NASCER E CRESCER
BIRTH AND GROWTH MEDICAL JOURNAL
year 2017, vol XXVI, n.º 2

editorial

# Epilepsy in female adolescents: issues concerning epilepsy and antiepileptic drugs, contraception and pregnancy

*Rui Chorão*[I]

With the enlargement of "paediatric ages" to adolescence, new problems have emerged to child neurologists concerning epileptic patients, especially the girls. The main related issues are the interactions between antiepileptic drugs (AEDs) and hormonal contraceptives, and the questions related to the future possibility of motherhood.

Pregnancy in epileptic patients is of high-risk, but obstetric complications are relatively rare. Seizure frequency may change or not during pregnancy, perhaps related to changes in the serum drugs levels. But treatment with AEDs should always be maintained, because the risk of uncontrolled seizures, namely tonic-clonic, is considered more harmful to the foetus than those drugs.

The problem of teratogenicity is of great importance and has been extensively investigated for the last decades of the twentieth century, and numerous national and international registries have been undertaken since.

All AEDs should be considered as potentially hazardous, but the oldest ones are at greater risk and their deleterious effects more extensively known. Among the AEDs frequently used nowadays valproic acid (VPA), has been found to be the most teratogenic. This is the most widely used AED in children and maybe also in adolescents, at least in developed countries. Their most serious related congenital malformations are neural tube defects, but acid folic supplementation seems to be protective to some extent. Some studies have also shown possible negative cognitive and behavioural effects in the offspring of mothers taking VPA during pregnancy. Carbamazepine, more recently used levetiracetam and even lamotrigine (LTG), previously considered the best choice for women at childbearing age, are also associated with congenital malformations, although in a smaller proportion. Both phenobarbital and phenytoin are also associated with malformations, but are rarely used at these ages.

Pregnancy should always be planned, and some measures that should be tried before conception may be discussed or started in some adolescent patients. Whenever possible, monotherapy should be tried, the lowest effective dose of any drug tried to be found, or even consider gradual withdrawn of a drug if epilepsy is in remission and the risk of recurrence considered relatively low. But this poses questions of a relapse of seizures in adolescents, like the permission to get a driving license when they are young adults.

Interactions between oral contraceptives and antiepileptic drugs are known since the 1970s and have been successively studied. Virtually all combined oral contraceptives (COCs) have ethinylestradiol (EE) as the estrogen compound, which undergoes extensive hepatic metabolism into inactivated compounds, being predominantly catalyzed by cytochrome P450, mostly CYP3A4; but the metabolism of progestins also involves CYP enzymes. Enzyme-inducing antiepileptic drugs (EIAEDs) can accelerate the metabolism of hormonal contraceptives, in most cases both EE and progestin (carbamazepine, oxcarbazepine, eslicarbazepine, pheno-

[I] Department of Neurophysiology and Outpatient Clinic of Paediatric Epilepsy, Centro Hospitalar do Porto.
4099-001 Porto, Portugal.
rui.chorao@gmail.com

barbital, phenytoin, rufinamide), of the estrogen component only (as topiramate in a dose-dependent way, with doses higher than 200 mg daily) or the progestative (lamotrigine, with a not clinical significant effect, and the more recently available perampanel with a clinical significant effect with 12 mg or higher doses). COCs have been progressively reducing their hormonal compounds, in order to minimize adverse events as thromboembolic complications or breast cancer, so modern preparations contain 20-35 µg of EE and less than 1 mg of progestogen. In order to be effective in association with EIAEDs, the estrogen component it must contain at least 50 µg of estradiol; sometimes patients are counselled to take two pills, preferably divided twice a day. Other contraceptives that are affected by these AEDs are combined contraceptive patches, vaginal ring, progestogen-only pills and progestogen implants. The latter are commonly used in adolescents, in particular in some mentally retarded epileptic patients, and one must alert for its ineffectiveness as the only contraceptive method in girls taking EIAEDs. Additional contraception, as with barrier barrier methods, is advised. Intrauterine devices are a safe option for patients taking EIAEDs, both levonorgestrel device (because its hormonal effect is mainly local) and those with copper that has a spermicide effect. Interestingly, medroxyprogesterone acetate depot injection seems not to be altered by those AEDs, because of the vitally 100% clearance on the first pass through the liver. Not much is known about EIAEDs and emergency contraception ("after day pill"), but they seem to reduce its efficacy.

Valproic acid, levetiracetam, ethosuximide, vigabatin, zonisamide and lacosamide are among the AED that are not enzyme-inducers, thought they do not interfere with the efficacy of hormonal contraceptives.

On the other hand, COCs have been found to interact with the metabolism of some AEDs, the most significant of which is lamotrigine, its blood level being reduced to 50% or more. It is advised to increase the dose of LTG when hormonal contraception is initiated, some authors clamming up to double the dose. Progestin-only methods do not interfere with LTG.

In summary, adolescence, as a transition phase to adulthood and with some health problems that are very different to those found in childhood, may be a very challenging period for paediatricians and other medical doctors that follow patients under the age of 18 years old. In the case of girls with epilepsy, the above-mentioned situations are of great importance, and knowledge experienced neurologists and gynaecologists may have a role, both in treating these patients and in clarifying both paediatricians and general practitioners.