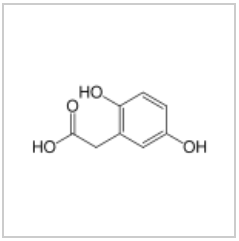
Alkaptonuria

Overview

Alkaptonuria is an inborn error of metabolism that presents most notably with the occurrence of black urine when the urine is exposed to air for a certain period of time. For this reason, it is also called the “black urine” disease. It is an autosomal recessive disorder and is therefore inherited genetically. Alkaptonuria is very rare, with a presentation of about 1:250,000. The causality behind Alkaptonuria is a deficiency in **homogentisic acid 1,2 dioxygenase**, an enzyme that is found in the liver and plays a key role in the catabolism of amino acids such as *phenylalanine* and *tyrosine*. Due to the lack of homogentisic acid 1,2 dioxygenase, the affected individual will experience a build-up of homogentisic acid in the body, namely in fibrous and cartilaginous tissue. Homogentisic acid is part of the catabolic chain from phenylalanine and tyrosine to fumarate and acetoacetic acid. Alkaptonuria received its title from the early name for homogentisic acid, *alkapton*.



Structure of Homogentisic Acid

Genetics

Alkaptonuria is an autosomal recessive disorder that is genetically inherited in a Mendelian fashion within a family. It arises when individuals inherit two defective HGD genes from their parents. The gene HGD is located on the long arm of chromosome 3 and encodes homogentisic acid 1,2 dioxygenase. Although it is first and foremost a genetically linked condition, Alkaptonuria has also been observed in a patient who, following a liver transplant, began to show symptoms of the disease. This confirmed that the location of homogentisic acid production is, in fact, the liver.

Signs and Diagnostics

The alternate name for Alkaptonuria is the “black urine” disease, which is informative in the nature of the presentation of this disease. When exposed to air, the urine of the affected will turn a dark brown-black color. In newborns, the urine discoloration can be observed by the parents and is an immediate cause for concern. Fresh urine, however, does not undergo immediate discoloration so this telling symptom can sometimes go unnoticed. Additional symptoms often occur later in life and include ochronosis of the sclerae (Osler’s sign), skin pigmentation which presents earliest in regions of high cartilaginous content such as the ear, and arthropathy due to ochronotic accumulation. These symptoms often arise in the third or fourth decades of life. Diagnosis can be carried out by measurement of homogentisic acid levels in the urine, where it would not be found in the case of a healthy individual.

Treatment

Treatment of Alkaptonuria is similar to that of metabolic disorders of a similar nature, which means that treatment should be primarily diet based. Additional introduction of Vitamin C into the diet can prove to be beneficial due to the antioxidant nature of ascorbic acid. Nitisinone (an inhibitor of an enzyme that mediates homogentisic acid formation) can prove to be beneficial. However, its effects over prolonged use have not been well studied. As with other inborn errors of metabolism of a similar nature, the most effective method of treatment is a limit in the intake of phenylalanine and tyrosine in the diet.

History

Alkaptonuria was one of four inborn metabolic disorders described by Sir Archibald Edward Garrod in his 1908 book titled *Inborn Errors of Metabolism*. In his writing, Garrod recounted an early case described in 1649 that revolved around a young boy who passed black urine. In this case, techniques of medical intervention of the time did nothing to alleviate the symptom. However, the young man lived a healthy life save for the fact that he lived it while continuing to pass black urine. Garrod’s interest in the biochemistry of the disease led him to deduce that it was the inability of the patient to break down the phenyl ring of homogentisic acid that caused the dark urine symptom. Despite his major interest in the biochemical nature of the disease, Garrod correctly evaluated that the

disease showed a pattern of genetic linkage and followed rules of basic Mendelian inheritance. Garrod's correct assumption that it was an enzymatic defect in a metabolic pathway that caused the inability of the affected to properly digest amino acids containing phenyl rings led to many further studies and revelations as to the full nature of genetically caused errors of metabolism.

Links

- Disorders of aromatic and branched chain amino acid metabolism

References

1. VERMA, Shyam. Early detection of alkaptonuria. *Indian J Dermatol Venereol Leprol* [online]. 2005, y. 2005, vol. 71, no. 3, p. 189-191, Available from <http://www.ijdvl.com/article.asp?issn=0378-6323;year=2005;volume=71;issue=3;spage=189;epage=191;aulast=Verma>.

2. HARTL, Daniel L – RUVOLO, Maryellen. *Genetics : Analysis of Genes and Genomes.* 8. edition. Burlington, MA : Jones & Bartlett Learning, 2012. ISBN 978-1-4496-3596-1.

3. KOBAK, AC – ODER, G – ARGIN, M. Orchronotic arthropathy: disappearance of alkaptonuria and liver transplant for hepatitis B related cirrhosis. *Journal of Clinical Rheumatology.* 2005, y. 2005, vol. 11, no. 6, p. 323-5, PMID: 16371803 (http://www.ncbi.nlm.nih.gov/pubmed/16371803).DOI: 10.1097/01.rhu.0000191157.25894.55 (http://dx.doi.org/10.1097%2F01.rhu.0000191157.25894.55).

4. ROTH, Karl – BUEHLER, Bruce. *Alkaptonuria Treatment and Management* [online]. The last revision 19 Aug. 2011, [cit. 2012-12-05]. <http://emedicine.medscape.com/article/941530-treatment>.