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PHENYTOIN AS THE FIRST OPTION IN FEMALE EPILEPTIC PATIENTS?

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ABSTRACT – Objective: Phenytoin (PHT) is one of the first-choice drugs in several epileptic syndromes, mostly in partial epilepsies, in which case it is effective as carbamazepine and phenobarbital. However, like any other anti-epileptic drug (AED), unpleasant side-effects are not rare. The aim of this study is the evaluation of dermatological troubles related to chronic PHT usage in female patients. Method: Between 1990-93, 731 new patients underwent investigation for epilepsy at the Multidisciplinary Clinic for Epilepsy in our State. In this sample 283 were AED users at the time of the first assessment. Sixty one female patients taking PHT were identified. They were taking PHT in a dosage ranging from 100 to 300 mg daily, in mono or polytherapy regimen, during 1-5 previous years. Results: More than 50% of the sample showed coarse facial features made by the combination of several degrees of acne, hirsutism and gingival hyperplasia. Conclusion: Except in emergency situations, PHT should not be prescribed as the first option to the treatment of female epileptic patients, because not uncommonly the cosmetic side-effects are more socially handicapping than the epileptic syndrome by itself.

KEY WORDS: epilepsy, phenytoin, gingival hyperplasia, hirsutism.

Fenitoína como primeira opção em mulheres com epilepsia ?

RESUMO – Objetivo: Fenitoína (PHT) é uma das principais drogas no tratamento de epilepsias diversas, principalmente as parciais, para a qual ela é tão eficaz quanto carbamazepina e fenobarbital. Entretanto, como qualquer outra droga anti-epiléptica (DAE) da atualidade, efeitos desagradáveis não são raros. O alvo deste estudo é a avaliação dos efeitos dermatológicos relacionados com o uso prolongado de PHT em pacientes femininas. Método: Entre 1990-93, foram admitidos para avaliação 731 novos pacientes na Clínica Multidisciplinar de Epilepsia/SUS, Florianópolis/SC. Destes, 238 já estavam em uso de DAE, sendo que 61 eram mulheres usuárias de fenitoína, numa dosagem que variava de 100-300 mg/dia, em mono ou politerapia, por um período prévio de 1-5 anos. Resultados: Mais de 50 % das pacientes exibiam alterações faciais grosseiras, decorrentes da combinação em diferentes níveis de severidade de acne, hirsutismo e hiperplasia gengival,. Conclusão: Exceto em situações de emergência, PHT não deveria ser usada como primeira escolha no tratamento de mulheres com epilepsia; seus frequentes efeitos colaterais dermatológicos causam mais transtornos médico-sociais que a epilepsia por si própria.

PALAVRAS-CHAVE: epilepsia, fenitoína, hiperplasia gengival, hirsutismo.

Overall, phenytoin (PHT) is known to be effective in the treatment of several epileptic syndromes, specially in partial epilepsies[1]. However it has been associated with a lot of undesirable bad effects and cosmetic-dermatological troubles are quite common. Since Kimball, 1939, first reported gingival hiperplasia (GH) as a side-effect of PHT, many efforts have been done to approach this manifestation. The pathogenesis of the GH is still debatable and several theories have been

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developed in an attempt to elucidate such issue. The most reasonables are IgA deficiency in serum and saliva leading to local immune reactions[2]; decreased serum levels of folic acid causing deterioration of the gingival saccular epitelium[3] and low Ca^{+} in gingival fibroblasts[4].

Moreover PHT may generate a sizeable list of unpleasant side-effects, such as teratogenies, cognitive impairment, cutaneous syndromes, metabolic and hematologic disorders; however cosmetic side-effects are some of the most socially undesirable[5-7]. Hirsutism for instance, is a common undisguiseable trait of PHT long-term use and the first criticism on it was made by Kerr in 1975[8]. Since then very few neurologists have done comments on this important negative aspect and paradoxically it has never been taken into account on evaluating epileptic patient´s quality of life.

We hope to add few inroads into the era of the modern epileptology, and allow the idea of socially stigmatising sequelae as a result of PHT use.

METHOD

In a cohort study with 3-years of longitudinal follow-up, 1990-93, 731 new patients were assessed in the outpatient Multidisciplinary Clinic of Epilepsy (MCE) of the Brazilian National Health Service for investigation of seizures. All this sample was screened by a multidisciplinary team consisting of neurology, psychiatry, psychology, nursing and social workers. All patients previously taking anti-epileptic drugs (AEDs) were identified. Those female patients who presented unequivocal dermatological troubles were separated and correlation with previous treatment was made. As the mainstain inclusion criteria, the presence of PHT as the solely causative factor for the cluster of dermatologic side-effects was identified together with a minucious assessment of the clinical findings by a multidisciplinary team.

RESULTS

Among the 283 patients using AEDs, 61 were female PHT users in mono or polytherapy, in a dosage ranging from 100 to 300 mg daily. Mean time of PHT use prior to the initial assessment was 3 years and 7 months. Mean age was 32 years (14 to 56). Most of the sample, 52.46% (32 patients), exhibited bizarre facial features in a gamut of severity. Essentially they were a combination of acne, hirsutism and gum hyperplasia (Fig 1). Halitosis secondary to gingival bleeding was remarkable in the vast majority of this group.

DISCUSSION

Initially, we would like to emphasize our agreement that PHT is a major and accessible anti-epileptic drug. Actually, we use to prescribe PHT as the first choice drug to many patients suffering

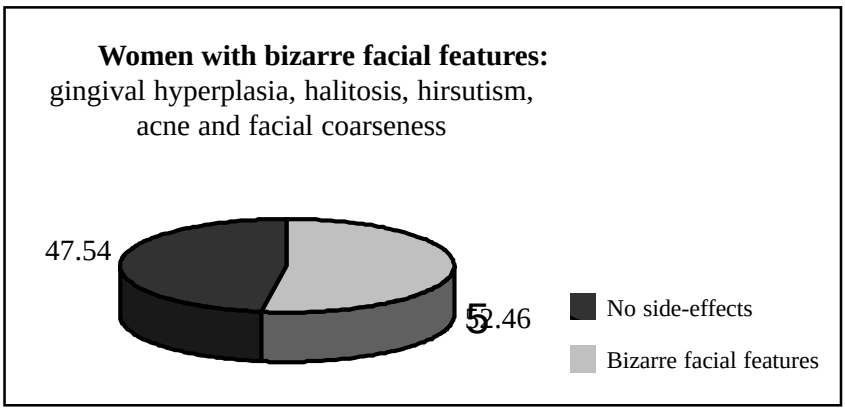

Fig 1. Women with bizarre facial features.

from epilepsy at the MCE. Unfortunately there is no safe side, being the list of side effects of PHT, like any other AED, manifold. The crippling combination of hirsutism and facial coarsening with thickening of the subcutaneous tissue, have been reported as common long-term complications PHT use. Also, there is a tendency for GH to be associated with high serum levels of the drug and duration of treatment[9]. However was noteworthy to see very few reports on this important subject. In our study for example, more than 50% of the female epileptic users showed undesirable features as a deplorable consequence of treatment. Unlike changes frequently seen, these unpleasant side-effects did not return to normal, keeping the patients with this lifetime scar. And now, these already stigmatised patients have to live not only with *abnormal phenomena* of *their brain*, but also with these iatrogenical and social limiting side-effects. Many unfortunate patients showed an "ugly-man" appearance that we defined as rasputinian facies. Most of them were unsuccessfully attempting to keep a charming feminine look, with endless shavings, as a result of the grossly deformed hairy face. The odd appearance was made by coarsened facial features, where GH was a clear cause of several bleeding episodes triggered by chewing or tooth brushing. Thus, halitosis became a *natural aroma* exhibited by most of these patients. Also, it was something surreal to notice that no one, including doctors, had paid attention to these symptoms. A considerable slice of these sample was exposed to chronic and enormously expensive psychological, dental and dermatological treatments, which gives testimony of a good deal of our reigning ignorance and consequent failure to recognize such obvious aetiology. Perhaps, for many doctors, patients and their relatives as well, epilepsy is still been identified as a *terrible lifetime condition*. So, these vulgar side-effects are usually neglected or misenterpreted as a kind of *natural tribute* that epileptic patients must pay to get freedom from seizures[10].

The association between those cosmetic effects and the lack of knowledge about epilepsy made even worse the psychological scenery among patients with epilepsy and their interaction in society. Medical and social importance given to these alterations differ from place to place, and doctors are prone to give attention or not to these side effects depending on the environment they grew up and learned their medical skills. So, we can not expect physicians from different lineages to have the same attitude and opinion before such situation.

Finally, our readers should noticed that as brazilians we belong to *latin tribe*, where good look is important to get active social life. Maybe, this aspect represents the bias side of our study. However, we suspect that artificial ugliness does not help people suffering from epilepsy to get better quality of life, does not matter which society they are living. For these reasons, we believe that except on an emergency basis, PHT should not be used as the first option in the treatment of female epileptic patients, because usually the dermatological side-effects are more socially handicapping than the epileptic syndrome by itself.

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