Clinical Investigation

Bacterial quality of urinary tract in patients with alkaptonuria

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Abstract

Background
The aim of the current study was to determine whether there is an association between alkaptonuria (AKU) and urinary tract infection (UTI) by exploring the bacterial quality of the urinary tract, as most of the patients with AKU present with frequent occurrence of urinary tract symptoms such as incomplete emptying of urinary bladder, dysuria and nocturia.

Methods
Study samples were collected from 22 participants; 9 from patients with AKU, 9 from individuals who were AKU carriers, and 4 people served as control. Confirmation of AKU diagnosis was established by the ferric chloride test and quantitative determination of urinary homogentisic acid (HGA) levels.

Results
In the ferric chloride test, the urine samples of AKU patients showed a characteristic black ring upon addition of few drops of ferric chloride solution. During urinary HGA determination, patients with AKU had increased levels of urinary HGA as compared to carriers and controls. The following 10 bacterial species were isolated from the urinary tract of AKU patients, carriers and controls: Sphingomonas paucimobilis, Escherichia coli, Francisella tularensis, Staphylococcus hominis, Staphylococcus haemolyticus, Leuconostoc mesenteroides, Dermacoccus nishingiomiyaensis, Rytococcus sedentarius, Serratia fonticola and Granulicatella adiacens. The presence of S. paucimobilis was found in three male patients, and one female each from the carrier and control groups. Almost all study samples were positive for D. nishingiomiyaensis and K. sedentarius. S. fonticola and G. adiacens were found only in AKU carrier females.

Conclusions
The results deduced that males show symptoms of arthritis early and more severely than females and by this it appears that there is an association between these symptoms and the percentage of bacterial infection in males that requires more accurate diagnosis and treatment to clarify such relationship. In the current study, males (patients, carriers, and controls) were more likely to have bacterial infections than females (64% vs. 36%). The 16 and 2 bacterial isolates, detected in 7 males and 2 females AKU patients, respectively, revealed that male AKU patients had a 2.3-fold greater rate of bacterial infection than female AKU patients. Therefore, further studies are needed.
warranted to investigate if there's any relationship between higher incidence of bacterial infections and development of AKU-related clinical symptoms in the male population.

Introduction

Alkaptonuria (AKU) (OMIM: 203500) also known as the “black urine disease”, was first described by the British physician Sir Archibald Garrod in 1908, while he was illustrating the concept of inborn errors of metabolism. It is a genetic disorder inherited in an autosomal recessive manner and caused by mutation in homogentisate 1,2-dioxygenase (HGD, EC.1.13.11.5) gene which maps to the human chromosome 3q21–q23. This mutation leads to a deficiency in homogentisate 1,2-dioxygenase (HGD) activity which is involved in the catabolism of homogentisic acid (HGA), an intermediary product of amino acid (phenylalanine and tyrosine) metabolism. This condition is characterized by accumulation of HGA in the body and the excess amount is excreted in the urine, imparting a distinct black color to the urine. The urine formed turns black upon exposure to air or alkali due to formation of a dark polymerized product.

In the body, HGA undergoes oxidation and subsequent dimerization to form a melanin-like pigment that gets deposited in the connective and cartilaginous tissues throughout the body. The deposition of this pigment in the tissues leads to ochronosis, the hallmark of AKU. The molecular mechanism of ochronosis was recently elucidated using redox-proteomic analyses which provided a potential pharmacological basis for its treatment.

AKU is a rare disease with a prevalence rate of approximately 1:250,000–1,000,000 in most ethnic groups. However, the incidence is higher in countries like Slovakia and the Dominican Republic where it is estimated to rise up to 1:19,000. Recent studies have reported 40 cases of AKU in South Jordan. However, the incidence of AKU in Jordan remains unknown. The features of ochronosis begin to appear usually around the third decade of life. Patients with AKU suffer from joint and spine arthritis and in more severe cases the cardiovascular system gets affected causing damage to the cardiac valves. As the disease progresses, most patients develop renal stones; male patients are at an increased risk of developing prostate stones. In a recent finding, a Jordanian male patient with AKU was admitted to the hospital for severe lower urinary tract symptoms (LUTS). Urine analysis was normal and free of bacterial growth. Clinical examination, non-contrast urinary tract computed tomography (CT), and a Kidney, Ureter and Bladder (KUB) plain film revealed numerous stones in the bladder and prostate gland particularly deposited in the paraprostatic diverticulum.

The current study aims to investigate if there is an association between AKU and the bacterial quality of the urinary tract (UT).

Section snippets

Ethical consideration

This study was approved by the Institutional Ethics Committee (IEC) in The Deanship of Scientific/Academic Research & Quality Assurance at Mutah University. The study abided by the Declaration of Helsinki (DOH). Written informed consent was obtained from all participants.

Study sample

The target population was selected based on surveys, interviews, and review of medical history. Study samples were collected from affected individuals and carriers of AKU who complained of recurrent LUTS. No antibiotic therapy...

Results

The urine samples of affected individuals showed a characteristic black ring upon addition of a few drops of ferric chloride solution (Fig. 1a, b and c). Another diagnostic tool used was quantitative determination of urinary HGA levels by GC-MS analysis (Table 1). AKU patients had higher levels of urinary HGA when compared to carriers and controls. Further diagnosis was made on the basis of medical signs and symptoms. All the clinical manifestations observed in patients, carriers and controls...

Discussion

Urine samples from patients with a diagnosis of AKU turned black, whereas those collected from AKU carriers and controls did not show any color change (Fig. 1a, b and c). Furthermore, AKU patients showed a clear rise in their urinary HGA levels as compared to carriers and controls (Table 1). These results thus confirm the validity of the study samples.

It was noticed in the current study that 7 out of 9 AKU patients were suffering from morning stiffness, pain in weight-bearing joints such as...

Conclusions
Our study could not establish any association between AKU and the type of bacterial species inhabiting the UT despite the fact that most AKU patients reported recurrent UT symptoms. The UT symptoms like incomplete emptying of urinary bladder, dysuria and nocturia might be secondary to obstruction and irritation caused by HGA as it passes through the kidneys during its removal. The incidence of AKU is equal in males and females. However, arthritic symptoms occur earlier and with a greater degree...

Ethical consideration

The study abided by the Declaration of Helsinki (DOH). All ethical principles for medical research involving human subjects were enforced. The human subjects' confidentiality and rights were preserved throughout the study.

Authors Contributions

Amjad and Muhamad recruited the patients and collected the samples. Amjad, Ali and Ibrahim analysed the samples. Nesrin, Khaled and Hussam designed the experiments and screened the relevant literature review. Nesrin, Amjad, Moath and Hussam revised and interpreted the patients' medical records and drafted the manuscript. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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