that there is a genetic substrate for this frequent comorbidity [40,41]. A possible reason for the lower prevalence of epilepsy in our group of patients (15.2%), compared to other clinical-based studies, could be younger age of participants, as mean age of the patients on study entry was around 6 years (Table 1). According to the literature, there were two peak periods of seizure onset in autism: early childhood [42] and adolescence [43]. This is also in accordance with our results of first peak of epilepsy onset in the first year of life, and second peak that occurred at the age of 11–14 years. According to results of the cross-sectional population-based study, evaluating 5815 people with ASD [37], where prevalence rate was 12.5% in children between the age of 2 and 17 years, but 26.2% in those at the age of 13 years or older, we could expect an increase of epilepsy frequency with follow-up of our patients, as the majority of our patients were between the age of 3 and 8 years (77%).

We did not find significant difference of the gender distribution in the three groups ($\chi^2 = 1.34$; df = 2; $p > 0.05$), but there was a trend toward higher male to female ratio (4.79:1) in patients without epilepsy and without epileptiform EEG discharges, than in the group with epilepsy (2.4:1). Other authors, also, found that the risk of developing epilepsy is higher in girls than in boys with ASD [44,45]. Amiet et al. [10] carried out a meta-analysis on data available from published reports between 1963 and 2006 on autism with respect to intellectual disability and gender. They noted that the male to female ratio of autism in those with epilepsy was close to 2:1, compared with a ratio of 3.5:1 in those without epilepsy, similarly as we found.

4.2. Epileptiform abnormalities

Interictal epileptic discharges are common among patients with epilepsy but are rare (1 to 4%) in healthy individuals [46,47]. Conversely, in patients with autism, there is a high rate of IEDs even in the absence of definite clinical seizures. The research interest has newly been focused on epileptiform abnormalities, which could be important for the understanding of ASD [14,48,49]. By repeated EEG examinations, we found epileptiform discharges in 20.4% of awake and 41.3% of sleep recordings. This finding is similar to previous studies, which reported a prevalence of epileptiform abnormalities in 20–70% of children with autism and of epilepsy in 10–40% of them [6,11–16,42,50–54]. The frequency of epileptiform EEG abnormalities in our sample (20.4% in awake and 41.3% in sleep condition) was almost twice as high as the frequency of epilepsy (15%), as in the case of Hrdlicka et al.'s [51] and Giannotti's [52] studies. However, given the relatively young age of our sample, one might postulate that epilepsy might develop in later years, because early childhood and adolescence have been indicated as the two peak ages of onset of epilepsy in autism [42,43].

Our results confirm the importance of EEG recording in sleep, which showed significantly higher sensitivity for epileptiform discharges, especially generalized spike-waves and multiple spike-waves complexes (Table 1). Other authors, also, emphasized the use of sleep EEG for correct detection of the epileptiform abnormalities [12,52,53]. Unfortunately, there was a number of patients that could not fell asleep despite melatonin induction (n = 66) and partial sleep deprivation. In the majority of them (n = 53), there were no epileptiform activity during wakefulness, and we cannot predict generalized IEDs in their sleep recordings. In those and other patients, it will be useful to perform the prolonged (overnight) EEG.

According to our results, neither epilepsy nor epileptic discharges had a significant effect on autistic core symptoms assessed by ADI-R scores (Table 2). A few studies evaluated the prevalence of IEDs based on intellectual and language function. Some reports found a high correlation between the presence of IEDs and lower IQ [35,55], but other studies failed to replicate this finding [15,51,54].

According to our results, subclinical epileptiform discharges, as well as clinical diagnosis of epilepsy, were not significantly, but somewhat frequently distributed in the nonverbal group of patients with autism (15.8%; 21.0%, respectively) than in verbal ones (7.5%; 11.3%, respectively), but symptoms of autism were not more pronounced in patients with epileptic discharges and/or epilepsy (Table 2). Abnormal electrical activity or epilepsy when associated with developmental delay or ASD can cause some cognitive, behavioral, or language abnormalities, but the relationships are still far to be clear. The most difficult is to understand which comes first and whether if we can talk about the added effect or already compromised brain [55–57]. Also, as earlier in the development we have epileptiform EEG it would be more delay in evaluated skills [58–60].

4.3. Adaptive behavior

The assessment of adaptive behavior is intended to determine individual abilities in everyday life in terms of functional Communication, Socialization, Motor, and Daily Living Skills [61–63]. Using within-participants research designs and standard scores a profile including very substantial delays in Socialization, moderate delays in Communication, and relative strengths in Daily Living, and Motor Skills have generally been found in individuals with high or average cognitive level, i.e., the so-called "typical autism profile" [64–66]. A different profile with Socialization higher than Communication (Communication\Socialization\Daily Living Skills\Motor Skills) has generally been observed in individuals with below-average cognitive levels [67]. It is interesting that, in both groups, Motor Skills are minimally affected. According to our results, on the contrary, there was a small and, in some cases, marginally significant correlation between motor ability, as measured by the VABS-II motor scores, and the presence of IEDs and/or epilepsy (Table 2), while we did not find any correlations with Communication/Socialization/Daily Living Skills.

Viscidi et al. [19], in a large population-based study, found that patients with ASD with epilepsy had poorer adaptive functioning as evidenced by significantly lower mean Adaptive Behavior Composite score and lower Motor Skills standard score, which is similar to what we found. Also, motor problems were found to be more prevalent in individuals with ASD who had comorbid epilepsy in two other studies, although they used a different battery (Diagnostic Interview for Social and Communication Disorders, DISCO-11) to investigate motor functioning [17]. The patients with epilepsy showed more difficulties with gross and fine motor skills and with daily living skills [17]. The severity of social impairments in children with ASD is related to practical motor abilities in everyday life [68], and motor skill development delays were more obvious as the children got older. In our study group, patients with autism without clinical diagnosis of epilepsy and subclinical epileptic discharges showed slight tendency to have higher motor skills scores compared to the group with ASD with epilepsy and with subclinical epileptic discharges. Also, there was a tendency for participants with higher motor skills to have slightly lower odds for epileptic discharge appearance. It has been suggested that the most common reason for the association of ASD and epilepsy is that the same brain pathology, such as metabolic or mitochondrial, causes both disorders [69,70]. Turk et al. [17] found that children with ASD and epilepsy were more likely to receive a later ASD diagnosis and have intellectual disability, motor difficulties, developmental delays, and challenging behaviors, compared with children with ASD only. Autism associated with epilepsy, language regression, or motor deficits, may represent genetic as well as clinical subtypes, and may also be helpful to genetic research of ASD etiology.

4.4. Limitations and strengths

Our sample included consecutive referrals (convenience sample) that might have led to sampling bias, due to the fact that our

patients were lower-functioning. This is under the assumption that parents of higher-functioning children are less prone to seek help at our clinic. Limitations could be the young age of our patients and relatively short follow-up that consecutively could result in lower frequency rate of epilepsy. In further investigations, we should continue longitudinal follow-up to determine the predictive value of an abnormal EEG and other possible risk factors in the development of later epilepsy.

The strength of our prospective study is that the v-EEG recordings were done at the time of diagnosis of ASD in all patients with unknown etiology, regardless of seizure history or concern. This would yield unbiased prevalence data. In most other retrospective studies, EEG recordings were performed only on patients with epilepsy, possibly leading to sampling bias. Also, our estimates were verified by clinical and electroencephalographic evaluation and were not based on parent report or on previous medical records. Since patients with ASDs often exhibit behaviors that clinically might appear concerning for seizures and every seizure type occurs in individuals with ASD, the differential diagnosis between epileptic and behavioral spell requires expertise.

5. Conclusion

According to our results, we were not able to detect differences in the ADI-R and VABS-II Communication/Socialization/Daily Living Skills between the three populations with ASD, all with unknown etiology. Motor ability, measured by the VABS-II motor scores, showed a trend toward being lower in patients with ASDs with IEDs and/or epilepsy than in those without, which can indicate some underlining brain pathology in those patients.

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Competing interests' statement

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Data sharing statement

All data are published as part of this study. No additional data are available.

Author statement

Maja Milovanovic — research design, organization, epilepsy diagnosis, EEG recordings and interpretations, writing paper. Milica Pejovic-Milovancevic — research design, recruiting patients, ASD diagnosis, organization and conduct of the study, and a guarantor. Vlada Radivojevic — EEG recordings and interpretations, epilepsy diagnosis, data collecting. Jelena Radosavljev-Kircanski — psychological testing of patients and data collecting. Roberto Grujicic — interviewing the patients, data collecting, literature research, writing the article. Oliver Toskovic — statistics. Olivera Aleksic-Hill — recruiting patients, ASD diagnosis, testing. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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