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Review article

Adverse effects of prenatal and early postnatal exposure to antiepileptic drugs: Validation from clinical and basic researches

Kimino Fujimura, Takayuki Mitsuhashi, Takao Takahashi *

Department of Pediatrics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

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Abstract

Epilepsy requires the long-term administration of antiepileptic drugs (AEDs), and thus, we must consider the effects of prenatal AED exposure on fetus when treating female patients of child bearing age. Large prospective clinical researches in humans have demonstrated the following: (1) prenatal exposure to valproic acid (VPA), carbamazepine, and phenobarbital increases the risk of congenital malformations in a dose-dependent manner and (2) prenatal exposure to VPA increases the risk of higher brain function impairments including intellectual disabilities and autistic spectrum disorders in the offspring. Furthermore, basic researches in animals have shown that prenatal exposure to specific AEDs causes microscopic structural abnormalities in the fetal brain. Specifically, prenatal exposure to VPA has been reported to inhibit the differentiation of neural progenitor cells during the early to middle phases of neuronogenesis, leading to increased number of projection neurons in the superficial layers of postnatal neocortices in mice. It is indispensable to prescribe AEDs that are associated with lower risk of congenital malformations and impairment of higher brain functions as well as to administer them at requisite minimum doses.

Keywords: Antiepileptic drugs; Congenital malformation; Neurodevelopmental disorders; Breastfeeding; Epigenetics

1. Introduction

Epilepsy is the most common chronic neurological condition, with a prevalence of 4–10 people per 1000 population [1,2]. Treatment for epilepsy generally requires the long-term administration of antiepileptic drugs (AEDs). Since most AEDs pass through the placenta at their specific concentrations [3], consideration of the maternal and fetal risks associated with uncontrolled seizures against the potential undesired effects from exposure to AEDs is indispensable when treating pregnant epileptic mothers [4,5]. These undesired effects include miscarriages, stillbirths, intrauterine growth retardation (IUGR), congenital malformations, and neurodevelopmental disabilities [6]. According to a report from the International Registry of Antiepileptic Drugs in Pregnancy (EURAP), an international registry that covers countries in Europe, Asia, Oceania, Latin America, and Africa, the most frequently administered AEDs during pregnancy are lamotrigine (LTG), carbamazepine (CBZ), valproic acid (VPA), and levetiracetam (LEV), accounting for approximately 80% of all AED monotherapies for epileptic mothers [7]. In North American countries, topiramate (TPM) is also frequently used in addition to the aforementioned AEDs [8].

In the late 1990s, several independent research groups established registries for epileptic mothers in an attempt to analyze large numbers of pregnancy outcomes after exposure to AEDs in a prospective manner, and are

* Corresponding author.
E-mail address: ttakahashi@keio.jp (T. Takahashi).

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now reporting long-term outcomes [9–11]. Furthermore, prenatal and early postnatal AED exposure is also an important research target in the area of basic biological science, since such exposure may lead to structural and/or functional impairments, referred to as "developmental origin of health and disease (DOHaD)" [12–15].

In this article, we shall summarize our current knowledge of prenatal and early postnatal AED exposure, from both clinical and basic research aspects. Moreover, we aim to propose future research questions that may arise based on current knowledge.

2. Observations from clinical registries

Epilepsy and pregnancy registries include national registries (e.g., United Kingdom Epilepsy and Pregnancy Register [UKEPR]; Australian Register of Antiepileptic Drugs in Pregnancy [APR]), regional registries (e.g., North American AED Pregnancy Registry [NAAPR]; Neurodevelopmental Effects of Antiepileptic Drugs [NEAD] study group), and broadly international registries (e.g., EURAP). In this section, we shall discuss the outcomes of AED-exposed pregnancy based on these clinical researches, focusing especially on major congenital malformations (MCMs) and neurodevelopmental disorders. Additionally, we shall discuss early postnatal exposure to AEDs through breastfeeding, which is another important issue during the peripartum period.

2.1. Major congenital malformations

Prenatal exposure to older-generation AEDs (i.e., VPA, CBZ, phenobarbital (PB), and phenytoin (PHT)) has been widely accepted to increase the risk of MCMs to 4–10% compared with 1–5% in the general population [4,16–18] (Fig. 1). The incidence is higher when AEDs are administered (1) during the first trimester [16], (2) at high-dose [2,4,8,19], and 3) in combination with other AEDs [4,16,20].

The most common major congenital malformations in AED-exposed offspring are heart defects, neural tube defects, hypospadias, clubfoot, and cleft lip or palate [2,16]. Among these MCMs, neural tube defects are especially associated with prenatal exposure to VPA (1–5% of exposed offspring) and CBZ (0.5–1.0% of exposed offspring) [4,16].

A dose-dependency of the incidence of MCMs has been observed for prenatal exposure to VPA [2,4,8,19], CBZ [2,4,19] and PB [4]. The incidence is particularly high (23%) when VPA is administered at 1500 mg/day or higher-doses [4,8]. Thus, the International League Against Epilepsy recommends avoiding the administration of VPA to women of childbearing age [21].

There is limited data with regard to zonisamide (ZNS) that is mainly used in Japan and the United States. The NAAPR has reported that ZNS did not increase the risk for MCMs, although the study population was small and the results, thus, require future investigation [8].

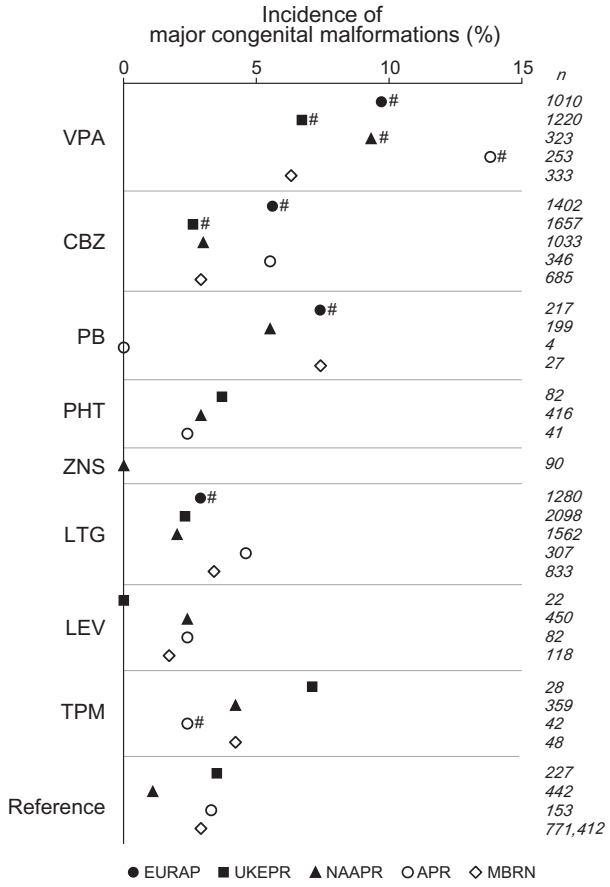

Fig. 1. Incidence of major congenital malformations after prenatal exposure to valproic acid (VPA), carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), zonisamide (ZNS), lamotrigine (LTG), levetiracetam (LEV), topiramate (TPM), and reference. Data reported from the International Registry of Antiepileptic Drugs in Pregnancy (EURAP), closed circles [4]; United Kingdom Epilepsy and Pregnancy Register (UKEPR), closed squares [2,19]; North American AED Pregnancy Registry (NAAPR), closed triangles [8]; Australian Register of Antiepileptic Drugs in Pregnancy (APR), open circles [20]; and the Medical Birth Registry of Norway (MBRN), open squares [23]. Numbers shown to the right are the size of each study population. Note that the reference is the results of pregnancy without AED exposure, although the presence of epilepsy in the mother differs among each research group. #, dose-dependency reported.

Among the newer-generation AEDs (i.e., LTG, LEV, and TPM), LTG has been the most widely investigated. Several studies have reported that the MCM incidence after prenatal exposure to LTG is equivalent to that in the general population when administered at low-dose (less than 200–300 mg/day) [4,19,22]. These MCM incidence were reported to increase to 4–5% when LTG is administered at higher-doses (200–300 mg/day or higher) [2,4], though another study reported no dose-dependent increase [22].