

Alkaptonuria: a disease with dark brown urine

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Alkaptonuria is a rare hereditary autosomal recessive metabolic disorder with the global average prevalence of 1:100000 to 1:250000 births. It is endemic in Slovakia (1:19000 births), Czech Republic, and the Dominican Republic.¹ Ochronosis is a disorder occurring during alkaptonuria and is caused by homogentisic acid accumulation in the connective tissue (skin, eye, ear, endocardium, etc.), manifesting as bluish/grey/black tissue discoloration and dark brown urine. It leads to organ damage. The discoloration is visible in superficially located structures with high content of connective tissue: earlobe, nose, eye cornea, cartilages, and tendons.²

There is no causal treatment of alkaptonuria. Restrict consumption of products containing tyrosine and phenylalanine and administration of high doses of vitamin C are proposed to slow symptom progression. However, complete elimination of phenylalanine from diet is impossible as it is an essential exogenous amino acid. Prophylaxis except genetic counseling is unavailable, while symptomatic treatment includes nonsteroidal anti-inflammatory drugs, physiotherapy, rehabilitation, and surgery.³

It has been proposed to treat alkaptonuria with medication used in tyrosinemia type 1, nitisinone, which inhibits the enzyme producing homogentisic acid. This treatment reduces homogentisic acid excretion by nearly 70%, but requires dietary restriction as its side effect is hypertyrosinemia. Long-term safety and efficacy of nitisinone treatment are unknown.⁴

A 62-year-old patient with a 30-year history of back pain, knee joint pain, as well as brain aneurysm surgery in 2003, was admitted to an orthopedic ward in 2013 for total knee joint replacement surgery. Left knee arthroscopy that was performed in 2011 showed lateral and medial meniscus damage as well as degenerative changes with cartilage necrosis of the medial femoral condyle. The patient was classified for total knee

replacement surgery due to intensified pain and difficulties in movement. After opening the left knee joint, a black-colored articular cartilage was revealed with multiple black crystals in the synovial membrane and articular capsule (FIGURE 1A). Past medical history was collected by a consultant in nephrology. The patient reported frequent hospitalizations due to abnormalities in the left ear canal and middle ear development, unilateral occurrence of black earwax and left hearing impairment, and black diaper syndrome until the age of 2 years. Bluish discoloration of the earlobes and sclera discoloration of both eyes were found (FIGURE 1B). A preliminary diagnosis of ochronosis was made. A urinalysis showed the blackening of specimen within 3 days of observation (FIGURE 1C). Supplied X-ray documentation demonstrated ochronotic spondylosis.

Blood samples for genetic testing were taken from the patient and his family members. Direct sequencing revealed that the patient carried a homozygous missense mutation in the *HGD* gene encoding homogentisate-1,2-dioxygenase (OMIM *607474). This known c.481G>A transition, located in the 8 exon of the *HGD* gene, leads to a glycine-to-arginine substitution at amino acid position 161 (p.Gly161Arg). The patient carried mutation characteristic for the Slovak population. The patient's 2 unaffected sons and 2 of 6 grandchildren were heterozygous carriers. None of the controls (384 chromosomes) presented with this nucleotide substitution. The PolyPhen-2 analysis (<http://genetics.bwh.harvard.edu/pph2/>) predicted that the p.Gly161Arg mutation is probably damaging to protein function with a score of 1.000. Ambulatory 24-hour urine collection was performed to explore homogentisic acid excretion (5.6 g/l; 5.88 g/d; normal <0.1 g/l). Clinical findings, genetic test results, and urine homogentisic acid concentration led to a diagnosis of alkaptonuria.

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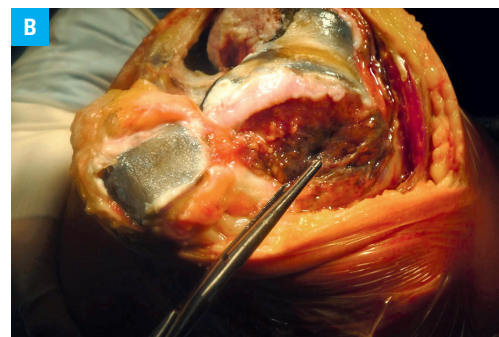
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FIGURE 1 A patient with alkaptonuria:

A – bluish earlobe discoloration; **B** – black-colored articular cartilage; **C** – dark discoloration of urine



When alkaptonuria is suspected, both medical history and physical examination are relevant. Patients usually seek medical assistance after they observe dark-colored urine. In some cases, the disease is identified when changes in the skeletal system occur. For patients who plan to have children and come from families or communities with high frequency of alkaptonuria, genetic counseling is recommended.

REFERENCES

- 1 Zatková A, de Bernabé DB, Poláková H, et al. High frequency of alkaptonuria in Slovakia: evidence for the appearance of multiple mutations in HGO involving different mutational hot spots. *Am J Hum Genet.* 2000; 5: 1333-1339.
- 2 Rizzo S, Basso C, Bottio T. A 61-year-old man with hyperpigmentation. *Ochronosis.* *Heart.* 2015; 101: 1412-1421.
- 3 Oláh AV, Llyés I, Szoke A, et al. Urinary homogentisic acid in alkaptonuric and healthy children. *Clin Chem Lab Med.* 2003; 41: 356-359.
- 4 Phomphutkul C, Introne WJ, Perry MB, et al. Natural history of alkaptonuria. *N Engl J Med.* 2002; 347: 2111-2121.