SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

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PROJECT REPORT

NAME : **Dr. SAJITH. S**

PROGRAM : **DM (NEUROLOGY)**

MONTH AND YEAR OF SUBMISSION : **NOVEMBER 2005**

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Intellectual and Language Functions in Children of Mothers with Epilepsy

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CERTIFICATE

I, Dr. Sajith. S hereby declare that I have actually carried out the project under report.

Place: Thiruvananthapuram

Signature:

Date: 29-10-05

Dr. Sajith. S

Forwarded. He has carried out the project under report.

Signature:

Prof (Dr). K. Radhakrishnan

Head of The Department

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I express my gratitude towards all children and their parents who took part in this study.

Dr.Sajith. S

CONTENTS

Introduction

INTRODUCTION

There are about 2.5 million women with epilepsy in India; half of them are in the reproductive age group. Women with epilepsy tend to get married almost as frequently as others but experience several problems related to epilepsy, pregnancy and health of their children[1]. They may have more abortions, smaller family size and increased frequency of infertility. Their offspring are at increased risk of congenital malformations and developmental delay. Health status of infants of mothers with epilepsy had been the focus of scientific scrutiny for several decades in the past. Extensive data had been compiled through national and international registries of pregnancy in women with epilepsy. There is considerable evidence that in utero exposure to antiepileptic drugs (AEDs) increases the incidence of major malformations in the offspring. Maternal epilepsy or its treatment may lead to other subtle and delayed effects on the infants such as delayed cognitive development that need further evaluation.

Normal growth and development

Growth and development represent two different aspects of the dynamic changes that happen from fertilization until maturity. Growth refers to the quantitative changes while development denotes the qualitative changes, particularly acquisition of new functionality. The various factors affecting growth and development can be broadly divided into intrinsic and extrinsic factors. Intrinsic factors include parental genotypic traits and other genetic factors, parental intelligence quotient, sex of the offspring etc. Extrinsic factors include maternal nutrition, medical illness particularly antenatal infections and exposure to teratogens such as radiation, chemicals, drugs and toxins. In the postnatal period, different biological functions are acquired at predetermined stages with some physiological variations. Several psychosocial and environmental factors are likely to influence development after birth. These aspects need careful consideration while assessing growth and development of infants.

Neuropsychological Tests and Methodological issues

There are several methodological issues that need to be reconciled with while interpreting data on development of children born to mothers with epilepsy. In the early stages it is difficult to ascertain subtle impairments, unless detailed neuropsychological test batteries are employed. Several confounding factors such as psychosocial and economic environment may modify the neurodevelopment in the subsequent period to the extent that it is difficult to attribute any impairment to antenatal exposure to AEDs alone.

A variety of scales have been developed to assess development of children at different ages. (See table.1 in Appendix). Test batteries employed by different groups vary depending upon the age of the children and the specific developmental aspect that is addressed. Each test has its own strengths and weaknesses. It is important that only tests that are standardized on the specific age group and regional population are adopted in such studies.

Review of Literature

REVIEW OF LITERATURE

The effects of epilepsy and AEDs on the offspring can be broadly classified in to physiological, anthropometric, minor anomalies, major malformations and late developmental effects. One of the earliest reports on the effect of AEDs on the fetus was by Janz et al in German language.[2] This was soon followed by a detailed report on the teratogenic effect of AEDs by Meadow.[3] They had in a subsequent report raised the possibility of mental subnormality due to AEDs.[4]Increased infant mortality[5,6] and low birth weight[7,8] were reported in the subsequent years. However, developmental problems of infants of mothers with epilepsy (IME) were recognized only recently.

Controversies

The earliest reports on the effect of AEDs on the cognitive outcome of IME were based on retrospective case series. In 1972 Speidel and Meadow found mental retardation in 1.5% of 427 children of mothers with epilepsy compared 0.2% of controls.[4] Several other groups also have demonstrated similar changes.[6, 9] On the contrary, Steinhausen and co-workers[10] in 1982 found no impairment in intelligence, visual perception of psycholinguistic abilities in 19 children of mothers with epilepsy when compared with general population standards. Delay in development of IME raised the issue, whether there were confounding factors such as low IQ of parents, peri-natal insults, or poor psychosocial environment. The chronological age of the child at the time of evaluation is also likely to

influences the findings. Janz[11] had demonstrated that children of mothers with epilepsy had early developmental delay but had caught up with peers by school age. Though inconclusive, suggestion of developmental delay was noted in other earlier studies. [12,13,14,15,16,17]

After 1990 the issue of psychomotor developmental delay due to in utero AED exposure was addressed in about 15 studies, two third of them were prospective studies (see table 2 in Appendix).

Early development under one year of age

The infant attains a certain level of motor, language and other skills by the end of one year. In a prospective study by Leavitt et al[18] (1992) involving 43 exposed children with 41 controls, there was no significant difference in growth parameters at 12 months of age. Their assessment using Bayley scale showed significantly low (p=0.017) mental development index (MDI) in exposed children (MDI =113) when compared to controls (MDI =119), denoting low cognitive skills in the exposed children. There was no significant difference in the psychomotor development index (p=0.325), which measures functional motor competence and locomotor skills. Further analysis showed that the MDI was lowest for infants exposed to polytherapy (MDI=108) when compared to monotherapy (MDI=116). These differences were statistically significant. The MDI for infants exposed to phenytoin and phenobarbitone monotherapy were 113 and 115 respectively while for carbamazepine monotherapy it was 122. Their data suggest that these infants have the potential risk of mental rather than motor developmental

delay, which is more marked for polytherapy and for phenobarbitone and phenytoin. However, the numbers were small to make any definitive conclusions.

However Wide et al[19] in a prospective population based study failed to demonstrate developmental delay in exposed infants (n=100) in comparison to unexposed matched control (n=100) infants at 9 months of age. Their test battery (Griffiths' test) consisted of 6 subsets: locomotor function, personal and social behavior, hearing and speech, eye and hand coordination, performance, and practical reasoning. Though the exposed infants had significant increase (31 compared with 18 control children; odds ratio 2.4, CI 1.15 to 5.02, P=0.02), in the number of minor anomalies (a marker of AED effect on structural development) there was no influence on the Griffiths' score. In the exposed cases, minimum possible number of AEDs in the lowest possible dose was used during pregnancy and drug levels were monitored on a monthly basis. They concluded that with meticulous AED treatment strategy during pregnancy, short-term psychomotor development may be spared but the increased risk for minor anomalies cannot be eliminated.

In a preliminary study from SCTIMST, the development of infants at one year of age, Thomas S V et al had observed mild impairment in mental and motor development for the exposed group when compared to controls. In this study[20], 84 exposed infants were compared with equal number of controls on DASII (Development Assessment Scale in Indian Infants), a scale based on Bayley's Scale of Infant Development. The mean mental

and motor development quotients (MODQ & MEDQ) of the cases were 99.79 ± 32.82 and 90.33± 38.59 respectively. The corresponding figures of controls were 119.54 ± 32.73 and 116.00 ± 33.46 respectively Thus mental and motor development of cases appeared to be significantly compromised (p= 0.003 and 0.001 respectively) compared with the controls.

Development between 1 to 3 years

Various studies have documented psychomotor delay in AED exposed children well beyond the first year of life. Parisi et al in 2003[21]prospectively followed up AED exposed children of born to women with epilepsy (n=11) until 30 months of age. The children were assessed using general movement observation (GM) at 1, 4 and 13 weeks, traditional neurological examination at 1, 4 and 13 weeks and then at 6, 9 and 12 months and Brunet- Lezine test at 30 months. They observed psychomotor retardation in the exposed children in all the test modalities. They also found that GM at 4 weeks was predictive of psychomotor impairment and performance on Brunet- Lezine test at 30 months. However the small number of index cases makes it difficult to draw meaningful conclusions.

In a study from SCTIMST, Thomas SV et al had examined the expressive and receptive language development according to REELS test battery at the age of 30 to 36 months in a cohort of children exposed antenatally to AEDs (n=75) and compared it with a control group (n=130) matched for age and socio economic background (unpublished data). This comparison failed to demonstrate any significant language impairment for

the exposed cohort. The cases were the follow up cohort of those who were examined at one year of age. Majority (14) of the subgroup with MEDQ less than 25th centile at one year age (n=18) had caught up in language development in the next two years and had REEL score comparable to others with higher MEDQ.

Development between 3 and 6 years

Wide and co workers in 2002[22] assessed the psychomotor development in AED exposed (in utero) and non-exposed preschool children at 4 ½ - 5 years of age (67 exposed and 66 unexposed children). The two groups had similar socio economic status except for a slightly lower level of education in the AED treated mothers. The study could not demonstrate any difference in global scores of Griffith test between the two groups. However children exposed to phenytoin (n=16) showed a significant but subtle reduction in the scores of locomotor function compared with the unexposed children (mean scores: 98 vs. 106: 95% confidence interval for the difference in mean scores: -14.0 to -0.4). There was no such difference in children exposed to carbamazepine (n=35). It appears that different AEDs may possibly have differential effect on psychomotor outcome of exposed infants and children.

Intellectual performance at five and half years of age was studied by Gaily et al in 1988[23].Their study group comprised of 148 children born to epileptic mothers enrolled in a prospective study during pregnancy, and 105 control children. The intelligence parameters of all but a few children were

assessed by both verbal (WPPSI- Wechsler Preschool and Primary Scale of Intelligence) and nonverbal (Leiter International Performance Scale) methods. Thirty-two study children were assessed on the basis of psychological tests done outside the study, or school achievement, or both. Of the 148 study group children, 131 had been exposed in utero to antiepileptic drugs. The study group had significantly lower intelligence quotient than the control group. But fetal exposure either to antiepileptic drugs below toxic levels or to brief maternal convulsions did not appear to be associated with poor outcome. In a subsequent report, this group in 1990 [24] had described specific cognitive abilities and motor functions at 5.5 years in 104 children with epileptic mothers and in 105 control children. Majority (89 per cent) of children born to mothers with epilepsy were exposed to anti-epileptic drugs during pregnancy, most commonly phenytoin. They found a significant difference, with poorer performance in the study group, on block design (WPPSI). But the subgroup analysis showed that low scores on block design correlated with maternal seizures during pregnancy and low maternal education rather than with AED exposure. This observation is in contrast to their earlier observations. The effect of parental IQ and socioeconomic status needs further evaluation.

Late development beyond 6 years

Mental development and acquisition of higher cognitive functions continue into late childhood in human beings. Several groups have examined the late developmental consequences of exposure to AEDs during antenatal period. But earlier studies did not control for socio

economic status or parental intelligence. Adab et al[25] in 2001 compared the language development in children (aged 4 –18 years) exposed in utero to AEDs with that of control children and found that monotherapy or polytherapy with valproate during pregnancy carried particular risks for additional educational needs.

Similarly Gaily et al[26] in 2004 observed a differential impact of in utero AED exposure on the cognitive outcome. They assessed the intelligence of 182 children of mothers with epilepsy (study group) and 141 control children of non-epileptic mothers matched for socioeconomic class, age and parity in a blinded setting at preschool or school age. The mean age of the study and the control children were 7.0 and 7.4 years respectively. The neuropsychological examination included assessment of Verbal, nonverbal, and full-scale IQs using six subtests (Information, Arithmetic, Similarities, Picture Completion, Block Design, and Animal Houses/Picture Arrangement) of Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (children aged <6 years) or Wechsler Intelligence Scale for Children-Revised (WISC-R) (aged 6 years). One hundred seven children were exposed to monotherapy: 86 to carbamazepine and 13 to valproate and 30 children were exposed to polytherapy: The mean verbal and nonverbal IQ scores in the children exposed in utero to carbamazepine monotherapy were 96 and 103 which did not differ from control subjects (95 and 102 respectively). On the other hand, children exposed to valproate or polytherapy had significantly reduced mean verbal IQ scores (82 and 85) compared with the rest in the

study group and control subjects. Carbamazepine monotherapy with maternal serum levels within the reference range had a more favorable verbal intelligence outcome when compared to valproate or polytheray. Data was insufficient to comment on other drugs.

Similar long-term neuropsychological consequences were observed in a prospective study by Koch [27]et al (1999). Sixty seven school age and adolescent children born to mothers with epilepsy (no drugs during pregnancy (n=13), monotherapy (n=31), polytherapy (n=23) and 49 control children were assessed using an intelligence test (Wechsler), a neurological examination and an EEG. Data analysis was controlled for parental social status, type of maternal drug therapy and dosage, and type and frequency of epilepsy. They found that type of maternal epilepsy and the kind of AED exposure had long-term neuropsychological consequences in terms of abnormal EEG patterns, low intellectual performance and minor neurological dysfunction. Maternal seizures during pregnancy did not correlate with abnormal EEG patterns. The adverse neuropsychological effects were least when not exposed to AEDs and worsened from monotherapy to polytherapy groups. The lowest scores were observed with polytherapy containing primidone.

Dean and colleagues[28] in a population based retrospective study in 2002 showed significant impact on cognitive outcome following AED exposure in utero. The study group comprised of 149 mothers and their 293 children. 144 mothers had epilepsy and 5 others took AEDs for other indications. 255 children had in utero exposure to AEDs and their 38

siblings were not exposed to AEDs (in 16 cases, the mother had epilepsy but took no treatment and in 22 the child was born before epilepsy developed). The children ranged in age from 2 days to 39 years. Developmental delay was classified as speech delay, motor delay or global delay. Those with apparently normal preschool developmental history, but special educational needs were classified as having a school age learning disorder. Comparing the neurodevelopmental outcomes in AED exposed and non-exposed siblings (after adjusting for family history of developmental delay) they found a developmental delay 19% for the study group and 3% for the control group. Monotherapy with carbamazepine, valproate, phenytoin and polytherapy were associated with significant ($p=0.001$) developmental delay. Surprisingly, phenobarbitone did not show similar effect. Speech delay was common following exposure to valproate (29%) or carbamazepine (22%) monotherapy and to polytherapy (23%). The frequency of global delay was highest in the polytherapy group. For the carbamazepine-exposed group, there was a correlation between maternal AED levels and developmental delay.

Exposure to phenobarbitone in nonepileptic mothers can lead to long term effects on cognitive performance in the offspring as shown by Reinisch [29]and colleagues. Last trimester exposure and low socio economic status were found to magnify the negative outcomes.

Special educational problems

The requirement for additional educational needs (AEN) probably indicates long-term neuropsychological adverse outcome. Adab et al in 2001 studied AEN in children exposed to antiepileptic drug in utero. They retrospectively collected data from 330 women who had given birth to at least one live-born child. Information was collected on 594 children, 400 of whom were of school age (4-18). 150 (37.5%) had been exposed to monotherapy in utero, 74 (18.5%) were exposed to polytherapy, and 176 were not exposed to any AEDs. The odds ratio of AENs for all children exposed to AEDs in utero compared with those unexposed was 1.49. Odds ratios for AENs for each therapy subgroup compared with those unexposed were- 3.4 for valproate monotherapy, 0.26 for carbamazepine monotherapy, 2.51 for polytherapy including valproate and 1.51 for polytherapy excluding valproate. This shows the differential impact of various AEDs on the long-term cognitive outcome following in utero exposure.

Thus most of the available literature shows evidence for impairment in various domains of development. However well structured prospective studies, recruiting adequate number of cases and specifically addressing both intelligence as well as language functions are largely lacking. The present study is an attempt for the same, keeping the confounding factors at the least possible level.

Objectives

OBJECTIVES

1) To assess the intellectual and language functions in children of mothers with epilepsy, at 6 years of age and

2) To compare with controls matched for age, sex and socio economic status.

Material and Methods

MATERIAL AND METHODS

Setting

Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, is Tertiary care centre for Neurology in South India. R Madhavan Nair Centre for Comprehensive Epilepsy care under the department of Neurology provides specialized care to patients with epilepsy. The Kerala Registry of Epilepsy and Pregnancy (KREP), which was started under the same in 1998, caters to women with epilepsy, who are in the reproductive age group and provides neurological care, with special emphasis during pregnancy, counseling and regular systematic follow up of these patients and their offspring. There are about 700 mothers covered till 2005 under this registry. In the year 2004-05 there were about 100 children aged 6-61/2 years, under follow up.

Design

Prospective controlled study, enrolling these children, with detailed neuropsychological and language evaluation and comparing the results with controls from the general population, matched for age, sex and socioeconomic status. Study was done during 2004 – 05.

Cases

Children (of mothers with epilepsy) aged 6-61/2 years; followed up under Kerala Registry of Epilepsy and Pregnancy (KREP) constituted the cases. The diagnosis of epilepsy in mothers was made by reviewing data obtained from hospital charts on seizure phenomenology, EEG, etiologic

studies including neuroimaging, past and present medication, and family history. All mothers (of cases) were confirmed to have epilepsy that was classified according to the proposal for revised classification of epilepsies and epileptic syndromes [34].

Inclusion criteria

1) Maternal epilepsy diagnosis antedating pregnancy , irrespective of AED exposure status.
2) Age of offspring 6- 6 ½ years
3) Infant under study should have been prospectively followed up under the KREP from pregnancy until the time of study.

Exclusion criteria

1) Any acquired neurological disorders in infancy or childhood.

Most of the children belonged to middle socioeconomic families. All study children at the age of 6- 61/2 years and their parents were invited by letter to participate in the study. A second invitation was sent to those who failed to answer the first letter.

Controls

Children, matched for age and socioeconomic status were selected randomly from local schools in Trivandrum. Different category of schools, private sector schools catering mainly to children belonging to middle/upper middle class and Government sector schools catering to low middle/low socioeconomic class were selected.

Inclusion criteria

1) Age 6- 6 ½ years

Exclusion criteria

1) History of maternal epilepsy.
2) Any acquired neurological disorders in infancy or childhood.

All controls and cases underwent detailed clinical examination in addition to neuropsychological and Language tests. These were administered by Neurologist, Child psychologist and Language expert respectively.

Outcome Measures

The cognitive evaluation - Intelligence and Language - are tested in detail. The Performance IQ, Verbal IQ, Full scale IQ and different language functions were assessed employing appropriate tests.

Neuropsychological and Language tests

The neuropsychological examination was done in a single session lasting 1.5 to 2 hours. The neuropsychologists were blinded to the drug exposure status. Verbal, nonverbal, and full-scale IQs were estimated using MISIC- Malin's Intelligence Scale for Indian Children (Indian adaptation of Wechsler Intelligence Scale for Children -WISC by Dr. Arthur J. Malin)[32]. MISIC is well validated and accepted and in use for the last 20 years. It includes subtests for assessing Verbal and Performance IQ from which the Full scale IQ (FIQ) is calculated. The following are the various subtests that are used.

Verbal Tests

1. Information
2. Comprehension
3. Arithmetic
4. Similarities
5. Vocabulary
6. Digit span

Performance tests

1. Picture completion
2. Block design
3. Object assembly
4. Coding
5. Mazes

Language Test (LT)

The Language test battery used was adapted from Language Proficiency Test (LPT) developed from All India Institute of Speech and Hearing, Mysore[33] and was standardized with normative data on 200 subjects from Trivandrum. The different Language domains tested include

1. Semantics
2. Semantic similarity
3. Naming
4. Lexical category
5. Antonymy
6. Syntagmatic relations
7. Plural forms
8. Tenses
9. PNG (Plural, Noun and Gender) markers
10. Case markers
11. Comparatives
12. Reading
13. Reading comprehension
14. Writing

Statistical Methods

STATISTICAL METHODS

Outliers in each category (two cases and one control) were excluded statistically taking IQR (Inter Quartile range) into consideration. ANOVA was used for analysis of the data using the SPSS statistical package. p Values <0.05 were considered significant.

Results

RESULTS

A total of 40 cases and 201 controls were enrolled. Outliers (two cases and one control) were excluded statistically. Data on 38 cases (26 males and 12 females) and 200 controls (86 males and 114 females) was analysed. The following is the data on AED intake and seizure characteristics during pregnancy. Among the 38 cases, 37 had in utero AED exposure - 28 to monotherapy and 9 to polytherapy. The individual drug exposure (number of cases) in the monotherapy group was 9, 8, 6, 3 and 2 for valproate, carbamazepine, phenobarbitone, phenytoin and other drugs respectively.

Seizure characteristics

Idiopathic generalized epilepsy was diagnosed in 14 mothers. Sixteen mothers had localization related (partial) epilepsy. Epilepsy was confirmed but could not be classified in 8 mothers.

Seizures during pregnancy

Partial/generalized maternal seizures had occurred during gestation in 18 participating children while 12 did not. None of the mothers had status epilepticus during pregnancy.

Performance IQ

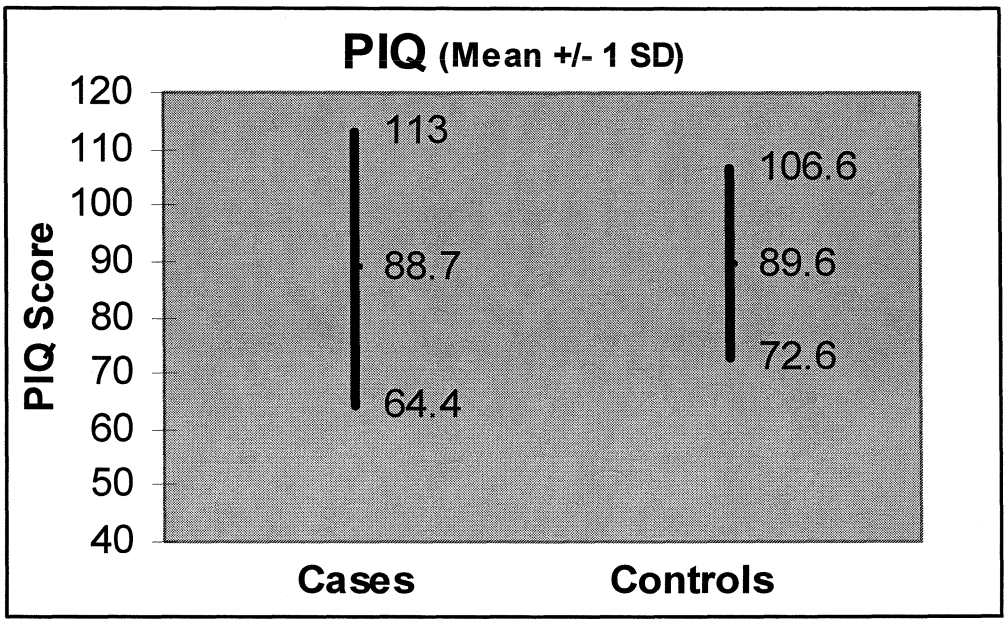
The mean Performance IQ (PIQ) was lower for the cases (Mean ± SD were 88.7 ± 24.3 and 89.6 ± 17 for cases and controls respectively) However the difference was not statistically significant (p= 0.8).

PIQ subtest analysis showed statistically significant lower scores for the coding subtest (79.3 ± 22.3 Vs 87.9 ± 10.4, $p < 0.001$). No significant difference was noted in case of other PIQ subtests (See Table.1)

Table.1

Performance IQ

Subtest	**Case** Mean score (SD)	**Control** Mean score (SD)	p value
Picture Completion	90.9 (20.3)	86.5 (21.9)	0.2
Block design	89.4 (36.0)	89.5 (26.9)	1.0
Object Assembly	83.6 (37.0)	85.5 (21.5)	0.7
Coding	79.3 (22.3)	87.9 (10.4)	<0.001
Mazes	97.2 (39.9)	99.3 (39.7)	0.8
Composite PIQ Score	**88.7 (24.3)**	**89.6 (17.0)**	**0.8**



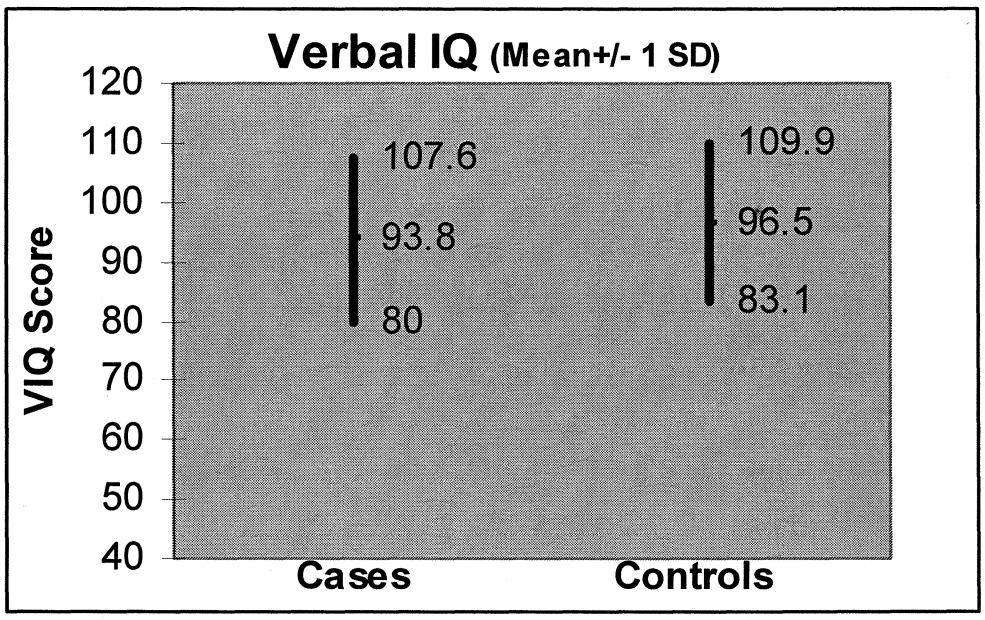
Verbal IQ

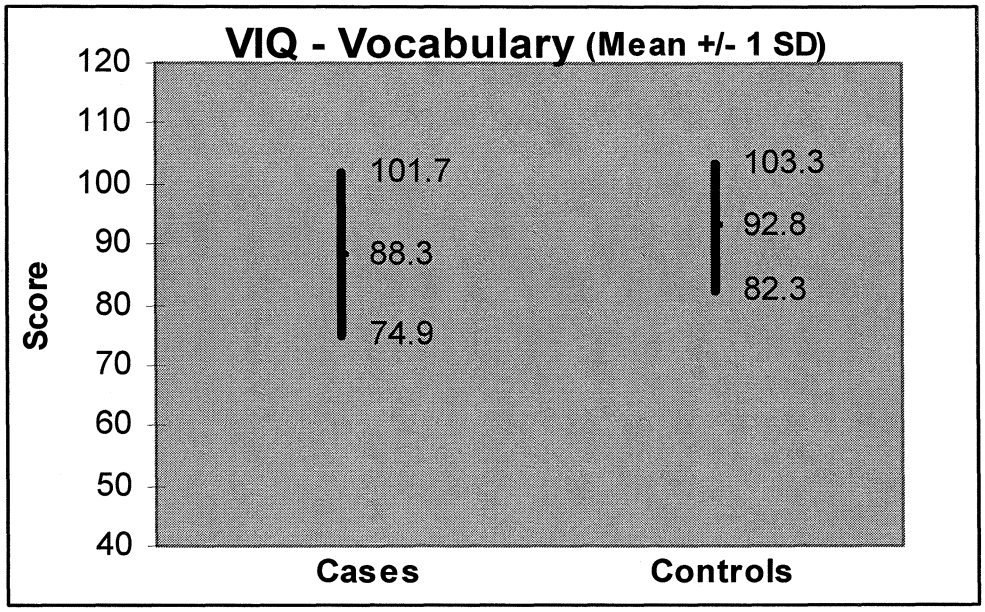
Mean Verbal IQ (VIQ) was lower for cases, however not reaching statistical significance (93.8± 13.8 Vs 96.5 ±13.4, p= 0.2). However, statistically significant poor performance noted in two VIQ subtests namely vocabulary and digit span (see table.2). Other subtests did not show any statistically significant difference.

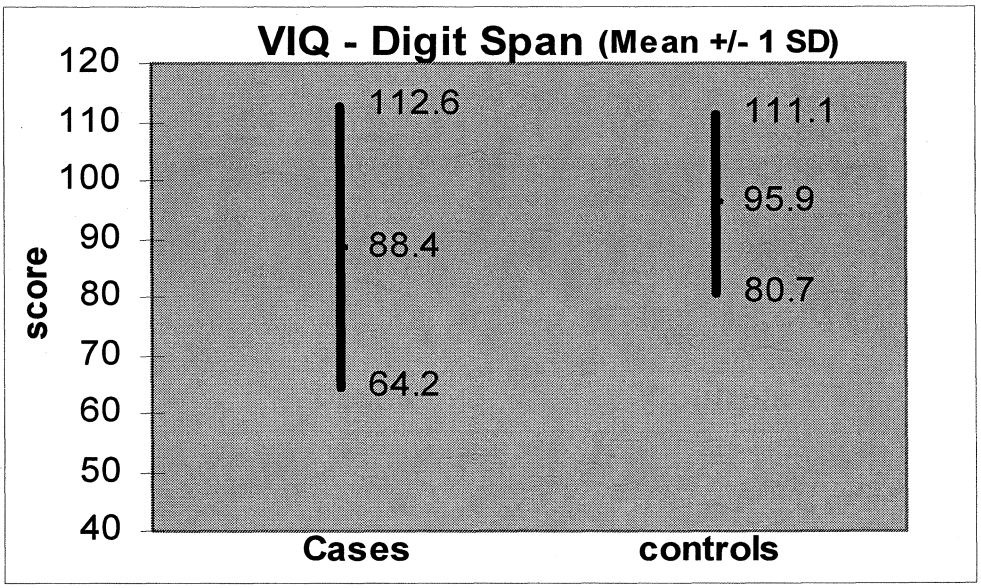
Table.2

Verbal IQ

Subtest	**Case** Mean score (SD)	**Control** Mean score (SD)	p value
Information	91.9 (14.9)	94.8 (13.4)	0.2
Comprehension	96.7 (18.3)	94.5 (26.8)	0.6
Arithmetic	94.7 (21.4)	96.4 (19.0)	0.6
Similarities	106.8 (34.3)	103.2 (31.3)	0.5
Vocabulary	88.3 (13.4)	92.8 (10.4)	0.02
Digit span	88.4 (24.2)	95.9 (15.2)	0.01
Composite VIQ Score	**93.8 (13.8)**	**96.5 (13.5)**	**0.2**




VIQ - Vocabulary (Mean +/- 1 SD)
120
110
100
90
80
70
60
50
40
Score
101.7
88.3
74.9
103.3
92.8
82.3
Cases
Controls


VIQ - Digit Span (Mean +/- 1 SD)
120
110
100
90
80
70
60
50
40
score
112.6
88.4
64.2
111.1
95.9
80.7
Cases
controls

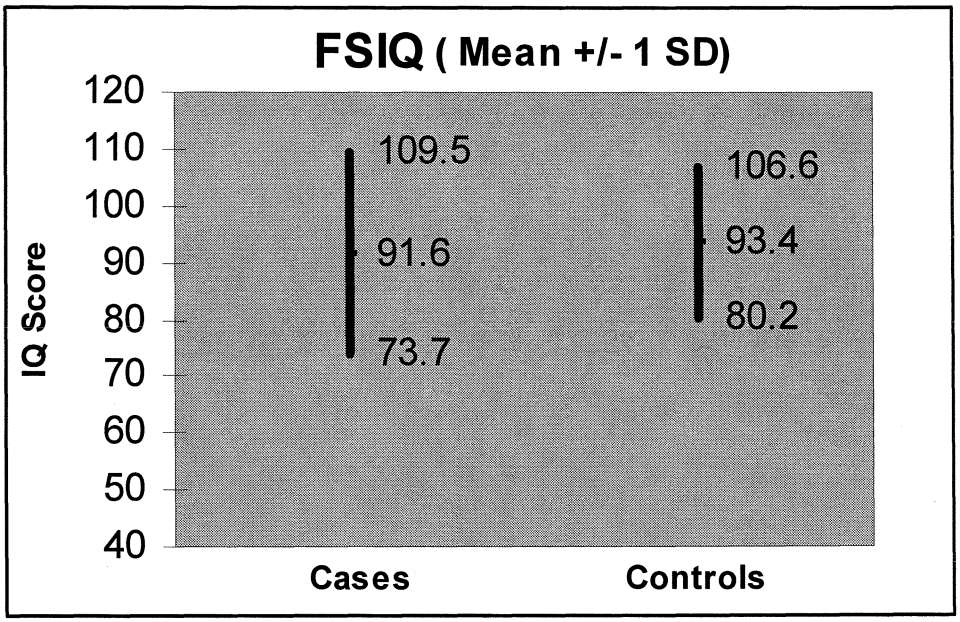
Full scale IQ

The lower mean Full scale IQ noted for cases was not statistically significant (Mean score 91.5 and 93.4 with SD 17.9 and 13.2 for cases and controls respectively, p=0.4).

Table.3

Composite IQ Scores

	Case Mean score (SD)	**Control** Mean score (SD)	p value
PIQ	88.7 (24.3)	89.6 (17.0)	0.8
VIQ	93.8 (13.8)	96.5 (13.5)	0.2
Full Scale IQ	91.6 (17.9)	93.4 (13.2)	0.4



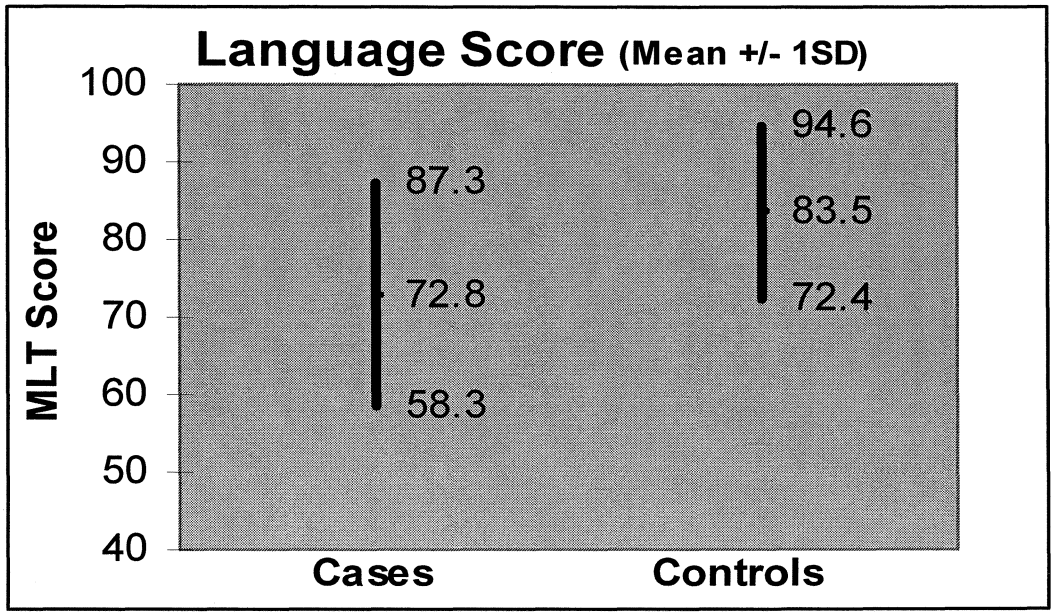
Thus sparing a few subtests, there were no statistically significant difference in PIQ, VIQ or FIQ scores between cases and controls.

Most striking difference was in the language functions as evidenced by statistically significant lower scores obtained by the cases in all language subtests (except coding) and composite language scores (see Table 4).

Table 4

Language scores

Subtest	**Case** Mean score (SD)	**Control** Mean score (SD)	p value
Semantics	9.2 (1.7)	9.8 (0.8	0.001
Semantic similarity	3.8 (0.7)	4.0 (0.3)	0.01
Naming	8.0 (0.0)	8.0 (0.2)	0.6
Lexical category	18.2 (3.5)	20.0 (2.0)	0.001
Antonymy	3.5 (0.7)	3.8 (0.5)	0.003
Syntagmatic relations	3.6 (0.7)	3.8 (0.4)	0.002
Plural forms	3.4 (1.0)	3.8 (0.5)	<0.001
Tenses	3.5 (0.8)	3.8 (0.4)	0.002
PNG markers	3.6 (0.7)	3.9 (0.3)	<0.001
Case markers	3.5 (0.7)	3.9 (0.3)	<0.001
Comparatives	3.7 (0.5)	3.9 (0.3)	<0.001
Reading	4.1 (4.2)	6.9 (3.9)	<0.001
Reading comprehension	1.3 (1.8)	2.4 (1.8)	0.001
Writing	3.3 (3.8)	5.8 (3.8)	<0.001
Composite score	**72.8 (14.5)**	**83.5 (12.3)**	**<0.001**


Language Score (Mean +/- 1SD)
MLT Score
100
90
80
70
60
50
40
87.3
72.8
58.3
94.6
83.5
72.4
Cases
Controls

No statistically significant difference was noted in VIQ, PIQ, FIQ or composite language scores when monotherapy Vs polytherapy or individual drug exposure Vs rest of the monotherapy as a whole were compared. Due to small number of cases with individual drug exposure, the comparison between different monotherapy subgroups was not done.

Table 5

Monotherapy Vs Polytherapy

	Monotherapy	**Polytherapy**	**p value**
PIQ Mean (SD)	88.9 (26.5)	88.4 (19.0)	0.9
VIQ Mean (SD)	94.8 (14.1)	92.5 (13.1)	0.7
FIQ Mean (SD)	92.1 (19.0)	90.8 (15.6)	0.8
Language score Mean (SD)	72.4 (15.2)	74.6 (13.3)	0.7

Exposure to maternal seizures during pregnancy was not associated with reduced intelligence or language scores.

Table 6

Maternal seizures Vs no seizures in pregnancy

	No seizures in pregnancy	**Seizures in pregnancy**	**p value**
PIQ Mean (SD)	93.6 (19.4)	83.3 (28.3)	0.2
VIQ Mean (SD)	94.9 (12.5)	92.7 (15.4)	0.6
FIQ Mean (SD)	94.5 (15.0)	88.3 (20.5)	0.3
Language score Mean (SD)	71.9 (14.7)	73.7 (14.5)	0.7

Discussion

DISCUSSION

This prospective study was conducted to evaluate the long-term cognitive functioning in children of mothers with epilepsy. This was achieved by assessing their intellectual and language functions at a specified age and comparing with matched controls without maternal epilepsy.

The present study included more children belonging to a particular age group than any other similar study. It was also unique in that detailed evaluation of different domains of IQ and language functions were tested together. The language test battery used was comprehensive and was adapted to the regional population and included subtests for testing various language domains in detail. Similarly the Intelligence test was also adapted for the Indian settings. The age selected for study also appeared appropriate as the cognitive functions are more reliably tested at preschool to school age than a younger age. [13, 16]

When selected cognitive functions were investigated, it was found that there was no statistically significant difference in PIQ, VIQ or FIQ (except a few subtest especially in verbal IQ) between cases and controls. The significant poor performance in Vocabulary and Digit span subtests of VIQ could suggest impairment in language functions.

Lower Intellectual performance for children of mothers with epilepsy at five and half years of age was previously reported Gaily et al in 1988[23]. However in a subsequent study, the same author[26] observed a differential

impact of various AEDs on intelligence, with impairment in those exposed to valproate and polytherapy, while those exposed to carbamazepine having normal performance. Differential drug effect was not analysed in the present study.

Some previous studies have reported that prenatal AED exposure is associated with impaired verbal functioning.[23, 25, 35, 36] However most of them derive conclusions from the data on performance on Verbal IQ tests rather than employing a comprehensive language test battery. Other evidences of probable language impairment was noted by Dean and colleagues[28] and Adab et al[25]. The former group noted a delay in speech while the latter showed the need for additional educational needs especially after valproate exposure.

In the present study, a comprehensive language test battery was used rather than depending on VIQ subtests. It was shown that there could be a striking impairment in language functions when compared to controls. The poor performance by the cases in almost all sub domains of language subtests had amply confirmed this aspect. The only remaining subtest (naming) showed an equal performance by both groups.

Thus children of mothers with epilepsy showed a selective cognitive dysfunction in language, in spite of the absence of any significant differences in Intelligence Quotient. However, the effect of individual drugs

could not be evaluated properly due to the small number of cases in each group.

Because language functions develop postnataly, their impairment perhaps denote a " functional teratogenic effect" that disturbs the in utero formation of neural substrate needed later for the development verbal abilities. The development of language and general verbal functions has significant implications for the child, particularly in respect to general learning processes where a substantial amount of information particularly in the early years is verbally mediated. The development of language skills is also an important prerequisite to social integration and a delay may hinder a child's social development.

As in some of the previous studies, [23,26] we could not find any effect of brief maternal seizures in the prenatal period on cognitive development in the offspring. Nevertheless prolonged maternal seizures or status epilpeticus were not encountered in our study.

Although the study had a comprehensive test methodology, it is not without its limitations. There is a potential bias because of the possibility that those parents with children having developmental difficulties answered our letter more readily than those who had not. The study would have benefited from having information on parental educational level, paternal/maternal IQ, breast feeding (which could potentially result in continued AED exposure to the offspring postnatally) etc.

Despite these limitations, the results show that children of mothers with epilepsy have a significant and rather selective impairment of language functions. Further large-scale prospective studies are needed in order to adequately quantify the adverse cognitive effects of specific AEDs on selective cognitive functioning.

Conclusion

CONCLUSION

This study shows significant and rather selective impairment of language functions in children of mothers with epilepsy, even when their IQ was comparable to those children without maternal epilepsy. It appears that children of mothers with epilepsy have high risk of impaired language development. The specific role of AEDs in this regard needs further evaluation.

Reference

REFERENCE

1. Thomas SV, Deetha TD, Kurup JR, Reghunath B, Radhakrishnan K, Sarma PS. Pregnancy among women with epilepsy. Ann Indian Acad Neurol. 1999; 2: 123-128.

2. Janz D, Fuchs U. Sind antiepileptische Medikamente während der Schwangerscht schädlich? Dtsch. Med. Wschr., 1964, 89: 241-243.

3. Meadow SR. Anticonvulsant drugs and congenital abnormalities. Lancet 1968: 2: 1296.

4. Speidel BD, Meadow SR. Maternal epilepsy and abnormalities of the fetus and newborn. Lancet. 1972; 2(7782): 839-43.

5. Bjerkedal T, Bahna SL. The course and outcome of pregnancy in women with epilepsy. Acta Obstet Gynecol Scand. 1973; 52: 245-8.

6. Nelson KB, Ellenberg JH. Maternal seizure disorder, outcome of pregnancy, and neurologic abnormalities in the children. Neurology. 1982; 32: 1247-54.

7. Annegers JF, Elveback LR, Hauser WA, Kurland LT. Do anticonvulsants have a teratogenic effect? Arch Neurol. 1974; 31: 364-73.

8. Svigos JM.Aust N Z. Epilepsy and pregnancy. J Obstet Gynaecol. 1984; 24: 182-5.

9. Hill RM, Verniaud WM, Horning MG, McCulley LB, Morgan NF. Infants exposed in utero to antiepileptic drugs. A prospective study. Am J Dis Child. 1974; 127: 645-53.

10. Steinhausen HC, Nestler V, Huth H. Psychopathology and mental functions in the offspring of alcoholic and epileptic mothers. J Am Acad Child Psychiatry. 1982; 21: 268-73.

11. Beck-Mannagetta G, Janz D. In Janz D, Dam M, Richens A et al. Data on psychomotor and mental development in children of epileptic parents: a retrospective study. Epilepsy, Pregnancy and the child. New York: Raven Press, 1982:443-45.

12. Jones KLJ, Lacro RV, Johnson KA, Adams J. Pattern of malformations in the children of women treated with carbamazepine during pregnancy. N Eng J Med 1989; 320:1661–6.

13. Nulman I, Scolnik D, Chitayat D, Farkas LD, Koren G. Findings in children exposed in utero to phenytoin and carbamazepine monotherapy: independent effects of epilepsy and medications. Am J Med Genet 1997; 68:18–24.

14. Scolnik D, Nulman I, Rovet J, Gladstone D et al. Neurodevelopment of children exposed in utero to phenytoin and carbamazepine monotherapy. JAMA 1994; 271:767–70.

15. D'Souza SW, Robertson IG, Donnai D, Mawer G. Fetal phenytoin exposure, hypoplastic nails, and jitteriness. Arch Dis Child 1990; 65:320–4.

16. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. Arch Dis Child 1996; 75:517–20.

17. Perniola T, Buttiglione M, Margari L. Antiepileptic drugs in pregnancy: late effects on the children's cognitive abilities. Preliminary data. Acta Neurol (Napoli). 1992; 14: 543-6.

18. Leavitt AM, Yerby MS, Robinson N, Sells CJ, Erickson DM. Epilepsy in pregnancy: developmental outcome of offspring at 12 months. Neurology. 1992; 42 (Suppl 5): 141-3.

19. Wide K, Winbladh B, Tomson T, Sars-Zimmer K, Berggren. Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero:a prospective population-based study. Dev Med Child Neurol. 2000; 42: 87-92.

20. Thomas SV, Nair MK, George B, Prasanna GL et al. Motor and mental development of infants of mothers with epilepsy. Epilepsia 2001; 42 (Suppl.7) 293.

21. Parisi P, Francia A, Vanacore N, Fiore S, Giallonardo AT, Manfredi M. Psychomotor development and general movements in offspring of

women with epilepsy and anticonvulsant therapy. Early Hum Dev. 2003; 74: 97-108.

22. Wide K, Henning E, Tomson T, Winbladh. Psychomotor development in preschool children exposed to antiepileptic drugs in utero. Acta Paediatr. 2002; 91: 409-14.

23. Gaily E, Kantola-Sorsa E, Granstrom ML. Intelligence of children of epileptic mothers. J Pediatr. 1988 Oct; 113: 677-84.

24. Gaily,E.,Kantola-Sorsa E, Granstrom ML. Specific cognitive dysfunction in children with epileptic mothers. Dev Med Child Neurol. 1990; 32:403-14.

25. Adab N, Jacoby A, Smith D, Chadwick D. Additional educational needs in children born to mothers with epilepsy. J Neurol Neurosurg Psychiatry. 2001; 70: 15-21.

26. Gaily E, Kantola-Sorsa E, Hiilesmaa V, Isoaho M et al. Normal intelligence in children with prenatal exposure to carbamazepine. Neurology. 2004; 62: 28-32.

27. Koch S, Titze K, Zimmermann RB, Schroder M, Lehmkuhl U, Rauh H. Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents. Epilepsia. 1999; 40:1237-43.

28. Dean JC, Hailey H, Moore SJ, Lloyd DJ, Turnpenny PD, Little J. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. J Med Genet. 2002; 39: 251-9.

29. Reinisch JM, Sanders SA, Mortensen EL, Rubin DB. In utero exposure to phenobarbital and intelligence deficits in adult men. JAMA. 1995; 274: 1518-25.

30. Dansky LV, Rosenblatt DS, Andermann E. Mechanisms of teratogenesis: folic acid and antiepileptic therapy. Neurology.1992; 42(Suppl 5): 32-42.

31. Yerby MS. Clinical care of pregnant women with epilepsy: neural tube defects and folic acid supplementation. Epilepsia. 2003; 44 Suppl 3:33-40.

32. Malin,A.J. Malin's intelligence scale for Indian children. Indian Journal of Mental Retardation. 1971; 4, 15-25

33. Language Proficiency Test, Karanth P, All India Speech and Hearing Institute, Mysore, 1986 (unpublished data)

34. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989; 30: 389–399.

35. Rovet J, Cole S, Nulman I. Effects of maternal epilepsy on children's neurodevelopment. Child Neuropsychol 1995;1:150–157.

36. Vanoverloop D, Schnell RP, Harvey EA, et al. The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age. Neurotoxicol Teratol 1992;14:329–335.

Appendix

APPENDIX

Table 1

Development Assessment Scales

No.	Test	Applicable age group	Domains tested
A	**Global Developmental Screening tools**		
1	Denver Developmental Screening Test II (DDST II)	0-6 years	Fine motor, gross motor, language and general social.
2	Griffith's Test	0-6 years	Locomotor, personal social, hearing and speech, eye and hand co-ordination, performance and practical reasoning
3	Bayley Scale Infant Development (BSID II)	1-42 months	Cognition, language personal social, fine motor, behavior rating.
4	Bayley Infant neuro development screener (modified BSID II)	3-24 months	Cognition, language personal social, fine motor, behavior rating.
5	Development Assessment Scale in Indian Infants (DASII) Indian adaptation of BSID)	<30 months	Cognition, language personal social, fine motor, behavior rating.
6	Binet Kamath (Indian adaptation of Stanford Binet test)	≥3 years	Fluid reasoning, knowledge, quantitative reasoning, visual-Spatial processing, working memory and verbal and nonverbal performance
7	Nursery evaluation Scale Trivandrum (NEST)	3-6 years	Fine motor, gross motor, receptive and expressive language, social and cognitive skills
B	**Intelligence Tests**		
1	Wechsler Preschool Primary Scale Intelligence (WPPSI-R)	3 to 7 years	Verbal and Performance Intelligence quotient
2	Wechsler Intelligence Scale for Children (WISC III)	6 to 16 years	Verbal and Performance Intelligence quotient
3	Wechsler Adult Intelligence Scale (WAIS-R)	16 years and older	Verbal and Performance Intelligence Quotient
4	MISIC – Malin's Intelligence scale for Indian Children (Indian adaptation of WISC)	6-16 years	Verbal and Performance Intelligence Quotient
C	**Language development screening tests**		
1	REELS (Receptive Expressive Language Scale)	Age adapted	Receptive Language and Expressive Language
2	Language Test (used in the present study)	Age adapted	Receptive Language and Expressive Language

Table 2

Developmental outcome of offspring exposed in utero to AEDs

Authors	Year of study	Age of evaluation	Effect of in utero AED exposure
Gaily et al [23]	1988	5 ½ years	Exposure to lower levels of AEDs likely not associated with psychomotor delay.
Leavitt et al [18]	1992	One year	Risk of mental rather than motor developmental delay, more marked for polytherapy and for phenobarbitone and phenytoin.
Scolnik et al [14]	1994	Children	Impaired neurobehavioral outcome with phenytoin, but not with carbamazepine.
Reinisch et al[29]	1995	Adults	Low verbal intelligence
Koch et al [27]	1999	School age and adolescents	Minor neurological dysfunction and low IQ, more risk with polytherapy than monotherapy.
Wide et al [19]	2000	9 months	Short-term psychomotor development may be unaffected by meticulous AED treatment strategy during pregnancy.
Adab et al [25]	2001	4-18 years	Effect on long-term cognitive outcome as evidenced by additional educational needs following in utero exposure to valproate.
Thomas et al [20]	2001	One year	Mild impairment in mental and motor development
Wide et al [22]	2002	4-5 years	Probable effect on locomotor development with phenytoin.
Dean et al [28]	2002	Up to 39 years	Significant impact on cognitive outcome, more risk with polytherapy than monotherapy.
Parisi et al [21]	2003	Up to 30 months	Psychomotor delay present
Thomas et al (unpublished data)	2004	30-36 months	No significant language impairment.
Gaily et al [26]	2004	7-7.4 years	Low verbal intelligence score with valproate and polytherapy, but not with carbamazepine.