VALPROIC ACID, POLYCYSTIC OVARY SYNDROME AND THE ADOLESCENT WITH EPILEPSY

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Abstract

When treating epilepsy with antiepileptic drugs (AEDs) the physician will choose the most effective drug according to the electro-clinical syndrome and aetiology, with a minimum of side effects. Valproic acid (VPA) is in clinical use for almost 50 years and is often recommended because of its efficacy and broad spectrum of action. Recent years have brought new information about its possible side effects, some still debated and others definitely proven. The aim of the present paper was to discuss the association between epilepsy, chronic treatment with valproic acid in adolescence and the polycystic ovary syndrome and to conclude with proposals on the assessment of adolescents with epilepsy who need valproic acid as their treatment.

Rezumat

Tratamentul farmacologic al epilepsiei are ca obiectiv alegerea medicamentului cel mai eficient, în funcție de sindromul electro-clinic și etiologie, cu minimum de reacții adverse. Acidul valproic este folosit de aproape 50 ani, fiind frecvent recomandat datorită eficacității sale și spectrului larg de acțiune. Ultimii ani au adus însă informații noi despre posibilele sale reacții adverse, unele încă discutate, altele cert dovedite. Scopul lucrării este de a discuta asocierea între epilepsie, tratamentul cronic cu acid valproic în adolescență și sindromul ovarului policistic și de a propune modalitatea de supraveghere a adolescentelor cu epilepsie care au nevoie de tratamentul cu acid valproic.

Keywords: valproic acid, polycystic ovary syndrome, polycystic ovary, adolescence, generalized genetic epilepsy

Introduction

Epilepsy is a chronic neurological condition and long lasting pharmacological treatment is usually necessary, according to the electro-clinical syndrome and aetiology. There is no perfect antiepileptic drug (AED), although many AEDs with improved efficacy and side effects profile have been developed in the last decades. Valproic acid (VPA), one of the most frequently recommended AEDs, mainly because of its efficacy, was marketed starting 1967, being used for almost 50 years now [26]. Several significant side effects of VPA have been brought into discussion last year, new practice recommendations being published in 2015, especially warning against the use of VPA in adolescents and women of childbearing age due to the risk of malformations, cognitive deficit and autism in offsprings [31]. The discussion remains open for other previously discussed possible side effects, among them also the polycystic ovary syndrome (PCOS) [32].

Valproic acid treatment for the adolescent with epilepsy

Valproic acid is a short-chain fatty-acid with a broad spectrum of activity against multiple seizure types [20]. VPA is often recommended in the paediatric population due to its efficacy in many of the electro-clinical syndromes with onset in infancy, childhood or adolescence [20, 27]. It is a valuable treatment option in generalized genetic epilepsy, in which VPA shows the best evidence of efficacy, at least in some phenotypes [19, 27, 30]. Even if an “old” drug, its principal mechanism of action is not fully understood, and is now considered that more than one mechanism are involved [18]. The mechanisms demonstrated until now are: (i) VPA potentiates the inhibitory neurotransmitter γ-aminobutyric acid (GABA), but this occurs at brain concentrations higher than expected with common therapeutic levels, so it seems that this mechanism does not fully explain the action of valproic acid; (ii) VPA limits the sustained repetitive firing of neurons by action on the voltage-gated sodium channels, at different sites than carbamazepine and phenytoin, and also inhibits the T-type calcium channels; (iii) other potential mechanisms would include: potentiation of calcium-activated potassium channels, reduction in the release of gamma-hydroxy-butyrate, decreased brain concentrations of the excitatory amino acid aspartate and an alteration in the expression of glutamate transporters in the
adolescence polycystic syndrome (PCOS) and polycystic ovary (PCO) in adolescence - the role of epilepsy and of the treatment with valproic acid

PCOS is a disorder which becomes active mainly during adolescence and is characterized by ovulatory dysfunctions and hyperandrogenism. It is caused by an excess production of androgens by the ovaries. The pathogenesis of PCOS is believed to be multifactorial, with involvement of genetic and environmental factors [32]. The concept now agreed is that PCOS is the result of one of a number of intrinsic ovarian genetic characteristics that interact with one or more other congenital or environmental factors to cause dysregulation of steroidogenesis - a “two-hit” model [6].

Criteria used for diagnosing PCOS in adults (Rotterdam criteria) include two of the following: (i) oligo-ovulation or anovulation; (ii) clinical and/or biochemical signs of hyperandrogenization; (iii) ultrasonographic evidence of polycystic ovaries (PCO), with exclusion of other causes of hyperandrogenism (such as: adrenal or ovarian tumours, thyroid dysfunction, non-classical congenital adrenal hyperplasia, hyperprolactinemia, acromegaly, Cushing syndrome) [17].

There is controversy regarding the criteria used for diagnosing PCOS in adolescent girls, for whom the following criteria are proposed: (i) hyperandrogenism, preferably confirmed by specific biochemical findings and (ii) a menstrual pattern that is abnormal for gynaecologic age (years since menarche) [17]. This above mentioned suggestion does not include PCO as a diagnostic criteria due to the fact that in adolescence polycystic – appearing ovaries are often a normal finding and appropriate ultrasonographic criteria for defining PCO in adolescence are unclear [1, 17].

PCOS is more common in women with epilepsy (13 - 25%) than in general female population (4 - 6%), even if not treated with AEDs [20, 32, 33], through several mechanisms. The function of hypothalamic-pituitary axis (HPA), including production of luteinizing hormone (LH), follicle-stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH), prolactin (PRL) and their end-products (oestrogen, testosterone and dehydroepiandrosterone) is modified in female patients with epilepsy [2, 5, 11, 24].

PCOS is listed among adverse reactions of valproic acid treatment but still debated if significant and reproducible [20, 30]. First association between PCOS and VPA was published in 1993 [13] and was much debated during the following years, with contradictory results [4, 7, 8, 10, 14, 24, 28, 34]. The discrepancies noted might relate also to the criteria used for defining of PCOS. It is however acknowledged that the initial discovery of Isojärvi et al. that VPA can induce changes in ovarian structure was extremely important [13].

Even if the data vary, a metaanalysis of PCOS in women with epilepsy treated with VPA suggested that women with epilepsy receiving VPA are twice more likely to develop PCOS than those receiving other AEDs [12], so VPA seems to be involved in the aetiology of reproductive abnormalities. VPA may induce hyperandrogenism or hyperandrogenemia in postmenarcheal girls, as in adult women, and not in the girls before menarche [4, 9, 15]. VPA determines high androgen concentrations by direct stimulation of the ovarian production and also through a decreased hepatic metabolism of sex hormones [33]. VPA-induced ovarian androgen biosynthesis might result from augmented transcription of steroidogenic genes, through one of the VPA actions, as histone deacetylase inhibitor [25]. VPA contributes to polycystic changes in the ovaries, high serum testosterone concentrations and menstrual disorders, especially among women who gained weight during VPA treatment [35]. In summary there is evidence now to support the hypotheses that the development of PCOS and PCO needs a genetic predisposition, but VPA might contribute to the increased prevalence of reproductive disorders in women with epilepsy taking it [33]. The reproductive endocrine effects of VPA are reversible after the treatment is discontinued [16, 23].

Practical recommendations for the follow-up of reproductive function of adolescent girls who need treatment with valproic acid

Due to the fact that reproductive system abnormalities seem to be more frequent in adolescents and women with epilepsy, regular follow-up of the
reproductive function is important. This could be done in adolescent girls by the treating physician, at baseline and after starting VPA treatment, mainly through monitoring the body weight and the menstrual cycle length. Persistent menstrual cycle duration outside the interval 21 - 45 days for more than 1 year after menarche is unusual in adolescence [29]. In order to identify POCs the physician should question about menstrual abnormalities such as amenorrhea or oligo-menorrhea which persists 2 years beyond menarche [17], hirsutism and other signs of hyperandrogenism. Evaluation through a multidisciplinary team would be recommended when abnormalities are present [22]. When clinically indicated, serum testosterone level will be assessed and also complementary tests for exclusion of other causes of hyperandrogenemia [17, 32, 33]. Pelvic ultrasonography in adolescence could be less useful for the diagnosis of POCs [17], but might be recommended in girls with epilepsy requiring AEDs before commencement of treatment, especially with VPA, and during the follow-up [32, 33].

Conclusions

Physicians treating girls and adolescents with epilepsy should follow EMA and CEA-ILAE/EAN recommendations to avoid VPA treatment during the fertility period, whenever possible. The benefits and adverse effects of VPA treatment have to be carefully discussed with female patients with generalized genetic epilepsy, taking into consideration that VPA shows in these cases the best evidence of efficacy. VPA remains an important AED for epilepsy treatment in the pediatric age including adolescence. Physicians should be aware of the dysfunctions of the reproductive system, increased in adolescent girls and women with epilepsy, which can be due to epilepsy itself or AEDs, especially VPA, and regularly check this system at diagnosis and in the follow-up period, through a multi-disciplinary approach.

References


