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BONY AND DENTAL RADIOGRAPHIC FEATURES OF TYPE I AND TYPE III GAUCHER DISEASED CHILDREN

Yomna Said Abdel Azim Mohamed *, Mohamed Khalifa Zayet ** *and* Khaled Eid***

ABSTRACT

Background: Gaucher disease (GD) is a lysosomal storage disease caused by an autosomal recessive inherited deficiency of the lysosomal enzyme glucocerebrosidase. The aim of this study was to describe jaw bones involvement and dental radiographic features in pediatric Gaucher disease patients (type I and type III). **Subjects and Methods:** The study population of this case-control study included 42 Gaucher patients (study group) and 84 medically free children (control group). Panoramic radiographic images of both groups were taken and analyzed for the following findings: generalized bone rarefaction, localized rarefaction, enlarged bone marrow spaces, thinning of cortex, pseudo-cystic radiolucent lesions, anodontia, and dental anomalies. **Results:** Generalized rarefaction showed almost similar percentages in both types of Gaucher disease cases. Localized rarefaction was noted in 30.77% and 18.75%, of Gaucher disease type III and type I respectively. Pseudo-cystic radiolucent lesions, thinning of cortex, anodontia and dental anomalies were more prevalent in type III Gaucher patients. **Conclusion:** Thinning of cortex, localized rarefaction and generalized rarefaction are the most common jaw bone findings in Gaucher patients.

KEYWORDS: Gaucher disease – Pediatric - Radiographic

INTRODUCTION

Gaucher disease (GD) is a lysosomal storage disease caused by an autosomal recessive inherited deficiency of one of the lysosomal enzymes, namely glucocerebrosidase [1]. This results in accumulation of the lipid glucocerebroside in lysosomal macrophages which become dilated cells called Gaucher cells relative to its discoverer, Philippe Gaucher in 1882 [2]. Those cells can be deposited in different organs leading to several systemic manifestations such as thrombocytopenia, anemia hepatosplenomegaly as well as skeletal involvement [3]. Gaucher cases occur in 1 per 50,000 to 100,000 people in the general population and increases in communities with consanguineous marriages, inbreeding or geographic isolates [4,5]. It manifests with broad phenotypic variation, ranging from neonatal lethality to asymptomatic octogenarians [6]. Three clinical forms or types of the disease are defined based on

* Lecturer - Pediatric Dentistry, Faculty of Dentistry, October 6 University,
** Assistant Professor - Oral and Maxillofacial Radiology, Faculty of Dentistry, Cairo University
*** Professor - Pediatric Hematology, Faculty of Medicine, Cairo University

the absence (type I) or presence (types II and III) of neurological signs [7].

Type I, is the most common type, with an ethnic predisposition in Ashkenazi Jews. Patients of this type show diverse variation in the extent of symptoms and are sometimes asymptomatic. The onset of symptoms can occur at any age [8]. While type II is more acute and shows high mortality rate by the age of two years old [9]. Regarding type III, it is the chronic form of the disease that encompasses different phenotypes, where patients present some features in childhood with at least one neurological sign. Symptoms also include bone involvement, visceral enlargement as well as central nervous system findings [10].

Bone association is one of the most common symptoms attributed to GD which is characterized by recurrent and sudden onset of painful episodes "bone crisis". Pathological fractures or fractures even after minor trauma are common complications of GD [11]. Osteopenia is prevalent among type I GD patients and low bone density becomes evident by the age of five years with the highest prevalence rate in adolescence [12]. Long bone involvement is common in GD, whereas maxillofacial bone involvements are less commonly seen. These manifestations can be detected incidentally in routine dental radiographic images. The mandible which shares long bones in cartilaginous bone type; has been reported to be a nidus of Gaucher cell infiltration and/or bone crisis in several case reports [13-16]

Studies reporting maxillofacial bones involvement among Gaucher disease patients are relatively few and include small number of patients, mainly case reports and case-series. The aim of this study was to describe jaw bones involvement and dental radiographic features in Egyptian Gaucher diseased children (type I and type III) and to compare the radiographic findings of them with an age and sex-matched control group.

SUBJECTS AND METHODS

This case control study was approved by the Research Ethics Committee, Faculty of Medicine, Cairo University. Additionally, informed consents were signed by children's guardians after explaining the purpose and procedures of the research.

The population of this study included a total of 126 children divided into two groups. Study group included 42 patients diagnosed with GD through laboratory investigations, and were recruited from Abu El Reesh children Hospital, Cairo, Egypt. While control group included 84 medically free children with matching age and sex, who are recruited from the outpatient clinic of the Oral and Maxillofacial Radiology department, Faculty of Dentistry, Cairo University; for screening and diagnostic purposes.

Dental history, extra-oral and intra-oral examination were recorded by a single pediatric dentist at Abu-El Reesh children hospital. Visceral and hematological involvement data was recorded from the patient's records as part of their routine follow-up.

Digital panoramic radiographic examination was performed for every child using Proline XC machine (Planmeca, Helsinki-Finland) with 60-68 kVp, 5-7 mA according to child's age and 18 sec exposure time.

The radiographic assessment for panoramic images was performed by an oral and maxillofacial radiologist of 16 year experience for bony and dental abnormalities. Assessment was done twice with two weeks interval, and in case of presence of inconsistent radiographic findings in some cases, a third assessment was done two weeks later. Each assessment session was of half an hour duration with haphazard arrangement of digital images.

The radiographic images of both groups were analyzed for the following findings: generalized bone rarefaction, localized rarefaction, enlarged bone marrow spaces, thinning of cortex, pseudo-cystic radiolucent lesions, anodontia and dental anomalies **(Figure 1)**.

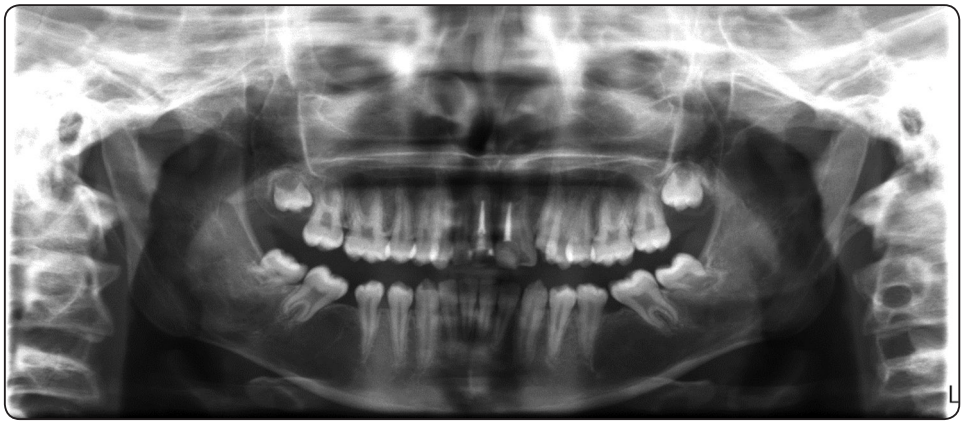

Fig. (1): Panoramic radiograph for Gaucher diseased child showing rarefaction of bone, pseudocyst in molar region, thinning of inferior border of the mandible anteriorly, and abnormal root morphology of lower third molars.

Statistical analysis: all variables were described in terms of frequencies and percentages. Pearson's Chi-squared test was used to determine whether any of the radiographic variable data were related to presence of GD. Odds ratios were calculated using multinomial regression models, where GD is the dependent variable and radiographic signs are the independent variables. Also interactions between different radiographic signs were examined. The results of all tests were considered to be statistically significant if *p*-value was ≤ 0.05. Statistical package used for this study: R statistical package, version 3.3.1 (2016-06-21). Copyright (C) 2016.

RESULTS

The study sample of the current study involved 42 patients with GD in the study group; 26 boys and 16 girls with a mean age of 9.54 ± 4.25 years, and the control group was consisted of 84 medically free children as reported in medical history taken from their guardians; 45 boys and 39 girls with a mean age of 11.37±1.83 years. The study group was further subdivided into two subgroups according to GD type (type I: 16 children, and type III: 26 children).

Analysis of the radiographic findings for GD cases versus control cases are presented in (Table 1); generalized rarefaction showed almost similar percentages in both type I and type III GD cases, while localized rarefaction was more prevalent in type III GD and wide bone marrow spaces was more prevalent in type I GD. Pseudo-cystic radiolucent lesions, thinning of cortex, anodontia and dental anomalies were more prevalent in type III GD.

Chi-squared test results showed that there was a significant association between both types of GD and generalized rarefaction, wide bone marrow spaces, pseudo-cystic radiolucencies, thinning of cortex, dental anomalies and absence of any of previous signs (normal radiographic features) (p-value < 0.05).

Regression model analysis revealed that patients with generalized rarefaction, wide bone marrow spaces, thinning of cortex are more likely to have type I GD. While, presence of pseudo-cystic radiolucencies and dental anomalies are not associated with type I GD (Table 2).

Patients with no abnormal radiographic signs have a lower risk for type I GD compared to those who have previous signs with an odds ratio of 0.1 (95% CI = 0.03 - 0.39, p-value = 0.0009). On the other hand, patients with generalized rarefaction, pseudo-cystic radiolucent lesions, thinning of cortex and dental anomalies are more likely to have type III GD. While, wide bone marrow spaces are not associated with type III GD (p-value = 0.3464). Patients with no abnormal radiographic signs are less likely to have type III GD compared to those who have normal radiographic features with an odds ratio of 0.13 (95% CI = 0.05 - 0.37, p-value = 0.0001).

TABLE (1): Multi-variate descriptive analysis of the radiographic signs regarding Gaucher's disease (frequencies and percentages) and results of the Pearson's Chi-squared test (x^2 and p-value) – [Control group n=84, Gaucher's disease Type I n=16, Gaucher's disease Type III n=26]

Variable		Control group n (%)	Gaucher's disease		Pearson's Chi-squared test	
			Type I n (%)	Type III n (%)	x^2	p-value*
Generalized rarefaction	Absent	84 (100%)	13(81.25%)	21(80.77%)	17.09	0.0002
	Present	0 (0%)	3(18.75%)	5(19.23%)		
Localized rarefaction	Absent	72 (85.71%)	13(81.25%)	18(69.23%)	3.62	0.1638
	Present	12 (14.29%)	3(18.75%)	8(30.77%)		
Wide bone marrow spaces	Absent	79 (94.05%)	11 (68.75%)	23 (88.46%)	9.35	0.0093
	Present	5 (5.95%)	5(31.25%)	3(11.54%)		
Pseudo-cysts	Absent	83 (98.81%)	15(93.75%)	22(84.62%)	8.9	0.01162
	Present	1 (1.19%)	1(6.25%)	4(15.38%)		
Thinning of cortex (anteriorly)	Absent	81 (96.43%)	12 (75%)	16 (61.54%)	22.79	<0.0001
	Present	3 (3.57%)	4 (25%)	10 (38.46%)		
Anodontia	Absent	71 (84.52%)	13 (81.25%)	19 (73.08%)	1.75	0.4176
	Present	13 (15.48%)	3 (18.75%)	7 (26.92%)		
Dental anomalies	Absent	83 (98.81%)	16 (100%)	21 (80.77%)	15.16	0.0005
	Present	1 (1.19%)	0 (0%)	5 (19.23%)		
Absence of any of previous signs	Absent	26 (30.95%)	13(81.25%)	20 (76.92%)	25.57	<0.0001
	Present	58 (69.05%)	3 (18.75%)	6 (23.08%)		

TABLE (2): Univariate multinomial regression models – Outcome variable: Gaucher's disease

Independent variable		Odds Ratio	95% CI	p-value
Generalized rarefaction	Type I	27.74	2.85 - 269.93	0.0042
	Type III	24.96	2.84 - 219.68	0.0037
Wide bone marrow spaces	Type I	7.18	1.79 - 28.85	0.0055
	Type III	2.06	0.46 - 9.28	0.3464
Cysts	Type I	5.53	0.33 - 93.37	0.2354
	Type III	15.09	1.6 - 141.92	0.0176
Thinning of cortex	Type I	9	1.79 - 45.25	<0.0001
	Type III	16.88	4.17 - 68.24	<0.0001
Dental anomalies	Type I	2.73	0.23 - 32.01	0.8689
	Type III	19.77	2.19 - 178.39	0.0078
Absence of any of previous signs	Type I	0.1	0.03 - 0.39	0.0009
	Type III	0.13	0.05 - 0.37	0.0001

The results of Multinomial regression models using interaction terms showed that there was no interaction between different radiographic signs among both groups of type I and type III GD (Table 3).

TABLE (3): Multinimial regression models using interaction terms– Outcome variable: Gaucher's disease.

Independent variables Interaction		p-value
Generalized rarefaction + Wide bone marrow spaces	Type I	0.9413
	Type III	0.9964
Generalized rarefaction + Pseudo-cysts	Type I	0.998
	Type III	0.9643
Generalized rarefaction + Thinning of cortex	Type I	0.6755
	Type III	0.9666
Generalized rarefaction + Dental anomalies	Type I	0.9988
	Type III	0.9733
Generalized rarefaction + Absence of any of previous signs	Type I	0.9223
	Type III	0.9582
Wide bone marrow spaces + Pseudo-cysts	Type I	0.9983795
	Type III	0.9646491
Wide bone marrow spaces + Thinning of cortex	Type I	0.9621295
	Type III	0.9627281
Wide bone marrow spaces + Dental anomalies	Type I	0.9906959
	Type III	0.9846022
Wide bone marrow spaces + Absence of any of previous signs	Type I	1
	Type III	1
Pseudo-cysts + Thinning of cortex	Type I	0.7543444
	Type III	0.9736419
Pseudo-cysts+ Dental anomalies	Type I	0.7744741
	Type III	0.9754025
Pseudo-cysts+ Absence of any of previous signs	Type I	1
	Type III	1
Thinning of cortex + Dental anomalies	Type I	0.8141335
	Type III	0.9763405
Thinning of cortex + Absence of any of previous signs	Type I	1
	Type III	1
Dental anomalies + Absence of any of previous signs	Type I	0.9604835
	Type III	0.8175843

DISCUSSION

Gaucher disease is a rare genetic disease manifesting in three major types according to presence or absence of neurological manifestations. Type I is the most common type while type III is seen in 5% of patients and is mainly seen in Northern Europe, Egypt and East Asia [17].

Panoramic images revealed that most of jaw manifestations in the current study were present in the mandible not in maxilla. This may be due to that mandible partially resembles long bones in their development, thus it is considered a potential reservoir for Gaucher cell infiltration [18, 19]. Comparing Gaucher patients type III and type I with the control group showed that four manifestations had statistically significant differences, which were generalized rarefaction, wide bone marrow spaces, thinning of cortex and dental anomalies.

Generalized rarefaction showed almost similar percentages in both type III (19.23 %) and type I (18.75%) GD cases which agreed with the results of Bender and Bender (1996) who observed generalized rarefactions in only five out of 28 Gaucher type I patients. However, it disagrees with some previous studies [13, 21, 22], who found that rarefactions were detected in all Gaucher cases. Wide bone marrow spaces were noted in 31.25% of the cases with type I GD, which contradicts with the results of Nobre et al. (2012) who recognized enlarged marrow spaces in nine out of 10 cases, and also disagreed with the findings of two earlier [20, 22].

Thinning of cortex was more prevalent in type III Gaucher patients (38.46%) than type I patients (25%) which disagrees with others studies that showed that this manifestation is one of the most prevalent findings [13, 21].

Pseudo-cystic radiolucent lesions were more prevalent in type III Gaucher patients (15.38%) versus (6.25%) in type I patients which partially agrees with smaller size similar study[20], in which they observed pseudo-cystic lesions in one panoramic radiograph. However, the results

of this study disagree with other studies where the most common radiographic observation in an affected mandible is the presence of pseudo-cystic or honeycombed radiolucent lesions mainly in the premolar-molar regions [14, 23]. The expression "pseudocyst" is related to its radiographic appearance of being cyst-like radiolucent lesion, and "pseudo" because it is not lined by epithelium. Its presence of such disease may be attributed to presence of thin bone trabeculae and multiple wide bone spaces which may coalesce together giving that appearance. Nevertheless, biopsy may be required for more definitive diagnosis of cystic lesions which was not performed in the current study as all the lesions were asymptomatic.

Anodontia (26.92%) and dental anomalies (19.23%) were more prevalent in type III Gaucher patients which may be explained by the accumulation of Gaucher cells, which increase intraosseous pressure and compromise the vascularity of the area by extrinsic compression or occlusion of these vessels [20, 23].

Qualitative assessment of panoramic images revealed similar findings to previous studies concerned with GD, but with different percentages in some of these findings. These variations may be attributed to more than one factor, different types and races, different samples size, or the point that in the current study 95% of Gaucher cases were on ERT which might have improved bone rarefaction as stated by Bender and Bender 1996, although this opinion was contradicted by Saranjam et al 2012. Moreover, four children were under treatment of bisphosphonate which may alter the remodeling pattern of the bone [24].

CONCLUSION

Localized rarefaction and generalized rarefaction are the most common jaw bone findings in both types of Gaucher Disease (GD). Presence of pseudo-cystic radiolucencies and dental anomalies is more prevalent in type III GD while wide bone marrow spaces are more prevalent in type I GD.

Clinical significance

Current results offer pediatric dentists an overview of the possible systemic and dental manifestations accompanying GD, which is crucial information when planning for dental management of those cases.

Conflicts of interest

All authors declare that they have no conflicts of interest

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