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Mandible bone density in adolescents with cerebral palsy using antiepileptic drugs

Densidade óssea da mandíbula em adolescentes com paralisia cerebral em uso de drogas antiepilépticas

Andrea PAVANELLO[1], Antonio Francisco DAVID[1], Andre Luiz Ferreira COSTA[2]; Maria Teresa Botti Rodrigues SANTOS[2]

1 - Universidade Cruzeiro do Sul, Department of Dentistry; São Paulo, SP, Brazil.
2 - Universidade Cruzeiro do Sul, Postgraduate Program in Dentistry; São Paulo, SP, Brazil.

ABSTRACT

Objective: The aim of this study was to assess the bone density of the mandible in adolescents with cerebral palsy (CP) treated with antiepileptic drugs using one beam computed tomography (CBCT). **Methods**: The study was carried out with 18 adolescents aged 12–18 years, undergoing routine dental treatment at the dental clinic of APCD-São Caetano do Sul. CBCT scans were of divided into two groups: G1 adolescents with CP using antiepileptic drugs and G2 normoactive adolescents. A single dentomaxillofacial radiologist assessed and evaluated the images using Dental Slice software and Image J. Fisher's exact tests as well as paired and unpaired Student's t-tests were performed. **Results:** Groups differed significantly with regard in the values of density ($p < 0.001$), with G1 presenting lower values compare to G2. G1 showed significantly lower density means on the right side, left side, and right/left sides of the mandible edge than G2 ($p < 0.001$). **Conclusion**: CP patients using antiepileptic drugs show evidence of bone mineral density loss of the mandible.

KEYWORDS

Antiepileptic drugs; Bone mineral density; Cone beam computed tomography; Mandibular indices; Osteoporosis.

RESUMO

Objetivo: O objetivo deste estudo foi avaliar a densidade ótica óssea da mandíbula em adolescentes com paralisia cerebral (PC) tratados com drogas antiepilépticas por meio de tomográfica computadorizada de feixe cônico (TCFC). **Métodos**: O estudo foi realizado com 18 adolescentes de 12 a 18 anos, em tratamento odontológico de rotina na clínica odontológica da APCD-São Caetano do Sul. As TCFC foram divididas em dois grupos: G1 adolescentes com PC em uso de antiepilépticos e G2 adolescentes normoativos. Um único radiologista dentomaxilofacial assessou e avaliou as imagens usando usando os softwares Dental Slice e Image J. Os testes exatos de Fisher, bem como os testes t de Student pareados e não pareados foram realizados. **Resultados:** Os grupos diferiram significativamente quanto aos valores de densidade óptica ($p <0{,}001$), com o grupo G1 apresentando valores menores em relação ao G2. O grupo G1 apresentou médias de densidade óptica significativamente menores nos lados direito, esquerdo e direito / esquerdo da borda da mandíbula do que o G2 ($p <0{,}001$). **Conclusão:** Pacientes com PC em uso de drogas antiepilépticas apresentam evidências de perda de densidade óssea da mandíbula.

PALAVRAS-CHAVE

Antiepilépticos; Densidade mineral óssea; Tomografia computadorizada de feixe cônico; Índices mandibulares; Osteoporose.

INTRODUCTION

Cerebral palsy (CP) is a prevalent and permanent, non-progressive neuromotor disability that is associated with alterations of movement and posture and is caused by injury to the immature or developing brain. These neuromotor alterations have an impact on the daily life and activities of such individuals [1]. Furthermore, epilepsy as well as behavioral and cognitive disorders may be present together with motor alterations [1].

Epilepsy is characterized by recurrent seizures and is one of the most prevalent comorbidities in individuals with CP, in whom it is considered a marker of CP severity [2]. The prevalence of epilepsy is estimated to be 77% in individuals with CP [3]. This results from an imbalance in the excitatory and inhibitory neuronal networks in the brain [4] and requires clinical treatment based on continuous drug therapy with antiepileptic drugs (AEDs).

The control of excitatory and inhibitory neuronal networks in the brain is carried out by post-synaptic ion channels and AEDs modulate these channels. AEDs act on potassium channels, T-type calcium channels, and sodium channels as phenytoin carbamazepine, oxcarbazepine and lamotrigine. Furthermore, phenobarbital, primidone, benzodiazepines, valproic acid, and topiramate inhibit gamma aminobutyric acid (GABA). Finally, the AED levetiracetam binds to the synaptic vesicle protein SV2A in the brain [5].

The effects of phenobarbital, carbamazepine, and phenytoin are correlated with bone mineral density (BMD) reduction related to cytochrome P450 (CYP450) induction, resulting in vitamin D reduction, hyperparathyroidism, increased bone remodeling, and consequent BMD reduction. Although sodium valproate is a CYP450 inhibitor, this AED also promotes BMD reduction [6,7].

In addition to neurological problems, subjects with CP in general develop nutritional disorders, whose prevalence varies between 19 and 50.9% [8]. This condition results from a poor nutritional intake of calcium and vitamin D, Oral-motor dysfunction, swallowing problems, malnutrition, food intolerance, gastroesophageal reflux and constipation, among the most commons [9-11].

These nutritional disorders could be associated with complications related to low bone mineral density (BMD), increasing the risk of developing osteoporosis, due to decreased exposure to sunlight, physical inactivity, medication or treatment that can lower BMD (e.g., AEDs, glucocorticoids, and ketogenic diet) and poor nutrition [10]. However, the majority of these effects remains subclinical for a long time and may take years to manifest clinically, thus explaining the limited attention given to this issue [12,13]. Due to the risk of osteoporosis in CP children and adolescents in use of AEDs, is recommended routine evaluations serum 1.25(OH)2D levels, maintenance of adequate calcium intake, vitamin D supplementation, physiotherapy or bisphosphonate therapy [10].

Cone beam computed tomography (CBCT) is a low-cost diagnostic imaging method that permits easy positioning of the subject in the device, requires little exposure time, and has a lower emitted radiation index than that of other methods such as panoramic, periapical, or computed tomography (CT) [14,15].

With the development of CBCT, complete sampling (360°) is possible without increasing the radiation dose to which the patient is exposed, and which is kept within acceptable limits [16]. CBCT uses the Hounsfield unit (HU) as the unit of measurement [17]. This is a numerical value of interpretation used in CT that characterizes tissue density in the anatomical image acquired. The accuracy of integrating laser-scanned dental models into CBCT images is greater with a high relative Hounsfield unit (RHU) threshold setting (voxel sizes 0.20 and 0.40 mm) [17,18].

The aim of this study was to assess the bone density of the edge of the mandible in adolescents with CP treated with AEDs using CBCT and compare to normoactive adolescents. The hypothesis of the study was that the CBCT could evidence the bone mineral density loss at the edge of the mandible in adolescents with cerebral palsy in use of antiepileptic drugs.

MATERIAL AND METHODS

Ethics statement

The study was approved by the Institutional Review Board of UNICSUL according to protocol number 2.093.884. The study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. Written informed consent was obtained from the guardian of each participant, after informed about the study.

Subjects

Subjects for this study were recruited from a previous research study in Orthodontics who had a diagnosis of CP. Twelve adolescents with a medical, attending the School of Professional Development of the Paulista Association of Dental Surgeons, (APCD-SCS), participated in this study. Data were collected from February to December 2018. Inclusion criteria were diagnosis of spastic CP, ranging from 12–18 years, both male and female and treated with AEDs (G1). Subjects who presented progressive or neurodegenerative lesions or uncooperative behavior during clinical oral examinations were excluded. The control group consisted of nine normactive adolescents who attended the same School of Professional Development of the APCD-SCS not using AEDs (G2). Sociodemographic data, including gender, age, medical diagnosis, clinical pattern of CP, and AED used, were collected.

Image acquisition

CBCT was performed using an i-CAT scanner (Imaging Sciences International, Hatfield, PA, USA) operating at 120 Kvp and 9.65 mA for 10 s with a field of view (FOV) for the mandible of 0.40 slice voxel (17), which involved a lower risk of radiation to exposed individuals. The images were generated in the digital imaging and communications in medicine (DICOM). CBCT was performed at the Department of Radiology and Imaging of the APCD-SCS. The adolescents were positioned sitting in the tomography chair, protected against radiation by a lead apron, and stabilized in supine position for image acquisition. G1 adolescents were restrained with Velcro strips in the frontal sinus region and thorax before scan acquisition.

The inclusion criteria were: patients with no history of trauma or surgical procedure, or undergoing orthodontic treatment; no pathologies in the region of the head and neck.

The exclusion criteria were: images with low sharpness and artifacts resulting from the patients' movements.

Image analysis

Under dim lighting conditions, images were assessed by one previously calibrated dentomaxillofacial radiologist with seven years of experience in CBCT imaging diagnosis using a Sansung notebook, model NP270ESG (Samsung Electronics, Republic of Korea). Images were evaluated using the Dental Slice software (Bioparts Prototipagem Biomédica, Brasilia-DF, Brazil, Version 214 E), which allows for use of the Hounsfield scale. This software classifies bone into type I, compact cortical bone; type II, small medullary bone covered by a thick layer of cortical bone; type III, fine layer of cortical bone lining bone marrow with small trabeculae; and type IV, fine layer of cortical bone lining medullary bone with large trabeculae.

Measurements were recorded from the inner edge to the outer edge of the mandible in the region of the anterior wall of the mental foramen on both the right and left sides. The ImageJ software, (U. S. National Institutes of Health, Bethesda, MA, USA), (Figure 1) and the Histogram panel in Photoshop software (Version 11.0 Adobe Photoshop CS4 software; Adobe System Inc., San Jose, CA). (Figure 2) were used to assess the density of the mandible. Figure 3 shows CBCT panoramic view of a patient (A) and a control (B).

Statistical analysis

Descriptive analyses were performed to analyze demographic data. Inferential analyses were performed using Fisher's exact test and paired and unpaired Student's t-tests to assess intra- and inter-group differences, respectively. The level of significance was set at 5%.

RESULTS

Among the 12 adolescents with CP initially evaluated for inclusion in the study, three participants were excluded from the analysis due to uncooperative behavior during the oral exams. Thus, nine adolescents with spastic CP were included in this study (G1; n=9) of which four were females and five were males aged 12-18 years (15.9 ± 1.6). The normoactive group (G2; n=9), of which five were females and four were males aged 12-18 years (15.6 ± 2.4) were included. There were no differences between

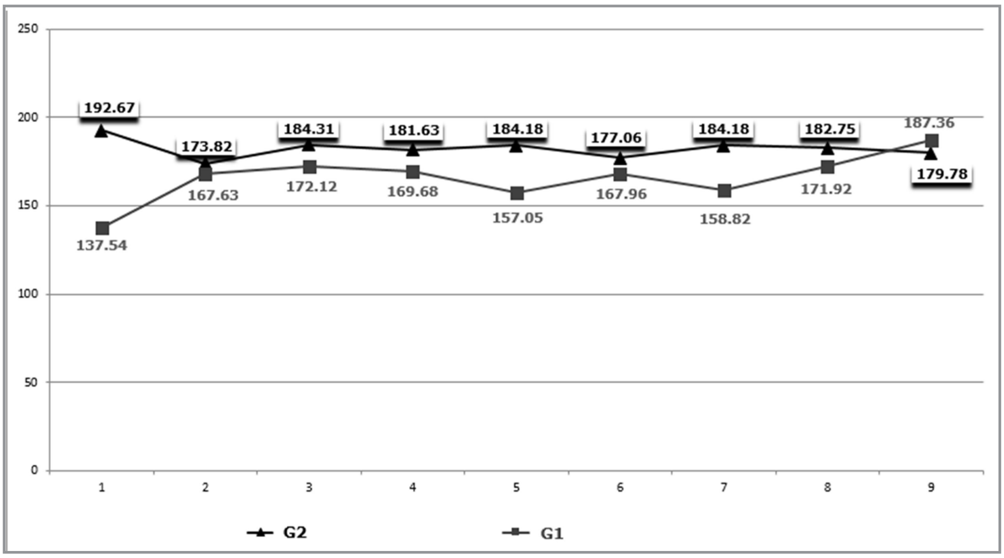

Figure 1 - Image J - Mean density values for adolescents with cerebral palsy using antiepileptic drugs (G1), and normoactive adolescents not using antiepileptic drugs (G2).

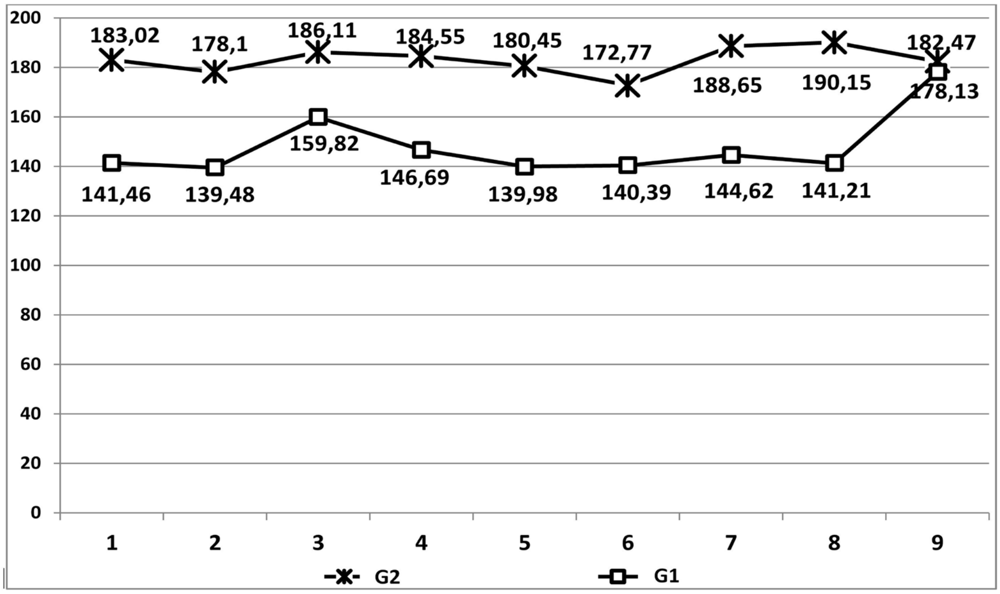

Figure 2 - Mean density for adolescents with cerebral palsy using antiepileptic drugs (G1), and normoactive not using antiepileptic drugs (G2).

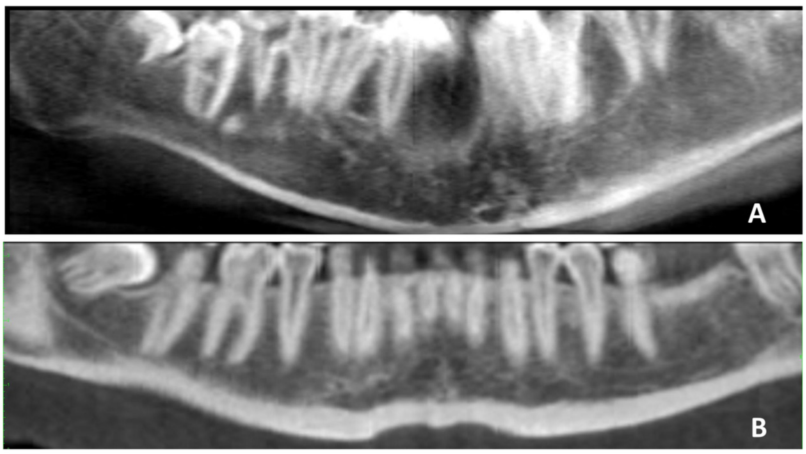

Figure 3 - CBCT panoramic view showing: (A) Thinned smooth edge of the mandible in a CP patient, G1; (B) thick mildly edge of the mandible in a control subject, G2.

groups regarding gender (p = 0.6374) and age (p= 0.9393), (Table I).

As the number of participants in this study was small (n = 18), statistical power was calculated using the density means and standard deviations of G1 (mean ± SD: 149.81 ± 10.93) and G2 (mean ± SD: 183.06 ± 6.23). Results showed that power was 100.00% (95% confidence interval) [19].

Almost 45% of the adolescents with CP presented quadriplegic clinical pattern. Regarding the use of antiepileptic drugs, the adolescents were treated with carbamazepine, lamotrigine, levetiracetam, phenytoin, oxcarbazepine, topiramate, and valproic acid. Three participants (33.3%) used monotherapy and six polytherapy (66.7%). The most AEDs used was topiramato (28.6%) and carbamazepine (21.4%) polytherapy. (Table I). Only one adolescent was treated levetiracetam and presented lower BMD loss.

Regarding bone density and Hounsfield scale, the groups differed significantly (p < 0.001), with G1 presenting lower values for the right side, left side, and both sides, compared to G2. However, individual results from the right and left sides of adolescents in each group did not differ (G1: p = 0.307 and G2: p = 0.513; Table 2).

In order to compare the density of the mandible base between G1 and G2, it was used the Photoshop CS4 at the exact region measured by the previous test. The groups differed significantly with regard to mean densities in the right, left, and right/left sides. G1 showed significantly lower values than G2 (p < 0.001, Table 3).

DISCUSSION

This study demonstrated that the CBCT could evidence the bone mineral density loss at the edge of the mandible in adolescents with

Table I - Characteristics of adolescents with cerebral palsy in use of antiepileptic drugs (G1) and normoactive adolescents without cerebral palsy (G2)

Variables	G1 (n = 9)	G2 (n = 9)	p value*
Gender (n, %)			
Female	4 (44.4)	5 (55.6)	0.6374[a]
Male	5 (55.6)	4 (44.4)	
Age in years (mean ± SD)	15.9± 1.6	15.6 ± 2.4	0.9393[b]
Clinical pattern (n, %)			
Quadriplegic	4 (44.4)	not applicable	
Diplegic	3 (33.3)		
Hemiplegic	2 (22.3)		
Antiepileptic drugs used (n, %)			
Carbamazepine	3 (21.4)	not applicable	
Lamotrigine	2 (14.2)		
Levetiracetam	1 (7.2)		
Phenytoin	2 (14.2)		
Oxcarbazepine	1 (7.2)		
Topiramate	4 (28.6)		
Valproic acid	1(7.2)		

*Statistically significant with p < 0.05; [a,b]: Different superscript lowercase letters indicate statistically significant differences; SD: standard deviation

Table 2 - Image J - Optical density in adolescents with cerebral palsy using antiepileptic drugs (G1) and normoactive not using antiepileptic drugs (G2)

Area thickness	2.00±0.0	2.00±0.0	1
Length area right side - height	10.33±1.58	16.22±5.01	0.004*
Length area left side - height	11.33±1.93	17.00±5,47	0.008*
Mean right side	165.87±13.54	182.60±5,52	0.003*
Mean left side	165.26±13,98	181.93 ±5,50	0.003*
Mean right and left sides	65.56±13.64	182.26±5,30	0.003*

*Statistically significant at p< 0.05; Unpaired Student's t-test

Table 3 - Histogram Photoshop CS4 - Optical density in adolescents with cerebral palsy using antiepileptic drugs (G1) and normoactive not using antiepileptic drugs (G2)

Variables	G1 (n = 9)	G2 (n = 9)	p-value*
Area thickness	0.07 ± 0.0	0.07 ± 0.0	1
Length area right side - height	0.35 ± 0.41	0.38 ± 0.10	0.347
Length area left side - height	0.36 ± 0.10	0.41 ± 0.20	0.261
Mean right side	146.14 ± 17.4	183.06 ± 6.23	<0.001*
Mean left side	149.81 ± 10.93	182.78 ± 5.33	<0.001*
Mean right and left sides	149.81 ± 10.93	182.92 ± 5.37	<0.001*

*Statistically significant at p< 0.05; Unpaired Student's t-test; n: number of subjects

cerebral palsy in use of AEDs. To best of our knowledge, this is the first study to demonstrated this possibility.

Although the overall prevalence of CP in the developed countries decreased from 1.90 to 1.77 per 1000 live births [19], in Brazil no recent data are available.

Spasticity affects the majority of individuals with CP (85% - 90%), acts as a negative factor, and results of an abnormal increase in muscle tone, caused by injury of nerve pathways within the brain, responsible for muscle movement control [1]. The clinical patterns of involvement in these individuals are related to the affected limbs and classified as quadriplegic (the highest level of motor impairment, with all limbs affected), diplegic (lesser severity of arm involvement compared to leg involvement), or hemiplegic (with the involvement of one side of the body) [1]. The adolescents of this study were all spastic and almost 45% quadriplegic, being the most common type [19]. Due to the extent of neurological damage, they also presented epilepsy and were treated with AEDs.

With regard to gender, there are a higher percentage of males with a diagnosis of CP than females, as was reported in the literature [20], and observed in this study. This higher prevalence in males is related to variants in the interleukin (IL)-6 gene, greater vulnerability with regard to the protective function of hormones, polymorphisms, and brain structure [2,20], with higher susceptibility for the default quadriplegic pattern [19].

CBCT was used in this study as an appropriate option for high-quality image resolution and is feasible for use in adolescents with CP, considering the ease in positioning of the patient, low cost, rapid acquisition, and lower amount of radiation emitted. Studies have shown that exposure to radiation with CBCT corresponds to 20% of exposure generated in fan-beam computed tomography (FBCT) and is equivalent to a complete periapical radiographic series (14 periapical radiographs) [21]. The results of this study were obtained using CBCT images, as this technique allows for bone and density measurements at the edge of the mandible and is feasible for use in adolescents with CP.

Non-invasive techniques currently available to analyze skeletal mass or density include DEXA, single-energy x-ray absorptiometry (SXA), and quantitative CT. The U.S. Food and Drug Administration (FDA) approved these techniques for the measurement of BMD because of their ability to predict the risk of fractures. Individuals with osteoporosis are more likely to present erosion on the lower edge of the jaw and there is a correlation between the thickness of the mandibular cortex below the mental foramen and the thickness of the lumbar spine and the proximal femur [22]. In adolescents with CP using AEDs, it is essential to evaluate the edge of the mandible in order to prevent damage and minimize possible deleterious effects of this condition.

First-generation AEDs, phenobarbital, phenytoin, carbamazepine, valproic acid, primidone induce CYP450 isoenzymes that may cause vitamin D deficiency, hypocalcemia, BMD reduction, and bone remodeling alteration, increasing the risk of fracture. Currently, new drugs have been prescribed such as oxcarbazepine, lamotrigine, gabapentin, eslicarbazepine acetate, brivaracetam, felbamate, lacosamide, levetiracetam, pregabalin, rufinamide, stiripentol, sulthiame, thiamatiamate considered safers and better tolerated than classic AEDs and shows more broad-spectrum activity [23].

AEDs, including levetiracetam used both in monotherapy and polytherapy, are deleterious to bone metabolism, contrary to the effects of lamotrigine monotherapy [24]. Based on the results of this study, association of levetiracetam and lamotrigine, did not result in significant BMD loss, in contrast with the effects of other AEDs such as valproic acid, oxcarbazepine, carbamazepine, and benzodiazepine and BZD in monotherapypoly or polytherapy, which has highlighted the need for new studies evaluating the effects of these new-generation AEDs [25-27].

The adolescents with CP of this study have been using AEDs for more than three years and showed significant BMD loss. As most of the effects of AEDs are not clinically detectable for a long period, and may manifest later [12,13], it is important to call the attention of the dental surgeon to include radiographic evaluations of the the mandible in individuals receiving AEDs for treatment of epilepsy.

An early diagnosis of bone mineral loss in the mandible of adolescents using AEDs requires of the dental professionals to establish a channel of communication with medical professionals to control and prevent the effects of AEDs on the bone tissue of these individuals. Further studies are needed to evaluate the impact of the new generation of AEDs on bone and optic density at the edge of the mandible in adolescents with CP.

This study has some limitation which need to be addressed: the sample size was small. Furthermore, CBCT images may be useful for assessments of bone mineral density loss, although they should not be used solely for that goal.

CONCLUSION

CP patients receiving AEDs showed more decrease in bone mineral density at the edge of the mandible.

Authors' Contributions

AP, MTBRS: study conception and design, analyses and interpretation of the data; final approval of the version to be published. AFD: study conception and design, acquisition of the data; final approval of the version to be published. ALFC: drafting the article; final approval of the version to be published

Conflict of Interest

All authors of this work declare no conflict of interest.

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Regulatory Statement

The study was approved by the Institutional Review Board of UNICSUL, according to protocol number 2.093.884. Informed consent: Written informed consent was obtained from the guardian of each participant, after informed about the study.

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Andrea Pavanello
(Corresponding address)
Universidade Cruzeiro do Sul, São Paulo, SP, Brazil.
Email: deiapavan8@hotmail.com.br

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