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Research Article

Correlating gingival overgrowth (GO) with risk factors in a group of Nigerian epileptics on anticonvulsants.

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SUMMARY

Introduction: Gingival overgrowth (GO) is the most widespread oral adverse effect reported with the use of anticonvulsants for the treatment of epilepsy. Since not all patients on anticonvulsants develop GO, exploration of the relationship between various reported risk factors and drug induced GO may establish a trend.

Objective: The aim of this study is to determinec relationship between gingival overgrowth (GO) and risk factors in epileptic patients on anticonvulsants.

Methods: The study was a cross-sectional study carried out at the Neurology Clinic of the Lagos University Teaching Hospital (LUTH) from 2009-2012. Participants were consecutive epileptic patients who had been on regular anticonvulsant therapy for at least three months preceding this study. Patients who had periodontal treatment six months prior to commencement of this study, those with systemic diseases or on drugs known to cause GO were excluded. A self-administered structured questionnaire was used to collect biodata, medical and drug history. This was followed by clinical examination. Simplified Oral Hygiene Index (OHI-S), Gingival Index (GI) and New Clinical Index for DIGO were used to assess the periodontium.

Results: 54 females and 96 males, mean age 31.5±16.5 years participated. Phenytoin therapy (p=0.013), Primidone therapy (p=0.009), gingival index score (p=0.000), degree of gingival inflammation (p=0.000) and frequency of plaque removal (p=0.039) showed statistically significant relationship with presence of GO.

Conclusion: Gingival inflammation, phenytoin and primidone therapy, as well as frequency of plaque removal may be significant risk factor in the development of gingival overgrowth (GO) among patients receiving anticonvulsant therapy.

INTRODUCTION

Gingival overgrowth (GO) is the current accepted term for all medication induced gingival enlargement. The three classes of drugs most implicated are anticonvulsants, immunosuppressant and calcium channel blockers.[1-3] GO resulting from use of medications is denominated Drug-induced GO (DIGO).

The most common neurological disorder seen in humans is epilepsy; a chronic disorder characterized by recurrent seizures of cerebral origin.[4,5] The treatment to control the seizures is predicated on the use of anticonvulsants like phenytoin, carbamazepine, valproic acid and phenobarbitone. More than 61% of the patients receiving anticonvulsants develop unwanted reactionswith GO as the most reported oral adverse reaction.[4,6,7] Phenytoin is the commonest implicated agent.[8,9]

Clinical manifestation of gingival enlargement frequently appears within the first three months of treatment, beginning as enlargement of the interdental papilla.[6,10] The gingival enlargements induced by different drugs are clinically indistinguishable, and occur more in the facial and lingual aspects of maxillary and mandibular anterior teeth.[1,4,9-11] It presents in areas with teeth and rarely in edentulous mouths.[2,9,10] Currently, the aetiology and pathogenesis of DIGO is not entirely understood hence several possible mechanisms and pathways have been proposed.[12] However, it is agreed that DIGO has a multifactorial nature.[10]

Recent studies demonstrated elevated levels of cytokines and growth factors, suggesting the role of abnormal balance of cytokines in gingival tissues in the pathogenesis of DIGO.[1]

It has also been proposed that susceptibility or resistance to DIGO may be governed by the existence of differential proportions of fibroblast subsets in each individual.[10]

Other etiological hypothesis includes depression of local immune response due to deficiency of IgA in serum and saliva; and reduced serum folate which causes low calcium ion in gingival fibroblasts.[9] Because cellular production of collagenase is modulated by calcium influx, it was postulated that the negative effects of these drugs on calcium ion influx across cell membranes may result in production of an inactive form of collagenase, being responsible for an increase in extra-cellular matrix.[3,5,13] Dental plaque and gingival inflammation are considered important risk factors for exaggeration of gingival overgrowth.[14,15] Several authors have suggested that plaque accumulation is an essential part of the development of GO. However, no clear correlation has been established, hence the role of plaque in DIGO remains controversial.[1]

DIGO causes aesthetic, functional, and psychological disturbance which may result in severe reduction in the quality of life of the affected individual.[2,4,5,13]

The overgrown tissue creates pockets that harbour pathogenic bacteria and impair optimal oral hygiene leading to an increased host susceptibility to oral infections and periodontal disease.[5,16]

Since not all patients on anticonvulsants develop gingival overgrowth, it is necessary to explore the relationship between various possible risk factors and DIGO. More so, there is paucity of studies that explore the relation between risk factors and GO in epileptic patients in this environment. Therefore, this study aims to determine relationship between GO and possible risk factors such as age, gender, oral hygiene status, degree of gingival inflammation as well as the anticonvulsants used in the control of epilepsy in patients in our environment.

MATERIALS AND METHODS

A cross-sectional study of 150 epileptic patients was carried out. An initial pilot survey was conducted among 20 patients using the questionnaire designed for the study. The patients were made to complete the questionnaires on two different occasions after which ambiguous questions were modified to suit the objectives of the study.

The study was carried out on patients with epilepsy who were being followed up at the Neurology Clinic of the Lagos University Teaching Hospital (LUTH) between 2009 and 2012. Patient must have been on regular therapy with antiepileptic drugs at least in the last three months preceding this study and with at least 16 permanent teeth with not less than 10 standing anterior teeth.

Patients who have had gingival surgery or periodontal treatment six months prior to commencement of this study were excluded. Other criteria for exclusion were presence of mental retardation and systemic diseases affecting the gingiva (endocrine disorders-diabetes, hematologic disorders-thrombocytopenic purpura or leukaemia and immunodeficiency states) as well as evidence of being on treatment with other drugs known to cause gingival enlargement (immunosuppressant and calcium antagonists).
Approval to carry out the study was obtained from the Ethical Review Committee of LUTH. Verbal consent to participate in the study was obtained from each subject after the nature of the procedure, possible benefits and risks were fully explained and understood by the subjects.

Information on bio-data and medical history including drug history was obtained using a structured self-administered questionnaire pretested on twenty subjects and adjusted to remove ambiguity. The drug history was confirmed from patients' clinical case notes.

Clinical examination was carried out by one examiner with the subject seated on a chair with a straight back in a brightly lit room using a plain mouth mirror and periodontal probe. The Simplified Oral Hygiene Index (OHI-S) of Greene and Vermillion was used to assess the oral hygiene status.[17] Six tooth surfaces were examined in each participant and scoring for Simplified Debris Index (DI-S) and Calculus Index (CI-S) was done on a scale of 0-3. The sum of DI-S and CL-S scores gives the OHI-S score for each subject. The subjects according to their OHI-S scores were grouped into three clinical oral hygiene levels using the following criteria: good: OHI-S score 0.0 to 1.2, fair: 1.3 to 3.0 and poor: 3.1 to 6.0.

The degree of gingival inflammation was assessed using the Gingival Index (GI) by Löe and Silness.[17] The GI-scores of the subjects were categorized into: 0.1-1; Mild gingivitis, 1.1-2; Moderate gingivitis and 2.1-3; Severe gingivitis.

GO was assessed using New Clinical Index for Drug-Induced Gingival Overgrowth (DIGO).[18] This method consists of clinical evaluation of the vestibular and lingual papillae which are scored 0 to 4 as follows: 0: no overgrowth or inflammation, 1: no overgrowth but inflammation present, 2: mild overgrowth (thickening of marginal gingiva not requiring treatment), 3: moderate overgrowth (covering gingiva not more than one-third of any of the crowns, but requiring treatment; and 4 severe overgrowth extending onto the coronal two thirds of one or more crowns. The subjects were divided into two groups according to; score 2 and below: GO absent and score greater than 2: GO present.

Data obtained was analysed using SPSS (version 20) statistical software. Chi square and Fisher's test were used to test for association between categorical variables. The level of significance was set at $P \leq 0.05$.

RESULTS

Socio-demographic characteristic

There were 54 females and 96 males, ratio 1:1.8 with mean age being 31.5 (±16.5) years. There were more subjects; 76 (50.7%) in the early adulthood (15-29 years) age groups. The detail is displayed in Table 1.

Medical and drug history

Eighty-three (55.3%) of the subjects have had epilepsy for over five years and 101 (67.3%) had been receiving anti-epileptic drugs for a minimum of two years. One-hundred and nineteen (79.3%) were treated with single anticonvulsant (monotherapy) and thirty-one (20.7%) with a combination of anticonvulsants (polytherapy). The drug distribution of subjects receiving monotherapy was: carbamazepine, seventy-four (62%); phenytoin, twenty-four (20%); phenobarbitone, sixteen (13%); sodium valproate, six (5%); and primidone, one (1%). In those that had polytherapy; more than 60% took carbamazepine or phenytoin in addition to other anti-epileptics. Sixty-eight (45.3%) of the cases received folic acid supplement in addition to anticonvulsant. (Table 1)

Table 1: Distribution according to variables

Age group (Years)	**Children 10-14**	**Early Adulthood 15-29**	**Late Adulthood >29**	**Total**
	12 (8.0%)	**76 (50.7%)**	**62 (41.3%)**	**150 (100%)**
Sex				
Male	8 (66.7%)	49 (64.5%)	39 (62.9%)	96 (64.0%)
Female	4 (33.3%)	27 (35.5%)	23 (37.1%)	54 (36.0%)
Anticonvulsant				
Monotherapy	11 (91.7%)	59 (77.6%)	49 (79.0%)	119 (79.3%)
Polytherapy	1 (8.3%)	17 (22.4%)	13 (21.0%)	31 (20.7%)
Carbamazepine	8(8.6%)	47 (50.5%)	38(40.9%)	93 (62%)
Phenytoin	2 (5.1%)	19 (48.7%)	18 (46.2%)	39 (26%)
Phenobarbitone	2 (5.6%)	22 (61.1%)	12 (33.3%)	36 (24%)
Primidone	0	2 (25.0%)	6 (75.0%)	8 (5.3%)
Sodium Valproate	0	2 (25.0%)	6 (75.0%)	8 (5.3%)
Anticonvulsant use Duration				
<2 years	6 (12.2%)	25 (51.2%)	18 (36.7%)	49 (32.7%)
2 – 5years	4 (9.5%)	27 (64.3%)	11 (26.1%)	42 (28.0%)
>5years	2 (3.4%)	24 (40.7%)	33 (55.9%)	59 (39.3%)
Frequency of cleaning mouth				
Once a day	10 (83.3%)	70 (92.1%)	48 (77.4%)	128(85.3%)
Twice a day	2 (16.7%)	6 (7.9%)	14 (22.6%)	22 (14.7%)
Oral Hygiene (OH) Status				
Good	3 (9.7%)	21 (67.7%)	7 (22.6%)	31 (20.7%)
Fair	8 (7.1%)	52 (46.0%)	53 (46.9%)	113 (75.3%)
Poor	1 (16.7%)	3 (50.0%)	2 (33.3%)	6 (4.0%)
Degree of gingival inflammation				
None	0	7 (9.2%)	4 (6.5%)	11 (7.3%)
Mild	10 (83.3%)	45(59.2%)	31(50.0%)	86 (57.3%)
Moderate	2 (16.7%)	24 (31.6%)	26 (41.9%)	52 (34.7%)
Severe	0	0	1(1.6%)	1 (0.7%)
Gingival Overgrowth Present				
No	9 (75.0%)	48 (63.2%)	44 (71.0%)	101(67.3%)
Yes	3 (25.0%)	28 (36.8%)	18 (29.0%)	49 (32.7%)

Oral hygiene practice and status

Most of the subjects (128; 85.3%) clean their mouth once daily and the remaining (22; 14.7%) twice daily. The mean oral hygiene index (OHI-S) score was 1.89+0.76 with good, fair and poor oral hygiene (OH) recorded in 31 (20.7%), 113(75.3%) and six (4%) respectively.

Degree of gingival inflammation

The mean gingival index (GI) score was 0.98+0.533, with only 11(7.3%) having healthy gingiva. Mild, moderate and severe inflammation was observed in 86 (57.3%), 52 (34.7%) and one (0.7%) subjects respectively. (Table 1)

Expression of GO

Presence of gingival overgrowth (GO) was observed in 49 (32.7%) of the subjects. The location of GO in one or both jaws was generalized in 11 (22.4%), anterior region only in 38 (77.6%) and none in posterior region only. (Table 1)

Relationship of presence of GO and risk factors

The GI score and degree of gingival inflammation showed a highly significant association with the presence of GO (P = 0.000) (Table 2). Significant relationship (P = 0.039) also existed between GO and frequency mouth cleaning. Presence of GO shows statistically significant relationship with only two of the anticonvulsants used by the patients; phenytoin (P = 0.013) and primidone (P = 0.009) (Table 2). However, there was lack of statistically significant relationship between GO and age (P = 0.523), gender (P = 0.392), oral hygiene status (P = 0.889), duration of treatment (P = 0.114), monotherapy or polytherapy drug administration (P = 0.421) and folic acid supplementation (P = 0.532)

Table 2: Relationship between risk factors and presence of Gingival Overgrowth (GO)

Risk factors	GO absent	GO present	P-value
Sex			
Male	67	29	0.3920
Female	34	20	
Age			
Children 10-14years	9	3	
Early adulthood 15-29years	48	28	0.5232
Late adulthood	44	18	
Previous Dental Visit			
None	74	37	0.7689
Have visited previously	27	12	
Frequency of cleaning mouth			
Once a day	82	46	
Twice a day	19	3	0.0394*
Duration of anticonvulsant therapy			
<2years	38	11	
2 – 5years	24	18	0.1136
>5years	39	20	
Gingival Index Score			
0.00	9	2	
0.01-1.0	68	18	0.0003*
1.01-1.59	16	16	
1.6-3.0	8	13	
Degree of gingival inflammation			
No inflammation	9	2	
Mild inflammation	68	18	0.0001*
Moderate – Severe inflammation	24	29	
Oral Hygiene (OH) Status			
Good	22	9	
Fair	75	38	0.8891
Poor	4	2	
Folic acid (FA) supplementation			
No	57	25	0.5321
Yes	44	24	
Anticonvulsant therapy			
Monotherapy	82	37	0.4205
Polytherapy	19	12	
Carbamazepine use			
No	36	21	
Yes	65	28	0.3933
Carbamazepine			
Monotherapy	53	21	
Polytherapy	12	7	0.4731
Phenytoin use			
No	81	30	
Yes	20	19	0.0129*
Phenytoin			
Monotherapy	13	11	
Polytherapy	7	8	0.2078
Phenytoin with FA supplementation			
No	4	8	
Yes	16	11	0.1349
Phenobarbitone use			
No	73	41	
Yes	28	8	0.1253
Phenobarbitone			
Monotherapy	13	3	
Polytherapy	15	5	0.6540
Primidone use			
No	99	43	
Yes	2	6	0.0087*
Primidone			
Monotherapy	0	1	
Polytherapy	2	5	1.0000$_F$
Sodium Valproate use			
No	95	46	
Yes	6	3	0.9649
Sodium Valproate			
Monotherapy	5	1	
Polytherapy	1	2	0.1336

* Statistically significant ($P < 0.05$)

DISCUSSION

Gingival overgrowth (GO) is the most frequent oral side effect of anticonvulsant drugs used in the treatment of patients with seizure disorders.[6,14] The overgrown tissue creates pseudopockets which harbour pathogenic bacteria that are beyond the reach of a toothbrush and dental floss. The resultant increase in plaque accumulation and retention can induce inflammation and periodontitis with eventual tooth loss.The pathogenesis of drug induced gingival overgrowth (DIGO) is still not completely understood. Gingival enlargement has a multifactorial nature and may be affected by factors such as demographic variables, genetic predisposition and oral hygiene status; pharmacokinetic variables including molecular and cellular changes in gingival tissues.

The prevalence of GO was found to be 32.7% among the subjects in agreement with previous studies.[19-21] However, studies which involve more or only patients receiving phenytoin reported higher figures ranging from 40% - 80%.[22,23] In this study, carbamazepine (Tegretol) was the most commonly used anticonvulsant drug among the subjects with 93 (62%) taking it either as monotherapy or polytherapy. Only 39 (26%) of the subjects in this study were taking phenytoin; the most common drug incriminated in the development of GO. This may explain the low prevalence of GO (32.7%) recorded in this study in contrast to 80% reported by Ojehanon,[22] in which 69% of the patients were receiving phenytoin.Phenytoin is widely distributed in all the body fluids including Cerebrospinal fluid (CSF) and also secreted in saliva where dental plaque acts as a reservoir for the drug.[24] It has been suggested that phenytoin selects for a subpopulation of fibroblasts that have increased protein synthesis and collagen production.[9] The incidence of GO was found to be predominantly in the upper and lower anterior teeth region in agreement with previous report.[25] However, a few cases of GO have been reported on edentulous ridges and in denture wearing epileptic patients on phenytoin therapy.[4,9]

In conformity with some previous reports,[22,23] non-statistically significant relationship was recorded between age, gender; and GO in this study. Nayyar *et al*. described young age as risk factor for DIGO,[4] but other studies have not confirmed such finding.[12] Hence, age and sex may not be important factors in the development of GO.

Although positive association has been reported between oral hygiene status and severity of GO by many authors,[22,23,25,26] oral hygiene status did not appear to influence development of GO in this study. This may suggest that other factors may play more prominent roles in the genesis of GO. It has been suggested that susceptibility or resistance to DIGO may be due to the proportions of fibroblast subsets in each individual which exhibit a fibrogenic response to the offending medications.[10] This proportion is suggested to be genetically determined.[10] The existence of functional heterogeneity in gingival fibroblasts in response to various stimuli is in support of this hypothesis.[10,27,28] A direct effect of cyclosporine, phenytoin and nifedipine (or metabolites) on the activity of gingival fibroblasts has been demonstrated.[28] Phenytoin has been shown to induce gingival overgrowth by its interaction with a subpopulation of sensitive fibroblasts.[16,28,29] It has been demonstrated that high frequency of particular HLA antigens and genetic markers (cytochrome P450, HLA-DR2) was present in patients developing gingival lesions while those patients who expressed genetic markers such as HLA-B3 or HLA-DR1, have some degree of protection against GO.[15,20]

The percentage of patients who presented with GO is higher among those that brush once daily (35.9%) than in those that brush twice daily (13.6%) and the difference is statistically significant (P = 0.0394). This relationship to the best of our knowledge has not been previously evaluated or reported. The possible explanation is that frequent brushing reduces the exposure time of gingiva to plaque which is a prerequisites for gingival inflammation that can precipitate gingival overgrowth. GO is almost exclusively related to dentate areas suggesting that factors attached to the dentition, such as bacterial dental plaque, have a role in gingival enlargements.[16] Frequent plaque and calculus removal procedure with the use of chlorhexidine oral rinses could help to prevent or reduce the degree of gingival overgrowth as the presence of dental plaque may provide a reservoir for the accumulation of the responsible drugs especially phenytoin.[27,30] However, further studies are required to establish whether these lesions can be prevented by instituting professional tooth cleaning and instituting good oral hygiene practices before commencement of drug treatment in these patients. In this study, Gingival Index (GI) score showed a significant association with the presence of GO (P=0.000) in agreement with previous reportsthus confirming that gingival inflammation may be a significant risk factor for development of GO.[26,27,31-34] A review of existing literature shows that a cofactor is needed to induce GO and several studies point to a modulation of inflammatory processes.[9,28,30] Pro-inflammatory cytokines, such as interleukin-1b and interleukin-6 seem to have a synergistic effect in the enhancement of collagen synthesis by human gingival fibroblasts.[16,30] In addition, Interleukin-6 has been shown to enhance proliferation of fibroblasts and increase collagen production and glycosaminoglycan synthesis.[10,16] Elevated levels of these cytokines and growth factors found in DIGO suggest the role of abnormal balance of cytokines in gingival tissues in the pathogenesis of DIGO.[1,30] The non-significant relationship found in this study between drug taken as monotherapy or polytherapy; and GO (P=0.421) agrees with the report of Kamali *et al*.[35] Significant association recorded in this study between the use of phenytoin and presence of GO (P=0.013) conforms with report from previous studies.[22,36-39] This finding may be due to the fact that Phenytoin is widely distributed in all the body fluids including CSF. It is also secreted in saliva where dental plaque may acts as a reservoir hence increasing the concentration of the drug in the gingival tissues.[24,30] The major metabolite of phenytoin 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) forms locally in the gingiva due to presence of one or more CYPs (cytochrome-P). This in turn cause cell injury and activates inflammatory response and fibroblastic proliferation.[24] It was also postulated that phenytoin may interfere negatively with the synthesis and function of collagenases by inducing a reduction in the influx of Ca^{2+} into cells with resultant production of an inactive form of collagenase.[15] The resultant imbalance in production and degradation of collagen is believed to results in the over accumulation from decreased collagen degradation rather

than an increase on its synthesis.[8,10,13,16]

The significant association (P = 0.009) recorded in this study between primidone and GO has not been reported in earlier studies to the best of our knowledge. Few cases of GO after chronic use of valproic acid, carbamazepine, or phenobarbitone in adult patients have been reported but very rarely with primidone or may have been poorly documented.[10] Further studies are required among larger number of patients on primidone to reconfirm this association. In this study there was no significant association between duration of treatment and presence of GO (P=0.252) in concurrence with previous studies.[22,27,31,32] Sixty-eight (45.3%) of the patients received folic acid tablet (5mg/day) supplementation with the anti-epileptic drugs to avoid depletive effect of phenytoin, one of the mechanism implicated in the pathogenesis of GO. Although folic acid deficiency had been reported in conjunction with chronic phenytoin therapy,[4,37,40] this study did not record any significant relationship between folic acid supplementation and GO (P = 0.532). This observation may be explained by the fact that only a few (39 of 150) of the subjects in this study were receiving phenytoin. Due to the cross-sectional study design used, pre-existing GO could not be assessed and controlled because the patients were not examined before commencement of anticonvulsant drug therapy, hence further study is required in which this is incorporated.

CONCLUSION

The result of this study suggests that gingival inflammation, phenytoin and primidone therapy, as well as frequency of plaque removal may be significant risk factors in the development of gingival overgrowth (GO) among patients receiving anticonvulsant therapy. The presence of GO does not appear to be affected by age, gender, oral hygiene status, folic acid supplementation or duration of antiepileptic drug therapy.

We therefore recommend the following:

- All patients who are been treated with anticonvulsants should be informed of the possibility of GO as a side-effect and regular dental visits should be encouraged.
- All patients on anticonvulsants should be educated on the importance of frequent plaque removal and be encouraged to brush more frequently; at least twice a day.
- Physicians and dentists should adopt a multidisciplinary treatment plan for the patients who need to undergo these drug therapies.
- Further studies should be undertaken to confirm the association found in this study between GO and risk factors such as primidone therapy and frequency of mouth cleaning.

Conflict of Interest

The authors declare that there is no conflict of interest.

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