

CERVICAL VERTEBRAL MATURATION AND DENTAL AGE IN COELIAC PATIENTS

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SUMMARY

Cervical vertebral maturation and dental age in coeliac patients.

Aim. The aim of the study was to evaluate the cervical vertebral maturation and dental age, in group of patients with coeliac disease (CD), in comparison with a control group of healthy subjects.

Methods. At the Paediatric Dentistry Unit of PTV Hospital, "Tor Vergata" University of Rome, 120 female patients, age range 12.0-12.9 years were recruited. Among them, 60 subjects (Group 1) were affected by CD, while the control group (Group 2) consisted of 60 healthy subjects, sex and age-matched. The Group 1 was subdivided, according to the period of CD diagnosis, in Group A (early diagnosis) and Group B (late diagnosis).

The skeletal age was determined by assessing the cervical vertebral maturation, while the dental age has been determined using the method codified by Demirijyan.

Statistics. The analyses were performed using the SPSS software (version 16; SPSS Inc., Chicago IL, USA). In all the assessments a significant level of $\alpha = 0.05$ was considered.

Results. There are no statistically significant differences between Group 1 and Group 2 as for chronological age ($p=0.122$).

Instead, from the assessment of skeletal-dental age, there are statistically significant differences between Group 1 - Group 2 ($p<0.001$) and Group A - Group B ($p<0.001$). The statistical analysis carried out to assess the differences between chronological and skeletal-dental age within the single groups, show a statistically significant difference in Group 1 ($p<0.001$) and in Group B ($p<0.001$), while there are no statistically significant differences in Group 2 ($p=0.538$) and in Group A ($p=0.475$).

A correlation between skeletal and dental age was registered; for Groups 1-2 and for Groups A-B the Pearson coefficient was respectively equal to 0.967 and 0.969, with $p<0.001$.

Through the analysis of data it is possible to assess that the percentage of subjects with skeletal and dental age delay corresponds to 20% in healthy subjects, 56.7% in coeliac subjects, 23% in coeliac subjects with early diagnosis and 90% in coeliac subjects with late diagnosis. From

RIASSUNTO

Maturazione delle vertebre cervicali ed età dentale nei pazienti celiaci.

Obiettivi. Lo scopo del presente studio è stato quello di effettuare una valutazione della maturazione delle vertebre cervicali e dell'età dentale, in un gruppo di pazienti con malattia celiaca (CD) ed in gruppo controllo di soggetti sani.

Metodi. Nell'Unità Operativa di Odontoiatria Pediatrica dell'Ospedale PTV, Università degli Studi di Roma "Tor Vergata", sono stati selezionati 120 pazienti di sesso femminile, di età compresa tra 12.0-12.9 anni. Tra questi, 60 soggetti (Gruppo 1) presentavano CD, mentre il gruppo controllo (Gruppo 2) era costituito da 60 soggetti sani, di pari sesso ed età. Il Gruppo 1 è stato suddiviso, in base al periodo della diagnosi di CD, nel Gruppo A (diagnosi precoce) e Gruppo B (diagnosi tardiva).

L'età scheletrica è stata determinata valutando la maturazione delle vertebre cervicali, mentre l'età dentale è stata calcolata con il metodo codificato da Demirijyan.

Statistica. Le analisi statistiche sono state effettuate utilizzando il software SPSS (versione 16; SPSS Inc., Chicago, IL, USA). In tutte le valutazioni è stato considerato un livello significativo di $\alpha = 0.05$.

Risultati. Non ci sono differenze statisticamente significative tra Gruppo 1 e Gruppo 2, in rapporto all'età cronologica ($p=0.122$). Invece, dalla valutazione dell'età scheletrica-dentale, ci sono differenze statisticamente significative tra Gruppo 1 - Gruppo 2 ($p<0.001$) e Gruppo A - Gruppo B ($p<0.001$).

L'analisi statistica effettuata per valutare le differenze tra età cronologica e l'età scheletrica-dentale nei singoli gruppi, mostra una differenza statisticamente significativa nel Gruppo 1 ($p<0.001$) e nel Gruppo B ($p<0.001$), mentre non ci sono differenze statisticamente significative nel Gruppo 2 ($p=0.538$) e nel Gruppo A ($p=0.475$).

È stata evidenziata una correlazione tra età scheletrica e dentale; per i Gruppi 1-2 e A-B il coefficiente di Pearson è stato rispettivamente pari a 0.967 e 0.969, con $p<0.001$. Attraverso l'analisi dei dati è possibile valutare che la percentuale di soggetti con ritardo dell'età scheletrica e dentale corrisponde al 20% nei soggetti sani, 56.7% nei soggetti celiaci, 23% nei soggetti celiaci con diagnosi precoce e 90% nei soggetti celiaci con diagnosi tardiva. Dal con-

the comparison between Group 2 and Group A there are no statistically significant differences ($p=0.951$).
Conclusions. The skeletal age and dental age delay may be two predictive indexes for a CD diagnosis. The dental age and cervical vertebral maturity can be assessed with a low cost, non invasive, easy to perform exam carried out through the routine radiographic examinations such as orthopantomogram and lateral telerradiography.

Key words: cervical vertebrae, dental age, skeletal maturation, coeliac disease.

fronto tra il Gruppo 2 e Gruppo A non ci sono differenze statisticamente significative ($p=0.951$).

Conclusioni. Un ritardo dell'età scheletrica e dell'età dentale può essere un indice predittivo per la diagnosi di CD. L'età dentale e la maturità delle vertebre cervicali possono essere valutate a basso costo, con una metodica non invasiva, facile da eseguire attraverso l'analisi degli esami radiografici di routine come l'ortopantomografia e la telerradiografia latero-laterale del cranio.

Parole chiave: vertebre cervicali, età dentale, maturazione scheletrica, malattia celiaca.

Introduction

Coeliac disease (CD) may be defined as an inflammatory condition of the small intestinal mucosa which appears with alterations of the proximal intestinal villi in genetically susceptible individuals consequent to the intake of gluten in the diet (1).

The major CD-predisposing genes are located in HLA region, namely the HLA-DQ2 and DQ8 genotypes, found in almost all CD patients and in 30% of the general population (1).

The CD prevalence has remarkably increased over the last years, fluctuating within a range from 1:85 up to 1:300 in relation to the study considered (1,2-5). This is attributable to a more frequent serological screening on children (measurement of anti-endomysium antibodies EMA, anti-gliadin antibodies AGA and anti-transglutaminase antibodies tTG), that, if positive, is followed by small intestine biopsy and an histological examination (1).

Nonetheless, CD still is diagnosed with a delay, because recently the typical form of CD, characterized by malabsorption and gastrointestinal symptoms, is less frequent respect to atypical, silent, potential, latent forms, often asymptomatic and involving extra-intestinal clinical manifestations (6).

Among the extra-intestinal CD manifestations it is possible to find: short stature, somatic growth retardation, anaemia, (normochromic normocytic anaemia, megaloblastic anaemia, sideropenic anaemia), retarded puberty, female infertility, early menopause, miscarriages, high percentage of preterm newborns or with reduced body weight at birth, reduction of the breast-feeding period, neurological di-

sorders (epilepsy, ataxia, neuropathy-myelopathy, memory disorders, tremors), appearance of dermatological manifestations (dermatitis herpetiformis) and intra-oral manifestations (enamel hypoplasia, atrophic glossitis, recurrent aphthous stomatitis, dental age alterations) (1,6,7).

The aim of this study was to evaluate the cervical vertebral maturation (CVM) and dental age, in group of CD patients, in comparison with a control group of healthy subjects.

Material and methods

At the Paediatric Dentistry Unit of PTV Hospital, "Tor Vergata" University of Rome, 120 female patients, age range 12.0-12.9 years were recruited. Among them, 60 subjects (Group 1) were affected by CD and came from the Paediatric Gastroenterological Unit of the PTV Hospital, "Tor Vergata" University of Rome, while the control group (Group 2) consisted of 60 healthy subjects, sex and age-matched, recruited from the Paediatric Dentistry Unit. Inclusion criteria for coeliac patients participating in this study were positivity towards serological tests (Ab-htTG IgA, Ab-htTG IgG, AGA IgA, AGA IgG, EMA IgA, EMA IgG), small-bowel biopsy through esophago-gastro-duodenoscopy (EGDS), and histological evidence of intestinal villous atrophy, crypt hyperplasia and increased intra-epithelial lymphocytes. Exclusion criteria for control group enrolment were malnutrition status, body growth delay, gastrointestinal diseases and/or familiar coeliac diseases. For each subject a medical records reporting specific information for subjects affected by CD (period

of CD diagnosis, period of beginning of the gluten-free diet GFD, anti-tTG-EMA antibodies seric values in the follow-ups) was filled in.

The Group 1 was subdivided, according to the period of CD diagnosis, in Group A (early diagnosis made within the first two years of life) and Group B (late diagnosis made after the age of 8).

It was also required the written consent by parents and radiographs (lateral cephalograms, panoramic radiographs) to assess skeletal maturation and dental age.

The skeletal age was determined by assessing the CVM, using the lateral cephalometric radiographs and by following the below detailed methods:

- the method codified by Franchi and Baccetti (8,9) providing for the morphological analysis of C2, C3, C4 vertebra and the subdivision into five stages (CVMS I, II, III, IV, V);
- the mathematical formulas of Caldas (10,11) considering the measurement of C3 and C4 vertebra:
 Female cervical vertebral bone age = $1.3523 + 6.7691 \times AH3/AP3 + 8.6408 \times AH4/AP4$;
 Male cervical vertebral bone age = $1.4892 + 11.3736 \times AH3/AP3 + 4.8726 \times AH4/AP4$.

The dental age has been determined using the method codified by Demirjiyan (12,13) and panoramic radiographs. In practice, each tooth except for the third molar on the left side of the mandible, is assigned a letter from A to H; each letter corresponds to a score and the total score of all the 7 teeth represents the dental maturity score (14). Subsequently, the dental maturity score is converted into dental age using conversion tables according to the gender.

Statistical analysis

The assessment of differences through the means of continuous variables (chronological age, dental and skeletal age) between patients and control subjects and between subjects with early and late diagnosis were analysed using Students' t test for independent samples. Furthermore, a Student's t test was also applied for each group of subjects considering chronological and skeletal-dental age. In addition, the Fisher's exact test was performed for the categorical variable CVMS.

Besides, to assess the association between skeletal and dental age, the Pearson correlation coefficient was calculated. In all the assessments a significant level of $\alpha = 0.05$ was considered.

The analyses were performed using the SPSS software (version 16; SPSS Inc., Chicago IL, USA).

Results

A total of 120 female patients, age range 12.0 to 12.9 years, mean age 12.4, were analysed.

There are no statistically significant differences between Group 1 and Group 2 as for chronological age ($p=0.122$). The subjects belonging to Group 1-2 had a mean age and a standard deviation respectively equal to 12.4 ± 0.28 and 12.5 ± 0.27 (Tab.1).

Instead, from the assessment of skeletal age, according to Caldas, and of dental age, according to the Demirjiyan method, there are statistically significant differences between Group 1 and Group 2 ($p < 0.001$) (Table 1).

In addition, among the coeliac subjects, the difference between mean chronological age and mean skeletal-dental age is respectively of 7 and 6 months, while among non coeliac subjects it is equal to 1 month. The Students' t test showed statistically significant differences in Group 1, between Group A and Group B as for chronological age, skeletal and dental age (detected according to Caldas-Demirjiyan methods) ($p \leq 0.001$) (Table 2).

Among coeliac subjects with early diagnosis it is highlighted that the difference between mean chronological age and mean skeletal age is 1 month, while it is absent for what concerns dental age. Among coeliac subjects with late diagnosis it is pointed out that the difference between mean chronological age and mean skeletal age is 13 months, while the difference between mean chronological age and mean dental age is 11 months (Table 2).

The statistical analysis carried out to assess the differences between chronological and skeletal-dental age within the single groups, show a statistically significant difference in Group 1 ($p < 0.001$) and in Group B ($p < 0.001$), while there are no statistically significant differences in Group 2 ($p = 0.538$) and in Group A ($p = 0.475$) (Table 3).

Table 1 - Mean and Standard Deviation (SD) of chronological, skeletal and dental age for Groups 1-2.

	Group 1		Group 2		p-value (Student's t test)
	Mean	SD	Mean	SD	
Chronological Age	12.4	0.28	12.5	0.27	0.122
Skeletal Age	11.8	0.89	12.4	0.41	<0.001
Dental Age	11.9	0.83	12.4	0.42	<0.001

Table 2 - Mean and Standard Deviation (SD) of chronological, skeletal and dental age for Groups A-B.

	Group A		Group B		p-value (Student's t test)
	Mean	SD	Mean	SD	
Chronological Age	12.5	0.27	12.3	0.25	0.001
Skeletal Age	12.4	0.45	11.2	0.78	<0.001
Dental Age	12.5	0.43	11.4	0.77	<0.001

Table 3 - Mean and Standard Deviation (SD) of chronological and skeletal-dental age in Groups 1, 2, A, B.

	Chronological Age		Skeletal-Dental Age		p-value (Student's t test)
	Mean	SD	Mean	SD	
Group 1	12.4	0.28	11.9	0.83	<0.001
Group 2	12.5	0.27	12.4	0.42	0.538
Group A	12.5	0.27	12.4	0.43	0.475
Group B	12.3	0.24	11.4	0.77	<0.001

A correlation between skeletal and dental age was registered; for Groups 1-2 and for Groups A-B the Pearson coefficient was respectively equal to 0.967 and 0.969, with $p < 0.001$.

Through the analysis of data it is possible to assess that the percentage of subjects with skeletal and dental age delay corresponds to 20% in healthy subjects, 56.7% in coeliac subjects, 23% in coeliac subjects

with early diagnosis and 90% in coeliac subjects with late diagnosis. From the comparison between Group 2 and Group A there are no statistically significant differences ($p = 0.951$) (Table 4).

For what concerns the determination of the skeletal age using the Franchi and Baccetti method, it is highlighted how in Group B there is a significant delay (20% of subjects at stage CVMS I, and 33.3%

Table 4 - Percentage, Mean and Standard Deviation (SD) of skeletal-dental age delay respect to chronological age in comparison between Groups 2-A and A-B.

	Percentage (%)	Mean	SD	p-value (Student's t test)
Group 2	20%	0.53	0.47	0.951
Group A	23%	0.51	0.55	<0.001
Group B	90%	1.04	0.64	

Table 5 - Percentage (%) of subjects at the different stage of CVMS in Groups 2, A, B.

	Percentage (%) of subjects					Total
	CVMS I	CVMS II	CVMS III	CVMS IV	CVMS V	
Group 2	0,0	3,3	31,7	61,7	3,3	100
Group A	0,0	3,3	36,7	56,7	3,3	100
Group B	20,0	33,3	36,7	10,0	0,0	100
Total	5,0	10,8	34,2	47,5	2,5	100

at stage CVMS II) with respect to Group 2 and Group A (Table 5). The Fisher's exact test for the categorical variable CVMS revealed that there are no statistically significant differences just between Group A and Group 2 ($p=0.926$).

Discussion and conclusion

The skeletal maturation was assessed through the CVM using both Franchi and Baccetti method and the mathematical formulas of Caldas, in order to obtain a double analysis capable of combining the operator's ability in carrying out the assessment of vertebral morphology with an objective calculation. The whole sample group was made uniform as for gender and age; in fact, only female with a chronological age between 12.0 and 12.09 were recruited. The analysis of the results points out that the skeletal age in coeliac subjects present statistically significant differences with respect to the control group, both using the Franchi and Baccetti method and the Caldas formulas ($p<0.001$).

The percentage of coeliac subjects with a skeletal age delay (56.7%) is in line with other studies included in the literature and reporting a delay of 60% (15), and 81% (16). Probably such percentages differ among them with respect to the percentage of patients with early and late CD diagnosis recruited in the sample.

For this reason, in this study, an additional assessment has been carried out pointing out a skeletal age delay of 23% in celiac subjects with early diagnosis and of 90% in celiac subjects with late diagnosis.

Already in 1978, Exner concluded that in the differential diagnosis of retarded growth and bone age CD should always be considered (15).

A subsequent study underlined the importance of monitoring children presenting axiological alterations and bone age delay because these elements are potential predictive indexes of a CD early diagnosis (17).

CD in fact, being characterized by the malabsorption of different nutrients (calcium, iron, Vitamin A,D,E,K,B12), if not early diagnosed can determine a severe condition of malnutrition until slowing down the body growth (18).

The pathogenesis of CD-associated short stature is still unclear (18,19).

According to several Authors (18,19), the skeletal age delay is not only due to poor nutrition-malabsorption but also to an endocrine system dysfunction. Generally a GFD leads to a rapid catch-up in growth and to normalization of the pituitary function (19). A significant increase in height velocity is often noticed, especially during the first year of GFD (18). However, the catch-up growth is not always complete, despite reversion to seronegativity for CD markers (19). Furthermore, children in which a catch-up growth, at least incomplete, is not reached could present some endocrinological abnormalities, such as growth hormone deficiency (prevalence 0,23%) (18).

Other Authors (20), instead, state that, in some patients, CD may be characterized by growth hormone (GH) resistance, as suggested by normal or elevated GH levels and low insulin-like growth factor-I (IGF-I) levels.

Besides the involvement of the growth hormone (GH)/insulin-like growth factor-I axis, a role for ghrelin was recently proposed (19).

In this study there aren't statistically significant differences among coeliac subjects with early diagnosis and healthy subjects with regard to skeletal-dental age ($p=0.951$). Thus, observing the statistical data,

a prompt diagnosis and a rigorous GFD precociously begun seem to allow the celiac subjects to have a skeletal growth and the development of permanent teeth correlated to that observed in healthy subjects. The dental age in celiac subjects (Group 1) presents statistically significant differences ($p < 0.001$) with respect to the control group; the difference between chronological age and dental age, in fact, is 6 months while for the Group 2 it is 1 month.

Such datum is in line with other studies published in the literature (17,21-23), even if a literature review is numerically limited with regard to this topic.

According to some studies there is a correlation between dental maturity and cervical vertebral maturity (14,24) and between malabsorption-poor nutrition protracted over time in patient with undiagnosed CD and alteration of dental age (17,21,22). GDF, in fact, may have a positive effect both on the skeletal and dental maturity (21).

Other Authors, on the other hand, state that the skeletal and dental development are subordinated to different control mechanisms (25).

The results of the study highlight a correlation between skeletal age and dental age underlining that subjects with late CD diagnosis present a dental delay of 11 months with respect to coeliac subjects with early diagnosis presenting a development of permanent teeth that may be correlated to the one pointed out in healthy subjects.

From this study it is possible to observe how the skeletal age and dental age delay may be two predictive indexes for a CD diagnosis. In addition the dental age and cervical vertebral maturity can be assessed with a low cost, non invasive, easy to perform exam carried out through the routine radiographic examinations such as orthopantomogram and telerradiography.

The dentist visit, aimed at analysing the alterations of enamel structure, recurrent aphthous stomatitis, glossitis (7) but also the dental and skeletal delays can represent a diagnostic instrument to identify CD and prevent possible complications by promptly beginning a GFD.

In this way dental screening may be fundamental to identify subjects affected by atypical forms of CD disease otherwise not diagnosable due to the lack of typical symptomatology and clinical picture.

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