Rare Disease Reviews – Alkaptonuria

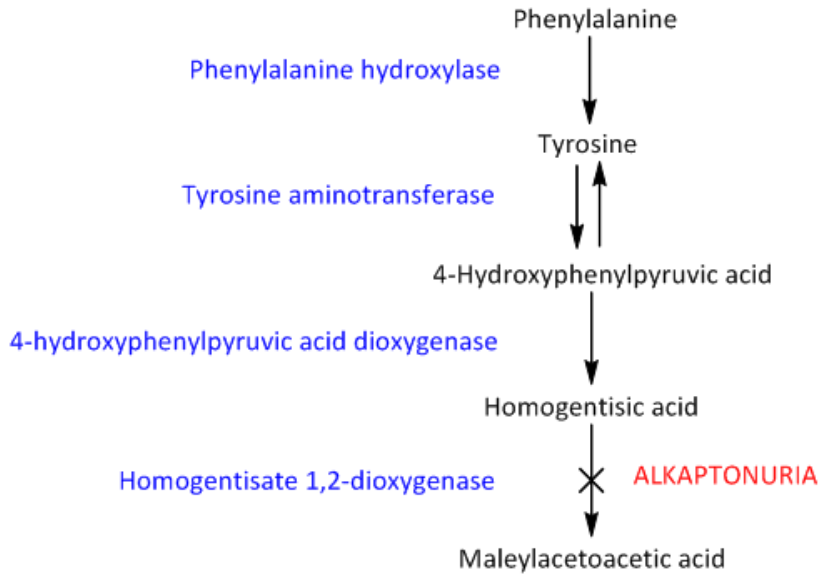
Alkaptonuria (AKU, Black Bone Disease or Black Urine Disease), was the first disease to be seen as following a pattern of inheritance. It was first described by Sir Archibald Garrod as an 'inborn error of metabolism' in 1901 in London.[1]

Alkaptonuria is an autosomal recessive genetic disease, meaning that patients have inherited two defective copies of a gene; one from each parent. The defects have been mapped to chromosome 3, between regions $3q_{21}$-q_{23}.[2] In humans, this is the site of the homogentisate 1,2-dioxygenase (HGD) enzyme, which play a key role in the metabolism of one of the twenty common amino acids, tyrosine. The HGD enzyme catalyses the conversion of homogentisic acid (HGA) into maleylacetoacetic acid (see Fig.1). Therefore, Alkaptonuria results in the accumulation of HGA at 2000 times the normal rate.

Homogentisic acid (HGA), is a systemic molecule that initially only accumulates in the blood. In childhood, this results in only one symptom: urine that turns black upon standing (hence the name black urine disease). This is due to the excretion of HGA, which oxidises to a black pigment when left to stand in air. Over time proportionally less HGA is excreted and so is deposited in cartilage and bone. Once deposited, HGA polymerises to benzoquinones and binds to the individual collagen fibres in cartilage in a characteristic pattern; resulting in a pigmentation known as ochronosis.[3] This change in structure makes cartilage more stiff, brittle and black (hence the name black bone disease). This presents in the patient as joint pain (usually first starting in the lower back) becoming progressively worse as the cartilage deteriorates and allows bone-on-bone contact.[4] At this stage Alkaptonuria is, now, seen to resemble a severe form of early-onset osteoarthritis. As joints degrade and collapse, the only current medical treatment is joint replacement surgery.

While the most severe and well-documented effects of Alkaptonuria is seen in the cartilage and bone, HGA can also accumulate elsewhere in the body, causing further complications. One of the more obvious signs of Alkaptonuria is the discolouration under the skin, particularly in the pinna of the ears. This is due to ochronosis of the auricular cartilage and giving it a black appearance. Some patients have reported hearing loss due to Alkaptonuria-associated damage to the small bones of the ear. Ochronotic pigmentation has been seen in the ligaments, tendons, blood vessels, kidneys, lungs and the prostate.[4-6] Black spots are known to appear in the whites of the eye.

Fig 1. Metabolic Pathway of Tyrosine Metabolism, showing enzymatic defect present in Alkaptonuria.



Symptoms

During childhood, there are no symptoms of AKU other than the urine turning black when left to stand for a few minutes. Typically, the pain associated with AKU starts around the second decade of life. Joint pain typically starts in the weight-bearing joints, especially the lower back, hips and knees.[4-7] By the fifth decade of life, many patients will have had at least one joint replaced through surgery.

Other symptoms would include the darkening of skin, especially at the ears, to a blue/black colour. Black spots will appear in the whites of the eyes. Pigmentations have been seen in ligaments, tendons, blood vessels, kidneys, lungs and the prostate. These commonly present as kidney stones, prostate stones, muscle tears and cardiovascular problems. CVD complications are usually due to a hardening on the blood vessels due to ochrosis and may require surgery.[8] Ochronosis has also been documented in the larynx and trachea[9] which may lead to a change in the sound of the voice.

Diagnosis

Diagnosis typically either happens in early childhood or much later in life. In early childhood, diagnosis is suspected due to the urine turning black when exposed to air. Diagnosis later in life is usually first suspected due to back pain and joint pain. In both cases, the diagnosis is confirmed through urine tests, examined by chromatography-mass spectrometry analysis.[10] A positive diagnosis is seen when the results show elevated levels of homogentisic acid, usually between 1 and 8 grams.[4]

Treatment

There is no cure for AKU. The biggest hope for a future treatment of Alkaptonuria lies with a drug, Nitisinone (NTBC). This blocks the HGD enzyme, thereby blocking production of HGA.[(11)] It should provide an effective treatment.[(12)] However it is going through clinical studies, with further clinical trials planned. Patients on the drug report an improvement in their condition, but at the moment, it is not licensed for use in Alkaptonuria. The AKU Society estimates 1% of the AKU population are taking the drug off-label.

Currently, the only treatment offered to patients is palliative; pain management until joints collapse, and then joint replacement surgery. As a patient organisation, the AKU Society has gathered several recommendations to delay damage to joints:

1. Since Alkaptonuria damages cartilage, it is important to avoid sports and exercises that put too much strain on joints. Instead, the society advises patients to do more gentle exercises, such as swimming, yoga, pilates or cycling. Avoid contact sports such as football and martial arts.
2. The AKU Society does not recommend a low protein diet that restricts diet severely. However, it is best to avoid eating too much red meat, instead replace it with white meats, such as chicken.
3. The AKU Society does not recommend increasing ascorbic acid intake with vitamin C dietary supplements. There is no evidence that they work in Alkaptonuria and since ascorbic acid increases synthesis of tyrosine, may actually contribute to the formation of HGA.

Frequency

In the UK and USA, the frequency of Alkaptonuria is roughly 1 in 500,000.[(4)] However it seems to be much more common in certain other countries, notably in Slovakia[(13)], the Dominican Republic[(14)], and the Middle East[(15)] where frequency is closer to 25 in 500,000. The reason for this seems to be that intermarriage is more common. Recent work from Jordan, for example, identified nine cases of Alkaptonuria within one family.[(15)] Marrying within your own family increases the risk of children inheriting genetic diseases so, if possible, it is best avoided.

Historical information

The disease was first described in 1901 in London by Sir Archibald Garrod.[(1)] The first known patient with Alkaptonuria is an Egyptian Mummy dated from circa 1500BC.[(16)] Previous reviews of the history of Alkaptonuria[(7)] have shown cases throughout history, beginning in 1584 with the examination of a young boy whose urine turned black when exposed to air.

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References

(1) Garrod, AE. The incidence of alkaptonuria: a study in chemical individuality. Mol Med. 1996 May;2(3):274-82

(2) Fernandez-Canon, JM et al. The molecular basis of alkaptonuria. Nat Genet. 1996 Sep;14(1):19-24

(3) Taylor, AM et al. Ultrastructural examination of tissue in a patient with alkaptonuric arthropathy reveals a distinct pattern of binding of ochronotic pigment. Rheumatology. 2010 Jul;49(7):1412-4

(4) Phornphutkal, C et al. Natural history of alkaptonuria. N Engl J Med. 2002 Dec 26;347(26):2111-21

(5) Helliwell, TR et al. Alkaptonuria – a review of surgical and autopsy pathology. Histopathology. 2008 Nov;53(5):503-12

(6) Schumacher HR et al. Ochronotic arthropathy. 1. Clinicopathologic studies. Semin Arthritis Rheum. 1977 Feb;6(3):207-46

(7) O'Brien WM et al. Biochemical, pathologic and clinical aspects of alcaptonuria, ochronosis and ochronotic arthropathy: review of world literature (1584-1962) Am J Med. 1963;34;813-838

(8) Kragel, AH et al. Cardivascular findings in alkaptonuric ochronosis. Am Heart J. 1990 Dec;120(6 Pt1):1460-3

(9) McClure J et al. Calcium pyrophosphate dehydrate (CPPD) deposition in ochronotic arthropathy. J Clin Pathol. 1983 Aug;36(8):894-902

(10) Introne WJ et al. Alkaptonuria. In: GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2003 May 9 [updated 2009 Jul 2]

(11) Hall, MG et al. Pharmacokinetics and pharmacodynamics of NTBC (2-(2-nitro-fluoromethylbenzoyl)-1,3-cyclohexanedione) and mesotrione, inhibitors of 4-hydroxyphenyl pyruvate dioxygenase (HPPD) following a single dose to healthy male volunteers. Br J Clin Pharmacol. 2001 Aug;52(2):169-77

(12) Suwannarat, P et al. Use of Nitisinone in patients with Alkaptonuria. Metabolism. 2005 Jun;54(6):719-28

(13) Zatkova, A 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 Nov;67(5):1333-9

(14) Milch, RA. Studies of Alcaptonuria: Inheritance of 47 cases in eight highly inter-related Dominican kindreds. Am J Hum Genet. 1960 Mar;12(1):76-85

(15) Al-Sbou, M et al. Nine cases of Alkaptonuria in one family in southern Jordan. Rheumatol Int. 2010 Dec 3 [Epub ahead of print]

(16) Stenn, FF et al. Biochemical identification of homogentisic acid pigment in an ochronotic Egyptian mummy. Science. 1977 Aug 5;197(4903):566-8