Glycogen Storage Disease type Ib: a paediatric case report

A. BARTOLI, M. BOSSÙ, G. SFASCIOTTI, A. POLIMENI

ABSTRACT. Aim This paper addresses the need of the dental literature to document cases of Glycogen Storage Disease (GSD) type Ib with focus on the paediatric management of oral and dental problems and the potential complications arising from the increased susceptibility to bacterial infections, cariogenicity, and blood diathesis. Methods Previous medical and dental papers on GSD type Ib published from 1980 to 2006 have been searched in the electronic databases PubMed and EMBASE using keywords of the NLM’s Thesaurus, with the aim to retrieve important implications of treatment and preventive measures for an evidence-based multidisciplinary medical and dental management of the oral health problems of a 9-year old boy affected by GSD type Ib. Case report Oral and dental manifestations observed during a period of two years and relative treatments are reported from our case. Data on pharmacologic, oral hygienic, dietary, and surgical preventive measures for the control of recurrent oral infections, dental caries, gingival inflammation and risk of surgical bleeding are described. In addition, an electronic microscope structural analysis at SEM of the enamel tooth surface was conducted to identify any characteristic difference in the enamel architecture of this GSD type Ib affected patient compared with the normal enamel structure Conclusion The oral manifestations of our case included uncommon findings such as multiple deep oral ulcers of the tongue, labial and vestibular mucosa, which could be related with a severe impairment of the neutrophil-related immune system of the patient. At SEM, the enamel of the deciduous teeth showed dark spots of hypomineralisation which are the first published data of an enamel-related susceptibility to dental caries. The quality of life of our patient increased thanks to the oral and dental treatments and preventive oral health measures given at clinical appointments. The dentist should be prepared to face the possible complications of surgery in these patients and the hospital setting seems to allow for this clinical safety. Keywords: Glycogen Storage Disease type I, Intraoperative complications, Dental anesthesia, Diet therapy, Fluorides.

Introduction

Glycogen Storage Disease (GSD) is a group of rare metabolic disorders caused by a genetically inherited deficiency of one of the enzymes, or transporters, involved in glycogen metabolism. While GSD types II, V and VII affect muscles, GSD types I, III, IV and IX affect the liver causing hepatomegaly and hypoglycemia.

The overall prevalence of GSD has been reported to account for 1:20,000 to 1:25,000 live births [Scrimer, 1995]. Two forms of GSD type I (Ia and Ib) were distinguished on a molecular basis by Narisawa et al. [Narisawa et al., 1986]. A defect of the microsomal hydrolasis glucose-6-phosphatase (G6Pase), which catalyses the utilisation of glucose-6-phosphate (G6P), is responsible for GSD type Ia, whereas GSD type Ib is caused by an enzymatic defect of the G6Pbidirectional translocase (G6PT1), which is located on the microsomal membrane where it ensures the transport of G6P into the endoplasmic reticulum where G6P can be utilised by the cell. GSD Ia and Ib both reveals with indistinguishable clinical patterns of varying degrees of glycogen accumulation.

Diagnosis of GSD type I can be biochemical, requiring a liver biopsy to detect the enzymatic defects of the G6Pase system [Maire et al., 1991], or molecular, requiring the identification of the gene of G6PT1 on chromosome 11 at 11q23 [Annabi et al., 1998]. Neutropenia with dysfunction of neutrophil migration is a common and exclusive finding of GSD Ib [Visser et al., 2000] in which there is an increased susceptibility to recurrent bacterial infections [Ambruso et al., 1985; Visser et al., 2000]. Characteristic oral lesions of GSD Ib are oral ulcers, gingivitis and periodontal disease, that may be related.
to the limited intake of glucose into polymorphonuclear leucocytes [Ambruso et al., 1985; Barrett et al., 1990; Dougherty and Gataletto, 1995]. Frequent epistaxis, ecchymoses and prolonged bleeding can be complications of minimal trauma or after dental procedures, as a result of the acquired reduced platelet adhesiveness and aggregation [Ambruso et al., 1985; Dellinger et al., 1998]. The published data on dental manifestations associated with GSD Ib, such as dental caries, delayed dental maturation and eruption, and taurodontism are limited to case series or isolated case reports [Baccetti et al., 1994; Dellinger et al., 1998; Katz et al., 1997; Kidd et al., 2002; Loeyv et al., 1983].

Between 1980 and 2005, 54 cases of GSD Ib have been reported in the published literature with oral manifestations [McCabe et al., 1980; Beaudet et al., 1980; Ambruso et al., 1985; Barrett et al., 1990; Salapata et al., 1995; Dougherty and Gataletto, 1995; Farrington et al., 1995; Katz et al., 1997; Dellinger et al., 1998; Kidd et al., 2002; Mortellaro et al., 2005]. The oral findings of previously published cases of GSD Ib are summarised in Table 1.

The purpose of this study is to add a new case to the dental literature by reporting a 9-year old child affected by GSD Ib in which oral hygiene and dental restorative and surgical procedures have been performed during a period of two years.

### Methods

Previous medical and dental papers on GSD type Ib published from 1980 to 2006 have been searched in electronic databases PubMed and EMBASE using keywords of the NLM’s Thesaurus. The aim of the literature search was to retrieve data on implications of treatment and preventive measures for an evidence-based multidisciplinary approach to the oral health problems and prevention of possible complications of our 9-year old boy affected by GSD Ib. The patient was followed at our Paediatric Dental Department for a period of two years.

### Case report

A 9-year old boy (BC) affected by GSD Ib was accepted at the Department of Paediatrics of the Dental University Hospital in May 2004 for dental caries. BC an only son. There is no consanguinity between his parents. He was born after a normal pregnancy with a weight of 2,900 g. During his first six months of life he was breast fed with a normal weight gain. After this period, he was given suitable food and he developed diarrhoea, had hypoglicemic events and occasional night convulsions. The diagnosis of GSD Ib was confirmed by assay of the G6P enzyme system on a fresh liver tissue sample. He was started to be fed every three hour with soy milk during the day and at night. He was forbidden lactose and fructose as sugars and received only long-chain carbohydrates that could be slowly absorbed. He received allopurinol because of the hyperuricemia and azitromycin therapeutically and prophylactically because of recurrent infections of the lungs.

At three years of life uncooked cornstarch was introduced in his diet as supplement on a 3.5-hourly daily diet and for the 5-hourly nasogastric meals during the night. At the age of 9 years he has a normal stature (133 cm), low body weight (32 Kg), abdominal distention due to hepatomegaly, and shoulder adiposity. The mental development is slightly down the normal. The percentage of polymorphonuclear leukocytes generally accounts to 30-35% and recurrent infections, such as oral candidiasis, have been frequent along the two years follow-up.

Extraoral examination revealed thick and soft skin of the face and neck without craniofacial dysmorphysms. Intraoral examinations during the two years revealed a normal vermilion border of the lips, while the mucosal side was recurrently ulcerated with little (up to 10 mm diameter), painful, plain ulcers which were repeatedly bitten by the patient.

### Table 1 - Oral findings of published cases of Glycogen Storage Disease type Ib.

<table>
<thead>
<tr>
<th>Author</th>
<th>Clinical sign</th>
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<tbody>
<tr>
<td>McCabe et al. (1980)</td>
<td>recurrent ulcerative stomatitis, candidiasis</td>
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<tr>
<td>Beaudet et al. (1980)</td>
<td>gingivitis, stomatitis</td>
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<tr>
<td>Ambruso et al. (1985)</td>
<td>oral ulcers, gingival bleeding</td>
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<tr>
<td>Barrett et al. (1990)</td>
<td>oral ulcers, periodontal disease</td>
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<tr>
<td>Salapata et al. (1994)</td>
<td>oral ulcers, gingivitis, deep and narrow palate</td>
</tr>
<tr>
<td>Dougherty and Gataletto (1995)</td>
<td>gingivitis, alveolar bone loss</td>
</tr>
<tr>
<td>Farrington et al. (1995)</td>
<td>oral ulcers, dental caries</td>
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<td>Katz et al. (1997)</td>
<td>dental caries</td>
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<td>Dellinger et al. (1998)</td>
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<td>Kidd et al. (2002)</td>
<td>dental caries</td>
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<tr>
<td>Mortellaro et al. (2005)</td>
<td>hyperplastic-hypertrophic gingival epulis</td>
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<tr>
<td>Bartoli et al. (2006)*</td>
<td>oral ulcers, dental caries, gingivitis, periodontal disease</td>
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* present case
(Fig. 1). Similar but deeper ulcers were visible on the side of the tongue and on the vestibular mucosa (Fig. 2, 3). Usually the ulcerations healed after three weeks of topic cortisones or by antibiotic therapy given to the child for organ infections, but never healed spontaneously possibly because of the repeated dental trauma by crown spikes and overbite.

The oral ulcers were a constant finding at any of the four annual visits (every three months) to our department, probably because of the neutropoenia and impaired neutrophil migration which typically affects the immunogenic system of patients with GSD Ib.

At the age of 7 years, when the patient first came to observation, there were no missing or filled teeth. A swelling for dental abscess (tooth 1.6) was treated through dental drainage and local incision of the dentoalveolar membrane after anesthetic local infiltration (mepivacaine with adrenaline 1.100.000). A perioperative antibiotic prophylaxis was given (one dose Azytromicine 500 mg 1 hour before and 8 hours after the intervention). Gingival inflammation and plaque accumulation were severe during the first year and then decreased up to mild during the second year, in relation with the increasing compliance of the child about our instructions on procedures of good daily toothbrushing and oral hygiene. Gingival inflammation and plaque deposits were treated as primary aim at every visit by means of manual removal of the supragingival plaque using a periodontal probe and sterilised gauze and by ultrasonic scalers. Tartar deposits were never present.

A full dental arch periodontal probing revealed the presence of infra- and supra-osseous bone defect sites both at deciduous and permanent teeth, as was confirmed by intraoral x-rays of the deepest sites (mean PPD= 4 mm; range: 4-8 mm). Because of the young age of the patient, the periodontal bone defect sites and gingival pockets were treated by conservative methods of root curettage and use of metronidazole-embedded fibers placed into the pockets. The alveolar bone during the two years of treatment remained at a constant level.

Before the hospitalisation, the patient had never used fluoride supplements but he lives in an area with a discrete fluoride level in the domestic water (0.3 ppm), which could be responsible for the low caries prevalence that accounted to only four caries on four teeth (1.6, 2.6, 5.3, 8.5). The tooth 1.6 was endodontically treated for an abscess and then was reconstructed with a fiber post. Endodontics was
performed five days after the abscess drainage by infiltration of local anaesthesia (mepivacaine 1.100.000) with vasoconstrictor to prolong the pain relief after treatment.

At the age of 9 years, the child had to be extracted five teeth of the deciduous dentition (5.4, 5.5, 6.4, 7.4, 7.5) to prevent the delayed eruption of the relative permanent teeth. Blood analysis revealed a reduced platelet count (135,000/dL) and impaired blood coagulation (INR=2.5). After a preoperative antibiotic prophylaxis (Azitromicine 500 mg dose), the extractions were performed in one day-surgery in a sterile surgery under sedation (30 minutes’ time) with infiltrative (not nerve block) local anesthesia. Alveolar emostasis was aided by surgical haemostatic foam. Another antibiotic dose was given at 24 hours for two days postoperatively. No postoperative bleeding was observed as complication, thus proving the efficacy of the measures used for reducing the risk of bleeding (gingival plaque removal, vasoconstrictor, haemostatic foam and suture). A structural analysis at SEM of the enamel architecture of the extracted deciduous teeth was conducted to assess any possible relevant difference in the structure and spatial distribution of the prisms of the enamel of this GSD type Ib affected patient compared with the normal enamel structure. The deciduous teeth compromised by untreatable caries (and it was too early to be substituted by the permanent teeth) were extracted and put into plastic tubes containing 10% formaline. At the Department of Oral Sciences of the University of Chieti, Italy, each sample was dehydrated into alcoholic solutions with increasing concentrations, mounted on a stub and given metal treatment (Emitech K 550, Emitech Ltd, Ashford, Kent, UK), and finally treated with 37% orthophosphoric acid for 30 seconds. The latter procedure enabled to analyse the enamel prismatic crystals at SEM (LEO 435 Vp, LEO Electron Microscopy Ltd, Cambridge, UK). At SEM, the enamel surfaces resulted having prismatic crystals with a normal parallel pattern and a normal dimension and spatial distribution (Fig. 4). Notably, the finding of dark spots between the crystals was interpreted as a scarce quantity of interprismatic matrix, which is possibly to be related with the hypomineralisation of the teeth in such patients (Fig. 5, 6). This finding is the first published data to reveal an enamel-related susceptibility of these teeth to dental caries.

Parents of the patient and the child were given reinforcement of advices on toothbrushing and oral hygienic and dietary preventive measures to reduce the risk of dental caries because of the possible enamel dissolution at low salivary pH for the repetitive daily intake of carbohydrates. The parents were not recommended to give systemic fluoride supplements to the child because of its good concentration supply in the domestic water. Recently, the patient has started an orthodontic treatment for the resolution of dental malocclusions (right molar relationship and overbite) in another dental hospital.

**Fig. 4 -** Enamel sample from an extracted deciduous teeth at SEM. The prismatic crystals are parallel between them and the scarce quantity of interprismatic matrix is possibly to be related with the hypomineralisation of Glicogen Storage Disease type Ib.

**Fig. 5 -** Enamel sample from an extracted deciduous teeth at SEM. Dark spots in the enamel structure between enamel prismatic crystals and the interprismatic matrix are to be related with the hypomineralization of the tooth in a Glicogen Storage Disease type Ib affected patient.
Discussion and conclusion

The ulcerative lesions caused by impaired neutrophil count and function are constant findings of cases of GSD Type Ib reported in literature. Our neutropoenic GSD Ib affected child presented oral ulcers and gingival inflammation at every visit during the two-year follow-up, thus confirming the observed relationship of previous studies of the increased susceptibility to bacterial infections and the presence of a systemic disorder characterised by neutropoenia and impaired neutrophil chemotaxis [Ambruso et al., 1985; Barrett et al., 1990; Beaudet et al., 1980; McCabe et al., 1980; Narisawa et al., 1986; Salapata et al., 1995].

In literature a significant reduction of infections as well as oral ulcers in these patients has been reported by the use of granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF), which stimulate the proliferation and differentiation of committed granulocyte progenitor cells thus increasing the neutrophil count [McCawley et al., 1994; Mortellaro et al., 2005; Schroten et al., 1991]. The clinical presentation of the ulcers in our patient was characterized by healing of one lesion while developing of another. As opposed to the neutropenic ulcers described in the literature as having a unique presentation with deep involvement of the epithelium [Ambruso et al., 1985; Barrett et al., 1990; McCabe et al., 1980], our case presented multiple deep ulcers on the tongue, labial mucosa and dentoalveolar mucosa, possibly in relation also with the spikes of the decayed crowns and the traumatic overbite on the lower lip, and in relation with the qualitative impairment of the immunogenic system. However, an early diagnosis of the potentially traumatic intraoral sites, such as destroyed crowns, or bad habits, such as lower lip chewing, is recommended to remove possible causes of ulcerations. The treatment of ulcers using topical corticosteroid agents resulted to be successful in decreasing the duration of ulcers on the tongue and lip which never healed spontaneously. The importance of an effective toothbrushing after any meal should be particularly emphasized to the patient and parents because it is the most effective way to maintain good oral health conditions during visits.

Professional plaque removal should be a primary aim of every visit to enable an effective reduction of the risk of dental caries and periodontal disease at a young age. Indeed, an effective control of the gingival health can minimise the risk of bleeding during dental procedures and surgery. Supply of fluoride treatments and early use of systemic fluoride supplements should be part of a specific oral health preventive programme for patients affected by GSD type I because of their increased cariogenicity. In fact, frequent rich-carbohydrate meals result in a prolonged fall in the salivary pH below the critical value 5.5, thus enabling the development of dental caries for dissolution of the enamel [Dougherty and Gataletto, 1995; Farrington et al., 1995; Moynihan et al., 1996].

In children over 2-years-old the frequency of glucose polymers-based meals (generally every 3 - 3.5 hours) can be reduced by the use of uncooked cornstarch that acts as a slow glucose-releasing source [Moynihan et al., 1996]. This is an important advantage for the quality of life of these patients which should be fed three times per night. Another advantage of cornstarch is that its cariogenic potential is lower than that of glucose [Bowen et al., 1980]. This therapeutic dietary regimen may minimise the impairment of dental development and normalise dental eruption [Loey et al., 1983]. However, since cornstarch is adherent to the enamel surface forming a film around the teeth, beneath which caries may develop, this dental plaque must carefully be removed each day by frequent and effective toothbrushing [Farrington et al., 1995]. Vitamin supplements and calcium also should be included in the diet to ensure normal skeletal growth and to prevent long-term complications, such as osteopenia [Lee et al., 1995].

An early treatment of the jaw abscess is
recommended to avoid the risk of bone fractures which can result from osteopenia and osteoporosis. Also the enamel samples of the extracted deciduous teeth analysed at SEM revealed a hypomineralisation of this tissue because of a scarce quantity of interprismatic matrix and dark spots between the prisms. This finding would be the first proven data of the increased caries susceptibility of teeth of such patients. The cariogenicity of hypomineralised teeth together with the increased cariogenicity of the diet advocate for an early supply of fluoride dental treatments and systemic prophylaxis, also with the aim to minimise the risk of developing periodontal disease at young age and bone fractures as adults.

Local infiltrative anesthesia is preferable to an inferior alveolar nerve block because of the risk of bleeding along the pharingeal fascial spaces up to the patient’s airways and mediastinum [Ralls and Marshall, 1985]. The dentist should be prepared to afford the possible complications of surgery in such patients in which the bleeding diathesis makes the management of oral surgery more difficult.

The need for treating GSD type I affected patients in a sterile hospital setting with suitable equipment to monitor the vital signs is advocated. Furthermore, the hospital setting seems to allow for this clinical safety, as well as being the unique place where these chronically ill patients may receive the specific advantages of any specialty engaged in their multidisciplinary treatment.

References


Moynihan PJ, Gould MEL, Huntley N, Thoraman S. Effect of glucose polymers in water, milk and a milk substitute on