

## A CASE OF PHENYTOIN INDUCED GUM ENLARGEMENT

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## ABSTRACT

Phenytoin is commonly used antiepileptic drug (AED) and used for grand mal and psychomotor epilepsy. Adverse drug reaction due to phenytoin ranges from adverse effects at therapeutic dose to toxic dose. Herein we present a case of gum hypertrophy caused by Phenytoin in child.

**Key Words** – AED, Phenytoin, Gum Enlargement

## INTRODUCTION

Epilepsy is the most common chronic neurological disorder in human<sup>1</sup>. Epilepsy treatment is based on drug-therapies which aim to help patients to achieve seizure freedom without adverse effects. However, in several cases the first-choice drug fails in the treatment due to a lack of efficacy or to the patient failure to tolerate the medication side effects<sup>2,3</sup>. Phenytoin remains the drug of choice for treatment for grand mal, temporal lobe, and psychomotor epilepsy since it was first introduced in the 1930s<sup>4</sup>. The first reported case of phenytoin associated enlargement appeared more than 6 decades ago<sup>4</sup>. There are conflicting reports regarding incidence of phenytoin induced GE. One study says, it is estimated that about 30 to 50% of patients taking phenytoin develop significant gingival alterations<sup>5</sup> while another says Gingival hyperplasia occurs in approximately 20% of all patients during chronic therapy and is probably most common manifestation of phenytoin toxicity in children and young adolescents<sup>6</sup>. Other side effects of phenytoin are sedation, ataxia, skin rash, agranulocytosis and Steven-Johnson syndrome.

As oral hygiene is an important risk factor for GE, still no precaution is taken to prevent this ADR especially in rural set up like ours. Hence we decided to highlight this case as an eye opener.

We present a case of phenytoin induced gum hypertrophy.

## CASE REPORT

A 10 year old male child, a known case of seizure disorder since 1½ year presented for routine follow up in the pediatrics OPD and during examination complained of tender and swollen gums. He was on Tab Phenytoin 50mg thrice daily @ 7.5mg/kg/day since same duration. Tablet is of ABBOTT pharma, manufacturing date March 2011; expiry dated Feb 2014 and batch no WAF4C01A. Patient was on medicine regularly.

On oral examination there is generalised fibrotic gingival enlargement seen in upper and lower jaw. Enlargement is upto the coronal one third of upper right canine, 1<sup>st</sup> and 2<sup>nd</sup> premolar. Crowding is present in lower anterior teeth. Gingiva is inflamed, bright red in colour with irregular margins. There was bleeding on probing with scalloping of the interdental gingiva and presence of stippling. Plaque present +, no caries, no calculus, overall oral mucosa was healthy.

On investigation Complete blood count shows Hb 13.1g/dl, WBC 17.3 /cmm, Platelets 3lakh, and liver function test (AST- 31IU/L, ALT- 9IU/L) were done and found to be within normal limits. Therapeutic drug monitoring of Phenytoin showed concentration of 29.61mcg/dl which is way above the therapeutic concentration of 10-20mcg/dl. X-ray imaging IOPA (Intraoral periapical radiograph) view reveals partially erupted canine, first and second permanent premolars. There was also presence of malocclusion. After ruling out the other causes of generalized gingival enlargement, child was diagnosed as a case of Phenytoin induced gingival hypertrophy. The child was switched over to another antiepileptic drug i.e Sodium valproate in the dose of 300 mg OD, after tapering the dose of phenytoin for fifteen days.

It was observed that at no point of time during the treatment with Phenytoin the patient or his relatives were instructed about oral hygiene and its role in preventing this ADR.

The Naranjo's criteria is frequently used for determination of causality for suspected ADRs<sup>14</sup>. Causality assessment of this ADR using the Naranjo's criteria revealed that adverse drug reaction due to phenytoin in this case is probable (overall score, 8). In this case rechallenge is not feasible as above mentioned adverse drug reaction is slow to progress and slow to regress hence causality score falls short of being definite.

## DISCUSSION

Gingival enlargement is an abnormal growth of the periodontal tissue. Several causes of gingival enlargement are known, and the most recognized is drug-induced (iatrogenic) gingival enlargement (GE)<sup>7</sup>. Among the causes for drug induced GE, PNT is the most common agent<sup>7, 8</sup>. Other causative drugs are phenobarbitone, amlodipine, nifedipine and cyclosporine. Drug-induced gingival enlargement associated with chronic use of the AED phenytoin was first reported in 1939 by Kimball<sup>9</sup>. Factors affecting the occurrence of GE may include gender, with males being three times as likely to develop overgrowth<sup>8</sup>. Children & adults younger than 30 yrs of age are more susceptible<sup>8</sup>. Roughly 50 % of the patients on PNT therapy develop this ADR within 1 year of commencing therapy and is probably the most common ADR in children and young adults receiving PNT<sup>7, 8</sup>. All patients on phenytoin do not develop gum hypertrophy hence there are certain risk factors associated. The adverse effects of PNT depend on the duration of exposure, and the dosage. There is no clearcut correlation between the plasma concentration and GE. The other risk factors are poor oral hygiene, poor socioeconomic class and poor educational status. Dental plaque, as it acts as a reservoir for accumulation of drug, is commonly associated with this condition<sup>10</sup>. The local risk factors are mal-positioned teeth, gingivitis and mouth breathing. Physical irritants like orthodontic appliances, implants, filling also play their role in the causation of this ADR<sup>7</sup>

PNT accumulates in brain, liver, muscle, and fat. Its metabolism gets saturated and its rate of elimination varies as a function of its concentration (*i.e.*, the rate is nonlinear). The plasma  $t_{1/2}$  ranges between 6 and 24 hours at plasma concentrations <10 µg/ml but increases with higher concentrations. As a result, plasma concentration increases disproportionately even with the small increments in the dose. PNT is largely metabolized in liver (95%) and principal metabolite is a para-hydroxyphenyl derivative 5-(4Hydroxyphenyl)-5-phenylhydantoin (HPPH), is excreted in urine<sup>11</sup>.

GE appears to be a result of interaction of susceptible subpopulation of fibroblasts, keratinocytes and collagen present in gums with PNT & its metabolite<sup>8, 10</sup>. Matrix metalloproteinases (MMP's) because of their major role in cellular proliferation, migration, differentiation, and angiogenesis might play a role here also<sup>12, 13</sup>.

## TREATMENT OF GE

The management of GE requires multidisciplinary approach which includes medical, surgical and supportive care.

### Medical Care

The most effective treatment of drug induced gingival enlargement is withdrawal or substitution of medication i.e. PNT. Unfortunately, not all patients respond to this mode of treatment, especially those with longstanding gingival lesions<sup>2,15</sup>.

Antimicrobials like macrolides and tetracyclines which interfere with collagen synthesis and also lead to increased degradation of collagen. Antiseptic mouth wash - Chlorhexidine gluconate, Biotene and Folic acid 1 mg one to three times a day is to be supplemented to take care of PNT induced folate deficiency.

### Surgical Care

Needed in moderate to severe cases which do not resolving even after decreasing the dose of the offending drug, maintaining proper oral hygiene, debridement with scaling or root planning. It includes Flap procedures<sup>1</sup>, Gingivectomy but, there is rapid recurrence<sup>(2, 7)</sup>. The preferred method is the use of CO<sub>2</sub> or YAG Laser<sup>1,2</sup>

### Supportive Care

Informing patients of the risk of developing GE secondary to PNT therapy.

Role of oral health in minimizing complications should be stressed at regular intervals.

Routine dental examination is recommended to control development of dental plaque which is a major predisposing factor.

## PROGNOSIS

The prognosis is better if patients maintain regular oral hygiene and plaque control.

## CONCLUSION

GE is the most common ADR in the young adults and children receiving PNT as antiepileptic therapy. Though poor oral hygiene and dental plaque are considered important risk factors in pathogenesis of GE, meticulous oral hygiene can minimize but not prevent the occurrence of GE<sup>(2)</sup>. Antimicrobials are found useful in alleviating the symptoms of GE. Considering alternatives to PNT or discontinuing it if feasible can definitely arrest or lessen the severity. Surgical correction remains the resort for those who have not responded well to these modalities. The importance of oral hygiene in preventing this ADR should not be underrated as this is probably the best, cheapest and practical option.



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