

Research article

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Dental profile of patients with Gaucher disease

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Abstract

Background: This study was conducted to determine whether patients with Gaucher disease had significant dental pathology because of abnormal bone structure, pancytopenia, and coagulation abnormalities.

Methods: Each patient received a complete oral and periodontal examination in addition to a routine hematological evaluation.

Results: Gaucher patients had significantly fewer carious lesions than otherwise healthy carriers. Despite prevalence of anemia, there was no increase in gingival disease; despite the high incidence of thrombocytopenia, gingival bleeding was not noted; and despite radiological evidence of bone involvement, there was no greater incidence loss of teeth or clinical tooth mobility.

Conclusions: These data represent the first survey of the oral health of a large cohort of patients with Gaucher disease. It is a pilot study of a unique population and the results of the investigation are indications for further research. Based on our findings, we recommend regular oral examinations with appropriate dental treatment for patients with Gaucher disease as for other individuals. Consultation between the dentist and physician, preferably one with experience with Gaucher disease, should be considered when surgical procedures are planned.

Background

Gaucher disease, the most prevalent lysosomal storage disorder, is a result of the genetic defect in production of the enzyme β -glucocerebrosidase, and the consequent accumulation of the glycolipid, glucocerebroside, in the cells of the monocyte-macrophage system [1]. The clinical heterogeneity, which marks all forms of Gaucher disease, is attributable, to a large extent, to the more than 200 mutations, including point mutations, insertions, deletions, and cross-overs, within the glucocerebrosidase gene [2]. Classically, three clinical forms have been delineated,

based on the absence (type I) or presence (types II and III) of neurological signs.

Type I, the non-neuronopathic form, is the most common, with an ethnic predilection for Ashkenazi Jews. Onset of symptoms is noted in all ages; neonates as well as in the elderly. Clinical heterogeneity is characteristic of type I and the course of the disease is variable. Many patients with this type are virtually asymptomatic all of their lives and are diagnosed because of evaluation for an unrelated medical problem or because of a family

screening of a symptomatic relative [3]. The presence of the single most common mutation, N370S (1226G) on one allele appears to be protective of development of a neuronopathic form, and the genotype N370S/N370S is the most common among type I patients [2]. Most other Ashkenazi Jewish patients are compound heterozygotes for the N370S (1226G) mutation.

Type II presentation is more acute and typically more uniform, with onset of both visceral signs and neurological involvement during the first six months of life. This includes hypertonic posturing, strabismus, trismus, and retroflexion of the head [4]. Aspiration pneumonia and laryngospasm are often the cause of death, which generally occurs by two years of age.

Type III may be considered a heterogeneous conglomerate of patients who present some features in childhood and who demonstrate at least one neurological sign. Early cases of this "sub-acute" form of Gaucher disease were recognized in the Norrbottnian-Vesterbottnian territories in northern Sweden. Symptoms were of mild to moderate severity and included bone involvement and visceral enlargement as well as central nervous system findings of spasticity, seizures, and oculomotor apraxia. A new variant, called type IIIc, has been described in a few families from Japan, Israel, and Spain. These patients present with none of the above common visceral signs, but only with oculomotor apraxia and a progressive calcification of the aortic and/or mitral heart valves which has proven to be fatal in all of the non-Israeli cases [5].

The earliest sign of Gaucher disease is splenomegaly. In cases where the spleen may not be palpable, this will be demonstrable on ultrasound examination [6]. Untreated, there may be progressive organ enlargement, leading to hypersplenism. In children, growth retardation may be seen [7]. Anemia and thrombocytopenia, causing easy fatigability and a tendency towards bleeding, are among the earliest presenting signs and most prominent features of Gaucher disease [1]. Most symptomatic patients have some degree of liver involvement, usually presenting as hepatomegaly with or without abnormal liver function tests. The severity of liver involvement appears to be correlated with severe manifestations in other organs [8].

Bone involvement is among the more variable of the symptoms attributed to Gaucher disease. It is probably the most debilitating, particularly the recurrent and sudden onset of painful "bone crises" that may require narcotic medication for relief. The occurrence of pathological fractures or fractures following slight trauma (e.g., broken ribs after an embrace), avascular necrosis of the heads of femur and humerus, and compression fractures of the

spine are well-documented complications of Gaucher disease [9].

There are no markers that accurately predict which symptoms will occur in any particular patient. The degree of bone involvement may not be correlated with the severity of organomegaly or any of the hematological parameters of Gaucher disease [10,11]. Conversely, asymptomatic bone disease, such as the Erlenmeyer flask deformity of the distal femur, medullary infarcts, and osteopenia, are often only secondary findings in cases of massive visceral involvement. Thus, bone involvement may or may not be a presenting feature of Gaucher disease.

The mandible, a long bone, has been noted in anecdotal case reports as a nidus of Gaucher cell infiltration and/or bone crisis [12-17]. In our study of a subset of 28 patients with Gaucher disease (of an initial cohort of 87 patients), 25 patients displayed radiologic evidence of bone involvement in the jaw, including widening of the marrow spaces, endosteal scalloping, and cortical thinning [18]. A tendency to bleeding is one of the more common presenting signs; hence, prolonged or excessive bleeding after tooth extraction or other similar invasive dental procedures may induce a patient to seek medical attention. Therefore, we initiated this study to ascertain whether patients with Gaucher disease demonstrate greater dental pathology because of poor underlying bone structure, whether pancytopenia affects gingival health, and whether these features of symptomatic Gaucher disease affect oral health.

Methods

The Shaare Zedek Medical Center referral clinic includes more than 350 patients with Gaucher disease. All Ashkenazi Jewish patients who appeared for routine medical follow-up examination between March and June of 1996 were invited to participate in the study. Of these 146 patients, 87 consented to have an oral examination. This study received approval of the Helsinki Committee (Institutional Review Board). Patients were also asked to sign an informed consent form.

The diagnosis of Gaucher disease was based on bone marrow aspirate and/or enzyme assay, and confirmed by molecular analysis. The severity of the disease was assessed by the use of a severity score index (SSI) ranging from 0-30; indicative of asymptomatic to very severe involvement [19].

Carriers of Gaucher disease were also enrolled in the study. Patients were accompanied by first degree relatives who had previously been diagnosed as carriers of Gaucher disease both by enzyme analysis and molecular analysis.

Each patient received a complete oral examination by an oral pathologist, using a portable dental chair, with a dental examining light. The oral examination procedure consisted of a complete soft tissue examination and a clinical examination for decayed, missing and filled surfaces of teeth (DMFS). As recommended by the World Health Organization, the DMFS index did not include radiographs [20]. Patients were encouraged to present for panoramic radiographic examination. Twenty eight of the 87 patients agreed. A periodontal examination (GI) was performed, using a modification of the Löe and Sillness Index [21]. Gingival probing was not done. Hematological tests were conducted as part of the routine Gaucher-related follow-up, including complete blood count and coagulation tests, prothrombin time (PT) and partial thromboplastin time (PTT). No additional hematologic tests were ordered other than those customarily required for the routine medical evaluation.

Results

The population studied consisted of 87 patients with Gaucher disease (37 males and 50 females). The mean age was 30.7 (range: 4–68) years. Twenty-eight patients (32%) had been splenectomized prior to the time of the oral examination. Fifty-three (61%) of these patients were receiving enzyme replacement therapy with Cerezyme® (Genzyme Therapeutics Inc., Cambridge MA), the recom-

binant form. [22]. Thirty-one carriers (14 males and 17 females) were examined. Their mean age was 43.7 (range 26–68) years.

The hematological parameters of the patients are presented in Table 1. Some patients presented with an abnormally prolonged PTT (65%), thrombocytopenia (42%) and anemia (38%). Although a few patients reported a history of oral bleeding associated with dental extractions and/or shedding of deciduous teeth, spontaneous oral bleeding was not reported.

The oral health status of the patients with Gaucher disease, as compared to the carriers, is presented in Table 2. For most dental parameters measured, the findings in the patients were better than those of the carriers. Patients had lower levels of caries experience (DMFS) than carriers (36.8 as compared to 49.4). This difference was statistically significant at a level of $p = 0.048$. The largest difference was for the MS component (missing surfaces). Among patients, this was 9.5, half the level found among carriers (18.9). This difference reached high statistical significance ($p = 0.008$). The differences for the filled and decayed surface components of the DMFS index did not reach statistical significance. There was no difference in gingival disease between the patients and the carriers.

Table 1: Hematological parameters of patients with Gaucher disease

Parameter (units)	Number of patients*	Mean (+/- SD)	Normal range	Number patients < normal (%)	Number patients > normal (%)
PT (%)	82	78.1 (+/-19.2)	66 – 100	18 (22%)	13 (16%)
PTT (seconds)	79	39.8 (+/-11.8)	20 – 32	0	51 (65%)
Platelet count (10 ³ /μl)	86	169,500 (+/-113,700)	120,000 – 350,000	36 (42%)	4 (5%)
Hemoglobin (g/dl)	86	12.3 (+/-1.6)	12 – 16	33 (38%)	0
WBC (10 ³ /μl)	86	7.7 (+/-3.8)	3.9 – 9.6	8 (9%)	21 (24%)

SD = standard deviation; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell count. *data not available for all patients

Table 2: Age adjusted mean oral health indices (+/- SD) for patients and carriers of Gaucher disease.

	Patients n = 87	Carriers n = 31	p value
DMFS*	36.8 (+/- 31.3)	49.4(+/- 35.5)	.048
DS*	0.8 (+/- 2.3)	1.5(+/- 4.2)	.026
MS*	9.5 (+/- 20.3)	18.9(+/- 32.7)	.008
FS*	21.5(+/- 21.8)	28.9(+/- 19.6)	NS
GI**	0.7 (+/- 0.48)	0.8 (+/- 0.45)	NS

SD = standard deviation; DMFS = decayed, missing and filled surfaces of permanent and deciduous teeth; DS = decayed surfaces; MS = missing surfaces; FS = filled surfaces; GI = gingival index. *DMFS, DS, MS, FS, parametric variables were analyzed employing ANOVA. Mean levels were adjusted for age. **GI, a non-parametric variable, was analyzed employing the Mann-Whitney test. Due to differences in age distribution, the test was applied separately for three age groups (<18, 19–40, and >41 years).

No correlation was detected between the DMFS and GI indices and the clinical signs of Gaucher disease, including anemia, thrombocytopenia, status post-splenectomy, and decreased coagulation times; nor with the SSI.

Discussion

The dental health of the patients, as measured by the DMFS index, was better than that of the carriers. The patients had approximately half the number of carious surfaces and half the number of missing surfaces compared to the carrier cohort. Since the carriers and the patients are members of the same families, one might assume a similar socio-economic environment and access to oral health care. The insignificant difference in filled surfaces, a measure of dental treatment, supports this hypothesis. The patients, however, were aware of their Gaucher disease status and may have had a higher health awareness, including a greater concern for their oral health. A healthier diet and better personal oral hygiene might explain the observed differences in DS and MS scores.

As Gaucher disease results in anemia, tendency to bleeding, and poor healing, a correlation between Gaucher disease and gingival disease was anticipated, but no such association was found. As suggested above, the reason for this could be that the patients were aware of their "at risk" status and may have practiced better oral hygiene.

A certain selection bias is recognized in this study. The patients were told that an American professor of dentistry was conducting a project related to oral health. This introduction implicitly suggested an "expert consultation", and may have induced some patients to participate. At the same time, patients satisfied with their current level of oral care may have declined this invitation. The sample was taken only from those patients under care of the Shaare Zedek Medical Center Gaucher Disease clinic.

This is a "pathfinder investigation" and the authors are aware of the limitations. An initial study will have many imperfections and represents a compromise with optimal design. Such a study need not be perfect. [23]. Considering the rarity of Gaucher disease and the unique opportunity to study this population in this specialized clinic, never the less these results are of interest and we believe of significant value.

These data represent the first survey of the oral health of a large cohort of patients with Gaucher disease. Although the literature cites case reports of oral signs and symptoms, this population was devoid of significant abnormalities, suggesting that patients previously reported in the literature represent those who sought consultation for

oral symptoms and were not typical of this special need population.

These results are preliminary, but valuable, indications of the oral health status of Gaucher disease patients. Future studies should include an evaluation of the oral hygiene status (plaque level and calculus scores), oral health education, and a disciplined review of the patients' professional dental care. A comparison of oral health findings in a cohort of healthy Israeli Ashkenazi Jews is also indicated.

Conclusions

Based on these findings, we recommend regular and thorough oral examination, with appropriate dental treatment, for patients with Gaucher disease as for other individuals. Enzyme replacement therapy, either with the placental-derivative Ceredase® (Genzyme Therapeutics Inc, Cambridge MA) or the recombinant product Cerezyme®, reduces the complications of hypersplenism, improving hemoglobin and increasing platelet counts [24,25], as well as decreasing the tendency to infections [26].

Because many of the Gaucher disease patients (42%) had thrombocytopenia, the dentist should consult with the patient's primary care physician when the treatment plan includes procedures likely to cause bleeding. This would include scaling, root planing and curettage, extractions, periodontal surgery, and other oral surgical procedures. It would be preferable for this consultation to include a physician experienced in managing Gaucher disease or a hematologist. In addition, partial factor deficiencies, such as of factors IX and XI, are not uncommon in Ashkenazi Jews [27]. This deficiency should also be considered in patients with Gaucher disease. Antibiotic prophylaxis before and after deep scaling and similar procedures has been suggested for splenectomized patients as well as in patients with a history of systemic infections [28].

Competing interests

none declared

Authors' contributions

SF participated in the design of the study, performed the clinical examinations, and drafted the manuscript.

DE participated in the design of the study and assisted in preparation of the manuscript.

H S-C participated in the design of the study, the review and analysis of the data, and drafting of the manuscript.

JM participated in the design of the study, provided financial support for the study, and assisted in preparation of the manuscript.

AZ directs the Gaucher clinic at the Shaare-Zedek Medical Center. He participated in the design of the study, provided the medical data for the patients, and assisted in preparation of the manuscript.

All authors read and approved the final manuscript.

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References

- Beutler E and Grabowski G: **Glucosylceramide lipidoses** In: *The metabolic basis of inherited disease* Edited by: Scriver C, Beudet A, Sly W. New York: McGraw-Hill; 1995:2641-2670.
- Grabowski GA and Horowitz M: **Gaucher's disease: molecular, genetic and enzymological aspects** *Baillieres Clin Haematol* 1997, **10**:635-656.
- Azuri J, Elstein D, Lahad A, Abrahamov A, Hadas-Halpern I and Zimran A: **Asymptomatic Gaucher disease: Implications for large-scale screening** *Genet Testing* 1998, **2**:297-299.
- Brady RO, Barton NW and Grabowski GA: **The role of neurogenetics in Gaucher disease** *Arch Neurol* 1993, **50**:1212-1224.
- Abrahamov A, Elstein D, Gross-Tsur V, Farber B, Glaser Y, Hadas-Halpern I, Ronen S, Tafakjdi M, Horowitz M and Zimran A: **Gaucher's disease variant characterized by progressive calcification of heart valves and unique genotype** *Lancet* 1995, **346**:1000-1003.
- Hill SC, Reinig JN and Barranger JA *et al.*: **Gaucher disease: Sonographic appearance of the spleen** *Radiology* 1986, **160**:631-634.
- Mistry PK and Abrahamov A: **A practical approach to diagnosis and management of Gaucher's disease** *Baillieres Clin Haematol* 1997, **10**:817-38.
- Hill SC, Damaska BM and Lin A *et al.*: **Gaucher disease: Abdominal MR Imaging findings in 46 patients** *Radiology* 1992, **184**:561-566.
- Elstein D, Itzhaki M and Mankin HJ: **Skeletal involvement in Gaucher disease** *Baillieres Clin Haematol* 1997, **10**:793-816.
- Stowens DW, Teitelbaum SL, Kahn AJ and Barranger JA: **Skeletal complications of Gaucher's disease** *Medicine* 1985, **64**:310-322.
- Pastakia B, Brower AC, Chang VH and Barranger JA: **Skeletal manifestations of Gaucher's disease** *Seminars in Roentgenology* 1986, **21**:264-274.
- Sela J, Polliack A and Ulmansky M: **Involvement of the mandible in Gaucher's disease. Report of a case with post-mortem findings** *Br J Oral Surg* 1972, **9**:246-250.
- Bender I: **Dental observations in Gaucher's disease** *Oral Surg Oral Med Oral Pathol* 1959, **12**:546-561.
- Heasman PA: **Mandibular lesions in Gaucher disease** *Oral Surg Oral Med Oral Pathol* 1991, **72**:506.
- Schwartz M, Weycer J and McGavran M: **Gaucher's disease involving the maxillary sinuses** *Arch Otolaryngol Head Neck Surg* 1988, **114**:203-206.
- Lustmann J, Ben-Yehuda D, Somer M and Ulmansky M: **Gaucher's disease affecting the mandible and maxilla** *Int J Oral Maxillofac Surg* 1991, **20**:7-8.
- Bender I and Bender A: **Dental observations in Gaucher's disease. Review of the literature and two case reports with 13- and 60-year follow-ups** *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996, **82**:650-659.
- Carter L, Fischman S, Mann J, Elstein D, Stabholz A and Zimran A: **The nature and extent of jaw involvement in Gaucher disease: observations in a series of 28 patients** *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998, **85**:233-239.
- Zimran A, Sorge J and Gross E: **Prediction of severity of Gaucher's disease by identification of mutations at DNA level** *Lancet* 1989, **2**:349-353.
- World Health Organization: **Oral Health Surveys, Basic Methods, World Health Organization** Geneva 41977.
- Löe H and Sillness J: **Periodontal disease in pregnancy: prevalence and severity** *Acta Odont Scand* 1963, **21**:533-551.
- Elstein D, Abrahamov A, Hadas-Halpern I, Meyer A and Zimran A: **Low-dose low frequency imiglucerase as a starting regimen of enzyme replacement therapy for patients with type I Gaucher disease** *QJM* 1998, **91**:483-488.
- Abramson JH and Abramson ZH: **Survey Methods in Community Medicine** Churchill Livingston, NY 51999, **3**:42.
- Barton NW, Brady RO, Dambrosia JM, DiBisceglie AM, Doppelt SH, Hill SC and Mankin HJ *et al.*: **Replacement therapy for inherited enzyme deficiency: macrophage-targeted glucocerebrosidase for Gaucher's disease** *N Eng J Med* 1991, **324**:1464-1470.
- Grabowski GA, Barton NW, Pastores G, Dambrosia JM, Banerjee TK, McKee MA and Parker C *et al.*: **Enzyme therapy in type I Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources** *Ann Intern Med* 1995, **122**:33-39.
- Zimran A, Abrahamov A, Aker M and Matzner Y: **Correction of neutrophil chemotaxis defect in patients with Gaucher disease by low-dose enzyme replacement therapy** *Am J Hematol* 1993, **43**:69-71.
- Aerts JMFG and Hollak CEM: **Plasma and metabolic abnormalities in Gaucher's disease** *Baillieres Clin Haematol* 1997, **10**:691-709.
- Aker M, Zimran A, Abrahamov A, Horowitz M and Matzner Y: **Abnormal neutrophil chemotaxis in Gaucher disease** *Br J Haematol* 1993, **83**:187-191.

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