Effects of anti-epileptic drugs on the oral health of paediatric patients

D. Tripodi, G. Cacciagrano, S. D'Ercole, A. Verrotti, M. Tieri

Department of Medical, Oral and Biotechnological Sciences, University of Chieti-Pescara, Chieti, Italy

e-mail: giuliaccgrn@hotmail.it

DOI 10.23804/ejpd.2023.24.01.08

Abstract

Aim To evaluate the effects of epilepsy therapy on the oral health in paediatrics patients.

Materials and methods The test has involved 57 patients. The patients were stratified in three groups: monotherapy group, politherapy group and control group. They were examined and after that the test groups were compared with the control group.

Results Statistical results show the absence of significant differences between test and control groups.

Conclusions Paediatric epileptic patients seem to have a greater risk of having a worse oral health status compared with healthy patients. However, if the patient is well monitored and undergoes regular dental checks, the oral condition is comparable to a healthy subject.

KEYWORDS Anti-epileptic drugs, Paediatric patients, Oral health.

Introduction

Epilepsy is a chronic disease that affects around 50 million people worldwide. It is characterised by recurrent seizures, which are not recognisable by an external observer and which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalised) and are sometimes accompanied by loss of consciousness and bowel control or bladder function [World Health Organization, 2019].

There are many types [Araiche and Brode, 1959] and many causes [Ercoli et al., 2015] of epilepsy: it is very important determine the type of seizure to guide differential diagnosis, choose the right therapy and establish prognosis. However, not all seizures may fit easily into classification schemes, especially those occurring during infancy [Boutiouet al., 2020]. According to a recent study, the lifetime prevalence is 7.60 per 1,000 persons (95% CI 6.17–9.38) while the incidence rate is 61.44 per 100,000 person-years (95% CI 50.75–74.38) [Fiest et al., 2020].

Pharmacological therapy can be very effective in reducing or even eliminating seizures. The treatment goal is to employ a drug with the least side effects, while monitoring the patient and adjusting the dosage if needed.[Nevitt et al., 2017].

For a long time, the only therapeutic option was to employ some "classic" anti-epileptic drugs (AEDs), which have many side effects [Suneja et al., 2016].

Recently, new drugs have been made available. In addition, the modern approach involves the use of different protocols, such as monotherapy and polytherapy, where, as always, the choice of drug is a crucial.

AEDs are generally well tolerated in therapeutic doses; however, they may have very important toxic and side effects that are both systemic and neurological [De Negri, 2004]. One common side effect is gingival fibromatosis, which can be caused by three classes of systemic drugs, such as anticonvulsants, calcium channel blockers and immunosuppressants [Ercoli, 2015]. It is characterised by the accumulation of extracellular matrix in the gingival connective tissue, caused by a reduced phagocytosis of collagen by gingival fibroblasts [Boutiou et al., 2020]. In fact, some drugs act as intracellular calcium antagonists, which is involved in regulating the affinity of the bond between $\alpha 2\beta 1$ integrin (on the surface of fibroblasts) and collagen [López-González, 2017]; however, the cause of this side effect in children with epilepsy was unclear [Yeung et al., 2017]. In addition, teenagers and subjects under 30 years show worst reactions than older patients [Ercoli, 2015].

The aim of present study is to evaluate the effects of epilepsy treatment on the oral health in paediatric patients to assess the presence or the absence of intraoral side effects.

Materials and methods

The sample consisted of 57 patients, grouped as follows.

Tests groups: 21 patients in monotherapy with valproic acid, levetiracetam, oxcarbazepine, topimarate or lamotrigine; 18 patients in politheraphy with the above mentioned AEDs.

Control group: 18 healthy patients.

The inclusion criteria were the following.

Epileptic Paediatric patients.

Patients with teeth.

Patients under 1–3 months (therapeutic dose) monotherapy or politherapy with valproic acid or levetiracetam or oxcarbazepine or topimarate or lamotrigine.

The exclusion criteria were:

0	Healthy gingiva
1	Mild inflammation-no bleeding on probing
2	Moderate inflammation-bleeding on probing
3	Severe inflammation

TABLE 1 Gingival index (Loe, 1967)

0	No plaque
1	A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen in situ only after application of disclosing solution or by using the probe on the tooth surface.
2	Moderate accumulation of soft deposits within the gingival pocket or the tooth and gingival margin visible to the naked eye.
3	Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin

TABLE 2 Plaque index (Silness and Loe, 1964)

Patients without teeth;
Epileptic patients who had already suspended antiepileptic therapy with other drugs;
Patients with other systemic diseases and/or disability.

Patients underwent dental examination, and the following parameters were recorded.
Plaque index (PI) [Silness and Löe, 1964] (Table 1).
Gingival index (GI) [Löe, 1967] (Table 2).
Angle's class of malocclusion.
Use of fluoride (such as fluorinated toothpaste).
DMFT and dmft indexes.

At T0 patients had optimal hygiene conditions: they had a professional dental hygiene before starting pharmacological therapy (IP = 0; IG= 0) and they had been motivated to oral hygiene at home.
The DMFT remained unchanged from T0 to the subsequent controls, with p=0.2649.
The AEDs included in this paper, the mechanisms of action and the effects are reported in Table 3.
Parental informed consent was obtained for all patients before they were examined (Italian Personal Data Protection Code - Legislative Decree no. 196 of 30 June 2003). The selected subjects participated voluntarily in the study.
In this study, the approval from the Ethics Committee was not required since the research protocol was based on a clinical protocol previously approved by the Department of Medical, Oral and Biotechnological Sciences, University of Chieti-Pescara, Chieti (Italy) for medical use.
Kruskal-Wallis test was used to perform statistical analysis to assess the presence of statistically significant differences between groups: monotherapy, politherapy and control group. In addition, a statistical comparison was made between patients using valproic acid and the other ones.
Data were expressed as: mean ± Standard Deviation. We used t-Student test and p value <0.05 was considered statistically significant.

Results

Regarding the type of occlusion recorded in the patients, data are as follows.

CLONAZEPAM	Increases the action of the GABA inhibitory neurotransmitter	Sedative effect; in the child, changes in behaviuor and increase in salivation
TOPIRAMATE	Blockage of dependent sodium-voltage channels, enhancement of GABAergic transmission, attenuation of excitatory activity of AMPA-Kainate neurotransmitters O receptors?	Sedation, difficult concentration, reduced mental performance, decreased appetite, dizziness, behavioural disorders, may favor kidney stones, contraindicated in those who have suffered from renal colic
LEVETIRACETAM	Binds to the synaptic sites of the central nervous system cells. It is possible that it forms paroxysmal neuronal discharges and inhibits the propagation of the epileptogenic discharge	Drowsiness and asthenia, dizziness, NB: transient side effects, well tolerated
OXCARBAZEPINE	Dependent sodium-voltage channel blocker, potassium conductance modulation, differential inhibition of dependent calcium-voltage channels	Dizziness, asthenia, ataxia, headache, hyponatremia; in patients with allergic reactions to carbamazepine, it can be very well tolerated
VALPROIC ACID	Increased inhibitory activity of the neurotransmitter GABA, modulation of permeability of sodium channels	Nausea, vomiting, gastralgia, subsequently increased appetite and weight; possible increase in hair loss and menstrual disorders; in predisposed subjects, increased ammonium in the blood with confusional state, very rarely severe toxic hepatopathy
VIGABATRIN	Increased the action of the inhibiting amino acid GABA, in combination with other drugs	Drowsiness, weight gain psychiatric disorders, narrowing of the field of vision, campimetric examination should be regularly practiced every six months

TABLE 3 AEDs used in this work, their mechanisms of action and effects

Class I, 66% of cases.
Class II, 17% of cases.
Class III, 17% of cases.
Most patients, 83%, declared to use fluoride substances.
As for PI, we did not find any significant difference between monotherapy group, politherapy group and control group (p=0.0728).
About GI, we did not find any significant difference between monotherapy group, politherapy group and control group (p=0.1847).
About DMFT and dmft index, we did not find any significant

difference between monotherapy group, politherapy group and control group (p=0.2649).

About PI, we did not find any significant difference between valproic acid group, second generation AEDs (clobazam, levetiracetam, oxcarbazepine, topiramate, vigabatrin) group and control group (p=0.3530).

About GI, we did not find any significant difference between valproic acid group, second generation AED (clobazam, levetiracetam, oxcarbazepine, topiramate, vigabatrin) group and control group (p=0.0940).

About DMFT and dmft, we did not find any significant difference between valproic acid group, second generation AED (clobazam, levetiracetam, oxcarbazepine, topiramate, vigabatrin) group and control group (p=0.1408).

Discussion and conclusion

The most common side effects of AEDs are of neurological concern, such as dizziness, motor incoordination, diplopia, sleep disorders and mood, cognitive function and memory disorders; they arise at the beginning of treatment, they are proportional to serum levels of the drug and they are reversible by reduction or interruption of therapy. Newer drugs may adversely affect kidney, hematopoietic, liver, digestive, metabolic and endocrine systems; these side effects are less common, are not always proportional to serum levels of the drug dose, are generally idiosincratic, can alter the course of treatment and may be as severe as to be life-threatening. Early identification of these side effects is crucial to avoid long-lasting consequences [Liu et al., 2017; Moavero et al., 2017].

Gingival hypertrophy has long been recognised as an adverse effect of chronic phenytoin therapy [Gerret and Gerret, 2014; Ercoli, 2015; Thomason et al., 2020]. When it occurs, it is present for the whole course of treatment, and the prevalence of PHT-induced gingival hyperplasia vary from 13% to 50%, in community-based studies on institutionalized patients [Candotto et al., 2019]. For other AEDs, such as valproate, oxcarbazepine, levetiracetam, topiramate, lamotrigine, this aspect has not been investigated sufficiently or the old studies claim no oral adverse effects. For example, about leviracetam there is no recent literature (less than 5 years) about paediatric patients, the only reference available is not specifically about epileptic patients [Korporowicz et al., 2020], but there is a study on adult patients [Gallo et al., 2021]; carbamazepine can be considered a safe drug in children in relation to gingival overgrowth [Suneja et al., 2016]. Some articles found that disabled patients may be prone to bad oral health [Ogunbodede et al., 1998; Ferreira et al , 2011; Murthy et al 2011; Morgan et al., 2019; Bagattoni et al., 2020; Carli et al., 2021]. However, many authors believe that this is due not only to the therapy but to a lack of attention to oral health: in fact, in this paper it was found that the patients under AEDs did not exhibit any intraoral adverse effects. It was also noted that these patients paid great attention to oral hygiene because they knew they were under strict clinical control. The cause of bad oral health is often unknown [Yeung et al., 2019; Paglia, 2022; Giuca et al., 2021] or it may be due to a period of no oral health care.

In addition, some authors believe that some side effects, such as oral trauma, may be due to uncontrolled seizures due to the inconsistent (desultory or absent) intake of the medication [Ghafoor et al., 2014]; in fact, in our paper, in which the patients were compliant with the therapy, no trauma was found.

There are not significant difference between monotherapy group, politherapy group and control group regarding PI and GI. In addition, there are not significant differences between valproic acid - group, second generation AED group and control group. A better oral care prevents cavities: it has been proven that poor to oral care, typical of patients undergoing this therapy, is correleted to a higher dmft/DMFT [Ghafoor et al., 2014]. Patients under strict clinical monitoring, such as our sample of patients, may have the same dmft/DMFT of completely healthy patients [Gurbuz and Tan, 2010; Ferrazzano et al., 2020].

The occurrence of possible oral side effects caused by new and old-generation drugs in patients who have been in therapy for at least three months has been evaluated, and there is a negative response, in accordance with literature. Despite the numerous side effects, such as gingival hypertrophy, reported in patients treated with valproic acid [Suneja et al., 2016], those effects were related to syndromes associated with epilepsy and were not the direct result of the drug itself on the gingival tissue; therefore, having excluded "patients with systemic diseases" in this paper, we found no case of gingival hypertrophy.

Based on our findings and those from the literature, it can be concluded that paediatric epileptic patients and those who use AEDs would seem at greater risk [Ferreira et al., 2019] for a worse oral health status compared with healthy patients.

However, as evidenced by this paper, if the patient is well monitored from the point of view of antiepileptic therapy and undergoes regular dental checkups, the oral status is comparable to that of a healthy subjects, because in this case oral side effects are not attributable to the drug therapy.

To achieve this, a good cooperation between the different health professionals who follow these patients and the patients' families is needed.

Further studies shall be carried out.

References

- Araiche M, Brode H. A case of fibromatosis gingivae. Oral Surg Oral Med Oral Pathol 1959 Nov;12:1307-10.
- Bagattoni S, Lardani L, D'Alessandro G, Piana G. Oral health status of Italian children with Autism Spectrum Disorder. Eur J Paediatr Dent 2021 Sep;22(3):243-247.
- Boutiou E, Ziogas IA, Giannis D, Doufexi AE. Hereditary gingival fibromatosis in children: a systematic review of the literature. Clin Oral Investig 2021 Jun;25(6):3599-3607.
- Candotto V, Pezzetti F, Baj A, Beltramini G, Lauritano D, Di Girolamo M, Cura F. Phenytoin and gingival mucosa: A molecular investigation. Int J Immunopathol Pharmacol 2019 Jan-Dec;33:2058738419828259.
- Carli E, Pasini M, Lardani L, Giuca G, Miceli M. Impact of self-ligating orthodontic brackets on dental biofilm and periodontal pathogens in adolescents. J Biol Regul Homeost Agents 2021 May-Jun;35(3 Suppl. 1):107-115.
- De Negri M. Neuropsichiatria dell'età evolutiva. Piccin edizioni: 2004. pp 324->325.
- Ercoli C, Bartolino M, Montesani L, Docimo R. Gingival fibromatosis: a case report. Eur J Paediatr Dent 2015 Sep;16(3):233-5.
- errazzano GF, Sangianantoni G, Desiderio F, Ingenito A, Iorio R, Di Dato F, Matarazzo M, Cantile T. Oral health conditions in Wilson's disease patients: A clinical diagnostic study. Eur J Paediatr Dent 2020 Jun;21(2):137-142.
- Ferreira MC, Guare RO, Prokopowitsch I, Santos MT. Prevalence of dental trauma in individuals with special needs. Dent Traumatol 2011;27:113- 116.
- Ferreira A, Mayer A, Kawamoto D, Santos M. Constipation, antiepileptic drugs, and gingivitis in children and adolescents with cerebral palsy. Int J Paediatr Dent 2019 Sep;29(5):635-6.
- Fiest K, Sauro K, Wiebe S, Patten S, Kwon C, Dykeman J, Pringsheim T, Lorenzetti D, Jetté N. Prevalence and incidence of epilepsy A systematic review and meta-analysis of international studies. Neurology 2017 Jan;88(3):296-303.
- Gallo C, Bonvento G, Zagotto G, Mucignat-Caretta C. Gingival overgrowth induced by anticonvulsant drugs: A cross-sectional study on epileptic patients. J Periodontal Res

2021 Apr;56(2):363-369.
› Gerreth K, Gerreth P. Occurrence of oral trauma in young epileptic patients. Eur J Paediatr Dent 2014 Mar;15(1):13-6.
› Ghafoor PA, Rafeeq M, Dubey A. Assessment of oral side effects of Antiepileptic drugs and traumatic oro-facial injuries encountered in Epileptic children. J Int Oral Health 2014 Apr;6(2):126-8.
› Giuca MR, Carli E, Lardani L, Pasini M, Miceli M, Fambrini E. Pediatric Obstructive Sleep Apnea Syndrome: Emerging evidence and treatment approach. Scientific World Journal 2021 Apr 23;2021:5591251.
› Gurbuz T, Tan H. Oral health status in epileptic children. Pediatr Int 2010 Apr;52(2):279-83.
› Korporowicz E, Olczak-Kowalczyk D, Lipiec M, Słowińska M, Gozdowski D, Jóźwiak S. Oral findings in children, adolescents and adults with tuberous sclerosis complex. J Clin Pediatr Dent 2020;44(3):190-195.
› Liu G, Slater N, Perkins A. Epilepsy: Treatment Options. Am Fam Physician 2017 Jul 15;96(2):87-96
› Löe H. The Gingival Index, the Plaque Index and the Retention Index Systems. J Periodontol. 1967 Nov-Dec;38(6):Suppl:610-6
› López-González MJ, Luis E, Fajardo O, Meseguer V, Gers-Barlag K, Niñerola S, Viana F. TRPA1 Channels mediate human gingival fibroblast response to phenytoin. J Dent Res 2017 Jul;96(7):832-839.
› Moavero R, Pisani L, Pisani F, Curatolo P. Safety and tolerability profile of new antiepileptic drug treatment in children with epilepsy. Expert Opin Drug Saf 2018 Oct;17(10):1015-1028.
› Murthy AK, Chandrakala B, Pramila M, Ranganath S. Dental trauma in children with disabilities in India: a comparative study. Eur Arch Paediatr Dent 2013;14:221–225.
› Morgan H, El Fadl R, Kabil S, Elagouza I. Assessment of oral health status of children with epilepsy: A retrospective cohort study. Int J Paediatr Dent 2019 Jan;29(1):79-85.
› Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev 2017 Dec 15;12(12):CD011412.
› Ogunbodede EO, Adamolekun B, Akintomide AO. Oral health and dental treatment needs in Nigerian patients with epilepsy. Epilepsia 1998 Jun;39(6):590-4.
› Paglia L. The first thousand days of mother and child: a lifelong investment in oral health! Eur J Paediatr Dent 2022;23(1):5.
› Percival T, Aylett SE, Pool F, Bloch-Zupan A, Roberts GJ, Lucas VS. Oral health of children with intractable epilepsy attending the UK National Centre for Young People with Epilepsy. Eur Arch Paediatr Dent 2009 Jan;10(1):19-24.
› Silness, J., Löe, H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964; 22: 121-135.
› Suneja B, Chopra S, Thomas AM, Jeyraj Pandian. A clinical evaluation of gingival overgrowth in children on antiepileptic drug therapy. J Clin Diagn Res 2016 Jan;10(1):ZC32-6.
› Thomason J, Seymour R, Rawlins M. Incidence and severity of phenytoin-induced gingival overgrowth in epileptic patients in general medical practice. Community Dent Oral Epidemiol 1992 Oct;20(5):288-91.
› World Health Organization,WHO. Web Site: https://www.who.int/news-room/fact-sheets/detail/epilepsy, 20 june 2019.
› Yeung PM, Wong VCN, McGrath CP, Yiu CKY, Lee GHM. Oral health status of children with epilepsy in Hong Kong. J Investig Clin Dent 2019 Nov;10(4):e12479.