Available online at www.sciencedirect.com
ScienceDirect
Epilepsy & Behavior 13 (2008) 229–236
Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Motor and mental development of infants exposed to antiepileptic drugs in utero

Sanjeev V. Thomas [a,*], B. Ajaykumar [a], K. Sindhu [a], M.K.C. Nair [b], Babu George [b], P.S. Sarma [a]

[a] *Kerala Registry of Epilepsy and Pregnancy, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India*
[b] *Institute of Child Development, Trivandrum, India*

Received 26 September 2007; revised 17 January 2008; accepted 19 January 2008
Available online 17 March 2008

Abstract

We prospectively evaluated the mental (MeDQ) and motor (MoDQ) developmental quotients of 395 (67.5% of the eligible) infants of mothers with epilepsy (IME) (mean age: 15 months) enrolled in the Kerala Registry of Epilepsy and Pregnancy between 1998 and 2004. The same developmental pediatricians, blinded to antiepileptic drug (AED) exposure, evaluated the children using the Indian adaptation of the Bayley Scale of Infant Development: Their mean MeDQ was 89.1 ± 29.9 and mean MoDQ was 90.7 ± 26.9. The MeDQ and MoDQ were impaired (<84) for 150 (37.6%) and 133 (33.5%) IME, respectively. Maternal age, type of epilepsy, seizure frequency, or use of folic acid did not correlate with the mean MeDQ or MoDQ. Maternal education was significantly correlated with the MoDQ, but not with the MeDQ, of the infants. Infants not exposed to AEDs ($n = 32$) had a higher MeDQ (mean: 92.3, 95% CI: 81.4–103.2) and MoDQ (mean 94.7; 95% CI 84.9–104.5) than those exposed to AEDs (MeDQ—mean: 88.6, 95% CI: 85.5–91.6; MoDQ—mean: 90.0, 95% CI: 87.3–92.8). Those exposed to polytherapy had significantly lower developmental quotients than those exposed to monotherapy. Cumulative AED scores during pregnancy had an inverse relationship with developmental quotients. On multiple regression analysis, polytherapy was a stronger predictor of lower developmental quotients than dosage. Compared with carbamazepine monotherapy, valproate monotherapy was associated with significantly lower MeDQ and MoDQ in IME (93.1 and 95 vs 86.9 and 86.1), but the differences between other AEDs were not significant for IME exposed to valproate monotherapy. A limitation of the study is that the influence of maternal intelligence on developmental quotients was not evaluated.

Keywords: Infant development; Epilepsy; Antiepileptic drugs; Late adverse effect; Developmental toxicology; Pregnancy registry

1. Introduction

There is a growing concern that infants of mothers with epilepsy (IME) may experience developmental delay. It is widely recognized that IME are at increased risk of congenital malformations, especially when they are exposed to polytherapy or higher doses of antiepileptic drugs (AEDs) [1]. Yet much less is known about the long-term developmental consequences of antenatal exposure to AEDs. Certain studies in animals have demonstrated that antenatal exposure to AEDs can lead to developmental delay [2,3]. There is less consistency in human studies. Some of the earlier studies did not reveal any significant developmental impairment in IME, whereas more recent studies have pointed toward significant impairment [4]. There are several reports on the developmental outcome of older children of mothers with epilepsy, but there are only a few prospective studies on the developmental outcome of IME under 2 years of age. A population-based study from Sweden reported that antenatal AED exposure can lead to reduced anthropometric measurements in infants [5], but

* Corresponding author. Present address: Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011. India. Fax: +91 471 2446433.
E-mail address: sanjeev.v.thomas@gmail.com (S.V. Thomas).

1525-5050/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2008.01.010

early development at 9 months of age was not different from that of unexposed infants in the community [6]. A follow-up study of these children demonstrated motor impairment in those exposed to phenytoin (PHT) [7]. Another study on a smaller number of infants from Germany did not reveal any significant developmental impairment for IME exposed in utero to AEDs [8]. The results for a population-based cohort of AED-exposed infants followed up in Finland [9–13] indicate that IME exposed to AEDs are at risk of developmental impairment. Studies of older children exposed prenatally to AEDs have demonstrated lower intelligence, cognitive impairments, and educational problems [14]. The precise pathogenesis of neurodevelopmental problems is rather unclear. The factors that may possibly influence neurocognitive development in infants include maternal epilepsy syndrome, occurrence of seizures during pregnancy, folate and other nutritional deficiency states, exposure to AEDs in utero, maternal IQ, and the social environment in which the children grow up. Granstrom and Gaily, in an earlier review of the topic, observed that lower scores on developmental or neurological assessments were more common among IME in the first 2 years of life [15]. A more recent review pointed out that most studies have failed to provide conclusive results or have provided conflicting results because of poor design, small sample size, or lack of uniformity in methodologies [16]. We aimed to evaluate prospectively the motor and mental development of a cohort of IME and to ascertain any correlation between impaired neurological development and antenatal exposure to AEDs or other maternal characteristics.

2. Material and methods

2.1. Setting

This study was carried out in the Kerala Registry of Epilepsy and Pregnancy (KREP) at a tertiary referral epilepsy center in Trivandrum, Kerala State, India. This registry examines the diverse problems related to pregnancy, delivery, and health status of their infants including late developmental outcome until 6 years of age. The detailed protocol of the registry was published earlier [17,18]. We enroll women with epilepsy (WWE) prospectively in the preconception period or during early pregnancy before the fetal outcome is known. The women were monitored with a standard proforma regarding AED and folic acid usage, exposure to teratogens (pharmaceutical or radiation), substance abuse, and seizure frequency during the entire course of pregnancy. All pregnant WWE are screened for fetal malformations with the serum α-fetoprotein test and ultrasonography (in the fourth month) and are administered vitamin K injections (in the last months of pregnancy). Documented use of folic acid during the first trimester was accepted as folic acid usage. Generalized and partial seizures were recorded separately for each month. All infants are subjected to a clinical examination at birth, echocardiography, and abdominal ultrasonography at 3 months of age and developmental assessment after 1 year of age. Data related to maternal epilepsy, pregnancy, delivery, and neonatal characteristics were abstracted from the records of the registry.

2.2. AED exposure

Use of AEDs anytime during the pregnancy was considered exposure. The daily dosage of AED(s) for each month of pregnancy was recorded. To make comparisons we also expressed the dosage of each AED as a drug score. A drug score of 1 unit was defined as one-tenth of the daily defined dose of the AED as recommended by the WHO Collaborative Center for Drug Statistics methodology [19]. Accordingly, one drug score for phenobarbital (PB) was 10 mg/day; for PHT, 30 mg/day; for carbamazepine (CBZ), 100 mg/day; and for sodium valproate (VPA), 150 mg/day. The drug score for each drug for every month of pregnancy was calculated. The cumulative drug score for the entire period of pregnancy was the sum of scores for each month of pregnancy derived from the score for each day.

2.3. Outcome measures

The outcome measures were the Mental Developmental Quotient (MeDQ) and Motor Developmental Quotient (MoDQ) after 12 months of age. The same team of developmental pediatrician and clinical psychologist (blinded to AED exposure) evaluated all children. The Developmental Assessment Scale for Indian Infants (DASII), an adaptation of the Bayley Scale of Infant Development standardized for Indian infants [20], was administered to each infant under standard conditions. The motor test comprises 5 clusters, that is, tests for neck control, body control, locomotion (coordinated movements, locomotion), skills, and manipulations. The test for mental development comprises 10 clusters: (1) visual cognition; (2) auditory cognition; (3) reaching, manipulation, and exploring; (4) memory; (5) social interaction and imitative behavior; (6) language (vocalization, speech, and communication); (7) language (vocabulary and comprehension); (8) understanding of relationship; (9) differentiation by use, shape, and movements; and (10) manual dexterity. DASII provides scores of mental and motor development with a standardized mean of 100 and SD of 16. MeDQ and MoDQ greater than 100 indicate advanced development for age. Development was considered severely impaired at scores less than 52 (mean – 3SD), moderately impaired at scores between 53 and 67, and mildly impaired at scores between 68 and 83. Scores above 83 (mean – 1SD) were considered normal.

2.4. Statistical analysis

All data were exported to an Excel spreadsheet and analyzed statistically with the SPSS for Windows package. The t test, χ^2 test, and Pearson's likelihood ratio were used to determine statistical significance ($P < 0.05$) of differences in means and proportions. Logistic regression and multiple regression were employed to ascertain the significance of putative predictors (number of AEDs used during pregnancy, cumulative exposure to AEDs, and other maternal and infant factors) for impaired development (scores < 84 for MeDQ and MoDQ).

Between April 1998 and December 2004 there were 635 live births, 585 of whom were 12 months or older in December 2005. We had completed developmental assessments on 395 children (62.2%). Tests were technically unsatisfactory for 5 children and could not be done in the others because they had moved to other stations, had declined to participate, or had reported for examination after 2 years of age. There were no differences with respect to maternal epilepsy characteristics, AED exposure, or immediate neonatal outcome between those who were evaluated and those who were not evaluated.

3. Results

We evaluated the motor and mental development of 395 infants (206 males) born to mothers with epilepsy. The mean age of the infants at the time of developmental assessment was 15.3 ± 4.4 months. The distribution of infants according to their MeDQ and MoDQ is given in Table 1. Maternal epilepsy classification, AED usage, seizure frequency during pregnancy, folic acid usage, and other characteristics are given in Table 2. Juvenile myoclonic epilepsy (JME) constituted 52.2% of the generalized