CASE REPORT

Journal of Pre-Clinical and Clinical Research 2024, Vol 18, No 2, 135-138
www.jpccr.eu

Gingival enlargement induced by anticonvulsant drugs in children with microcephaly – Case Report

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Maislla Mayara Silva Ramos, Anna Liz Oliveira, Maria Letícia Velame, Adriano Monteiro d'Almeida Monteiro, Rita de Cássia Andrade, Maria da Conceição Freitas. Gingival enlargement induced by anticonvulsant drugs in children with microcephaly: case reports. J Pre-Clin Clin Res. 2024; 18(2): 135–138. doi: 10.26444/jpccr/187945

Abstract

Microcephaly, in addition to craniofacial disproportion, can lead to skeletal muscle dysfunctions in the foetus, hearing and visual alterations, as well as seizures and epilepsy. It is additionally important to note that the oral health of these children can be compromised due to the difficulty in controlling mouth movements and chewing. Children have been taking anticonvulsant drugs to control seizures and epilepsy since the first year of life. But will children with microcephaly who take these drugs long term have oral manifestations from these substances? Could the delay in dental development be related to a possible excess of gingival growth, preventing tooth eruption? Based on these questions, five clinical cases of children with severe microcephaly, aged between seven and eight years in the mixed dentition stage, are presented, focusing on gingival health and dental development.

Key words

epilepsy, children, gingival hyperplasia, microcephaly

INTRODUCTION

Microcephaly is a clinical condition manifested within the first 24–48 hours of life of a newborn, who shows a smaller occipital-frontal circumference compared to others of the same gender and age by the normatives referred in the patterns of growth from the INTERGROWTH table, which relies on the measurement of the child's cephalic perimeter in order to monitor their brain growth [1, 2]. In addition to craniofacial disproportions, newborns exhibit visual and auditive complications, spasms, seizure and early epilepsy. Carvalho et al. (2020) observed that in children with Zika-related microcephaly, a higher incidence of epilepsy occurred during the first year and provided new insights regarding the development of spams in the second year of life [1].

According to the literature, antiepileptic drugs, such as phenytoin and sodium valproate, are strongly related to an enlargement in free and attached gingiva [3]. Medicines that inhibit the intracellular influx of calcium ions provoke an enhanced accumulation of collagen inducing a fibrotic gingival disorder. Displaying a similar mechanism of action on a cellular level, carbamazepine, valproic acid, phenobarbital and primidone are also antiepileptics that promote gingival enlargement in a lower range [4, 5]. Patients on polytherapy with these medications might experience a synergistic interaction, showing aggravation of the side-effects [5]. In fact, those drug classes can cause hypertrophy as a result from the buildup of compounds of the extracellular matrix amongst the cells, thus leading to an increase in the gingival volume. The American Academy of Periodontology and the European Federation of Periodontology have established a new classification for this clinical condition, including it in the gingival diseases induced by dental plaque and modified by drug stimulation. Nevertheless, in the total absence of a plaque index, the hypertrophic state remains undeveloped [6].

The latest studies highlight that children with microcephaly showed poor oral hygiene during the mixed detention stage, evidenced by the build-up of calcified biofilm in the region of the deciduous molars, and by the high risk of dental caries development [8]. Regarding dental development, studies have reported delayed eruption of the deciduous teeth besides changes in the eruption sequence [8, 9]. As a result of the extended use of antiepileptic drugs in order to control seizures and epilepsy, along with a significant dental plaque index, would the children with microcephaly show high levels of generalized gingival enlargement? Would the delay on the dental development be related to a possible gingival overgrowth which hinders tooth eruption? With these questions, five clinical cases of children with microcephaly and with mixed dentition are presented, with an approach to gingival health and dental development.

CASE REPORTS

All of the cases presented below were conducted at the dental clinic of the Southwest Bahia State University in Jaquié, Brazil, and were followed-up for 2 years. Ethical approval for this study was provided by the Human Research Ethics

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Received: 25.02.2024; accepted: 25.04.2024

Committee of the State University of Southwest Bahia (Approval No. 09430519700000055O). The patients consisted of 5 children, between 6–7 years old, from both genders, with severe microcephaly, as severe motor, cognitive, and sensory impairment, and presented negative laboratory results for congenital infections. Children's neuroimaging findings of the first year of life presented corticosubcortical calcifications, cortical developmental disorders with simplification of the gyral pattern lissencephaly, or polymicrogyria, and/or diffuse atrophy of the cerebral volume. All the children had infantile spasms with the first seizures occurring at the age of 2 and 3 months. They were on long-term use – at least two years – of the following antiepileptic and anticonvulsant drugs: Phenobarbital, Carbamazepine, Topiramate, Valproate sodium, Benzodiazepine, Levetiracetam and Oxcarbazepine. Throughout the use of such drugs, there were no changes in the patients' medical prescriptions.

Intraoral examination showed that the patients were in the first period of the mixed dentition. Halitosis, presence in biofilm on the upper and lower teeth, dental calculus on the upper and lower deciduous molars, lack of passive lip seal, atypical lingual interposition, excessive production of saliva and generalized gingival enlargement, were observed. The treatment plan suggested was: removal of calculus, oral prophylaxis and application of sodium fluoride, together with guidance on oral hygiene, with a follow-up every 2 months.

As for the gingival enlargement induced by drugs, an analysis according to the degree of coverage of the tooth crown by gingival tissue was adopted [3]: Grade 0 – no enlargement; Grade 1 – initial change in gingival aspect, which loses its orange peel appearance, the gingival margins look modified with no increase in papillary volume; Grade 2 – increased volume of the interdental papillae; Grade 3 – gingival enlargement up to half the anatomical crown of the tooth in both apical-coronal and mesio-distal directions; Grade 4 – gingival enlargement beyond half of the tooth crown, in apicalcoronal and mesial-distal directions; Grade 5 – gingival enlargement that interferes with teeth function. In intrabucal clinical examination, in 4 patients the enlarged gingiva of the upper and lower anterior teeth was red, smooth and shiny, which bled easily on probing. The gingival enlargement was mostly marked around the labial portion increased volume of the interdental papillae (Fig. 1).

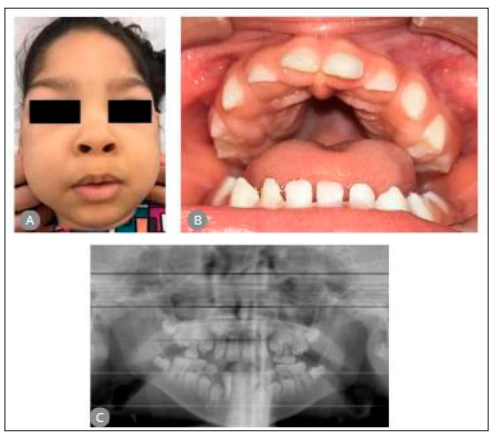

Figure 1 (A,B,C). Intraoral photographs of a patient, 7 years and 6 months of age, with severe microcephaly. Generalized gingival enlargement can be seen on the upper tooth surfaces. Panoramic radiographs of primary and mixed dentitions revealed alterations in the sequence of tooth eruption

There were crowns with dental plaque in cervical surfaces. In a male patient, the gingival were enlarged up to half the anatomical crown of the tooth (Fig. 2). All the patients showed in posterior teeth, especially in the region of the permanent upper and lower first molars, gingival enlargement beyond half of the tooth crown that interfered with teeth function. There were crowns with dental plaque in cervical surfaces and calculus in cervical and occlusal surfaces (Tab. 1).

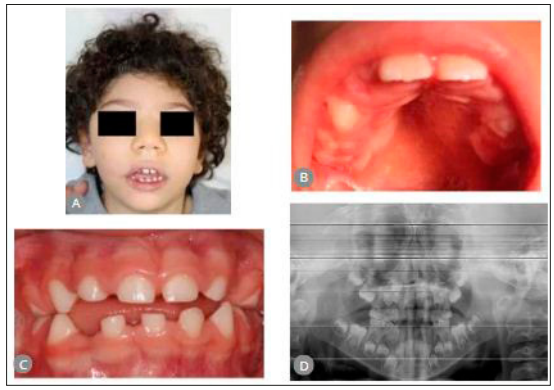

Figure 2 (A,B,C,D). Intraoral photographs and panoramic radiography of a patient with severe microcephaly, male, 6 years and 11 months of age, with primary dentition. In the mixed dentition, generalized gingival enlargement on the occlusal surfaces of the un-erupted upper permanent first molar can be seen

Table 1. Distribution of patients regarding the use of antiepileptic drugs, presence of biofilm and gingival growth

Patient and degree of microcephaly (WHO)	Sex	Age	Biofilm	Drugs/ Dosage	Terapy	Time of use	Gingival Growth (GRADE)
1 Severe Microcephaly	Female	6 years and 10 months	Anterior and posterior tooth surfaces	1-Carbamazepine (200mg/day), 2-Topiramato (50mg/day)	Polytherapy	1-6 years old 2-3 years old	Anterior teeth- 2 Posterior teeth - 4 and 5
2 Severe Microcephaly	Female	7 years and 04 months	Anterior and posterior tooth surfaces	1-Carbamazepine (200mg/day), 2- Sodium Valproate (40mg/ml/day)	Polytherapy	1-3 years old 2-5 years old	Anterior Teeth -2 Posterior Teeth -3
3 Severe Microcephaly	Male	7 years and 07 months	Anterior and posterior tooth surfaces	1-Carbamazepine (200mg/day), 2-Benzodiazepine (10 mg/day)	Polytherapy	1-7 years old 2-4 years old	Anterior Teeth -2 Back Teeth - 4 and 5
4 Severe Microcephaly	Female	7 years and 06 months	Anterior and posterior tooth surfaces	Levetiracetam (250mg/day)	Monotherapy	1-2 years old	Anterior teeth -2 Back Teeth -3 and 4
5 Severe Microcephaly	Male	6 years and 11 months	Anterior and posterior tooth surfaces	1-Phenobarbital (40mg/day), 2-Oxcarbazepine (60 mg/day)	Polytherapy	1-6 years old 2-4 years old	Anterior Teeth -3 Back Teeth - 4 and 5

The treatment plan for antiepileptic-induced gingival enlargement for all patients consisted of biofilm control and oral hygiene. In grade 4–5 cases, a report was previously sent to the neuropediatrician in charge, stating the need for a surgical approach, the performance of which was encouraged in the surgical centre.

Data on the patients, the use of antiepileptic/anticonvulsant drugs, presence of biofilm, and antiepileptic-induced gingival growth, are shown in Table 1.

Clinical follow-ups and monitoring by means of panoramic and periapical radiographs showed that the patients presented delayed tooth eruption, specifically of the permanent

maxillary and mandibular first molars, as well as a disrupted eruption sequence of those teeth. In 3 children, mean age of six years, the sequence of permanent teeth eruption was: lower central and lateral incisors; upper central and lateral incisors and lower and upper first molars. A male child, 7 years and 7 months of age, did not exhibit permanent lower incisors in the oral cavity. A female child, 7 years and 6 months of age, exhibited a severe alteration in the sequence of eruption: early loss of the first primary molar and the beginning of the eruptive process of the first premolar in the right side (Fig. 1).

DISCUSSION

About 70 million people are affected by epilepsy, and around 10–40% of the children worldwide suffer from seizures. The treatment suggested consists of the use of antiepileptics, which, on the other hand, might be associated with significant enlargement of the gingival tissue. This clinical condition may present itself within the first 3 months of use of the drugs, being initially noticed in the papilla [11]. The susceptibility to this drug-induced gingival response also depends on the presence of microbial biofilm. As highlighted in the data presented in this case report, there is an association between generalized gingival overgrowth and biofilm accumulation, mainly on the posterior teeth of all paediatric patients with microcephaly on long-term use of antiepileptics since their first year of life. These findings, however, differ from those by Gallo et al. [3]. Analyzing paediatric patients (<15 years old) and adults separately, they verified that the correlation between gingival overgrowth and plaque index in children was not significant, $r(18) = 0.276$ (critical value = 0.444); whereas, for adults this correlation was indeed significant, $r(40) = 0.357$; $P < 0.05$.

Muramaki et al. [12] have highlighted that the regular clinical characteristics of the antiepileptics-induced gingival overgrowth might present a variability in its extension and severity, which is related to the patient's genetic predisposition. In the higher occurrence observed in the anterior gingiva and a higher prevalence in the younger group ages, there is no probable association with periodontal attachment loss or dental loss. In this case report, all the children displayed symptoms of halitosis, bleeding after brushing the teeth, gingival swelling and redness; the periodontium did not exhibit bone loss; an increase was seen in the volume of interdental papillae in the anterior teeth, with aggravation of the gingival enlargement beyond half of the tooth crown of posterior teeth, in apical-coronal and mesial-distal directions, compromising tooth function. According to Doufexi et al [13], the jeopardy of oral function and delay in the eruption of permanent teeth are the major complications from the drug-induced gingival overgrowth in epileptic kids, reinforcing the evidence found in the current report on microcephalic children.

Among the antiepileptic drugs, those of the the first generation, such as phenytoin and phenobarbital, have a strong potential for inducing gingival overgrowth. New, second generation medications have been developed in order to soften this potential interaction and adverse effects [5] – carbamazepine, valproic acid and clobazam, as well as third generation medications – oxcarbazepine, topiramate and levetiracetam [14].

Studies indicate that the effect of the antiepileptic-induced gingival enlargement manifests itself after the first 3 months of use and reaches a plateau stage in 9–12 months [15]. This clinical condition may be seen in the patients of this case report (Tab. 1), who have used the earliest antiepileptic drugs, such as phenobarbital and sodium valproate, as well as those with less adverse effects, e.g. levetiracetam and topiramate for more than one year.

The presence of gingival enlargement induced by plaque and modified by the use of medication is easily justified in patients with microcephaly and inappropriate plaque control in mixed dentition with partially erupted teeth. Nevertheless, the presence of fibrotic gingiva covering all teeth before eruption is intriguing. As the teeth crowns are not exposed in the oral cavity and therefore not colonized by bacteria, how does plaque influence gingival growth, and consequently on tooth eruption?

Studies on the isolated use or use in combination of valproic acid, carbamazepine, levetiracetam, lamotrigine, phenobarbital and oxcarbazepine, verified that the prevalence of gingival overgrowth associated with only one medication, occurred in 37% and 45% of patients under polytherapy. The most commonly administered drug was valproic acid in mono- or polytherapy, while a higher occurrence of gingival enlargement was seen with oxcarbazepine [3]. Contrasting the data obtained in the present report, of the 5 patients followed, only one was on monotherapy (Levetiracetam); 3 patients were undergoing polytherapy, associating carbamazepine with topiramate or sodium valproate or benzodiazepines, and the fifth patient was on polytherapy with phenobarbital and oxcarbazepine. The grade of gingival growth induced by antiepileptic drugs in the anterior teeth ranged from 2–3, with grade 3 in only one patient who used phenobarbital and oxcarbazepine. In the posterior teeth, the grade was higher in the patients taking polytherapy, grades 4 and 5; only one patient (patient 3) did not take polytherapy of 2 anticonvulsants. In the patient using only levetiracetam, there was moderate gingival enlargement, grade 2 in the anterior teeth and grades 3–4 in the posterior teeth. Levitiracetum is a medication indicated in literature as one of the drugs that causes the least collateral damage. Polytherapy using 2 antiepileptics or one antiepileptic associated with a calcium channel blocker or a immunosuppressant, increases the drug-induced gingival response [16].

The withdrawal or exchange of the drug for epilepsy seizure control is directly related to the patient and to the evaluation of the neurologist, who can diagnose individuals with drug-resistant epilepsy, and optimize the therapy, adopting, for example, a rational polytherapy with antiepileptic drugs to find more effective combinations with fewer adverse effects [17].

In dentistry, the non-surgical approach is the first line of treatment for antiepileptic-induced gingival enlargement, with proper control of the microbial biofilm, and consists of the performance of tooth scaling and root planing, instruction on oral hygiene and the use of antimicrobial mouthrinses [5]. Persistent or relapsing cases require surgical intervention for complete resolution [18].

In the presented report, a strong correlation was observed between biofilm accumulation and gingival enlargement. Since there could be no reduction or change in medication, the treatment adopted was based on the elimination of the microbial biofilm with sporadic sessions every 2 months. In

cases of heavy severity, the patient was advised to undergo surgery in a hospital environment.

CONCLUSION

The presented series of cases demonstrates that through the medical history and through the clinical intraoral examination, children with microcephaly exhibit significant growth of the gingival volume induced by an expressive presence of plaque, modified by the stimulus of prolonged use of first, second and third generation antiepileptic drugs either in poly- or monotherapy. Regarding dental development, the children presented delayed tooth eruption, specifically of the permanent maxillary and mandibular first molars, as well as a disrupted eruption sequence of those teeth.

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