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Clinical management of phenytoin-induced gingival overgrowth in handicapped children

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Abstract

Phenytoin (PHT)-induced gingival overgrowth (PIGO) due to chronic administration remains an unsolved problem. The prevalence of PIGO in the general population is around 40% of those taking the drug. Younger age groups experience more lesions than adults and in the handicapped the prevalence appears to be highest. Oral hygiene modifies PIGO and it is suggested that minimal plaque drug levels (of salivary origin) and/or metabolite levels may be important for lesion production by having a direct affect on the gingiva. The most satisfactory treatment is the elimination of the drug, if possible. Patients who must be maintained on PHT respond well to a program of meticulous oral hygiene at home along with frequent professional prophylaxes. Surgical removal is indicated when the severity of the lesion is such that esthetics, mastication or secondary inflammation becomes a problem. Use of a positive pressure appliance and maintenance of good oral care after surgery has been shown to control resurgence of the gingival overgrowth.

Introduction

In 1937 Merritt and Putnam[1] introduced the first successful anticonvulsant or antiepileptic drug, Phenytoin (PHT). Drugs that preceded PHT, bromide and phenobarbital, were not specific for epilepsy and had a broad central nervous system effect. PHT was not a sedative and was not addictive, but controlled convulsions by modifying the bioelectrical activity of the affected central nervous system cells. Because of this ability to regulate cellular bioelectrical activity PHT has proven to be effective not only in epilepsy, but in a variety of other disorders. These include mood and behavior problems, stuttering, migraine and other headaches, neuromuscular pathologies, cardiac problems, and a variety of other maladies where cellular bioelectrical activity require regulation.[2]

Because of its wide therapeutic range, it is now estimated that in the United States there are well over two million persons using this drug on a chronic daily basis.[3] The usual adult dosage of PHT is 300mg per day taken orally. It is slowly absorbed by the intestines and reaches a peak plasma level in four to 12 hours. Serum levels of 10-15ug/ml are usually required for seizure control. Generally, there are no side-effects at serum levels below 15ug/ml.[4]

PHT, which has been tested by continuous use over long periods, and by a very large number of individuals, has proven to be one of the safest of the anticonvulsants currently being used. This drug has remarkably few side-effects, but of those reported, gastric distress, skin rash, minor central nervous system reactions and gingival overgrowth are the most common.[4]

Since this review is limited to a discussion of PIGO in handicapped children, it is appropriate to identify briefly some handicapping disorders in which PHT therapy may be used. Patients having cerebral palsy may have cerebral cortical damage which cause seizures. PHT may be used to treat certain types of psychotic patients, children with behavior disorders, various neuromuscular disorders (e.g., choreas and neuromyotonic syndromes), and infections and traumas affecting cortical cells.[2]

PHT therapy initiated before the eruption of the permanent teeth may delay eruption. It may reach a point where surgical intervention is necessary for eruption to occur. A delayed passive eruption may also occur leaving only a partially exposed anatomical crown making the teeth appear short.

The lesion assumes a different form when PHT therapy is started after the eruption of the permanent teeth. The first sign of the overgrowth is usually a painless enlargement of the interdental papillae which may be accompanied by swelling of the gingival margin. If there is no secondary inflammation, the gingiva is pink, firm and does not bleed easily. Gradually the gingival changes become more prominent and with enlargement, the interdental papillae become mulberry-like in appearance. These interdental lobulations extend labially and, less often, lingually. If growth continues, they meet at the center of the labial of the tooth surface, separated by a small cleft. With further enlargement the lobulations may coalesce at the mid-

line of the labial or lingual tooth surface and gradually encroach on the crowns of the teeth. In extreme cases, the gingival tissue may completely cover the anatomical crown with a solid mass of firmly resilient tissue.

As can be expected, these tissue masses become traps for debris and plaque, are difficult to clean and enhance secondary inflammation. With such involvement, esthetics becomes a serious problem and can only worsen the psychological difficulty already experienced by patients with epilepsy or other handicaps. Furthermore, with such masses of tissue extending onto the tooth biting surfaces, mastication becomes difficult and tissue trauma can occur. These lesions may usually be classified as purefibrotic or inflammatory type of gingival overgrowth. In the mentally retarded, where oral hygiene is limited, we appear to encounter the latter lesion more frequently.

Gingival overgrowth can be induced by factors other than PHT (e.g., mouth breathing, irritations along the necks of teeth or hormonal alterations such as those at puberty). These same factors appear to enhance the size of lesions in a PIGO. No matter what the etiology, the lesions appear grossly and histologically similar.

Any irritant to the gingival tissues, such as an orthodontic band or defective dental restoration, appears to encourage an earlier onset and an enhanced reaction of the gingival tissues to PHT. Similarily, irritation or inflammation induced by mechanical means in experimental animals receiving PHT aids in producing the lesion.[5,6]

Oral hygiene modifies the gingival overgrowth, but the degree of the fibrosis and its relationship to oral hygiene is disputed in the literature. Glickman and Lewitus[7] found that removing plaque, calculus and other local irritations eliminated inflammation, but only reduced the severity of the changes caused by PHT. My own clinical observations indicated that once the overgrowth condition begins it can be reduced with good oral hygiene, but is extremely difficult to eliminate completely without surgical intervention or eliminating drug intake. The relationship between oral hygiene and gingival overgrowth is complicated by the possibility that it is the lesion that causes the poor local hygiene. Several investigators maintain that elimination of plaque and gingival irritation prior to the initiation of PHT therapy will prevent the development of the lesion.[8,9] Their work supports the view that inflammation is a prerequisite for the development of the pathology and the prevention must be directed toward eliminating the causes of this inflammatory component.

Prevalence

Depending on the study quoted, from 3% to 78% of those on PHT will experience gingival overgrowth, with most investigators placing the rate at about 40%.[5] My observations at the epilepsy clinic at the University of Illinois indicate a much lower prevalence (around 25%) and, of those so affected, approximately 20% will have a reaction severe enough to warrant surgical correction. This lower prevalence may be due to the older population that was observed. Most investigators indicate a higher incidence of gingival overgrowth in children and adolescents than in adults, with few lesions seen after the age of 40.[5] The wide prevalence range may, therefore, be due to age difference in the groups studied, as well as differences in other parameters such as oral hygiene.

In a recent study[10] on institutionalized, severely retarded children, ages 4-15, we found that 94% of the patients (18 to 19) receiving PHT had a PIGO. Gardner et al.,[11] reported 78% of a mentally retarded group exhibited some PIGO and Kapur et al.,[12] reported 68% of a similar group had PIGO. The high prevalence in our study may, among other factors, be due to the poor oral hygiene and limited masticatory ability of this population. In the initial examination a significant relationship was noted between the degree of PIGO and the plaque index. 39% of these patients had a slight overgrowth, 11% had a moderate involvement, while 50% had a severe PIGO. In normal, non-institutionalized populations the degree of PIGO was found to be approximately 45% with a slight overgrowth, 40% had a moderate involvement and only 15% had a severe reaction.[13,14] Thus, it appears that in the mentally retarded there was a higher percentage of patients with a severe involvement of the gingiva. This finding may be due to the poorer oral hygiene of the patients and higher drug levels.

No race or sex difference in PIGO have been reported.[11,15] Opinions differ regarding the relationship between therapy duration, dosage and the severity of the gingival overgrowth.[5,16] There is also conflicting evidence concerning the role of plasma[12,17,18,19,20] and salivary levels[18,19,20,21] of PHT in relation to gingival enlargement. Such variation may be due to the para-hydroxy metabolite of PHT being a responsible factor.[19,22]

Clinical Manifestations

The time between the initiation of phenytoin therapy and the onset of gingival overgrowth varies. First clinical signs of fibrosis have been reported as early as two weeks after the beginning of therapy;[23] however, several months usually elapse. The factors responsible for such variability are unknown. It has also been reported that from two to four years are required for the overgrowth to reach its peak.[24]

Most investigators agree that the gingival overgrowth is most marked in the anterior region of the

mouth, with the labial or buccal surfaces of all teeth having a greater involvement than the lingual surfaces.[5,11] It has been suggested that this is due to the pressure exerted on these tissues by the tongue. The severity of the overgrowth can vary within the same individual, with both normal and pathological areas found in the same mouth. No lesion is usually observed in edentulous areas. However, occasionally such cases are reported.[25]

In the severely mentally retarded group we studied[10] we found that the pattern of gingival overgrowth was not the same as that generally observed in normal individuals. We found that the PIGO was most marked on the posterior teeth even though the majority of the patients were mouth breathers. It was difficult to ascertain the cause of this discrepancy. We speculate that severe retardation was important and that it limited masticatory abilities, resulting in food being swallowed whole. In addition, oral hygiene procedures were limited and, due to lack of cooperation, appeared to be restricted to the anterior teeth. This factor alone may have been responsible for our observation.

Etiology of PIGO

Among the many suggested theories regarding the etiology of PIGO are serum vitamin C deficiency,[5] direct local effect of the drug or metabolite,[26] depression of the pituitary — adrenal axis,[27] and immunological reaction.[5,28] It has also been proposed that PHT-induced folic acid deficiency could render the gingival tissues more susceptible to local factors (e.g., plaque), thus enhancing the response of the gingiva to specific exaggerated inflammatory reactions as in gingival overgrowth.[29]

It is postulated that PHT is a folic acid antagonist, interferes with normal metabolism of these tissues, and may decrease PHT metabolite production. Vogel[29] reported that administration of folic acid with PHT to cats, markedly decreased the occurrence of PIGO when compared to a group administered PHT alone. An isolated report has claimed a decrease in PIGO lesions in humans receiving 3mg of folic acid daily along with PHT.[30] This report, however, was not a controlled clinical study.

The uniqueness of plaque around the gingival sulcular area and the maintenance of minimal PHT or metabolite levels in blood, and/or saliva, appear to be important parameters. It has already been stated that inflammation or an immune response to plaque may be a factor in the production of this lesion. It is possible that phenytoin or a metabolite may affect the plaque bacteria by either limiting the population of bacteria or by altering the metabolism of plaque bacteria. Staple et al.,[31] in a recent investigation in monkeys, showed some bacterial population alteration in plaque from gingival overgrowth as compared to non-overgrowth areas. However, such an alteration in bacterial population may not be causally related to the gingival overgrowth. It was also observed that the amount of gingival plaque was not always directly related to the severity of overgrowth. Apparently the type as well as the quantity of dental plaque may be crucial to the development of the lesion. It is also possible that plaque bacteria metabolize PHT, producing a metabolite which, when absorbed into the sulcular tissue, induces the lesion.

Connective Tissue Changes

Pathological changes occur in connective tissue other than gingiva, but at lower frequency. A dermal reaction to PHT administration has been described in rats[32] and acceleration of wound healing has also been noted when this drug is administered.[33] Thickening of the bone of the cranial vault of children on long-term drug therapy has been described.[34] Swelling of lips, broadened nose, and a general thickening of subcutaneous tissues of the face have also occasionally been observed, especially if PHT has been initiated early in life and maintained for a long time period.[34,35]

Lefebvre et al.,[35] observed that among 222 institutionalized mentally retarded individuals with seizures, approximately 1/3 had obvious facial changes, another 1/3 had questionable facial changes, and 1/3 had no changes. PHT was the principal drug used by all, with the affected groups exhibiting a greater number of seizures, significantly higher serum drug levels, hyperphosphatasia, and increased lethargy. It was also noted that the affected group had a greater severity of PIGO. These mentally retarded patient's varied etiologies and early normal photographs indicated that the features were acquired, implying a high long-term dose response. Thus, long-term anticonvulsant therapy, initiated at an early age, may not only have a profound affect on the developing skull and craniofacial growth, but also affect the position of teeth and supporting bone.[36]

PHT appears to affect other connective tissues, but on a limited basis, suggesting that all the parameters which may enhance the prevalence of the lesion in gingiva are present only on a limited basis in other tissues.

Mechanism of Gingival Overgrowth

To date, none of these theories can explain the two major questions remaining unanswered. First, what is the mechanism by which phenytoin can stimulate gingival overgrowth? Second, why is gingiva the primary tissue in the body so involved?

Animal and clinical studies in my laboratory[19,26,37,38,39] have resulted in a hypothesis to explain why this unique reaction of the connective tissue predominates in the gingiva. According to pharmacokinetic princi-

ples, only the unbound or free fraction of the drug carried by blood is therapeutically active. For PHT this amounts to approximately 10%.[19] This unbound fraction found in serum is dispersed through the various body tissues, including gingiva. A number of investigators have demonstrated PHT in saliva of patients on long-term administration of the drug.[21,40,41] Our studies indicate that the level of PHT in human saliva is about 10% that of the blood level,[19] and Horning et al.[40] have reported that PHT secreted by saliva is in the unbound form. We have also shown that both PHT and its primary metabolite, the para-hydroxyl form, are present in human plaque.[42] Furthermore, our human studies suggest that the severity of gingival overgrowth tends to be associated with higher PHT levels in gingiva and with lower tissue levels of the para-hydroxyl metabolite.[19]

Saliva is a contributor to plaque formation and may be implicated in the production of this condition by serving as a reservoir, concentrating PHT in, and adjacent to, the gingival sulcular area. In addition, it is possible that plaque may metabolize PHT.

Our animal studies have demonstrated the absorption or diffusion of PHT through the gingival sulcular epithelium into the underlying connective tissue and into the circulation.[39,43] We have also shown a prolonged retention of PHT in the gingival sulcular tissue after local, topical application in the gingival sulcus.[44] These data indicate the presence of a pathway for the reabsorption of PHT from saliva into plaque and through the sulcular epithelium into the underlying connective tissue.

I believe that the combined effects of the unbound drug from saliva (10% of serum levels) reabsorbed into the gingival connective tissues and the unbound PHT delivered to the gingival connective tissues from the systemic circulation (10% of serum levels), combine to produce levels of unbound PHT, or a metabolite, which under prolonged exposure, may be important in altering collagen production by the local fibroblasts. Thus, the unique parameters of plaque, local inflammation and concentration of the drug or metabolite around the gingival sulcular tissue may make this tissue more susceptible to the gingival overgrowth than is any other tissue in the body.

Treatment

It is customary in medical practice to treat untoward drug reactions by eliminating the drug causing the problem. This is probably the most satisfactory treatment of PIGO. In patients where the gingival overgrowth is severe and difficult to control, the patient's physician should be warned of the situation and consulted about the feasibility of changing the anticonvulsant drug. In many cases PHT proves to be the drug of choice for seizure control and this usually takes precedence over the gingival overgrowth. It then becomes the dentist's responsibility to control the overgrowth as best he can. Withdrawal of the drug will usually result in a spontaneous disappearance of the gingival overgrowth within three to six months, if the lesions are moderate in size. It may take up to a year or longer if the lesions are large.[45]

Over the years a variety of theories regarding the etiology of this disorder have been presented and a variety of treatments relating to these theories have been attempted. Vitamin C administration,[5,46] antihistamine administration,[47,48] alkaline mouthwash,[15,48] topical hydrocortisones,[49] and diuretics[50] have all been attempted. These treatments have been shown to be ineffective.

The only treatment that has proved consistently effective has been the institution of a program of meticulous oral hygiene[5,8,9,18,20] along with a deep, soft tissue curettage to help further reduce secondarily inflamed tissues. Several investigators[8,9,20] have suggested that initiation of meticulous oral care with the beginning of PHT therapy will prevent the gingival overgrowth from occurring. Similar results have been reported in Macaque monkeys.[31] The elimination of plaque after the lesion is present appears to only modify the size of the gingival overgrowth.[5,24]

In the severely retarded children,[10] we attempted to control plaque in one of two ways. During one study period no oral hygiene procedures were used and 1 ml of a .325% stannous fluoride gel was applied topically once a day for five months. This resulted in a significant decrease in plaque and PIGO. Gingival index was, however, not reduced significantly. In the second phase of this investigation, an electric toothbrush was used to remove plaque and massage the gingival tissue for three minutes. This resulted in a very significant decrease in plaque scores, gingival index and PIGO. Findings of interest in this latter phase of the study were that the majority of the children had diminished seizure activity and greater food intake with a noted increase in weight and a decrease in constipation.

Surgical removal is indicated when the severity of the gingival overgrowth is such that an esthetic problem exists, speech or mastication is impeded, severe secondary inflammation is occurring, and when oral hygiene procedures have not succeeded in controlling the overgrowth. Surgery is not a permanent solution. If the PHT therapy continues, the gingival overgrowth will invariably recur. Repeated gingivectomies may be necessary in these patients and recurrence of the lesion has been observed as early as three weeks after surgery.[51] Meticulous oral care will, however, markedly delay the recurrence.

Donnenfeld, et al.,[52] using supervised oral hygiene

after gingivectomy, prevented PIGO from recurring during a nine month observation period in a number of patients. When early small interproximal tissue growths do begin to recur, they can easily be removed by a small curved surgical scissors.[51]

This procedure can be performed using a blade, which many practitioners feel provides better control for the restoration of normal gingival architecture. Following surgery a periodontal dressing is worn for a week over the wound as protection and as an anodyne. Electrosurgery is used by many practitioners because of the ease with which large amounts of tissue can be removed. A periodontal dressing is normally not required with this procedure.

The excess tissue removal can also be achieved using an internal bevel technique in which a flap is elevated and "thinned" of excess collagenous tissues. The flap is then contoured, apically repositioned and sutured securely to the necks of the teeth.[53] The surgical flap procedure heals faster than the external bevel since it leads to primary healing. In addition, this procedure gives better control of post-operative bleeding and does not necessitate the use of a periodontal pack which may be a problem to maintain in a handicapped patient. The external bevel procedure heals slower since it heals by secondary intention, even though patients on PHT therapy appear to have accelerated wound healing.[53] In all cases, the implementation of a presurgical oral hygiene program and prophylaxis is suggested, if possible, to minimize secondary inflammation (and resulting bleeding) and decrease the size of the lesion.

Positive Pressure Appliance

Recently, use of a positive pressure appliance after surgery has been shown to be a beneficial adjunct to daily oral care in controlling the resurgence of the gingival overgrowth. Successful control has been reported for from seven[54,55] to 23[56] months following surgery by the use of a pressure appliance. Immediately after surgery, alginate impressions of the upper and lower arches are taken and stone casts made for the fabrication of a latex tooth positioner.[57] The interproximal and attached gingival areas are accentuated to exert active pressure on the attached gingival and interproximal papilla.[53]

For this appliance to be successful, the patient must wear it when asleep and about four additional hours a day while maintaining meticulous oral care. In the severely handicapped, I have found such an appliance of limited value because of lack of cooperation.

The exact mechanism by which pressure appliances work is not known. Babcock[54] suggests three possibilities: 1. The pressure or stimulation on the gingival tissues, 2. Better oral hygiene habits developed in these patients due to an awareness created by wearing the appliance, and/or 3. Minimized gingival tissue exposure to saliva. Only one, or all of these factors, may be responsible for the reported success.

Occasionally patients have severe PIGO and, due to systemic conditions, surgery is contraindicated. An effort was made to ascertain how successful a series of pressure appliances, without surgery, might be in reducing the gingival overgrowth in one of our clinical patients. The patient had first undergone three weeks of meticulous oral care and weekly professional prophylaxes to reduce inflammation and lesion size. Impressions were taken of the upper and lower arches, stone casts were made and the gingival overgrowth area on the casts trimmed about 2mm. These casts were sent to a dental laboratory for the construction of a latex tooth positioner.[57] She wore this appliance about four hours during the day and during sleep. After four weeks, impressions were taken again, casts relieved again by about 2mm, and a second latex appliance constructed which she wore for four weeks. Comparing the initial condition with results after eight weeks revealed a marked decrease in lesion size. The results suggest that a series of such appliances could succeed in regressing a gingival overgrowth to clinically tolerable limits. Such a procedure is too time consuming for the average patient, but may prove valuable in those patients where systemic conditions contraindicate surgery.

Conclusion

We may summarize the approach to treatment of gingival overgrowth as follows:

1. Where a mild gingival overgrowth exists, initiating meticulous oral care along with four yearly professional prophylaxes and topical SnF_2 applications will do much to control the lesion. The patient can usually function well with a mild gingival overgrowth if oral care is maintained and secondary inflammation prevented.
2. With a moderate gingival overgrowth, initiation of meticulous oral care is again indicated along with four office visits (one week apart for professional prophylaxes and topical SnF_2 treatment). Such a regimen will usually decrease the size of the lesion to a clinically tolerable size, but only with complete patient cooperation. These patients are then seen five times each year for prophylaxes and SnF_2 treatment.

   Where the patient does not cooperate, or the lesion will not regress, contact should be made with the patient's physician to obtain the serum levels of PHT and discuss possible alterations of drug therapy from PHT to another anti-convulsant drug. Oral care by these patients should be monitored, not only by the dentist, but also by other professionals involved in treating the patient.

3. In the severe gingival overgrowth condition, the steps outlined in #2 should be initiated and the patient seen by the dentist on a weekly basis for curettage, professional prophylaxes, topical fluoride and monitoring of oral care for about four weeks. An evaluation is then made as to the success of the conservative therapy. If drug substitution is not possible and/or regression of the lesion is not to a tolerable size, surgery will be required. With meticulous oral care it has been shown that lesion recurrence after surgery can be prevented for up to nine months[52] and probably longer. If the lesions recur to previous levels and surgery is again required, a pressure appliance should be considered as an adjunct to oral care when there is sufficient patient cooperation.

Meticulous oral care must be initiated in all patients prior to initiation of PHT therapy. The patients and parents must be made aware, not only by the dentist, but by all professionals involved in their care, of the means at hand to control this untoward reaction to PHT. In the severely handicapped, oral care by parent or guardian is required. There will be a number of handicapped patients where the gingival overgrowth will not be controlled because of a lack of oral care. In these cases, treatment of a severe lesion is indeed a problem. Drug substitution is most successful here. It is hoped that future research will elucidate the mechanism by which PHT induces gingival overgrowth and provide better means of controlling this untoward reaction of a very useful drug.

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