

Pyrex Journal of Dentistry and Oral Hygiene
Vol 1 (4) pp. 029-033 September, 2015
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Original Research Article

Frequency of drugs-induced oral pathologies in patients with epilepsy

LM Loeb¹, D Mattei¹, LO Caboclo², M Rodrigues², TC Ladalardo³, EO Lima³, LC Villanova², C Hirata³, LM Weckx³, EM Yacubian², MG Naffah-Mazzacoratti¹ and D Amado^{1*}

¹Disciplina de Neurologia Experimental, Departamento de Neurologia e Neurocirurgia UNIFESP/EPM

²UNIPETE – Unidade de Pesquisa e Tratamento da Epilepsia

³Departamento de Otorrinolaringologia e Distúrbios da Comunicação Humana UNIFESP/EPM; HSP- Hospital São Paulo; SPDM- Sociedade para o Desenvolvimento da Medicina, São Paulo, Brasil

Accepted 8th September, 2015

The treatment of epilepsy with antiepileptic drugs (AEDs) is generally a chronic procedure and may be lifelong. Although necessary to decrease the number of seizures, AEDs have been associated with significant adverse effects on several tissues. Thus, the purpose of this study was to identify in 100 patients the prevalence of gingival hypertrophy due to AEDs used to treat seizures. The frequency of dental fracture in these patients as well as other oral alterations was also investigated. Around 50% of patients treated with polytherapy showed gingival hypertrophy being 22% fibrous and 28% inflammatory. Among all patients with inflammatory gingival hypertrophy, 25% have been treated with a cocktail containing PHT and PB. In addition, the highest incidence (27%) of fibrous hypertrophy was observed in those patients using PB, CBZ and CLB. The prevalence of gingival hypertrophy was higher in patients treated with polytherapy, when compared with monotherapy (Qui-Square test $p=0.004$).

Key words: Epilepsy, gingival hypertrophy, AEDs.

INTRODUCTION

Epilepsy is one of the major public health problem affecting nearly 50 million people worldwide and comprises a collection of disorders, whose common feature is a persistent increase in neuronal excitability. Among the epilepsies, the temporal lobe epilepsy (TLE) with mesial temporal sclerosis (MTS) is the most common chronic seizure disorder during adulthood. Treatment with antiepileptic drugs (AEDs) is generally a chronic procedure and may be lifelong. Although necessary to decrease the number of seizures, AEDs have been associated with significant adverse effects on several tissues such as in the skin, lips, bones, liver metabolism, hormonal release and gingival hypertrophy. However, the latter is also associated with other factors, including acute and chronic inflammatory processes, neoplastic processes due to benign or malignant tumors, hormonal disturbances, ascorbic acid deficiency, abnormal dental eruption or disturbance on bone metabolism.

Dental injuries have been also recognized as a complication of epilepsy and may occur during episodes of seizures, through falling forwards or jaw clenching. It is also recognized that the occurrence and the aspect of dental injury seen to be related to the type of the seizure. The authors

reported that dental injury occurs in approximately 1% of all patients with epilepsy, but is significantly more often in patients with juvenile myoclonic epilepsy (JME), where it occurs in about 10%, most frequently involving injury of frontal teeth. These authors also identified other factors of risk for dental injury, such as sudden onset of seizures and absence of aura, which prevents any sort of precaution to be taken. Other factors contributing to this association are those seizures occurring more often in the morning, shortly awakening or in the bathroom, providing more hard surface to fall against than other setting (Thomas RH et al., 2009).

Another adverse effect is the gingival hyperplasia, which could be idiopathic or induced by other drugs, beside AEDs (Lin K et al., 2007; Pack AM, 2003). In this context, three different classes of drugs can be responsible for the majority of drug-induced gingival enlargement and several patients have been suffering of this adverse effect. These drugs are AEDs, several antihypertensive, drugs related to calcium antagonism and immunosuppressants, such as cyclosporine (Lin K et al., 2007). "Gingival enlargement" is the term now used to describe medication-related gingival overgrowth or gingival hypertrophy

and can be defined as an abnormal growth of the periodontal tissue. The term "gingival hyperplasia" is not appropriate since the produced enlargement is not the result of an increase in the number of cells, but rather of an increase in the extracellular tissue volume (Lin K et al, 2007). This gingival enlargement may occur either by simple hypertrophy or can be associated with an inflammatory process due to accumulation of dental plaque (Majola MP et al., 2000; Brunet L et al., 2001). The overgrowth of the gingival tissue can result in an accumulation of oral bacteria on the blunted margins.

Therefore, the level of this overgrowth is further increased when it is associated with inflammatory processes, induced by microbial dental plaque, which is related to pain, bleeding and odor (Dogan A, 2001). Numerous studies on gingival lesions have been conducted and they show that the enlargement induced by AEDs was also associated with factors relating to genetic predisposition, multiple therapies, and reduced serum folate levels (Majola MP et al., 2000). Drugs associated with gingival enlargement include cyclosporine and calcium antagonists, such as dihydropyridines, verapamil and diltiazem (Garzino-Demo et al., 1998; Brunet L et al., 2001). To control seizures a great variety AEDs have been used and some of them may induce gingival overgrowth alone or in association with other drugs. They are the benzodiazepines (BD), carbamazepine (CBZ), clonazepam (CZP), valproic acid (VPA), phenytoin (PHT), oxcarbazepine (OXC), phenobarbital (PB), lamotrigine (LTG), topiramate (TPM), primidone (PRM) and clobazam (CLB).

Currently available AEDs act by depressing the neuronal activity in the focus or by blocking the seizure spreading mechanisms. According to their mechanism of action this wide group of drugs is classified as: 1- Drugs that block the maintenance of high frequency repetitive discharges (PHT, CBZ, VPA, LMT) 2- Drugs that increase the inhibitory activity induced by the neurotransmitter GABA (VPA, PB, BD) 3- Drugs that alter the functions of the calcium channels (PHT, PB, BD) (Garzino-Demo et al., 1998; Brunet L et al., 2001). PHT is an AED is causing a large number of adverse effects, including skeletal alteration, endocrine dysfunction, immunological reaction and disturbances in connective tissues. One of them is the gingival overgrowth, which is characterized by an increased amount of non-collagenous extracellular matrix, associated with gingival inflammation, due to an increased synthesis of glycosaminoglycans (Mooder T et al., 1992). Other AEDs have also been linked to gingival overgrowth, specifically VPA and PB. Furthermore, zonisamide and PHT may alter the dentin formation and the bone mineral density of the mandible in growing rats (Takahashi A et al, 2004). In addition, the polytherapy has shown to be associated with a higher risk of bone metabolism abnormalities and gingival overgrowth, when compared with monotherapy (Pack AM et al., 2003). In this context, the purpose of this study was to identify the prevalence of gingival hypertrophy due to AEDs used to treat seizures at UNIPETE/UNIFESP/SPDM as well as the prevalence of dental fracture in patients of a center specialized in the treatment of refractory epilepsies.

Methods

One hundred patients, with age between 1 and 80 years old, being treated at UNIPETE/UNIFESP/SPDM were analyzed. These patients were examined by neurologists and dentists and several parameters were evaluated such as type of epilepsy, employed drugs, facilities to dentist access, brushing

tooth habits, fracture of teeth, previous oral surgery, parafunctional habits (bruxism, nail gnaw), dentition types, respiratory habits and the presence of inflammatory and/or fibrous gingival hypertrophy and dental fractures. Modified Gingival Index (MGI) was used to assess gingival condition of participants (Lobene RR et al., 1986) and scores ranging from 0 to 4 were employed, as described in Table 1. MGI has been used by several authors since it is based on visual inspection, eliminating the use of probing or pressure to establish the presence or absence of inflammation. MGI also makes it possible to detect and record earlier, more subtle visual changes in gingival inflammation, allows the intra and inter calibration of examiners and is noninvasive, upon repeated evaluations.

Results

In this study were evaluated 100 patients with focal epilepsies being 56% with TLE associated with MTS, 19% extra-temporal epilepsies and 25% other types of epilepsy. Clinical examination showed that 50% of all patients presented gingival hypertrophy being 22% fibrous (Fig 1-A) and 28% inflammatory (Fig 1-B). Clinically, there was an enlargement of the gingival tissue, beginning in the region of the Interdental papillae increasing gradually in size and extending laterally to the adjacent papillae. For all patients with inflammatory gingival hypertrophy (28% of total), around 85% of patients showed MGI index level 3, suggesting the presence of moderate inflammation, glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit. The remaining 15% showed level 4, which was compatible with severe inflammation, marked redness, edema, and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration.

The mandibular anterior teeth were frequently involved in both types of gingival hypertrophy. Patients with fibrous gingival hypertrophy (22%) presented MGI score level 0, showing only the presence of fibrous tissue, without inflammation. Patients treated with polytherapy (two or three drugs) including CBZ, VPA, PHT, OXC, PB, LTG, TPM, PRM, CLB and CZP, showed a higher prevalence of gingival hypertrophy, when compared with those treated with monotherapy (Qui-Square test $p=0.004$). The Fig 2-A shows the percentage of patients presenting fibrous gingival hypertrophy versus the employed drugs (AEDs), used to reduce the number of seizures. This data show that the highest incidence (27%) was observed in those patients using a cocktail including PB, CBZ and CLB. In addition, around 13% of patients presenting fibrous gingival hypertrophy have been treated with PHT, PB and CLB and 14% CBZ, LMT, TPM and CLB. Among patients with inflammatory gingival hypertrophy (Fig 2-B), 25% have been treated with a cocktail containing PHT and PB; around 18% used PHT, PB and PRM and others 11% used PHT, PB and CLB or PHT, PB, CLB and CBZ. Fifty two percent of all patients presented dental injuries, being 34% during seizure episodes and 18% of these patients reported dental injury due to other causes (Fig 3) Together these data suggest the presence of this comorbidity in these patients.

This study also showed that 58% of patients were adults, with permanent dentition. Sixty eight percent of them have previously been submitted to some type of oral surgery such as gingival surgery and tooth extraction. Fifty patients showed signs suggestive of oral breathing and 25% presented atypical swallowing and 45% presented parafunctional habits.

Figure 1.A: Fibrous Gingival Hypertrophy, Figure 1.B: Inflammatory Gingival Hypertrophy

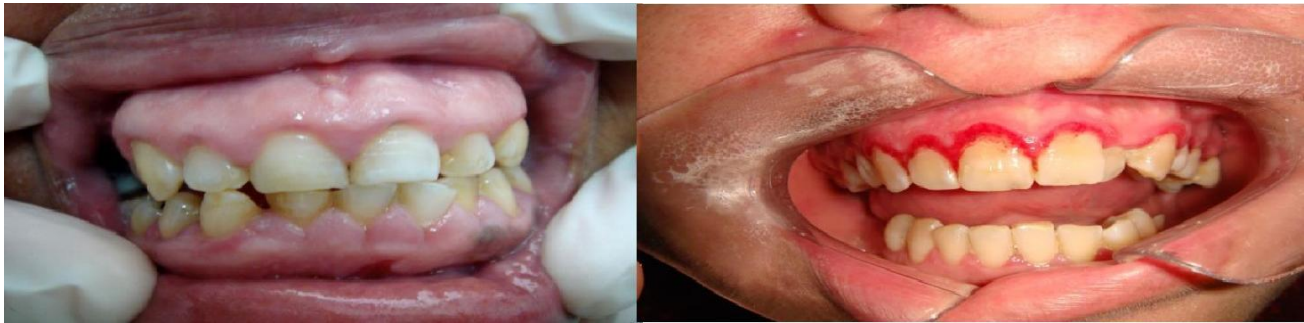


Table 1: The modified gingival index used to assess gingival condition of participants

Score	Definition
0	Absence of Inflammation
1	Mild inflammation; slight change color, little change in texture of any portion of but not entire marginal or papillary gingival unit
2	Mild inflammation; criteria as above but involving the entire marginal or papillary gingival unit
3	Moderate inflammation; glazing, redness, edema, and pain /or hypertrophy of the marginal or papillary gingival unit
4	Severe inflammation; marked redness, edema, and pain /or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding congestion, or ulceration

Figure 2.A: Patients with Fibrous Gingival Hypertrophy versus the employed drugs used to reduce the number of seizure, Figure 2.B: Patients with Inflammatory Gingival Hypertrophy versus the employed drugs used to reduce the number of seizure

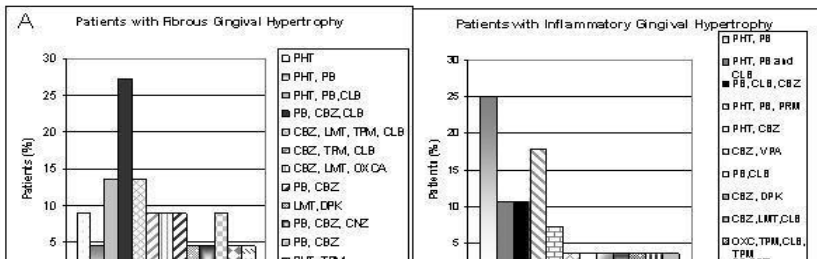
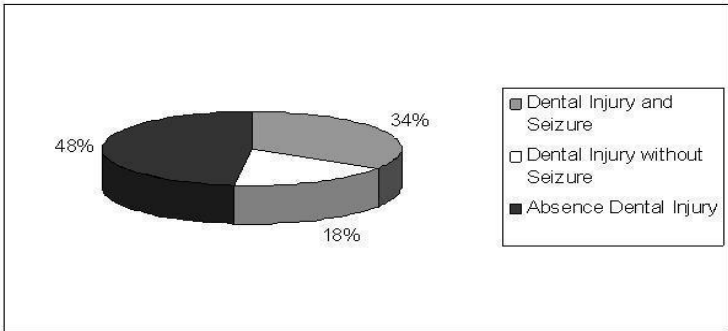


Figure 3: Patients with dental injury



Discussion

This study showed a high incidence of dental injury, high prevalence of gingival hypertrophy associated with several oral dysfunctions in patients attending the epilepsy clinic at UNIPETE/UNIFESP/SPDM. Some authors believe that gingival enlargement is a phenotypic presentation of the host's genetic response/susceptibility to the mitotic effect of phenytoin. Their argument was substantiated by the observation that some patients with high plaque levels had a normal gingival tissue, while others with no detectable plaque, exhibited clinically obvious gingival enlargement (Majola MP *et al.*, 2000).

However, our results are in accordance with previous reports (Vorkas CK *et al.*, 2008), which have suggested an association between an increase in gingival hypertrophy and the polytherapy, used to treat several types of epilepsies. Furthermore, each drug per se already shows its proper adverse effects profile such as: CBZ causes ulceration, xerostomia, glossitis and stomatitis; LTG induces thrombocytopenia and decreased platelets aggregation. In addition, some cases of the leucopenia have been related to patients on CBZ, LTG, OXC, PB, PHT, PRM, TPM and VPA treatment (Vorkas CK *et al.*, 2008). Since 1939, when gingival hypertrophy was first described by Kimball, several works have reported the risk factors for gingival overgrowth, associated with polytherapy such as: high risk (PB and PHT or VPA and PHT), medium risk (PRM and PHT) and low risk (CBZ and PHT) [6;13]. Studying 37 patients Brunet *et al.* (2001) observed that, from 14 patients taking only low doses of PHT (300mg/day) without another drug and from 23 patients receiving PHT plus PB around 58% developed gingival hypertrophy. According to these authors, the intake of PHT would be the main factor to the appearance of gingival hypertrophy.

Furthermore, some types of AEDs are more linked to gingival overgrowth, specifically VPA, PB and PHT. Other AEDs as zonisamide and PHT alter the dentin formation and the bone mineral density of the mandible in growing rats (Takahashi A *et al.*, 2004). Another adverse factor, induced by AEDs in these patients was the oral breathing, which can predispose to other types of lesions in gingival tissue (Vorkas CK *et al.*, 2008; Guimarães JJ, 2007). The data obtained after examination estimate a rate 52% of dental lesions in patients with active epilepsy, showing a high incidence of this morbidity. These tooth fractures may occur due to falls during seizures episodes or due to the action of drug cocktail in calcium metabolism or alteration in the dentin formation and changes in mineral density of the teeth (Takahashi *et al.*, 2004). Falls can accompany many seizure types, causing soft tissue lacerations, facial fractures, temporomandibular joint subluxation and desvitalization, fractures and subluxation or avulsion of teeth (Vorkas CK *et al.*, 2008). However, the high incidence of tooth fracture far from an ictal period may suggest the presence of alteration in mineral tooth and dentin of these patients, since polytherapy has been associated with a higher risk of bone metabolism abnormalities. In this context, few studies investigating bone diseases associated with AEDs have suggested the use of a specific therapy for bone disease, including calcium and vitamin D supplementation (Pack AM, 2003).

This study confirms the strong relationship between polytherapy with AEDs and gingival overgrowth and tooth fracture, during or after seizures. Patients that used a cocktail with PB, CBZ and CLB; PHT, PB and CLB; CBZ, LMT, TPM and CLB showed several fibrous gingival hypertrophy.

However, patients with inflammatory gingival hypertrophy using a cocktail with PHT and PB; PHT, PB and PRM and others that used PHT, PB and CLB or PHT, PB, CLB and CBZ, also showed several inflammatory gingival hypertrophy (score 4). Others studies confirmed the higher prevalence of gingival hypertrophy observed in anticonvulsant polytherapy. This fact has been related to the interaction of PHT with PB or with CBZ. Kamali (1999) reported that chronic comedication with other DAEs that induce PHT metabolism (such PB, PRM or CBZ), does not affect the plasma or saliva 5-(4-hydroxyphenyl)-5-phenylhydantoin (4-HPPH) steady-state levels, nor the degree of gingival hypertrophy in adult epileptic patients treated with PHT).

Thus, our data showed that some of these drugs, alone or in association could induce gingival overgrowth and severe inflammation, marked redness, edema, pain, spontaneous bleeding, congestion or gingival ulceration. Our data also showed that the worst association between drugs was PB+CBZ+CLB (25-30%) for generating of fibrous gingival hypertrophy and PHT + PB for inflammatory gingival hypertrophy (25%). Indeed, the treatment for gingival hypertrophy should be the discontinuation of the polytherapy but unfortunately this approach is often not possible due to uncontrolled seizures. In this case the best association between drugs with a minor grade of gingival hypertrophy could be CBZ+VPA (<5%) followed by PB+CBZ (5-10%). The other associations between drugs such as PHT+ PB +CLB; PHT+PB and PB + CBZ+ CLB evolve a percentage of 10-30% of fibrous or inflammatory gingival hyperplasia presence. In this sense, although the control of seizures should be the priority of medical care, when possible, less aggressive association between drugs could be employed.

Soga (2004) reported that patients with severe gingival hypertrophy exhibited significantly higher serum PHT concentration than those without overgrowth. Therefore, the patients with CYP2C9*3 (responsible for the hydroxylation of up to 90 % of serum PHT) carriers may easily be led to carry high serum PHT, and thus, should be considered to be at high risk for developing severe gingival overgrowth. This study indicated that other genetic and environmental factors influenced the severity of the disease (Soga Y *et al.*, 2004). In addition, the effective treatment involves surgical elimination of gingival tissue excess (gingivectomy) or periodontal flap approach, plaque removal and correction of parafunctional habits. Thus, multidisciplinary activities are very important to eliminate local irritants as oral breathing and atypical swallowing. As gingival hypertrophy is a process associated with pain, edema, infections and an increase in caries incidence, the treatment with AEDs should be followed by a dentist to prevent or treat the gingival hypertrophy and to correct oral breathing or other incorrect habits as well as other related oral pathologies.

Acknowledgments

The authors are grateful to all professionals from UNIFESP/SPDM and UNIPETE, responsible for the clinical care and surgery of all patients. This work was supported by Brazilian grant agencies (FAPESP, CInAPCe, FADA, CNPq, CAPES), MCT-INNT and DMC®.

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