Oral manifestations in paediatric patients with hepatobiliary diseases: a review

M.R. Giuca, L. Lardani, S. Ligori, E. Carli, G. Giuca and M. Miceli

Department of Surgical, Medical, Molecular and Critical Area Pathology, Unit of Pediatric Dentistry, University of Pisa, Pisa, Italy.

It is well known that greenish pigmentation of the teeth is seen in children following remission of severe jaundice and clinical and serum bilirubin, a degradation product of haemoglobin, may be permanently trapped in forming dental hard tissues causing discolouration and enamel and dentine hypoplasia. Neonatal jaundice is the most common cause of hyperbilirubinemia and pigmentation of the deciduous teeth is the consequence of this condition. Various hepatobiliary pathologies may have a clinical finding in the oral cavity; furthermore, oral manifestations of hepatic pathologies are not just limited to the pigmentation of the deciduous teeth but also the permanent dentition and the mucous membranes can be affected.

Some hepatobiliary disorders might be associated with oral manifestations; Langmead (1) and Thursfield (2), first proposed, in 1912, that dental changes could be the result of jaundice. First of all, hyperbilirubinemia, defined as a serum concentration of bilirubin greater than 1.5mg/100mL (3), must be considered, as the cause of intrinsic greenish pigmentation of human teeth. Plasma bilirubin in normal subjects is virtually all in the unconjugated form and ranges from 0.3 to 1.0 mg/dL (3) but when the serum bilirubin concentration rises above normal, the clinical condition called *jaundice* occurs, with yellow-green pigmentation of the mucous membranes, skin and sclera. Bilirubin is extensively deposited throughout the body during hyperbilirubinemia, dispersing caudally as the level increases, altough it disappears from soft tissue after remission (4). Nevertheless, in hard tissues bilirubin is permanently trapped,because after maturation these tissues lose metabolic activity (3).

Types of jaundice

There are different forms of jaundice: the clinical condition in which the yellow pigmentation is visible only at the level of the sclera and lingual frenulum is defined as latent jaundice (bilirubin concentration >1.5mg/dL), while the full-blown form of jaundice (bilirubin concentration > 2mg/dL) is clinically more widespread, also affecting the skin. Jaundice can be obstructive, hepatocellular or haemolytic in origin.

Etiopathogenesis

The obstructive jaundice, characterized by an high serum concentration of conjugated bilirubin, is caused by a lack of outflow of bile from the liver, linked to an intrahepatic or extrahepatic obstruction of the bile ducts, associated with cirrhosis or cholestasis, which in young child is often caused by biliary atresia but it could be also caused by other conditions such as infections (4) ,cystic malformation of the biliary tree (5) and Alagylle Syndrome (6).

The second form of jaundice, caused by an impaired function of liver cells (e.g., Gilbert or Crigler-Najjar or Lucey-Driscoll syndromes) is characterized by a high serum level of unconjugated bilirubin, as well as in the hemolytic form. The latter

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Corresponding author:
Prof. Maria Rita Giuca,
Department of Surgical, Medical, Molecular and Critical Area Pathology,
Unit of Pediatric Dentistry,
University of Pisa, Pisa, Italy
e-mail: mariarita.giuca@unipi.it

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is caused by massive destruction of erythrocytes which occurs in the following medical conditions: haemolytic anemia associated with infections or diseases such as galactosemia or favism; ineffective erythropoiesis or splenic hyperfunctionality.

Even drug-induced liver diseases can lead to hepatocellular or colestatic jaundice because of a liver failure and children can also be affected by this condition, often linked to the use of paracetamol (7).

Neonatal hyperbilirubinemia

Neonatal hyperbilirubinemia occurs in 60% of newborns during the first week and this medical condition is called neonatal jaundice. This appears to be a physiological condition linked both to the increased synthesis of indirect bilirubin and to the still ineffective activity of the liver enzymes destined for its metabolism. Indeed, at the time of birth, the onset of lung function and the increased availability of oxygen lead the spleen to dispose of many aged and superfluous erythrocytes, producing large quantities of unconjugated bilirubin. One of the main risk factors for neonatal jaundice is premature birth. This condition is physiological if it occurs from the second day of life and lasts for a maximum of two weeks. It is considered pathological jaundice if it appears in the first 24 hours of life and persists for more than two weeks, associated with comorbidities. Unconjugated hyperbilirubinemia can be associated with neonatal anemias, intoxications or infections in cases of jaundice due to increased hemolysis or associated with metabolic diseases and hypothyroidism in icteric forms due to reduced hepatic conjugation of bilirubin. The most common cause of haemolytic neonatal jaundice is maternal-fetal AB0 or Rh incompatibility. So, all the possible causes of hyperbilirubinemia listed so far must be taken into consideration in the case in which a patient with greenish pigmentation of the deciduous (or more rarely permanent) dentition comes to the dentist.

Green pigmentation of teeth due to hyperbilirubinemia

There is no estimate, but the prevalence of green teeth is low and some findings suggested a lack of gender susceptibility (8-15). From the knowledge emerged from the literature it appears that the primary dentition is most frequently affected and that when the permanent dentition is affected, all patients are found to have had a history of biliary atresia. The explanation for this is that the degree and localization of tooth staining is linked to the severity and duration of hyperbilirubinemia in correlation with dental maturation. Knowledge of the chronologic development of teeth is essential, in conjunction with the history of total bilirubin levels, to predict the degree and pattern of greenish pigmentation that will be found in the dentition.

Further oral manifestations of hepatobiliary pathologies

Hepatobiliary diseases can also affect the oral cavity in other ways. Up-to-date publications suggest that children with liver failure are more prone to oral mucosa lesions than generally healthy children, which might result from hypoproteinaemia, coagulopathy, malnutrition or immunodeficiencies (16-17). In previous studies the prevalence of angular cheilitis, strawberry lip with erosions and geographic or smooth tongue, petechiae and yellow discolouration was statistically significant in children with liver diseases. Patients with severe liver diseases (class B/C according to the Child-Plug scale) are more frequently prone to oral candidiasis and this is also indicated by the bacterial and fungal dysbiosis typical of cirrhotic patients who ,due to the overuse of antibiotics and immunosuppressants, are subject to frequent infections and characterized by an unfavourable gut microbiome, with a lower autochthnous bacterial taxa and a low fungal diversity.

Some dental defects, such as opacities and hypoplasia, have also been associated with hepatic pathology and this is presumably due to the state of malnutrition typical of these patients. Indeed, when bile passage to the intestine is decreased or completely blocked, malabsorption of fat-soluble vitamins A, D and K occurs. Bleeding due to inadequate vitamin K absorption and inadequate synthesis of clotting factors is common as are rachitic changes in bone and mineralized dental tissues due to inadequate vitamin D.

DISCUSSION

Tooth discoloration may manifest as different

colours, with green pigmentation being uncommon. Its etiology is classified into extrinsic and intrinsic causative factors. The known extrinsic causes include chromogenic bacteria, systemic antibiotics (e.g., minocycline), copper salts contained in mouth rinse, and copper and nickel metal ions (19-23). Intrinsic causes include hyperbilirubinemia and drugs such as minocycline and ciprofloxacin. There are various phenotypes of tooth pigmentation by bilirubin, ranging from a mild yellow to a darker green shade. Green is the most frequently reported, followed by brown, yellow, and gray. The degree of pigmentation is known to be proportional to the serum bilirubin level but there is no direct correlation between the degree of green discoloration and the duration of hyperbilirubinemia. It is considered that the degree and location of pigmentation is determined by the timing of hyperbilirubinemia so that the crown portion with a normal hue developed when the bilirubin level is normal and the green portion of the teeth formed during the hyperbilirubinemia period, are always clearly distinguished by lines, as it can be seen in Fig. 1.

Occasionally, green teeth are also affected by enamel hypoplasia, which could be due to the effects of osteopenia and other disturbances of calcium and phosphate metabolism encountered in chronic liver disease or due to intubation in neonatal periods, so that this clinical aspect could be not directly linked to the liver disease but related to a life-saving maneuver that may be necessary especially in premature babies (24-29).

In regard to the pigment responsible for greenish pigmentation of teeth, Shibata's study demonstrated by spectrophometric analysis the presence of bilirubin in artificially pigmented teeth of some rats, and this has undermined the hypothesis according to which the colour of green staining was due to biliverdin, an oxidation product of bilirubin. Furthermore, the histological analysis of murin pigmented teeth showed the presence of a green stripe in the dentine running parallel to the incremental line. These observations were subsequently validated also by a histological study carried out on human teeth extracted from patients with severe liver dysfunction and hyperbilirubinemia. Also, in human teeth pigmented stripes running parallel to the dentinal

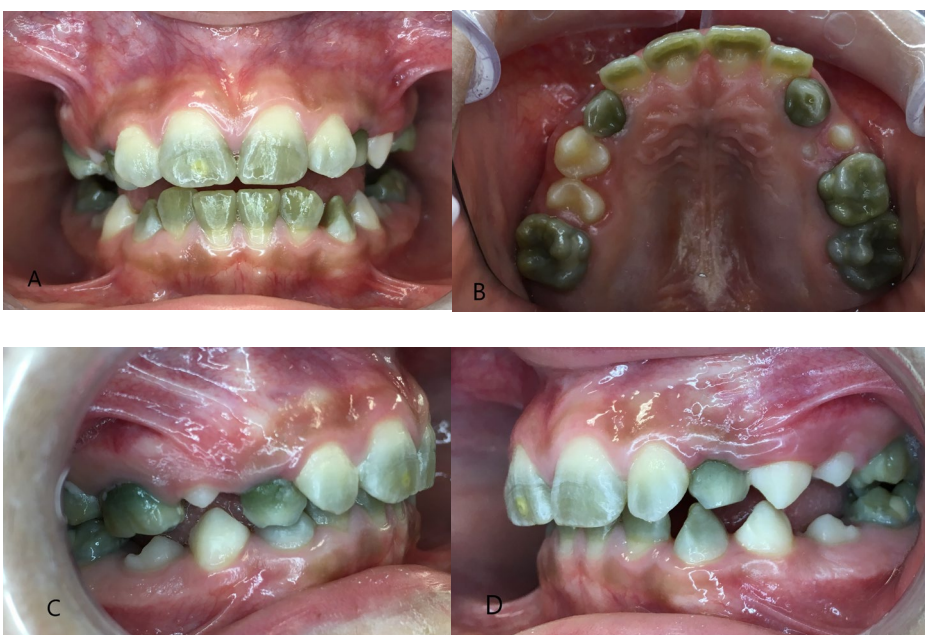

Fig. 1. *Green pigmentation of deciduous and permanent teeth in a 11 years old male child diagnosed with an intrahepatic cholestasis: most of the permanent teeth were characterized by a green pigmentation and also the attached gingiva of deciduos teeth showed yellow-greenish pigmentation. Liver transplant was performed after 2 years from birth therefore teeth showed white (mineralisation >2 years old) and green (mineralisation <2 years old) enamel colour changes (18).* ***A****: front view;* ***B****: upper arch in occlusal view;* ***C****: view of the first and fourth quadrants;* ***D****: view of the second and third quadrants.*

incremental lines were observed histologically, and the correlation between childhood hyperbilirubinemia and changes in dentin morphology seems to include even a decrease in the density of the dentin tubules and a reduction in the thickness of peritubular dentin in green teeth (30-33).

There are a lot of causes of green teeth reported in Literature and we have summarized the main causes of pathological hyperbilirubinemia in Table I. However, the most common cause appears to be biliary atresia that is the result of progressive bile duct destruction from an inflammatory disease of unknown cause. It is related to the persistence or lack of remodeling of the embryonic ductal plate and consists of both intrahepatic and extrahepatic biliary atresia. The damage causes obstruction of bile flow and if left untreated, this can result in cirrhosis and hepatic failure. This is the reason why the primary diagnosis for liver transplant was mainly biliary atresia (57.5%) followed by other causes of cholestasis (22.5%) (34-41).

In Literature it is reported that children with liver disease are at high risk of developing dental caries, possibly due to the need of continuous feeding to compensate for the low intestinal absorption of nutrients or due to an inadequate

Table I. *Schematization of the various pathologies causing hyperbilirubinemia.*

Pathologic hyperbilirubinemia
1) increased bilirubin load -hemolytic a. immune mediated (e.g. rh factor incompatibility; AB0 incompatibility) b. RBC enzyme defects (e.g. G6PD deficiency; pyruvate kinase deficiency) c. RBC membrane defects (e.g. spherocytosis; elliptocytosis) d. d. Hemoglobinopathies (e.g. thalassemia; sickle cell disease)
2) increased bilirubin load-non hemolytic a. extravascular blood (e.g. hematomas) b. polycythemia (e.g. delayed cord clamping; transfusion; increased intrauterine erythropoiesis caused by placental insufficiency or intrauterine hypoxia) c. exaggerated enterohepatic circulation (e.g. breast milk jaundice; cystic fibrosis)
3) impaired bilirubin conjugation a. physiologic hyperbilirubinemia b. Crigler-Najjar syndrome c. Gilbert syndrome d. congenital hypothyroidism e. breastfeeding jaundice f. breast milk jaundice (in the second week of life)
4) impaired bilirubin excretion a. biliary obstruction (e.g. genetic biliary atresia; Alagylle syndrome; drug-induced liver disease) b. infection (e.g. cytomegalovirus; reovirus type 3) c. chromosomal abnormalities (e.g. Turner's syndrome; trisomy 18; trisomy 21) d. metabolic disorders

absorption of macronutrients and micronutrients indispensable for dental development. As regards the differential diagnosis, the anamnesis is of fundamental importance for the clinician because teeth pigmentation could be caused even by chromogenic bacteria, medicaments, dentinogenesis imperfecta, amelogenesis imperfecta, tetraciclyne or congenital erythropoietic porphyria. The anamnesis reported by the parents is therefore a fundamental therapeutic moment for the management of the clinical case, when clinicians have to treat a patient with liver disease: it is important to plan the prevention of carious pathology with regular visits that allow the early identification of any oral problem caused by liver diseases, as well as aesthetically improve the appearance of damaged teeth (42-52).

It is important to underline that green dentin pigmentation is clearly visible through translucent enamel and can cause great anxiety for the families involved and significant peer problems for children. The pigmentation is not easily disguised with restorative materials, however, cosmetic improvements to these teeth may increase the chances of normal physical, psychological, and social development of the patient. In order to plan for the most appropriate treatment, it is important for clinicians to understand that the pigmentation is confined to dentin and dental bleaching is unlikely to be effective even if some authors suggested a bleaching technique with the use of transillumination with ultraviolet light to accelerate the breakdown and dissipation of bilirubin products (, 53-65).

Direct composite veneers could be placed but indirect veneers provide a more uniform opaque layer to disguise the green pigmentation. Porcelain or Belleglass could be used to mask the underlying pigmentation and the latter are recommended for a temporary restoration in children because Belleglass veneers don't require any tooth preparation prior to bonding, have a wear resistance comparable to that of human enamel and are less abrasive on the opposing natural dentition (66-72).

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