CASE REPORT

Global developmental delay with sodium valproate-induced gingival hyperplasia

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SUMMARY

Global developmental delay (GDD) refers to a disturbance in an individual child across one or more developmental domains, which include motor, cognition, daily activities, speech and language. The present case discusses a 5-year-old child with GDD associated with infantile spasms treated with sodium valproate. Delay in the widespread acquisition of skills, epilepsy and poor oral hygiene with gingival enlargement was the main concern to seek medical aid. This case is special as the child was suffering from GDD associated with sodium valproate-induced gingival enlargement.

BACKGROUND

Neurodevelopmental disabilities found in children are a group of chronic clinically distinct disorders that share a documented disturbance, quantitative, qualitative, or both, in developmental progress in one or more developmental domains compared with established norms. These domains, although not mutually independent or exclusive, include (1) motor (gross or fine), (2) speech and language, (3) cognition, (4) personal-social and (5) activities of daily living.

Global developmental delay (GDD) refers to neurodevelopmental disturbance in an individual child across one or more developmental domains, which is defined as a significant delay in >2 of the major developmental domains, although most affected patients have impairment evident in all five of the domains.¹ The prevalence of GDD in the paediatric population is not precisely known; however, estimates of affected children range between 1% and 3%.²

The aetiology includes (in descending order of apparent frequency)³

1. Intrapartum asphyxia;
2. Cerebral dysgenesis;
3. Early severe psychosocial deprivation (attachment disorder);
4. Antenatal toxin exposure (ie, alcohol or multidrug).

Although several disorders can be recognised in infancy, it is unusual to diagnose speech impairments, hyperactivity or emotional disorders before 3 or 4 years of age, and learning disabilities are rarely identified before children start school, as a result most of the parents do not seek early medical intervention.

Clinical features commonly associated with GDD are the child's build is generally of a short stature, macrocephaly, generalised hair growth anomalies, face shape may be striking with facial asymmetry,

coarseness attributed to thickened facial tissues, flat facial profile and mid-face hypoplasia. Eyes may appear to be deeply set or prominent associated with visual field defects such as pupillary abnormalities. Facial paresis, dysarthria and head tilt are seen with reduced muscle bulk, tone, stretch reflexes and plantar responses. The skin is generally associated with a neurocutaneous disorder. Bipolar disorders with frequent epileptic attacks are reported.

Drug-induced gingival enlargement is the term used to describe medication-related gingival hypertrophy or hyperplasia, a condition commonly induced by three main classes of drugs: anticonvulsants, antihypertensives, calcium channel blockers and immune suppressants. Among the anticonvulsants gingival enlargement is seen mostly with diphenylhydantoin. The other anticonvulsants that have the same effect are vigabatrin, primidone, phenobarbital and sodium valproate.⁴

However, the prevalence of sodium valproate-induced gingival enlargement in children remains less documented. Sodium valproate or valproate sodium is the sodium salt of valproic acid. It is an anticonvulsant used in the treatment of epilepsy and bipolar disorder. The drug is metabolised by P450 (CYP) enzymes with a half-life of 9–18 h and 20% of the drug is excreted as glucuronide. Some of the common adverse effects of sodium valproate include tiredness, tremor, sedation and gastrointestinal disturbances. In addition, about 10% of the users experience reversible hair loss and, rarely, gingival enlargement.

The aim of this case is to educate readers about GDD in children with sodium valproate-induced gingival enlargement.

CASE PRESENTATION

A 5-year-old girl presented with loss of teeth and bleeding gingiva. She was the only child of a non-consanguineous Indian couple and was born after a trouble-free pregnancy. The child weighted 1.25 kg at birth and did not cry till half an hour after birth. The Apgar score for the child was noted to be 6 at the time of birth and the appropriate medical attention was provided. The child is currently being treated for GDD associated with epilepsy. There was no familial history of any neurological problem. The entire set of her deciduous teeth had erupted normally by the age of 2 years 6 months. Three months later the teeth started to chip off gradually, associated with bleeding and swollen gingiva, which resulted in difficulty to chew food. The child was unable to speak, understand or reciprocate to commands. She was unable to hold her

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Figure 1 Head tilt.

head straight in prone, stand, sit or walk without support. There was an absence of any type of physical activity from the time of birth. Infantile spasms were observed since 8 months of birth and she had been on anticonvulsants, that is, sodium valproate 5 mL twice daily.

The general condition of the patient appeared compromised. She is of a short stature and exhibits the absence of deep tendon reflexes. Reactions to touch, tickling, pressure and thermal stimuli are abnormal. Right-sided weakness with extrapyramidal problems was more prominent. Difficulty to sit or stand upright with head tilt was noted.

Extraoral examination showed features of a high frontal hair-line with deep seated eyes, poor vision and small alae nasi with a depressed nasal bridge. Bimaxillary protrusion was prominent (figures 1 and 2). Intraoral examination revealed an increased depth of the palatal vault. The mandibular ridge was irregular, with reduced thickness and alveolar bone height at the anterior

Figure 2 Flat nasal bridge, bimaxillary protrusion.

Figure 3 Generalised bleeding and fibromatous gingiva.

region (figure 3). Bleeding fibromatous gingiva was a marked feature. Maxillary right and left second deciduous molars and mandibular right and left canines were the only teeth present and the remaining teeth were grossly decayed and had sharp edges (figures 4 and 5).

INVESTIGATIONS

The child was subjected to complete blood investigations with the serum valproate level estimation. Gingival biopsy was also performed as part of the investigations. As the patient exhibited head tilt and lack of neck stiffness, obtaining the orthopantomograph proved to be difficult.

Gingival biopsy was sent to the pathology laboratory where the microscopic examination of the H&E- stained section showed histological features suggestive of gingival hyperplasia. The serum valproate levels were higher than normal which helped in the confirmation of drug-induced gingival enlargement.

TREATMENT

The drug treatment plan of the neurophysician at the National Institute of Mental Health and Neurosciences managing the epilepsy was discussed. The physician tapered the valproate dose for the first 3 weeks and substituted carbamazepine after the required neurological assessment. The dental treatment approach included the elimination of sharp surfaces of the molars which was carried out by selective grinding and restorations for the molars. Thorough oral prophylaxis followed by vigorous gingival massage coupled with efficient tooth brushing instructions was taught to the parent. Extraction of the root

Figure 4 Root stumps in relation to all maxillary teeth except maxillary second molars.

Figure 5 Reduced ridge height at the mandibular anterior region.

stumps was carried out under local anaesthesia. Maintenance of meticulous oral hygiene was reinforced at every visit.

OUTCOME AND FOLLOW-UP

Follow-up after every 6 months up to the age of 8 years showed the absence of gingival inflammation and eruption of the upper and lower central incisors (figures 6 and 7). The child is currently receiving physiotherapy and has shown improvements in motor skills.

DISCUSSION

This case demonstrates features consistent with GDD. The heterogeneous nature of GDD is a peculiar challenge for a child to develop cognitive skills. The functional milestones that the child develops at the age of 3 years include to walk up and down stairs, play, read two-letter words, write, draw toilet training, finger feeds, brushing teeth, etc, whereas in this case, the child lacked any of these skills and required complete assistance from the parents.

The treatment of a child with GDD is a time-intensive process. As reviewed by Shevell³ there are multiple treatment objectives, which include the following elements: (1) confirming and classifying the precise neurodevelopmental disability; (2) through history, physical examination and selective laboratory testing, ascertaining a possible underlying aetiology; (3) identifying and arranging rehabilitation service interventions; (4) counselling the family regarding the implications of the diagnosis from individual and familial perspectives, including a discussion of the possible recurrence risks and possible outcomes and (5) identifying possible behavioural conditions that may require specific medical or other interventions to optimise the realisation of the child's full developmental and cognitive potential.

Most studies to evaluate the pathogenesis of drug-induced gingival enlargement involving anticonvulsants have been carried out with phenytoin, as sodium valproate is rarely

Figure 6 Absence of gingival inflammation.

Figure 7 Eruption of the upper and lower central incisors.

associated with gingival enlargement.⁴ According to one study however, epileptic children on valproate are at risk of periodontal problems.⁵ Seymour reviewed the pathogenesis of drug induced gingival overgrowth and consider it as a multifactorial model involving an interaction of several factors like drug metabolism with gingival fibroblasts, age, genetic predisposition, inflammatory changes.⁶

Comprehensive history revealed that the child was receiving valproate syrup 5 mL twice daily from the age of 8 months. Drug-induced gingival enlargement begins to appear as early as 2–3 weeks after initiation of therapy and peaks at 18–24 months. The initial clinical appearance is a painless enlargement of the interproximal gingiva. The buccal and anterior segments are more affected than the lingual and posterior segments. The affected areas are isolated at first but can become more generalised later. Unless a secondary infection or inflammation is present, the gingiva appears pink and firm and does not bleed easily on probing. More frequently, however, inflammation superimposes and a combined type of inflammatory enlargement ensues.

In the present case, as the adverse effect of valproate had been overlooked and no effective treatment or prophylaxis was carried out, the oral hygiene of the patient was severely compromised. As a result the first line of treatment was oral prophylaxis, the initial tapering and further discontinuation of valproate and substituting the drug with carbamazepine after the gingival and the higher serum valproate levels were discussed with the physician. The parent was instructed to follow meticulous oral hygiene and the ascorbic acid supplements helped to reduce the inflammation.

Gingival enlargement produces aesthetic changes and clinical symptoms including pain, tenderness, bleeding, speech disturbances, abnormal tooth movement and dental occlusion problems. As a result it becomes the responsibility of the paedodontist in identifying the cause for enlargement and the follow-up of the case to help establish the proper occlusion.

Learning points

- ▶ Developmental delays are common and can involve different domains of a child's functioning.
- ▶ Sodium valproate-induced gingival enlargement is a rare phenomenon.
- ▶ Early intervention and management provides the best opportunity for positive outcomes for the child and the family.

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Competing interests None.

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