Periodontal and Mucosal Findings in Glycogen-Storage Disease Type Ib: A 12-Year Case Report

Else Hornecker

Some genetic disorders are associated with recurrent inflammation of the oral mucosa and with periodontal disease. Of the various incarnations of glycogen-storage diseases (GSD), type Ib is such a disorder. It is caused by a lack of polymorphous nuclear neutrophilic granulocytes (PMN) and PMN dysfunction. The present case report relates to a patient suffering from GSD type Ib and describes the oral findings between the ages of seven and 19 years. His oral situation was characterized by frequent ulcerations in various regions of the oral mucosa, persistent gingivitis, and advanced periodontal disease, initially affecting the deciduous molars (F3 furcation involvement). A comprehensive preventive dental-care program and excellent compliance on the part of the patient could not prevent periodontal destruction of the mandibular right first permanent molar (4 mm attachment loss, F2 furcation involvement).

Key words: GSD type Ib, glycogen-storage disease type Ib, neutropenia, neutrophilic dysfunction, immunodeficiency, periodontitis, oral complications

INTRODUCTION

In the 1999 "Classification System for Periodontal Diseases and Conditions" the conditions associated with genetic disorders including the glycogen-storage disease (GSD) are listed under group IV (Periodontitis as a Manifestation of Systemic Diseases) (AAP, 1999; Neue Klassifizierung, 2000; DGP, 2002). Of the different types of GSD, however, only one – type Ib – is associated with periodontal symptoms (Hara et al, 1987; Kinane, 1999).
This case report describes the oral and periodontal situation of a GSD type Ib patient under a comprehensive preventive dental care program.

Glycogen Storage Disease Type I

Glycogen storage diseases (GSD) are a group of innate metabolic disorders associated with enzyme dysfunction (inheritance: usually autosomal recessive), where glycogen is not or insufficiently converted to glucose or where glycogen synthesis is limited (Chen, 2003; Kugel et al, 2003; Ullrich and Schaub, 2001). There are more than twelve different incarnations, depending on which enzymatic deficiency is present and which organ is primarily affected or where the disease primarily manifests itself clinically. There are hepatic GSD and muscular GSD (Chen, 2003).
GSD type I are hepatic GSD. In GSD type Ia (according to von Gierke), the enzymatic deficiency is related to glucose-6-phosphatase, whereas in GSD type Ib, the enzymatic deficiency is related to the glucose-6-phosphate transport gene, resulting in a glucose-6-phosphate translocase deficiency (Figure 1) (Bashan et al, 1987; Lange et al, 1980; Narisawa et al, 1982; Schaub and Heyne, 1983). Both types result in serious long-term damage if left untreated: Retarded growth, gout, reduced bone density, hepatomegaly and nephromegaly, renal insufficiency, hepatic adenomas and malignomas, and degenerative cerebral disease. Clinically, we find increased blood levels of lactate, cholesterol, triglycerides, phospholipids, uric acid, and especially depressed blood glucose levels (Chen,

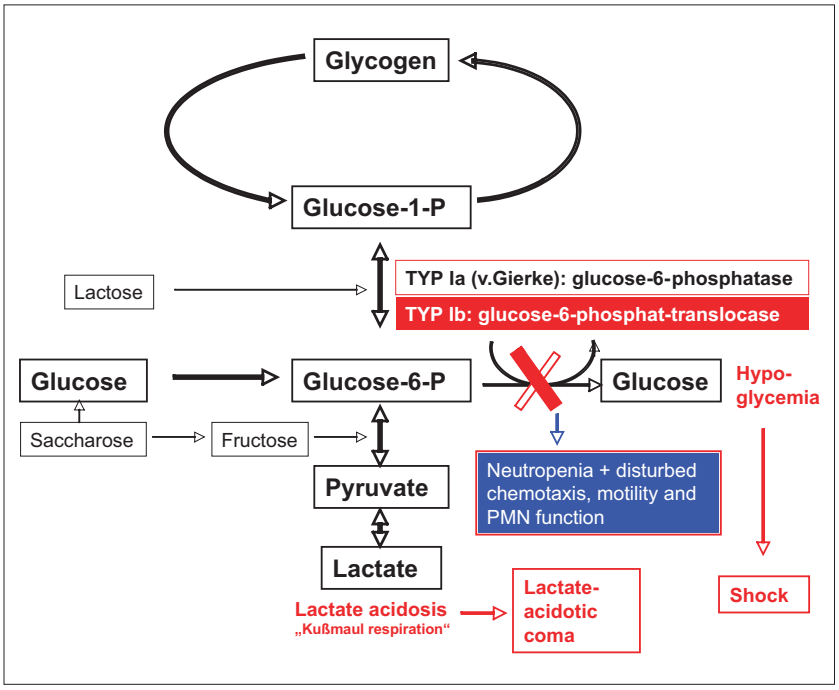

Fig 1 Diagram of the decomposition of glycogen with the enzyme deficiencies typical of GSD type I. Emergency situations are shown in red. PMN dysfunction in GSD type Ib is shown in the blue box.

2003; Talente et al, 1994; Ullrich and Schaub, 2001). As a result of the reduced activity of hepatic enzymes – where glycogen storage is pathologically increased – blood glucose levels cannot be maintained within the normal range in phases in which the patient does not eat, and severe hypoglycemia may be the result (Chen, 2003; Ullrich and Schaub, 2001). In some cases, however, metabolic decompensation first manifests itself in the form of lactate acidosis (Fig 1).

An approximately normal metabolic situation – avoiding serious long-term damage – can be achieved during the day by consistently following certain dietetic rules (GSD diet) (Rake et al, 2002a, 2002b; Visser et al, 2002). There are two strategies that can be followed during the night. In one of them, an infusion pump continuously provides nutrition by way of a gastric probe. This method is primarily used in children (Michels et al, 1982; Visser et al, 2002). The second strategy – most suitable for adolescents and adults – consists in the administration of an uncooked aqueous cornstarch solution. With this method, the patient is able to maintain blood glucose levels in the normal range for approximately six hours (Chen et al, 1984; Phillips, 2002; Rake et al, 2002a, 2002b; Schaub and Heyne, 1983; Smit et al, 1984; Visser et al, 2002). In addition, intake of nutritional supplements consisting of vitamins and minerals is recommended in order to help prevent nutritional deficiencies (Chen, 2003; Kishnani et al, 1999; Rake et al, 2002a).

In addition to the general problems and treatment aspects described for GSD type I, most GSD type Ib patients suffer additional aggravations due to a lack of polymorphous nuclear neutrophilic granulocytes (PMN) and functional impairment of existing PMN caused by deficiencies in microsomal transport of glucose-6-phosphate (Fig 1) (Anderson et al, 1981; Bartram et al, 1981; Bashan et al, 1987, Beaudet et al, 1980; Boxer, 2003; Christopher and Shetty, 1997; Di Rocco et al, 1984; Gahr and Heyne, 1983; Gitzelmann and Bosshard, 1993; Lange et al, 1980; Narisawa et al, 1981, 1982; Schaub and Heyne, 1983; Ueno et al, 1986; Ullrich and Schaub, 2001). In addition to from recurring bacterial infection e.g. of the respiratory tract (Bartram et al, 1981; Corbeel et al, 1983; Schaub and Heyne, 1983; Ullrich and Schaub, 2001) and multiple abscesses (Bartram et al, 1981), inflammatory bowel disease (IBD) or Crohn's-like disease (Chen, 2003; Garty et al, 1996; Melis et al, 2003; Roe et al, 1986; Ullrich and Schaub, 2001; Visser et al, 2000; Wendel et al, 1993) and ulcerations in the oral cavity (Ambruso et al, 1985; Barrett et al, 1990; Bartram et al, 1981; Boneh et al, 2001; Chen, 2003; Di Rocco et al, 1984; Dougherty and Gataletto, 1995; Garty et al, 1996; Katz et al,

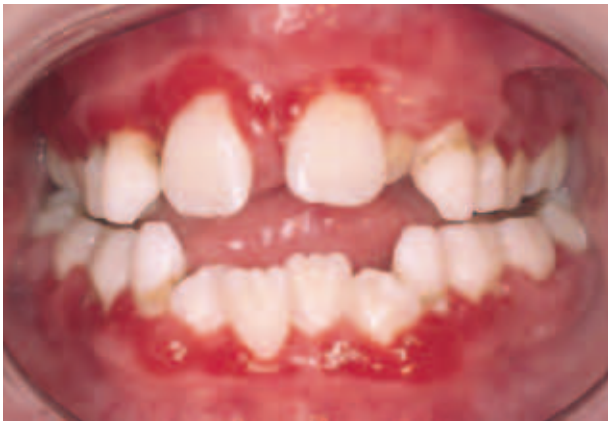

Fig 2a Extreme gingival reddening, bleeding at the slightest touch, bad oral hygiene, concrements on the deciduous dentition (August 3, 1992).

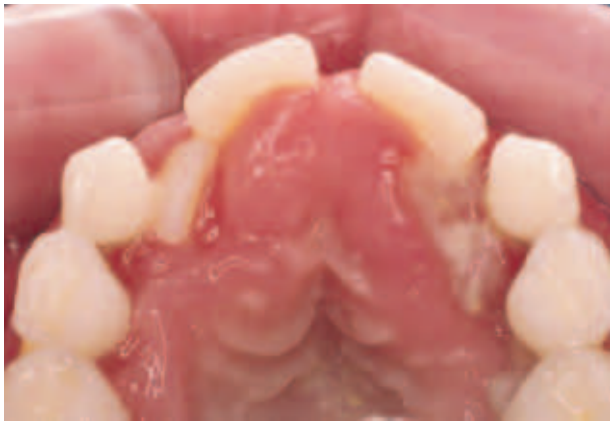

Fig 2b Severe swelling and large ulcerations on the hart palate (same date).

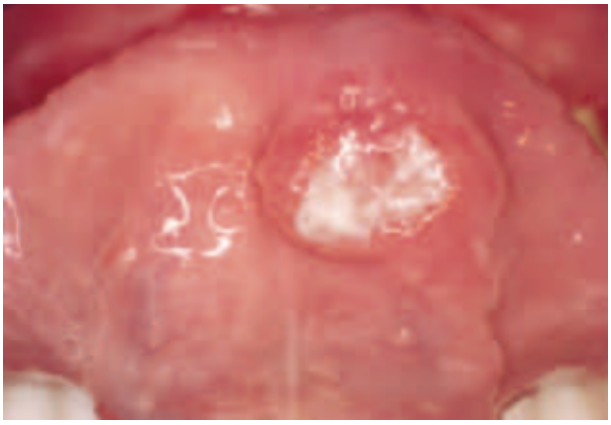

Fig 2c Large ulcer at the bottom of the tongue (same date).

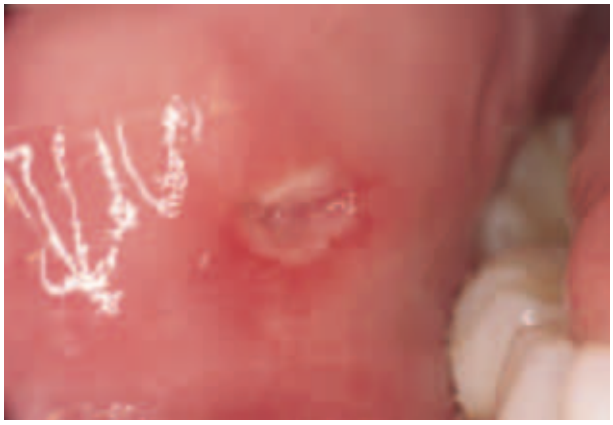

Fig 2d Large ulcer on the buccal mucosa, right side (same date).

1997; Ullrich and Schaub, 2001) as well as gingivitis (Katz et al, 1997; Talente et al, 1994) and periodontal disease (Barrett et al, 1990; Hara et al, 1987; Koven et al, 1986; Kugel et al, 2003; Laskaris and Scully, 2003) frequently occur.
Treatment with granulocyte colony-stimulating factor (G-CSF) has shown positive results. An improvement was observed with regard to neutropenia and PMN dysfunction, as well as a decrease in the frequency and severity of infection (Chen, 2003; Ishiguro et al, 1993; Melis et al, 2003; Schroten et al, 1991; Talente et al, 1994). G-CSF treatment is now part of the therapeutic arsenal for GSD type Ib patients (Ishiguro, 1993); however, severe adverse reactions may occur, such as massive splenomegaly, ultimately requiring splenectomy (Boneh et al, 2001; Visser et al, 1999).

CASE REPORT

The male patient, born in January 1985, had been referred to the department of periodontology of the University Dental School and Hospital of Göttingen, Germany, by the Pediatric Clinic at the same institution with a suspected ulcerative stomatitis. The patient was seven years old at the time. Figs 2a to 2d show the oral situation, while Fig 3 is the orthopantomograph taken on the day of admission (August 3, 1992).
The patient was hospitalized at the Pediatric Clinic. During this time, he received antibiotics and daily professional tooth cleaning. During the next half year, recall appointments were scheduled at two-week intervals (Figs 4 und 5). A monthly recall pattern was maintained through 1999 (Figs 6 to 9).

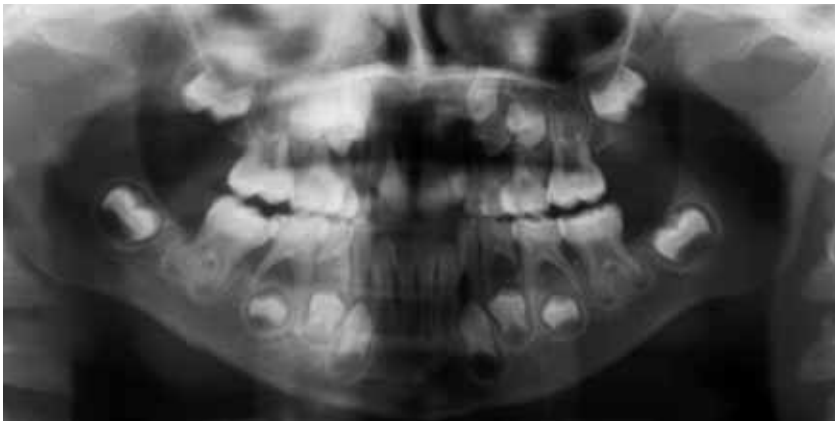

Fig 3 Orthopantomograph of August 3, 1992: The mandibular deciduous molars show F3 furcation involvement.

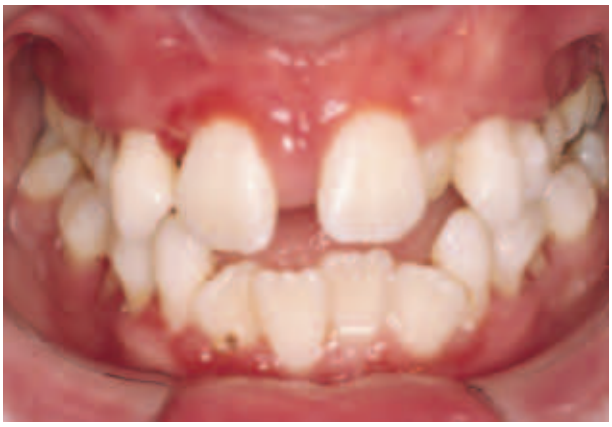

Fig 4 Less swelling and reddening of the gingival margin compared to Fig 2a after two weeks of local therapy.

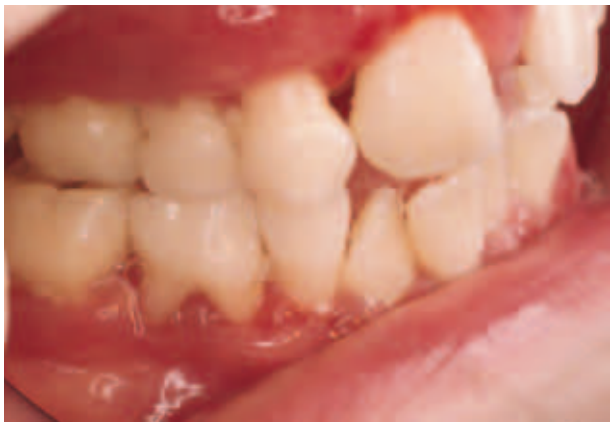

Fig 5 Pronounced clinical attachment loss and furcation involvement on the mandibular right second deciduous molar, despite multiple recalls.

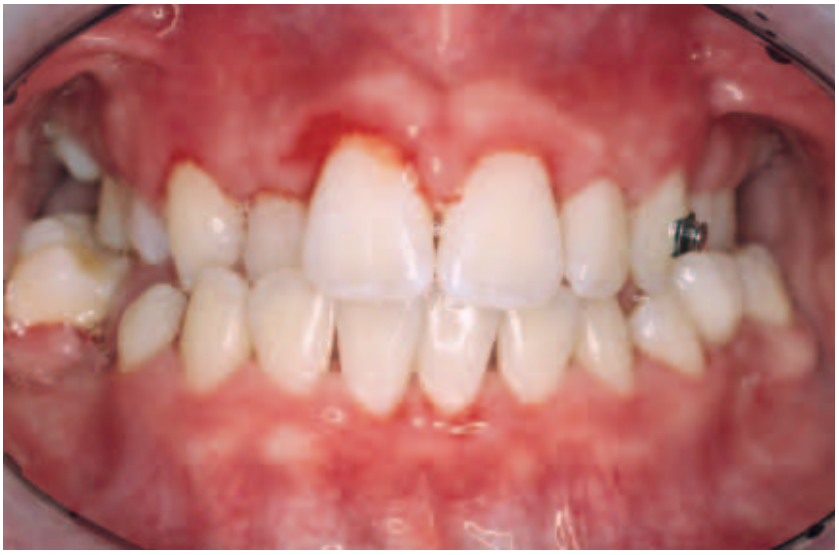

Fig 6 Four years later. Reddening and bleeding at the gingival margin of the maxillary right central incisor. (Orthodontic treatment had been initiated, see the maxillary left canine.)

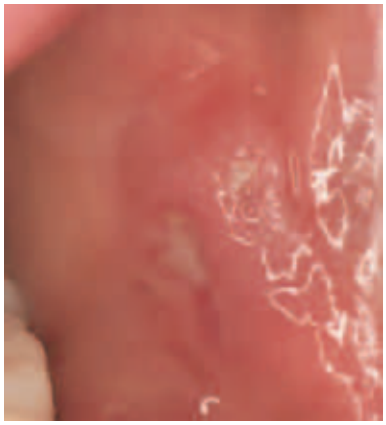

Fig 7a Recurring ulcers on the buccal mucosa (neutropenic ulcers).

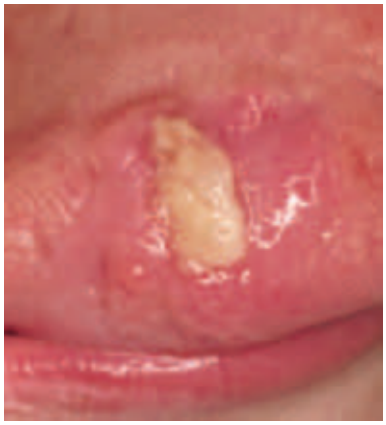

Fig 7b Recurring ulcers on the lingual margin (neutropenic ulcers).

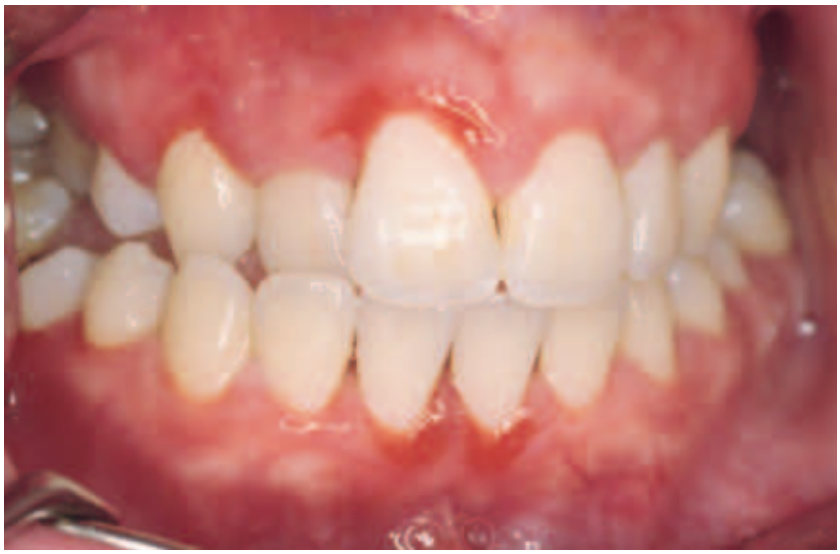

Fig 8 Reddening at the gingival margin, especially of the maxillary right central incisor and the mandibular central incisors, after six years.

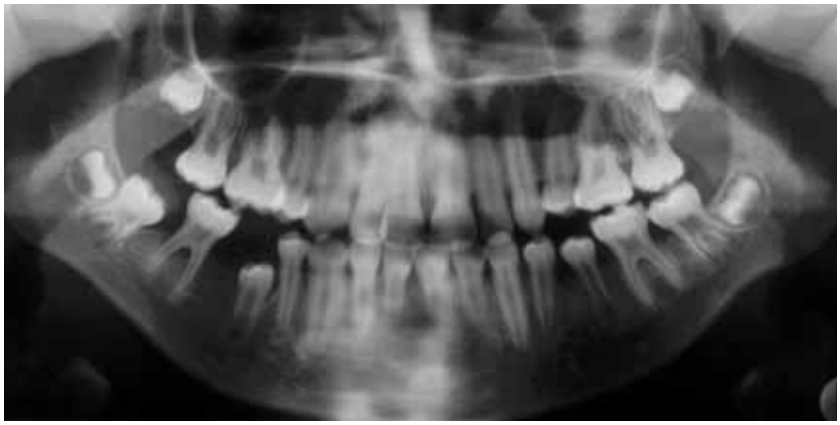

Fig 9 Orthopantomograph of December 8, 1997: The mandibular right first molar shows attachment loss proximally and in the furcation region.

Since 2000, the recall interval has been three months (Figs 10 to 15). Despite the excellent level of oral hygiene that has been attained, the bleeding tendency continues to be strong, with gingival margins showing pronounced reddening in many areas. A splinting/chlorhexidine gel therapy conducted in 2002 over a period of two weeks had no effect on clinical appearance (Figs 11 and 12). The mandibular right first molar has developed a clinical attachment loss of 4mm and a F2 furcation involve-

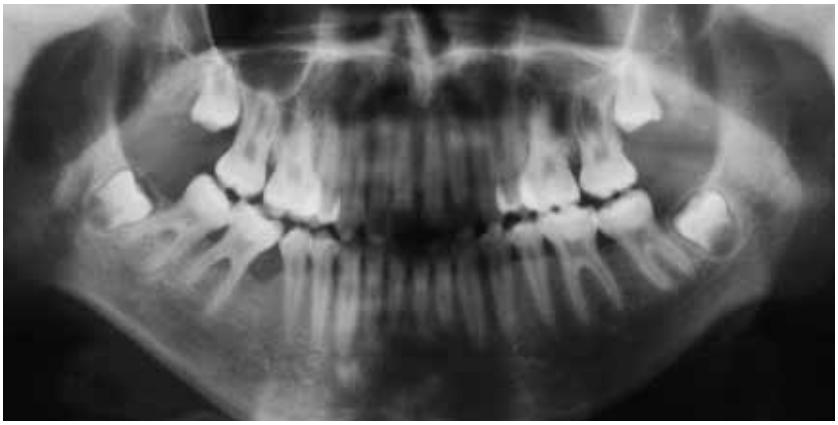

Fig 10 Orthopantomograph of January 15, 2001: With the exception of the third molars, all permanent teeth are fully erupted. The attachment loss at the mandibular right first molar has not been exacerbated compared to Fig 9.

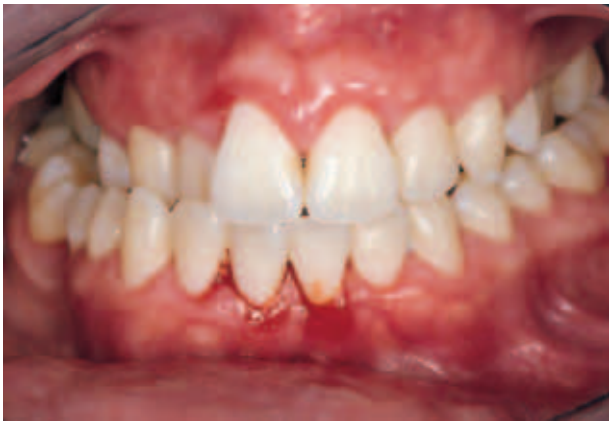

Fig 11 Before the two-week course of chlorhexidine gel therapy: Reddening of the gingival margin of the maxillary right central incisor and bleeding on the mandibular right incisors and the mandibular left central incisor (May 13, 2002).

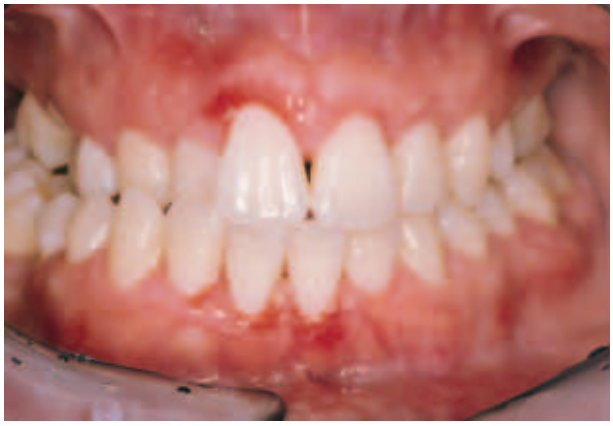

Fig 12 After the course of chlorhexidine gel treatment: Reddening of the gingival margin unchanged, possibly even exacerbated at the maxillary right central incisor (May 5, 2002).

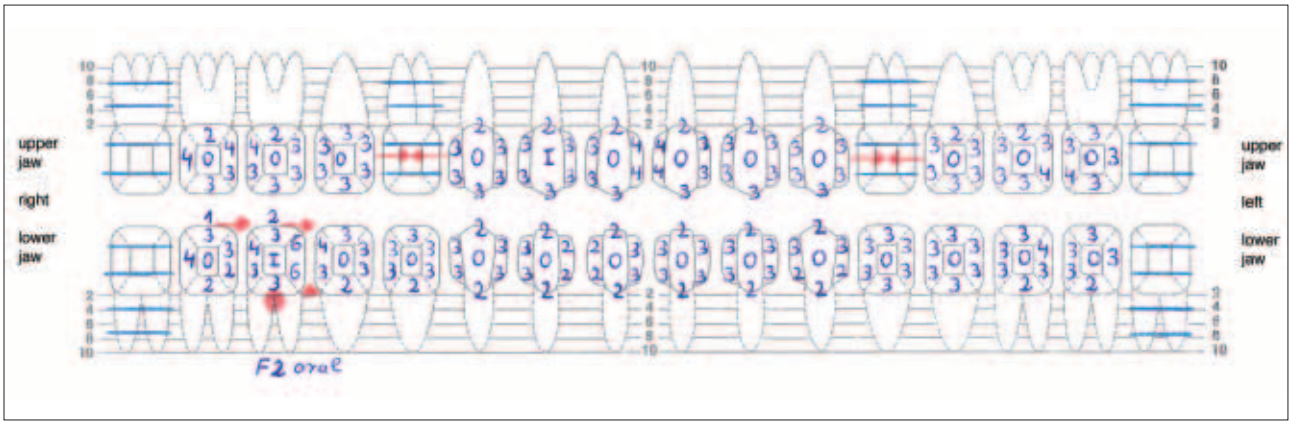

Fig 13 The periodontal status of May 29, 2002 shows the probing depths. The mandibular right first molar shows a F2 furcation involvement and a clinically exposed cervix (2 mm). On the lingual side of the mandibular right second molar, the cervix is exposed by 1 mm on the oral side.

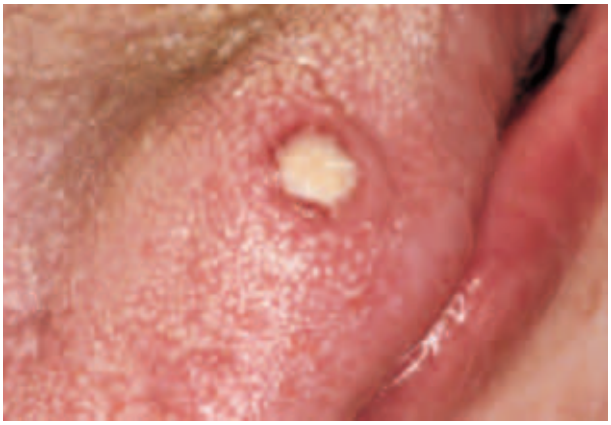

Fig 14 Large ulcer on the top of the tongue (May 29, 2002).

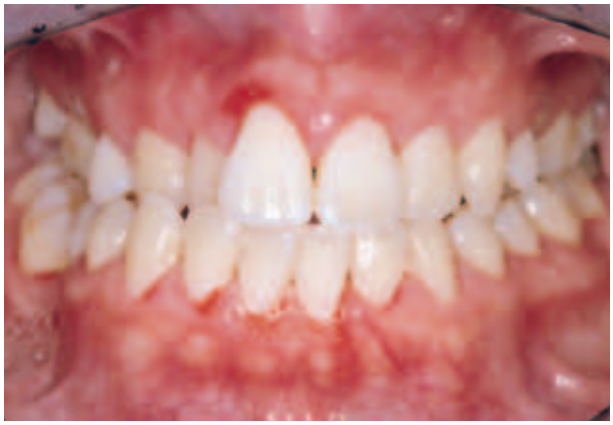

Fig 15 Reddening at the gingival margin, especially at the maxillary right central incisor and the mandibular anterior teeth twelve years after the initial diagnosis.

ment orally (Fig 13). At present, however, no progressive tendencies are noted. Large ulcerative processes form intermittently on the buccal wall of the oral cavity and on the tongue, which develop coarse infiltrate before starting to heal slowly. A course of orthodontic therapy initiated in 1995 (Angle Class II, frontal open bite, bilateral crossbite; the extraction of the two maxillary first premolars resulted in no problems) was repeatedly interrupted because of the large ulcerative processes on the buccal wall of the oral cavity and on the tongue (Figs 7a and 7b as well as Fig 14). It was finally discontinued in 2002.

General Medical History and Pediatric Findings

A diagnosis of GSD type Ib was first made in 1986 following a second biopsy of the liver, after the boy, following a first biopsy at the age of six months, had initially been given a diagnosis of GSD type Ia. Since that time, the GSD diet guidelines were meticulously followed (a special meal every two to three hours, no sucrose or sucrose-containing beverages, only small quantities of fat, etc.). According to the patient's parents, there had been some hypoglycemic episodes, mostly in connection with severe diarrhea in the years around 1990. Emergency treatment had been performed in these cases. No Crohn's-like disease of the intestine (see above) was detected. As a result of a failure of the infusion pump (for the nightly feeding by gastric probe), the patient suffered a hypoglycemic shock in 1995 and was comatose for two days. No serious hypoglycemic metabolic decompensation occurred after that event. Up to this point, the nightly nutrient supply is still primarily delivered by a gastric probe. Occasionally, the patient also uses an uncooked cornstarch solution (see above), which gives him a respite of approximately five hours. Because the necessary lifestyle rules required for GSD type I patients were meticulously followed, first by the patient's parents and later by the patient himself, his development was largely normal. Growth was not retarded – something that had been listed above as long-term detrimental effect of GSD type 1b: The patient is 176cm in height, the same height as his brother, who is one year younger and does not suffer from a metabolic disease. Having graduated from school, the patient – now 19 years old – was able to successfully complete his vocational training as a technical assistant.

Medically, the patient has been treated with a long-term (permanent) course of a granulocyte colony-stimulating factor (GCSE; Neupogen® 30, $^1/_2$ vial s.c. every other day) since his hospitalization in August of 1992. By contrast with other case reports (Ishiguro et al, 1993; Wendel et al, 1993), this treatment has not resulted in any improvement in the percentage of neutrophiles. One possible explanation for this might be the dosage: due to the, sometimes massive, adverse effects, the dosage is now being kept as low as possible. Table 1 shows the number of leukocytes and the percentage of polymorphous nuclear neutrophilic granulocytes (PMN) between August of 1992 and March of 2004; both values are consistently below normal, sometimes by a considerable margin. In 2002, the patient was briefly hospitalized for furunculosis.

Table 1 Normal values for leukocyte levels and the percentage of polymorphous nuclear neutrophilic granulocytes (PMN) and the patient's values between August of 1992 and March of 2004. (These figures were obtained from the patient's records at the Pediatric Clinic at Göttingen.)

Normal ranges: Leukocytes (x 1.000)/µl: **4,8 – 10;** PMN percentage[%]: **50 – 70**

Time		Leukocytes (x 1.000)/µl	Percentage of PMN [%]
August	1992	4,7	5
December	1992	5,5	30
June	1993	3,5	24
October	1993	3,3	18
February	1994	5	34
April	1994	3,6	7
July	1994	4,6	26
May	1995	2,5	6
December	1995	2,8	22
March	1996	3,5	14
August	1996	2,7	7
April	1997	3,4	24
October	1997	2,5	3
December	1997	2,5	6
May	1998	4	14
June	1998	2,9	9
February	1999	4,2	26
May	1999	2,9	25
November	1999	3,4	no information
March	2000	2,9	11
January	2001	2,4	no information
June	2001	2,5	6
January	2002	2	no information
September	2002	2,6	3
March	2003	1,8	2
September	2003	2,2	8
March	2004	2,1	6

DISCUSSION

GSD type Ib is a very rare disease. In a multicenter study of GSD type I in which 16 centers in 12 European countries participated, all known GSD type Ib patients born between 1960 and 1995 were retrospectively covered. There were a total of 57 patients; another 231 patients suffered from GSD type Ia (European Study on Glycogen Storage Disease Type I – ESGDS I) (Rake et al, 2002a; Visser al, 2000). Germany was the home of 13 type Ib patients and 54 type Ia patients. The study examined the incidence and severity of GSD type Ib, the progression of neutropenia and PMN dysfunction, and the occurrence of intestinal inflammation (inflammatory bowel disease, IBD). Neutropenia was present in 54 patients. (The fact that neutropenia was not present in a few type Ib patients is ascribed to a variant of the disease) (Kure et al, 2000). It generally manifested itself as intermittent severe neutropenia without any specific recurrence pattern. PMN dysfunction was present in all 18 patients for whom this had been investigated. Perioral infection – including abscesses, aphthous ulcers, labial and gingival edema – as well as perianal infection and IBD were frequently found, but invariably in patients with concurrent neutropenia. Even though this was not examined or mentioned, one might well speculate that a considerable number of these patients probably suffered from more or less pronounced periodontal destruction.

CONCLUSIONS

The present case report shows that in pronounced neutropenia and PMN dysfunction, as presented in this case of GSD type Ib, periodontal destruction cannot be prevented but certainly limited by intensive preventive dental treatment at close intervals. What was particularly salient about this case was the high incidence of ulcers on the oral mucosa. These finding once again underline the importance of polymorphous nuclear neutrophilic granulocytes (PMN) as the first and most important natural line of defense against acute infection. Since genetic defects associated with neutropenia and PMN dysfunction usually become manifest in childhood, pediatricians and dentists should cooperate closely. The dental treatment should be preventive in outlook and take place at close intervals.

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Reprint request:
Dr. med. dent. Else Hornecker
Dept. of Operative Dentistry, Preventive Dentistry and Periodontology
University Dental School and Hospital
University of Göttingen
Robert-Koch-Straße 40
D-37075 Göttingen
Germany
E-mail: else.hornecker@med.uni-goettingen.de