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Prenatal exposure to an antiepileptic combination (levetiracetam and valproic acid) throughout gestation and postnatal sensorimotor development in mice

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Introduction: Treatment of epilepsy always has an individual and unique path. Despite effective classical and novel antiepileptic drugs (AEDs), monotherapy is limited and insufficient in some cases, such as refractory epilepsy. Pregnant women with epilepsy are a population that requires a special approach. Protocol guidelines and experience dictate the rational use of AEDs during pregnancy, which means that monotherapy and the lowest therapeutic (curable) dose should be used. Epilepsy as a multifactorial condition involving different categories of epileptic disorders sometimes requires treatment with highly potent therapeutic drugs, such as valproic acid (VPA), which is known to be teratogenic. In some cases, not only can it not be substituted, but it must also be combined with another drug. The combination of VPA and levetiracetam (LEV), at a dosage of 1:1, achieves additive efficacy with no evidence of toxicity.

Aim: Thus, the aim of the present study was to investigate the sensorimotor development of mice whose mothers were treated with a combination of VPA and LEV (1:1 ratio) during breeding and gestation.

Method: Adult, 8-week-old female NMRI mice were used in this study. Two groups of animals were formed: one group (8 females) treated with a combination of LEV at a dose of 211 mg/kg/day (LEV-211) and VPA at a dose of 200 mg/kg/day (VPA-200), and a control group (8 females) receiving an equivalent amount of saline. The doses administered correspond to human doses of 1000 mg/day for both antiepileptic drugs. All animals were treated subcutaneously into the loose skin on the back of the neck twice daily. Treatment was initiated at the mating of males and females and continued throughout the entire period of breeding and gestation. After the females gave birth, each of them was housed separately with her litter. Offspring were separated by sex on postnatal day (PND) 21. Sensorimotor system performance and conditional learning were assessed on PND25 and PND32 in the hot plate test (HPT).

Results: Female and male offspring treated prenatally with a combination of AEDs (LEV-211 + VPA-200) showed a significantly faster response than the control group on PND32, whereas female offspring also showed a faster response than the control group on the first day of testing, PND25.

Conclusion: Considering the results of the HPT and the different sensorimotor responses in offspring prenatally treated with antiepileptic drug combinations in animal models, it would be necessary for the human practice to continuously monitor (until the end of adolescence) the children prenatally exposed to this antiepileptic drug therapy.

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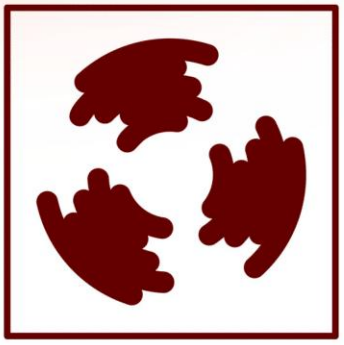

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