The Blue Man: Pediatric Diseases with Implications for Adulthood

Karuna Dewan[1], Charles MacDonald[2], and Courtney Shires[3]

[1]Affiliation not available
[2]University of Tennseess Health Science Center
[3]West Cancer Center

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Abstract

Blue discoloration of the skin and cartilage, or ochronosis, is a rare physical examination finding. Here are two cases of childhood onset ochronosis, one exogenous and one endogenous in etiology.

Introduction

Ochronosis is a rare condition caused by the accumulation of homogentisic acid in the connective tissues throughout the body. This accumulation results in the discoloration of tissues to a blue-yellow hue. This can be seen in the sclera of the eyes[1], nails[2], bones[3], skin[2-5], thyroid gland[6], substantia niagra[6], coronary arteries[6] and cardiac valves[6]. This discoloration makes for interesting physical examination findings. The associated differential diagnosis is quite narrow. Causes of ochronosis are either exogenous or endogenous. Those that are exogenous include chemical exposure or ingestion, whereas endogenous causes include inborn errors of metabolism.

Case Reports

Patient 1: A 29 year-old female with Meniere's disease presented with dizziness, hearing loss, nausea and vomiting. On physical examination her pinnae appeared dark blue (Figure 1A). She ultimately underwent endolymphatic sac decompression to treat Meniere's disease. Intraoperatively her temporal bone was noted to appear blue-black (Figure 1B). Upon further investigation the patient revealed that she had taken Minocycline for severe acne for 8 years.

Patient 2: A 44 year-old mentally disabled male presented for precipitous hearing loss. The patient's tympanic membranes (Figure 2A), sclera (Figure 2B), pinnae (Figure 2C), nail beds (Figure 2D), and gingiva (Figure 2E) were dark blue. Initially, thought to be hemotympanum, Computerized Tomography (CT) demonstrated clear middle ear spaces. Audiometric examination demonstrated left high-frequency sensorineural hearing loss and right moderate to profound mixed hearing loss. The patient's urine darkened when oxidized (Figure 2F).

Discussion

Multiple causes of pigmented bone and cartilage exist, including ochronisis, metabolic bone diseases, metal deposits, sequestrum, and metastatic disease. Ochronosis as described here, can be exogenous or endogenous.

Exogenous ochronosis results from prolonged exposure to certain chemicals. Patient 1 took Minocycline for severe acne for 8 years. Minocycline, a yellow-colored, semi-synthetic tetracycline antibiotic turns black when oxidized, causing disfiguring discoloration of the skin, lips, nails, oral mucous, ear cartilage, conjunctiva, teeth, bones, thyroid gland, and pigmentation of heart valves in a dose-dependent manner. The

incidence ranges between 3 and 15%[7]. Used for the treatment of a wide range of gram positive and negative infections, onchronisis is most often seen in patients receiving a dose of 100-200mg/day for as little as one year. Minocycline-induced hyperpigmentation can be severely disfiguring and is more likely to occur in certain populations of patients (eg: those with phemphigus, pemphigoid, atopic dermatitis, or cystic acne). Pigmentation is a commonly recognized adverse reaction associated with most of the drugs in the tetracycline family, affecting the skin, nails, teeth, oral mucosa, bone in the oral cavity, ocular structures, cartilage, thyroid, and other visceral structures. Minocycline-induced hyperpigmentation should be considered in the differential diagnosis of ochronosis. Other medications that may cause changes in skin pigmentation include anti-malarias, amiodarone, bleomycin and chlorpromazine[8]. Suwannarat et al. in 2004 published a case series of 5 patients who presented with findings consistent with ochronosis, including pigmentary changes of the ear and mild degenerative changes of the spine and large joints. These patients were clinically diagnosed as having alkaptonuria, but the diagnosis was withdrawn based on normal urine HGA levels. All 5 patients were women who had taken minocycline for dermatologic or rheumatologic disorders for extended periods[7].

Endogenous ochronosis results from alkaptonuria (AKU), an autosomal recessive mutation in the HGD gene resulting in a disorder of tyrosine metabolism due to deficiency of homogentisate 1,2 dioxygenase (HGD) activity. This causes an accumulation of homogentisic acid (HGA), ochronosis, and destruction of connective tissue resulting in joint disease. AKU, the working diagnosis for patient 2, is progressive, with dark urine, onchronsis of eyes and ears, and severe ochronotic arthropathy. It is diagnosed near birth with lifelong implications. Ocular pigmentation is especially prominent and appears in 70% of ACU patients. Referred to as the Osler sign, ochronotic pigment deposition becomes evident in the third decade of life. There is no literature to suggest that scleral pigment deposition is associated with any effects on visual function. If urine of an alkaptonuric patient is alkalinized or allowed to stand, the homogentisic acid metabolizes to a melanin-like substance, and the urine appears brown to black[9]. Aciduria causing darkly stained diapers in infancy is one method of diagnosis. Ochronotic pigment appears in cartilage, intervertebral disks, skin, and sclera[10]. Currently, no available treatment has been conclusively shown to prevent complications of alkaptonuria. Restriction of dietary protein in pediatric patients has been advocated, with the aim of reducing HGA excretion. Treatment is currently based on symptomatology.

The differential diagnosis for blue discoloration of the skin and cartilage is broad, these two patients presented with blue ears and sclera of two different pediatric onset etiologies. While they have different etiologies for their ochronosis both patients demonstrate the adulthood implications of conditions with childhood onset.

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Figure Legends:

Figure 1

A: Blue pinna, B: Blue discoloration of mastoid bone

Figure 2

A: Blue tympanic membrane, B: Blue discoloration of the sclera, C: Blue Pinna, D: Blue discoloration of nail beds, E: Blue discoloration of teeth, F: Urine before (left) and after (right) oxidation, much darker in color.

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