Original Article

Epileptiform activity in the electroencephalogram of 6-year-old children of women with epilepsy

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Abstract

Purpose: To study the epileptiform discharges (EDs) in the electroencephalogram (EEG) of 6-8-year-old children of women with epilepsy (WWE). **Materials and Methods:** All children born to women with epilepsy and prospectively followed up through the Kerala Registry of Epilepsy and Pregnancy (KREP), aged 6–8 years, were invited (n = 532). Out of the 254 children who responded, clinical evaluations and a 30-min digital 18 channel EEG were completed in 185 children. **Results:** Of the 185 children examined, 37 (20%) children (19 males, 18 females) had ED in their EEG. The EDs were generalized in 7 children, and focal in 30 children. The EDs were present in the sleep record only of 16 (43%) children and in the awake record only of 6 (16%) children. Out of the 94 children for whom seizure history was available, 7 children (7.4%) had seizures (neonatal seizures: 4, febrile seizure: 1, and single nonfebrile seizure: 2) and none had history of epilepsy or recurrent nonfebrile seizures. The odds ratio (OR) for occurrence of ED in the EEG was significantly higher for children of WWE [OR = 3.5, 95% confidence interval (CI) 2.3-6.0] when compared to the published data for age-matched children of mothers without epilepsy. There was no association between the occurrence of ED and the children's maternal characteristics [epilepsy syndrome, seizures during pregnancy, maternal intelligence quotient (IQ)] or the children's characteristics [antenatal exposure to specific antiepileptic drugs (AEDs), birth weight, malformations, IQ]. **Conclusion:** Children of WWE have a higher risk of epileptiform activity in their EEG when compared to healthy children in the community though none had recurrent seizures.

Key Words

Electroencephalogram (EEG), epileptiform discharges (EDs), women with epilepsy (WWE)

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Introduction

Women with epilepsy (WWE) have a major concern about whether their children will inherit epilepsy (May *et al*. 2009,[1] Helbig *et al*. 2010[2]). Epidemiological data indicate that 2.4-4.6% of the children of parents with epilepsy would have epilepsy (Winawer *et al*. 2005).[3] It had been shown that there is increased risk of epilepsy for the children of the mothers with epilepsy when compared to fathers with epilepsy. (Ottman *et al.*1988).[4] The pedigree analysis in the Kerala Registry of Epilepsy and Pregnancy (KREP) revealed that 1.58% of enrolled WWE had a history of maternal or paternal epilepsy (Nair and Thomas 2004).[5] Electroencephalogram (EEG) is the standard investigation to support a diagnosis of epilepsy although a small proportion of children without epilepsy may also show epileptiform discharges (EDs) in the EEG (Zivin *et al.* 1968).[6] An EEG would reveal EDs in about 50% of persons with epilepsy when recorded for the first time and the yield increases on repeated records (Salinsky *et al.* 1987).[7] The objective of the present study was to ascertain the EEG patterns of 6-year-old children of WWE and its relationship with maternal characteristics or the children's characteristics

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of the children who were prospectively followed up in a pregnancy registry.

Materials and Methods

This study was conducted through KREP at Sree Chitra Tirunal Institute for Medical Sciences and Technology, which is a tertiary referral neurological center in South India. KREP is a unique program that enrolls WWE in the preconception period or first trimester of pregnancy and prospectively follows them up through pregnancy and delivery. The infants born under the program are followed up prospectively as a cohort, according to a standard protocol. The details of the registry and its protocol are published elsewhere (Thomas *et al.* 2001).[8] As per the protocol, all live-born babies are examined at birth (clinical examination), at 3 months of age (with echocardiogram and ultrasonogram for the presence of birth defects), and at 1 year, 6 years, and 12 years of age. The developmental outcome at 1 year and intelligence quotient (IQ) and language function at 6 years had been published earlier. (Thomas *et al.* 2007,[9] 2008[10]). This paper pertains to the EEG findings of these children at 6 years of age.

For the purpose of this study, we considered all babies born alive between April 1998 and December 2005 who were aged 5-7 years at the time of data collection (n = 532). We had sent invitation letters to all the children to participate, to which 254 children responded. We visited a sample of nonresponders at their homes (n = 28) who cited the following reasons for not responding to the invitation: Failure to receive the correspondence, change of address, subsequent pregnancies for the mother at the appointed time, commitment to attend to younger babies, logistic difficulties in traveling a long distance, engagement with other priorities, financial difficulties, or unwillingness to participate in this study. Out of the 254 responders, EEG was performed for 185 children and for the others EEG could not be done due to technical and logistic reasons.

A digital EEG was acquired with a standard 21-electrode 10-20 electrode placement. The record included 20 min of awake recording, activation procedures of hyperventilation, photic stimulation, and 20 min sleep record. Natural sleep was attempted first and the sleep record was abandoned if the child failed to sleep in spite of the administration of chloral hydrate. All EEGs were read by neurophysiologists attending to the EEG laboratory who were blinded to the clinical details of the children. Abnormality in the form of spikes, sharp, slow waves, or persistent slowing were reported according to the guidelines of the International Federation of Clinical Physiology (Noachtar *et al.* 1999).[11] Epileptiform discharges (spikes or sharp waves) were classified into generalized, lateralized, focal, and mutifocal. Lateralized or focal EDs with maximum negativity over F7/F8 or T3/T4 were classified as temporal, T5/T6 or O1/O2 were classified as occipital, P3/P4 were classified as parietal, C3/C4 were classified as central, and Fp1/Fp2 or F3/F4 were classified as frontal.

The birth and developmental details of the children were extracted from the clinical records. A speech therapist performed the language evaluation [Malayalam Language Test, which is an adaptation of Language Proficiency Test (Karanth *et al.* 1986)][12] and a neuropsychologist performed the neuropsychological evaluation (Malin's Intelligence Scale for Indian children, which is the Indian adaptation of Wechsler Intelligence Scale for Children) (Malin 1971).[13] The detailed seizure history and other medical histories for each child were obtained from the mother. The clinical data pertaining to the mothers [epilepsy, antiepileptic drug (AED) exposure, seizure control during pregnancy, IQ] were abstracted from the clinical records of the registry.

The data were entered on to a spreadsheet and analyzed with Statistical Package for the Social Sciences (SPSS) (SPSS Statistics 17.0, IBM, Armonk, New York, USA). We compared the prevalence of EDs in the study group with the prevalence reported for healthy children in the published literature (Okubo *et al.* 1994[14] and Cavazzuti *et al.* 1980[15]). Chi-square test was used to compare the proportions and analysis of variance (ANOVA) was used to compare multiple variables. This registry has the approval of the Institutional Ethics Committee and informed consent was obtained.

Results

One hundred and eighty five children (84 boys and 101 girls) born to 181 mothers (8 children were twins) were evaluated during the study period. The maternal epilepsy syndromes were generalized epilepsy for 99 children, localization-related epilepsy for 79 children, and unspecified epilepsy for 7 children. The maternal AED usage was carbamazepine (76), phenobarbitone (60), valproate (52), phenytoin (40), lamotrigine (3), clonazepam (3), and primidone (1). There were 14 children with no AED exposure in the antenatal period; others were exposed to monotherapy (109) or polytherapy (62). There were 94 WWE who had seizures during pregnancy. The maternal IQ ranged 60-118.

The mean age of the children at the time of EEG examination was 6.65 ± 1 years. Their birth weight ranged 1.75-3.9 kg, the Apgar score was 9 or more for 176 children and less than 7 for 9 children. There were 18 children with major malformations involving the cardiac system (14), nervous system (2), and genitourinary system (2). Only three of them had ED in the EEG. All children had normal neurological examination except for one child who had static encephalopathy. The data on motor and mental developments at 1 year were available for 116 children, out of whom 26 (22.4%) had delayed development. The proportion of children with ED in the EEG (5/26) was not increased among those with delayed development. The full scale IQ test done at 6 years was as follows: Mean 91.2 ± 18.1, median 94.0, 5th centile 53.6, 95th centile 114).

Awake and sleep EEG records were obtained for 166 of the 185 children and for the rest, only the awake records were available. The EEG showed EDs for 37 (20%) children (19 boys and 18 girls). The distribution of ED was generalized in 7 children, focal in 28 children, and multifocal in 2 children. The location of the focal discharges were over the centrotemporal area for 14 children, frontal area for 6 children, occipital area for 4 children, parietal area for 3 children, and temporal area for 1 child [Figures 1 and 2]. The EDs were present in sleep record

only for 16 (43%) children and in the awake record only for 6 (16%) children. Hyperventilation or photic stimulation did not evoke ED in any child. Considering the background activity in 185 children, 4 children had background activity of 7 Hz, and one of them also showed focal ED.

Out of the 94 children for whom seizure history was available, 7 children (7.4%) had seizures (neonatal seizures: 4, febrile seizure: 1, and single nonfebrile seizure: 2) and none had history of epilepsy or recurrent nonfebrile seizures. The proportion of children with ED in the EEG was not increased for those with history of seizures (28.6%; 95% CI .1-64.1) when compared to those without history of seizures (19.6%; 95% CI 12.6-29.1).

There was no statistically significant association between the presence of ED and any maternal characteristics such as maternal seizure type, epilepsy syndrome, maternal IQ, occurrence of seizures during pregnancy, or usage of any specific AED during pregnancy. The presence of ED in the EEG had no association with birth weight, Apgar score, malformation status or, developmental quotient at 1 year or IQ at 6 years.

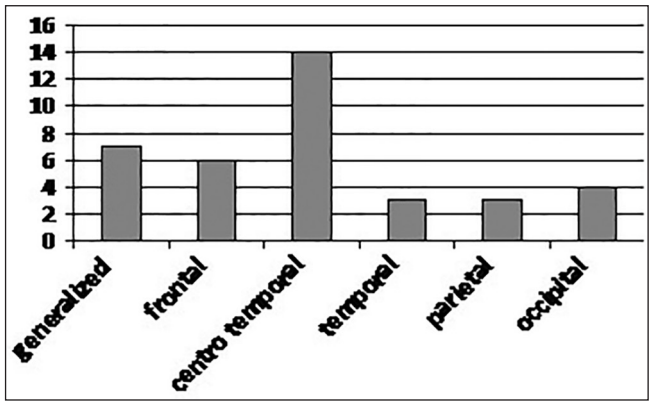

Figure 1: Lobar distribution of epileptiform discharges

Discussion

The setting of the pregnancy registry provided a unique opportunity to follow up a cohort of children of WWE prospectively over several years. We could complete the evaluations on 48% of potentially eligible children. In a developing country setting, long-term follow-up of apparently normal children is a demanding task. The maternal epilepsy characteristics (type of epilepsy, AED exposure, socioeconomic background) and infant characteristics of those who responded and those who did not respond were similar. Hence, it is likely that there is no selection bias in this sample.

The salient feature of this study is that one-fifth of children revealed ED in their EEG although none of them had seizures that could be classified as epilepsy. We noticed that the epileptiform activity was focal in a majority of our children [Figure 1] and its distribution was similar to what was reported in previous studies (Okubo *et al.*1994.[14] Cavazutti *et al.* 1980[15] and Borusiak *et al.* 2010[16]) in normal subjects [Table 1]. The design of our pregnancy registry did not have provision for follow-up of a cohort of children born to women without epilepsy. Hence, we had to resort to published data on the prevalence of ED in the EEG for the community (Okubo *et al.*1994[14] and Cavazutti *et al.* 1980[15]). A comparison with these published figures indicated that children of WWE have an odds ratio (OR) of 3.7 and 6.5 for the presence of EDs in the EEG compared to age-matched children [Table 2]. There was no association between the presence of ED in the EEG and any maternal characteristics such as maternal epilepsy classification and seizures during pregnancy or infant characteristics such as the presence of malformations, neonatal seizures, or developmental delay.

This is the first report on the EEG outcome of women with epilepsy being prospectively followed up as a part of the epilepsy and pregnancy registry. The data are of clinical significance in that a higher proportion of children of women with epilepsy can have epileptiform activity in their EEG even when they have no active epilepsy. Unrecognized epilepsy,

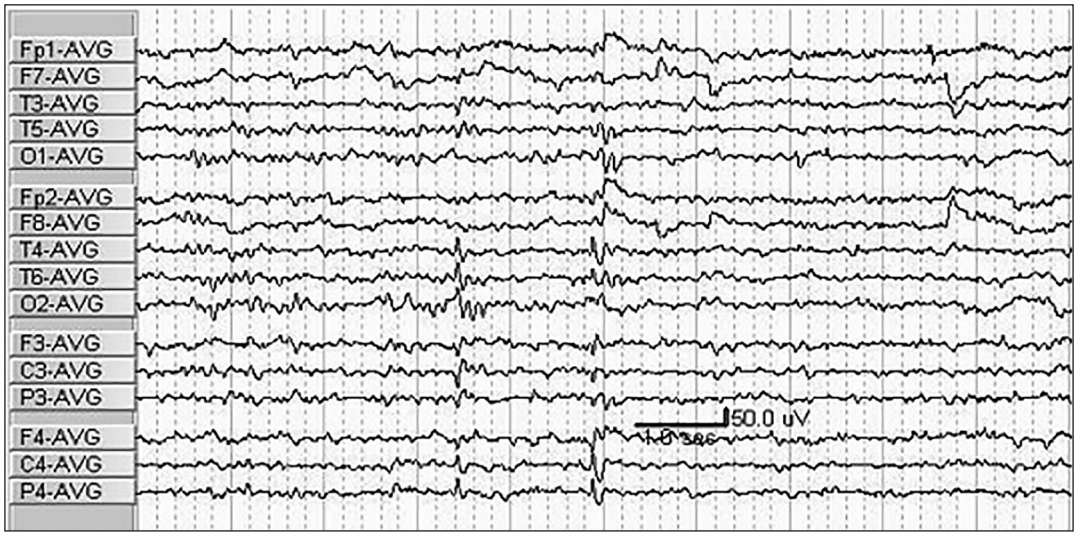

Figure 2: EEG of a 6-year-old child with right centrotemporal spike and wave discharges. The field extends to the right parietal region also

Table 1: Comparison of distribution ED in the EEG for children of WWE in this study to previous studies on normal children at 6 years

Author (year)	Generalized IED† (%)	Focal IED (total) (%)	Multifocal IED (%)	Rolandic IED (%)
Cavazzuti (1980)[15] *N*=131	41 (31.2)	79 (60.3)	11 (8.3)	27 (20.6)
Okubo (1994)[14] *N*=53	10 (18.8)	41 (77.3)	2 (3.7)	37 (69.8)
Borusiak (2010)[16] *N*=25	4 (16)	12 (48)	9 (36)	7 (28)
Present study *N*=37	7 (18.9)	28 (75.6)	2 (5.4)	14 (37.8)

†IED = Interictal epileptiform discharge

Table 2: Prevalence and OR for ED in the EEG for children of WWE in this study compared to previous studies on normal children at 6 years

Author	*N*	ED† (*n*)	%	CI‡ low	CI high	OR	CI low	CI high
Present	185	37	20.4	15.2	26.9			
Okubo	615	40	6.5	4.8	8.7	3.7	2.3	6.0
Cavazzuti	316	12	3.7	2.1	6.5	6.5	3.3	12.9

†ED = Epileptiform discharge, ‡CI = Confidence interval

attention disorder hyperactive disorder, autism spectrum disorders, and subtle encephalopathies other causes of unexpected epileptiform activity in the EEG of a child with no history of epilepsy. Technical aspects of EEG such as very short duration of recording, utilization of a limited number of electrodes, and failure to include activation procedures such as hyperventilation, photic stimulation, and sleep record have led to low yield of EDs in previous studies among healthy volunteers (Elson So 2010).[17] The risk of epilepsy in the children of women with epilepsy is a major concern for the parents. In a study from a tertiary care hospital with neurological disorders and epilepsy, 14% of the persons with ED in the EEG had subsequently developed clinical seizures (Zivin 1968).[6] In another study involving healthy volunteers from the community, only 6.3% of the subjects subsequently went on to develop seizures (provoked). None of the subjects in that series developed unprovoked seizures (Elson So 2001).[18] It is too early to predict the risk of epilepsy as the evaluation was performed when the children were less than 7 years of age. It is widely known that all children who demonstrate EDs in the EEG need not manifest seizures (Cavazutti *et al.* 1980).[15] It appears that these EEG changes are expressed independent of the maternal seizures. These EEG findings may indicate a perturbance in the normal electrophysiological maturation. The reason for EDs being more prevalent in children of WWE compared to normal children remains uncertain. It is hypothesized that clinical epilepsy may occur following an acquired cerebral insult in persons with a broad genetic background predisposition to epilepsy. The role of genetic factors and acquired factors such as antenatal AED exposure require further elucidation. EEG studies in immature rats have demonstrated abnormal discharges but only a small proportion of them went on to develop generalized ictal activity (Holmes *et al.* 1997).[19] Animal studies show that phenobarbital, phenytoin, and valproic acid exposures during early life can alter neuronal development through changes in gene expression, neuronal migration, differentiation, survival, and synaptic organization (Marsh *et al.* 2006).[20] This could alter the normal circuitry, increase seizure susceptibility, and produce EDs. The clinical outcome of these children, particularly with regard to EEG evolution and risk of seizures, are being monitored as part of the ongoing study.

Conclusion

Young children of WWE have increased probability of having epileptiform activity in the EEG although they may not have epilepsy at that point of time. This may have an association with other nonepileptic conditions such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, or risk of epilepsy as they grow up.

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Conflicts of interest
There are no conflicts of interest.

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