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A Review on Alkaptonuria a Rare Genetic Disorder

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ABSTRACT: The deficiency of the enzyme homo gentisate dioxygenase causes excessive accumulation of homogentisic acid in bodily fluids, which causes alkaptonuria (AKU). This leads to a variety of clinical symptoms, primarily from the conversion of HGA to ochronosis, a polymeric pigment that resembles melanin. One possible remedy is a medication called nitisinone, which reduces the production of HGA. But in order to successfully show that it is helpful in changing the natural history of AKU, a useful quantitative evaluation method is needed. Two possible instruments for measuring the disease burden in AKU have been discussed. The clinical aspects of 15 AKU patients, including clinical evaluations, investigations, and questionnaires, are scored using one instrument. A scoring method that just incorporates items derived from questionnaires is described in the second tool. Patients with Alkaptonuria (AKU), an extremely rare autosomal recessive genetic disorder, can benefit from the multifunctional digital platform ApreciseKUre, which makes data gathering, integration, and analysis easier. To establish a Precision Medicine Ecosystem (PME), it comprises genetic, biochemical, histopathological, clinical, therapeutic, and quality of life scores that doctors and registered researchers can exchange. Combining machine learning with ApreciseKUre data analysis and reinterpretation demonstrates the potential immediate benefits of patient classification and the ensuing customization of care and therapies for a particular patient subgroup. We have created a tool in this study that can examine the best course of action for AKU patients based on their quality-of-life scores, which show alterations in their health.

KEY WORDS:

HGA- Homo gentisate dioxygenase

AKU- Alkaptonuria

Ochrosonis- Bluish black discoloration of certain tissues, such as the ear cartilage.

I. INTRODUCTION

Alkaptonuria is one of a rare autosomal recessive genetic condition caused by homo gentisate 1,2dioxygenase (HGD). The liver, kidney, prostate, small intestine, and colon all express the HGD gene [1]. It is termed as an "Inborn error of metabolism" by sir Archbald Garrod [2], which is frequently regarded as an autosomal recessive condition [3], with an estimated prevalence ranging from 1:250,000 live births in the USA, to 1:19,000 in Slovakia [4]. The term refers to the bluish or grayish pigmentation of skin and eyes occurs in this condition. The brownish grey sclera, dark skin, kidney stones are the most frequent clinical presentations.

As of right now, AKU has no recognized treatment. Nonetheless, studies on the mechanism of disease progression have shown that there is HGA pigment deposition in structurally undamaged cartilage. The study found that ochrotonic osteoarthopathy and joint failure seem to develop after localized changes in the calcified cartilage and subchondral bone, which are vulnerable to injury after focal alterations. This has raised the possibility of a significant overlap between the pathophysiology of ochrotonic osteoarthopathy and OA, expanding the possible research directions [5].

Due to continuous HGA accumulation, the severity of the disease varies from patient to patient and even within siblings. It also gets worse with age. While life expectancy is typically not reduced in AKU, quality of life is significantly impacted, primarily because of the excruciating degeneration of the joints as a result of ochrotonis changing their mechanical characteristics [9].

II. HISTORY OF AKU

Ancient AKU (OMIM 203500) has been reported in multiple accounts of possible ochronosis and spondyloarthropathy in Egyptian mummies, such as Harwa (c.1500 BC; currently on display at the field museum, Chicago) [7]. The first documented instance of a person passing dark urine dates back to Scribonius (1584), who described a schoolboy’s pee as “as dark as ink”. A Carmelite monk was the subject of a similar event, which was recounted by Schenck (1609) 25 years later. Over the next 200 years, reports of similar incidents were made [8].

The term alkaptonuria is derived from the Arabic word “alkali” and the Greek word meaning “to stuck up oxygen greedily in alkali” [9]. Boedeker originally coined the term “alkaptonuria” in 1859[10] after analyzing the urine of a 44year old man who had severe backpain and limited movement.

The oldest known account of someone passing dark pee was given by Scribonius in 1584, when a schoolboy passed urine that was "as dark as ink." A Carmelite monk exhibited a similar phenomenon, which Schenck (1609) documented 25 years later. The following 200 years saw the reporting of similar incidents.

AKU's Natural History:

Ochronosis can begin in AKU patients before the age of 20, as evidenced by the detection of pigmentation in an ear sample from a 20-year-old female. Eye ochronosis was initially identified at age 22, and it grew with age. Ear ochronosis that was evident from the outside was only discovered after the age of 34.

Additionally, analysis revealed that starting in the third decade, the quality of life seems to be significantly declining. Regardless of sex, AKU patients score higher on the qAKUSSI as they age, indicating a deteriorating disease burden. Though a pediatric study is required to determine the earliest age at which ochronosis may begin, it can be concluded that it begins early, before adulthood. In order to determine the precise age at which damage begins and, consequently, the ideal age to begin nitisinone therapy, this new study will concentrate on youngsters under the age of sixteen [12].

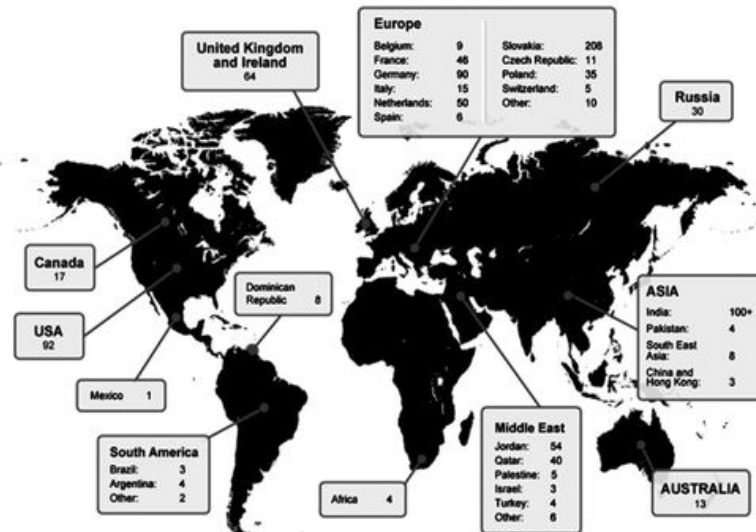


Figure 1. The map illustrates the current number of AKU patients identified worldwide

Osteoarthropathy in AKU:

As a result of early joint and spine pathology, AKU causes significant pain and incapacity in the prime of adulthood, which seems to inevitably lead to joint ochronosis and the osteoarthritis that follows. Progression of kyphoscoliosis and excruciating pain are symptoms of ochronotic illness of the intervertebral disc, which appears in the third decade of life. Respiratory issues result from disc degeneration's impact on thoracic and spinal movement.

Connection between genotype and phenotype:

There is currently no data on the relationship between AKU genotype and phenotype. These types of research are challenging, particularly in patients with two distinct mutations, because of the intricate hexameric structure of the HGD enzyme. Additional research is required. Proportion of individual mutation types identified in AKU patients, however it has been demonstrated that certain mutations result in distinct residual HGD enzymatic activity. Furthermore, the AKUSSI, an efficient system for assessing AKU severity, was only recently created. The Develop AKU are initiative will provide comprehensive clinical characterizations of AKU patients, including mutations, a range of metabolic indicators, and AKUSSI. This will help to clarify the importance of various HGD variations [13].

The exact localization of HGD expression has been made possible by the inclusion of a β -galactosidase (lacZ) gene trap into the Hgd gene locus in this model. The HGD enzyme's active form is a dynamic, extremely complex hexamer made up of two disk-like trimers. Identification of such factors may be aided by the examination of AKU siblings[14]. In-depth phenotyping (molecular characterization) of the disease and pharmacogenomic prediction of the patient's response to planned medical therapy are two common and successful applications of whole genome or exome DNA analysis.

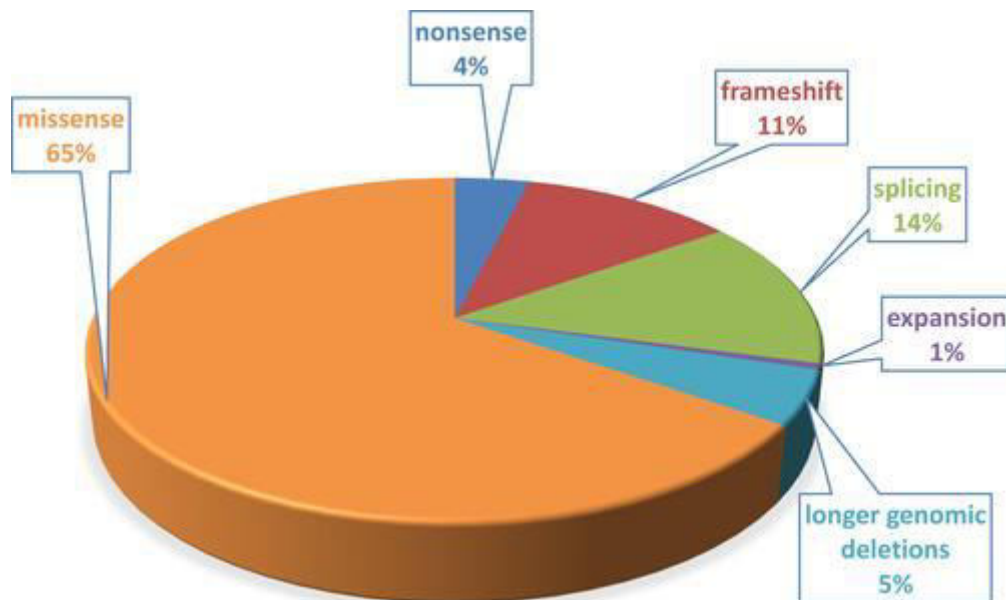


Figure 2: percentages of 13 HGD gene mutations found in 121 AKU chromosomes from Slovakia. The grey-shaded mutations most likely came from Slovakia.

SYMPTOMS:

Dark pee: When exposed to air, the urine can turn brown or black, making it one of the most prevalent and distinctive signs of alkaptonuria.

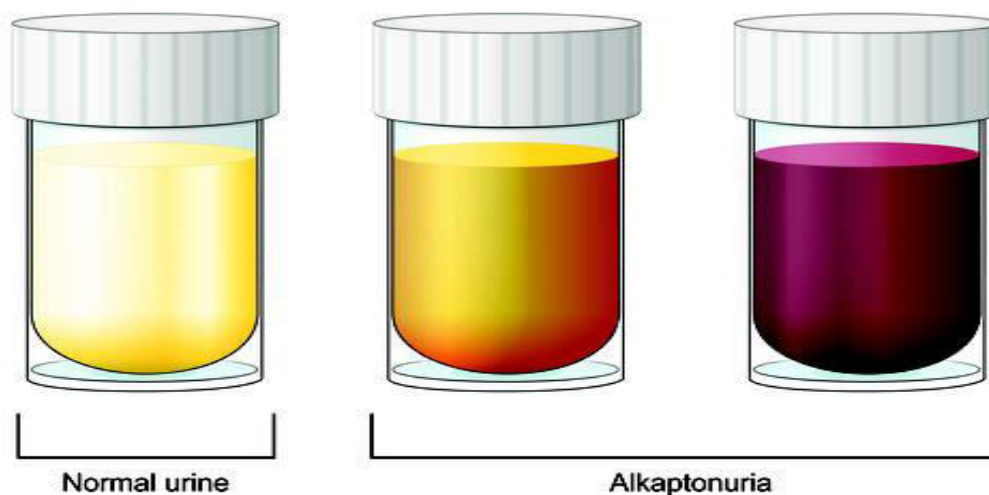
Joint stiffness and discomfort: Alkaptonuria can lead to stiffness and soreness in the joints, particularly in the knees, hips, and spine.

Damage to connective tissues and cartilage: An accumulation of HGA can harm the body's connective tissues and cartilage, resulting in osteoarthritis.

Long-term Complications:

- **Arthropathy:** The buildup of homogentisic acid can cause severe joint damage, leading to chronic pain and mobility issues.
- **Cardiovascular Issues:** Calcification of heart valves and arteries can lead to cardiovascular complications.
- **Kidney Stones:** Increased risk of developing kidney and bladder stones due to the accumulation of homogentisic acid.

ALKAPTONURIA



III. METHODOLOGY

1. Identification of the target:

Genes and Genomes (KEGG) pathway Using PubMed, the target for drug design was chosen from the literature; additionally, the Kyoto Encyclopedia of and the literature were used to identify the mutant protein in AKU. In order to shed light on the relative size and level of overlap of metabolic pathways, KEGG is a database that includes reference pathway databases [15]. The Protein Data Bank (PDB) database, the only global repository of experimentally resolved 3D structures of big molecules, provided the target's 3D structure for download. Protein resolution (less than 2.5 Å), structural completion (more than 90%), and ligand availability were taken into account when choosing this protein.

2. Analysis of ADME:

Swiss ADME, an online program that takes SMILES of compounds as input and interprets results in the form of graphs, tables, and even spreadsheets, was used to analyze the hits' absorption, distribution, metabolism, and excretion (ADME) characteristics. Each input's physiochemical characteristics, lipophilicity, solubility, pharmacokinetics, drug-likeness, medicinal chemistry, structure and bioavailability radar, and physiochemical properties are all interpreted [16]. Furthermore, CYP450 inhibition, blood-brain barrier permeability, and protein binding are also anticipated. A drug candidate's chances of success in clinical trials, as well as its potential for efficacy and safety, can be evaluated using this data.

3. Ligand-Protein Interactions:

The molecular visualization program Discovery Studio 2021, which depicts the two-dimensional interactions between ligand atoms and particular amino acids in the active site, was used to further analyze and examine docked complexes [17]. Van der Waal forces, electrostatic interactions, hydrogen bonds, and hydrophobic interactions are some examples of these interactions, which are shown by dotted lines of particular colors [18].

INTERPRETATION:

BMI:

In the UK, 63% of adults are overweight or obese²⁸; however, the mean BMI for AKU women was 26.3 and for AKU males was 26.9. While this cohort only has one female, national data would indicate that at least one guy and two women fall into the morbidly obese group. With trends showing a decline in body weight during the fourth and fifth decades, the prevalence of underweight is greater than the 2.3% national expectation and is not regularly distributed].

Body fat percentage:

The percentage of body fat in male AKU patients is higher than the percentage in a nationally representative sample that has been adjusted for age and ethnicity. According to centiles based on bioimpedance measurements, the male mean is in the 75th centile, with an IQR ranging from the 50th to more than the 95th centile (). A call on nutritional reserves may be indicated at this stage, as the numbers are too small to stratify by age but show a persistent pattern of above-average fat scores until the sixth decade, when they drop to average norms and then below expectations [19].

IV. DISCUSSION

According to reviews, ochronotic ear and scleral pigmentations—two physical indications of AKU—almost always manifest beyond the age of thirty, and as people age, they have gradual organ and arthritic alterations. At the age of 12, our patient unexpectedly developed ear ochronosis, which is significantly earlier than typical presentations. As early as age 25, the tetrad of physical diagnostic signs of AKU—dark urine, black scleral pigmentation, black/blue ear pigmentation, and clinical arthritis (accompanied by lower back pain)—were indeed present in this patient. As children or young adults, AKU sufferers do not exhibit any symptoms. There was not the lengthy "disease-free" period that is typical of classical AKU patients, which lasts until the patient is 28 to 30 years old and is characterized by no physical symptoms other than dark standing.

AKU currently has no recognized effective treatment; instead, symptomatic care is the main focus. AKU is a rare progressive condition for which there is no known cure, necessitating improved diagnostic techniques. Recent studies using nitisinone, a medication that inhibits the formation of HGA, have demonstrated that it efficiently lowers HGA levels but raises plasma tyrosine. Tyrosinemia's clinical and pathophysiological significance is uncertain. After undergoing right shoulder replacement surgery, our patient's shoulder pain subsided and some range of motion was restored. Patients can also benefit from lifestyle counseling that focuses on hobbies and activities that reduce the strain on main joints, controls food, and teaches pain management techniques.

V. FUTURE PERSPECTIVES

One of the most significant advances in AKU research has been the discovery that nitisinone, a medication derived from hereditary tyrosinemia 1 (HT1) (OMIM 276600), another rare condition, may be a useful treatment. Despite the fact that there isn't a licensed treatment for AKU at the moment, there is hope that nitisinone will totally stop ochronosis and diminish HGA in AKU mice. Additionally, nitisinone has been demonstrated to reduce circulating HGA in patients with AKU.

Patient organizations, such as the AKU society, are playing a crucial role in promoting research, providing support and information to patients and families, and advocating for access to effective care. There is still much to be learned about alkaptonuria, the progress being made in research and treatment of the rare disease.

VI. CONCLUSION

As of right now, there is no proven cure for AKU; instead, symptomatic care is the primary goal. There is currently no cure for AKU, a rare progressive illness that calls for better diagnosis methods. Nitisinone, a drug that prevents the production of HGA, has been shown in recent research to effectively reduce HGA levels while increasing plasma tyrosine. The pathophysiology and clinical relevance of tyrosinemia is unknown. Following surgery to replace the right shoulder, our patient's shoulder pain decreased and some range of motion returned. Lifestyle counseling that teaches pain management skills, regulates food intake, and emphasizes pastimes and activities that ease the strain on major joints can also be beneficial to patients. Psychotherapy, which allows a patient to talk about their suffering, might be helpful in addition to lifestyle counseling.

Since there is still much to learn about AKU, we advise treating it as a complex illness with developing neurological, psychosocial, and physiological symptoms. Patients with this uncommon illness may have a higher quality of life if they receive early diagnosis, have a better knowledge of their prognosis, and prioritize their mental health.

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