Autistic Spectrum Disorder: What Video EEG Can Reveal about Its Pathophysiology

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Abstract

Objective: The autistic spectrum disorder (ASD) is a lifelong disorder characterized by a defect in communication, social interaction and stereotype patterns of behavior. The etiology of ASD is probably heterogeneous. EEG abnormalities were observed in autistic patients, but these findings are mostly based on the visual analysis and scarce studies used quantified EEG parameters. Changes in connectivity of various parts of brain cortex were described in some studies and that is why we decided to investigate an EEG measure which is capable to evaluate the connectivity: The coherence. Study aims are to,

1. Assess the hypothesis of connectivity changes;
2. Assess the impact of epileptiform discharges on neuropsychological development.

Methods: We present a small study of 24 children with ASD who underwent complex neuropsychological, neurological, sleep video-EEG (whole night and part-day) and MRI of brain investigations. The video EEG and MRI data are compared with quasi-normal EEG and MRI data from the control group. The EEG data were evaluated by experienced EEG reader and then the parts of EEG in relaxed wakefulness were quantified in terms of inter-channel coherence in several EEG channels.

Results: A coherence analysis across several EEG channels revealed a statistically significant correlation between inter hemispheric coherence of the rear temporal regions (T5-T6) at 16-31 Hz and Childhood Autism Rating Scale raw scores.

Conclusion: The changes in connectivity measured by the coherence might be a part of pathophysiology of the ASD.

Keywords: Autism; Video EEG; Coherence; Connectivity; Epileptiform discharges

Abbreviations

ASD: Autism Spectrum Disorder; CARS: Childhood Autism Rating Scale; CI: Confidence Interval; EEG: Electroencephalography; FFT: Fast Fourier Transform; MRI: Magnetic Resonance Imaging.

Objective

The autistic spectrum disorder (ASD) is a lifelong disorder characterized by defect in communication, social interaction and stereotype patterns of behavior [1]. The first symptoms are observed in early childhood. The prevalence studies in different geographical regions done by different teams, converge to estimates to a median of 17/10 000 [2]. The etiology of ASD is unknown, probably heterogeneous and it includes genetic, immunologic and environmental factors [3-7].

Atypicalities in EEG signal are more frequent in ASD than in other neurodevelopmental conditions [8]. Coherence counted as a cross-spectral density by the FFT is a parameter that estimates the consistency of relative amplitude and phase between any pair of signals in each frequency band [9]. Its value is 0 for two independent signals and 1 for completely dependent signals. Thus, coherence is an indirect measure of functional connectivity between two areas of the cerebral cortex. In addition, coherence is a function of frequency and can vary depending on the different frequency components of the two signals [9]. The coherence of EEG signals between the temporal and frontal lobes of the dominant hemisphere is lower in autistic children compared to unaffected controls [10]. In addition, the most prominent changes in coherence in ASD children are in the gamma band of the EEG (25-100 Hz) [11].

One study of ASD children, comparing EEGs between subgroups with and without developmental regression, found a higher frequency of epileptiform discharges in sleep [12]. Other authors have reported slightly different results, with no significant correlation between interictal epileptiform discharges and regression but a correlation between clinically manifest epilepsy and regression [13].

It is still under debate if early treatment with antiepileptic drugs might improve communication and social skills in children with ASD and epileptiform discharges, but this was not proven by statistical


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analysis and that’s why the AEDs are mostly not used in patients with subclinical epileptiform discharges without seizures [14].

Morphologic and neuro-pathologic changes have been identified in ASD, including in some cases a larger head and brain size as measured by MRI volumetry [15]. The enlargement is more prominent in the white matter and this finding supports the changes in connectivity as a pathophysiological factor of ASD [16,17].

Methods

Here we performed a complex neurological investigation, including sleep video EEG and brain magnetic resonance imaging (MRI), as part of a project analysing the immune profiles of children with ASD. The study aims to (a) Assess the hypothesis of connectivity changes, especially in the temporal regions; (b) Assess the impact of epileptiform discharges on neuropsychological development. The patients were pre-selected among the patients of the paediatric psychiatry unit of our hospital.

Informed consent and ethical aspects

The parents of all the patients in the autistic group signed an informed consent which was as like as the whole study approved by the local Ethical Committee of our hospital. The control group was selected retrospectively from the regular patients and all of them had signed proper informed consent for that procedures performed in the treatment regime.

Inclusion criteria

Children 3 to 6 years of age with a diagnosis of childhood autism or atypical autism by a psychologist and paediatric psychiatrist according to the ICD-10 were recruited to our study. Children with a clear genetic basis for the ASD, epilepsy and/or using antiepileptic drugs, or haematological, autoimmune, or infectious disease and other known diseases or malformation were excluded.

Psychological and pedopsychiatric examination

A structured interview was conducted with parents. It was oriented to family history, general health state, and medication used. The paediatric psychiatrist performed the examination and evaluation with respect to ICD-10 criteria. Intensity of autism symptoms was evaluated using the Autism Diagnostic Observation Schedule (ADOS), 2nd revision, and the Childhood Autism Rating Scale (CARS) [18,19]. The ADOS is a semi-structured standardized evaluation of communication, social interaction, play and imaginative use of memory materials, and specific and repetitive behavioral patterns in children with suspicion of ASD [20]. The CARS is a broadly accepted evaluation scale for childhood autism based not only on the frequency of behavioral patterns but also on their intensity, peculiarity, and duration. The result is expressed as a raw score (Table 1). The psychologist determined the laterality of the patient.

Complex neurological evaluation and video EEG

The complex neurological investigation, including clinical neurological evaluation and long-term video EEG (evening and whole night) recording, was performed in 24 children (20 boys, 4 girls; average age 4 years, 10 months; standard deviation 1 year and 3 months). The video EEG was recorded using the TruScan EEG 2/32, in the standard montage with 19 EEG channels and a sampling frequency of 256 Hz. The EEG cap was used in all cases.

We retrospectively selected 24 daytime recordings from non-
Video EEG

The waking EEG was normal in 14 patients (58%). In 10 children (42%), the visual analysis revealed some abnormality of the basic relaxed–wake basal activity (nine children with mild abnormality in terms of unstable activity). The slowing of the basal activity was identified in six children (25%), mostly generalized in 4 from 6 cases. Epileptiform activity in the wake state was not detected in any children, but the wake period was limited to only the evening before night recording. The disruption of normal sleep structure as detected by visual analysis (sleep fragmentation, absence of typical sleep patterns, and suppression of delta sleep N3) was seen in seven children (29%). Epileptiform discharges were noted in six (25%), all generalized (95% CI of probability of epileptiform discharges in sleep is 9.8% to 46% which is clearly higher than in general population). The electrical status epilepticus in slow-wave sleep (ESES) was not recorded in any of our patients, and we did not see any clinical epileptic seizure.

Comparison of wake EEG between ASD children and unaffected controls

We found higher coherences in wake EEG between frontal (F7-F8) temporal (T3-T4) in all 4 frequency bands (0.1Hz-3Hz, 4Hz-7Hz, 8Hz-15Hz, 16Hz-31Hz) by the Wilcoxon–Mann–Whitney U-test (F7-F8/0.1-4Hz, p=0.013; F7-F8/4-7Hz, p<0.05; F7-F8/8-15Hz, p=0.02; F7-F8/16-31Hz, p<0.05; T3-T4/0.1-4Hz, p<0.05; T3-T4/4-7Hz, p<0.05; T3-T4/8-15Hz, p<0.05; T3-T4/16-31Hz, p<0.05) and no statistically significant difference of coherences was found between the occipital electrodes O1 and O2.

Correlation between coherence and CARS

We found a statistically significant correlation between CARS raw scores and the coherence between the rear temporal regions (T5 and T6) in the beta frequency range (16-31 Hz) (Figures 1 and 2). The Pearson’s r is -0.4423 and the correlation is statistically significant (p=0.031).

Relationship between epileptiform discharges and CARS

We compared the subgroup of the six children with epileptiform discharges in sleep with the other subgroup of 18 patients without them. Patients with the discharges had higher CARS scores (average value 38.25 compared with 35.19), but this difference was not statistically significant (Wilcoxon–Mann–Whitney U-test, p=0.224).

Relationship between epileptiform activity and laterality

In the subgroup without epileptiform discharges in sleep, right-handedness was more frequent compared to left-handedness/ambidexterity (ratio 13:5). In the subgroup with epileptiform discharges, this ratio was 2:4. As distinct as this difference appears, however, with this small number of patients, it was not statistically significant (Fisher’s exact test, p=0.150).

Brain MRI

The visual analysis of the MRI results was mostly normal, with only three cases involving abnormal findings (one pontocerebellar cyst, one arachnoid cyst, one gliosis). The functional anisotropy in the regions of genu, truncus, splenium, cingulum, and uncinate gyrus was compared with imaging of four controls of corresponding sex and age. These controls were not selected from the EEG controls. The children with ASD did not differ significantly from controls in values of functional anisotropy (Wilcoxon–Mann–Whitney U-test, p values (according to the selected region): 0.298, 0.883, 0.617, 1.0 and 0.220, respectively).

Conclusion

We found a statistically significant negative correlation between CARS raw scores and the interhemispherical coherence of signals from the rear temporal regions at the frequency band 16-31 Hz. This finding corresponds with the observation of connectivity differences in people with ASD [16,17]: Close connections have higher connectivity in those with ASD compared with controls, and long-distance connections have lower connectivity. We found this correlation only in the inter-
temporal coherence, which supports the hypothesis that the temporal lobes have a special role in ASD pathogenesis. The clinical observation that ASD patients perform quite well on tasks requiring focus on a narrow segment of reality (short connections) but not with associations on a broader spectrum of input (long connections) seems to be linked to this electrophysiological finding.

We identified higher interhemispheral coherences in ASD patients compared to controls in the frontal and anterior temporal regions. This might support the hypothesis of altered connectivity in brain of the ASD patients. We found an increased frequency of interictal epileptiform discharges in the sleep EEG (6 in 24, 95% CI of probability 9.8% to 46%). The proportion is higher than in general population and this finding is in agreement with previous studies [21]. It is generally accepted that epileptiform discharges, even if interictal, can affect psycho-neurological development [22]. One important factor in our study design that probably decreased the strength of the statistical association between interictal discharges and psychological measures is that patients with active epilepsy (with seizures) were excluded.

Our finding of a statistically significant negative correlation between the interhemispheral coherence of the rear temporal regions and CARS raw scores corresponds with previously identified changes in local and long-distance connectivity in children with ASD. It seems that this feature is more prominent in higher EEG frequencies. The presence of epileptiform discharges in sleep appears to be part of the pathophysiological process of ASD. Possible associations would be better analysed with a larger series of patients in a larger study.

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References