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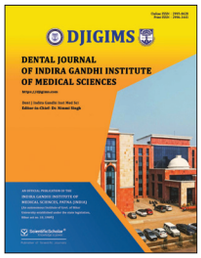

Review Article

Congenital Hematological and Metabolic Disorders Causing Intrinsic Discoloration of Pediatric Dentition at Pre-Eruptive Stage

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ABSTRACT

The current review assesses the literature and depicts the hematological and metabolic diseases of newborns resulting in intrinsic stains of primary dentition. The appearance of dentition is an esthetic concern to the child as well as to the caregivers. The correct diagnosis claims prime importance to the dentist as it has profound value in deciding the appropriate treatment protocol and describing it to the patient. The review describes the hematological and metabolic diseases of newborns which can affect the color of normal pediatric dentition. Erythroblastosis fetalis, icterus gravis neonatorum, congenital erythropoietic porphyria, thalassemia, sickle cell anemia, and alkaptonuria are found to have a definite impact on the intrinsic discoloration of deciduous teeth. The article is an overview of those congenital hematological and metabolic disorders and their direct and indirect effects on primary dentition at the pre-eruptive stage resulting in discoloration.

Keywords: Erythroblastosis fetalis (EBF), Icterus gravis neonatorum (IGN), Congenital erythropoietic porphyria (CEP), Thalassemia, Sickle cell anemia (SCA), Alkaptonuria, Benzoquinoneacetate (BQA)

INTRODUCTION

Understanding the etiological factors of staining and discoloration of deciduous dentition is necessary for patient education as well as framing proper treatment approaches. Increasing population knowledge about the discoloration etiology, especially the systemic diseases that influence the staining of primary teeth, enhances maternal and pediatric care and improves the quality of life of the child.[1] Color is a combination of the psychophysiological response to the physical interaction of light energy with an object and the subjective experience of an individual observer. Discoloration is defined as a variation from a normal accepted color. The surface of the primary tooth can be divided into three halves, namely, incisal, middle, and cervical third. Moving from incisal third towards cervical third discoloration is more intense in an individual tooth.[2] There are two types of staining observed in primary tooth; intrinsic and extrinsic stains. The normal color of the tooth is governed by blue, pink, and green tints of enamel, which is reinforced by yellow to brown shades of underlying dentine. Extrinsic lies outside the external tooth surface or is incorporated in the acquired pellicle. Internalized discoloration is the incorporation of metabolites or blood-borne stains into the tooth bud in the developmental stage.[3] The causes of intrinsic staining in pediatric dentition are due to developmental defects like amelogenesis and dentinogenesis imperfecta; drugs and minerals like tetracycline, iron, and fluorides, trauma, or due to some hematological or metabolic causes. Tooth color varies based on the color of internal deposits incorporated in the enamel, dentinal, or pulpal tissue.[4]

CONGENITAL HYPERBILIRUBINEMIA – YELLOW AND GREEN TEETH

Erythroblastosis fetalis (EBF) is a type of hemolytic anemia of the fetus or newborn infant caused by the transplacental transmission of a maternally generated antibody. Usually, it is secondary to the incompatibility between the blood groups of mother and her offspring characterized by upregulation of the number of nucleated red blood cells in the peripheral bloodstream, resulting in hyperbilirubinemia and extramedullary hematopoiesis (icterus gravis neonatorum). It is the lysis of fetal erythrocytes resulting from incompatibility between sensitized maternal and fetal blood cells. The sensitization antigens are most commonly Rhesus (Rh) factor, AB0, and Kell system. This happens in the first week of life affecting approximately 70% of term babies and almost all premature babies. Bilirubin is the end product of heme resulting from hemocaterese.[5] When the liver fails to eliminate bilirubin produced by the body, it is deposited in certain organs like skin, sclera, ameloblasts, kidney, etc. Clinical neonatal jaundice is usually detected with 5–7 mg/dl bilirubin level. Unmonitored bilirubin may lead to acute bilirubin encephalopathy (Kernicterus) which causes neurological impairments. Unconjugated hyperbilirubinemia is also associated with other syndromes, namely, Crigler–Najjar syndrome, Gilbert's syndrome which is related to hemolysis and also affects the primary teeth.[6,7]

It is proposed that hyperbilirubinemia may lead to intrinsic yellow staining due to overproduction of bilirubin and biliverdin which also interferes with the process of amelogenesis and tooth matrix formation. The blood vessels of dental papilla are the nutritional source of the ameloblasts which are the precursors of enamel. So, in hyperbilirubinemia, feeding vessels are the source of deposition of bilirubin in ameloblasts which are further oxidized to biliverdin, which is a green pigment. This may lead to hypocalcified, opaque, and stained hypoplastic enamel.[7,8] The maturation stage of primary teeth is dependent on the albumin and globulin ratio, which indirectly suggests that the increment of unconjugated bilirubin is supposed to be a predominant factor in hampering ameloblasts.

Deciduous tooth calcification begins at the fourth month of intrauterine life and is completed at birth. The crowns of deciduous incisors are completed within one month after birth, canines and molars six months after birth. Formation of enamel takes place in two phases; first, ameloblasts secretes an organic protein matrix, which contains 25% of hydroxyapatite crystals (secretory phase), and at the maturation stage the protein matrix is resorbed and embedding of the thickness of hydroxyapatite crystals takes place until the inorganic mineral content of enamel reaches up to 96%.[9,10] The typical appearance of the affected tooth varies from yellow to greenish yellow staining with a hypoplastic look generally involving the cervical and mid portion of central and lateral incisors, cusp tips of cuspids, occlusal and cervical area of the deciduous first molar, and cusp tips of the deciduous second molar. The affected teeth are usually called "green teeth." The teeth are histochemically positive to bilirubin up to the second year of life of the child.[11]

THALASSEMIA AND BROWN TEETH

Thalassemia stands for a group of inherited hemolytic anemic diseases that involve defects in the synthesis of hemoglobin (Hb) alpha- or beta-polypeptide chains, called as alpha and beta thalassemia. In India, the prevalence of β-thalassemia is 3% to 4% with an estimate of around 8,000–10,000 new births with this major disease each year.[12] Reduction in the synthesis of one of the two globin polypeptides results in decreased Hb production that leads to hypochromic microcytic anemia along with erythrocyte dysplasia and destruction. Thalassemia encompasses different subtypes with diverse clinical characteristics. Beta-thalassemias are generally classified into thalassemia major (TM), thalassemia intermedia, and thalassemia minor. According to genetic heterogeneity and clinical and hematologic variability, thalassemia is further classified as homozygous, heterozygous, or compound heterozygous. Homozygous beta-thalassemia (also known as TM, Cooley anemia, or Mediterranean anemia) is manifested with the most severe signs and symptoms.[13,14] Anemia stimulates the bone marrow to produce erythropoiesis by erythropoietin activation to maintain adequate oxygenation; however, erythrocyte production is abnormal, which is called "ineffective erythropoiesis" causing hypertrophy and expansion of the erythroid marrow cavity, impaired growth of bones, and increased bone resorption. As a result, osteopenia or osteoporosis, decreased calcification, and increased osteoclastic activity are common findings.[15] Expansion of bone marrow causes mechanical irritation, cortical thickening, and fragility of bone. Ineffective erythropoiesis leads to iron overproduction in cells which is called hemosiderosis. Iron overload which is known as hemochromatosis may be due to chronic hemolysis of erythrocytes, regular blood transfusions, and increased iron absorption in response to the anemic state. Clinical manifestations are relevant to iron overload and deposition in organs and endocrine glands. Due to chronic jaundice associated with thalassemia, incorporation of bilirubin and iron deposition in the dentinal tubules during the maturation phase results in brownish-yellow or sometimes grayish discoloration of teeth. The enamel and dentine are the best indicators of iron deposition. Moreover, pediatric patients and patients of adult dentition of beta thalassemia major contain five times more iron concentration

than normal individual dentition. Most of the patients lack the sparkle of milk teeth. Short crowns and roots with mucosal pallor, pale colored gums are other clinical features of the thalassemic patient.[15, 16]

CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP) AND ERYTHRODONTIA (RED TEETH)

Porphyria is a rare congenital metabolic disease presented with declined activities of enzymes of the heme pathway, leading to unwanted deposition of metabolites in tissues. Congenital erythropoietic porphyria (CEP) is a severe autosomal recessive form of the disease characterized by an acute deficiency of synthesis of Uroporphyrinogen 3, which is one of the key enzymes of heme biosynthesis.[17] Accumulation of porphyrins leads to visceral symptoms of hemolysis, hypo-/hyperpigmented areas, hypertrichosis, scarring, bullae, and vesicles on the sun-exposed areas of skin and erythrodontia. The most reliable diagnosis of CEP is red-colored urine, which is the consistent sign in early infancy.[18] Skin blisters after sun exposure, bullae, and vesicles along with reddish urine suggest the incidence of CEP. The most striking feature of CEP is reddish brown discoloration of primary dentition due to porphyrin deposition in the tooth buds. The discoloration is most intense in the cervical region which gradually fades towards the incisal and occlusal area. The affected teeth exhibits red fluorescence under ultraviolet light.[19] The porphyrin accumulation in deciduous teeth is higher in dentin than enamel because of the high affinity of porphyrin toward calcium phosphate. In some instances, discoloration and inadvertent deposition of porphyrin can affect the maturation and calcification which may lead to hypoplastic tooth. Chromogenic materials usually appear first within enamel or dentin either during odontoclastoma or the post-eruption period. There is marked thinning of enamel which can be detected radiographically which in turn increases the risk of childhood caries in patients with CEP.[20] CEP is usually misdiagnosed as porphyria cutanea tarda (PCT) or erythropoietic protoporphyria (EPP) as cutaneous manifestations resemble to some extent. Although symptoms of EPP occur during infancy and early childhood like CEP, non blistering photosensitivity, persistent edema, and erythema give some clues about differential diagnosis. However, transfusion-dependent hemolytic anemia, hypersplenism, or erythrodontia never accompany EPP.[21]

SICKLE CELL ANEMIA AND YELLOW TEETH

Sickle cell anemia (SCA) is a genetic disorder caused by replacement of glutamic acid by valine in position 6 at the N-terminus of beta chain of globin.[22] This genetic alteration leads to HbS formation. Deoxygenation (hypoxia) results in shape alterations of erythrocytes predominantly containing Hb S, which changes to the sickle shape.[23] Hypoxia may lead to circulatory difficulties like vaso-occlusive conditions which minimizes the average lifespan of erythrocytes to 20 days. The sickled erythrocytes have a greater affinity to adhere to the endothelium of the blood vessels causing microvascular obstruction, which leads to limitation of the blood flow, resulting in hazardous situations like pain, hypoxia, and tissue necrosis.[24] Iatrogenic pulp necrosis and calcification is one of the most consistent signs of SCA. Pulp necrosis is thought to be originate from the vaso-occlusive incident of pulpal vessels which hampers the blood supply. The general appearance of teeth is opaque and yellowish. Gingiva and oral mucosa also exhibits pallor and altered yellowish appearance because of decreased hematocrit value or may be due to the existence of hemolytic anemia.[25, 26]

ALKAPTONURIA AND BLACK TEETH (OCHRONOSIS)

Alkaptonuria (AKU) is an autosomal recessive metabolic disorder where incomplete metabolism of phenylalanine and tyrosine promotes aggregation of homogentisic acid (HGA) in organs.[27] It is a hereditary disorder and results from the absence of homogentisate 1,2 dioxygenase (HGD), the enzyme that is predominantly produced by hepatocytes in the liver and within the kidney and is responsible for the breakdown of HGA.[28] AKU has three distinct clinical features, namely, homogentisic aciduria, ochronosis, and ochronotic osteoarthropathy. These clinical manifestations appear in different stages of life; however, the earliest sign is the passing of black urine which confirms the possibility of AKU.[29] The darkening of urine occurs because the HGA pigment oxidizes to Benzoquinone Acetate (BQA) which forms a melanin-like polymer, which slowly turns the urine black.[30,31] Ochronosis develops as BQA deposits in both intra- and extracellular connective tissue. The accumulation of BQA in pulpal connective tissue turns the tooth brownish black. Necrosis of pulp tissue is also observed in some incidences. Pulp vitality tests sometimes give false-negative results. AKU generally affects the permanent dentition; rarely pediatric patients suffering from AKU reported black teeth. Maximum manifestations of AKU are revealed in the third to fifth decade of life.[32]

CONCLUSION

From the foregoing discussion, the mechanisms of internal staining of deciduous dentition and relevant diseases are quite important to understand for a dental practitioner. The knowledge behind the staining of teeth is equally important to decide the treatment plan as well as the underlying disease as they claim special dental care. As intrinsic stains due to developmental or systemic diseases are unavoidable, a dentist

should explain the consequences to the parents at the pre-eruptive session of the child and should prepare for esthetic remedies to improve the quality of life of the child.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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