RESEARCH

Dentomaxillofacial manifestations of Gaucher's disease: preliminary clinical and radiographic findings

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Objectives: A wide variety of manifestations is presented in patients with Gaucher's disease (GD), including bone, haematology and visceral disturbances. This study was conducted to ascertain the main maxillofacial abnormalities by means of clinical survey, panoramic and cone beam CT (CBCT); to compare the patient's group with an age–sex matched control group; and to correlate clinical and radiological data.

Methods: Ten patients previously diagnosed with GD were submitted to clinical and radiological surveys (CBCT and panoramic radiographs). The examination consisted of anamnesis, extra- and intraoral examinations and analyses of each patient's records. Imaging data were collected from the point of view of 3 observers, and the results compared with a healthy group (20 individuals) by means of statistical analysis (Fisher's exact test).

Results: Gaucher patients had significantly more manifestations than otherwise healthy carriers. The most prevalent findings were enlarged marrow spaces, generalized osteopenia and effacement of jaw structures (mandibular canal, lamina dura and mental foramen). Here we describe a case in which thickening of the maxillary sinus mucosa was observed on CBCT rather than opacification of the sinus as seen on panoramic radiographs. Pathological fractures, root resorption and delay on tooth eruption were not observed.

Conclusions: A poor relationship could be observed between clinical and radiological data. Patients showed important bone manifestations, which require careful diagnostic and surgical planning whenever necessary. Although panoramic radiographs have shown significant differences, CBCT is more effective in pointing out differences between patients and a control group, thus showing it as an important tool for evaluation of Gaucher patients. *Dentomaxillofacial Radiology* (2012) 41, 541–547. doi: 10.1259/dmfr/43023353

Keywords: Gaucher disease; maxillofacial abnormalities; cone beam computed tomography; dental radiography

Introduction

Gaucher's disease (GD) is a lysosomal deficiency storage disease characterized by absence or decreased activity of B-glucosidase with systemic manifestations, including pancytopenia, hepatosplenomegaly and bone lesions.^{1,2}

Global prevalence of the disease is 1:50 000, but among Ashkenazi Jews prevalence is 50 times greater than in the general population.³ The involvement of the maxillo-mandibular complex in GD is probably more common than realized, considering that the vast majority of patients recover asymptotically.^{1,4–6}

In the course of the disease, many clinical and radiographic findings are expected; however, it is not known whether clinical data have correlations with radiological ones. Some studies have shown changes in the maxillomandibular complex. However, the lack

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Table 1 Clinical characteristics in patients with Gaucher's disease ($n = 10$)

Patient	1♀	2♂	3♀	4♀	5♂	6♀	7♂	8♀	9♂	10♀	Mean
Age (years)	11	9	9	16	17	26	22	41	39	42	23.2
Age at start of ERT (years)	8	1	6	14	15	16	12	31	29	32	16.4
Length of ERT (years)	3	8	3	3	3	10	10	10	10	10	7
Type of disease	I	I	I	I	I	I	I	I	I	I	—
Visceral enlargement	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	70%
Haematological complications	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	70%
Haemorrhagic episodes	No	No	No	No	No	No	No	No	No	No	0%
Bone symptoms	Yes	No	No	No	No	Yes	No	Yes	Yes	No	40%
Facial bone symptoms	No	No	No	No	No	No	No	Yes	Yes	No	40%
Type of occlusion	I	II	II	I	I	I	I	^a	I	I	Type I—70%
Facial fracture	No	No	No	No	No ^b	No	No	No	No ^b	No	0%

^aPatient using total dental prosthesis in maxilla and removable partial dental prosthesis in mandible.^bPatients with facial trauma history, but no fracture.

of a control group consisting of healthy patients in these studies does provide accurate evidence of these changes.

The aim of this study is to analyse maxillofacial involvement by means of clinical examinations, panoramic radiographs and cone beam CT (CBCT) in a group of patients with GD and compare them with an age- and sex-matched control group of 20 individuals, and then correlate clinical and radiological data.

Materials and methods

This study was approved by the Ethics Committee of the Pará Haematology and Haemotherapy Foundation. Patients were invited to participate in the study, and after agreement they were asked to sign an informed consent form.

All clinical examinations were carried out by the same dentist at the Pará Haematology and Haemotherapy Foundation at the time the patients agreed to participate. The patients were then examined radiographically at the clinic in Belém, Pará, Brazil.

Out of the 14 individuals, 10 patients agreed to participate. General information, such as age, gender, age at the beginning of enzyme replacement therapy (ERT), type of disease, and visceral and haematological involvement was obtained from the patients' records. The survey was conducted by a doctor of dental surgery. The examination consisted of anamnesis, extra- and intraoral examinations and analysis of patients' records. Patients were asked about history of haemorrhagic episodes (spontaneous or after surgery), post-operative infection and facial fracture, and the presence of bone symptoms such as pain.

CBCT and conventional panoramic radiographs were carried out using the same type of equipment for all patients. Panoramic radiographs were obtained with an Orthopantomograph® OP200 (Instrumentarium Dental, Tuusula, Finland) and CBCT using the i-CAT® Cone Beam 3D Dental Imaging System (Imaging Sciences International, Hatfield, PA): voxel size 0.3 mm, 110 kVp, 15 mA, field of view (FOV) 16×12 cm (diameter×height), and 40 s for acquisition of raw data. A control

group consisting of 20 individuals was necessary to compare data. This group was obtained from the files of the same radiology clinic where Gaucher patients were examined, so images had already been taken for other purposes.

The following findings were observed: generalized bone rarefaction, enlarged marrow spaces, cortical thinning, osteosclerosis, radiolucency as pseudocystic lesions, root resorption, demineralization of the mental region, temporomandibular joint (TMJ) involvement, delay in tooth eruption, effacement of maxilla and/or mandible structures and maxillary sinus involvement.

Three observers were blinded and calibrated prior to analysing the images individually. After collection, data were tabulated in Microsoft Office Excel® (Microsoft Corporation, Albuquerque, NM) for statistical analysis. The kappa test was used among the observers to assess reliability of sample results and to validate the study. Because there were two nominal variables, Fisher's exact test was used to compare the radiological findings between the patient group and the carrier cohort.

Results

Of the patients examined, there were 4 males and 6 females, mean age 21.1 (9–42) years, carrying GD Type I under ERT at the time of the study (age at start 1–32 years, mean 14.7 years). They had been undergoing therapy for about 6.7 years (minimum 3 years and maximum 10 years). These characteristics are presented in Table 1.

Radiographic characteristics of the sample are presented in Tables 2 and 3. The kappa test showed inter-rater significant correlation ($\kappa = 0.684$ for conventional radiography and $\kappa = 0.73$ for CBCT).

Although seven patients had an increase in spleen and/or liver volume or haematological disturbances such as thrombocytopenia, anaemia and leukopenia, bleeding and poor wound healing were not described. Even though all ten patients had radiological evidence of bone involvement, only four complained about symptoms, and none had pathological fractures or delays in tooth eruption.

Table 2 Panoramic radiograph findings in patients with Gaucher's disease ($n = 10$)

Patient	Age (years)	Generalized rarefaction	Enlarged marrow spaces	Cortical thinning	Osteosclerosis	Pseudocystic lesions	Root resorption	Mental demineralization	TMJ involvement	Delay in tooth eruption	Effacement of anatomical structures	Maxillary sinus involvement	Bone involved
1♀	11	No	Yes	Yes	No	No	No	No	No	No	No	Yes	Maxilla mandible
2♂	9	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Maxilla mandible
3♀	9	No	No	Yes	Yes	No	No	No	Yes	No	No	No	Mandible
4♀	16	No	Yes	Yes	No	No	No	No	No	No	No	Yes	Maxilla mandible
5♂	17	No	Yes	Yes	Yes	No	No	No	Yes	No	No	No	Mandible
6♀	26	Yes	Yes	Yes	No	No	No	No	Yes	–	Yes	Yes	Maxilla mandible
7♂	22	Yes	Yes	Yes	Yes	No	No	Yes	Yes	–	No	Yes	Maxilla mandible
8♀	41	Yes	Yes	No	No	No	No	No	Yes	–	No	Yes	Maxilla mandible
9♂	39	Yes	Yes	Yes	Yes	Yes	No	No	Yes	–	Yes	Yes	Maxilla mandible
10♀	42	Yes	Yes	Yes	Yes	No	No	Yes	Yes	–	Yes	Yes	Maxilla mandible

TMJ, temporomandibular joint.

Table 3 Cone beam CT findings in patients with Gaucher's disease ($n = 10$)

Patient	Age (years)	Generalized rarefaction	Enlarged marrow spaces	Cortical thinning	Osteosclerosis	Pseudocystic lesions	Root resorption	Mental demineralization	TMJ involvement	Delay in tooth eruption	Effacement of anatomical structures	Maxillary sinus involvement	Bone involved
1♀	11	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Maxilla mandible
2♂	9	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	Maxilla mandible
3♀	9	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	No	Mandible
4♀	16	Yes	Yes	No	No	Yes	No	No	No	No	Yes	No	Mandible
5♂	17	Yes	Yes	Yes	No	No	No	No	No	No	Yes	No	Maxilla mandible
6♀	26	Yes	Yes	Yes	Yes	Yes	No	Yes	No	–	Yes	No	Mandible
7♂	22	Yes	Yes	No	Yes	Yes	No	Yes	No	–	Yes	No	Maxilla mandible
8♀	41	Yes	Yes	No	No	Yes	No	No	No	–	Yes	No	Mandible
9♂	39	Yes	Yes	Yes	Yes	Yes	No	Yes	No	–	No	Yes	maxilla mandible
10♀	42	Yes	Yes	Yes	Yes	Yes	No	Yes	No	–	Yes	Yes	Maxilla mandible

Figure 1 Sagittal cone beam CT images in mandible molar region show unclear cortical borders of the mandibular canal, pseudocystic radiolucent lesions and enlarged marrow spaces

The CBCT images showed that the mandible was affected in all cases, and the maxilla in six. Generalized rarefaction and enlarged marrow spaces could be seen in all patients, cortical thinning and osteosclerosis in five, pseudocystic lesions in nine, mental demineralization in seven, flattening in the head of the condyle in one case, effacement of anatomical structures in eight (Figure 1), and thickening of maxillary sinus mucosa in three individuals (Figure 2b,c). No matches were found for pathological fractures, root resorption related to the disease or delay in the chronology of tooth eruption.

On panoramic radiographs, the mandible was affected in all cases, and both the maxilla and the mandible in eight. Generalized rarefaction was seen in

six individuals, enlarged marrow spaces and cortical thinning in nine, osteosclerosis in six, pseudocystic lesions in one, mental demineralization in three, flattening in the head of the condyle in seven and partial or total obliteration of the maxillary sinus in eight. Effacement of anatomical structures was seen in four cases: path of the mandibular canal, mental foramen, maxillary sinus floor (Figure 2a) and lamina dura. Root resorption was not observed.

Fisher's exact test was used for statistical analysis to compare CBCT and panoramic findings between the patient group and the control group ($p < 0.05$). Generalized bone rarefaction, enlarged marrow spaces and effacement of jaw structures had significant differences on plain radiographs ($p = 0.0038$, 0.0010 and 0.0259 , respectively). CBCT differences were statistically significant for the following: generalized bone rarefaction ($p < 0.0001$), enlarged marrow spaces ($p = 0.0082$), cortical thinning ($p = 0.0050$), pseudocystic lesions ($p < 0.0001$), mental demineralization ($p = 0.0002$), TMJ involvement ($p < 0.0001$) and effacement of jaw structures ($p < 0.0001$).

In short, panoramic radiographs show significant differences as generalized bone rarefaction, enlarged

Figure 2 Panoramic radiograph (a) shows partial opacification of maxillary sinuses and effacement of cortical sinus floor. Axial cone beam CT (b) shows thickening of maxillary sinus mucosa, probably due to environmental reasons, which had improved after 6 months (c)

marrow spaces and effacement jaw structures, but CBCT is more effective in pointing out differences between the GD group and the control group, thus showing it to be an important tool for the evaluation of patients with GD.

Discussion

Of the 10 patients studied, who were aged 9–42 years (mean 23.2 years), 6 were female and 4 were male. This fact corroborates findings reported in the literature that prevalence is higher in females than males.^{1,2,7} There were three children, two teenagers and five adults.

All patients were carriers of Type I disease (non-neurological), which agrees with other studies showing that it is the most prevalent type, (95–99% of cases).^{7,8} During the study, all patients were being treated with ERT, as in most other studies.^{4,7,9}

Clinical and radiographic findings varied greatly in the sample. Some clinical data showed no correlation with radiographic images; this is probably owing to the numerous phenotypic manifestations of Type I disease, a fact also reported in the literature.^{8,9}

According to literature findings,^{2,3,10} the disease is characterized by the classical triad of visceral enlargement (liver and/or splenomegaly), haematological changes and a high incidence of bone changes. Visceral enlargement and haematological changes were present in seven cases. Haematological thrombocytopenia was present in six of the ten patients, but none of them reported prior episodes of bleeding, as had been previously described.⁹

Only two individuals complained of bone pain, demonstrating the asymptomatic feature of the disease, as mentioned in other studies.^{8,9} However, the presence of pain, generalized rarefactions and pseudocystic areas adjacent to the periapical region of the maxillofacial complex should be taken into account when diagnosing this disease, and that makes it important to disseminate these findings, especially when pain is not related to periapical lesions.

There were no clinical findings of the following oral manifestations: yellowish pigmentation or petechiae in the mucosa, delayed eruption of permanent teeth, pathological fracture, delay in bone deposition in wound healing, post-operative infection, spontaneous bleeding (epistaxis or gingival bleeding) and post-surgical bleeding, contradicting some authors who have reported one or more of these as findings.^{1,4,5,7,9,10}

The most relevant radiographic manifestations included generalized bone rarefaction, enlarged marrow spaces, cortical thinning, osteosclerosis, radiolucent pseudocystic lesions, demineralization of the mental region, effacement of anatomical structures and the maxillary sinus and TMJ involvement, which is in agreement with several studies.^{1,3,4,5,7,9}

Panoramic radiographs revealed mandible changes in all cases and maxillary complications in eight. In

CBCT, manifestations were observed in the mandible in all samples and in the maxilla in six, with no cases of maxillary involvement alone. These findings are consistent with other studies that showed the mandible as the most affected bone in almost 100% of the sample, with no cases of maxillary involvement alone.^{4,5,7} These data suggested that some plain radiographic findings were not observed in CT images, probably because of overlapping structures on the plain radiographs.

The most common findings on plain radiographs were enlarged marrow spaces and cortical thinning, also seen on previous findings,^{4,5} whereas CBCT images showed a high incidence of generalized rarefaction, enlarged marrow spaces and pseudocystic lesions.

Generalized rarefactions were presented on 6 plain radiographs and 10 CBCT images, agreeing with the findings that rarefactions were detected in all cases,^{5,7} but disagreeing with Bender and Bender,⁴ who observed generalized rarefactions in only 5 of 28 patients. Enlarged marrow spaces were observed in ten CBCT and nine plain radiographs, agreeing with other studies.^{4,7}

Cortical thinning was observed in nine plain radiographs, but in only five CT images. It has not been reported in the literature,⁷ but was observed in only 2 of 28 cases.⁴ However, this study agrees with another paper that showed this manifestation as one of the most prevalent findings at both early and advanced stages.⁵

Pseudocystic lesions were presented in one panoramic radiograph, but visualized in nine cases by means of CBCT images. This could be a result of overlapping characteristics of the panoramic images yielding a false-negative result. Lesions with a pseudocystic pattern represent the increase in pathognomonic marrow spaces due to the accumulation of Gaucher cells, which increase intraosseous pressure and compromise the vascularity of the area by extrinsic compression or occlusion of these vessels.^{4,6}

Another unusual finding was mental demineralization, present in three plain radiographs and seven CBCT images, probably because of the overlapping explained above. The presence of demineralization corroborates with other clinical cases.⁴

These results have clinical significance. The presence of generalized rarefactions, enlarged marrow spaces, pseudocystic lesions, cortical thinning and mental demineralization in GD patients may have important significance in surgical procedures such as fixation of implants, removal of bone grafting, orthognathic surgery and other procedures. It is critical that the dentist knows of these bone changes in patients with GD.

Effacement of anatomical structures such as the path of the mandibular canal, mental foramen, maxillary sinus floor and lamina dura was observed in four plain radiographs, although in CBCT such difficulties occurred in eight cases. The most commonly affected structure was the mandibular canal, which disappeared

in areas of intense radiolucency. This result corroborates previous findings of effacement of the mandibular canal in more than 50% of samples.^{4,7}

Signs of osteosclerosis were present on six panoramic radiographies and five CBCT images, most commonly in the mandible, probably due to a chronic widespread reaction against the initial infiltration of Gaucher cells. This fact concurs with a few findings⁶ and differs from others.^{4,5,7} Areas of radio-opacity may suggest infiltration of cells or a temporary reaction against the bone (cases of tooth extractions or recent splenectomy),⁵ but such situations do not apply to any cases in our sample. However, we found no statistically significant differences between the GD group and the control group, which may suggest attenuated involvement, or non-participation of Gaucher cells in this phenomenon.

Flattening of the condyle was the predominant TMJ manifestation, which occurred in seven panoramic radiographs and in only one CBCT image. Thus, many cases that might suggest flattening of the condyle have been demystified by the visualization of sagittal and axial slices in tomography, implying that panoramic views give false-positive results. Comparing the control group with the GD group, we observed a statistically significant difference for changes in TMJ CBCT. Some previous work has highlighted that tomography seems to have a minimal effect on the diagnosis or management of temporomandibular disorders.^{11,12} Therefore, other methods of diagnostic imaging associated with clinical examination should be used to validate our findings in relation to the TMJ. No previous study has analysed this condition among Gaucher patients.

The presence of radio-opaque images suggesting partial or total obliteration was observed in the maxillary sinus region, agreeing with other clinical cases previously described,^{8,13} but disagreeing with others that did not detect involvement of the paranasal sinuses.⁴ This finding occurred on eight plain radiographs, but was confirmed in only three cases by CBCT images. Authors who have used panoramic radiographs^{3,7,8} usually suggest that partial or total obliteration of the maxillary sinus is due to hyperplasia of the medullary portion by infiltration of Gaucher cells. But this study also found thickening of the maxillary sinus mucosa using CBCT and effacement on the limits of the cortical floor of the maxillary sinus (probably owing to

environmental causes). These findings were previously unreported.

Comparing the patient group with the control group by means of panoramic images, three manifestations had statistically significant differences: generalized osteopenia, enlarged marrow spaces and effacement of anatomical structures. On the other hand, when CBCT was analysed, 7 of the 11 findings studied had a higher incidence in the patient group than in the healthy population: generalized osteopenia, enlarged marrow spaces, cortical thinning, pseudocystic lesions, mental demineralization, TMJ involvement and effacement of anatomical structures. Therefore, it is easy to provide evidence of CBCT superiority for diagnostic efficacy expressed as sensitivity, specificity and predictive values.

The literature in this area consists of case reports or studies with very small sample groups.^{1,5,6,8} Another difficulty concerns the methodology used to obtain such reports, the majority being chiefly made up of plain radiographs (panoramic and cephalometric). From this point of view, this study is the first to use CBCT to analyse the details of the images in a group of patients with GD. A few other isolated case report studies have used conventional computer-based tomography and periapical radiographs.^{11,12}

Finally, the results of the study agree largely with clinical and imaging findings described in the literature. Flattening of the condyle, thickening of the maxillary sinus mucosa and effacement of the cortical floor of the maxillary sinus were first described in these patients. Although these findings can be observed in the general population, the incidence among Gaucher patients was higher, probably because the disease exacerbated the condition, owing to bone involvement.

In conclusion, patients showed important bone manifestations in 100% of the survey. CBCT can accurately help in evaluating maxillofacial manifestations in GD, establishing data which are not clear in conventional radiographs, especially for the diagnosis and surgical planning of patients with GD. Some clinical data such as visceral and haematological involvement could not be correlated with the radiological findings of bone changes, probably for two reasons: multiple phenotypes of the disease and its asymptomatic course. Finally, a multi-centre study is necessary to better comprehend GD maxillofacial involvement.

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