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Phenytoin Induced Gingival Enlargement - A Case Report and Review

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Abstract

The potential of phenytoin to induce gingival enlargement has been well established, since it was first reported in the early 1960s in institutionalized epileptic children who were receiving therapy with phenytoin for the treatment of seizures. High levels of dental plaque and calculus have been reported as a critical co-factor for the development and severity of phenytoin induced gingival enlargement. This report documents a severe generalized gingival enlargement in a medically compromised patient who is on phenytoin.

Keywords: Phenytoin, Gingival enlargement, Epileptic attacks.

Introduction

Phenytoin (sodium 5, 5-diphenylhydantoin) has been the drug of choice in the suppression of grand mal seizures & other convulsive disorders for about 6 decades. Phenytoin has also been used to treat migraine, neuropathic pain, anxiety & bipolar disorders.[1] The adverse effects can be broadly classified into those that are reversible and dose dependant (ataxia, sedation, dizziness, cognitive dysfunction) and those that are chronic and not rapidly reversible (such as changes in the body weight, hirsutism and gingival enlargement).[1] Drug induced gingival overgrowth was first reported in 1939 and is associated with the chronic usage of the anti-epileptic drug phenytoin. Gingival changes can occur within 3 months of dosage.[2,3]

This report demonstrates the value of consultative planning between oral care practitioners and physicians for the prevention & treatment of gingival lesions in medically compromised patients.

Case Report

A 10 year old boy with cerebral palsy and gingival enlargement presented to Department of Periodontics, Goa Dental College and Hospital. Medical history revealed prolonged labour followed by a breach delivery. There were no antenatal complications. He had his first grandmal epileptic attack on the 18th day after birth. History revealed delayed milestone, could turn

from supine to prone position at 6 weeks and achieve head control at the age of 1 and able to crawl at the age of 2 years. He allows himself to be fed, but is unable to grasp objects. Speech development is impaired. Extraoral examination revealed incompetent lips due to generalized massive gingival enlargement, which protruded from the mouth, resulting in an esthetic disfigurement (Figure 1, 2).

Intraoral examination revealed generalized gross gingival enlargement covering all erupted teeth resulting in the presence of pseudoclefts (Figure 3,4). The vertical and horizontal growth was more severe in the maxillary anterior region (Figure 2,3,4). The enlargement was mulberry shaped and firm in consistency. In some areas the gingiva was bright red, soft, friable and painful thus showing signs of inflammation (Figure 2,3,4). The enlargement started approximately 4 months after commencement of phenytoin therapy.

Discussion

Phenytoin (5-diphenylphenytoin) has been used to control seizure disorders in patients with epilepsy since its clinical introduction by Merrit and Putnam in 1938.[4] Due to the effectiveness of this medication in controlling convulsive seizure disorders and its low cost, availability and frequency of administration phenytoin is being used for the more than six decades.[1] Within a year of its initial clinical use, reports linking phenytoin to gingival overgrowth appeared in the literature. Phenytoin induced Gingival enlargement is known to begin in the interdental papillae within 3 months of use. With time the enlargement becomes generalized and develops a characteristically lobulated, thickened appearance, thus partially or completely covering the tooth surface and the occlusal surface thus making it esthetically displeasing. In severe cases it may disrupt the functions of speech and mastication. There is a tendency for the gingival enlargement to be distributed symmetrically and for the anterior teeth to be more severely affected than the posterior teeth, as is seen in our patient. It is rare in edentulous areas and known to disappear after extraction of teeth.[1,4]

It has been reported that gingival enlargement has a multifactorial nature and is affected by factors such as age, demographic variables, genetic predisposition, oral hygiene status, pharmacokinetic variables, molecular and cellular changes in gingival tissues. Most studies have shown an association between oral hygiene status and both the prevalence and severity of drug induced gingival overgrowth. This suggests that plaque induced gingival inflammation may be a critical co-factor in the development and expression of the gingival changes, thus leading to edematous and hyperemic gingiva. When this is the case, plaque removal is made more difficult by the distorted contours of the gingival tissues thus perpetuating the cycle.[4]

While the physiology behind Drug Induced Gingival Enlargement has not been definitely elucidated, histopathology studies have shown that the gingival tissue volume increase is due to an excessive accumulation of extracellular matrix proteins including collagen & plasma cells.[2] Hence, the enlargement is primarily a connective tissue response. A role of genetic factors has also been investigated. It has been suggested that human gingiva contains genetically predetermined phenytoin sensitive sub-populations of fibroblasts, as a result, phenytoin and its major metabolite 5-(p-hydroxyphenyl)-5-phenylhydantoin (pHPPH) reacts with some cells stimulating greater collagen and protein production.[2,3] Some studies have demonstrated that patients developing gingival lesions have a high frequency of particular Human leukocyte antigens (HLA) and genetic markers (cytochrome P450, HLA-

DR2) and this appears to be related to a genetic predisposition for pathology. Cytochrome P450 is responsible for metabolism of phenytoin in the liver associated with gingival enlargement.[5] Furthermore, it has also been reported that patients who expressed genetic markers such as HLA-B37 or HLA-DR1 are afforded some degrees of protection against gingival overgrowth. Early in vitro studies showed that phenytoin induced gingival enlargement may be more related to a lack of collagen breakdown as opposed to an increase in collagen production.[6] Drug induced gingival enlargement is more common in children and could cause significant disfigurement & functional difficulty as it impairs speech, mastication & can disturb occlusal contact. Furthermore, it promotes plaque accumulation and causes tremendous difficulties during self or professional plaque control especially in children with disabilities who are under anticonvulsant therapy, as was in the above mentioned case. It has also been reported that tooth migration might occur due to severe drug induced gingival enlargement, along with delayed eruption of primary teeth.[6] Also, phenytoin has been known to induce deficiency of salivary Ig A, which can result in increased susceptibility to gingival inflammation which is considered to be one of the predisposing factors for the development of gingival hyperplasia.[7] The number of Langerhans cells also increase in gingival epithelium in patients with phenytoin induced gingival enlargement.[8] The relationship between such an increase in Langerhans cells and gingival overgrowth remains speculative.

It has been shown that an increase in IL-1 is related to increase in Langerhans cells in chronically inflamed gingival.[8] IL-1 can stimulate fibroblast proliferation in the presence of primary growth factors thus, phenytoin induced gingival enlargement and increase in Langerhans cells may be mediated via IL-1/growth factor interaction. Phenytoin may also interfere with folic acid absorption and metabolism and lead to a significant decline in folate levels. This phenomenon is also one of the most important promoters of phenytoin induced gingival enlargement. Folic acid is known to interfere with the production of pHPPH, a byproduct of phenytoin metabolism which is basically responsible for the gingival overgrowth. Thus, systemic folic acid & folate based mouthwash prescribed along with phenytoin can delay the onset & reduce the severity of gingival enlargement.[9.10,11] Intraoral examination too revealed generalized gross gingival enlargement, covering all the erupted teeth resulting in the presence of pseudoclefts (Figure 3,4). The vertical and horizontal growth was more severe in the maxillary anterior region (Figure 2,3,4). Enlargement was mulberry shaped, firm, In some areas the gingiva was soft, friable, bright red, painful, thus showing signs of inflammation (Figure 2,3,4). The enlargement started approximately four months after the commencement of phenytoin therapy.

Conclusion

In the above presented case maintenance of a healthy periodontium was difficult as the patient was physically & mentally challenged & the gingival enlargement was gross. Surgical resection of hypertrophied gingivae has been traditionally carried out, but owing to its insidiously progressive nature, the overgrowth recurs. Thus, despite our great understanding of the pathogenesis of Drug Induced Gingival Enlargement, treatment still remains a challenge. The reluctance of the neurologist or of the patient to change an ongoing anti-convulsant program is often a response to a long history of tedious steps in medication adjustments to establish a level of seizure control without sacrificing alertness and mood control. Moreover, it's important to assess the

status of periodontal health before the initiation of the drug therapy.

Thus, role of the periodontist & neurologist in monitoring gingival health, epileptic attacks & controlling gingival inflammation is very important.

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Figure Legends

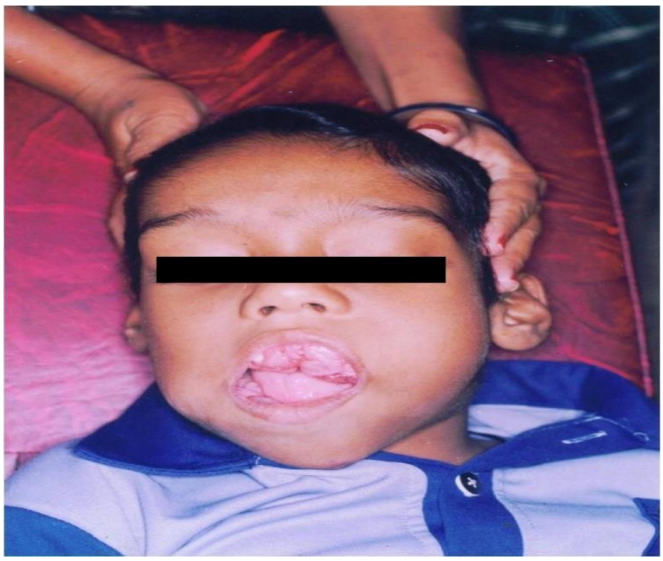

Figure 1: Extraoral view

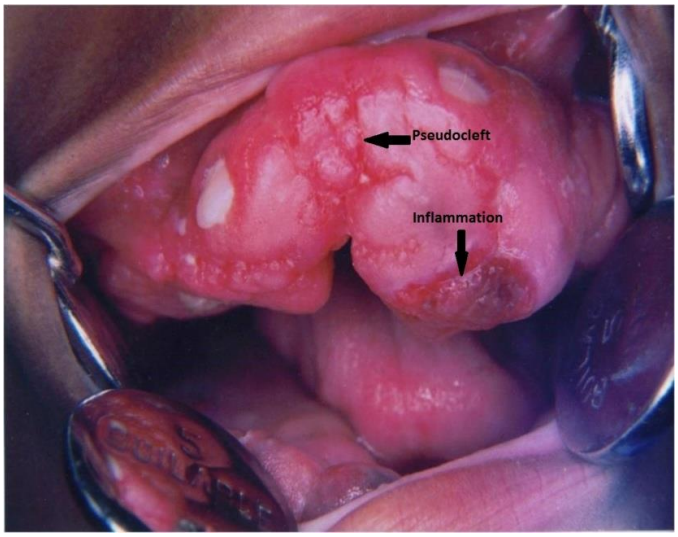

Figure 2: Maxillary anterior view

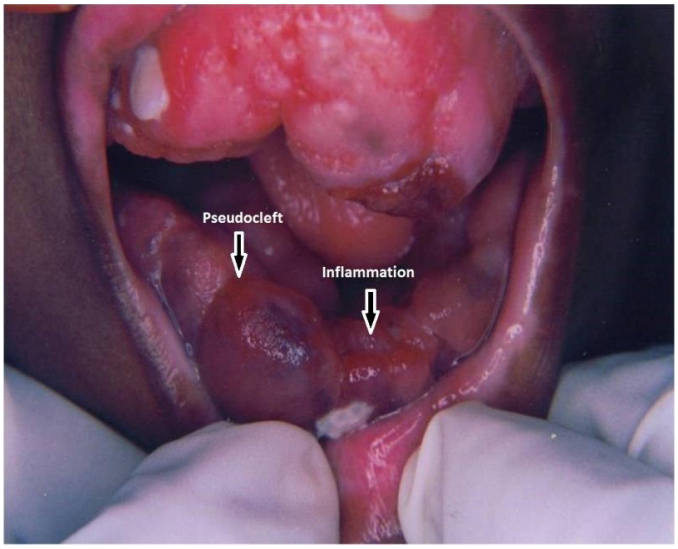

Figure 3: Maxillary and Mandibular view

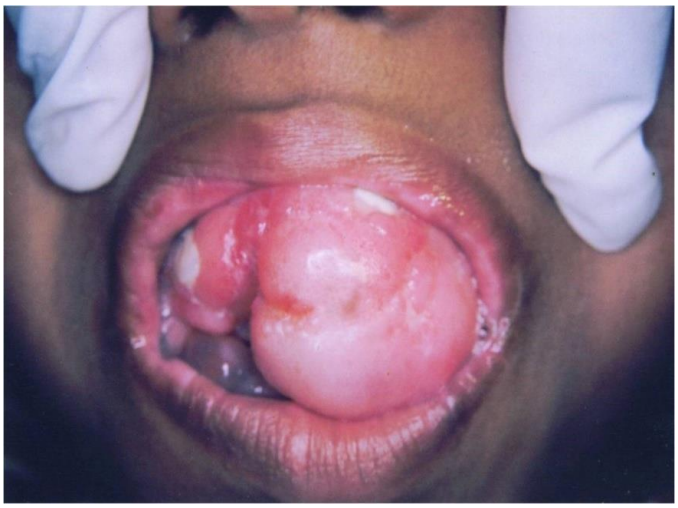

Figure 4: Gingival enlargement protruding from the mouth