Two-Year Follow-up of Isolated Epileptiform Discharges in Autism: An Endophenotypic Biomarker?

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ABSTRACT

Context: A significant subset of autistic children exhibit abnormal isolated epileptiform discharges (IEDs) in the absence of clinical epilepsy. The etiological significance of such IEDs is under much debate. Aims: The aim is to study the relationship between IEDs with risk factors, clinical severity, behavioral problems, and social-quotient and follow-up for the occurrence of new seizures. Settings and Design: This study was a prospective double-blind comparative study of autistic children with and without IEDs. Subjects and Methods: All autistic children attending Child Psychiatry Department of tertiary care postgraduate teaching hospital in April 2013 were included in the study. Electroencephalography, risk factors, and clinical severity were assessed. The same cohort of 72 children was followed for 2 years and reassessed. Statistical Analysis Used: Independent sample t-test, Chi-square test, Pearson correlation, and linear by linear association were the statistical methods used. Results: Twenty-four (42%) of the followed up sample exhibited IEDs. 10.52% had converted to clinical seizures within the follow-up period. While there was no difference between risk factors and age at diagnosis between the IED and non-IED groups, there was a significant difference between disease severity, behavioral problems and social quotient between the groups. Conclusions: IED in a subgroup of autistic children point to more severe illness, severe behavioral problems, and severe social impairment over a 2-year follow-up period. Can IED be considered a neurobehavioral endophenotype in autism?

Key words: Autism, behavioral problems, electroencephalography, endophenotype, epilepsy, isolated epileptiform discharges, risk factors, social functioning

INTRODUCTION

Autistic spectrum disorders (ASD) encompass a...
heterogeneous group of children with deficits in social interaction, language development, and stereotyped pattern of interests and activities manifesting with a wide range of cognitive skills ranging from severe deficits to high functioning individuals.[1] Neurobiological underpinnings of the disorder were given as early as 1943 by Kanner. In his original description of 11 cases, one child had seizures, three children were mute, and five children were macrocephalic.[2] However, despite a large body of pharmacological, pathological, electrophysiological, and functional imaging investigations, the etiology of ASD still remains unclear.[3] Known medical conditions account only for quarter (or less) of the diagnosed cases of ASD.[4-6]

One of the best known associations is increased risk of developing epilepsy and is commonly reported to occur in one-third of individuals with ASD. The occurrence of epilepsy in ASD has been extensively investigated.[7-10] Evidence suggests that epilepsy itself is a risk factor for autism, independent of other central nervous system dysfunction. Infantile spasms are an independent risk factor in tuberous sclerosis complex for ASD suggesting a etiopathologic role for epilepsy in the development of ASD.[11] Furthermore, epilepsy seems to be a major factor contributing to the severity of behavioral problems in ASD and is strongly correlated with worse cognitive functioning.[12]

Nonspecific electroencephalography (EEG) changes, such as slowing or asymmetry, and epileptiform discharges, consisting of spikes or sharp wave discharges, sharp slow waves, generalized spike-wave, and generalized polyspikes are common among patients with active epilepsy,[3] but are reportedly rare (1%-4%) in healthy children.[1,3,11,14] In contrast, children with ASD exhibit high rates of these abnormalities even in the absence of epilepsy[1,3] and their presence should not be considered as evidence of epilepsy.[3] The term isolated epileptiform discharges (IEDs) is commonly used to denote the occurrence of epileptiform discharges in the complete absence of identifiable seizures as opposed to interictal spike discharges occurring between seizures.[1]

Several studies have reported IED rates of approximately 30% in ASD.[15-17] One of the earlier studies (1975), reported 40% in a single recording, whereas two recordings showed IED in 60% and three showed IED in 80% of the sample (n = 147), highlighting the importance of prolonged or repeated monitoring to detect IED.[18] Another study of children with ASD referred for video EEG monitoring to evaluate possible seizures found IED in 59%.[19] A retrospective review of almost 900 children with ASD who had no known history of epilepsy, found 61% with epileptiform EEG (IED) activity. One of the most important findings of this investigation was that, in this population, IEDs were detected only during sleep.[20]

Approximately one-third of children with ASD present with insidious regression in language, behavior, social, and play skills, that is, autistic regression (AR). A smaller percentage of autistic children will experience late severe regression, usually between 2 and 10 years.[21,22] In a study, examining the relationship between IEDs, epilepsy, and regression in 585 children with ASD concluded that IED (not epilepsy) is a risk factor for the development of AR. The presence of focal IED suggest the possibility of causative relationship, that is AR can be considered as a form of epileptic encephalopathy.[23] Although fundamental questions regarding the relationship of IED to the cognitive, language, and behavioral deficits seen in autism are still not evaluated in large-scale population-based studies, presumptive evidence from hospital-based samples indicate that it may give an important clue to an underlying neurological abnormality, at least for a subset of autism patients.[1,3,21,24]

It has long been known that interictal discharges can interfere with normal neural processing.[25,26] Recently, there has been more attention to the concept of deleterious transient cognitive impairment due to the presence of background epileptiform discharges in patients with epilepsy.[27,28] This is important to highlight because of treatment implications, as large number of individuals with ASD could conceivably benefit from treatment of IEDs.[3] However, most of the reviews point out that there is lack of “convincing evidence” with regard to the treatment of IEDs.[29,30]

SUBJECTS AND METHODS

Study design
This study was a prospective double-blind comparative study of children of Autism with those exhibiting IEDs group with no abnormal EEG (non-IED). The investigator assessing the clinical and psychobiological variables is blind to the EEG status of the children. The same cohort is followed up 2 years later and assessed for seizure status, clinical severity, and behavioral problems [Figure 1]. Ethical committee approval was obtained before the start of the study and written informed consent was obtained from both the parents in their native language.

Participants
All the children who attended child psychiatric outpatient department in April 2013 were screened
for the presence of autistic symptoms and those children who satisfied DSM IV-TR criterion for Autism or pervasive developmental disorder-NOS by the structured clinical tool INCLEN were included in the study \((n = 72)\). Children with known seizure disorder, other neurological illnesses, and specific genetic syndromes were excluded from the study.

**Scales, electroencephalography, and measurements**

A semi-structured tool was devised to collect sociodemographic data of all the participants and their parents. A literature search was made using the keywords “prenatal, postnatal, perinatal, autism, and risk factors” between 2000 and 2010 in PubMed and Google Scholar and separate list of all the obstetric complications was compiled from the results. This list was used to as a reference point to collect information regarding the risk factors from both the parents.

EEG was done in the Department of Pediatric Neurology by an EEG technician who was blind to the diagnosis or seizure status of these children. EEG interpretation was done by a senior professor of pediatric neurology who is blind to clinical diagnosis and seizure status of these children. The same cohort of these children was followed up regularly for new onset of seizures and reassessment was done for 57 children in April 2015 [Figure 1]. Childhood Autism Rating Scale 2 (CARS2) was used to assess the severity of autism, and Vineland Social Maturity Scale (VSMS) was used to assess the social functioning in these children. Behavioral problems, both internalizing and externalizing were measured using Child Behavior Check List (CBCL).

**RESULTS**

**Statistics**

Descriptive data were analyzed using the total sample of 72 children. Rest of the analysis were done using the reassessment sample \((n = 57)\). Children were divided into two groups based on the presence or absence of IEDs. Continuous variables were assessed using independent sample \(t\)-tests whereas Chi-square analysis was performed for categorical variables. Pearson correlation was used for clinical severity, behavioral problems, and social functioning within the groups and linear by linear association was used for assessing the significance for the new occurrence of seizures between the groups.

**Sociodemographic details**

Seventy-two children were included in the study based on the selection criterion in April 2013. Thirty-six (50%) children were males and the rest 36 (50%) were females. Most of these children \((n = 51, 72\%)\) were from lower socioeconomic strata. Average age at diagnosis of these children were 28 months (standard deviation [SD] =6 months). Boys are diagnosed on an average 3 months later than girls. Severity of Autism as per CARS2 revealed a mean score of 35.5 (SD = 3.25). Social functioning of these children as assessed by VSMS points to an average social functioning of 27 months (SD = 6 months). CBCL was used to assess the behavioral problems in the categories of externalizing, internalizing, and others. Externalizing scores were significant in 40 (53%) of the children whereas internalizing scores were significant in 27 (37.5%) of the children. Most of these children \((n = 58, 81\%)\) were subjected to psychosocial interventions (either speech, occupational, and/or behavior therapy).
Follow-up
Fifty-seven cases from the original cohort were reassessed after 2 years (April 2015). Disease severity, social functioning, and behavioral problems of these children were assessed using the same instruments as before. Thirty-three (58%) children had no abnormal EEG activity whereas 24 (42%) exhibited isolated epileptiform activity [Figure 1]. Nineteen children (33%) exhibited sharp waves in contrast to five children (9%) exhibited other abnormal wave patterns. Alternatively, 80% of the 24 children exhibited sharp waves [Figure 2].

Inter group comparison
IED group (n = 24) was compared with normal EEG group (n = 33) on clinical, risk factors and sociodemographic variables. Results indicate that both groups were unremarkable with respect to age, age at diagnosis [Table 1], head circumference, gender distribution, and interventions (both pharmacological and nonpharmacological). Similarly, there were no significant difference in the presence of antenatal (n = 5), perinatal (n = 6), and postnatal (n = 7) risk factors [Table 2] between the groups. IED group exhibited more severe autistic features (P < 0.001), severe social impairment (P < 0.001), and more behavioral problems (P < 0.001) when compared to normal EEG group [Table 3]. Five children (20%) exhibited clinical seizures in the IED group when compared to one (3%) in the normal EEG group during the follow-up period indicating a significant difference (P = 0.032).

Correlations
Children with IED exhibited strong correlations with autism severity, social impairment, and behavioral problems (both internalizing and externalizing) whereas children without IED there were correlation only with autism severity and social impairment. When IED group (n = 24) was subdivided into seizures (converted within 2 years) and not (n = 5 vs. 19, respectively), there was no difference in clinical severity, social impairment, and behavior problems [Table 4]. Sharp waves were present in 19 children (79%) of IED group and other abnormal wave patterns (spike, sharp, bilateral generalized epileptic discharges) were present in 5 (21%) of children. When the clinical severity, social impairment, and behavioral problems were compared

Table 1: Comparison of sociodemographic variables between Non-IED and IED groups

| Variable                  | Non-IED (n=33) | IED (n=24) | Total | 2 | P     |
|---------------------------|----------------|------------|-------|---|-------|
| Gender                    |                |            |       |   |       |
| Male                      | 29             | 17         | 46    | 2.592 | 0.1074 |
| Female                    | 4              | 7          | 11    |   |       |
| Head circumference        |                |            |       |   |       |
| Normal                    | 31             | 20         | 51    | 1.660 | 0.4362 |
| Microcephaly              | 1              | 2          | 3     |   |       |
| Macrocephaly              | 1              | 2          | 3     |   |       |
| Medications               |                |            |       |   |       |
| Present                   | 13             | 14         | 27    | 1.999 | 0.1574 |
| Absent                    | 20             | 10         | 30    |   |       |
| Therapies                 |                |            |       |   |       |
| OT                        | 1              | 3          | 4     | 2.645 | 0.6189 |
| Speech                    | 2              | 2          | 4     |   |       |
| Special school            | 7              | 3          | 10    |   |       |
| Combined                  | 21             | 14         | 35    |   |       |
| No therapy                | 2              | 2          | 4     |   |       |

| Variable                  | Mean (SD)     | t     | df  | P     |
|---------------------------|---------------|-------|-----|-------|
| Age (years)               | 7.8 (2.6)     | 6.8 (2.3) | 1.50 | 55 | 0.138 |
| Age at diagnosis          | 3.4 (1.3)     | 3.0 (0.7) | 1.38 | 55 | 0.174 |

SD – Standard deviation; IED – Isolated epileptiform discharge; OT – Occupational therapy

Table 2: Prenatal, perinatal, and postnatal risk factors between both groups

| Risk factors               | Chi-sq value (df) | P     |
|----------------------------|-------------------|-------|
| Prenatal risk factors      |                   |       |
| Mother age at conception   | 6.465 (3)         | 0.091 |
| Paternal age at conception | 1.595 (4)         | 0.810 |
| Pregnancy complications    | 3.256 (3)         | 0.354 |
| Consanguinous/nonconsanguous marriage | 0.247 (1) | 0.619 |
| Previous psychiatric illness in family | 1.606 (1) | 0.205 |
| Drug intake                | 2.116 (2)         | 0.347 |
| Antenatal infections       | 1.469 (1)         | 0.225 |
| Birth order                | 5.026 (3)         | 0.170 |
| Gestational age            | 0.822 (2)         | 0.663 |
| Prolonged labor            | 2.826 (1)         | 0.093 |
| Mode of delivery           | 0.868 (2)         | 0.648 |
| Birth weight               | 2.245 (2)         | 0.325 |
| Cry at birth               | 2.880 (1)         | 0.090 |
| Multiple birth             | 1.683 (1)         | 0.195 |
| Neonatal hyperbilirubinemia| 0.257 (1)         | 0.612 |
| Neonatal seizures          | 0.724 (1)         | 0.395 |
| Congenital anomalies       | 0.724 (1)         | 0.325 |
The present study was mainly conducted to evaluate the presence of IED in autism, and its relationship to clinical variables, (mainly: clinical severity, social functioning, and behavior problems) prenatal, natal, and postnatal risk factors and new occurrence of seizures during the 2-year follow-up. Both groups (IED and non-IED) are unremarkable with respect to age, at diagnosis, and gender distribution. There was no significant difference between the groups in terms of interventions, either pharmacological or nonpharmacological. Essentially, both groups are similar to each other in almost all sociodemographic variables. Surprisingly, both groups also show a similar pattern of prenatal, perinatal or postnatal risk factors, head circumference, and any of the sociodemographic variables indicating that IED can be viewed as an endophenotype at least in a subgroup of ASD. Further studies with adequate sibling controls, long-term follow-up, quantitative computerized EEG, and neuroimaging will shed light on this neuroelectrophysiological signature of ASD.

**CONCLUSIONS**

The presence of IED in a subgroup of ASD children portends more severe autism, social impairment, and behavioral problems. IED is not related to prenatal, perinatal or postnatal risk factors, head circumference, or any of the sociodemographic variables indicating that IED can be viewed as an endophenotype at least in a subgroup of ASD. Further studies with adequate sibling controls, long-term follow-up, quantitative computerized EEG, and neuroimaging will shed light on this neuroelectrophysiological signature of ASD.

**Limitations**

Study is limited by small sample size. Another drawback is that IED is not related to prenatal, perinatal or postnatal risk factors, head circumference, and any of the sociodemographic variables indicating that IED can be viewed as an endophenotype at least in a subgroup of ASD. Further studies with adequate sibling controls, long-term follow-up, quantitative computerized EEG, and neuroimaging will shed light on this neuroelectrophysiological signature of ASD.

**Future directions**

1. Large sample size with quantitative computerized EEG with sibling and parents as controls may throw light on the genetic, epigenetic, and environmental factors in IED
2. EEG in well-baby clinics correlated with MCHAT in normal versus MCHAT-positive children may throw light on the occurrence of IED before clinical symptoms
3. Treatment of IED with AED may throw light on the prognostic and therapeutic options of IED in autism

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**Conflicts of interest**

There are no conflicts of interest.

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**Table 3: Clinical variables between isolated epileptiform discharge and nonisolated epileptiform discharge groups**

| Variable | Mean (SD) | t (df) | P    |
|----------|-----------|--------|------|
| IED (n=24) | Non-IED (n=33) |       |      |
| CARS 2   | 39.2 (5.0) | 34.3 (2.7) | -4.79 (55) | <0.001 |
| VSMS     | 50.5 (10.2) | 60.9 (8.2) | 4.22 (55) | <0.001 |
| Internalizing | 21.3 (10.3) | 12.0 (5.9) | -4.30 (55) | <0.001 |
| Externalizing | 21.6 (7.1) | 13.3 (5.3) | -5.30 (55) | <0.001 |
| Other    | 21.6 (7.1) | 13.3 (5.3) | -4.60 (55) | <0.001 |
| CBCL total | 66.9 (18.2) | 42.0 (11.6) | -6.30 (55) | <0.001 |

**Table 4: Intragroup comparison in IED: No seizures vs seizures and sharp waves vs other waves**

| Variable | No seizures (n=19) | Seizures (n=5) | t (df) | P    |
|----------|-------------------|---------------|--------|------|
| CARS 2   | 38.9 (5.3) | 40.4 (3.5) | 0.571 (22) | 0.574 |
| CBCL     | 65.5 (19.5) | 72.4 (11.8) | 0.752 (22) | 0.460 |
| VSMS     | 50.7 (10.2) | 49.8 (11.3) | 0.179 | 0.860 |

| Variable | Sharp waves (n=19) | Other waves (n=5) | t (df) | P    |
|----------|-------------------|-------------------|--------|------|
| CARS 2   | 39.3 (5.4) | 39.0 (3.7) | 0.123 (22) | 0.903 |
| CBCL     | 66.5 (16.2) | 83.6 (16.7) | -2.58 (22) | 0.017* |

*P<0.05. CARS – Childhood Autism Rating Scale; VSMS – Vineland Social Maturity Scale; CBCL – Child Behavior Check List.

between IED children exhibiting sharp waves with other waves there was significant difference (P < 0.017) in the behavior problems [Table 4].

**DISCUSSION**

The present study was mainly conducted to evaluate the presence of IED in autism, and its relationship to clinical variables, (mainly: clinical severity, social functioning, and behavior problems) prenatal, natal, and postnatal risk factors and new occurrence of seizures during the 2-year follow-up. Both groups (IED and non-IED) are unremarkable with respect to age, at diagnosis, and gender distribution. There was no significant difference between the groups in terms of interventions, either pharmacological or nonpharmacological. Essentially, both groups are similar to each other in almost all sociodemographic variables. Surprisingly, both groups also show a similar pattern of prenatal, perinatal or postnatal risk factors, head circumference, and any of the sociodemographic variables indicating that IED is independent of environmental variables. This indicates that IED was present (presumably) before birth that is well before the clinical manifestations of autism. IED group exhibits more intense autistic features, low social functioning, and more severe behavioral problems when compared to non-IED group (P < 0.005). Over the 2-year follow-up, 20% from the IED group exhibited new onset of seizures when compared to 3% from the non-IED group (P = 0.032) indicating that former has an increased chance of developing seizures. Despite this increased risk, intragroup comparison reveals that there is no significant difference in clinical severity, social functioning, and behavior problems between those converted to clinical seizures and those who had not. Thus, IED not (the presence or occurrence of) seizures is important with respect to clinical parameters. IED group can further be subdivided into those exhibiting sharp waves and those exhibiting other waves. Intragroup comparison reveals that both groups are similar in all clinical variables except in behavioral problems. Sharp waves are associated with more severe behavioral problems (P < 0.05) indicating that sharp waves may be distinct neuro-electrophysiological signature in a subgroup of autism patients.
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