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The Difference Between Matrix Metalloproteinase-8 Levels and The Severity of Periodontal Disease in Children with Cerebral Palsy Receiving Anticonvulsant Monotherapy and Polytherapy: A Cross-Sectional Study

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Abstract

Background

Children with cerebral palsy have increased periodontal risk because motor impairment limits oral hygiene and creates caregiver dependence. Long-term anticonvulsant use may affect periodontal inflammation and tissue remodelling. Matrix metalloproteinase-8 (MMP-8) in gingival crevicular fluid reflects collagen degradation.

Objective

This study aimed to analyse differences in gingival crevicular fluid MMP-8 levels and periodontal disease severity between children with cerebral palsy receiving anticonvulsant monotherapy and polytherapy.

Methods

This comparative analytical cross-sectional study was conducted at Yayasan Anak Bunda Istimewa and the RSP Eijkman laboratory, Bandung, from October to December 2025. Consecutive sampling enrolled children with physician-diagnosed cerebral palsy who received anticonvulsants, had periodontal disease, and whose parents provided consent. Noncooperative children were excluded. Sixty children aged 2–17 years were classified into monotherapy and polytherapy groups (n = 30 each). The minimum required sample was 25 per group. Six examiners, calibrated against a reference examiner (Friedman test, all $p > 0.05$), measured probing depth, clinical attachment loss, bleeding on probing, and periodontal disease severity using standardised procedures. Gingival crevicular fluid MMP-8 was quantified by enzyme-linked immunosorbent assay. Unadjusted comparisons used Mann–Whitney U, Fisher's exact, and chi-square tests, with $p < 0.05$. No missing outcome data, subgroup analyses, or sensitivity analyses were reported.

Results

All 60 participants, comprising 24 boys and 36 girls, were analysed. Mean age was 8.73 years in the monotherapy group and 8.50 years in the polytherapy group. Mean treatment duration was 5.34 and 5.98 years, respectively. Median MMP-8 was higher with polytherapy (4.42 ng/mL, range 3.36–6.68) than with monotherapy (3.47 ng/mL, range 2.20–4.48; $p < 0.001$). Median probing-depth and clinical attachment-loss scores were 3 in both groups. Bleeding on probing affected 28 monotherapy and 24 polytherapy participants. The groups did not differ in probing depth ($p = 0.503$), clinical attachment loss ($p = 0.114$), bleeding on probing ($p = 0.254$), or overall periodontal disease severity ($p = 0.368$).

Conclusions

Anticonvulsant polytherapy was associated with higher gingival crevicular fluid MMP-8 levels, but this was not accompanied by a corresponding difference in clinical periodontal disease severity. The cross-sectional, single-site, unadjusted design, small sample, and uncontrolled confounders limit causal interpretation and generalisability. MMP-8 may complement, but should not replace, conventional clinical periodontal assessment.

Background

Cerebral palsy is a permanent disorder of movement and posture caused by disturbances in the developing brain. Motor impairment, abnormal orofacial function, difficulty with toothbrushing, and dependence on parents or caregivers can increase plaque retention and periodontal risk in affected children [1–5]. These barriers persist through childhood and adolescence, making preventive oral care difficult, particularly for children with more severe functional limitations. Cerebral palsy is estimated to affect approximately 2 to 3 per 1,000 live births, and population-based surveillance indicates that this prevalence has remained relatively stable across recent birth cohorts, underscoring the sustained clinical relevance of oral and periodontal complications in this population [6].

Compared with the general paediatric population, children with cerebral palsy show a distinct pattern of oral morbidity. Periodontal disease, gingival hyperplasia, and gingival bleeding are reported more frequently in this group, reflecting a combination of difficulty maintaining oral hygiene, intraoral hypersensitivity, orofacial motor dysfunction, physical limitation, and malocclusion [3]. Long-term anticonvulsant medication is itself recognised as an important contributing factor to these periodontal changes, and recent evidence continues to link anticonvulsant drug therapy with adverse oral and periodontal outcomes in children with epilepsy [7]. This periodontal burden is disproportionately higher among children with intellectual and developmental disabilities, including cerebral palsy, than in the general paediatric population [8].

Periodontal tissue breakdown reflects both clinical changes and active molecular processes. Matrix metalloproteinase-8 (MMP-8), a neutrophil-derived collagenase, degrades type I and III collagen and contributes to extracellular matrix remodelling. Studies have identified MMP-8 in gingival crevicular fluid as a biomarker of periodontal inflammatory activity and collagen destruction [9–13]. Gingival crevicular fluid can therefore provide biochemical information that may appear before, or may not be fully represented by, probing depth, clinical attachment loss, and bleeding on probing.

Many children with cerebral palsy receive long-term anticonvulsant treatment for seizure disorders. Anticonvulsants can influence gingival fibroblast activity, collagen turnover, plaque retention, and inflammatory responses. Gingival enlargement and poorer oral health have been reported with several antiseizure medications, although findings vary by drug, dose, duration, oral hygiene, and regimen [14–18]. Polytherapy also increases pharmacological complexity and the potential for cumulative or interacting effects on gingival tissues.

Evidence directly comparing gingival crevicular fluid MMP-8 in children with cerebral palsy receiving anticonvulsant monotherapy and polytherapy remains limited. This study aims to analyse differences in MMP-8 levels and clinical periodontal disease severity between these regimens.

Methods

Study design and setting

This comparative analytical cross-sectional study was conducted at Yayasan Anak Bunda Istimewa, Bandung, Indonesia, with laboratory analyses performed at the RSP Eijkman laboratory in Bandung. Recruitment, clinical examinations, gingival crevicular fluid collection, and laboratory work took place from October to December 2025. The report follows the Strengthening the Reporting of Observational Studies in Epidemiology guidance for cross-sectional studies.

Participants and group classification

The source population comprised children with cerebral palsy attending Yayasan Anak Bunda Istimewa. Consecutive sampling was used during the study period. Eligible participants were boys and girls aged 0–18 years with cerebral palsy diagnosed by a pediatrician, current or previous anticonvulsant use, periodontal disease, and written parental or caregiver consent. Children who were uncooperative during clinical examination were excluded. The enrolled sample ranged from 2 to 17 years of age.

Current medication information was obtained from foundation documents and parent or caregiver interviews. Monotherapy was defined as one anticonvulsant drug and polytherapy as two or more anticonvulsant drugs. Participants were classified according to their current regimen at assessment.

Study size

Two sample-size calculations were performed with a two-sided significance level of 5% and 80% power. A two-proportion calculation using expected proportions of 0.80 and 0.40 yielded 23 participants per group. A two-independent-means calculation using a standardised effect size of 0.80 yielded 25 participants per group. The larger requirement was selected. The analysed sample included 30 participants in each group.

Variables and periodontal assessment

The exposure was anticonvulsant regimen, classified as monotherapy and polytherapy. Outcomes were gingival crevicular fluid MMP-8 level, periodontal pocket depth, clinical attachment loss, bleeding on probing, and overall periodontal disease severity. Age, sex, and duration of anticonvulsant use were identified as potential confounders. The analysis did not adjust for these or other confounders.

Six examiners, calibrated against one reference examiner, conducted all periodontal assessments using standardised scoring criteria. Inter-examiner reliability was acceptable: Friedman tests showed no significant difference among examiners for pocket depth, clinical attachment loss, or bleeding on probing (all $p > 0.05$, ranging from $p = 0.228$ to $p = 0.487$), and Spearman correlations indicated predominantly strong, significant agreement among examiners' scores. The same examination procedures were used in both exposure groups.

At the first visit, examiners assessed all teeth at six sites per tooth using a UNC15 periodontal probe: mesiobuccal, mid-buccal, distobuccal, mesiopalatal or mesiolingual, mid-palatal or mid-lingual, and distopalatal or distolingual. Pocket depth was categorised as score 0 for 1–2 mm, score 1 for 3–4 mm, and score 2 for at least 5 mm. Clinical attachment loss was categorised as score 1 for less than 1 mm, score 2 for 1–2 mm, score 3 for 3–4 mm, and score 4 for at least 5 mm. Bleeding on probing was scored 0 when absent and 1 when present. The highest clinical scores were used to classify overall disease as gingivitis, mild periodontitis, or advanced periodontal destruction with loss of masticatory function, using the study's predefined periodontal disease index [19, 20].

Gingival crevicular fluid collection

The second visit occurred one day after the initial examination. The tooth with the highest periodontal severity score was selected. Participants did not eat, drink anything other than water, brush their teeth, or chew gum during the 30 minutes before sampling. The site was cleaned, dried, and isolated with cotton rolls. A size 15 paper point (Gapadent) was inserted gently at the site with the highest probing value using a superficial intracrevicular technique and left in place for 30 seconds. Paper points contaminated by saliva or blood were not accepted as samples.

Each accepted paper point was transferred to a labelled 1.5-mL Eppendorf tube containing 1.25 microlitres of phosphate buffer, kept in a cooled container at 4°C for transport, and stored at − 80°C until analysis.

MMP-8 measurement

MMP-8 concentrations were measured with the MMP-8 BZ 08123090-EB enzyme-linked immunosorbent assay kit (Human Biotrak System, Amersham Biosciences) according to the study laboratory protocol. Standards and samples were loaded into prepared wells, incubated, washed three times, reacted with MMP-8 conjugate and substrate, and stopped before measurement. Absorbance was read at 450 nm with a microplate reader. Concentrations were reported in ng/mL.

Efforts to address bias

Consecutive recruitment reduced discretionary selection within the available population. Eligibility criteria and regimen definitions were applied before outcome comparison. Calibration, a common

reference examiner, identical six-site examination procedures, standardised pre-sampling restrictions, and the same laboratory protocol were used for both groups to reduce measurement variation. Selecting the site with the highest clinical score standardised the sampling rule across participants. Exclusion of non-cooperative children and unmeasured oral hygiene and clinical factors remained potential sources of bias.

Statistical analysis

Categorical variables were summarised as counts and percentages. Numerical variables were summarised with means and standard deviations and, where appropriate, medians and ranges. Normality was assessed with the Shapiro-Wilk test. MMP-8, pocket depth, and clinical attachment loss comparisons used the Mann-Whitney test. Bleeding on probing used Fisher's exact test, and overall periodontal disease severity used the chi-square test. All comparisons were unadjusted. No subgroup, interaction, multivariable, or sensitivity analyses were performed. All reported variables had complete data, so no imputation was used. The consecutive sampling strategy was not weighted. Analyses were performed with SPSS version 18, and statistical significance was defined as $p < 0.05$.

Ethical considerations

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Universitas Padjadjaran Research Ethics Committee (No. 1113/UN6.KEP/EC/2025). Parents or legal guardians received information regarding the study and provided written informed consent prior to their children's participation. Behaviour guidance using Tell-Show-Do and positive reinforcement was applied to reduce anxiety during examinations and sampling.

Results

Participants and descriptive characteristics

Sixty eligible children were enrolled and included in the reported analyses, with 30 in the monotherapy group and 30 in the polytherapy group. No post-enrolment exclusions or missing outcome values occurred in the reported dataset. The number of children screened before enrolment and reasons for non-participation before enrolment were not recorded in the source report, so a participant flow diagram was not constructed.

The monotherapy group included 13 boys and 17 girls, and the polytherapy group included 11 boys and 19 girls. Mean age was 8.73 years (SD 3.79) in the monotherapy group and 8.50 years (SD 3.22) in the polytherapy group. Mean treatment duration was 5.34 years (SD 3.54) and 5.98 years (SD 3.19), respectively. Valproic acid was the most frequently recorded medication in both groups (Table 1).

Table 1
Participant characteristics and anticonvulsant medications

Characteristic	Monotherapy (n = 30)	Polytherapy (n = 30)
Sex, n (%)		
Male	13 (43.3)	11 (36.7)
Female	17 (56.7)	19 (63.3)
Age, years, mean (SD)	8.73 (3.79)	8.50 (3.22)
Treatment duration, years, mean (SD)	5.34 (3.54)	5.98 (3.19)
Recorded medication, n		
Valproic acid	25	23
Depakene	2	2
Diazepam	1	0
Levetiracetam	1	0
Topiramate	1	2
Clobazam	0	3

SD, standard deviation.

Periodontal findings

The observed median pocket depth was 3 in both groups, with ranges of 1–4 in the monotherapy group and 1–6 in the polytherapy group. Median clinical attachment loss was also 3 in both groups, with ranges of 1–5 and 2–9, respectively. Bleeding on probing was present in 28 children (93.3%) receiving monotherapy and 24 (80.0%) receiving polytherapy. Across both groups, 5 children (8.3%) had gingivitis, 31 (51.7%) had mild periodontitis, and 24 (40.0%) had advanced periodontal destruction with loss of masticatory function.

The groups did not differ significantly in pocket depth ($p = 0.503$), clinical attachment loss ($p = 0.114$), bleeding on probing ($p = 0.254$), or overall periodontal disease severity ($p = 0.368$) (Table 2).

Table 2
Periodontal findings by anticonvulsant regimen

Variable	Monotherapy (n = 30)	Polytherapy (n = 30)	p value
Pocket depth category, n			
Score 0 (1–2 mm, mild)	6	6	
Score 1 (3–4 mm, moderate)	24	19	
Score 2 (≥ 5 mm, severe)	0	5	
Observed pocket depth, median (range)	3 (1–4)	3 (1–6)	0.503
Clinical attachment loss category, n			
Score 1 (< 1 mm, normal)	0	0	
Score 2 (1–2 mm, mild)	8	4	
Score 3 (3–4 mm, moderate)	20	17	
Score 4 (≥ 5 mm, severe)	2	9	
Observed clinical attachment loss, median (range)	3 (1–5)	3 (2–9)	0.114
Bleeding on probing, n			
Score 0 (absent)	2	6	0.254
Score 1 (present)	28	24	
Overall periodontal disease severity, n			
Gingivitis	4	1	0.368
Mild periodontitis	15	16	
Advanced destruction with loss of masticatory function	11	13	

Mann-Whitney test for pocket depth and clinical attachment loss; Fisher's exact test for bleeding on probing; chi-square test for overall periodontal disease severity.

MMP-8 levels

Mean MMP-8 was 3.34 ng/mL (SD 0.54) in the monotherapy group and 4.63 ng/mL (SD 0.92) in the polytherapy group. Median MMP-8 was 3.47 ng/mL (range 2.20–4.48) and 4.42 ng/mL (range 3.36–6.68), respectively. The Mann-Whitney test showed higher MMP-8 levels in the polytherapy group ($p < 0.001$) (Table 3).

Table 3
Gingival crevicular fluid MMP-8 levels by anticonvulsant regimen

MMP-8 (ng/mL)	Monotherapy (n = 30)	Polytherapy (n = 30)	p value
Mean (SD)	3.34 (0.54)	4.63 (0.92)	< 0.001
Median (range)	3.47 (2.20–4.48)	4.42 (3.36–6.68)	

MMP-8, matrix metalloproteinase-8; SD, standard deviation. p value from the Mann-Whitney test.

Discussion

Children receiving anticonvulsant polytherapy had higher gingival crevicular fluid MMP-8 levels than those receiving monotherapy. In contrast, pocket depth, clinical attachment loss, bleeding on probing, and overall periodontal disease severity did not differ significantly between groups. The high prevalence of mild periodontitis and advanced destruction in both groups also shows a substantial periodontal burden in this population.

Interpretation of MMP-8 findings

MMP-8 degrades fibrillar collagen and rises with active periodontal inflammation. Systematic and mechanistic evidence supports its use as an adjunctive marker of periodontal tissue breakdown [9–13, 21]. The higher concentration in the polytherapy group indicates greater collagenolytic or inflammatory activity at the sampled site. Because this was a cross-sectional study with an unadjusted comparison, the result identifies an association and does not prove that polytherapy caused the increase.

Anticonvulsants can affect the turnover of gingival collagen by impacting fibroblast function, folate metabolism, inflammatory signalling, and the balance between matrix metalloproteinases and tissue inhibitors of metalloproteinases [16, 22, 23, 24]. Polytherapy may add pharmacodynamic and pharmacokinetic interactions, but the direction and strength of these effects depend on the drugs and doses used [25, 26]. The heterogeneous combinations in this study prevent attribution of the MMP-8 difference to a specific medication or interaction.

MMP-8 also participates in inflammatory pathways outside periodontal tissues, including neuroinflammatory signalling [27, 28]. This broader biological understanding supports a cautious interpretation in children with a neurological disorder. The present measurement came from gingival crevicular fluid at a selected periodontal site, but systemic and local inflammatory conditions may both contribute to enzyme activity.

Interaction mechanisms among the anticonvulsants used

Pharmacodynamic interaction occurs when two or more drugs in a polytherapy regimen influence one another’s effects at the same or a related biological target, thereby increasing or decreasing the overall therapeutic or adverse effect; this differs from pharmacokinetic interaction in that it concerns the

combined effect at the site of action rather than drug disposition. Such interactions include additive effects, in which two drugs with similar therapeutic actions combine to produce an overall effect approximately equal to the sum of their individual effects; synergistic effects, in which the combined effect exceeds the sum of the individual effects; and antagonistic effects, in which one drug reduces or opposes the effect of another. Many of these interactions occur at the receptor level, where two drugs acting on the same receptor can potentiate (synergistic interaction) or inhibit (antagonistic interaction) one another [26, 34].

Applied to the medications recorded in this cohort, valproic acid combined with clobazam would be expected to act synergistically, because valproic acid raises gamma-aminobutyric acid (GABA) levels by inhibiting glutamic acid decarboxylase and GABA transaminase, while clobazam potentiates GABA-A receptor activity, together producing stronger neuronal inhibition. The combinations of valproic acid with diazepam and of valproic acid with topiramate instead suggest an antagonistic pattern, since topiramate both stimulates GABA-A receptors and blocks AMPA/kainate receptors. Clobazam combined with topiramate would likewise be expected to act synergistically, as both act on the GABA neurotransmission pathway, whereas levetiracetam, in whichever combination it is used, would be expected to behave additively because its unique synaptic vesicle protein 2A target has little mechanistic overlap with the other anticonvulsants recorded here. These theoretical pharmacodynamic relationships have not been verified biochemically in this study and cannot by themselves account for the higher MMP-8 levels observed with polytherapy, but they illustrate that the direction and strength of any interaction depend on the specific drugs combined rather than on the number of drugs alone.

Interpretation of clinical periodontal findings

The lack of significant differences in clinical periodontal severity agrees with reports in which the number of anticonvulsant medications did not clearly separate gingival or periodontal outcomes [18, 29]. Other studies have reported more gingival overgrowth with polytherapy or drug combinations [14, 17]. Variation in drug type, dosage, treatment duration, oral hygiene, motor impairment, and caregiver support can explain these different findings. Broader evidence from institutional populations with intellectual disabilities also shows a high periodontal burden [30].

Clinical indices and MMP-8 describe different aspects of disease. Pocket depth and clinical attachment loss reflect accumulated structural change, whereas bleeding on probing is a clinical sign of inflammation. Gingival crevicular fluid MMP-8 reflects current collagenolytic activity and may change before group differences become visible in tissue measurements [10, 31, 32, 33]. Therefore, the biochemical difference does not conflict with the similar clinical distributions.

Clinical implications

Children with cerebral palsy receiving long-term anticonvulsants require regular periodontal assessment regardless of regimen. The observed disease burden supports periodic pocket depth, clinical attachment loss, and bleeding on probing measurements, together with caregiver-focused oral hygiene instruction. MMP-8 testing may provide additional information for children at high risk, particularly those receiving

polytherapy, but the present study does not establish a diagnostic threshold or demonstrate that biomarker-guided care improves outcomes.

Conclusions

Children with cerebral palsy receiving anticonvulsant polytherapy had higher gingival crevicular fluid MMP-8 levels than those receiving monotherapy. Clinical periodontal disease severity did not differ significantly between regimens. MMP-8 may serve as an adjunctive biomarker of periodontal inflammatory activity and collagen destruction that clinical examination does not fully reflect. These findings support periodontal monitoring but do not prove causality of polytherapy.

Abbreviations

BOP
bleeding on probing
CAL
clinical attachment loss
CP
cerebral palsy
ELISA
enzyme-linked immunosorbent assay
GCF
gingival crevicular fluid
MMP-8
matrix metalloproteinase-8
PD
probing depth
SPSS
Statistical Package for the Social Sciences
TIMP
tissue inhibitor of metalloproteinases.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Universitas Padjadjaran Research Ethics Committee (No. 1113/UN6.KEP/EC/2025). Written informed consent was obtained from the parents or legal guardians of all participants, including participants aged 16 and 17 years. The participants were children

with cerebral palsy with developmental and/or cognitive limitations affecting their capacity to provide independent informed consent; therefore, consent was obtained from their parents or legal guardians in accordance with the ethical procedures approved for this study.

Consent for publication

Not applicable. The manuscript contains no identifiable individual participant data, images, or videos.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

AR, NBP, and ER conceived and designed the study. AR collected the clinical and laboratory data and performed the data analysis. AR drafted the manuscript. NBP and ER supervised the study and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request, subject to participant confidentiality and institutional requirements.

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