Reproductive Toxicology 41 (2013) 115–125

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Developmental outcomes at preschool age after fetal exposure to valproic acid and lamotrigine: Cognitive, motor, sensory and behavioral function

Tanya Rihtman[a,*], Shula Parush[a], Asher Ornoy[b]

[a] School of Occupational Therapy of Hadassah and the Faculty of Medicine, Hebrew University of Jerusalem, PO Box 24026, Mount Scopus, Jerusalem 91240, Israel
[b] Hebrew University Hadassah Medical School, Jerusalem, Israel

ARTICLE INFO

Article history:
Received 14 March 2013
Received in revised form 27 May 2013
Accepted 3 June 2013
Available online 17 June 2013

Keywords:
Valproic acid
Lamotrigine
Monotherapy
Intra-uterine AED exposure
Developmental outcomes

ABSTRACT

This prospective, observational study assessed the development of preschool children aged 3–6 years, 11 months ($n = 124$) after in-utero anti-epileptic drug (AED) monotherapy exposure to valproic acid (VPA) ($n = 30$, mean age 52.00[±15.22] months) and lamotrigine (LT) ($n = 42$, mean age 50.12[±12.77] months), compared to non-exposed control children ($n = 52$, mean age 59.96[±14.51] months). As a combined group, AED-exposed children showed reduced non-verbal IQ scores, and lower scores on motor measures, sensory measures, and parent-report executive function, behavioral and attentional measures. When the VPA- and LT-exposed groups were analyzed separately, no cognitive differences were found, but control-VPA and control-LT differences emerged for most motor and sensory measures as well as control-VPA parent-report behavioral and attentional differences. No differences were noted between the VPA and LT groups. These findings suggest that VPA- and LT-exposed children should be monitored on a wider range of developmental measures than currently used, and at differing developmental stages.

1. Introduction

Epilepsy is one of the most common chronic neurological conditions requiring continuous treatment during pregnancy [1]. Pregnancy in women with epilepsy is considered high risk [2] yet optimal treatment is controversial due to evidence of risk resulting from both seizures [3] as well as fetal exposure to anti-epileptic drugs (AEDs) [4]. Nonetheless, most practitioners continue to prescribe AEDs during pregnancy [5].

Much research investigating fetal outcomes after in-utero AED exposure has focused on physical outcomes [3,5–8]. Developmental assessment has usually focused on cognitive outcomes [9], commonly assessing younger cohorts [10], which may be problematic since developmental tests administered at young ages may have poor predictive power [3]. The thorough understanding of the effects of AED exposure is further complicated by the prescription of polytherapy [11], limiting the clear understanding of the effects of exposure to specific drugs.

Children in high-risk population groups require comprehensive measures to accurately assess their outcomes [12], and at various stages of their development. This includes AED-exposed children, for which there is a wealth of evidence of potentially detrimental effects. Standardized developmental tests are designed to assess childhood development by assessing individual ability within specific developmental domains, and enabling quantification of developmental difficulties in the defined population [12]. Furthermore, standardized tests enable the comparison between the performance of the child on the outcome of interest and that expected of other children of the same age [12]. The developmental assessment of children is an important facet of behavioral science, with extensive evidence supporting the use of well-structured tests in influencing decision-making process and outcomes for individuals [13]. While the few existing developmental studies with AED-exposed children have begun to shed light on certain developmental delays, including a potentially higher frequency of autism spectrum disorders amongst VPA- and AED polytherapy-exposed children [1,14], more extensive developmental testing of AED-exposed children is warranted.

The purpose of this prospective, observational study was to assess preschool-aged children on a broader range of functional, developmental outcomes than commonly employed, after in-utero AED monotherapy exposure to a classic AED (valproic acid [VPA]) [15] and a newer AED (lamotrigine [LT]) [16] as compared to a

* Corresponding author at: School of Occupational Therapy of Hadassah and the Faculty of Medicine, Hebrew University of Jerusalem, PO Box 24026, Mount Scopus, Jerusalem 91240, Israel. Tel.: +972 2 5845300; fax: +972 2 5324985.
E-mail addresses: tanya@tanya-branko.com (T. Rihtman), msshulap@pluto.huji.ac.il (S. Parush), asher.ornoy@mail.huji.ac.il (A. Ornoy).

0890-6238/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.reprotox.2013.06.001

non-exposed control group. Since few studies have assessed functional measures amongst this population at these ages, this study aimed to provide a broad overview of developmental measures, to establish which measures are abnormal and/or might justify further investigation.

2. Materials and methods

2.1. Participants

This prospective study included 124 preschool children aged 3 years to 6 years and 11 months, within three study groups: a control group, recruited via a convenience sample ($n = 52$ [one set of twins]; mean age 59.96 months [SD: 14.51]; 25 boys), a VPA-exposed group ($n = 30$ [one set of twins]; mean age 52.00 months [SD: 15.22]; 16 boys) and a LT-exposed group ($n = 42$ [two sets of twins]; mean age 50.12 months [SD: 12.77]; 18 boys). Inclusion criteria stipulated fluency in Hebrew (child and parents) (all groups) and exposure to VPA or LT monotherapy for a minimum of the first trimester of pregnancy (AED-exposed groups). Exclusion criteria (all groups) were genetic abnormalities and full scale IQ of less than 70; it is important to note that this criterion was selected during the study design phase in order to prevent potentially skewed results yet in the final analyses, no children were excluded for this reason. Based on Meador et al. [7] at an alpha of 0.05, for 80% power for the identification of IQ differences, a sample of 38 children per group was required while, for 70% power, a sample of 30 children per group was required.

The use of convenience sampling for the identification of the control group was selected due to its availability; children within the specified age-range of the study were identified via word-of-mouth and were invited to participate as control participants if they fulfilled the study criteria. While convenience sampling is more commonly used in pilot studies, it was selected in the current study which aimed to assess outcomes not previously investigated in depth with this population. However, due to the limitations of convenience sampling, it was essential to establish that it was representative of the population. To do so, the control group (C-AED; $n = 52$) was compared on overlapping variables to the control group of a different study (C-Random; $n = 98$) which employed a randomly selected control group representative of the Israeli population [17]. This randomly selected sample had been recruited through the *Israeli Teratogen Information Service*, through contacting callers who had contacted the service with benign queries. The two groups were compared using *t*-tests for continuous variables and chi-squared tests for categorical variables. Of the study variables, it was possible to compare groups on the SB5, Conners' Parent Questionnaire and a number of socio-demographic variables. The ages of the two groups differed, thus standardized scores were employed for between group comparisons. Results are presented in Table 1. The two control groups did not differ on any of the common study variables; it was thus concluded that the control group of the current study was representative of the population.

VPA dosage during pregnancy ranged from 100 to 1250 mg (mean daily dose: 546.3 mg). VPA was continued into the second and third trimesters for 24 of the 29 mothers (82.76%) while five mothers of singletons (17.24%) reported ceasing VPA exposure after the first trimester; 6 took VPA for non-epilepsy (psychiatric) indications. A range of epilepsy type was reported by the remaining 23 mothers (12 grand mal; 3 focal/temporal lobe; 2 petit mal; 5 other; 1 not reported). Two mothers reported seizures during the first trimester, three reported seizures during the second trimester and three reported seizures during the third trimester.

LT dosage during pregnancy ranged from 25 to 800 mg, with a mean daily dosage of 293.3 mg. LT was continued into the second and third trimesters for 36 of the 40 mothers (90.0%) and four mothers of singletons (10.0%) reported ceasing LT exposure after the first trimester; 4 took LT for non-epilepsy (psychiatric) indications. A range of epilepsy type was reported by the remaining 36 mothers (19 grand mal; 2 focal/temporal lobe; 5 petit mal; 8 other; 2 not reported). Five mothers reported seizures during the first trimester, seven reported seizures during the second trimester and four reported seizures during the third trimester. No information regarding changes in dosage during pregnancy was available. Additional participant data is presented in Table 2.

2.2. Instruments

The assessment battery employed in the current study was selected based on the suitability of all the instruments to the defined age-range of the study population.

2.2.1. Psycho-social intake

Non-standardized parent/caregiver questionnaire to attain socio-demographic information and to confirm inclusion and exclusion criteria.

2.2.2. Stanford-Binet Intelligence Scales, Fifth Edition (SB5) [18]

Valid and reliable, individually administered assessment of intelligence and cognitive (for ages 2 years to >85 years), generating two domain scores (Non-Verbal IQ [NVIQ] and Verbal IQ [VIQ]) and a full-scale General IQ score (GIQ).

2.2.3. Developmental Coordination Questionnaire'07 (DCDQ'07) [19] & Little Developmental Coordination Disorder Questionnaire (Little DCDQ) [20]

Standardized, valid and reliable 15-item parent questionnaires to identify motor coordination problems in children aged 3–4 (Little DCDQ) and 5-15 (DCDQ'07), generating a total score.

2.2.4. Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition (Beery) [21]

Standardized assessment of visual-motor skills (for ages 2–18), yielding visual motor integration (VMI), visual perception (VP) and motor coordination (MC) norm-referenced scores.

2.2.5. Miller Function & Participation Scales (M-FUN) [22,23]

Standardized, norm-referenced assessment (for ages 2.6–7.11), yielding a visual motor (VM), fine motor (FM) and gross motor (GM) score. In this study, the FM and GM components were administered since VM skills were comprehensively assessed using the Beery [21].

2.2.6. Sensory Profile (SP) [24,25] & Short Sensory Profile (SSP) [24]

Standardized parent-report measures of sensory processing abilities (for ages 3–10). The four quadrant scores (registration, seeking, sensitivity and avoiding) of the 125-item SP were used. The SSP was designed for use in screening and research protocols and generates a total score (derived from 38 of the SP items), providing a clear indication of the child's sensory processing ability; this score was used in the current study.

2.2.7. Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) [26] & Behavior Rating Inventory of Executive Function (BRIEF) [27]

Standardized parent and teacher questionnaires assessing executive functioning (EF) of children aged 2–5.11 (BRIEF-P) and 5–18 (BRIEF). For parent and teacher versions, both the BRIEF-P and BRIEF yield a comparable, norm-referenced Global Executive Composite (GEC), with higher scores indicative of greater deficit.