CASE REPORT

A well known and important adverse effect of phenytoin in a neurosurgical patient

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SUMMARY

Gum hypertrophy is a well-known and important adverse effect of phenytoin therapy in a neurosurgical patient. We present an interesting case of a 21-year-old man who, following head injury after a road traffic accident, developed status epilepticus diagnosed with gum hypertrophy in the jaws, with ongoing antiepileptics. He was managed conservatively as per hospital protocol.

BACKGROUND

Gum hypertrophy is a well-known and important adverse effect of phenytoin therapy in a neurosurgical patient. There are many aetiological factors attributed to gingival hypertrophy (table 1).

Management of this condition should include identifying and taking into account the offending drug prescribed. Clinical physicians and intensivists should be aware of routine medications in use that could cause gum enlargement in order to identify and manage this problem.

CASE PRESENTATION

We report an interesting case of a 21-year-old man who presented following head injury after a road traffic accident; he had a Glasgow Coma Scale score of E₄ V_T M₄. Initial CT of the head findings were suggestive of bilateral frontal contusion. The patient had no significant medical or surgical history and no associated injury. At admission, his physical and oral cavity examination, including gums, was non-significant except for poor oral hygiene. Subsequently, he developed status epilepticus in the intensive care unit, for which he was prescribed a phenytoin 100 mg injection three times a day intravenously for the first month, which was later switched to oral tablets for the next 5 months. He first underwent ventriculoperitoneal shunt implantation 3 months after the head injury in view of progressive hydrocephalus and midline shift during his hospital stay. Later, decompressive craniectomy followed by cranioplasty after 3 months was also carried out during his long course of hospital stay. Haemodynamically he was found to be stable during the perioperative period. On follow-up examination in the neurosurgical ward, we noticed gross hypertrophy of his gums in the upper and lower jaws (figure 1).

INVESTIGATIONS

We confirmed the offending drug's aetiology by assessing the plasma phenytoin level (35 µg/mL), which was considerably higher than normal therapeutic concentrations (10–20 µg/mL).

DIFFERENTIAL DIAGNOSIS

As evident with the plasma phenytoin concentration report, we ruled out other possible causes behind this pathology.

TREATMENT

We withdrew the offending drug and substituted it with another antiepileptic agent, levetiracetam. Maintenance of strict oral hygiene and regular use of a mouth wash containing chlorhexidine were continued with metronidazole 400 mg tablets three times a day via Ryle's tube for 21 days as additional treatment. Surgical removal of the gingival overgrowth (gingivectomy) was, as such, not planned in this case.

OUTCOME AND FOLLOW-UP

Follow-up over the next 2 months showed favourable progressive regression in enlargement of the gums (figure 2). However, the patient was dependent for routine feeding and nursing care, and was finally discharged home on a strict regimen of medication with instructions for nursing care.

DISCUSSION

Gum enlargement is one of the most common side effects associated with the administration of phenytoin, the most frequently used antiepileptic drug. The prevalence of phenytoin-induced gingival overgrowth has been shown to vary from 13% in a community-based study¹ to 50% in a study on institutionalised patients.² In India, 57% of epileptic children aged 8–13 years who were undergoing phenytoin monotherapy developed gingival overgrowth within 6 months of treatment.³ Poor oral hygiene is a primary risk factor for gum enlargement in these patients on antiepileptics. However, routine use of phenytoin or other antiepileptics such as carbamazepine, phenobarbital or valproate (though less evaluated in studies) is not recommended for preventing late post-traumatic seizures in patients with traumatic brain injury.^{4 5}

Presence of dental plaque can provide a reservoir for accumulation of drugs such as phenytoin.⁶ Gingival enlargement in these patients is not due to an increase in the number of periodontal cells but, instead, due to an increase in the extracellular volume.^{7 8} This increase in volume is caused by hyperplasia involving fibroblasts. Studies reveal that drug-induced gingival overgrowth usually occurs within the first 3 months of starting drug therapy with the offending drug.⁷ Several mechanisms are involved in the development of gingival overgrowth. Phenytoin induces a decrease in Ca²⁺ cell

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Table 1 Various categories of drugs and clinical conditions implicated in gum hypertrophy

Drugs/conditions causing gum hypertrophy	Names of the drugs
1. Antiepileptic drugs	Phenytoin, phenobarbitone, valproic acid, primidone, vigabatrin and carbamazepine
2. Calcium channel blockers	Nifedipine, verapamil, diltiazem, amlodipine
3. Immunosuppressive drugs	Cyclosporine
4. Miscellaneous drugs	Sertraline, erythromycin
5. Physiological conditions	Pregnancy, puberty
6. Pathological conditions	Vitamin C deficiency, leukaemia, Wegener's granulomatosis, sarcoidosis or orofacial Granulomatosis, Cancer

influx leading to a reduction in the uptake of folic acid, thus limiting the production of active collagenase. The drug decreases collagen endocytosis through induction of a lower expression of $\alpha_2\beta_1$ -integrin by fibroblasts. Myofibroblasts seem to be stimulated by phenytoin.⁹ Classically, gingival tissue adjacent to anterior teeth is more commonly affected than the tissue adjacent to posterior teeth. In the above case, the patient's poor oral hygiene had an adjunctive effect over phenytoin tissue response thereby causing gum enlargement. The predominant histological feature found in the hyperplastic tissue was a proliferation of collagen fibres in the corium.¹⁰

It is possible that drugs such as azithromycin and metronidazole have a common action inhibiting the proliferation of collagen fibres. The role of metronidazole in the management of gum hypertrophy is thought to be due to its antibacterial action, but this is controversial.¹¹ Wong *et al*¹² described four cases of cyclosporin-induced gingival hyperplasia that resolved after 7-day treatment with 400 mg/day of metronidazole. Gingival hyperplasia disappeared after 3–4 weeks of treatment. In two of these patients, gingival hyperplasia recurred 1 year later, but then it responded again to a second course of metronidazole therapy. Wahlstrom *et al*¹³ described two cases of gingival hyperplasia that improved after treatment with azithromycin. A systematic review revealed that a short course of azithromycin or metronidazole along with proper regular oral hygiene is helpful in reducing the degree of gingival overgrowth.¹⁴ There is a general agreement that an initial threshold serum

Figure 1 Oral cavity of patient on chronic use of phenytoin showing gum hypertrophy in upper and lower jaws.

Figure 2 Oral cavity of patient showing progressive regression of gum hypertrophy in both jaws.

Box 1 Summary of management strategy for gum hypertrophy in neurosurgical patients

Prevention

1. Strict oral hygiene: chlorhexidine (0.1%) 2–3 times/day (the interval between tooth-brushing and rinsing should be at least 30 min)
2. Oral folic acid 500 mg supplementation with antiepileptics (eg, phenytoin, etc)
3. Regular oral cavity examination for patients on offending medications¹⁶

Management

1. Stopping/substituting the offending medicine with alternative drugs (eg, levetiracetam)
2. Oral metronidazole 400 mg for 21 days or azithromycin 500 mg for 3–5 days
3. Laser or surgical removal of the gingival overgrowth (gingivectomy)^{17 18}

concentration of the offending drug (phenytoin) is required to initiate gum hypertrophy and it has been suggested that the higher the serum concentration the quicker gum hypertrophy develops.¹⁵

Learning points

To conclude, we reiterate the importance of:

- Oral hygiene in neurosurgical patients.
- Regular oral examination of neurosurgical patients on chronic use of antiepileptics with intermittent measurement of their plasma levels.
- Switching over or starting with a safer, more compliant complementary medicine, for example, levetiracetam.
- However, once diagnosed with this pathological condition, patients should be managed according to protocol (described in box 1).

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