SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA

ANTENATAL EXPOSURE TO ANTI EPILEPTIC DRUGS AND COGNITIVE, BEHAVIOURAL AND LANGUAGE FUNCTION IN CHILDREN OF WOMEN WITH EPILEPSY

Thesis submitted in partial fulfilment of the rules and regulations for DM Degree Examination of

Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

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Month and Year of Submission: July 2018

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DECLARATION

I, Dr. Vysakha K V , hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram
Date: 31-7-2018

Dr.Vysakha K V

Forwarded :

The candidate, Dr Vysakha K V, has completed the project under my guidance.

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INTRODUCTION

Introduction

The prevalence of seizure disorders among pregnant women ranges from 0.6 to 0.8 percent and treating them is a challenge considering the fact that frequency and recurrence of the event and foetal complications varies from patient to patient. (1) Around 50 million of world population suffers from epilepsy with half of them are women. One sixth of the women with epilepsy(WWE) are living in India contributing to number around 2.73million with half of them in the reproductive age group (15-49 years).

The social stigma of epilepsy affects women than other groups including men and children owing to various social circumstances. The issues of fertility, child rearing and the subsequent well-being of the child in terms of psycho social and cognitive development pose a major concern to WWE and their relatives.(2) WWE contribute to group of patients who experience a significant amount of psychosocial stress which is added on by the adjustment problems as well as impaired problem solving abilities associated with the disease per se.(3)

The issues start from the reduced rate of infertility among WWE, correlating with the AED exposure as well as the hormonal alterations induced by the AED. Among the AEDs, FDA has reclassified valproate under Class D risk during pregnancy, which states that its use in women in child bearing potential requires that the benefits of its use should be weighed against the risk of injury to the foetus and studies in pregnant women have demonstrated a risk to the foetus on the basis of animal models and teratogenic as well as developmental consequences in registries for WWE.(4)

Various schools of thought exist regarding the selection, appropriate dosing and monitoring among the WWE during pregnancy for optimal foetal outcome. Knowledge gap in this areas to be addressed include the effect of various drugs in the cognitive, language, social and behavioural function and the difference in various age groups. If the manifestations can be characterized and identified at an earlier age, interventions can be planned reducing the burden of stress both among the care takers and mothers who are Women with epilepsy.

In this background we planned our study to identify the burden of language, social dysfunction and autistic traits among children with antenatal exposure to AEDs. The burden of disease shall be identified with respect to the exposure to valproic acid and carbamazepine. By assessing this outcome we will be able to gather information regarding the safety of AED use in women with epilepsy with regard to the normal birth and development of their children .

REVIEW OF LITERATURE

1.Epilepsy and pregnancy:

Knight et al studied the relation of gestation to epilepsy in 153 pregnancies on 59 patients. Including both idiopathic and symptomatic epilepsy group, 45 percent had recurrence during pregnancy, whereas 50 percent remained in the pre pregnancy status and 5 percent had reduced seizure frequency. They also reported 4 to 10 times increased risk of congenital malformations as compared to the live birth among that area(5) The data from European pregnancy registry(EURAP),showed that close to 60 % remained seizure free throughout the pregnancy. The seizure frequency remained unchanged with respect to the trimester of pregnancy with the overall data indicating a good seizure control during pregnancy.(6)

2.Pregnancy and epilepsy:

Thomas et al reported complications during pregnancy after following up 643 completed pregnancies among WWE from Kerala Registry for epilepsy and Pregnancy(KREP). Except for anaemia, spontaneous abortions, ovarian cyst, fibroids and increase in seizure risk, there was no significant increase in risk of other complications. The frequency of caesarean section was 33.4 % as compared with 29.5% among the pregnancy in general population, concluding that there was no undue risk of pregnancy and childbirth in most WWE. (7)

In a population based cohort study from Norway, an investigation was done to identify the increased risk of complications during labour, where in they identified an increased risk of induction, caesarean section, post-partum haemorrhage as compared with women without epilepsy. However the overall rate of complication was lower than women without epilepsy.(8)

3. Effect of Epilepsy and AED on Foetus

The foetal complications due to AED use and epilepsy can be classified into:

(1) Anthropometric changes /physiological changes

(2) teratogenic effects

(3) Long term effects.

1.Anthropometric/Physiological changes:

A study spanning 6 years from Norway which covered 2,861 deliveries of WWE revealed that the bad of outcomes in pregnancy and child birth is mainly due to AED exposure. AED exposed foetus had more chance of preterm delivery, low birth weight, low APGAR score, low head circumference. The frequency of congenital malformations were 2.8% versus 2.5 % in epilepsy and control groups respectively. But, the incidence of major congenital malformations was significant only for valproate. (9) A Swedish study reported decreased anthropometric influence with small for gestational age babies were related to mother who had polytherapy as well as exposure to carbamazepine. (10)

Gailey et al (11) studied head circumference growth after first year of life, with respect to head circumference with lower values among children exposed to carbamazepine and barbiturates in utero. However the difference was non-significant when adjusted for family history and paternal details. The body weight adjusted head circumference was found to be low among kids exposed to carbamazepine and valproate as well as polytherapy with no effect for other drugs including phenytoin, clonazepam, lamotrigine and gabapentin as reported from Almgren et al. (12)

2. Teratogenic effects:

The risk of major congenital malformations in the children is the most important concern while using AEDs. The mechanism of teratogenesis is thought to be multifactorial, including genetic predisposition, effect of seizures, falls and injuries, standard of antenatal care and teratogenic effects of AEDs. Previously, data reported from Kerala registry of Epilepsy and Pregnancy(KREP) in study conducted with the registered women as proband and the unaffected spouse and family members as controls, among 573 probands, failed to demonstrate familial tendency for major congenital malformations(MCM)(13)

Foetal sequalae of maternal seizures postulated to be due to decreased placental blood flow and secondary ischemia. The restoration of circulation by reperfusion post ictally lead to elevated oxidative stress contributing to teratogenic risk. (4)

The single modifiable risk factor for teratogenesis is the exposure to AEDs. The exposed foetus carry increased risk of congenital malformation when compared with those without. Polytherapy and monotherapy with valproate and lamotrigine, folic acid deficiency, social and health support influence the risk of congenital malformations.

After the first literature description of congenital malformation by Janz (14)from Germany, with subsequent reports started coming including various drugs like, phenobarbitone, phenytoin, carbamazepine and sodium valproate. The predisposition to neural tube defects were identified to be due to folate deficiency.(15) Arene oxide, a metabolite of AEDs through the cytochrome p450 system in liver is a potent teratogen. Various other mechanisms including homeobox (HOX) genes, retinoic acid signalling pathways, histone deacetylators and polymorphisms of AED transporters has been postulated.(16) From the data, of KREP, an increased odds ratio for congenital malformation risk has been reported for sodium valproate (6) as compared with carbamazepine (1.2) or phenobarbitone (0.8).(17)

EUROCAT data demonstrated increased risk of neural tube defects, atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis for valproate exposure even as monotherapy when compared with other drugs.(18)

Mechanism

The mechanism by which inhibition of foetal brain development is brought about in CME is not well elucidated ; however three possibilities are proposed as described : genetic predisposition, seizure activity during pregnancy, and exposure to AEDs. Malformations have a constitutional or genetic basis related to the epilepsy itself, and AEDs serves only to increase the frequency of these anomalies in CME who are already genetically predisposed to develop them.

An animal study found that rats aged between 3 and 30 days that had received AEDs including PHT, CBZ, and VPA showed extensive and dose- dependent apoptotic neurodegeneration in the brain during brain growth spurts. AEDs led to a reduction in neurotrophin expression and a reduction in oestradiol, which stimulates neurotrophin activated pathways, and when oestradiol was administered to cells prior to the administration of AEDs there was a reduction in the degeneration of cells.(19) In this study VPA was associated with an increase in adverse effects, specifically for verbal intelligence.

3. **Long-term effects**

Cognitive disability among CME:

AEDs interfere with neuronal migration and synaptic organization leading to abnormal cell development in neonatal brain. (20)The subtle cognitive dysfunction among AED exposed children antenatally or postnatally is difficult to identify in children less than 5 years of age, owing to incomplete brain maturation as well as poor predictability of neuropsychological tests on intellectual functions. (21)(22)The number of simultaneous drugs used(polytherapy) prove more deleterious than monotherapy.(23)

Mechanism

Genetic predisposition, seizure activity during pregnancy, AED exposure contribute to the foetal brain development among CME. AED exposure is supposed to increase the frequency of anomalies among CME, who have a genetic as well as constitutional risk related to epilepsy. Dose dependent apoptotic neurodegeneration in the phase of brain growth spurts was shown in a dose dependent fashion in rats aged between 3 and 30 days, which received AEDs including PHT,CBZ,VPA. Reduced Neurotrophin expression and a reduction in oestradiol which stimulate neurotrophin activated pathways was demonstrated by exposure to AED. The significant finding was that , administration of oestradiol prior to AED lead to reduced degeneration of cells. (19)

Hormonal levels are affected by the AED exposure. AED effects on brain development supporting gonadal and extra gonadal hormones are well known. Right hemisphere development inhibits specific areas of left hemisphere, which is dominant for language abilities, and is enhanced by testosterone levels. Animals studies have shown that testosterone has trophic effect suppressing left cortical growth. (24)In humans and post-natal testosterone levels related to language abilities. Higher levels of testosterone were associated with diminished verbal abilities where as it was augmented by oestrogen levels. (25)(26)(27)

The mechanism by which AED induces adverse cognitive and psychotropic effects are poorly understood. The postulated mechanism are reduced sustained high-frequency repetitive firing, altered neuronal responses including effects on firing rate or threshold , reduced response speed , long term potentiation, or synaptogenesis and disruption of coherent activity. Animal models may be studied to provide further detailed mechanism.

Autism and Antiepileptic drugs in mother:

Autism spectrum disorder emerges during the time when developing child acquires communicative and social skills with affection of behaviour. Even though the

behaviour changes manifest at a later age, the brain alterations are thought to occur at an early age, with symptoms being discoverable as early as six months. During embryogenesis, critical environmental factors can increase the risk of subsequent autism. Early alteration in development points to co-existence of minor malformations and histological changes in brain in people with autism(28) .

Various maternal factors including maternal rubella infection, drugs including thalidomide, valproate, misoprostol and ethanol exposure has been linked with autism.

Valproate has been classified as category "D" as per FDA in pregnancy since it crosses placenta and is secreted through breast milk. Since at times, benefit to mother outweighs the risk to foetus as in epilepsy. Initially case reports came up sighting the risk of autism among VPA exposed children, later the first case series was reported in 2000. (29)(30) (31)(32)(33)

Moore et al reported 57 children with foetal AED exposure. Around 60 % had two or more features of autism with 11 % having a diagnosis of autism spectrum disorder and the risk of autism was linked to valproate exposure. (34) The time point of embryogenesis where valproate exerts its teratogenic effect is not clear, however in lines with the dysmorphic features with valproate exposure, including neural tube defects, congenital heart disease, craniofacial abnormalities, abnormally shaped or posteriorly rotated ears, genital abnormalities, and limb defects, the insult can be assumed to be occurring in the early part of gestation. (35)

Animal models studies on VPA exposure showed behavioural disturbances in rats. (36) Cerebellar abnormalities seen in human autism cases were demonstrated following VPA exposure in animals with similar abnormalities including reduced Purkinjee cell number in Lobules (VI-VIII and X) were reduced with normal anterior lobes. Imaging studies had shown reduced size of posterior cerebellar vermis .(37)(38) Among the cerebellar nuclei, interpositus nuclei showed reduced volume by 62% which is equivalent to globose and emboliform nucleus in humans. There was an overall reduction in the brain size too. (39) Behavioural and anatomic models of autism could be induced by exposing embryonic brain to valproate. (28)

Christensen et al studied around 6.5 lakh children and estimated an absolute risk of 1.53% for autism spectrum disorder(ASD) and 0.5% for childhood autism. On

considering the valproate exposed children, the absolute risk was 4.42% and 2.5 % respectively. When the cohort was constituted to CME, adjusted HR was 2.9 [95% CI, 1.4-6.0]) vs 2.44% (95% CI, 1.88%-3.16%) for ASD and childhood autism for VPA exposure and no exposure. (40)

Adaptive behaviour of CME were evaluated with respect to AED exposure as well as dose from a US based study. 256 children were identified from North American Anti-epileptic Drug Pregnancy Registry who had taken lamotrigine, valproate, or carbamazepine monotherapies during the period of pregnancy. Post the adjustment of confounding factors including maternal age, folic acid use, ethanol and cigarette use, adaptive behavioural scores showed lowest performance among VPA exposed children and highest among Lamotrigine exposed children. The higher dose of VPA showed lower adaptive behavioural scores, socialization and motor scores. They could not identify significant difference with carbamazepine and lamotrigine. (41)

From antenatal patients, a cohort was recruited including WWE and without epilepsy. Children born to this cohort was followed up till 6 years. On final analysis, most frequent disorder diagnosed with autism spectrum disorder. Neuro developmental disorders were related to therapy with sodium valproate, either as monotherapy or polytherapy. Similar to other studies, other AED including Carbamazepine and Lamotrigine had no effect. (42)

An Australian study which include 105 children aged 6-8 years, from Australian Pregnancy Register for Women on Antiepileptic Medication. 10.5 % had elevated Childhood Autism Rating Scale (CARS) among the whole cohort. When data was analysed by linear regression, mean valproate dose was a predictor of CARS score after controlling for polytherapy, use of folic acid ad seizures during pregnancy. There was no data for low dose VPA in this study group. Of the eleven, two exposed to Carbamazepine monotherapy as well had elevated CARS scores. (43)

Language abilities among CME:

Development of language abilities among children perinatally exposed to AED had been an area of research interest. Vinten et al studied 249 children from 6 to 16

years who had AED exposure in utero. On comparing verbal IQ, children exposed to VPA had lower score than those exposed to other AED or those with no exposure. VPA exposed children also had lower IQ below 69 and memory impairment. They identified that maternal IQ, sodium valproate, and number of tonic clonic seizures during pregnancy had prediction value in the verbal IQ scores.(44)

A study from the Liverpool and Manchester Neurodevelopment Group including children less than 2 years demonstrated a significant association between low verbal IQ scores and delayed early development. (45) In another study from same group conducted among patients aged 6 months to 16 years, identified valproate exposure as well as tonic clonic seizures during pregnancy predicted lower verbal IQ among CME thus indicating cognitive impairment. (46)

In a study comparing cognitive fluency and flexibility with respect to foetal exposure to AED, Mcvearry et al found significant effect of VPA. VPA group had a lower fluency as compared with lamotrigine and carbamazepine(mean-763.for VPA vs 93.76 Lamotrigine vs 95.5 Carbamazepine) with statistical significance. (47)

Nadebaum et al evaluated language among 102 AED exposed children from Australian Pregnancy Register for Women with Epilepsy and Allied Disorders with Clinical Evaluation of Language Fundamentals, fourth edition (CELF-4). Low scores were identified among valproate exposed children, both as monotherapy and polytherapy as compared with other AEDs including carbamazepine and lamotrigine. (48)

NEAD study group studied 309 children aged 3 years with respect to the AED, viz carbamazepine, lamotrigine, phenytoin, or valproate. Lower IQ scores were found in VPA exposed children than other AEDs. Mean IQ scores were 9 points lower for valproate with respect to lamotrigine, 6 with carbamazepine. The interesting fact was that the relation of IQ to valproate was dose dependent and maternal IQ correlated with the child IQ with regards to carbamazepine, lamotrigine, or phenytoin but not with valproate.(49)

Intelligence among CME:

Previously reported data from Kerala registry of epilepsy and pregnancy studying children with mean age of 15 months, between 1998 and 2004, showed that mental and motor developmental quotients were related inversely to polytherapy. Among monotherapy, valproate had less scores when compared with carbamazepine.(50)

The fact that more children with intrauterine valproate exposure (29%, RR=3.6, 95% CI 1.7–7.5) had values below the average range, indicating the reduction in cognitive development and functioning and is not a statistical coincidence.(51) The same cohort when reassessed at 6 years for IQ, learning, memory and attentional abilities, children with intrauterine valproate exposure differed form control children with visual attention being impaired most, and 36-46% falling below average range.(45)

Relation of perinatal AED exposure with respect to child IQ was studied by Liverpool and Manchester Neurodevelopment Group. The adjusted Mean IQ was 9.7 points lower for children exposed to high dose valproate(>800mg) than low dose. However even with low dose, there were impaired verbal abilities, need for educational intervention. Iq was not affected by carbamazepine and lamotrigine. The higher dose of VPA exposure(>800mg) had poor cognitive development. (52)

AIM AND OBJECTIVES

Aims and Objectives

1. To characterize the cognitive, behavioural and language function of children of women with epilepsy according to antenatal exposure to Anti-epileptic drugs.

2. To study the difference in outcome measures according to AED exposure

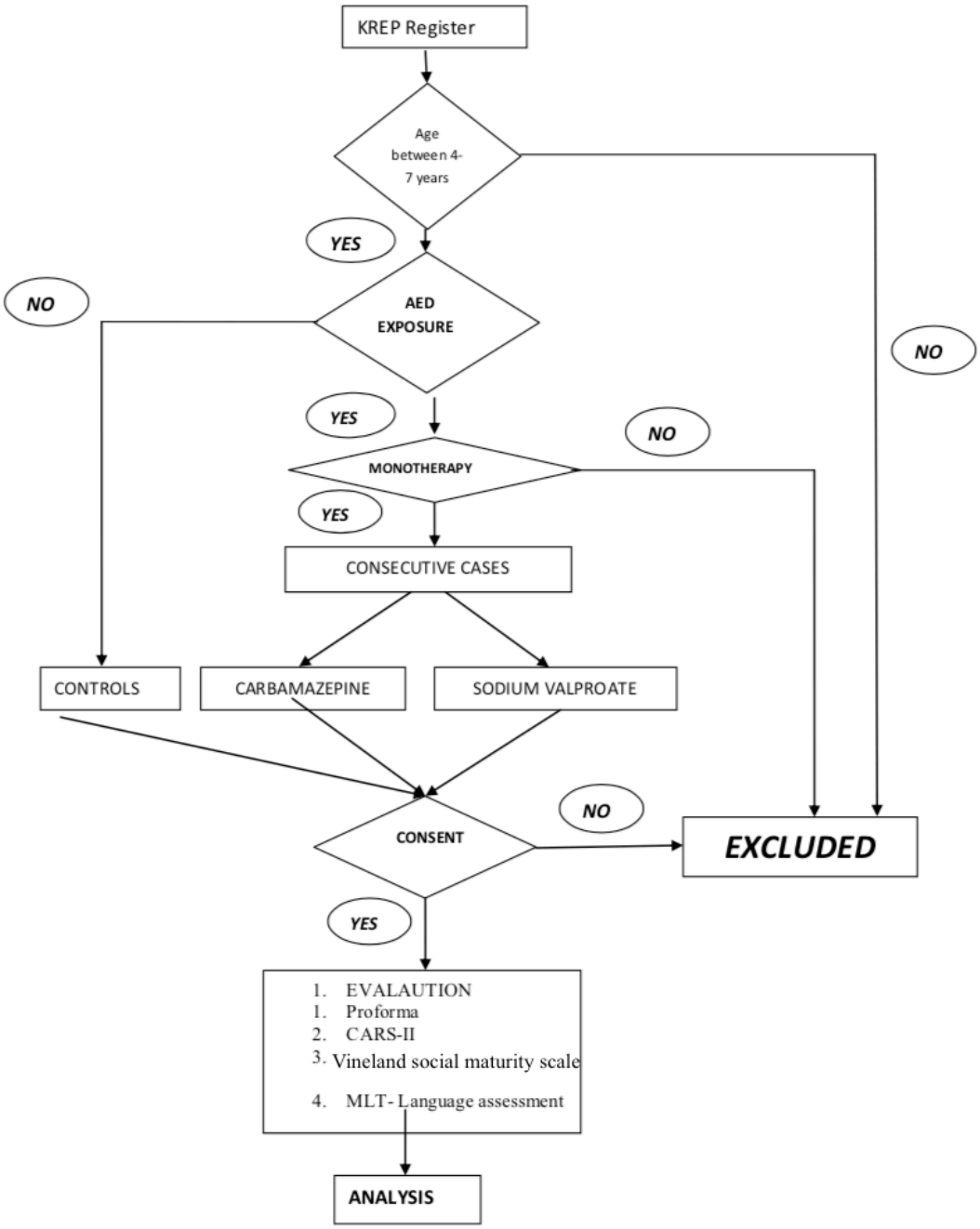
MATERIALS AND METHODS

Materials and Methods

Background:

The study was designed and executed in the Kerala Registry of Epilepsy and pregnancy at a tertiary referral epilepsy centre in Trivandrum, Kerala, India. The registry follows up the patient from the early stage of pregnancy as per protocol before the foetal outcome is known. A standard proforma is maintained which includes details of AED, folic acid use, exposure to pharmaceutical teratogens or radiations, substance abuse and seizure frequency during conceptional period. All Women with epilepsy undergo screening of foetal malformations by ultrasonography, serum alpha fetoprotein and are given vitamin K injections at last trimester. The type of seizure at each month is recorded separately. At 3 months of age, all the children are subjected for echocardiography and sonographic examination of abdomen and developmental quotient at 1 year. These children are further followed up till 18 years with periodic assessment.

Protocol:


KREP Register
Age between 4-7 years
YES
NO
AED EXPOSURE
NO
YES
NO
MONOTHERAPY
YES
CONSECUTIVE CASES
CONTROLS
CARBAMAZEPINE
SODIUM VALPROATE
NO
CONSENT
EXCLUDED
YES
1. EVALAUTION
1. Proforma
2. CARS-II
3. Vineland social maturity scale
4. MLT- Language assessment
ANALYSIS

Methodology :

Cases and controls: The subjects will be children of women with epilepsy of age group 4-7 years, from Kerala Registry of Epilepsy and Pregnancy(KREP) at SCTIMST. Those who give consent for the study will be included. Three groups will be identified as per the protocol detailed and studied

Methodology:

For the purpose of study, live children born in the cohort from June 2010-June 2014 who were in the age range of 4-7 years were considered. From this group, children with in utero exposure to monotherapy with valproate, carbamazepine as well as those with no exposure to AEDs were identified. Invitation letter addressed to the parents were sent by registered post to 126 eligible children of which 52 responded in the first letter. Patients who could be contacted telephonically was intimated over phone. A second letter was sent to those who did not respond. Total of 69 patients came for personal interview with their children. A total of 14 letters returned because of either wrong address or change of address. 8 patients declined the call, stating the following reasons: they were off AED, follow up from elsewhere, Logistic difficulties in long travel, financial difficulties, separated family.

The birth and developmental details of the children were taken as part of the history. The detailed seizure history and other medical history for each child was obtained from the mother. Socioeconomic score was calculated considering the paternal education, maternal education as well the job status of parents with 0 indicating worst, whereas 50 indicates best socioeconomic status. The clinical data pertaining to the mother like type of epilepsy, AED exposure were abstracted from the clinical records of the registry.

Inclusion criteria:

1. Age group of 4-7 years.
2. Children of women with epilepsy who had received mono therapy with either valproate or carbamazepine or no drug therapy antenatally.

Exclusion criteria:

1. Children of mother who received poly drug therapy will be excluded
2. Children with low developmental IQ at 1 year of age(Less than 2 standard deviations)
3. Children with significant perinatal insult and global developmental delay.
4. Those for whom Malayalam is not a native language.
5. Those who decline consent to undergo the study will be excluded.

Instruments

In age groups 4 and 7 years, CARS2(Childhood Autism Rating Scale 2) for autistic traits and Social quotient and mental age using the Vineland social maturity scale(VSMS), was used. Language development was assessed with MLT and Receptive-Expressive Emergent Language test (REELS) were administered to calculate receptive and expressive language age in children who were 4 years and those who had technical difficulties in doing MLT. CARS-2 and MLT was administered by speech and language pathologist. VSMS was administered by a single neuropsychologist.

CARS- 2 score consist of 15 scoring items assessing the autistic traits. Each trait has median score and an age based raw score. Final score obtained by adding up the items. A total score of 15-29 indicate minimal to no symptoms of autism, 30-36.5 suggest mild to moderate autistic spectrum disorder and any score more than 37 indicate severe autism. A detailed chart containing the item is described at annexure-c.

MLT was developed to assess the language proficiency of school age children. The test battery consists of 14 subtests pertaining to different language domains (Semantics, Semantic similarity, Naming, Lexical category, Antonymy, Syntagmatic relations, Plural forms, Tenses, Plural-Noun-Gender (PNG) markers, Case markers,

Comparatives, Reading aloud, Reading comprehension and Writing). The test was standardized previously on 200 healthy children of six years of age, matched for socioeconomic status and attending to the local schools. (53)

Method of analysis

The data were entered on to a spreadsheet and were analysed with SPSS (SPSS Statistics 21.0).Numerical variables are summarized as means and standard deviations, and compared using Kruskal Wallis tests (non-parametric alternative of ANOVA, as the sample size is small); Mann Whitney U test to compare between CBZ and VPA. Categorical variables are compared using Chi square tests/ Fisher exact test. A p value less than 0.05 is considered statistically significant.
Analysis was extended to look for confounders/ effect modifiers by comparing outcomes across observed values of independent variables – sex, chronological age, paternal age, birth order (proxy for maternal age), SES, DQ mental. Potential confounders and effect modifiers were further analysed using binary logistic regression after including AED group (no AED, CBZ, VPA).

Ethical considerations

This registry has the approval of the Institutional Ethics Committee and informed consent was obtained from the parent(either father or mother)

RESULTS

RESULTS:

1.Demographics of study population:

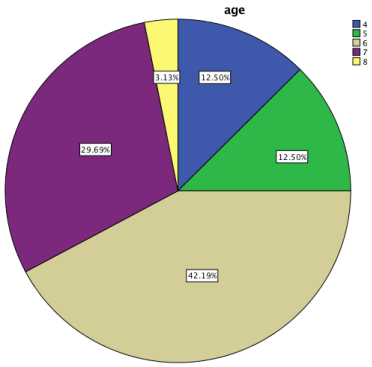


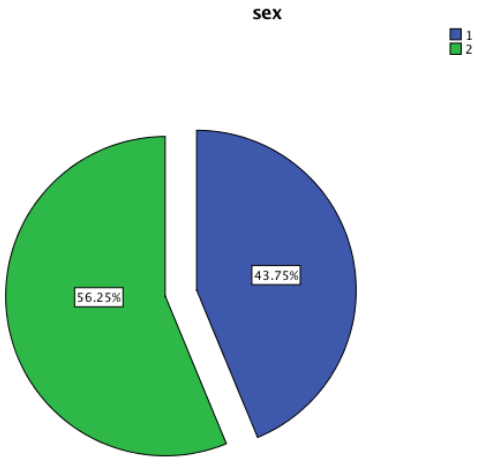
Figure 1:Age distribution of the study cohort

age		Frequency	Percent	Valid Percent	Cumulative Percent
	4	8	12.5	12.5	12.5
	5	8	12.5	12.5	25.0
	6	27	42.2	42.2	67.2
	7	19	29.7	29.7	96.9
	8	2	3.1	3.1	100.0
	Total	64	100.0	100.0	

Table 1:Age distribution

Out of the 64 subjects, 27 (42.2%) were of 6 years, followed by 19(30%) of seven years. 8(12.5%) each belonged to 4 and 5 years respectively.

Sex distribution:



There were 28 (43.8%)boys and 36(56%) girls in the study population.

Figure 2:sex distribution

sex					
		Frequency	Percent	Valid Percent	Cumulative Percent
	1	28	43.8	43.8	43.8
	2	36	56.3	56.3	100.0
	Total	64	100.0	100.0	

Table 2:Sex Distribution

Anti-epileptic drug exposure in the cohort:

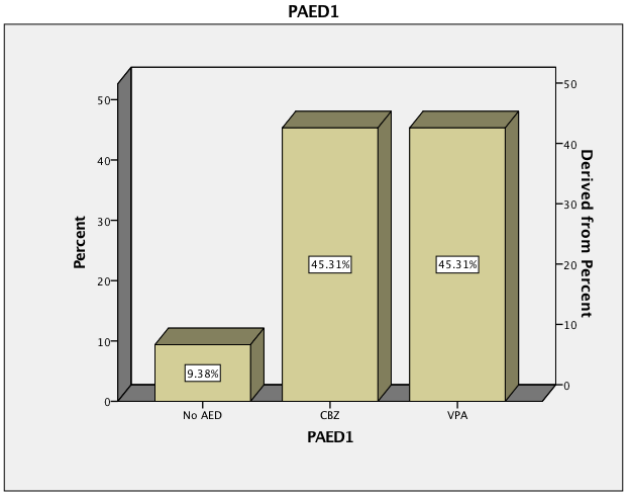


Figure 3:Anti-epileptic drug exposure in the cohort

Around 29(45.3%) each of the mothers were on carbamazepine and valproate at the time of pregnancy, whereas, 6 patients were not on anti-epileptic drugs during the pregnancy.

Antecedents:

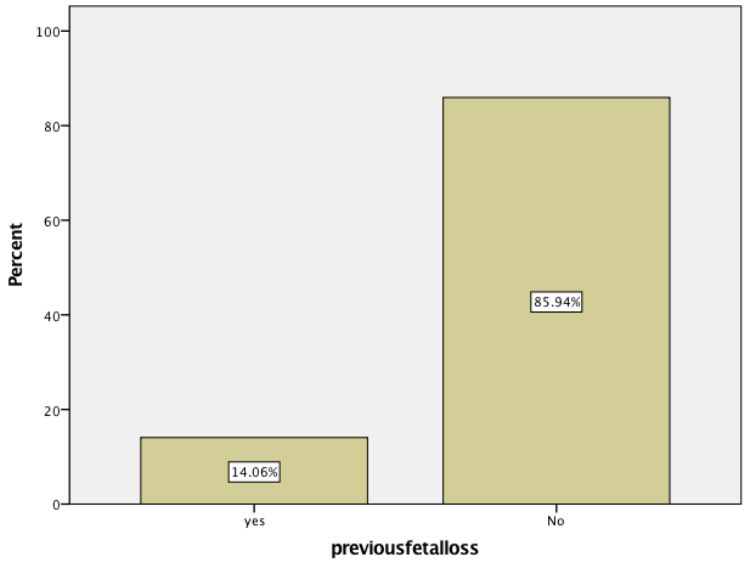


Figure 4:Previous fetal loss in cohort

Considering the previous fetal loss among mothers, 14.1%(9 of 64) had previous fetal loss. Of the 9 mothers, 7 had abortions, 3 had still births and two had pre-term twins leading to early death.

Folic acid use during pregnancy:

All the mothers in our cohort has received folic acid at a dose of 5mg during the entire period of pregnancy.

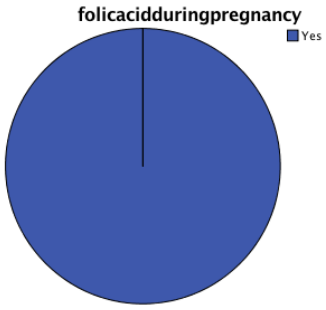


Figure 5:Folic Acid during pregnancy

Seizures in children:

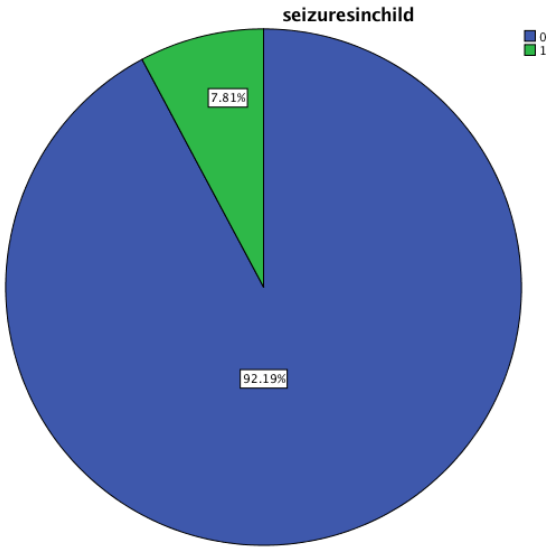


Figure 6: Seizures in the children

In the cohort, 5(7.8%) children had seizures, of which 4 had febrile seizures and 1 had afebrile seizures. 3 children had a diagnosis of febrile seizures, where as one each had a diagnosis of GEFS plus and absence seizure.

AED use:

2 patients of the whole cohort had AED usage at any time. One was on levetiracetam and child with absence seizure was on Valproate. At the time of evaluation, the child who had absence seizure continued to be on Valproate, and he had 3hz typical spike and wave discharges on SEEG recording.

Other diseases:

2 children in the cohort had atrial septal defect. One child had low birth weight and neonatal sepsis. One each had childhood asthma and pes cavus deformity.

Seizures in mother:

One patient each had seizures during pregnancy where as one had seizure during the time of delivery.

AED Dose in mother:

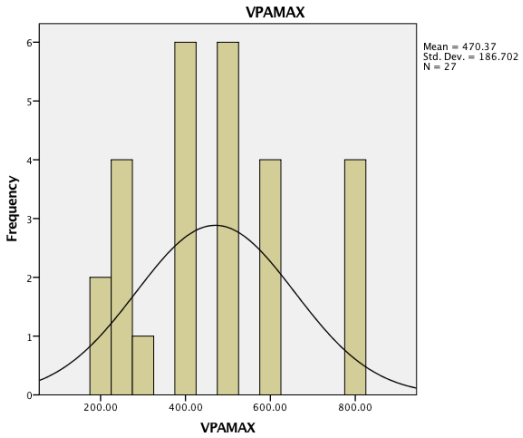


Figure 7: Dose distribution of VPA

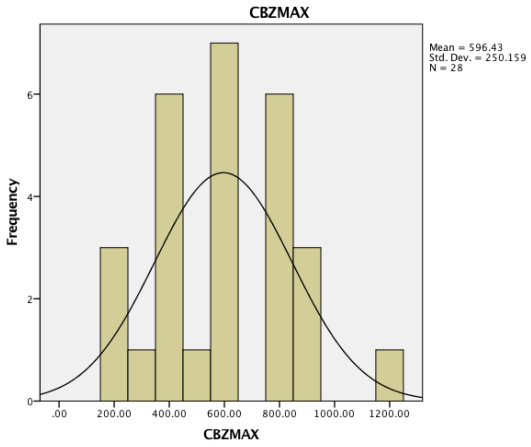


Figure 8:Dose Distribution of Carbamazepine

In the cohort studied, mean dose of Carbamazepine was 596.4 mg (range 200mg—1200mg) and valproate was 470mg (200mg-800mg).

CARS and MLT Score:

Mean CARS score in the cohort as 15.21 (15-19; SD-0.75) and mean MLT scores were 78.13 (34-94; SD 24.3).

	N	Minimum	Maximum	Mean	Std. Deviation
MLT score	60	34	94	78.13	14.346
Total CARS score	64	15.0	19.0	15.211	.7496

Table 3:Mean score of CARS and MLT

BASELINE DESCRIPTION OF STUDY GROUPS

		No AEDs	CBZ	VPA	Total	P value
Sex	Male	1 (16.7%)	15(51.7%)	12(41.4%)	28(43.8%)	0.325*
	Female	5(83.3%)	14(48.3%)	17(58.6%)	36(56.3%)	
Birth order	1	4(66.7%)	21(72.4%)	19(65.5%)	44(68.8%)	-
	2	1(16.7%)	6(20.7%)	7(24.1%)	14(21.9%)	
	3	1(16.7%)	2(6.9%)	2(6.9%)	5(7.8%)	
	4	0	0	1(3.4%)	1(1.6%)	
Previous foetal loss	Yes	1(16.7%)	4(13.8%)	4(13.8%)	9(14.1%)	1.0*
	No	5(83.3%)	25(86.2%)	25(86.2%)	64(85.9%)	
Folic acid before pregnancy	yes	6(100%)	29(96.6%)	29(100%)	63(98.4%)	-
	No	0	1(3.4%)	0	1(1.6%)	
Seizure class	1	1(16.7%)	8(27.6%)	25(86.2%)	34(53.1%)	-
	2	4(66.7%)	19(65.5%)	4(13.8%)	27(42.2%)	
	3	0	2(6.9%)	0	2(3.1%)	
	12	1(16.7%)	0	0	1(1.6%)	
Epilepsy class	1	1(16.7%)	8(27.6%)	24(82.8%)	33(51.6%)	-
	2	4(66.7%)	19(65.5%)	5(17.2%)	28(43.8%)	
	3	0	2(6.9%)	0	2(3.1%)	
	11	1(16.7%)	0	0	1(1.6%)	

Table 4:baseline description of study groups

*Fisher exact test

-P cannot be calculated due to small numbers.

Valproate exposed female children were slightly high as compared with carbamazepine exposure (58.6% versus 48. 3%).A total of 9 mothers in the cohort had previous fetal loss with 4 each in VPA and CBZ group and one without AED, however these results were not statistically significant.

		N	Mean	Std. Deviation	Minimum	Maximum	P value*
Mental developmental quotient at 1 year of age	No AED	6	130.23	23.42	97.89	160.90	0.364
	CBZ	29	113.40	31.36	42.71	167.25	
	VPA	25	109.28	33.17	31.47	162.30	
	Total	60	113.36	31.57	31.47	167.25	
Chronological Age(months)	No AED	6	63.00	12.11	48	76	0.148
	CBZ	27	74.70	14.41	40	99	
	VPA	29	74.07	13.72	44	96	
	Total	62	73.27	14.09	40	99	
Socio-economic Status Score	No AED	4	34.25	5.25	27	39	0.093
	CBZ	26	24.69	9.79	12	50	
	VPA	28	26.54	9.40	13	45	
	Total	58	26.24	9.53	12	50	
Paternal age(years)	No AED	6	31.50	4.97	26	40	0.547
	CBZ	28	33.04	3.93	27	42	
	VPA	28	32.04	4.20	25	40	
	Total	62	32.44	4.12	25	42	

Table 5: baseline description of study groups

*Independent sample Kruskal Wallis test (Non-parametric alternative of ANOVA)

Mean socioeconomic score was 34.25 in mothers not on AED where as it was 24.69 on Carbamazepine and valproate, which showed a trend towards significance. The relevance of the same could be identified through further analysis. As compared with children with no exposure to AED antenatally, those with exposure had a lower DQ at 1 year and was further low for VPA when compared with CBZ.

OUTCOME VARIABLES

1.CARS-2 SCORE:

		N	Mean	Std. Deviation	Minimum	Maximum	P value
Total CARS-2 score	No AED	6	15.17	.41	15.0	16.0	0.338
	CBZ	29	15.07	.37	15.0	17.0	
	VPA	29	15.36	1.03	15.0	19.0	
	Total	64	15.21	.75	15.0	19.0	

Table 6:Outcome variables-CARS 2 score

The Variation in CARS -2 score was found to be slightly high in the VPA group as compared with the CBZ and no AED group with no statistical significance.

2.Language Function and AED exposure:

Malayalam Language Testing score (MLT SCORE)	No AED	5	84.60	11.55	68	94	0.619
	CBZ	27	77.00	15.08	36	94	
	VPA	28	78.07	14.22	34	94	
	Total	60	78.13	14.35	34	94	
Receptive language AGE Quotient(REELS) (RLAQ)	No AED	1	95.00		95.00	95.00	0.453*
	CBZ	9	94.97	11.61	76.00	116.67	
	VPA	6	82.45	20.55	63.33	112.50	
	Total	16	90.27	15.87	63.33	116.67	
Expressive language AGE Quotient (REELS) (ELAQ)	No AED	1	95.00	.	95.00	95.00	0.392*
	CBZ	9	94.97	11.61	76.00	116.67	
	VPA	6	78.70	25.52	54.29	120.00	
	Total	16	88.87	18.84	54.29	120.00	

Table 7:Language function and AED exposure outcome

**Mann Whitney U test – CBZ vs VPA*

RLAQ - 0.224/ELAQ - 0.18

The receptive language quotient and expressive language quotient was found to be low among valproate than carbamazepine with no statistical significance. Additional Mann Whitney U test done to compare the two groups in term of receptive and expressive language assessment was not significant.

3.Behavioural function and AED

Social Quotient (VSMS) [SQ]	No AED	6	99.83	16.39	82	126	0.463
	CBZ	27	89.41	12.74	58	117	
	VPA	28	89.79	13.07	60	120	
	Total	61	90.61	13.38	58	126	
Mental Age quotient [MA] (VSMS)	No AED	6	101.16	8.73	91.67	110.53	0.142
	CBZ	27	92.62	10.6	60.87	106.25	
	VPA	29	92.48	10.13	61.73	111.11	
	Total	62	93.38	10.38	60.87	111.11	

Table 8:Behavioural outcome and AED exposure

The variation in the Social quotient and mental age score was minimal and not statistically significant.

ANALYSIS FOR CONFOUNDERS/ EFFECT MODIFIERS

Sex and outcomes

		N	Mean	Std. Deviation	Minimum	Maximum	P value
Total CARS score	Male	28	15.107	.4163	15.0	17.0	.556
	Female	36	15.292	.9287	15.0	19.0	
	Total	64	15.211	.7496	15.0	19.0	
MLT score	Male	27	79.04	13.921	36	94	.586
	Female	33	77.39	14.858	34	94	
	Total	60	78.13	14.346	34	94	
SQ	Male	26	93.19	14.291	58	126	.465
	Female	35	88.69	12.522	60	111	
	Total	61	90.61	13.379	58	126	
Mental Age quotient	Male	27	92.7147	11.65818	60.87	111.11	.604
	Female	35	93.8941	9.42740	61.73	109.09	
	Total	62	93.3805	10.38341	60.87	111.11	
RLAQ	Male	6	98.7897	16.95874	68.57	116.67	0.056
	Female	10	85.1643	13.51002	63.33	100.00	
	Total	16	90.2738	15.86794	63.33	116.67	
ELAQ	Male	6	100.0397	18.38762	68.57	120.00	**0.042**
	Female	10	82.1643	16.45475	54.29	100.00	
	Total	16	88.8676	18.84248	54.29	120.00	

Table 9:Sex and outcomes

The Expressive language age was found to be low among the girl children in the cohort with a statistical significance (p.042)

		Weighted mean	Std. Deviation
ELAQ	No AED	95.0000	.00000
	CBZ	92.6939	10.95759
	VPA	75.5810	22.62088
	Total	86.2894	17.93202

Table 10:ELAQ- weighted for sex

On weighing ELAQ scores for sex, VPA have significantly lower ELAQ scores in ANOVA (p=0.047) but not in Kruskal Wallis test (p=0.127).

BIRTH ORDER OF MOTHER

		N	Mean	Std. Deviation	Minimum	Maximum
Total CARS score	1	44	15.216	.6854	15.0	18.5
	2	14	15.286	1.0690	15.0	19.0
	3	5	15.000	.0000	15.0	15.0
	4	1	15.000	.	15.0	15.0
	Total	64	15.211	.7496	15.0	19.0
MLT score	1	41	80.24	12.387	50	94
	2	13	76.54	11.027	60	94
	3	5	73.80	23.921	36	94
	4	**1**	**34.00**	**.**	**34**	**34**
	Total	60	78.13	14.346	34	94
SQ	1	41	89.68	14.210	58	126
	2	14	93.79	11.477	80	120
	3	5	92.60	10.945	82	111
	4	**1**	**74.00**	**.**	**74**	**74**
	Total	61	90.61	13.379	58	126
Mental Age Quotient	1	42	93.6871	9.61725	60.87	110.53
	2	14	95.1546	8.75775	84.51	111.11
	3	5	92.1678	13.51183	76.60	109.09
	4	**1**	**61.7284**	**.**	**61.73**	**61.73**
	Total	62	93.3805	10.38341	60.87	111.11
RLAQ	1	12	92.4385	12.80316	68.57	116.67
	2	2	87.9167	34.76608	63.33	112.50
	3	1	95.0000	.	95.00	95.00
	4	**1**	**64.2857**	**.**	**64.29**	**64.29**
	Total	16	90.2738	15.86794	63.33	116.67
ELAQ	1	12	90.7718	14.85487	66.00	116.67
	2	2	91.6667	40.06938	63.33	120.00
	3	1	95.0000	.	95.00	95.00
	4	**1**	**54.2857**	**.**	**54.29**	**54.29**
	Total	16	88.8676	18.84248	54.29	120.00

Table 11:Birth order of mother and outcome

One of the mother was born as 4th child of her parents. The sibling of that child had lower scores on all the parameters tested. There was no significance for the other scores.

PREVIOUS FETAL LOSS

		N	Mean	Std. Deviation	Minimum	Maximum
Total CARS score	yes	9	15.111	.3333	15.0	16.0
	No	55	15.227	.7983	15.0	19.0
	Total	64	15.211	.7496	15.0	19.0
MLT score	**yes**	**9**	**70.78**	23.737	34	94
	No	51	79.43	11.885	50	94
	Total	60	78.13	14.346	34	94
SQ	yes	9	90.22	18.747	58	126
	No	52	90.67	12.468	60	120
	Total	61	90.61	13.379	58	126
Mental Age Quotient	yes	9	87.9934	17.97152	60.87	110.53
	No	53	94.2953	8.42088	73.56	111.11
	Total	62	93.3805	10.38341	60.87	111.11
RLAQ	**yes**	**2**	**79.6429**	21.71828	64.29	95.00
	No	14	91.7925	15.30928	63.33	116.67
	Total	16	90.2738	15.86794	63.33	116.67
ELAQ	**yes**	**2**	**74.6429**	28.78935	54.29	95.00
	No	14	90.8997	17.61613	63.33	120.00
	Total	16	88.8676	18.84248	54.29	120.00

Table 12:Previous fetal loss and outcome

On analysing the previous foetal loss as a confounding factor, there was a trend towards lower MLT scores, RLA and ELA scores.

Correlations

			Total CARS score	MLT score	SQ	Mental Age Quotient	RLAQ New	ELAQ
Spearman's rho	DQ Mental	Correlation Coefficient	-.185	.024	.260	.217	.002	.049
		Sig. (2-tailed)	.158	.858	**.051**	.102	.995	.863
		N	60	57	57	58	15	15
	Paternal age	Correlation Coefficient	-.153	.248	-.118	-.062	-.117	-.078
		Sig. (2-tailed)	.235	.061	.371	.638	.666	.773
		N	62	58	59	60	16	16
	CA	Correlation Coefficient	-.123	**.404****	.162	**.287***	.016	-.024
		Sig. (2-tailed)	.341	**.002**	.213	**.024**	.954	.928
		N	62	58	61	62	16	16
	SES	Correlation Coefficient	**-.241**	.068	.179	**.272***	**.484**	**.511**
		Sig. (2-tailed)	**.069**	.621	.187	**.041**	**.067**	**.051**
		N	58	55	56	57	15	15
	Maternal age	Correlation Coefficient	-.109	-.139	.142	.042	0.112	0.08
		Sig. (2-tailed)	.405	.286	.286	.752	0.689	0.76
		N	61	61	58	61	15	15
**. Correlation is significant at the 0.01 level (2-tailed).								
*. Correlation is significant at the 0.05 level (2-tailed).								

Table 13:Correlation study

When a correlational study was done using Spearman's rho, the social quotient seemed to be related to DQ at one year(P-0.051), chronological age had positive

correlation with Mental age score(0.024) and MLT score (0.002). The socioeconomic status had a trend towards negative correlation with CARS score(p-0.07), positive correlation to mental age score (p-0.041), expressive language age (p-0.05),and trend in receptive language score (p-0.07).

Regressions:

A binary regression analysis was done to assess the significance of the correlation analysis for the effect of AED. The cut off chosen for the analysis was Mean-1 standard deviation. All the regression was carried out with no drug as the reference category, with comparison to VPA and CBZ.

Total CARS score was regressed against socioeconomic status, MLT cut off was taken as "64" and was regressed against chronological age and drug, RLQ was regressed against Sex, SES and drug, ELQ<70 was regressed against Sex, Socioeconomic status and drug, SQ<77 was regressed against DQ mental at 1 year and drug, mental age score <83 was regressed against chronological age, socioeconomic status and drug. None of this analysis showed significance in linear regression analysis.

DISCUSSION

Discussion

64 children aged between 4-7 years; born to WWE were recruited for the study. There were 28 males (43.8%) and 36 females (56%) .This proportion was difference to that seen in previous studies of CME studying neuropsychiatric and cognitive effects (54)(45).

The Age group included were CME from 4 to 7 years. When the study population was split as per age, the major age group was 6 years (42.2%) followed by 7 years who constituted around 29.6% of the study population. The lesser number of children from 4 and 5 years could be related to the logistic difficulties of bringing younger children at a prescheduled time. Overall female children constituted the bulk of cohort (56%). The effect of epilepsy on the life of children are a concern for the WWE, with the concern whether they are less efficient in carrying out the burden adds on to the stress.(55)

We intended to include the CME in three groups of 40 patients each belonging to valproate, carbamazepine exposure and no drugs respectively. However, 29 each from the valproate and carbamazepine turned up, whereas only 6 who were not on AEDs during pregnancy turned up for follow up.

The rate of foetal loss among the mothers in the cohort was14.1%. Around 7 had early abortion and 3 had previous still births. The rate of foetal loss among WWE was previously reported from the Kerala registry for epilepsy and pregnancy was 8.65%. The risk of spontaneous abortion was 12.6 % for valproate and 7% for carbamazepine. Our cohort had slightly higher rate than previously reported which could be due to the inclusion of more WWE on Valproate and exclusion of less risky drugs like levetiracetam and lamotrigine .(56)

Folic acid is prescribed preconception to at least the end of the first trimester as for any women , for women on antiepileptics due to increased risk of neural tube defects associated with the intake of Carbamazepine and Valproic acid. There is existing controversy regarding whether women with epilepsy need higher doses of folic acid to prevent malformations .The certainty that whether folic acid actually reduces the risk of malformations associated with the use of antiepileptic medications. There were assumptions that folic acid could exacerbate seizures. In our study all patients received regular dose of folic acid during the whole period of pregnancy after conception.

In the whole cohort, 4(6.3%)had febrile seizures and one had afebrile seizures who had semiology suggestive of absence seizures. The concurrent AED use in the child could contribute to the cognitive slowing among kids. However only one child in our cohort was taking Valproate at the time of examination. Two children in our cohort had ostium secondum atrial septal defect whereas only one child had a bad perinatal history in the form of perinatal sepsis and low birthweight.

Only two mothers in our cohort had seizures during pregnancy, one had it antenatally and one had it during the delivery, indicating the good compliance as well as good control of seizures.Mean dose of Carbamazepine was 596.4 mg (range 200mg—1200mg) and valproate was 470mg (200mg-800mg) in the cohort.

The mental developmental quotient at 1 year of age was studied for the whole cohort. Valproate exposed children had lower DQ at one year as compared with other groups (109+/- 33.1 versus 113.4+/-31.3(CBZ) versus 130.23+/-23.42(no AED)p-0.364).

1.Autsim and AED exposure.

On evaluating for autistic traits with CARS 2 score, the result in valproate exposed children were 15.36(SD-1.03; 15-19) versus 15.07 (SD-0.37; 15-17) in the carbamazepine group and 15.17 (SD-0.41;15-16) [p-.338] in the group with no AED exposure. The score were minimally high in the valproate group, however with no statistical significance.

For diagnosing autism at any age, a score of more than 25.5 is considered to be sensitive and specific.(57) It was however interesting to note that valproate group

had 2 patients having relatively high score in the cohort. In a previous study evaluating 105 CME, wood et al(43) has identified a 10.5% increased prevalence of elevated CARS score(>27). The age group of the cohort was 6-8 years which was slightly different from our cohort. Elevated CARS score were identified in 7.7% of valproate monotherapy and 46.7% of valproate polytherapy group. Pre conceptional use of folic acid and mean dose of valproate correlated with the risk of autism. The mean dosage of valproate was 1585.7 (ranged : 300mg to 3gm) in this study cohort. The groups on polytherapy had a higher score in CARS -2. In addition two children exposed to carbamazepine monotherapy also had elevated CARS-2 score.

The mean dose of VPA in our cohort was 470mg (200-800mg) and all the patients received folic acid during the pregnancy. In our cohort, there was only two children with mildly elevated CARS score. This could suggest that a lower VPA dose and stringent use of folic acid might explain the lower prevalence of autism in our cohort. We compared the children exposed to valproate and carbamazepine instead of the newer AEDs with less risk including Lamotrigine and Levetiracetam. This could be one potential reason for less difference in the mean CARS-2 scores, as the previous study had shown that carbamazepine is associated with increased risk(43). However the sample size was small to make a significant comment on the result. Future studies to identify the prevalence of autism among AED exposed children is warranted.

The socioeconomic status of the parents seemed to show a trend towards the elevated CARS score with a negative correlation(p-0.067).This indicate that children from a poorer socio economic status had elevated Scores in CARS scale. The lower educational status of the parents could be a factor contributing to the elevated score in this cohort. However on regressing for the effect of socioeconomic status for anti-epileptic drug effect, there was no significant effect. The risk of autism in developed countries is found to be increasing with the rise in socioeconomic class, which in particular could be due to the increased number of professional visits and health seeking (58)(59).

2.Language development and AED exposure

The language assessment in the cohort was done using Malayalam language testing (MLT)score, which has been developed and used previously in Kerala registry of epilepsy and pregnancy. The test was developed to assess the Malayalam language proficiency of school age children. The test battery has been described previously. The reason for choosing MLT as the primary test over REELS was the ability to assess the skills of children directly by means of structured exercises whereas REELS asses the same based on parental interviews. The children who could not attempt MLT were assessed by REELS.

The Mean MLT score for the whole group was 78.13. There was no significant difference between the three groups(p-0.6). The score items when studied independently could not identify the areas of defect as previously reported.(53) MLT score increased with age(p-0.02) indicating a better language skills as age increases. However when binary regression analysis was done, there was no relation between drug and score, after adjusting for age.

REELS assessment of expressive and receptive language assessment was done for 18(28.1%) patients. The receptive and expressive language scores were lower for valproate exposed children than carbamazepine and those without exposure (p-0.392 for receptive language and 0.453 for expressive language). The socio economic status showed trend affecting expressive and receptive language(p-0.51 and 0.67 respectively). This trend indicated that, towards the higher socio economic strata, the language development was better. However there was no relation to the drug effect on regression analysis.

Our study did not indicate a relation between language performance and AED exposure among CME. There was no association between type of maternal epilepsy, occurrence of seizures during pregnancy and use of folic acid during pregnancy with language development in CME. The innate factors in the child, educational status of parents and genetic factors could play important role in the development of language than the AED exposure in CME. The MLT scores were higher for valproate than Carbamazepine, whereas the group with no AED exposure had a higher score compared to those on AED(84 [no AED] vs 77[CBZ] vs 78[VPA]; p-0.619), with

better scores indicating better skills. However the result was not significant. Previously reported data from KREP had shown that maternal IQ, education and polytherapy was associated with selective impairment of language skills.(53) The exclusion of children exposed to polytherapy could be one reason for the absence of interaction. Future study can be planned to assess the relation of language development with the dose as well as type of AED could provide more conclusive result.

3.Mental and social development with AED exposure

The mental and social development was assessed using Vineland social maturity scale. The social quotient and mental age in relation to chronological age was studied. The social quotient and mental age was similar in the carbamazepine and valproate exposed group, however it was low when compared to the group without AED exposure. It was notable that developmental quotient(DQ) at 1 year of age had a relation to subsequent social quotient (p-0.05). This could indicate an innate element with in the child playing a role in intellectual development than environmental factors. Eriksson et al, in his study of CME had postulated similar concept that in addition to drug effect, the genetic and environmental factors can influence the intellectual development in CME.(60)

When the regression analysis for mental age and social quotient was done after adjustment for DQ, there was no drug effect in the development of social cognition. Our analysis failed to identify defective social development with AED exposure antenatally. Previous studies have shown that CME with exposure to VPA in particular had lower IQ and language function as compared with others.(61)(62)(63)

Overall the changes were observed slightly higher in the language hemisphere among children assessed with REELS score than in social function or autistic traits. The result was not statistically significant. However further study has to be done so as to assess whether the language affection is earlier than the other spheres in children due to AED exposure antenatally.

Advantages of the study:

The study was conducted in the setting of an epilepsy and pregnancy registry which had helped us in evaluating the intellectual and language function in children ager 4-7 years and children without exposure to AED in utero. The study was also unique that it looked into the autistic traits in addition to the language and intellectual functions. The language test used was comprehensive covering all the aspect of the language and assessing the children directly rather than through structured interview to parents. Even though previous studies have looked into the intelligence and language functions of CME, this was the first study from KREP, which has also assessed the autistic traits in the children. The cohort had composed of CME, with monotherapy, who were chosen as an initial screening study, in particular, valproate and carbamazepine. The control group was children of WWE who were not on AEDs rather than the general paediatric population. Children were also regularly followed up from the antenatal period onwards with a strict protocol.

Limitations of the study

1.The major limitation of the study was the sample size. Though we intended to include 40 patients in each group, a lower proportion had turned up. The dropout was more evident in the group who were not on AEDs antenatally. Most of the patients in this group were free of AED use for longer period of time and were not coming for regular follow up.

2.The tool used for language assessment selectively evaluates the native Malayalam speaking population and the non-Keralite population had to be excluded from the study.

3.More objective scales for assessment autistic traits could be used to quantify the abnormality.

CONCLUSIONS

Conclusions and Summary

1. We intended to compare the cognitive, behavioural and language function among children with antenatal exposure to carbamazepine, valproate, and no drugs.

2. We used CARS -2 to asses autistic function, MLT and REELS for evaluating language function and VSMS for assessing the behavioural function. There were no significant difference between the three groups with regard to the functions assessed.

3. The subjects in this study were on lower dose of valproate. At lower dose, there is little difference between valproate, carbamazepine and no drug exposed children on CARS -2 scores. This is in contrast to the previous publication, where the dose exposure was high. This could be due to a possibility of dose dependency of VPA with autistic dysfunction. This is in tune with the previously demonstrated dose dependent relation of Valproate with malformation, cognition and language function.

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APPENDIX

1.ABBREVIATIONS:

AED-Anti Epileptic drug

CA-Chronological Age

CARS- Childhood autism rating scale

CBZ-Carbamazepine

CME-Children of mothers with Epilepsy

DQ-Developmental Quotient

ELA-Expressive Language Age

GE-Generalized Epilepsy

IQ-Intelligence Quotient

KREP-Kerala Registry of Epilepsy and pregnancy

MA-Mental age

MLT- Malayalam Language testing

REELS- Receptive and Expressive Emergent Language Test

RLA-Receptive language age

SQ-Social Quotient

VPA-Valproate

VSMS- Vineland Social Maturity Scale

WWE-Women with Epilepsy

2.Proforma

Thesis Proforma

1.Patient identification details- mother

Serial number:
Hospital number:
SCT number
KREP number
Name:
Name of mother:
Name of father:
1.4 Address:
1.5) Phone number: ----------

2. Demographic data- Child

2.1 Age : years
2.2 Sex : 1. Male 2. Female

3.Maternal details:

a) Antenatal details:
i. Birth order of mother :
ii. Previous foetal loss: yes/No
iii. If yes: abortion/ miscarriage/stillbirth/ Others( )
iv. Age at child birth
1. Maternal:
2. Paternal :
v. Maternal complications
1. Antenatal Bleeding : Yes /No
2. PIH- Yes /No
3. GDM- Yes /No
4. Infections- Yes /No
5. Other- specify:
b) Co morbidities
i. Maternal asthma:
ii. Prenatal stressors:

4.Birth history:

a) Term/Preterm :
b) Vaginal delivery /LSCS :
i. Reason for LSCCS :
c) Birth asphyxia Yes /No
d) ICU stay Yes /No
i. Indication
e) Jaundice Yes /No
f) Sepsis Yes /No
g) Seizures Yes /No

5.Details of epilepsy and antiepileptic treatment

3.1 Age of onset of epilepsy(KREP):

Age of onset of first seizure(KREP)

Etiological factors(KREP)

Type of seizure(KREP)

AED and seizure control in past(KREP)

AED and control of seizure in present pregnancy(KREP)

3.2 AED during pregnancy : (KREP)

a) Drug:
b) Dosage:
c) Dose Modification
d)

3.5 Duration of antiepileptic therapy initiation : years

4.Folic acid use:

a) Duration in months before pregnancy:
b) During pregnancy:

5.Child History:

a) DQ assessment at 1 year (KREP)

6.Seizures in child: yes/No

a) IF yes;
i. Febrile seizures-Yes/No
ii. Age of onset:
iii. Syndromic diagnosis:
iv. AED- use Yes/No
1. Drug:
2. Dosage

b) Siblings
i. History of developmental delay
ii. Genetic disease if any
iii. Seizures:
iv.

4.Neuropsychological evaluation

a) Developmental quotient at 1 year of age:

3.CARS – 2 SCORES

	Minimum
Relating to people score	1
imitation	1
Emotional response	1
Body use	1
Object use	1
Adaptation to change	1
Visual response	1
Listening response	1
Taste smell and touch response and use	1
Fear of nervousness	1
Verbal communication	1
Non verbal communication	1
Activity level	1
Level and consistency of intellectual response	1
General impressions	1

3.MLT scores:

	Minimum	Maximum
Semantics	0	10
naming	0	8
Lexical category	0	20
antonymy	0	4
Syntagmatic relation	0	4
Semantic similarity	0	4
Plural forms	0	4
tenses	0	4
PNG markers	0	4
Case markers	0	4
comparitives	0	4
Reading passage	0	10
Reading comprehension	0	4
writing	0	10

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/975/APRIL-2017 19.04.2017

Dr. Sanjeev V Thomas
Professor
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Sanjeev V Thomas,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "ANTENATAL EXPOSURE TO ANTI EPILEPTIC DRUGS AND COGNITIVE, BEHAVIOURAL AND LANGUAGE FUNCTION IN CHILDREN OF WOMEN WITH EPILEPSY (IEC/975)" on 15th April, 2017.

The following documents were reviewed:

1. Covering letter addressed to the Chairperson, IEC, SCTIMST, dated 23.01.2017 with checklist
2. TAC Approval Letter
3. IEC Application Form
4. Project Proposal
5. Patient Information Sheet and Consent Form in English and Malayalam
6. Proforma
7. CV of Principal Investigator and Co- Principal Investigator

The following members of the Ethics Committee were present at the meeting held on 15th April, 2017 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
3.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
4.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
5.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
6.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
7.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
8.	Dr. P. Manickam	BSMS, MSc (Epid)., PhD.,	Male	Health Science Expert/ Social Scientist	No
9.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
10.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
11	Dr.Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
12.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

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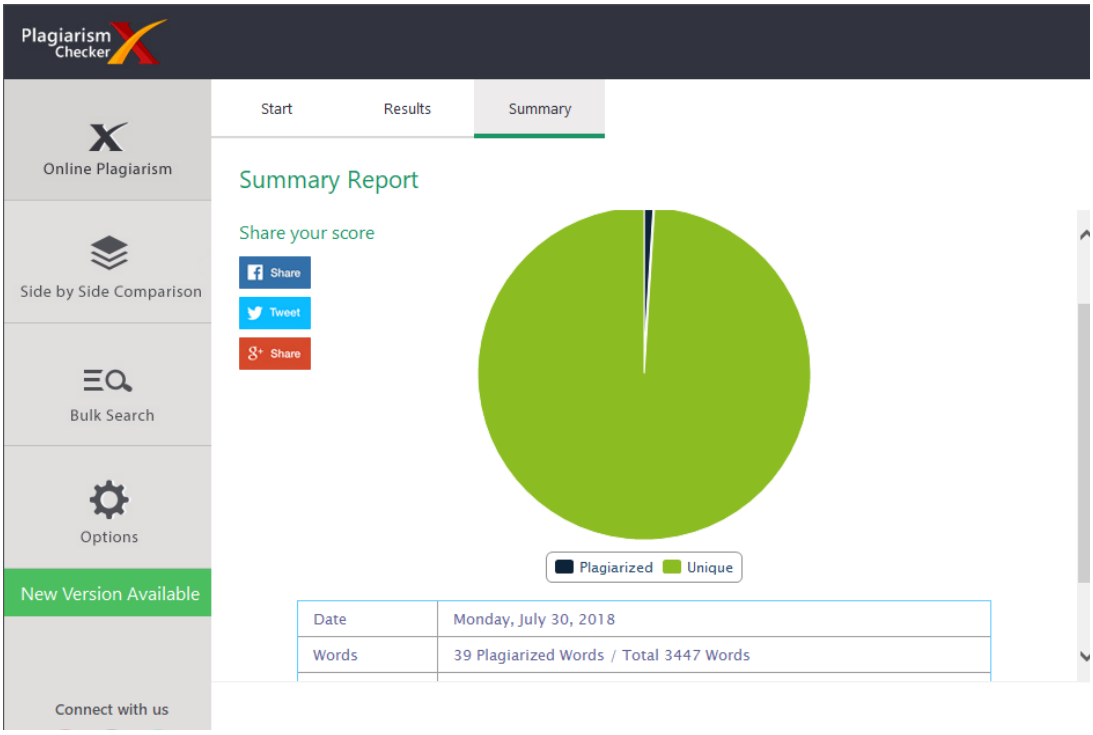
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