AUTISM SPECTRUM DISORDER AND EEG SPECIFICITY : A CROSS – SECTIONAL TUNISIAN STUDY

SPECIFICITE DE L'EEG DANS LE TROUBLE DU SPECTRE AUTISTIQUE : UNE ETUDE TRANSVERSALE TUNISIENNE

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Abstract

The goal of this survey is to evaluate the particularities of the EEG in children with ASD and to specify their correlations with clinical data.
Methods: This cross-sectional study was carried out over a period from April to September 2014. EEGs were obtained from children with ASD (n=39).
Results: Abnormal EEGs were found in 16 cases (41%) of children with ASD. Epileptiform discharges affected the frontal lobe in 11 cases, the temporal lobe in 4 cases and the occipital lobe in 1 case. There was a multifocal involvement in one case. These epileptiform discharges were more common in females (p=0.3), in intellectually disabled (p=0.3), and in severe autists (p=0.03).
The EEGs was well organized in 33 cases. Disorganized EEGs are correlated with a regression of language (p=0.02) and presence of behavioral problems such as instability and agitation (p=0.04).
Conclusion: This study demonstrates that the high prevalence of EEGs abnormalities in ASD's children was associated with an intellectual deficiency, behavioral problems and severe forms of autism.

Key - words: Autism spectrum disorder ; Electroencephalography; Epileptiform discharges; Epilepsy.

Résumé

Objectif : Evaluer les particularités de l'EEG chez les enfants avec TSA et de préciser leurs corrélations avec les données cliniques.
Méthodes : Cette étude transversale a été réalisée sur une période allant d'avril à septembre 2014. Des EEG des enfants avec TSA (n=39) ont été enregistrés.
Résultats : Des EEG pathologiques ont été trouvés dans 16 cas (41%) d'enfants atteints de TSA avec des décharges épileptiformes au niveau du lobe frontal (11 cas), du lobe temporal (4 cas), du lobe occipital (1 cas) et multifocale (1 cas). Ces décharges épileptiformes étaient plus fréquentes chez les autistes sévères (p=0,03). L'EEG était bien organisé dans 33 cas. Les EEG désorganisés étaient corrélés à une régression du langage (p=0.02) et à la présence de troubles du comportement tels que l'instabilité et l'agitation (p=0.04).
Conclusion : Cette étude démontre que la prévalence élevée des anomalies EEG chez les enfants avec TSA est associée à des problèmes de comportement et à des formes sévères d'autisme.

Mots - clés : Trouble du spectre autistique ; Electroencéphalographie ; Décharges épileptiformes; Epilepsie.

ملخص

الهدف من هذه الدراسة هو تقييم خصوصيات مخطط كهربية الدماغ لدى الأطفال المصابين بالتوحد وتوضيح ارتباطهم بالبيانات السريرية الطرق: أجريت هذه الدراسة المقطعية على مدى الفترة من أبريل إلى سبتمبر 2014
تم تسجيل39 تخطيط كهربية الدماغ للأطفال المصابين باضطراب طيف التوحد
النتائج: تم العثور على مخطط كهربية الدماغ غير طبيعى في 16 حالة (41٪) من الأطفال المصابين بالتوحد. أثرت الإفرازات الصرعية على الفص الجبهي في 11 حالة ، والفص الصدغي في 4 حالات والفص القذالي في حالة واحدة. ولوحظ تورط متعدد البؤر في حالة واحدة.كانت هذه الإفرازات الصرعية أكثر تواتراً في مرضى التوحد الشديد (ع = 0.03). تم تنظيم مخطط كهربية الدماغ بشكل جيد في 33 حالة. ارتبطت مخططات كهربية الدماغ غير المنظمة بانحدار اللغة (ع = 0.02) ووجود اضطرابات سلوكية مثل عدم الاستقرار والقلق (ع=0.04) الخلاصة: توضح هذه الدراسة أن ارتفاع معدل انتشار تشوهات مخطط كهربية الدماغ لدى الأطفال المصابين باضطراب طيف التوحد يرتبط بمشاكل سلوكية وأشكال حادة من التوحد.

كلمات المفاتيح: اضطراب طيف التوحد**;** تخطيط كهربية الدماغ**;** إفرازات صرع الشكل**;** الصرع

Background

Autism Spectrum Disorders (ASD) severely impairs neurological and developmental disorders. They are characterized by a persistent impairment in reciprocal social communication and social interaction, and restricted, repetitive patterns of behavior, interests or activities. These symptoms exist from early childhood and limit or impair everyday functioning [1].

The incidence of autism has increased over these last years. According to estimates from the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network [2], one in 68 children has been identified with ASD, with a prevalence 4.5 times higher in boys than girls. In Tunisia, the autism frequency rate among children with developmental disorders was documented as 11.5% [3,4].

Despite a large body of investigations, the etiology of ASD remains indeterminate. It is hypothesized that it is caused by a combination of genetic and environmental stimuli [5].

Children with ASD display associated features such as intellectual disability and co-occurring medical conditions, particularly epilepsy (5% to 40%) [6,7].

These children frequently have behaviors that are similar to complex partial seizures. Thus, it is difficult to determine if such behaviors result from epileptic seizures or are related to ASD symptomatic [8]. Moreover, epileptiform discharges (ED) in EEG in children with ASD are frequently found without a clinical history of seizures or epilepsy. The increased prevalence of epilepsy and/or ED in children with ASD may be an important sign of an underlying neurological abnormality.

The aim of this study is to evaluate the particularities of the EEG in children with ASD and to specify their correlations with clinical data.

MATERIALS AND METHODS

1. Study

The study was cross-sectional, descriptive and analytical. It was carried out over a 6 month period from April to September 2014.

It was performed in both the Child and Adolescent Psychiatry Department and Neuropediatric Department (Hedi Chaker Hospital, Sfax, Tunisia) and in the Functional Exploration Department (Habib Bourguiba Hospital,Sfax, Tunisia).

All study procedures were approved by the local Research Ethics Committee at Hedi Chaker Sfax University Hospital , according to Helsinki.

Data were collected by a properly – trained child psychiatrist.

A written consent from parents or legal guardians of participants was obtained after the nature of the procedures had been fully explained.

2. Population

The sample enrolled thirty nine[39] children with ASD previously identified and followed up regularly in the Child and Adolescent Psychiatry Department.

*** Inclusion criteria:**

- Children who met DSM 5 criteria [1] of ASD and whose score at the Child Autistic Rating Scale (CARS) was ≥ 30.
- Children who had normal neurological and physical examination

*** Non-inclusion criteria:**

known neurogenetic conditions (for example, tuberous sclerosis, neurofibromatosis, fragile X syndrome, Down syndrome) and epileptic children or children with a history of seizures.

3. Methods

3.1 DSM-5 Diagnostic Criteria for ASD

Diagnostic Criteria for ASD according to DSM-5 [1] were :

-Persistent deficits in social communication and social interaction across multiple contexts,
- Restricted, repetitive patterns of behavior, interests, or activities, currently or by history
- Presence of the symptoms in the early developmental period.
- Clinically significant impairment in social, occupational, or other important areas of current functioning.

3.2 CARS

The CARS evaluates the severity of autistic behaviors in 14 functional areas by assigning a score from 1 to 4. An overall score is calculated by adding all of these figures, to situate three levels: "Severely autistic" when the score is between 37 and 60; "Mildly to moderately autistic" when the

score is between 30 and 36.5, and "absence of ASD" when the score is less than 30 [9].

3.3 EEG

We chose to perform an EEG sleep (EEGs). In fact, the recording sleep could minimize artifacts and therefore could better identify ED. In addition, we studied and analysed sleep organization.
In our dataset, sleep was recorded in all cases and the recording time was 45 to 60 minutes.
Mild sleep deprivation (awaking the child 2–4 h prior to regular morning arousal) was recommended.
We used the digital EEG system: Neurofax Nihon Kohden. Recordings included an electrocardiogram using a standard clinical recording system.
In order to optimize near field activity and reduce electrical contamination from the physical reference, data was referenced according to the longitudinal bipolar montage of the original 8 electrode signals. This montage is considered as one of the best to improve spatial resolution in EEG with a limited number of electrodes and because of its effectiveness and widespread clinical usage.
Analysis of the data of these subjects included:
-The analysis of the physiological sleep graphoelements.
- The research of the ED, describing their patterns and specifying their location.

4. Statistical analysis

Statistical analysis of all factors was performed using Statistical Package for the Social Sciences (SPSS) in its 20th release. It included:
-A descriptive study: we observed frequencies of the quantitative variables and average with standard deviation of the qualitative variables.
-An analytical study: we used the Pearson correlation coefficient in order to establish correlations between EEG abnormalities and the severity of autism. The level of statistical significance was set at $p < 0.05$ (alpha level of 5%).

RESULTS

1-Demographic data

The study population included 39 Children with ASD (23 males and 16 females), mean age 5 years, ranging from 2 to 6 years old table 1.

Table 1: Demographic data (n = 39)

Demographic data	n (%)
Gender	
Male	23 (58.97%)
Female	16 (41.02%)
Area of residence	
Urban	22 (56.41%)
Rural	17 (43.59 %)
socio - economic level	
Good	7 (17.95 %)
Average	25 (64.10 %)
Low	7 (17.95 %)
Rank sibling	
Older	14 (35.90 %)
Younger	7 (17.95%)
Youngest	18 (46.15%)
Consanguinity	9(23.07%)

2-Clinical characteristics of patients

The clinical characteristics of patients are represented in table 2.

Table 2: Clinical characteristics (n = 39)

Clinical characteristics	n (%)
Psychomotor development	
Delayed	21 (53.84 %)
Normal	18 (46.15%)
Language	
Absence	31(79.48%)
Presence	1 (2.56%)
Regression	7 (17.95%)
Intellectual deficiency	
No	23(58.97%)
Yes	16 (41.03%)
Severity of autism	
Severely autistic	27 (69.23%)
Mildly autistic	12 (30.77%)
Instability and agitation	
Yes	21 (53.85%)
No	18 (46.15%)

3- Epileptiform discharge in sleep EEG

In EEGs, ED were noted in 16 cases (41%). Abnormalities were seen as spikes, polyspikes and polyspike waves (figure 1) that affected the frontal lobe in 11 cases, the temporal lobe in 4 cases and the occipital lobe in one case. There was a multifocal involvement in one case.

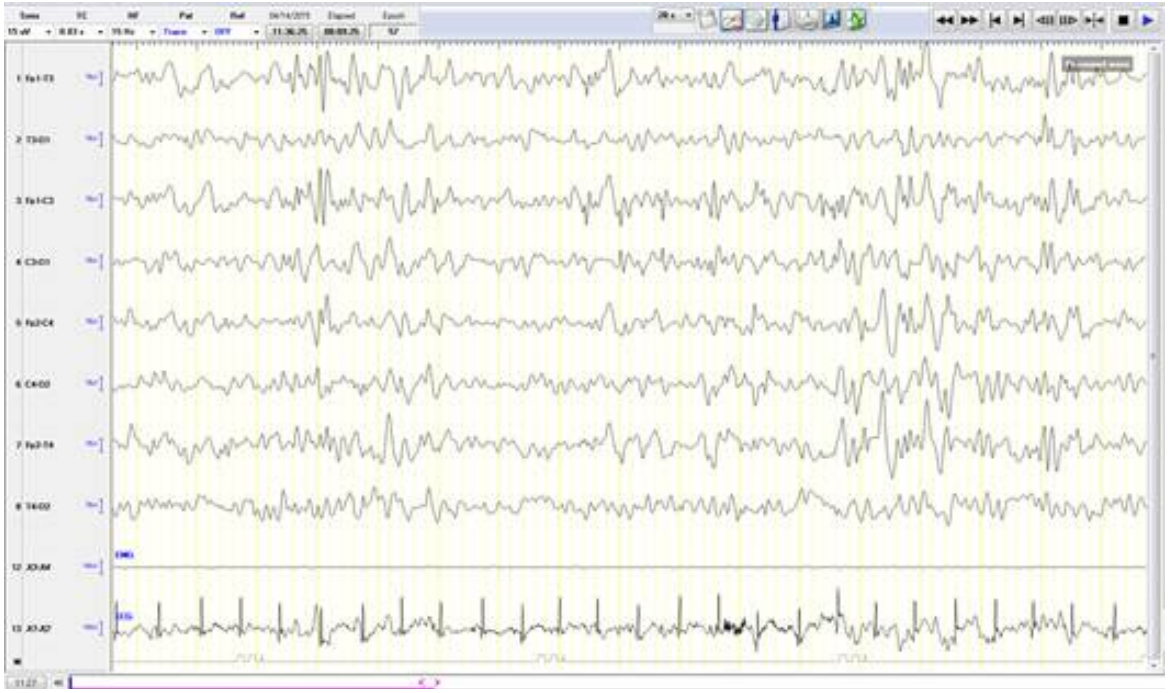

Fig 1: example of EEGs: biphasic spikes left frontopolair in a 4 – year boy with a severe form of autism.

ED in EEGs are more common in females, in patients with intellectual disability and in children with severe autism table3. Nevertheless, only the severity of ASD was significantly correlated to ED.

In addition, patients with behavioral disorders exhibited EEG abnormalities affecting the frontal lobe in 81.81% of cases. Children with an absence of language have ED which affects different cerebral lobes.

Table3 : Correlation between ED in EEGs and clinical characteristics of patients

Clinical characteristics	Epileptiform discharges	P
Gender		
Males	7	0.3
Females	9	
Severity of autism		
Severe autism	14	**0.03***
Moderate autism	2	
Instability		
yes	10	0.36
No	6	
Absence of language		0.5
yes	12	
No	4	
Regression of language		0.33
yes	4	
No	12	
Intellectual disability		0.30
yes	9	
No	7	

p: Pearson correlation coefficient, the level of statistical significance was set at $p < 0.05$ (alpha level of 5%).
*Significant result.

4-Sleep organization

The EEGs was properly organized in 34 cases. Sleep disorganization was observed in five cases: asynchrony of sleep spindles in three cases (figure 2), and two poorly organized EEGs.

The disorganized EEGs was correlated with regression of language (p=0.02) and the presence of behavioral problems (p=0.04).

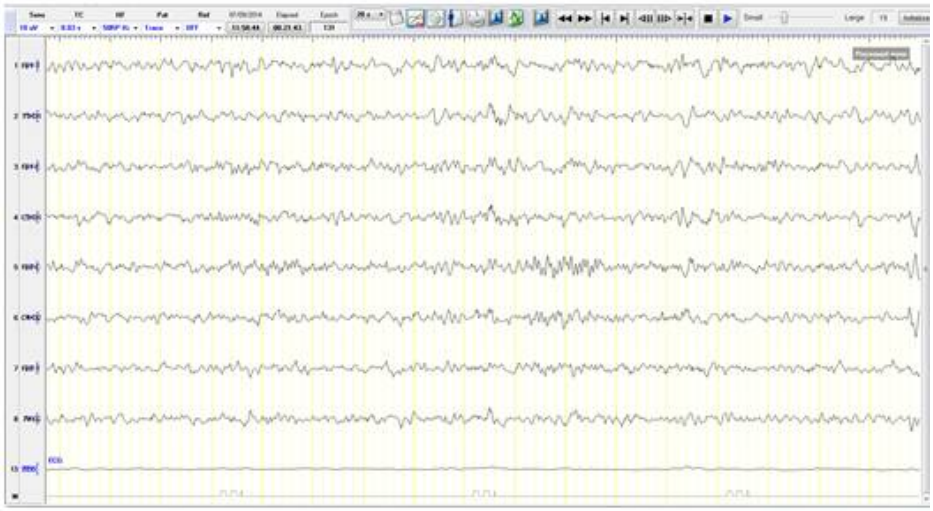

Fig 2 : example of sleep disorganized EEG: asynchrony of sleep spindles in a 6 – year old girl

DISCUSSION

The main results of this study show that 41% of patients with ASD have ED on their EEG without having definite clinical seizure. In 68.75% of cases the frontal lobe was affected.

A recent review showed a widely varying frequency of subclinical electroencephalographic abnormalities in patients with ASD and the most common site of abnormal electrical discharges seems to be the right temporal lobe [10]. Nicotera and al [11] conducted a retrospective study on a sample of 69 patients with ASD and evaluated: the phenotypic characteristics; the prevalence of EEG abnormalities; the correlations between behavioral and cognitive variables and EEG abnormalities. They found that EEG abnormalities were present in 39.13% of patients. Whereas, Chez and al [12] found higher rates than ours: 61% of individuals with ASD and without clinical history of seizure have ED on their EEG.

In Yasuhara's study [13], ED were found in 85.8% of the autistic children. These differences could be due to the use of prolonged EEG recordings.

The increased prevalence of ED in individuals with ASD may be an important sign to an underlying neurological anomaly.

The authors suggest that paroxysmal discharges in cortical areas undergoing rapid maturation may be involved in the development of autistic symptoms [5].

Concerning the pathophysiology of the association of ASD and ED, scientific studies are interested to understand the clinical and biological basis of this comorbidity. For this reason, many hypotheses have suggested: accidental co-occurrence considering the high frequency of both conditions [6]; common neuroanatomical and neurochemical events leading to a disrupted excitatory/inhibitory balance [14] and common genetic or neurodevelopmental risk factors; or similar brain pathology might underlie an autistic phenotype and epilepsy [6].

In the present survey, ED in the EEGs of children with ASD were heterogeneous. In fact, the localization of these abnormalities in EEGs was variable, ranging from centrotemporal spikes to similarities to benign focal epilepsies [12,15]. Many different localization patterns were observed in this study. Interestingly, the frontal site is the most common locus with a frequency of 68.75%. This may explain the frequency of behavioral problems in children with this type of abnormalities targeted in our study. The temporal lobe was concerned by ED in 25% of cases; this site can be involved in social deficits. Some authors showed that bitemporal and left temporal abnormalities are also consistent with sites of potential language dysfunction [12]. In another study, the frequency of frontal lobe epileptic activity was higher [5]. The significance of this observation needs further exploration, as it has

been suggested that the involvement of the frontal lobe may be important for the possible development of autistic symptom [5].

A primordial question concerns correlation between the location of the ED and the presence of specific cognitive or behavioral problems as not being properly addressed. In fact, nearly all patients with autism have impairment in social skills. Beside, several studies have revealed specific deficits in social cognition in patients with various forms of epilepsy [8]. The different localization of EEG abnormality seems to confirm that they represent an epiphenomenon of a cerebral dysfunction [16]. EEG epileptiform abnormalities may be a factor in the pathology of language delay and, possibly, the future development of clinical seizures [12]. A possible impact of epileptic activity not only on language neural networks but also on brain regions involved in the development of social skills [17].

In the present survey, some factors were associated with ED in the EEG: female sex, intellectual disability and the severity of autism and the absence of language. In Yasuhara' study [13], epileptic seizure discharges are most frequently developed from the frontal lobe (65.6%) and children with ASD having a lower intellectual quotient showed higher incidence of seizure waves. The effect of intellectual disability on the rate of isolated epileptiform EEGs is less well investigated, and the existing data are conflicting. Spence et al. [16] found no intellectual quotient differences between those with and without epileptiform EEGs.

Precenzano and al [10] showed that electroencephalographic abnormalities in ASD appear independent of age and gender, but they are frequently associated with severe dysfunctional behaviors and lower intellectual performance, and they are associated with a poor prognosis, probably because they reveal a severe brain dysfunction disrupting neuronal excitability.

Similarly, Nicotera et al. [11] found that EEG abnormalities correlated with autism severity, hyperactivity, aggression, anger outbursts, language impairment, self-harm, negative or destructive behavior, motor stereotypies and intellectual disability.

Capal et al. [18] in their retrospective study found evidence that patients with ASD and epileptiform discharge exhibited more impaired adaptive functioning (evaluated through Vineland Adaptive Behavior Scales) compared with normal EEG-ASD group ($p = 0.05$).

Ours study has also shown that disorganized EEGs is associated with regression of language and behavioral problems. Five children (12.82%) have disorganized EEGs.

In fact, sleep difficulties have proved to be associated with increased rates of over activity, disruption, non-compliance, aggression, irritability, and affective problems which are all problems that could significantly interfere with ASD [19]. Sleep deprivation is correlated with ASD severity such as social skill deficits, communication impairments, higher rates of stereotypic behaviors, and stricter adherence to non-functional routines [20].

Study limitations: The present study has some limitations which are mainly the relatively small size of our population, the lack of comparison of EEGs data with a control group, and the absence of history of epilepsy or seizure.

CONCLUSION

The high prevalence of EEG abnormalities in ASD's children concurs with literature findings. The most common site of abnormal electrical discharges was the frontal lobe and these abnormalities are associated with severe form of autism. They are considered as risk factors of developing epilepsy. So, there is a need to study these children early with electroencephalography to better understand the evolution of autism and the propensity to develop seizures in this population, and to improve understanding of the pathophysiological mechanisms of autism. Future electroencephalographic observations may offer insight into and treatment options for ASDs.

REFERENCES

[1]. American Psychiatric Association. Autistic Spectrum Disorders. In: Diagnostic and Statistical Manual of Mental disorders. *5th ed. Arlington VA: American Psychiatric Association.*2013;50-59

[2]. Christensen D, Van Naarden Braun K, Baio J, Bilder D, Charles J, Constantino J et al. "Prevalence and characteristics of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network". MMWR Surveill Summ.2016; 65.3:1–23.

[3]. A.Ouhtit, Y.Al-farsi, M.Al-sharbati, M.Waly, I.Gupta, O. Al-Farsi and al. Underlying Factors Behind the Low Prevalence of Autism Spectrum Disorders in Oman Sociocultural perspective. *Sultan Qaboos Univ Med.* 2015; 15: 213–217.

[4]. MO Bakare, KM Munir. Autism spectrum disorders (ASD) in Africa : a perspective. *Afr J Psychiatry*. 2011; *14*: 208–210.

[5]. Boutros N. Epileptiform discharges in psychiatric patients: a controversy in need of resurrection. Clin EEG Neurosci.2009; 40: 239–244.

[6]. C Amiet, I Gourfinkel-An, C Laurent, N Bodeau, B Génin, E Leguern, et al. Does epilepsy in multiplex autism pedigrees define a different subgroup in terms of clinical characteristics and genetic risk? *Molecular autism*. 2013; 4: 47.
[7]. Canitano R: Epilepsy in autism spectrum disorders. Eur *Child Adolesc Psychiatry*.2007; **16:** 61–66
[8]. Ghacibeh G & Fields C. Interictal epileptiform activity and autism. *Epilepsy & Behav*.2015
[9]. Schopler E, Reichler EJ, DeVellis RF, Daly K. Toward Objective classification of childhood autism: Childhood Autism Rating Scale (CARS). *J Autism Dev Disord*. 1980; 10: 91-103.
[10]. F Precenzano, L Parisi, V Lanzara, L Vetri, F Operto, G. M. G Pastorino et al. Electroencephalographic Abnormalities in Autism Spectrum Disorder: Characteristics and Therapeutic Implications. Medicina 2020, 56, 419
[11]. Nicotera, A.G.; Hagerman, R.J.; Catania, M.V.; Buono, S.; Di Nuovo, S.; Liprino, E.M.; et al. EEG Abnormalities as a Neurophysiological Biomarker of Severity in Autism Spectrum Disorder: A Pilot Cohort Study. J. Autism Dev. Disord. 2019; 49: 2337–2347
[12]. Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy Behav*. 2006; 8: 267- 271
[13]. Akihiro Yasuhara. Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). *Brain Dev JPN*. 2010; 32: 791–798
[14]. Marotta, R.; Risoleo, M.C.; Messina, G.; Parisi, L.; Carotenuto, M.; Vetri, L et al. The Neurochemistry of Autism. Brain Sci. 2020; 10: 163
[15]. A Parmeggiani , G Barcia, A Posar, E Raimondi, M Santucci, M Cristina Scaduto. Epilepsy and EEG paroxysmal abnormalities in autism spectrum disorders. *Brain Dev JPN*.2010; 32: 783–789
[16]. Spence SJ, Schneider MT. The role of epilepsy and epileptiform EEGs in autism spectrum disorders. *Pediatr Res*. 2009; 65: 599–606.
[17]. Hansen R. L., Ozonoff S., Krakowiak P and al. Regression in autism: Prevalence and associated factors in the charge study. *Ambul Pediatr*. 2008; 8: 25–31.
[18]. Capal, J.K.; Carosella, C.; Corbin, E.; Horn, P.S.; Caine, R.; Manning-Courtney, P. EEG endophenotypes in autism spectrum disorder. Epilepsy Behav. 2018; 88: 341–348.
[19]. S. Cohen, R. Conduit, S. W. Lockley, S. MWRajaratnam, K M Cornish. The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. *J Neurodev Disord*. 2014; 6: 14.
[20]. Richdale AL, Schreck KA: Sleep problems in autism spectrum disorders: prevalence, nature, & possible biopsychosocial aetiologies. *Sleep Med Rev*. 2009; 13: 403–411