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Original Research Article

EPILEPSY COMORBIDITY IN AUTISM SPECTRUM DISORDER IN ALBANIA

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Abstract

Introduction: The association between epilepsy and autism has been extensively described and documented during the past decade due to its therapeutic approach and clinical importance.

Objectives: This study aims to describe the comorbidity of epilepsy in autism spectrum disorder in Albania with a special focus on the effect of epilepsy on regression age and intellect (IQ).

Methods: In this retrospective study we reviewed 164 patients diagnosed with ASD at our clinic during 2011-2014. The chief complaints were developmental problems (speech delay, behavior problems, and developmental delay) and seizures. The children were evaluated by the child neurologist and the psychiatrist for children and adolescents.

Results: The comorbidity of epilepsy and ASD was found in 40 children (24%). In the comorbidity group, there was a significant positive correlation between lower IQ and early age of regression ($r=0.817$, $n=49$, $p<0.001$). Patients in the comorbidity group had a lower mean IQ than patients with ASD only (88.10 ± 6.94 vs. 65.54 ± 8.72; $p<0.001$).

Conclusion: Epilepsy in autism spectrum disorders is one of the additional problems to be to be dealt with in these patients. Major risk factors for seizure occurrence are mental retardation and additional neurological disorders, as well as some specific associated medical conditions.

Keywords: autism, epilepsy, comorbidity, intellectual, disability, Albania

Introduction

Epilepsy in autism spectrum disorders has been the subject of increasing interest and it is one of the additional problems to be to be dealt with in these patients. The association between epilepsy and autism has been extensively described and documented during the past decade due to its therapeutic approach and clinical importance. The rate of comorbidity varies, depending upon the age and type of disorder, and currently, the conservative estimate of comorbidity cases is 20–25% of the whole spectrum. Major risk factors for seizure occurrence are mental retardation and additional

neurological disorders, as well as some specific associated medical conditions**. [1]**

The association between autism and specific epileptiform electroencephalography (EEG) abnormalities is not firmly established; neither is the prevalence of epileptiform abnormalities in the broader range of pervasive developmental disorders (PDDs). The prevalence of both epilepsy and the abnormal (potentially epileptogenic) activity in children with PDD is gradually increasing. About 10% of children with confirmed autism are found to have either a paroxysmal EEG pattern, as seen in acquired epileptic aphasia (Landau–Klener syndrome), or electrical status epilepticus during sleep, as seen in some children with childhood disintegrative disorder.**[2]**

The correlation between ASD, neurologic dysfunction and epilepsy suggest an underlying encephalopathy which is presenting with a combination of neurologic abnormalities, including clinical epileptiform activity. Other lines of evidence suggest that epilepsy itself is a risk factor for autism, independent of other central nervous system underlying pathology. For example, among children with tuberous sclerosis complex, seizures, especially infantile spasms, are an independent risk factor for autism, suggesting a specific pathophysiologic role for epilepsy in development of ASD **(3).** However, the mechanisms responsible for increased seizure susceptibility in ASD are largely unknown. Clues to neural hyper-excitability in the autistic brain might be derived from disorders in which, single gene mutations, cause both epilepsy and an autistic phenotype, such as fragile X syndrome and tuberous sclerosis complex. **[3]**

Electroencephalographic (EEG) findings in ASD

All types of seizures have been detected in autism with some differences deriving from the population examined. All seizure types have been reported: simple, complex partial, atypical absences, tonic-clonic and myoclonic. There is no specificity to seizure type to be expected in children and adolescents with autism. Thus, the clinical approach is essential in recognizing any of these types of epileptic disorders. **[1,4,5]**

Requesting EEG studies only in children with autism is not a routine practice. EEG is not listed in the practice parameters for autism, either by pediatricians or by the American Psychiatric Association, unless, there is an evidence of the clinical seizures, regression, or a high index of suspicion for epilepsy. **[2]**

While normal EEGs are frequently seen, multiple types of EEG abnormalities have been described in patients with ASD, especially focal spikes. In early EEG-autism studies, the definition of EEG "abnormality" was broader than currently accepted and included not only epileptiform features (e.g., spikes and spike-wave discharges) but also less clearly abnormal features, such as "diffuse theta" "low-voltage fast" and "amorphous background". **[6]**

Abnormal electroencephalographic (EEG) findings and autistic regression

Approximately one-third of children with ASD present as toddlers or preschool children with insidious regression in language, behavior, social, and play skills, which is known with the term "autistic regression". A smaller percentage of autistic children will experience late severe regression, usually between 2 and 10 years, defined as a disintegrative disorder. The high frequency of associated focal EEG abnormalities suggests a link between abnormal brain electrical activity and autistic regression. **[7]**

Several explanations for this concurrence have been suggested: **[8]**

• The two conditions are independent.

- Epilepsy and ASD are both different clinical manifestations of the same brain pathology (e.g., fragile X syndrome).
- Epilepsy or related process occurring early in development interfere with developing the function of the brain; in the case of ASD, focused on brain networks associated with communications and social function (e.g., West syndrome)
- Focal CNS pathology that affects limbic systems can produce ASD and trigger epilepsy which in turn aggravates the autistic symptoms (e.g., hamartomas in tuberous sclerosis).
- Epilepsy or an "epileptic process" produces a specific sensory or cognitive dysfunction with "autistic withdrawal" in a "vulnerable child."

Methods

In this retrospective study, we reviewed 164 patients diagnosed with ASD at the clinic of Neuropediatric in University Medical Center of Tirana "Mother Teresa" during 2011-2014. The chief complaints were developmental problems (speech delay, behavior problems, and developmental delay) and seizures. The children were evaluated by the child neurologist and the psychiatrist for children and adolescents. Then, they were referred to the clinical psychologist to perform the IQ tests where applicable. The diagnosis for ASD was based on DSM-5 and ICD-10 guidelines. The diagnosis of epilepsy and epileptic syndromes were based on ILAE definitions and guidelines.

Results and Discussion

In this retrospective study, we reviewed 164 children with autism spectrum disorder presented at our clinic between 2011-2014. The comorbidity of epilepsy and ASD was found in 40 children (24%). Nine (9) children had genetic syndromes which manifest epilepsy and autistic features (Landau-Kleffner, Tuberous Sclerosis Complex, X-Fragile Syndrome, Rett Syndrome. (Figure 1).

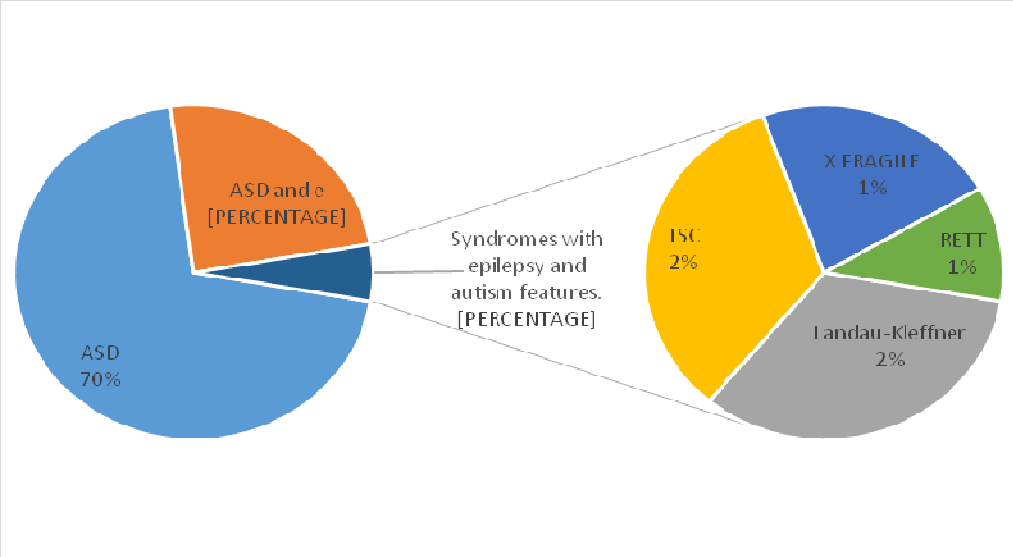

Figure 1. Distribution of diagnosis. (n=164)

The male to female ratio was 3.5:1. The mean age of regression for the whole group was 4.6 years old. The mean age of regression was 5.35 years in isolated ASD and 2.86 years old in comorbidity.

Abnormal electroencephalographic (EEG) findings were present in 30% of the patients

(n=115) with isolated ASD (ASD without clinical proof for epilepsy and seizures). (Figure 2)

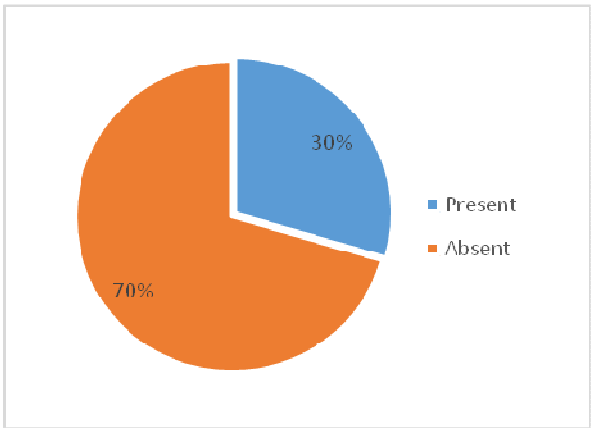

Figure 2. EEG abnormalities in ASD only group.

Forty-five percent (45%) of the abnormal findings in the comorbidity group were located in the centrotemporal region, thirty-eight percent (38%) in the temporoparietal region, ten percent (10%) in the frontotemporal region and eight percent (8%) in the posterior leads. The situation in the ASD group with abnormal findings in the EEG was similar; 41% in the centrotemporal region, 38% in the temporoparietal region, 12% in the frontotemporal region and 9% in posterior leads. (Figure 3)

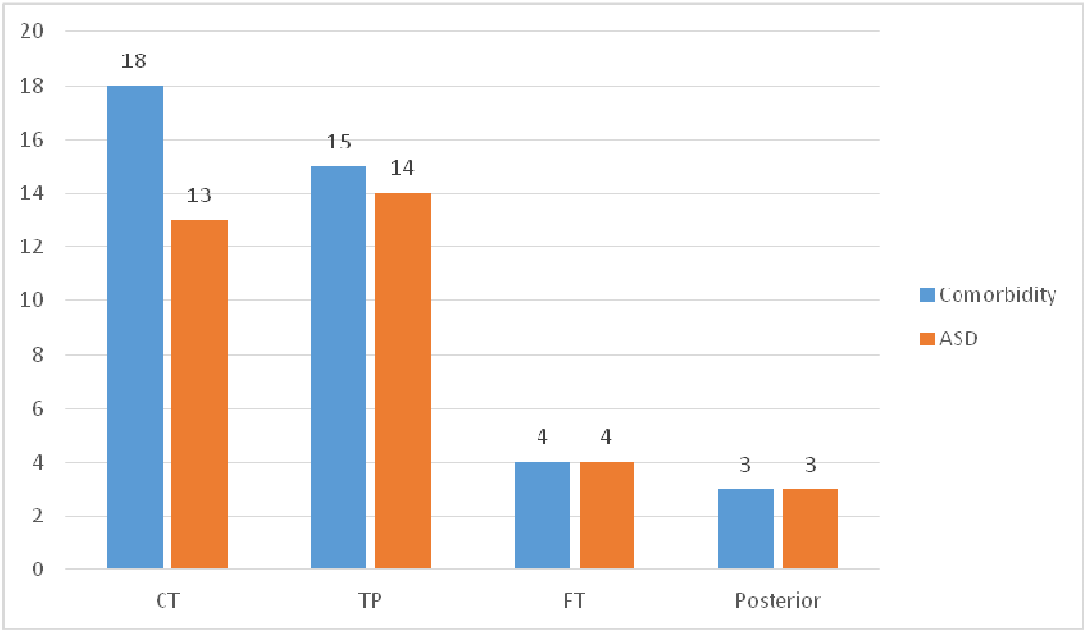

Figure 3. Abnormal EEG findings regarding the location in both groups in absolute number.

IQ tests were performed in 113 patients. In the ASD group (n=107), fifty-eight (58%) of the patients had an IQ more than 85% and the other 42% had an IQ between 70-85. In

the comorbidity group, seventy-seven (77%) of the patients had an IQ lower than 70 and the other 23% had an IQ between 70-85. This difference between two groups was statistically significant (88.10±6.94 vs. 65.54±8.72; p<0.001). (Figure 4)

We also compared the IQ difference between "group with ASD and abnormal EEG" and "group with ASD and normal EEG". The difference was not statistically significant (87.56±7.16 vs. 88.33±6.88, p=0.601).

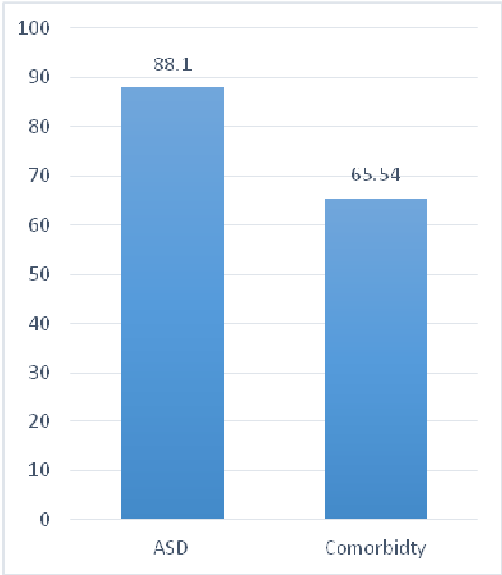

Figure 4. Mean IQ in ASD VS. Comorbidity groups. The Y-axis represents the IQ.

Regarding the age of autistic regression, we found a statistically significant positive correlation between low IQ and early age of autistic regression (r=0.316, n=133, p<0.001). (Figure 5)

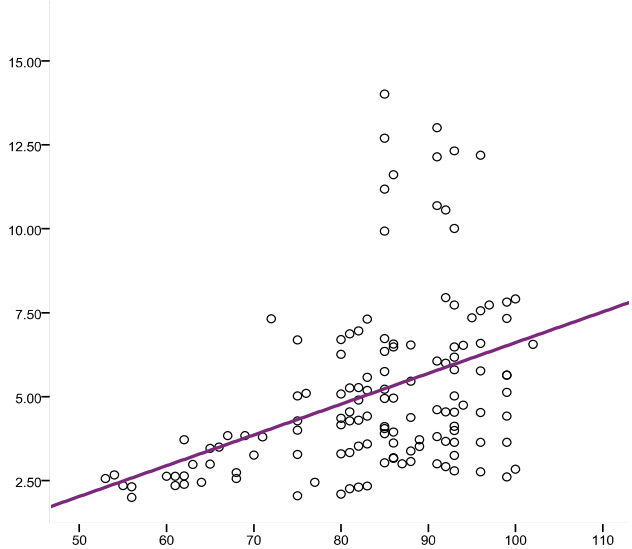

Figure 5. Scatter diagram describing the relationship between IQ and regression age. The Y-axis shows the regression age. The Y-axis shows the IQ.

Looking at the patients separately, there was no significant correlation between low IQ and early age of regression (r=0.154, n=115, p=0.112), while a (Figure 6)

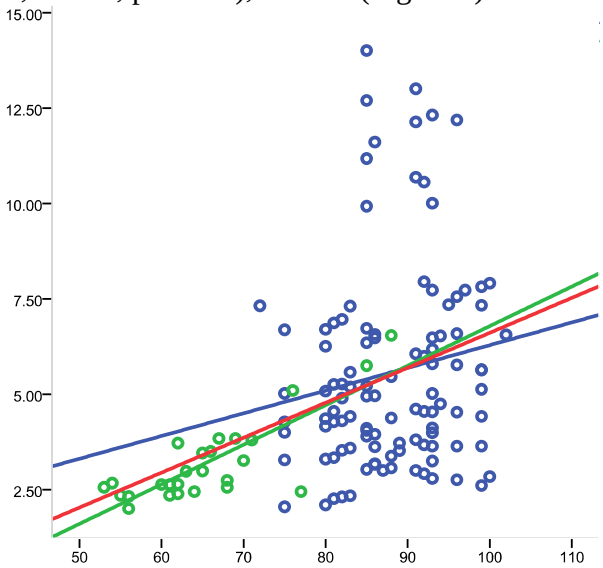

Figure 6. Scatter diagram describing the relationship between IQ and regression age. The Y-axis shows the regression age. The Y-axis shows the IQ. Green color represents the comorbidity group. Blue color represents ASD group. Red color represents all patients.

The treatment of epilepsy in the comorbidity group was the same as the treatment in the general pediatric population, following the protocols of our clinic. Valproate was used as a first-line anti-epileptic drug (AED). Sixty-seven percent of the patients achieved control of epilepsy while on monotherapy wish valproate. The other 33% required poly-therapy with a second AED, such as clobazam and topiramate. (Figure 7)

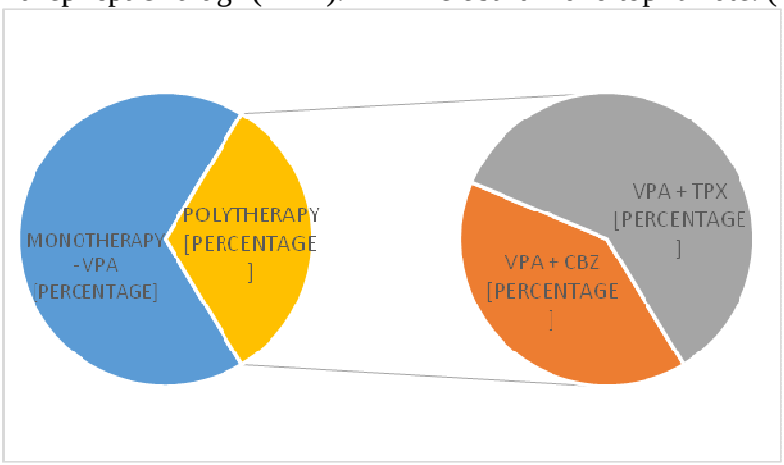

Figure 7 AED therapy. VPA=valproate. CBZ=Clobazam. TPX=Topiramate.

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