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Immunoglobulin A Levels in Serum and Saliva of Patients Treated with Phenytoin

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Abstract

A study was conducted to compare IgA levels in serum and saliva obtained from phenytoin-treated epileptic patients (PHT-TEPs) and a control group and to examine the correlation between IgA levels and clinical parameters. Eighteen epileptic patients treated with phenytoin and 18 periodontally healthy individuals with no systemic disease were included in the study. Clinical parameters were recorded, and samples of serum and saliva were obtained from each individual. IgA levels were determined by the radial immunodiffusion technique. Serum IgA levels were significantly lower in PHT-TEPs. No difference was found in salivary IgA levels between the PHT-TEP and control groups. Weak negative correlations were found between serum IgA level and gingival overgrowth index (GOI), and between salivary IgA level and GOI. None of the clinical parameters was significantly correlated with IgA level in the PHT-TEP group.

Introduction

Changes in immune system parameters have been frequently observed in epileptic patients undergoing long-term anticonvulsant therapy[1,2]. Although the contribution of anticonvulsant drugs to these changes is still uncertain, phenytoin (PHT) has been considered responsible for some specific immune alterations[3]. PHT has been utilized as an anticonvulsant agent since the late 1930s[4].

A correlation between chronic PHT administration and IgA reduction has been well documented[5]. SORRELL et al.[6] were first to report abnormally low concentrations of serum IgA in some patients receiving long-term PHT therapy. Since this initial report in 1971, several authors[7,8] have noted an association between PHT therapy and depression of serum IgA concentration. Such IgA depression has been reported in 12-70% of patients treated with PHT[9]. The treated patients with low IgA had a normal number of lymphocytes with surface IgA, suggesting that PHT causes failure of terminal differentiation of IgA-bearing B cells[10].

SMITH et al.[11] studied the influence of PHT on IgA in both serum and total and parotid saliva. They noted that PHT induced a significant decrease in serum IgA levels and a significant increase in both salivary IgA levels and the rate of IgA secretion by the parotid gland.

The use of PHT has been frequently associated with side effects[12]. Some of the effects do not appear to be dose-related, and include problems such as gingival hyperplasia, hypertrichosis and leukopenia[9]. VAN DER KWAST[13] suggested in 1956 that the immune system was involved in PHT-induced gingival hyperplasia (PHT-IGH). It has since been suggested that IgA is a factor in PHT-IGH[14-16]. On the other hand, the influence of dental plaque on drug-induced

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gingival hyperplasia (DIGH) is well documented[17–20]. A relationship between bacterial plaque-induced inflammation and DIGH has been clearly established[21]. Thus it is suggested that a bacterial inflammatory component is necessary for expression of the side effect. Several studies have demonstrated that dental prophylaxia and good oral hygiene can reduce or prevent DIGH[21].

Adhesion of bacteria to tissue surfaces may be prevented or reduced by secretory antibodies[22]. Patients lacking IgA may, therefore, manifest an increased susceptibility to gingival inflammation when the oral hygiene is insufficient[16]. Gingival inflammation in phenytoin-treated epileptic patients (PHT-TEPs) is intimately connected with gingival hyperplasia. The connective tissue repair process is altered by PHT, which causes fibroblast proliferation with subsequent hyperplasia[23].

The purpose of this study was to determine the serum and salivary levels of IgA in PHT-TEPs in comparison with those of healthy controls, and to correlate IgA levels with various clinical parameters.

Materials and Methods

The study was performed on PHT-TEPs who attended the clinic at the Department of Neurology, Faculty of Medicine, Hacettepe University, for their routine control medication, and also periodontally healthy individuals with no systemic disease.

The patient group comprised 18 individuals, 5 females and 13 males, with an age range of 14—49 yr with an average of 28.2 yr. The duration of PHT treatment ranged from 2 months to 12 years with a mean of 4.45 years for the whole group. The patients had not been taking any other drug and had not received any periodontal treatment during the 6 months prior to the study.

Clinical measurements were performed and the values of pocket depth (PD), gingival index (GI) (Löe and Sillness)[24], gingival overgrowth index (GO) (McGaw et al.)[25] and plaque index (PI) (Sillness and Löe)[24] were recorded.

Samples of total saliva and 5 ml of non-heparinized venous blood were obtained from each patient and healthy control. The blood was allowed to clot for 30 min at room temperature, stored at 4°C for 30 min and then centrifuged for 5 min. The separated serum was kept frozen at −40°C until assayed. Whole saliva samples from 18 individuals were collected into tubes directly without any stimulation (5 ml). Each tube of saliva was sealed with plasticine and centrifuged to spin down particulates and heavy mucus.

The salivary and serum IgA levels were determined using the single radial immunodiffusion technique[26]. The clinical and laboratory findings were then analyzed statistically. Significance of differences between the groups was determined by ANOVA (analysis of variance) and the correlations between the clinical parameters and IgA levels were determined by correlation and regression analysis.

Results

Clinical Measurements: The mean scores of clinical parameters (mean±S. E.) in the PHT-TEP group were, PD 2.89±0.27 mm, GI 1.59±0.22, GOI 0.97±0.11 and PI 1.61±0.16 (Table 1).

IgA Levels:

Serum: The mean values of serum IgA levels were 222.39±34.15 mg/dl in the PHT-TEP group and 308.52±20.62 mg/dl in the control group. The difference between the groups was statistically significant ($p<0.05$) (Table 2).

Saliva: The mean IgA levels were 5.25±0.57 mg/dl in the PHT-TEP group and 6.49±0.44 mg/dl in the control group. The difference between the groups was not statistically significant ($p>0.05$) (Table 2).

Correlations Between IgA Levels and Clinical Parameters:

A weak negative correlation was found between GOI and the serum IgA level ($r=-0.35$) ($p>0.05$) in the patient group (Table 3). A weak negative correlation was also found between the salivary IgA level and GOI ($r=-0.13$) ($p>0.05$) in the PHT-TEP group (Table 4). Salivary IgA level showed a weak positive correlation with PD ($r=0.16$) ($p>0.05$) and also with PI ($r=0.33$) ($p>0.05$) in the patient group (Table 4).

Table 1 Mean Scores of Clinical Parameters in the PHT-TEP Group

	$\bar{x}$	S.D.	S.E.
PD	2.89	1.15	0.27
GI	1.59	0.93	0.22
GOI	0.97	0.47	0.11
PI	1.61	0.68	0.16

$\bar{x}$=Mean value
S.D.=Standard deviation
S.E.=Standard error

Table 2 Mean Values of Serum and Salivary IgA Levels (mg/dl) in the PHT-TEP and Control Groups

	Serum			Saliva		
	$\bar{x}$	S.D.	S.E.	$\bar{x}$	S.D.	S.E.
PHT-TEP Group	222.39*	144.88	34.15	5.25	2.42	0.57
Control Group	308.52	85.02	20.62	6.49	1.85	0.44

* Significantly lower than the control group ($t=2.15$, $p<0.05$)
$\bar{x}$=Mean value
S.D.=Sandard deviation
S.E.=Standard error

Table 3 Correlations between Serum IgA Levels and Clinical Parameters

	r	p
PD - Serum IgA	−0.06	$p>0.05$
GI - Serum IgA	−0.08	$p>0.05$
GOI - Serum IgA	−0.35*	$p>0.05$
PI - Serum IgA	0.06	$p>0.05$

* Weak negative correlation between GOI and serum IgA levels

Table 4 Correlations between Salivary IgA Levels and Clinical Parameters

	r	p
PD - Salivary IgA	0.16*	$p>0.05$
GI - Salivary IgA	−0.05	$p>0.05$
GOI - Salivary IgA	−0.13**	$p>0.05$
PI - Salivary IgA	0.33†	$p>0.05$

* Weak positive correlation between PD and salivary IgA levels
** Weak negative correlation between GOI and salivary IgA levels
† Weak positive correlation between PI and salivary IgA levels

Discussion

The findings of the present study indicated that IgA levels in the sera of the PHT-TEPs were significantly lower than those of the controls, apparently in accord with previous reports[3,6,9,11,14–16,21,27–29]. Since SORRELL et al.[6] first noted the association between PHT therapy and depression of serum IgA concentration, various authors have confirmed this association in different patient populations treated with PHT and other anticonvulsants. Various degrees of IgA depression were described in these reports.

GILHUS and AARLI[29] followed up 32 epileptic patients treated with PHT, and 16 had depressed serum IgA concentrations. Another study[9] revealed that approximately 15% of PHT-treated epileptic children with seizure disorders had significant depression of serum IgA when compared with age-matched controls. Many studies have shown that a low serum concentration of IgA is a common finding in epileptic patients taking antiepileptic drugs, and that among them PHT seems to exhibit the highest capability of modifying immune responses[3].

The mechanism by which PHT induces an IgA-deficient state is unknown. Most PHT-TEPs have a normal number of circulating B lymphocytes with surface IgA[9]. Studies suggest that drug-induced IgA deficiency is a heterogeneous disorder[9,30]. Some investigators have noted decreased antibody responses in PHT-treated children[6,7] although this is not a uniform finding[31].

The present results revealed no significant difference in salivary IgA levels between the PHT-TEP and control groups. In a previous study[16], PHT-induced salivary IgA deficiency was demonstrated in PHT-TEPs. It was considered that this deficiency produced increased susceptibility to gingival inflammation, which in turn was a predisposing factor for the development of gingival hyperplasia. In contrast, another study[11] demonstrated that PHT induced a significant decrease in serum IgA levels and a significant increase in salivary IgA levels. The data showed increased quantities of salivary IgA relative to plasma IgA. It was concluded that levels of IgA in serum and saliva were at least partly under independent control, and that PHT did not appear to cause a deficiency in salivary IgA, or that decreased oral IgA with consequent enhanced susceptibility to inflammation seemed unlikely to contribute to PHT-IGH[11]. The present data indicating no significant difference in salivary IgA levels between the PHT-TEP and control groups and the weak negative correlation between GOI and the salivary IgA level in the PHT-TEP group seem to confirm this concept.

A literature review failed to locate any studies correlating serum and salivary IgA levels with clinical parameters. In the present study, no significant correlation could be found between IgA level and clinical parameters. However, weak positive correlations were found between PD and PI and salivary IgA levels. The influence of dental plaque on PHT-IGH is well documented[17–20]. The bacterial plaque causes inflammation, which in turn leads to increased gingival connective tissue production[21]. The inflammation that occurs secondary to bacterial plaque causes an increase in connective tissue, which is a normal physiologic response[21].

The mean GOI and PI scores in epileptic patients were 0.97 and 1.61, respectively. A GOI score of 0.97 cannot be regarded as high, according to the criteria of GOI[25], and the PI scores were also not high.

Further detailed studies categorizing the extent of gingival overgrowth in patients receiving PHT in comparison with IgA levels should be done to provide further information in this area.

Conclusions

1. Serum IgA levels were significantly lower in PHT-TEPs.
2. There was no difference in salivary IgA levels between the PHT-TEP and control groups.
3. Weak negative correlations were found between serum IgA levels and GOI, and between salivary IgA levels and GOI.

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