Review Article
Phenytoin-induced gingival overgrowth


Gingival overgrowth is a common adverse effect of therapy with Phenytoin, having important medical and cosmetic implications. Poor periodontal hygiene is an important risk factor for severity of Phenytoin-induced gingival overgrowth (PIGO), which is a time-dependent process. There is complex interplay of altered fibroblast biology, connective tissue turnover, inflammatory processes, and growth factors on a background of genetic susceptibility to produce increase in various components of interstitial matrix in PIGO tissue. Treatment options have included change of PHT to another anti-seizure drug, measures to improve periodontal hygiene and gingivectomy. There is conclusive evidence that folic acid supplementation significantly decreases the incidence of PIGO.

Gingival overgrowth was recognized as an adverse effect of Phenytoin (PHT) in 1939 (1), just a year after it was first used for the treatment of epilepsy (2). This phenomenon has several important cosmetic and medical implications. Because of increasing awareness and concern about appearance and self-image, especially among adolescents, Phenytoin-Induced Gingival Overgrowth (PIGO) may create compliance issues with failure of otherwise effective therapy. Gingival overgrowth also leads to the formation of pocket within gingivo-dental sulcus with potential accumulation of debris, leading to poor dental hygiene, halitosis, and gingival bleeding. The problem of PIGO is very relevant to developing countries because PHT is a very commonly prescribed medication because of cost and familiarity and is usually not substituted by other anti-epileptic drugs (AED) even where it is feasible. Also, a sizeable proportion of patients in any public health facility in developing countries lack acceptable dental hygiene. The present article has reviewed the problem statement, clinical features, pathogenesis, treatment, and prevention of this important entity (Table 1).

Epidemiology
A review of the studies from 1939 to 1972 found a median incidence of 52% (0–84.5%) (3). A community-based cross-sectional study in 1997 (n = 134) found the prevalence of PIGO to be 39% in patients on PHT for more than 1 year (4). Prospectively collected data from India have shown the incidence to be 57% in children aged 8–13 years (n = 30) over 6 months of follow-up (5). This variability is contributed by several factors including the definition(s) used, ascertainment method(s), and concomitant intake of other drugs (6). A recent prospective study showed that with careful observation some degree of PIGO was found in up to 89% of children aged 6–15 years on PHT for 6 months (7).

Risk factors
Phenytoin-Induced Gingival Overgrowth is mainly a problem of older children and young adults, being exceptionally rare in edentulous subjects (8). PIGO has a controversial relationship with the dose and serum levels of PHT (9, 10). Even local levels of PHT or its important metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (4-HPPH) in saliva (11) or gingival crevice fluid (12) have no clear correlation with the prevalence and severity of PIGO. Experimental models demonstrate that probably serum levels only have a permissive effect (13). It is believed that co-administration of other AED, especially phenobarbitone and carbamazepine, increases the risk of PIGO, probably by increasing the levels of certain PHT.
metabolites from hepatic enzyme induction (14); however, this has been challenged (15).

Periodontal hygiene is an important determinant of severity, but probably not the incidence of PIGO. Indices of gingival inflammation and plaque accumulation have shown significant correlation with grades of PIGO (16, 17). However, overgrowth itself distorts the gingival contour and impedes plaque removal leading to exacerbation of local inflammation and complicating PIGO (18). In actual clinical setting, several of the risk factors operate concurrently and different studies vary in their results regarding predictors of occurrence or severity of PIGO (19).

Clinical features

Gingival overgrowth is usually first noticed after 3–6 months of PHT therapy and reaches its maximal severity by 9–18 months. The first sign of enlargement is noticed in the inter-dental papilla region. Gradually, gingival lobulations extend along the labial, lingual, and coronal aspects to cover entire anatomic crowns of teeth (Fig. 1). The gum appears dense, resilient, and stippled (20). The effects are most apparent in the anterior part of mouth (8). Various grading systems are used for quantifying the severity of PIGO, which is important for therapeutic decision making and research purposes (Table 2).

Pathology

Routine microscopic examination of gingival tissue in patients with PIGO has shown decreased collagen volume density with increased interstitial ground substance (8). Immunohistochemistry has characterized this to result from proliferation of fibroblasts, formation of pro-collagen fibers and non-collagen proteins, especially glycosaminoglycans (GAGs) (21); and altered distribution of fibronectin, collagen types, and GAGs (22, 23). Increased synthesis of GAGs by gingival fibroblasts derived from patients with PIGO has, indeed, been documented (24). Electron microscopy has also shown decreased volume density of rough endoplasmic reticulum and nuclear–cytoplasmic ratio, suggestive of altered synthesis and release of connective tissue proteins (25).

Pathogenesis

The mechanisms of development of PIGO are multiple and complex including alterations at cellular and molecular level involving fibroblasts, cytokines, growth factors, and genetic susceptibility. For the purpose of easy understanding, these mutually overlapping, concurrently operational processes are described separately (Fig. 2).
Connective tissue dynamics

Fibroblast is a key player in the gingival connective tissue homeostasis. Human gingival fibroblasts can be said to consist of two sub-populations in response to PHT exposure: ones which proliferate and alter their protein synthesis (the responders) and those who do not (non-responders). Selection of the otherwise unusual responder phenotype in response to PHT has been demonstrated (26). Increase in collagen production and decrease in its degradation in response to PHT has been shown in gingival fibroblast monolayer cultures (24). The same experimental model also documented

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**Table 2. Grading systems for severity of Phenytoin-Induced Gingival Overgrowth**

<table>
<thead>
<tr>
<th>Grade</th>
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<tr>
<td>0</td>
<td>No hyperplasia, normal gingiva</td>
<td>0</td>
<td>No changes</td>
<td>a. No hyperplasia</td>
<td></td>
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<tr>
<td>1</td>
<td>Hyperplastic gingiva covering the cervical third or less of the anatomic crowns of anterior teeth</td>
<td>1</td>
<td>Qualitative changes only. Gums are firm and stippled with granular appearance</td>
<td>b. Minimal: increased density of gingiva with marked stippling and granular appearance</td>
<td></td>
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<tr>
<td>2</td>
<td>Hyperplastic gingiva extending anywhere in the middle third of the anatomic crowns of anterior teeth</td>
<td>2</td>
<td>Quantitative changes. Gingival enlargement with hyperplastic tissue covering less than half of the crown</td>
<td>c. Moderate: increase in the size of papilla or rolled gingival margins</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Hyperplastic gingiva covering more than two-thirds of the anatomic crowns of anterior teeth</td>
<td>3</td>
<td>Severe hyperplasia. Hyperplastic tissue covering more than half of the crown or interfering with mastication</td>
<td>d. Severe: profound thickening of gingiva covering a large percentage of the clinical crown</td>
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**Figure 2.** Pathophysiology of Phenytoin-Induced Gingival Overgrowth: Phenytoin leads to increased generation of inflammatory cytokines and matrix substance by gingival fibroblasts. Some of the cytokine mediators lead to gingival inflammation and set up a vicious cycle. PGE2 causes selection of the “responder phenotype” of fibroblasts. The net result of these processes is increase in matrix collagen and non-collagenous proteins. PHT, Phenytoin; PLA, Phospholipase A; COX, Cyclo-oxygenase; AA, Arachidonic Acid; IL, Interleukin; PG, Prostaglandin; GAG, Glycosaminoglycan; MMP, Matrix Metalloproteinase; TNF, Tumor Necrosis Factor.
increased GAG synthesis with corroborative ultrastructural changes in the cellular protein synthetic apparatus (24). One of the mechanisms for decreased collagen degradation is production of inactive collagenase by fibroblasts in response to PHT (27).

Another theme in the connective tissue biology of PIGO is alterations in interstitial matrix. It has been shown that PHT and Cyclosporin-A suppressed the expression of some matrix metalloproteinases (28). Some lysosomal cysteine proteinases (cathepsins) are also considered important for the digestion of matrix components. Depressed cathepsin activity in response to PHT may jeopardize intracellular degradation of nascent procollagen and increase the amount of matrix ground substance (28, 29). In fact, gingival overgrowth probably because of defective cathepsin activity is described in a lysosomal storage disorder mucolipidosis II (I cell disease). Hence, PIGO may also be considered as a consequence of acquired lysosomal dysfunction.

### Inflammation

The contribution of inflammation in the exacerbation of PIGO has been proposed very early (8), but the knowledge of cytokine chemistry remains incomplete. Substantial work in this field has come from the group of Prof. Thomas Modeer from Karolinska Institute, Sweden.

Exposure to PHT results in up-regulation of prostanoid formation in gingival fibroblasts because of increased activities of phospholipase-A2 and cyclo-oxygenase (30). In fibroblasts derived after 9 months of PHT therapy, interleukins (IL) 1α, 1β, and tumor necrosis factor (TNF)-α induced a significantly higher generation of prostaglandin (PG) E2 and increased release of arachidonic acid (AA) (30, 31). Also, there was increased PGE2 synthesis in response to exogenous AA. Further, IL-1β was reported to stimulate biosynthesis of hyaluronic acid and proteoglycans in gingival fibroblasts (32). These experiments offer attractive possibility of using PG synthesis inhibitors for the therapy of PIGO. Indeed, acetylsalicylic acid was found to reduce the incidence of cleft palate in PHT-treated mice (33). It has been further shown that 4-HPPH metabolite does not affect IL-1β production, which however, is induced by the co-exposure to PHT and TNF-α especially in the presence of PG endoperoxide synthase inhibitors like indomethacin (34). TNF-α also increases the release of AA in human dermal and rat gingival fibroblasts (35). PGE2, thus induced by IL-1, affects hyaluronic acid and GAG synthesis in extra-cellular matrix (36). Also, PGE2 induces selection of human gingival fibroblasts with enhanced matrix synthesis in cell cultures (37). Recently, PHT has also been shown to up-regulate production of other cytokines as well (IL 6 and 8) which are important for recruitment and activation of inflammatory cells (38). Hence, PHT may have an important role in the establishment of a complex interaction between inflammatory mediators and connective tissue cells in periodontal tissue.

### Growth factors

The role of altered growth factor metabolism in the pathogenesis of PIGO has been the subject of several recent investigations. A study demonstrated down-regulation of epidermal growth factor receptor (EGF-R) metabolism in a responder patient after exposure to PHT; as evidenced by reduced EGF-R mRNA in cultured fibroblasts (39). The probable mechanisms include decreased EGF-R synthesis and increased internalization. The pathogenic link to PIGO remains obscure; however, increased pretreatment levels of EGF-R mRNA in gingival fibroblasts may be a biomarker to identify patients at risk for developing PIGO (39). Increased expression of platelet-derived growth factor by accumulated macrophages and higher connective tissue growth factor immune-staining in PIGO tissue has also been documented (40–42). It is hypothesized that these alterations may be responsible for overproduction of matrix substance and fibrosis.

### Genetic susceptibility

At cellular level, normal human gingival fibroblasts include phenotypically distinct sub-populations synthesizing large (high activity) or low (low activity) amounts of collagen and other proteins, respectively. High activity fibroblasts appear to be more sensitive to PHT and 4-HPPH leading to selection of ‘the responder phenotype’ (43). At subcellular level, single-nucleotide polymorphisms in the coding region of cytochrome CYP 2C influencing PHT metabolism have been identified (44). Carriers of CYP 2C9*3 exhibited higher serum levels to dose ratio; however, as noted earlier, relationship between the drug levels and the development of PIGO is not exactly delineated.

### Management

It is known that lower grades of PIGO usually reverse after a mean duration of 4 months on stopping PHT, which may not be feasible many-a-
times (45). Grade 3 PIGO requires gingivectomy to establish normal contour of gums, but it may be complicated by recurrence on continued exposure to PHT. The other management options lie between these two extremes.

Plaque control

Poor periodontal hygiene correlates with severity of PIGO as supported by correlation between plaque index, gingival inflammation, and PIGO (16, 17). Also, there is evidence to support plaque control program as a palliative measure (17, 46). However, gingival overgrowth itself distorts the gingival contour that impedes plaque removal and exacerbates inflammation creating a vicious cycle (47). When starting PHT therapy, instructions should include intra-sulcular method of brushing and inter-dental cleansing (17, 47). Chlorhexidine mouth rinse was found to have some value in preventing PIGO in post-operative patients (48), however, a chlorhexidine toothpaste was not useful for therapeutic purpose (49).

Folic acid

Folate supplementation has shown considerable promise as a preventive (7) and therapeutic measure for PIGO. In an uncontrolled observation of nine individuals with PIGO, seven had sub-normal folate levels (1–2.9 ng/ml, mean 1.6). After 6 months of folate supplementation (5 mg/week), PIGO completely resolved in six and remained unchanged in one individual (50). However, a double-blind randomized controlled trial (RCT) comparing 3 mg/day folic acid for 16 weeks vs placebo (n = 20) concluded that folate supplementation is an inadequate therapy for established PIGO (51). This study had some methodological issues because the trial arms were not comparable and no suitable adjustment was made. Another three arm RCT compared daily two topical applications of 1 mg/ml folate solution, two daily doses of systemic folate, and placebo given for 6 months for the prevention of PIGO. Topical folate was found to significantly inhibit PIGO when compared with other two groups (52). Folate deficiency induced by PHT can cause degenerative changes in succular epithelium and exacerbate inflammation (20). Folate supplementation probably reduces gingival inflammation by binding to plaque-derived endotoxin; and additionally interferes with generation of 4-HPPH (53). It has been documented that folate is transported to gingival tissue in PIGO patients using sodium coupled active transport and passive diffusion (54).

Recently, the preventive role of oral folate supplementation has been established (Class I evidence) (7). This double-blind RCT (n = 120) showed that 0.5 mg/day folate supplementation significantly decreased in the incidence of PIGO (absolute risk reduction 67%, 95% confidence intervals 54–80%, \( P < 0.0001 \)) in children aged 6–15 years (7). It is recommended that folate may be co-prescribed in any patient being started on PHT therapy.

Other drugs

There is anecdotal evidence supporting some other drugs for treatment of PIGO. A single case report documented reduction in PIGO with isotretinoin (55). The probable mechanisms include effects on cyclic adenosine monophosphate, which is inhibitory to fibroblast growth; and on ornithine decarboxylase which is rate limiting enzyme for biosynthesis of polyamines associated with cell growth and division.

Azithromycin has been found to be effective for remission of cyclosporine-A induced gingival overgrowth in renal transplant recipients (56). The proposed mechanisms include blocking of cell proliferation, interference with collagen synthesis, and activation of matrix metalloproteinases. Because it is known that PHT encourages selective bacterial growth in periodontal tissue and has analogous mechanisms for the development of gingival overgrowth, it is hypothesized that azithromycin may have a role in therapy of PIGO.

Conclusion

Gingival overgrowth is a common adverse effect of Phenytoin therapy, which has cosmetic and medical significance particularly in developing countries. It results from complex biological mechanisms including selection of a sub-population of gingival fibroblasts, altered connective tissue turnover and inflammation. The role of genetic susceptibility is also being recognized. Maintenance of proper periodontal hygiene has a role in prevention. There is now conclusive evidence that oral folic acid supplementation should be routinely considered in children on Phenytoin therapy.

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Conflict of Interest

None of the authors have any conflict of interests to disclose.
References


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