Autistic Spectrum Disorders and Hyperactivity in Epileptic Children

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ABSTRACT

Background: It is well known that autistic disorders are associated with increased incidence of epilepsy, but very few studies investigate the incidence of autistic disorders and hyperactivity in epileptic patients. Objective: Study of the autistic spectrum disorders and hyperactivity in epileptic children. Methods: This study was carried out on 143 epileptic children, aged 2-15 years. They were subjected to complete neuropsychiatric examination, E.E.G. and examination for associated autistic disorder and hyperactivity through two stages study: in the first stage parents were asked to complete two scales, autism screening questionnaire and Rutter’s parent questionnaire. In the second stage autism diagnostic interview revised was done. Results: Of the 143 examined children, 23 cases (16%) were found to have autistic spectrum disorders. Children at risk of these disorders were found to have maternal and paternal ages more than 35 years, earlier onset of the first seizure, treated by more antiepileptic drugs, having more nocturnal seizures, more behavioral disorders, antisocial disorders and more hyperactivity symptoms than non autistic children. Conclusion: This study suggests that children with epilepsy are at greater risk of having autistic spectrum and behavioral disorders, and so there is a need for more clinical vigilance to identify these disorders, as they could affect patients’ quality of life and ability to learn.

Key Words: Autistic spectrum disorders, Hyperactivity, Epilepsy.

INTRODUCTION

There is a need to define the prevalence of the autistic spectrum disorders (ASD) in the pediatric epilepsy population, as these conditions have potential treatments, which may have a positive impact on quality of life1. Autistic Spectrum Disorders are spectrum of behaviorally defined disorders, characterized by impaired socialization, impaired verbal and nonverbal communication, and repetitive, restricted patterns of behavior2. Recent estimates of ASD range from 2 to 6/1,0003. It is suggested that the autistic trait may affect 14/1,000 boys and 3/1,000 girls4. Approximately one-third of cases of ASD will experience at least one seizure by adolescence5. One-third of cases of children with autism show normal early development prior to loss of their first words, often between the ages of 18 months and 2 years accompanied with behavioral changes, and autistic regression6. The association between autism and seizures had led the committee on children with disabilities of the American Academy of Pediatrics to recommend a prolonged sleep-deprived E.E.G. in autistic children with regression, or with a high suspicion of subclinical seizures7.

The association between attention deficit hyperactivity disorder (ADHD) and epilepsy has been the focus of numerous studies8,9. Epilepsy as well as ADHD can cause an important impact on the affected individuals’ social, school and emotional life, and they are highly prevalent disorders in childhood and adolescence10. People with epilepsy present high incidence of associated behavioral disorders. The presence of co morbidities can worsen the prognosis, making the treatment with antiepileptic drugs difficult and many times overshadowing the diagnosis of epilepsy11.

The aim of the present work is to study the ASD and hyperactivity symptoms in children with epilepsy to clarify the specific characteristics of these cases.

SUBJECTS AND METHODS

This study was carried out on 143 epileptic children, aged 2-15 years, accompanied by one of their Parents, selected from Neurology, Pediatric and Psychiatry outpatient clinics, Zagazig University Hospitals, after obtaining a written consent in the clinic. Children were excluded if they have severe physical or mental handicap and if they failed to complete any stage of the study.

The patients were subjected to:

1. Thorough history taking according to the epilepsy sheet, including specific characteristics
of epilepsy such as age of first seizure, seizure type, frequency of seizures and antiepileptic drugs. The age of the parents at time of birth of the child, their education, work and socio-economic state were also included.

2. Complete general and neuropsychiatric examination.

3. Electroencephalography (E.E.G.): E.E.G was done for all patients at the Neurology Department, Zagazig University Hospitals, using 32 channels digital E.E.G. Nicolet Biomedical, Alliance Works. Electrodes were arranged according to the international 10-20 system of surface electrode placement using mono and bipolar montages. Ethyl chloride hypnosis was used for young or non cooperative children. Hyperventilation for three minutes together with intermittent photic stimulation were used as provocation methods. The E.E.G. tracing was analyzed as regards: background activity, generalized or focal epileptic discharge or focal with secondary generalization discharge.

4. Assessment of autistic spectrum disorder and hyperactivity: This was done in two stages:
   A. The first stage: Parents were asked to complete two scales:
      i. Autism Screening Questionnaire (ASQ)\textsuperscript{12}: The ASQ has questions based on the Autism Diagnostic Interview Revised (ADI-R) algorithm used for the ICD-10 and DSM-IV diagnosis of autism. The ASQ consists of 40 questions concerning symptoms associated with autism spectrum disorders (ASD), with yes or no answers, scoring one for the yes and zero for the no answers respectively. It contains questions concerning reciprocal social interaction, language and conversation, and repetitive and stereotyped patterns of behavior. In addition, the ASQ includes questions about self-injurious behaviors\textsuperscript{1}. This scale was used as a screening measure for autistic spectrum disorders, the total scores of the scale ranged from 0-39 for the verbal children (item about the current language was omitted from the scoring). For the non verbal children the total score ranges from 0-34 as the 5 items concerning the language was omitted from the scoring. Any child scoring 15 (cut off point) or above and a random sample of those scoring below the cut-off point will pass to the second stage of ADI-R to diagnose cases of autistic spectrum disorders.
      ii. Rutter’s Parent Questionnaire (RPQ)\textsuperscript{13}: It is a reliable and widely used instrument for studying psychiatric disturbances. This scale consists of 31 brief statements concerning the children behavior. Each statement has to be checked whether it “certainly applies”, “applies somewhat” or “does not apply” to children behavior at home, they are given a weight of 2–1–0 respectively to produce a total score with a range of 0–62 by summation of the score of 31 items. This scale has 3 subscales:
         a. Hyperactivity subscale: It consists of 3 items, 1, 2, 14 (very restless, squirmy fidgety child, poor concentration and short attention span), these three items are used to test for hyperactivity and inattention in both autistic and non autistic spectrum children. Any child scoring 3 or above in this subscale has symptoms of hyperactivity and inattention\textsuperscript{14}.
         b. Neurotic subscale: It consists of 5 items, G, V, 6,15 (chest wheezing, weeping on arrival at school, sleep difficulty, often worries, fearful). Higher score means neurotic disorder\textsuperscript{15}.
         c. Antisocial subscale: It consists of 4 items, III, 3, 13, 18 (has stolen things, often destroys own or others belongings, disobedient, bullies other children). Higher score means an antisocial disorder\textsuperscript{16}. The cutoff point of this scale is 13, any child scoring 13 or above may has behavioral disorder, then by the summation of different subscales, if the child has a score in the antisocial subscale more than the neurotic subscale then he has an antisocial disorder, if he has a score in the neurotic subscale more than the antisocial subscale then he has a neurotic disorder, and if they equal each other then he has undifferentiated behavioral disorder.
   B. The second stage: Any child scoring 15 or above on the (ASQ) and random sample of those scoring below the cut-off point were subjected to Autism Diagnostic Interview-
Revised (ADI-R)\(^7\), which is a standardized, semi structured, investigator-based interview for caregivers of individuals with suspected autism. For a diagnosis of autism spectrum disorders, abnormality in development has to be evident at or before 36 months and the cut off must be reached or exceeded in all three symptom domains: (a) impaired social interaction, (b) impaired communication, and (c) stereotyped and repetitive actions.

5. **Statistical Analysis:** The collected data were statistically analyzed using EPI-INFO software version 6.1. Comparison between group means was done using student’s t-test, while Chi square test was used for qualitative data. The significance level was considered at \(P<0.05\).

## RESULTS

Two hundred and twenty epileptic children were followed up during the period of the study, seventy seven (35%) of them were excluded due to inadequate or non response of the scales and severe physical or mental handicapping. Of the remaining 143 children, 92 children had a score below 15, and 51 had a score equal to or above 15 in the Autism Screening Questionnaire (ASQ). By the Autism Diagnostic Interview-Revised (ADI-R), 23 of them were diagnosed as having one of the autistic spectrum disorders (ten with autistic disorder, five with childhood disintegrative disorder, three with Asperger syndrome, and five with autistic disorder not otherwise specified) (Figure 1).

Socio demographic characteristics of children identified as having autistic spectrum disorders (ASD) compared with other children without ASD, showed that children with ASD were younger compared with non autistic children, but this was not statistically significant. Maternal and paternal age at the time birth of the child (more than 35 years) was significantly higher in ASD group ([39%] versus [19%] and [43%] versus [22%] respectively, \(p<0.05\)). There was a high trend of urban living in ASD group, but not reaching statistical significance. Also there was no significant difference between the two groups regarding the gender, the number of years of education of father or mother, working of any parent and the economic status of the family (Table 1).

Regarding the epileptic characteristics of ASD and non ASD children, we found that the mean age of the first seizure was highly statistically significantly lower in ASD than in non autistic children (24 months versus 40 months, \(p<0.001\)), also the mean number of antiepileptic drugs was significantly higher in the autistic group ([2.01] versus [1.61], \(p<0.05\)) and a highly significant more nocturnal seizures in the autistic spectrum group ([30%] versus [13%], \(p<0.001\)). No significant difference between the two groups was found as regards the average seizure frequency/month, seizure type and E.E.G. abnormalities (Table 2).

We also found that 13 out of 23 (57%) of the ASD group versus 37 out of 120 (31%) of non autistic children were scoring above the cut off point of 13 in the RPQ, \(p<0.02\), 35% of autistic group had antisocial disorder versus 16% in the non autistic group, \(p<0.05\), also more neurotic disorders were found in the ASD children, but not reaching statistical significance. No significant difference between the two groups in the undifferentiated behavioral disorder was found. In the three items of hyperactivity subscale of RPQ, there was highly statistically significant higher scores in the ASD group than the non autistic children: very restless, one versus 0.33 \(p<0.001\), squirmy fidgety child, 1.17 versus 0.42 \(p<0.001\) and poor concentration and short attention span, 1.1 versus 0.38 \(p<0.001\) (Table 3).

| Table 1. Socio-demographic characteristics of autistic and non autistic spectrum children. |
|---------------------------------------|-----------------------------------|----------------|
| **Item**                             | **Autistic spectrum disorders (23)** | **Non Autistic spectrum disorders (120)** | **\(X^2\)** | **\(P\)** |
| Age of child years, mean ± (SD)      | 8.92±3.11                         | 9.07±3.16                 | 0.21       | 0.80     |
| Sex: male(%)                         | 11/23 (48%)                        | 52/120 (43%)              | 0.16       | 0.69     |
| Maternal age** >35 years.(%)         | 9/23(39%)                          | 23/120 (19%)              | 4.41       | 0.035*   |
| Paternal age** >35 years.(%)         | 10/23(43%)                         | 26/120 (22%)              | 4.87       | 0.027*   |
| Education of father >12years.(%)     | 10/23(43%)                         | 58/120 (48%)              | 0.18       | 0.66     |
| Education of mother >12years.(%)     | 7/23(30%)                          | 33/120 (28%)              | 0.08       | 0.77     |
| Working father (%)                   | 17/23(74%)                         | 78/120 (65%)              | 0.68       | 0.40     |
| Working mother (%)                   | 4/23(17%)                          | 12/120 (10%)              | 0.45       | 0.24     |
| Sufficient income(%)                 | 15/23(52%)                         | 66/120 (55%)              | 0.82       | 0.36     |
| Urban living (%)                     | 16/23(70%)                         | 69/120 (58%)              | 1.17       | 0.28     |

SD standard deviation, \(X^2\) chi square

* Statistically significant at \(p<0.05\) ** at time of birth of the child
**Figure 1.** Illustration of the assessment of ASD and hyperactivity in the epileptic children.

**Table 2.** Epileptic characteristics of autistic and non autistic spectrum children.

<table>
<thead>
<tr>
<th>Item</th>
<th>Autistic spectrum disorders (23)</th>
<th>Non Autistic spectrum disorders (120)</th>
<th>t-test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of 1st Sz ms, mean± (SD)</td>
<td>24.1±6.44</td>
<td>40.2±11.2</td>
<td>9.5</td>
<td>0.001*</td>
</tr>
<tr>
<td>Number of AEDs, mean± (SD)</td>
<td>2.01±0.76</td>
<td>1.61±0.86</td>
<td>2.26</td>
<td>0.03*</td>
</tr>
<tr>
<td>Sz frequency /month, mean±(SD)</td>
<td>4.8±2.93</td>
<td>5.3±2.79</td>
<td>0.76</td>
<td>0.44</td>
</tr>
<tr>
<td>Nocturnal Sz number (%)</td>
<td>7/23 (30%)</td>
<td>15/120 (13%)</td>
<td>4.77</td>
<td>0.028*</td>
</tr>
<tr>
<td>Seizure type:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>12/23 (52%)</td>
<td>50/120 (41.7%)</td>
<td>0.87</td>
<td>0.35</td>
</tr>
<tr>
<td>Focal</td>
<td>3/23 (13%)</td>
<td>20/120 (16.6%)</td>
<td>0.02</td>
<td>0.9</td>
</tr>
<tr>
<td>Focal with 2ry generalization</td>
<td>8/23 (35%)</td>
<td>50/120 (41.7%)</td>
<td>0.83</td>
<td>0.53</td>
</tr>
<tr>
<td>E. E. G. abnormality (%)</td>
<td>20/23 (48%)</td>
<td>102/120 (39%)</td>
<td>0.01</td>
<td>0.93</td>
</tr>
</tbody>
</table>

AEDs antiepileptic drugs, gen generalized, Sz Seizure.

*Statistically significant at p<0.05.

**Table 3.** Behavioral disorders and hyperactivity items of (RPQ) in autistic and non autistic children.

<table>
<thead>
<tr>
<th>Item</th>
<th>Autistic spectrum disorders (23)</th>
<th>Non Autistic spectrum disorders (120)</th>
<th>$X^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral disorders:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number above the cutoff point 13(%)</td>
<td>13/23 (57%)</td>
<td>37/120 (31%)</td>
<td>5.6</td>
<td>0.017*</td>
</tr>
<tr>
<td>Antisocial disorder (%)</td>
<td>8/23 (35%)</td>
<td>19/120 (16%)</td>
<td>4.52</td>
<td>0.03*</td>
</tr>
<tr>
<td>Neurotic disorder (%)</td>
<td>5/23 (22%)</td>
<td>15/120 (13%)</td>
<td>1.37</td>
<td>0.24</td>
</tr>
<tr>
<td>Undifferentiated disorder( %)</td>
<td>0/23 (0%)</td>
<td>3/120 (3%)</td>
<td>0.59</td>
<td>0.44</td>
</tr>
</tbody>
</table>

| Hyperactivity items:                      |                                  |                                      |        |       |
| 1- very restless, mean±SD                 | 1± 0.73                          | 0.33±0.67                           | 4.18*  | 0.001*|
| 2-squirmymidgety,mean±SD                  | 1.17±0.89                        | 0.42± 0.76                          | 3.81*  | 0.001*|
| 3- poor concentration and short attention span, mean±SD | 1.1 ±0.66                       | 0.38± 0.75                          | 4.8*   | 0.001*|

SD standard deviation

*Statistically significant at p<0.05
The relationship between epilepsy and autistic spectrum disorders (ASD) has captured the attention of neurologists for decades. The present work is one of the novel approaches to study the autistic disorders in known epileptic children.

We found that 16% of our epileptic children had at least one autistic spectrum disorder. This was lower than that reported by Clarke et al., who found that 32% of their epileptic children exhibited autism symptomatology. Steffenburg et al. studied children with mental retardation and active epilepsy, and found that the prevalence of ASD in their study was 38%. A prevalence of ASD found in children who had unprovoked seizures with onset in the first year of life was 6.0%-7.1%, exceeding the estimated 0.6%-1% prevalence of ASD in the general population. These variations in the prevalence rates may be attributed to the different methodology and different samples used. In our study we used the Autism Diagnostic Interview Revised for diagnosis and the Autism Questionnaire as a screening measure, also we excluded children with severe physical or mental handicapping and this may explain our lower prevalence rate.

Paternal and maternal ages were found to be significantly above 35 years at the time birth of the child in the autistic spectrum group. Although the association between autism and maternal age has been evaluated in multiple clinical and epidemiologic samples, some studies have reported a positive association and others reported no association. The association of ASD risk with paternal age has been less frequently investigated. In an Australian population, Glasson et al. found that increased paternal age, but not maternal age, was significantly associated with autism risk independent of other perinatal factors. In a Danish population, Lauritsen et al. found that the risk of autism was associated with increasing paternal but not maternal age, independent of the child's age, child's sex, parental psychiatric history, sibling autism status, parental country of birth, and degree of urbanization. A second Danish study by Larsson et al. reported no statistically significant association between risk of autism and either maternal or paternal age after adjustment of other perinatal factors and parental psychiatric history. In our study, no other socio demographic characteristics were found to be statistically significantly different between ASD and non ASD children, however, positive correlations between autism prevalence and various indicators of socioeconomic status have been consistently reported. Investigators have long suspected this association to be the result of ascertainment bias.

In our study, the children identified as having ASD had a younger mean age of the first seizure than non autistic children, approximately two years. This correlates to the known timing of autistic regression, which occurs before 3 years of age in over 90% of children with autism who have developmental regression. There may be a relationship between this early age of seizure onset causing an early epileptic encephalopathy, hence disrupting language, social, and/or behavioral development. As regards other characteristics of epilepsy, there was no statistically significant difference between ASD and non ASD children in seizure frequency or seizure type and E.E.G abnormalities but there was a statistically significant difference in the occurrence of nocturnal seizures and the number of antiepileptic drugs, with more nocturnal seizures and more antiepileptic drugs in the ASD group. This may be due to more intractability or the more severity of epilepsy in the autistic than non ASD group.

Regarding behavioral symptoms, a statistically significant more behavioral and antisocial disorders were found in the ASD than the non ASD group (57% and 35% versus 31% and 16% respectively), neurotic disorders were also found to be more in the autistic group (22% versus 13%), but not reaching statistical significance. The diagnosis of these disorders was according to the results of RPQ only and no specific interview was done to diagnose these disorders exactly. Several studies reported the presence of psychiatric co morbidities ranging from 40% to 70% in people with epilepsy. Hanssen-Bauer et al. investigated the occurrence of psychiatric disorders in 74 children and adolescents with epilepsy in Norway and found that 77% had possible or probable associated psychiatric disorders. In a population-based epidemiological study, in children and adolescents with epilepsy, Turky et al. found that epilepsy related factors appeared to be more closely related to emotional problems and depression, while cognitive impairment was related to behavioral problems, specifically conduct problems and ADHD. The association between ADHD and epilepsy related factors was also identified by Sherman et al.. In Brazil, Thome-Souza et al. studied the types of psychiatric disorders in a group of 78 children and adolescents with epilepsy and found that 70% had some psychiatric disorder, being depression (36.4%) and ADHD (29.1%) the most common, and partial epilepsy was the type of epilepsy most significantly associated with psychiatric disorders.

In the three items of hyperactivity subscales of Rutter's Parent Questionnaire (RPQ), ASD children also have significantly higher scores when compared with non ASD children, denoting that symptoms of hyperactivity and inattention are more severe in the
ASD children. This may partially reflect the poor socialization and distinctive patterns of behavior seen in these children. Epidemiological studies of people with epilepsy indicate a frequent association with ADHD, with rates ranging from 8% to 77%, depending on the sample and the criteria used for ADHD diagnosis, most studies showed a prevalence rate between 30%-40%. Dunn et al. diagnosed ADHD in 38.7% of epileptic children, Hermann et al. found that 31% of children with epilepsy had ADHD and McDermott et al. reported the symptoms of ADHD in 28% of children with epilepsy. Lower rates were reported by Davies et al. who observed the ADHD symptoms in 12% of children with epilepsy.

**Recommendations:** The observation that 16% of epileptic children suffered from one of the autistic spectrum disorders and the high occurrence of behavioral disorders in them, must warrant clinical vigilance to early diagnosis of these cases and the symptoms must not only be attributed to the epilepsy or to the treatment received.

[Disclosure: Authors report no conflicts of interest]

**REFERENCES**