REVIEW ARTICLE

Epilepsy drugs and effects on fetal development: Potential mechanisms

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Approximately 1% of all pregnancies are in woman with epilepsy. Although, the majority of children born to women with epilepsy are normal, they are at increased risk for malformations. Notably, the teratogenicity of antiepileptic drugs is a well-defined subject. The incidence of major malformations in offspring of mothers with epilepsy who were treated with AEDs is higher than women with untreated epilepsy and in the general population. These malformations include spina bifida, cleft palate, limb reduction defects, cardiac abnormalities, hypospadias, and gastrointestinal atresia. The exact mechanism by which the AEDs mediate abnormalities in the fetus is uncertain. However, there are several hypotheses to explain them. Some of the most important include folate-related actions, ischemia, reactive intermediates (e.g., free radicals), and genetic susceptibility. Thus, understanding the mechanisms of AED-related abnormalities is of vital importance for the care of epileptic women and their offspring.

Keywords: Anti-epileptic drugs, epilepsy, pregnancy, teratogen

INTRODUCTION

Although, the majority of children born to women with epilepsy are normal, they are at increased risk for malformations.[1] Antiepileptic drugs (AEDs) have the potential to affect fetal development throughout pregnancy. However, pregnant women should not stop their medication. The reasons are due to the frequency and severity of their underlying epileptic disorder and also the fact that avoidance of using any AED in women of childbearing age is not a reasonable or safe option for many patients with significant epilepsy.[2] Having seizures during pregnancy by affecting the mother's cardiovascular status can cause a risk to both the mother and the fetus.[3] Therefore, understanding the ways of preventing AED-related abnormalities is an important factor in the care of epileptic women and their offspring. This goal will be reached by examining the differential effects and mechanisms of AEDs teratogenesis.

Antiepileptic drugs in pregnancy and risk of teratogenicity

Several studies show that the antiepileptic drug therapy rather than the maternal disease or convulsions is the major cause of malformations identified at birth. Annergers and colleagues found that the rates of malformation in the offspring of mothers with epilepsy treated with AEDs are higher than in the children of group with no AED treatment.[4,5] In addition, mean plasma AED concentrations are higher in mothers with malformed infants than mothers with healthy children.[6] There is a higher risk in children of mothers with polytherapy compared to monotherapy and occasionally a clear relationship between daily dose and risk of malformations has been documented.[7] Selected drugs are thought to be associated with specific malformations.[8]

While a strong connection between anticonvulsant use in maternal epilepsy and the development of congenital malformations has been established, the question arises whether (or to what extent) maternal epilepsy itself contributes to the increased risk of major congenital abnormalities in the offspring. Maternal epilepsy may influence this risk by a genetic predisposition that goes together with the disease, by seizures occurring during pregnancy and causing an impairment of feto-placental circulation, or by transplacental effects of metabolic abnormalities underlying or associated with the maternal epilepsy. These findings were confirmed by few investigations.[9] However, more recent studies have not shown the relationship between maternal seizures during pregnancy and increasing the risk of congenital malformations.[10-12] In addition, many women are not allowed to stop the medication because having seizures

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during pregnancy for both the mother and child is usually more high-risk than exposure to drug during pregnancy.[3]

Teratogenic effects of AEDs

Several studies have afforded to evaluate the teratogenic effects of AEDs, since the first report of AED-induced birth defects was published 40 years ago.[13] Major congenital malformations (MCMs) (defined as defects of medical, surgical or cosmetic importance) as a possible outcome of using older AEDs and the scanty information about use of newer AEDs are discussed in this part.

Older AEDs and MCMs

Numerous studies have shown that the traditional antiepileptic drugs (e.g., phenobarbital, phenytoin, carbamezapine, valproate) increased risk of MCMs.[7,14,15] Fetal hydantoin syndrome is a rare disorder that is caused by exposure of a fetus to the anticonvulsant drug phenytoin (PHT). The symptoms of this disorder may include abnormalities of the fingers and toes, and/or mild developmental delays. Other findings occasionally associated with this syndrome include cleft lip and palate, having an unusually small head (microcephaly) and brain malformations with more significant developmental delays.[16,17] Barbiturates like phenobarbital (PHE) have also been associated with the same major and minor abnormalities and dysmorphic features as with PHT. These include congenital heart defects, facial clefts, craniofacial abnormalities and growth deficiency. Valproate (VPA) has a different pattern of congenital abnormalities from the previous ones. VPA has a clear link with increased risk of fetal abnormalities, particularly spina bifida and other neural tube defects, as well as hypospadias.[18] Other congenital malformations associated with the exposed fetus have included heart defects, oral clefts, genital abnormalities, and limb defects.[19] Furthermore, it has been estimated that there is a linkage between VPA dose and adverse outcome. Higher doses of VPA have been associated with a significantly greater risk than with lower doses.[20] Carbamazepine (CBZ) is also associated with major malformations.[21,22] Buehler believed that there is a similarity between CBZ and fetal hydantoin syndrome and concluded that they follow the same teratogenic mechanism.[23] Morrow and collaborates yielded contradictory results. In a prospective study on 3607 cases, they found that exposure to CBZ monotherapy was associated with the lowest risk of MCM. Individual AED results for MCMs included 2.2% for CBZ (1.4%-3.4%), 6.2% for VPA (4.6%-8.0%), 3.7% for PHT (1.3%-10.2%), and 3.5% for no AED exposure (1.8%-6.8%).[7] VPA monotherapy, among the various drug regimens have proportionally high relative risks of major congenital abnormalities in the offspring.[18]

Newer AEDs and MCMs

Currently, many new AEDs including lamotrigine, gabapentin, oxcarbamazepine topiramate, pregabalin and levetiracetam have been introduced into clinical practice. They are known for their better toleration. Some authors have believed that the use of newer AEDs in pregnancy may be preferred because they have a good safety and pharmacokinetic profile that makes their effects more predictable during pregnancy. In addition, they are also less likely metabolized to teratogenic compounds and most of them do not show antifolate properties.[14] However, systematic data and experience with the newer AEDs has not been extensive enough to determine risk. One of the most commonly prescribed drugs among the newer antiepileptic drugs is lamotrigine (LAM). A number of studies concerning the use of LAM in pregnancy have been reported. The North American Registry did not find any increased risk of malformations overall for LAM, although a specific increased risk for cleft lip/palate (0.73%) was reported.[24] The UK Registry also reported a positive dose response for MCMs with LAM exposure that was not seen in the North American Registry or the International LAM Registry.[24,25] An 18 years registration of women who had received lamothrigine did not detect an appreciable increase in MCM frequency following first-trimester lamotrigine monotherapy and also any additional risk for lamotrigine and valproic co-administration has not been reported.[26] However, a new survey on 1317 Australian women with epilepsy has reported that the incidence of malformations associated with lamotrigine monotherapy was 12/231 (5.2%), with topiramate 1/31 (3.2%) and with levetiracetam 0/22 (0%).[27] Human data examining the teratogenic potential of other new AEDs are limited. A retrospective study was carried out involving 12 pregnancies exposed to oxcarbazepine as mono- or polytherapy, showed three spontaneous abortions and nine healthy births without MCMs.[15] One literature review indicates that, receiving of oxcarbamazepine monotherapy during pregnancy do not appear to show an increased risk for malformations compared with general population. [28] We have shown that another new anti-epileptic drugs, gabapentin administration in mice during pregnancy can induce skeletal malformation.[29,30] The results of prospective and retrospective study concerning 51 fetuses were collected from 39 women exposed to gabapentin during pregnancy showed that the rates of maternal complication, miscarriage, low birth weight, and malformation were less than or similar to those seen in the general population or among women with epilepsy. [31] A preliminary study with levetiracetam did not show increased risk and preliminary studies with topiramate have had conflicting results. However, the sample sizes in these studies are too small to get confident conclusions.[32-34]

AED combinations and MCMs

In only 60% of epilepsy patients, monotherapy is sufficient to obtain adequate seizure control. Approximately,

40% of patients require polytherapy treatment. Higher malformation rate, in general, has been found with AEDs polytherapy than monotherapy. This finding has been confirmed in numerous studies. Holmes *et al*. found increased rates of growth retardation and microcephaly particularly with polytherapy, PHE, and CBZ.[10] On analyzing the results of 870 newborns body dimensions from Canada, Japan, and Italy, the researchers found greater risk for small head circumference with polytherapy. [35] Samrén *et al*. reported the relative risks for 1, 2, 3, and 4 or more AEDs to be 2.4, 3.3, 3.1 and 5.9, respectively.[18] The teratogenic potential of different AED combinations is different. Combination of PHE, PHT and primidone; CBZ, VPA; and CBZ, VPA and PHE, with or without PHT, are associated with high teratogenic risks.[18,36,37]

Potential mechanisms of AED teratogenesis

The mechanisms of teratogenicity are uncertain at the present time. Several mechanisms have been postulated to explain the teratogenicity of AEDs. Some of them may be teratogenic because of alteration in vitamin K metabolism, folate deficiency, bioactivation of PHT to a reactive toxic intermediate (epoxide) by cytochrome P450, co-oxidation of PHT to free radical intermediates, apoptosis and hypoxia-reoxygenation damage.[38-40] The most important theories are discussed below.

Reactive intermediates of AEDs and teratogenicity

The fetotoxicity of some AEDs may be mediated not by the parent compound, but by toxic intermediary metabolites. One of the suggested toxic intermediates is epoxide compounds. Arene oxides are unstable epoxides formed by aromatic compounds via the cytochrome P450 system. Various epoxides are highly reactive and may bind to fetal critical cell macromolecules. Arene oxides can be detoxified by epoxide hydrolase. An inhibition of this enzyme has shown to cause an increase of malformations in animals.

Low epoxide hydrolase activity in amniocytes correlates with subsequent dysmorphic features at term in children exposed to PHT.[41] Interestingly, some specific combinations of AEDs, particularly CBZ, PHE and VPA have been associated with a particularly high rate of malformations as a result of epoxides formation by CBZ and PHE and epoxide hydrolase inhibition by VPA.[42] However, there are some observations that cannot be completely explained by this fact. Trimethadione, as a potent teratogenic AED does not have phenyl rings and thus cannot form epoxide. Inhibition and potentiation of PHT teratogenesis by some cytochrome P450 inducer and inhibitor drugs (PHE and SKF 525 A, respectively) also argues against this hypothesis.[43]

Folate deficiency and AEDs teratogenicity

Folic acid (FA) appears to play a major role in the metabolism of the developing fetus because it is essential for DNA methylation, protein methylation, DNA synthesis, and maintenance of the overall integrity of DNA.[44] Also, there are some evidence that demonstrate FA deficiencies can cause alterations in the levels of proteins and genes.[45] Many studies have shown that folate deficiency can be induced in patients undergoing AED therapy. A relationship between FA deficiency and impairing in offspring development has been confirmed by some studies.[46]

Co-administration of FA alone or FA with several vitamins and PHT on day 9 to 11 of gestation reduced malformation rates and increased fetal weight and length in mice pups.[47] Neural tube defects have been reported to be a major teratogenic outcome after *in utero* exposure to VPA and to a lesser extent CBZ. One group stated that the incidence of VPA-induced neural tube defects in rodents could be reduced by 50% through supplementation with folinic acid (not folic acid). Also, Dansky *et al*. found a clear relationship between low blood folate concentrations in epileptic women with abnormal pregnancy outcomes.[6] Infants of mothers with epilepsy who did not take folate supplementation have shown a 15% malformation rate, whereas none of 33 folate supplemented children had congenital abnormalities.[48,49] However, not all research supports the association between folate deficiency and malformations. The effect of folate or folinic acid (metabolically active compound, tetrahydrofolate) with PHT administration in pregnant animals have shown results from no change to a protective effect or enhancement of PHT teratogenicity.[6,50,51] Hernández-Díaz and her collaborates reported that when pregnant women taking PHT, PHE or CBZ and a multivitamin supplement that included folic acid, a decrease in the incidence of cardiovascular or urinary tract abnormalities or oral clefts in their infants has not been observed.[52]

One current hypothesis for folate deficiency is an increased plasma and tissue concentration of homocysteine, that is responsible for the observed defects.[53] It remains to be established whether folate supplementation before and early in pregnancy is of any benefit to epileptic women undergoing AED therapy.

Hypoxia/Reoxygenation and AEDs teratogenicity

A more recent hypothesis suggests that many AEDs such as PHT, trimethadione, CBZ and PHE are exerting their developmental adverse effects by inducing episodes of embryonic cardiac arrhythmia during restricted periods of embryonic development.[54] According to this hypothesis, embryonic hypoxia is followed by reoxygenation and generation of reactive oxygen species, which will cause tissue damage.[55] All typical malformations such as orofacial clefts, heart defects, distal digital defects and growth retardation can be induced in experimental studies by hypoxia, and AEDs have been shown to affect the embryonic

heart in animal models. Additionally, in a series of studies, Danielsson and colleagues showed that administration of a teratogenic dose of PHT to pregnant rabbits had little or no effect on maternal heart rate or blood pressure. The induced malformations included distal digital reduction defects and orofacial cleft were preceded by edema, vascular disruption, hemorrhage and necrosis. These changes seen after PHT administration were almost the same as those seen after interrupted oxygen supply to the embryo.[56,57] Hence, the embryonic heart appears to be more sensitive than the adult heart to the effects of AEDs.

Apoptosis and AEDs teratogenicity

Apoptosis, a form of active cell death, is described morphologically by chromatin condensation, cytoplasmic shrinkage and membrane blabbing.[58] It is a common event in the pathogenesis associated with malformations induced by a variety of teratogens.[58-60] There is evidence that several AEDs may influence brain development by inducing neural apoptosis. One study showed that therapeutic concentrations of several common AEDs (VPA, PHT, clonazepam, PHE, vigabatrin, and diazepam) can have effects on rat brain development. They found that all drugs caused neuronal apoptosis through the suppression of an endogenous neuroprotective system.[61] One study indicated that VPA at low therapeutic concentrations in comparison to other AEDs can induce apoptosis. CBZ, levetiracetam, lamotrigine, or topiramate monotherapy did not show similar apoptotic effects. However, all of these AEDs, except levetiracetam are capable of enhancing PHT-induced apoptosis in polytherapy.[62]

Genetic susceptibility and AEDs teratogenicity

Only a small percentage of infants who are exposed in uterus to known or suspected teratogens are born with congenital birth defects. It is not clear why some fetuses are at increased risk. However, it is widely believed that an interaction between genetic sensitivity and teratogenic agent changes normal morphogenetic pathways and results in birth defects. Both, maternal and fetal genotypes can affect placental transport, absorption, metabolism, distribution and receptor binding of an agent, influencing its teratogenicity.[63]

Genetic sensitivity is believed to play an important role in antiepileptic drug-induced teratogenesis. Variable teratogenicity among different strains of laboratory mice suggests that genetic factors influence susceptibility. PHT induced cleft lip/palate in an A/J strain of mice whereas C57BL/6 mice were relatively resistant.[64] A difference in sensitivity of PHT arrhythmogenic effects on embryonic hearts has been documented.[56] It has also been suggested that genetic differences in folate metabolism may account for the increased risk of congenital anomalies, particularly neural tube defects, in the children of women with epilepsy treated with AEDs. In one study, epileptic mothers of children who were diagnosed with fetal anticonvulsant syndrome were more likely than epileptic mothers of unaffected children to be homozygous for the C677T variant of the MTHFR gene.[65]

Genetic differences can also influence the content and potency of antioxidant enzymes. These antioxidant compounds break down reactive species in the body into harmless substances like water or oxygen particles, which then leave the body without harming it. As mentioned above, there is evidence that Reactive Oxygen Species, generated in the embryo, may be directly responsible for certain teratogenic effects, such as cleft palate.[66] Jergil and his colleagues reported that they have recognized some gens which are positive predictive value for the teratogens of VPA.[67,68]

There are some pharmacovigilance differences on safety and response to AEDs.[69] Thus, the degree of fetal sensitivity is determined by the interaction of the teratogen with a susceptible genotype. These differences in susceptibility are important to interpreting the existing risk data.

Other mechanisms

Recently, other mechanisms for the teratogenicity of AEDs have been suggested. In one recent study, exposure to AEDs drugs during a sensitive postnatal period impaired physiological maturation of synapses in neurons that survived the initial drug insult in exposed rats.[70] Other interesting mechanism that might explain the teratogenicity of VPA was revealed in a study that showed epigenetic changes with VPA treatment and a relationship with neuropsychiatric disorders.[71]

CONCLUSION

The frequency of major malformations, growth retardation, and midline heart defects, hypoplasia of the midface and fingers, known as anticonvulsant embryopathy, is increased in infants exposed to anticonvulsant drugs *in utero*. Though data is limited on all AED, there are case reports of malformations for all of the commonly used medications. Although the exact mechanism of their teratogenicity is not very clear, however a variety of mechanisms have been suggested, including folate-related actions, ischemia, reactive intermediates (e.g., free radicals), and genetic susceptibility. It is important to know that additional research is needed to reveal the risks for all AEDs, find out the underlying mechanisms, and explain reasons for individual variance in outcomes.

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