Reminder of important clinical lesson

Generalised stunting of roots in an epileptic child: is long-term phenytoin therapy the cause?

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Summary

Long-term phenytoin therapy is known to cause disturbance in calcium and bone homeostasis. Dental tissues being calcified tissues can also be affected by this derangement of mineral metabolism, especially during developmental phases. This report describes a case of an epileptic child who presented with short roots, enlarged pulp chambers, blunt apices and delayed eruption of permanent dentition, which might be attributed to long-term phenytoin therapy. The purpose of this case report is to increase awareness among the clinicians about its possible dental implications and emphasise upon the need of regular dental check-ups in epileptic children.

BACKGROUND

Epilepsy is a neurological disorder associated with several comorbidities. The estimated number of epileptic patients in India is 5.5 million with approximately 4.1 million residing in rural areas. Anticonvulsant drugs are cornerstones in epilepsy treatment.¹ The effects of epilepsy and the various complications of the long-term anticonvulsant drug intake adversely affect the quality of life of the afflicted people. For many patients, the latter may be a major concern as the long-term adverse effects of the drug may be insidious.²

Long-term phenytoin therapy has been documented to produce hypocalcaemia and disturbances in bone metabolism which manifests as osteomalacia in adults and rickets in children.² The most common side effect seen in oral cavity is gingival hyperplasia, but its effect on the development of dentition is scarcely reported in the literature.³ The following paper describes the case of a child who presented with the disturbance in the development of permanent dentition which could possibly be due to long-term phenytoin therapy.

CASE PRESENTATION

A 14-year-old girl presented to the Department of Pediatric Dentistry with the chief complaint of malaligned teeth. The patient was a known epileptic and was on phenytoin therapy (100 mg twice daily) for 8 years with intermittent short-term use of valproate and carbamazepine. Despite being on regular medications, the frequency of seizures continued to be 3–4 per year. The medical records of the patient revealed that phenytoin was administered in dosage normal to the patient's age but for a prolonged duration of 8 years. The child also had myopia and wore corrective glasses. On anamnesis, the patient was found to have frequent episodes of muscle cramps and involuntary contractions in feet and hands. Family history was not significant.

Oral examination revealed retained left maxillary primary canine and second molar. The patient had fair oral hygiene and no carious lesions were detected. The

crowns of the erupted teeth appeared normal. Maxillary central incisors were proclined and slightly mobile. Radiographic examination revealed unerupted left maxillary canine and premolars of the same side. The striking feature on the Orthopantomograph x-ray was that permanent teeth had short, blunt roots with open apices (figures 1 and 2).

INVESTIGATIONS

Biochemical investigations of the patient revealed low serum calcium (6.4 mg/dl), elevated serum phosphorus (5.9 mg/dl) and high serum alkaline phosphatase (874 U/l) and normal parathormone level (47 pg/ml). Patients renal function tests and liver function tests were not deranged.

DIFFERENTIAL DIAGNOSIS

The dental features of the patient were shortening of roots, blunt apices, mobility of teeth and enlarged pulp canals. These features could have been the result of disturbances in tooth development because of trauma or root resorption following trauma. However, the patient and her parents could not recall any episode of trauma to the orofacial region, not even during the epileptic attacks and cramps.⁴

The enlarged pulp chamber is a characteristic feature of taurodontism. However, in taurodontism teeth involved

Figure 1 Panoramic x-ray showing generalised stunting of roots and blunt apices.

Figure 2 Intraoral periapical x-ray of permanent maxillary central incisors showing poor root formation.

are invariably molars and frequently tend to be rectangular in shape rather than taper towards the roots.⁵ However, radiographically most of the teeth showed usual pulpal constriction at the cervical of the teeth, thereby excluding the possibility of taurodontism in the present case.

The dental features on the radiograph most closely resemble the root anomalies seen in hypoparathyroidism and pseudohypoparathyroidism, which prompted us to investigate for the parathormone and calcium levels in the concerned patient. However, the biochemical investigations ruled out the possibility of hypoparathyroidism and the general features of pseudohypoparathyroidism such as cataract, basal ganglia calcification, short stature and metacarpal shortening were not seen in the present case. Harris *et al*³ reported an interesting case series of root abnormalities in epileptic patients in which occasional stumpy shortening to marked resorption of roots had been attributed to the phenytoin therapy.

Short root anomaly was also excluded as no positive family history could be ascertained in the present case. Other possible aetiologies in which short-rooted teeth are seen include orthodontic treatment, history of chemotherapy and radiation therapy to craniofacial area and neck, disorders such as scleroderma, Stevens-Johnson syndrome, Down syndrome. However, none of these conditions could be accounted for in the present case.⁴

TREATMENT

Patient was referred to a neurologist and an endocrinologist of our university and was started on oral calcium supplements with calcitriol. The retained deciduous teeth were extracted to allow for eruption of permanent teeth. The patient was kept on regular follow-up.

OUTCOME AND FOLLOW-UP

After 6 months of starting oral calcium therapy, the biochemical investigations were repeated and found to be within normal range. There was no history of seizures or cramps during that period. The left maxillary first premolar was erupting buccally inclined to normal position in the oral cavity (figures 3 and 4). Radiograph did not reveal any significant change in the shape and size of the roots of teeth when compared with the previous one.

DISCUSSION

It has been well documented that the long-term administration of phenytoin can produce metabolic disorder of calcium. At higher doses, phenytoin acts by blocking intracellular and transmembrane calcium transport by blocking calcium channels. This effect on calcium transport might be responsible for calcium antagonism causing an inhibitory effect on calcium secretory cells.⁶ It has also been postulated that the inhibitory effect of phenytoin on membrane permeability to sodium indirectly affects calcium transport and plays a role in the genesis and maintenance of phenytoin-induced hypocalcaemia.⁷ The odontoblasts being the secretory cells in dentinogenesis can be the target cells of the action of phenytoin during the developmental stages of teeth.⁸

The other proposed mechanism of the disturbance in calcium homeostasis by phenytoin is by induction of liver microsomal oxidase enzymes, with a consequent increased rate of catabolism of vitamin D and 25-hydroxyvitamin D to polar, presumably inactive metabolites.⁹ However, in a tropical country like India, where sunlight exposure is enough for adequate production of vitamin D, this mechanism seems less likely in our case.

Several clinical studies also report that phenytoin can cause end-organ resistance to the effects of parathyroid hormone, which is involved in maintenance of calcium homeostasis.⁷ Harris *et al* found phenytoin-induced root resorption and stumpy shortening in 14 of the 112 epileptic patients in a radiographic survey and followed it up with an *in vitro* study. They concluded that phenytoin appears to block the effect of parathyroid on bone, which was comparable to pseudohypoparathyroidism where

Figure 3 Intraoral clinical view of maxillary arch showing erupting first premolar after 6 months of calcium therapy.

Figure 4 Intraoral clinical view of mandibular arch.

bone is insensitive to high or normal levels of hormone.³ Another study by Robinson and Harvey reported extensive resorption of cementum and dentine in the molars of the phenytoin-treated and parathyroidectomised rats, but not in the rats fed on calcium-deficient diet or control groups. The authors concluded that phenytoin induces a condition similar to pseudohypoparathyroidism in which the resistance of tooth roots to resorption is reduced.¹⁰

The biochemical tests of the present case and dental features led us to a suspicion of a state mimicking pseudohypoparathyroidism. In the present case, the presence of short roots, blunt apices, large pulp chambers and delay in teeth eruption are seen, the dental features characteristic of pseudohypoparathyroidism. However, the general features of pseudohypoparathyroidism such as cataract, basal ganglia calcification, short stature and metacarpal shortening were not present in our case. The other dental characteristics of pseudohypoparathyroidism such as small crowns and thin hypoplastic enamel¹¹ were not found in the present case, the probable reason for which could be that calcium derangement might have started after the crown calcification was complete. Sunde and Hals¹² also found that the dentine changes are more pronounced than those in enamel and thought that this might be a manifestation of the gradual loss of the property of specialisation of the odontoblast as a result of the biochemical consequences of the condition. The arrested root development could be due to a defect in Hertwig's root sheath, the part of the tooth germ responsible for root formation. On the contrary, it has been claimed that the enamel hypoplastic changes are not an essential feature of pseudohypoparathyroidism.¹³

The most likely cause of hypocalcaemia seen in the present case was long-term phenytoin therapy. After careful evaluation and excluding all the possible known causes of stunted roots, hypocalcaemia induced by long-term phenytoin therapy could be considered as the most plausible aetiology in the present case. Calcium supplements should be prescribed with long-term phenytoin therapy to prevent calcium metabolic disturbance, although that is not routinely practised. This is illustrated by a survey of 624 neurologists, of whom only 28% were aware that anticonvulsant drugs are associated with reduced bone mass. In this cohort of neurologists, only

9% of paediatric neurologists and 7% of those treating adults prescribed prophylactic calcium and vitamin D supplements to their epileptic patients.¹⁴ Hypocalcaemia can also lead to tetany and seizures which can be confused with epileptic attacks. If misdiagnosed, hypocalcaemic seizures can erroneously be treated on the lines of epilepsy, which further aggravates the condition leading to a vicious cycle.¹⁵ In the present case also hypocalcaemia was seen in an epileptic child that could be attributed to long-term phenytoin therapy. The patient in the present case came from a rural background with poor medical facilities due to which this condition remained undetected for long.

In a child with long-term phenytoin therapy, defective mineral metabolism might alter the dental development and the defects already produced cannot be reverted back to normal. The purpose of this case report is to lay emphasis on regular dental monitoring and calcium levels of patients on long-term phenytoin therapy especially for paediatric patients so that the irreversible damage that can adversely affect developing teeth can be prevented.

Learning points

- Developmental disturbances in dental tissues can lead to irreversible defects in dentition.
- Regular calcium monitoring should be done in epileptic patients especially in children.
- Regular dental check-ups should be advised on patients on long-term phenytoin therapy.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Sridharan R, Murthy BN. Prevalence and pattern of epilepsy in India. *Epilepsia* 1999;**40**:631–6.
2. Nakken KO, Taubøll E. Bone loss associated with use of antiepileptic drugs. *Expert Opin Drug Saf* 2010;**9**:561–71.
3. Harris M, Goldhaber P. Root abnormalities in epileptics and the inhibition of parathyroid hormone induced bone resorption by diphenyl hydantoin in tissue culture. *Arch Oral Biol* 1974;**19**:981–4.
4. Apajalahti S, Hölttä P, Turtola L, et al. Prevalence of short-root anomaly in healthy young adults. *Acta Odontol Scand* 2002;**60**:56–9.
5. Shafer WG, Hine MK, Levy BM. A text book of oral pathology. In: Rajendran R, Sivapathasundaram B, eds. *Developmental disturbances of oral and paraoral structures*. Ch1. 6th edn. India: Elsevier; 2009:44.
6. Hassel TM. Epilepsy and the oral manifestations of phenytoin therapy. In: Myers HM, ed. *Monogr Oral Sci* 1981;**9**:1–205.
7. Harris M, Jenkins MV, Wills MR. Phenytoin inhibition of parathyroid hormone induced resorption in vitro. *Br J Pharmacol* 1974;**50**:405–8.
8. Larmas M, Tjäderhane L. The effect of phenytoin medication on dentin apposition, root length, and caries progression in rat molars. *Acta Odontol Scand* 1992;**50**:345–50.
9. Hahn TJ, Scharp CR, Richardson CA, et al. Interaction of diphenylhydantoin (phenytoin) and phenobarbital with hormonal mediation of fetal rat bone resorption in vitro. *J Clin Invest* 1978;**62**:406–14.
10. Robinson PB, Harvey W. Tooth root resorption induced in rats by diphenylhydantoin and parathyroidectomy. *Br J Exp Pathol* 1989;**70**:65–72.
11. Brown MD, Aaron G. Pseudohypoparathyroidism: case report. *Pediatr Dent* 1991;**13**:106–9.
12. Sunde OE, Hals E. Dental changes in a patient with hypoparathyroidism. *Br Dent J* 1961;**111**:112–17.
13. Glynn A, Hunter IP, Thomson JA. Pseudohypoparathyroidism with paradoxical increase in hypocalcaemic seizures due to long-term anticonvulsant therapy. *Postgrad Med J* 1972;**48**:632–6.

14. **Valmadril C**, Voorhees C, Litt B, *et al*. Practice patterns of neurologists regarding bone and mineral effects of antiepileptic drug therapy. *Arch Neurol* 2001;**58**:1369–74.
15. **Kelly A**, Pomarico L, de Souza IP. Cessation of dental development in a child with idiopathic hypoparathyroidism: a 5-year follow-up. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;**107**:673–7.

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