Alkaptonuria

An obscure disease

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LISTA DE ABREVIATURAS

4-HPPD – 4-hydroxyphenylpyruvate dioxygenase
AA – Ascorbic acid
AKU – Alkaptonuria
BQA – Benzoquinone acetic acid
HGA – Homogentisic acid
HGD – Homogentisate 1,2-dioxygenase
OOA – Ochronotic osteoarthropathy
uHGA – Urinary homogentisic acid
Abstract

Alkaptonuria (AKU) is a rare metabolic disease with an autosomal recessive inheritance. It is characterized by accumulation of homogentisic acid (HGA) as a consequence of the absence of the enzyme involved in the phenylalanine and tyrosine destruction pathway, homogentisate 1,2-dioxygenase (HGD). This deficiency results in accumulation in tissues and excretion of large quantities daily in urine of HGA, which are responsible for the triad of clinical features that characterized AKU: homogentisic aciduria, ochronosis and ochronotic osteoarthropathy.

Usually, its earlier feature is the darkening of urine when exposed to air, which can be present since birth and is a consequence of homogentisic aciduria. Other systemic manifestations resulting from ochronosis and ochronotic osteoarthropathy are more recognizable around the fourth decade of life and thereafter.

There is no currently approved cure for AKU, but nitisinone has been investigated as a potentially disease modifying therapy. Given these limitations, the symptomatic control of these patients is crucial and the most important approach, since AKU has a massive impact in patients’ quality of life.

Greater efforts to improve recognition and diagnosis of the disease will be worthwhile and this review pretends to reunite all the information known until the present about AKU, mainly in what concerns its history, genetics and metabolic pathways, epidemiology, clinical features and natural history, diagnosis, therapies and prognosis. Therefore, this literature review is intended to disclose this entity, mainly to allow for early diagnosis and proper monitoring of these patients in an attempt to improve their quality of life.

**Keywords:** alkaptonuria, ochronosis, ochronotic osteoarthropathy, homogentisic acid, homogentisate 1,2-dioxygenase
Resumo

A alcaptonúria é uma doença rara do metabolismo, de transmissão autossómica recessiva. Trata-se de uma aminoacidopatia que se caracteriza pela deficiência da enzima homogentisato 1,2-dioxidase, com acumulação subsequente de ácido homogentísico. A elevada excreção renal deste ácido e a sua deposição no tecido conjuntivo são responsáveis pela tríade associada à alcaptonúria de acidúria homogentísica, ocronose e osteoartropatia ocronótica.

Habitualmente, a manifestação que aparece mais precocemente é o escurecimento de uma amostra de urina quando é deixada a repousar, característica esta que pode estar presente desde o nascimento e é consequência da acidúria homogentísica. As outras manifestações sistémicas de ocronose e osteoartropatia ocronótica surgem perto da quarta década de vida ou posteriormente.

Atualmente não existe cura para a alcaptonúria, mas a nitisinona tem sido investigada como potencial terapêutica modificadora do curso da doença. Tendo em conta estas limitações, a abordagem terapêutica mais pertinente passa pelo controlo dos sintomas apresentados, que têm um grande impacto na qualidade de vida destes doentes.

São necessários mais estudos para melhorar o reconhecimento e a suspeita da doença, pelo que esta dissertação tem como objetivo rever a bibliografia existente até à data sobre a alcaptonúria, nomeadamente no que diz respeito à sua história, genética e via metabólica, epidemiologia, manifestações clínicas e evolução natural, diagnóstico, tratamento e prognóstico.

Assim, com esta revisão bibliográfica pretende-se divulgar esta entidade, sobretudo para que seja possível um diagnóstico precoce e um acompanhamento adequado destes doentes numa tentativa de melhorar a sua qualidade de vida.

**Palavras-chave:** alcaptonúria, ocronose, osteoartropatia ocronótica, ácido homogentísico, homogentisato 1,2-dioxidase
Introduction

AKU is a rare metabolic disease of autosomal recessive inheritance. Reviewed by Sir Archibald Garrod in 1908, it was considered the disorder responsible for the creation and evolution of the inherited metabolic disease branch of medicine.1

The disease is a consequence from absence of HGD, an enzyme responsible for the conversion of HGA in maleylacetoacetic acid. Therefore, the deficiency of this enzyme results in accumulation of HGA in tissues and excretion of large quantities daily in urine, which are responsible for the triad of clinical features that characterize AKU: homogentisic aciduria, ochronosis and ochronotic osteoarthropathy (OOA).2,3 The disease has a systemic involvement, with cardiovascular, musculoskeletal, genitourinary, ocular, cutaneous and respiratory manifestations.4 In fact, virtually all connective tissues are affected by AKU.5

Typically, all the characteristic symptoms appear during adulthood, with exception of homogentisic aciduria that is usually present since birth.2 This makes AKU a unique entity among other genetic metabolic diseases. Nowadays, the gold standard for the diagnosis of AKU is testing a urine sample for quantification and confirmation of high levels of HGA.6

Even though the disease is known for more than a century and is subject to massive investigation, there is currently no approved cure for AKU. Thus, the symptomatic control of these patients is crucial and the greatest approach given that the disease has a huge impact in patients’ quality of life.2 At this time, the most promising therapy is nitosine, an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) responsible for HGA production.

This article pretends to extensively review the bibliography known until the present about AKU, mainly in what concerns its history, genetics and metabolic pathways, epidemiology, clinical features and natural history, diagnosis, therapies and prognosis. Even though this is a rare entity, it is crucial to diagnose it as earlier as possible, since the repercussions can be very restrictive to patients’ quality of life.
Materials and Methods

All the articles cited in this review were found using the keywords ‘alkaptonuria’, ‘homogentisic acid’, ‘homogentisate 1,2-dioxygenase’, ‘ochronosis’ and ‘ochronotic osteoarthropathy’ associated with ‘natural history’, ‘genetics’ and ‘treatment’ in the international database PubMed (available at http://www.ncbi.nlm.nih.gov/pubmed) and in ScienceDirect (available at http://www.sciencedirect.com/).

There was no custom range of publication dates and the articles were selected based on the title and on the abstract. The cited articles are original articles, case reports and reviews.
History

The first case of alkaptonuria was found in the Egyptian mummy Harwa dating from 1500 BC. The roentgenograms of the mummy’s entire body revealed extensive calcification in all the intervertebral discs without secondary arthritic features and the biopsy of her right hip also showed black zones that in the modern patient would lead to the diagnosis of ochronosis. Further analysis of the black pigment found in Harwa's joints and bones confirmed it was derived from HGA. The description of the disease goes back to 1866 and was first made by Rudolf Virchow (1821-1902) that observed a patient with black intervertebral discs, larynx, tracheal rings, menisci and articular cartilages. Microscopically, the pigment appeared to be yellow-brown in color, and as a consequence he named it ochronosis from the Greek translation of ‘yellow disease’. In 1899, Sir Archibald Edward Garrod (1857-1936), through the study of pigments and different colors in urine of patients, first established that the disease was due to a chemical aberration and was thought to be congenital. He also observed an increased incidence of this condition in offsprings of consanguineous marriages, which suggested a Mendelian autosomal recessive inheritance. Years later, in 1908, Garrod delivered The Croonian lectures, the greatest breakthrough of his scientific career, and universally recognized AKU as a landmark in medicine, human genetics and biochemistry. He was the first person to use the term “inborn errors of metabolism” to describe alkaptonuria, among other diseases, such as albinism, cystinuria and pentosuria. Therefore, alkaptonuria is considered the disorder responsible for the creation and evolution of the inherited metabolic disease branch of medicine.

After Garrod’s findings, the curiosity about this condition increased. It was known that alkaptonuria resulted from a defect in oxidation of tyrosine, primarily in the enzyme system homogentisic acid oxidase, but only fifty years later, La Dou et al. (1958) were capable of determining the exact nature of the abnormality. It was established with reasonable certainty that the defect is limited to homogentisic acid oxidase, that there appears to occur a failure to synthesize active enzyme and that the metabolic block is essentially complete.
Genetics and Metabolic Pathway

In normal circumstances, less than 5% of dietary tyrosine is used to synthetize hormones such as thyroxine and catecholamines, melanin and new proteins. In fact, the majority of dietary tyrosine is metabolized via HGA to malate and acetoacetate and the products enter the intermediary metabolism.\(^6\)

In order to understand what happens in patients with AKU, it is important to be acquainted with the normal phenylalanine and tyrosine degradation pathway (figure I).

In this condition, there is absence of HGD, an enzyme responsible for the conversion of HGA in maleylacetoacetic acid, which results in accumulation of HGA.\(^2\) This enzyme has a hexamer subunit structure and a Fe\(^{2+}\) cofactor. Adjacent subunits
form a trimer and are arranged as a dimer of trimers. Primarily, HGD catalyzes the aromatic ring opening reaction, using Fe\(^{2+}\) to incorporate molecular oxygen into homogentisate. HGD is produced mainly by hepatocytes in the liver, but it is also present in the kidney, small intestine, colon, prostate and several compartments of central nervous system.

In 1995, the localization of the genetic defect was narrowed down and mapped to chromosome 3 (3q21-q23).

Beltrán-Valero de Bernabé et al. (1998) analyzed 29 AKU chromosomes from France, Spain, Germany, Italy, United Kingdom, Holland, Algeria and Turkey to screen mutations in HGD gene. Along with others studies, there were screened a total of 39 AKU chromosomes that demonstrated a large heterogeneity of HGD mutations distributed throughout the whole length of the gene sequence and no prevalence of a single mutation. Müller et al. (1999) extended the screening of mutations in Central Europe, primarily in Slovakia because of its high prevalence of AKU. Overall, the defects in HGD were attributed to inactivating missense and frame-shift mutations.

Years later, Vilboux et al. (2005) described new HGD mutations in patients with AKU, which along with the previously reported, consisted of 91 HGD variants, including 62 missense, 13 splice site, 10 frame-shift, 5 non-sense and 1 no-stop mutations. The same type of mutations was also found in the United Kingdom, by Usher et al. (2015).

More recently, in 2010, Andrea Zatkova created a database with all AKU mutations known to date (http://hgddatabase.cvtsr.sk/home.php). Until 2014, there were reported 115 mutations in the HGD gene. So far, 174 different mutations have been identified. While some variants are spread throughout the world, others are specific for some regions or countries.

All AKU mutations resulted in significant HGD loss of function, with some affecting the assembly of the hexamer, others interfering with the active site of HGD and others affecting the stability of the protomer.

HGD entails a complex pattern of intra and intersubunit interactions for activity and can be inactivated by single-residue substitutions at multiple levels. The majority of the missense mutations affect residues located in areas of contact between subunits, but the single residue substitutions are distributed uniformly in the HGD subunit.

There appears to not exist a clear correlation between the genotype’s patient and the phenotype, evaluated by excreted levels of HGA. In fact, a moderate decrease in HGD activity does not always explain the disease, and in order to have AKU symptoms, there has to be a loss of more than 99% of the enzyme activity, because
the liver produces enough HGD to convert 1.5 kg of homogentisic acid per day. It is difficult to predict the consequences of each mutation, mainly in missense mutations (the most frequent).\textsuperscript{18,23}

Generally, there is remarkable allelic heterogeneity and AKU patients are homozygotes or compound heterozygotes for loss of function mutations in the gene.\textsuperscript{13,22,24}
Epidemiology

Worldwide, the prevalence of this condition is low in all ethnic groups, 1 case in 250,000-1,000,000 births. However, it is more prevalent in regions like Slovakia, the Dominican Republic, India and Jordan, the highest being 1 case in 19,000 listed in the first. It is thought that this is explained by a founder effect as consequence of migration and genetic isolation.2,17,25

Being an autosomal recessive disease, AKU has more probability of happening in families or regions with a high degree of consanguinity.8

A careful study of large pedigrees revealed that there was no predominant sex in the affected patients, with AKU affecting both male and female in equal proportions.8 However, the progression of this condition is faster in males.26

Until now, there is no evidence that other metabolic diseases are consistently associated with AKU.8
Clinical Features and Natural History

As described previously, this disease results from a deficiency in HGD enzyme, involved in phenylalanine and tyrosine metabolism. This deficiency results in accumulation in tissues and excretion of large quantities daily in urine of HGA, which are responsible for the triad of clinical features that characterized AKU: homogentisic aciduria, ochronosis and ochronotic osteoarthropathy.²

Regardless of AKU being a genetic disease, normally, until adult life, the only expression of this condition is the discoloration of urine (figure IV). However there were cases of children with ocular pigmentation and teens with back pain.⁸ Overt ochronotic features typically begin after the fourth decade of life, but the reason for this delay remains unknown.⁵ Nonetheless, it is believed this happens as a consequence of the decreased renal clearance of homogentisic acid with age.²³

Homogentisic aciduria

The majority of HGA produced in the body is excreted by the kidneys through filtration and active secretion. Thus, the excreted HGA oxidizes in an alkaline pH or when exposed to open air by a long period of time causing darkening of the urine, referred as homogentisic aciduria.²⁷²⁸

This reaction is pH-dependent, which means that acidic urine may not darken after many hours of standing. This is one of the reasons why blackening of the urine may never be noted in an affected patient.²⁹³⁰

Ochronosis

Despite efficient urinary excretion of HGA, in the tissues, there is accumulation of ochronotic pigment, which results from oxidation of HGA to benzoquinone acetic acid (BQA), then converted to a melan ine-like product. The enzyme system responsible for this conversion, homogentisic acid polyphenol oxidase, has been identified in skin and cartilage.¹³³¹ Ochronosis is, therefore, a darkening of collagenous tissues resulting from binding of this pigment to connective tissue. The tissues become weak, brittle and prone to chipping, cracking and rupture, leading to rapid degeneration of the joints. It is the focal pathophysiological event in AKU and it is responsible for complications such as arthritis, valvular heart disease, stones (prostatic, renal, gall bladder and salivary), osteopenia, fractures and muscle, tendon and ligament ruptures. Ochronosis can also develop in other soft tissues sites, including the skin, eye, ear and throat.²⁵³²-³⁴ Virtually all connective tissues are affected by AKU.⁵
The characteristic external features of ochronosis are blue-black pigmentation of the ear cartilage and of the sclera of the eyes. Usually, first occurs a discoloration of the ear lobes, followed by the pigmentation of the sclera and for last the staining of the skin.\textsuperscript{8,33}

As previously referred, bluish discoloration of the ear cartilages (figure II)\textsuperscript{35} is one of the earliest signs of ochronosis and develops by the third and fourth decades of life. Usually, not only the external ear is involved, but also the middle ear, the internal structures and the cochlear nerve. This type of ochronosis can be asymptomatic or cause symptoms of tinnitus, impaired auditory acuity and even deafness.\textsuperscript{8} These patients commonly present with dark cerumen, which may be one of the earliest recognized clinical manifestations of AKU.\textsuperscript{4}

The ochronotic pigment can also be deposited in any of the outer structures of the eye, such as sclera, cornea, conjunctiva, tarsal plates and eyelids. Eye involvement develops earlier than OOA, starting around the third decade and it is clearly visible by the fifth decade of life. The pigmentation of the sclera, also known as Osler’s sign (figure III)\textsuperscript{36}, usually occurs in two phases. In early stages, there is a brownish pigment deposited in the nasal and temporal aspects of the sclera, about midway between corneal limbus and canthus. Later, the area of discoloration resembles a triangular shape, with the base near the limbus, and occupies most of the palpebral fissure. When present, corneal pigmentation has a characteristic profile of tiny oil drops scattered peripherally in the areas designated by three and nine o’clock. In the conjunctivas, sometimes can be seen inconspicuous ring-shaped deposits. The skin of the eyelids may exhibit slight brown discoloration and the tarsal plates may appear blue on transillumination.\textsuperscript{4,8,30} Despite all the possible alterations, there are no significant visual impairments.\textsuperscript{4,37}

In the skin, there is deposition of the pigment granules in the dermis and in the sweat glands. Given this, the discoloration of the skin is usually more prominent in sun exposed areas and in areas where there are the greatest concentration of sweat glands, whereby in advanced cases of AKU, malar areas of the face, axilla and genital regions can have a bluish or brownish coloration and the sweat is usually discolored, staining the clothing brown, mainly at the arm pits and groin. However, usually the discoloration of the skin is less noticeable and common than that of the sclera or ear lobes.\textsuperscript{4,8}

In the respiratory tract, the laryngeal, tracheal and bronchial cartilages have the greatest degree of discoloration. Some patients present with hoarseness, dryness of the throat and severe dysphagia. However, noticeable clinical involvement is rare.\textsuperscript{4,8}
Ochronotic Osteoarthropathy

Being one of the most defining features of AKU, it results from the deposition of the HGA polymer within hyaline articular cartilage.\(^2\)

OOA is rare and usually only appears in the fourth decade of life, but its symptoms manifest before. The first symptoms to appear are back pain and stiffness and are often the first ones suggestive of AKU in the majority of undiagnosed patients. According to the series of patients studied by Phornphutkul et al. (2002), 49% reported low back pain before the age of 30 years old.\(^8\)\(^{23}\)\(^{38}\)

The course of these manifestations is progressive and chronic.\(^8\) Weight-bearing joints such as the spinal column, hips and knees are predominantly affected. OOA has a characteristic anatomic distribution with sequential spinal and peripheral joint involvement. Usually, symptoms in the lumbar and thoracic spine usually precede those in the cervical spine (figure IV). The knees are involved almost ten years later, followed by the shoulders and hips, but sacroiliac joints and the small joints of the hands and feet are rarely affected. The physical ability of the patient becomes impaired and he can be totally disabled by 60 years of age. In advanced stages of the disease, the posture of these patients is characteristic: they have a stiffened spine with flexed hips and knees, resulting on a “goose gait” with a broad base.\(^6\)\(^8\)\(^{36-40}\)

The involvement of the spine results in height loss, kyphosis and decreased lumbar flexion. Phornphuktul et al. (2002) reported a mean decrement of 7.9 cm in the 43% of patients above 40 years old who had lost height and according to available data, the patient’s height might be diminished up to 15 cm.\(^{23}\)\(^ {38}\)\(^ {40}\) They also testified kyphosis in 53% of patients and an abnormal Schober test in 59% of the subjects.\(^{38}\)
Severe disc calcification, disc space narrowing, osteophytosis and sclerosis are spinal changes pathognomonic of ochronosis. Usually there is a progression from narrowing of the disk space to disk calcification and fusion of the disk and the typical radiologic findings are widespread narrowing of the intervertebral disc spaces, waferlike calcification and ossification of intervertebral discs, vacuum phenomena and osteoporosis.\textsuperscript{32, 38, 39}

In some patients, chest expansion can be restricted, resulting in an impaired respiratory function.\textsuperscript{8}

Overall, joint involvement, mostly the knee, is more frequent, more severe and develops at an earlier age in males. \textsuperscript{8, 38, 40} It decreases the range of motion and causes effusions.\textsuperscript{23, 38} The symptoms appear in the third or fourth decade of life and typically progress until chronic pain instigates a joint replacement, what happens at the mean age of 55 years old. According to Phornphuktul et al. (2002), 50\% of the patients studied had undergone at least one knee, hip or shoulder replacement by the age of 55.\textsuperscript{38}

The typical radiologic findings of peripheral joint involvement are similar to those of more common types of osteoarthritis, including joint space narrowing, subchondral bone sclerosis with cyst formation and minimal osteophytes. There may appear calcific deposits in the tendons and osteochondral bodies in the suprapatellar pouch or popliteal fossa, which are more frequently associated with ochronosis than osteoarthritis.\textsuperscript{8, 39}

**Cardiovascular Manifestations**

The deposition of ochronotic pigment within endocardium, heart valves, all layers of arterial walls and coronary arteries triggers dystrophic calcification, leading to the cardiovascular manifestations of AKU.\textsuperscript{4, 8, 41} It also can be present in areas of myocardial fibrosis, in arteriosclerotic plaques and, rarely, in the media of veins.\textsuperscript{4, 8}

Although it was thought that ochronosis promotes arteriosclerosis, there was no evidence of such correlation. As a matter of fact, the incidence of arteriosclerosis and coronary artery disease in these patients seems to be no greater than in the general population, which favors the hypothesis that AKU does not contribute significantly to the arteriosclerosis process or cause clinically discernible cardiac disease.\textsuperscript{8, 41}

Pettit et al. (2011) evaluated a series of patients with AKU in the United Kingdom, focusing on their cardiovascular system. They identified cardiovascular involvement in 38\% of patients, with the aortic valve being preferentially affected with mild or moderate disease. This result supported the finding of Phornphuktul et al. (2002) that 40\% of
patients had cardiovascular involvement. The disease was characterized by aortic stenosis, aortic regurgitation or mixed aortic valve disease. Contrary to other literature (Kragel et al., 1990; Phornphuktul et al., 2002; Wilke and Steverding, 2009), Pettit et al. did not find significant mitral, tricuspid, pulmonary valvular disease or aortic root dilatation. However, their study group consisted of only 16 subjects, opposing to the 58 of Phornphuktul et al., so Pettit’s results about the absence of other valvular involvement can’t be applied to all AKU patients. Therefore, aortic valvular stenosis is the most frequent cardiac manifestation of the disease, followed by involvement of the mitral and pulmonary valves. It is also possible that more than one valve is affected in the same patient.26 27 38 41

The reason why there is a predominant involvement of aortic valve remains unclear, but it is thought to be related with the higher pressures and sheer stress to which this valve is subjected.41

The age of onset of aortic valve disease was between 30 and 40 years old and, even though, it was more common with advancing age, not all people developed it. In the study made by Phornphuktul et al. (2002), the mean age at time of diagnosis of valvular heart disease was 54 years old and Hannoush et al. (2012) concluded that their patients developed aortic valve disease in their fifties and sixties (figure IV).38 41 42

Contrary to arteriosclerosis, there appears to be a higher prevalence of aortic valve disease in patients with AKU than in the general population.38 41

It was not demonstrated that standard cardiovascular risk factors, such as hypertension, dyslipidemia or smoking, were related with the development of aortic valve disease.41 42

Even though it was thought that ochronosis of the fibrous skeleton of the heart could lead to abnormalities of atrioventricular conduction, Pettit et al. did not identify any evidence of arrhythmias.41

The clinical manifestations of involvement of cardiovascular system by AKU include dyspnea, chest pain and cardiac murmurs.26 27 43 44

Despite all of the above, the cardiovascular ochronosis is a rare complication of AKU.26

Genito-urinary Manifestations

Being a systemic disease, AKU also presents in the genito-urinary tract, affecting mainly the prostate, which validates the fact that males are more commonly affected by this kind of manifestations than women.8

In fact, 5 in 7 patients examined and every biopsy postmortem revealed calculi in this gland without major alterations of the parenchyma, even though the prostate
appeared enlarged and nodular. These findings can be explained by the fact that alkaline secretions produced in the prostate lead to rapid polymerization of HGA, which, in turn, results in a nidus for stone formation. On rectal examination, the nodular aspect of the gland is evident, even before other symptoms of enlargement such as dysuria and pollakiuria manifest, and as the stones are characteristically soft, they can be crushed by the examining finger. In some cases, rectal examination suggested carcinoma of the prostate with a hard gland. Therefore, the radiographic diagnosis of prostatolithiasis is the most reliable one.

Furthermore, renal stones are known to occur and reoccur in ochronosis, usually in the fifth and sixth decades (figure IV), with 50% of patients with alkaptonuria having a history of renal stones by the age of 64 years old. The deposition of ochronotic pigment in the renal parenchyma, itself, does not lead to clinically evident renal disease and usually the renal function is preserved. However, in cases where an unrelated disease is present and the renal function is impaired, the clearance of HGA is decreased and the accumulation of the pigment in the tissues is increased, worsening the disease.

The kidney stones contained calcium oxalate, phosphate and carbonate, similar to calculi composition of the general population. Other less common locations for these calculi are the posterior and anterior urethra, the bladder and ureters.

All these stones can lead to urinary tract obstruction and infection, however the majority of patients is asymptomatic and the calculi are incidentally found.

As alkaptonuria has a typical dark coloration, this pigmentation is also present in the spermati c fluid, being possible to demonstrate the existence of HGA in concentrations ten times higher than in plasma. It is likely that this finding results from an active excretion of HGA by the prostate and seminal vesicles, but it can also be because of the contamination of the urethra by high concentrations of this acid in the urine.

Figure IV. Natural history of Alkaptonuria
Diagnosis

To recognize AKU is necessary a high clinical suspicion. At birth and during childhood, the discoloration of nappies is the earliest opportunity to suspect and diagnose AKU.6

According to Phornphutkul et al. (2002), the diagnosis of AKU was made before 1 year of age in 21% of the patients studied and the mean age of diagnosis was 29 years old. This suggests that it is missed or ignored at an earlier age. In most cases (55%), the dark urine was the finding that led to the diagnosis of the disease, while chronic joint pain represented the discovery that suggested the diagnosis in the other patients.38

However, occasionally the disease is only suspected when patients are submitted to joint replacement and the characteristic bluish-black discoloration of the tissue surrounding the joint is observed intraoperatively.23

Given that there are more than a hundred mutations responsible for AKU and possible a lot more, a genetic test is not the ideal way to diagnosis the disease. However, in areas where AKU has high prevalence or consanguinity is common, this test can be useful to determine whether patients are homozygous or compound heterozygotes and facilitate family counselling. In the same line of thought, the change in urine color upon alkalization is unpredictable and not specific for AKU. Thereupon, currently, the gold standard for the diagnosis of AKU is testing a urine sample for absence or presence of HGA. The amount of HGA in 24-hour urine can be detected and measured with gas liquid chromatography or thin-layer chromatography.6 30 38 The amount of HGA excreted per day in patients with AKU is usually between 1-8 g, contrary to a normal individual that excretes 20-30 mg per day of this acid.47

Measurement of HGA in random urine is sufficient for establishing the diagnosis of AKU.6 However, a further quantification of HGD’s residual activity through enzymatic spectrophotometry followed by a genetic test are useful to an additional evaluation of the patient’s disease.

Currently, newborn screening is not available in any country worldwide.2
Therapies

The treatment of AKU has mainly 3 goals: correction of the metabolic defect, restriction of the production of HGA and prevention of complications. However, until now there is no feasible option for the first aim, so the majority of available treatments focus on the restriction of the production of HGA (see further topics ‘low protein diet’ and ‘nitisinone’) and consequent prevention of complications (see further topics ‘antioxidants’ and ‘symptomatic control’).

Low Protein Diet

Since AKU is a metabolic disease involving primarily the metabolism of tyrosine and phenylalanine (two amino acids), one of the first therapies suggested to decrease the levels of HGA in the tissues and control the clinical manifestations was a low protein diet. Considering the hypothesis that the deposition of ochronotic pigment is proportional to HGA production rate, it is reasonable to expect that a lower production of HGA in childhood, will translate in milder clinical manifestations in adulthood.

De Haas et al. (1998) applied a 2-week program with different quantities of proteins in the diet (all patients received a low-protein diet with 1g/kg per day followed by an age-corrected high-protein diet with 3-5g/kg per day) to 12 patients between 4 and 27 years old. They proved that there was a significant decrease in the excretion of HGA after a diet with a lower protein intake. They also verified differences concerning the age of the subjects, with younger children (<12 years old) having an effect from increasing the protein intake, while older ones did not. Bearing this in mind and the fact that older patients had a lower compliance to change their usual protein intake, they concluded that protein restriction in older patients with AKU was probably useless.

Even though this is the most logical option to treat the disease, there are authors that believe it is useless. Also, restricting dietary protein for life has a low compliance in the long-term and requires intensive specialist supervision during growth. Trials with a large number of subjects and a longer duration are still missing, so the long-term effect of such a diet on the symptoms of AKU is still unknown.

Nitisinone

The most promising therapy is nitisinone, already used to treat other metabolic diseases involving the same pathway as AKU, for instance tyrosinemia type I caused by deficiency of fumarylacetoacetate hydrolase (figure I).
Its chemical name is 2-(2-nitro-4-trifluoromethylbenzoyl)-cyclohexane-1,3-dione and it is a triketone herbicide. This drug inhibits 4-HPPD enzyme, responsible for HGA production, with subsequently hypertyrosinemia (figure I).

The first time it was suggested as a potential treatment for AKU patients was in 1998. In the last couple of years, there have been a limited number of trials testing this drug, with all of them showing a decrease in urinary HGA (uHGA) excretion. According to Suwannarat et al. (2005), a dosage of 1.05 mg bid reduced by 94% the uHGA excretion and a bigger and longer trial supervised by Introne et al. (2011) using a dosage of 2 mg daily reduced it by 95%. Probably related to this reduction, some patients reported decreased joint pain, improved mobility, normal colored urine on standing and lighter cerumen, but there was no significant effect on clinical parameters.

Gertsman et al. (2015) studied the metabolic effects of increasing doses of nitisinone in patients with AKU and concluded that there was an insignificant change in plasma tyrosine concentrations in patients who are given a 4 mg/day as compared to a 2 mg/day dose, with a further decrease of 2.7-fold in uHGA excretion. They also verified that, compared to 4 mg/day, increased levels of 6 or 8 mg/day resulted in little or no benefit in achieving HGA reduction and sustaining tyrosine levels. However, Ranganath et al. (2016) in a larger study denominated Suitability Of Nitisinone In Alkaptonuria 1 (SONIA 1) revealed that the decreased urinary excretion of HGA is nitisinone dose-dependent up to serum concentrations of 3μmol/L (equivalent to 8 mg/day), and at this higher dose, there was a reduction of at least 99.4% of uHGA excretion. This information suggests that even higher doses of this drug could lead to a decrease in uHGA excretion of almost 100% in AKU patients. A longer trial, SONIA 2, is currently underway in order to define the effect of nitisinone on clinical symptoms and long-term safety.

The data collected by Introne et al. (2011) suggested that this drug may delay progression of aortic valve disease, but further investigation is necessary.

Overall, nitisinone has potential to prevent morbidity when started prior to the symptomatic phase and to prevent progression in those already symptomatic.

Complications from Nitisinone

One of the most known complications of the use of nitisinone and hypertyrosinemia is ocular alterations, namely corneal opacities, even though it is reversible upon discontinuing the drug.

Suwannarat et al. (2005) studied a series of patients with AKU treated with this drug for 3 to 4 months and they did not observed any ocular manifestations on weekly
ophthalmic examinations. On the other hand, 5% of the subjects of the study controlled by Introne et al. (2011) that were treated with the drug for a variable period between 3 and 4 years, experienced corneal toxicity regardless of plasma tyrosine level, suggesting that some predisposition to toxicity exists independent of the peak plasma tyrosine concentration. In fact, Olsson et al. (2015) reported that the increase in serum tyrosine levels is less clearly related to nitisinone concentrations compared with decreased levels of uHGA excretion.

Another notorious side effect of this treatment consists in the development of neurological problems, once more related to hypertryrosinemia. However, in the trial run by Suwannarat et al. (2005), none of the patients developed this kind of complication and MRI scans of the brain were normal, before and after the treatment.

Never stated before as a complication of the use of nitisinone or hypertryrosinemia, one of the patients treated with nitisinone had renal lithiasis, a well-known complication of AKU itself. The authors thought that it could be related to this treatment, being that the decrease in uHGA excretion resultant of the nitisinone treatment led to the dissolution of already present calculi and resulted in their passage. This could be considered both an adverse event and a long-term benefit of nitisinone therapy.

Suwannarat et al. (2005) and Introne et al. (2011) also verified an increase in serum levels of hepatic transaminases in a few patients, but whether this alteration is consequent of nitisinone or of other factors remains unclear since all of the subjects had other risk factors for hepatotoxicity.

**Antioxidants**

As explained before, ochronosis results from accumulation in the tissues of a melanin-like pigment produced by an oxidative process via BQA. Therefore, another option used to treat AKU is antioxidants, mainly ascorbic acid (AA), commonly known as vitamin C, and N-acetyl-cysteine.

In fact, AA supplementation was found to reduce significantly the levels of BQA in the urine. However, there were no alterations in the urinary excretion of HGA, even with a few studies showing an increase in its value, probably due to activation of the enzyme 4-HPPD by its cofactor ascorbic acid which resulted in an increased production of HGA.

It is believed that antioxidants have a moderate increased risk of cancer, whereby its clinical use should be discussed case by case.
However, because of their small cohort size and their short duration, none of the studies established whether AA could have a positive clinical effect, so different trials are needed.

Thus, even though there are no concrete proves of their benefits, a low protein diet associated with administration of ascorbic acid might be prudent and feasible.

**Symptomatic control**

Even though there is no cure for AKU, the symptomatic control of these patients is crucial and the most important approach given that, as further explained, the disease does not affect life expectancy but has a huge impact in patients' quality of life.

**Lifestyle counselling**

The severity of AKU diverges in siblings with the same mutation and the same gender, which suggests that other factors besides diet can be important in the evolution of the disease. Lifestyle topics such as hobbies, activities and career that minimize joint loading are more likely to be benefic to the patient. However, this subject is often not addressed and evidences to provide this theory are still lacking.\(^6\)\(^47\)

**Pain Control**

Pain is the most mentioned symptom by AKU patients. Its control can be achieved, even partially, by drugs and physical modalities. Paracetamol, non-steroidal anti-inflammatory drugs, opioids, anticonvulsants, local anaesthetics and gabapentin are examples of medications used to treat the pain in AKU patients, similar to patients without AKU. Usually, it is necessary a constant escalating pain relief. Other options to treat the pain are transcutaneous electrical nerve stimulation, acupuncture, physiotherapy and nerve blocks.\(^6\)

**Physiotherapy**

As one of the most important causes of disability in these patients is musculoskeletal incapacity with limitation of activity, this type of treatment is very important, namely in a palliative mode. It can promote optimal muscle strength and flexibility.\(^47\)

Introne et al. (2011), in a 3-year trial using nitisinone where patients were subjected to general exercises conceived specifically for them, and were also given instructions about individualized exercises targeting problematic areas, demonstrated that all AKU patients, even the ones in the control group, responded to consistent strengthening and flexibility exercises. The response to this therapy reflects the critical
role of physiotherapy in the rehabilitation of alkaptonuria and in the improvement of patients’ quality of life. Nevertheless, it is currently underused both by the doctors and the patients.

Ablative Laser Therapy

There is a case report illustrating the treatment of facial ochronosis in a patient with AKU using an erbium: yttrium aluminium garnet laser. Further studies of similar patients will aid in assessing this option as a treatment for ochronosis.

Renal Replacement Therapy

There is a case reported by Heng et al. (2010) where it was thought that renal replacement therapy, essentially hemodialysis, may be capable of eliminating the HGA in excess, but the intensive renal support used in the case failed to improve the outcome of the disease and it had a fatal outcome.

Other Options

Preparations containing glucosamine and chondroitin sulfate, intraarticular hyaluronic acid and steroids injections, arthroscopic debridement of the affected joint, and arthroplasty are other treatment options.

Even though the usual arthritic drugs reduce joint symptoms in the early stages of OOA, they do not decrease the degeneration rate of joints. There has been shown that arthroscopy can temporarily improve symptoms of OOA and the range of motion in these patients, consequently delaying the need for total joint arthroplasty.

Surveillance

Since AKU is untreatable, the best that we can do is treat its complications, namely of the heart, kidney and prostate, whereby its surveillance must start after the fourth decade of life.

Pettit et al. (2011) and Hannoush et al. (2012) recommend baseline echocardiogram screening after 40 years old in order to detect valvular heart disease and cardiac computed tomography to detect coronary artery calcifications. Patients with aortic regurgitation could be offered an angiotensin converting enzyme inhibitor, which may modify disease progression and surgical intervention is generally reserved for cases of severe symptomatic aortic valve disease.
Kidney function should be monitored every year in these patients and when they
develop chronic decreased kidney function, monitoring should be performed every
month to detect any rapid evolution of the disease.\textsuperscript{48}

**Organ Transplantation**

There is a case report suggestive of the cure of AKU with liver transplantation.\textsuperscript{64} Renal transplantation has also been associated with partial cure of AKU in a patient
with chronic kidney disease, given that there was a reduction of uHGA levels and
normalization of plasma HGA levels, thought to be related with the previously referred
activity of the kidney to produce HGD.\textsuperscript{28}

However, given that this is a disease with a preserved life expectancy, organ
transplantation seems unjustified.\textsuperscript{5}

Arnoux et al. (2015) proposed a sequential strategy to treat AKU patients since
childhood. According to them, during childhood it must be applied a vegetarian diet with
mineral and vitamin supplements if needed, while during adulthood the choice would
be an association of nitisinone with a mild protein restriction diet (e.g. vegetarian diet,
three dairy products per day). Before and during pregnancy, nitisinone should be
discontinued.\textsuperscript{50}

**Future Therapies**

The ideal treatment would be enzyme or gene replacement therapy, but they are
not currently available and a long way and much further investigation is necessary
before we can think about these options.
Prognosis

Many years ago, the effect of AKU in life expectancy was not determined, even though many lived until old ages, with one patient reaching to 99 years old. More recently, it is known that this condition is relatively benign and does not affect life expectancy. However, it affects significantly patients’ quality of life mainly due to osteoarticular repercussions. 2,13

Overall, this entity has a poor prognosis since it is progressive and it does not have an approved treatment to modify its natural history. 6,5

As in the general population, the most common causes of death in these patients are cardiovascular disease, cancer and infectious diseases. 6
Conclusion

AKU is a rare metabolic disease with an autosomal recessive inheritance, which has a characteristic triad of clinical features: homogentisic aciduria, ochronosis and ochronotic osteoarthropathy. Despite these typical findings, this pathology can have systemic manifestations, mostly affecting the ear, eye, skin, heart, prostate and kidney.

The fact that it is more exuberant and sometimes only suspected during adulthood brands it as a unique disease among all other genetic metabolic diseases.

In this way, AKU is a disease that cannot be ignored and given its systemic repercussions it must be known by physicians from a large variety of specialties. It also has a considerable impact in patients’ quality of life, mainly due to osteoarthropathy, whereby its correct diagnosis is crucial in order to allow proper monitoring of these patients.

In the last decades, there were scarce new findings about the disease with the most problematic area being related to the treatment. There are a variety of options currently in consideration, but the published studies report no specific conclusions and refer the importance of undertaking other trials. The most promising therapy to control AKU is nitisinone, but it is not currently approved and more studies are necessary before conclusions about the benefits in the progression of the disease can be made. The goal to cure AKU, although still distant, is enzyme or gene replacement therapy.
Resumo Circunstanciado

Introdução

A alcaptonúria é uma doença rara do metabolismo, de transmissão autossômica recessiva.

Estudada em 1908 por Archibald Garrod, foi a patologia responsável pela criação e evolução do ramo das doenças hereditárias do metabolismo na medicina.\(^1\)

Trata-se de uma aminoacidopatia que se caracteriza pela ausência de homogentisato 1,2-dioxidase, uma enzima responsável pela conversão de ácido homogentísico em ácido maleiloacetocético na via metabólica da tirosina e da fenilalanina. Consequentemente, a doença resulta da acumulação de ácido homogentísico nos tecidos e da elevada excreção renal deste ácido, que dão origem à tríade associada à alcaptonúria de acidúria homogentísica, ocrônose e osteoartropatia ocrônótica.\(^2\)\(^3\) A doença tem um atingimento sistémico, com manifestações cardiovasculares, músculo-esqueléticas, genito-urinárias, oculares, cutâneas e respiratórias.\(^4\) De facto, virtualmente todos os tecidos conjuntivos podem ser afetados por esta entidade.\(^5\)

As suas manifestações surgem habitualmente na idade adulta, com exceção da acidúria homogentísica que pode estar presente após o nascimento.\(^2\) Este facto torna a alcaptonúria uma entidade única entre as doenças metabólicas genéticas. O diagnóstico baseia-se na determinação de elevados níveis de ácido homogentísico na urina.\(^6\)

Apesar da alcaptonúria ter sido descrita há mais de um século e ser alvo de intensa investigação, ainda não existe nenhuma terapêutica eficaz. Assim, a abordagem atual mais importante passa pelo controlo dos sintomas, sobretudo devido ao grande impacto que estes têm na qualidade de vida dos doentes.\(^2\) Atualmente, a terapêutica mais promissora parece ser a nitisinona, inibidora da enzima responsável pela produção de ácido homogentísico, a 4-hidroxifenilpiruvato dioxidase.

Esta dissertação pretende, por conseguinte, rever extensivamente a bibliografia existente até à data sobre a alcaptonúria, nomeadamente no que diz respeito à sua história, genética e via metabólica, epidemiologia, manifestações clínicas e evolução natural, diagnóstico, tratamento e prognóstico. Apesar de ser uma entidade rara, a precocidade do seu diagnóstico é de máxima importância, para tentar minimizar a progressão/consequências da doença, que podem ser muito limitantes em termos de qualidade de vida dos doentes.
Materiais e Métodos


Não foi selecionado nenhum limite temporal relativo à data de publicação dos artigos, sendo que os mesmos foram selecionados com base no seu título e resumo. Os artigos citados incluem artigos originais, relatos de casos e artigos de revisão.

História

O primeiro caso de alcaptonúria foi descrito em 1500 AC na múmia egípcia Harwa que apresentava calcificação extensa de todos os discos intervertebrais e áreas hiperpigmentadas nos ossos e articulações que continham ácido homogentísico.7

A doença foi pela primeira vez descrita em 1866 por Rudolf Virchow após a observação de um doente com escurecimento das cartilagens articulares, laringe, anéis traqueais, meniscos e discos intervertebrais. Ao microscópio, o pigmento parecia ter uma coloração amarelo-acastanhado, pelo que Virchow atribuiu o termo ocronose a esta característica, em resultado da tradução da língua grega de ‘doença amarela’. Três anos depois, Archibal Edward Garrod estabeleceu que esta era consequência de uma anomalia bioquímica com transmissão genética sugestiva de uma doença autossómica recessiva, devido ao aumento da incidência da alcaptonúria em famílias com relações consanguíneas. Contudo, foi apenas em 1908 que Garrod conseguiu que a alcaptonúria fosse reconhecida mundialmente e na qualidade de doença por “erros hereditários do metabolismo”, onde também se incluíram outras patologias como o albinismo, a cistinúria e a pentosúria.9 Assim, a alcaptonúria foi a patologia responsável pela criação e evolução do ramo das doenças hereditárias do metabolismo na medicina.1

Genética e Vias Metabólicas

A alcaptonúria é caracterizada pela ausência de homogentisato 1,2-dioxidase, uma enzima envolvida na via de metabolismo dos aminoácidos fenilalanina e tirosina responsável pela conversão de ácido homogentísico em ácido maleiloacetoacético (figura I). A deficiência desta enzima resulta, por isso, na não metabolização e subsequente acumulação de ácido homogentísico, responsável pelas manifestações clínicas.2
Em 1995, o defeito genético foi localizado no cromossoma 3 (3q21-q23), estando identificadas até à data desta revisão 174 mutações associadas à doença.¹³¹⁵²¹

Parece não existir uma relação óbvia entre o genótipo e o fenótipo dos doentes, já que uma redução moderada da atividade da enzima nem sempre explica a doença e, para existirem sintomas da mesma, a atividade da enzima terá de estar diminuída em mais de 99%.¹⁸²³

**Epidemiologia**

A nível mundial, a prevalência desta entidade é baixa em todos os grupos étnicos, 1 caso em cada 250.000-1.000.000 nascimentos. Contudo, a alcaptonúria apresenta uma prevalência aumentada em regiões como a Eslováquia (1 caso em 19.000 nascimentos), a República Dominicana, a Índia e a Jordânia. Pensa-se que esta diferença seja explicada pelo efeito de fundador em sequência da migração e da perda de variação genética.²¹⁷²⁵

Não existe diferença na prevalência da alcaptonúria entre géneros, mas sabe-se que os homens têm uma progressão mais rápida da doença.²⁶

**Manifestações Clínicas e Evolução Natural**

Na sequência da ausência de homogentisato 1,2-dioxidase, ocorre elevada excreção renal e deposição no tecido conjuntivo de ácido homogentísico, que são responsáveis pela triade associada à alcaptonúria de acidúria homogentísica, ocronose e osteoartropatia ocronótica.²

Mesmo tratando-se de uma doença genética, a única expressão de alcaptonúria presente até à vida adulta na maioria dos casos é o escurecimento da urina resultante da acidúria homogentísica. As características próprias de ocronose tipicamente começam na quarta década de vida, tendo sido estipulado que este atraso relativamente ao aparecimento de acidúria homogentísica seja devido à diminuição da taxa de filtração dos rins associada à idade, com consequente diminuição da eliminação de ácido homogentísico e acumulação no tecido conjuntivo.⁵²³

**Acidúria Homogentísica**

A maioria do ácido homogentísico produzido pelo organismo é excretado pelos rins através de filtração e secreção ativa. Por conseguinte, em ambientes com pH alcalino ou quando a urina é exposta ao ar por longos períodos de tempo, o ácido oxida e provoca o escurecimento da urina.⁸²⁷²⁸ Esta reação é dependente do pH, pelo
que pode não ocorrer quando a urina tem pH ácido. Este facto é um dos motivos pelo qual o escurecimento da urina pode passar despercebido ao doente. 29 30

Ocronose

O escurecimento do tecido conjuntivo próprio da alcaptonúria resulta da deposição de ácido homogentísico com consequente oxidação e polimerização e denomina-se ocronose. Isto leva a que os tecidos se tornem frágeis e suscetíveis a fratura, conduzindo a uma rápida degeneração das articulações. A ocronose é, por isso, o principal evento fisiopatológico da doença e é responsável por complicações como artrite, doença cardíaca valvular, litíase, osteopenia, fraturas e rotura de músculos, tendões e ligamentos.2 3 5 32-34 Virtualmente todos os tecidos conjuntivos são afetados pela alcaptonúria, sendo a manifestação mais típica a hiperpigmentação da orelha, que adquire uma cor preto-azulada, seguida pela pigmentação da esclerótica e da pele.5 8 33

Estas alterações surgem na terceira e quarta décadas de vida com o envolvimento da orelha (figura II) a ser o sinal mais precoce de ocronose. Este pode ser assintomático ou provocar acufenos, diminuição da acuidade auditiva e surdez.8 Um dos sinais mais característicos de atingimento do olho é o sinal de Osler, que consiste na pigmentação acastanhada da esclerótica (figura III), inicialmente nas regiões temporal e nasal e posteriormente de toda a área entre a córnea e as regiões temporal e nasal.4 8 30 Geralmente não existe défice visual significativo associado.4 37 A alteração da pigmentação da pele é mais exuberante nas áreas de exposição solar e de maior concentração de glândulas sudoríparas, como a face, as axilas e os genitais, sendo que o suor pode manchar a roupa de tons acastanhados.4 8

Osteoartropatia Ocronótica

A deposição do ácido homogentísico na cartilagem articular hialina dá origem à osteoartropatia ocronótica, uma das características mais definidoras da doença e também a mais limitante para a qualidade de vida dos doentes.2

Surge habitualmente na terceira e quarta décadas de vida (figura IV) e apresenta uma evolução progressiva para a cronicidade.8 As articulações de suporte do peso, como a coluna, a anca e o joelho, são as que mais frequentemente são afetadas por esta patologia, sendo que habitualmente ocorre um envolvimento sequencial da coluna e das articulações periféricas. Sendo esta uma das características mais restritivas da doença, a diminuição da capacidade física do doente pode ser tal que este esteja totalmente incapacitado por volta dos 60 anos. Em estados avançados de
Alcaptonúria, os doentes podem apresentar uma postura típica caracterizada por coluna rígida e anca e joelho fletidos.\textsuperscript{6,38-40}

Outras Manifestações

À semelhança do que acontece noutros tecidos, o pigmento ocronótico também se pode depositar no endocárdio, nas válvulas cardíacas e nas artérias coronárias.\textsuperscript{4,8,41} A estenose da válvula aórtica é a manifestação cardíaca da doença mais frequente, seguida pelo atingimento das válvulas mitral e pulmonar.\textsuperscript{41} Por sua vez, a incidência de arteriosclerose e doença arterial coronária em doentes com alcaptonúria não parece ser maior do que na população geral, o que favorece a hipótese de que esta entidade não contribui significativamente para o processo arteriosclerótico.\textsuperscript{8,41} Da mesma forma, também não foram encontradas evidências de que a ocronose pudesse originar alterações da condução cardíaca.\textsuperscript{41}

Assim, as manifestações clínicas cardiovasculares da alcaptonúria incluem dispneia, dor torácica e sopros cardíacos.\textsuperscript{26,27,43,44}

Sendo a alcaptonúria uma doença sistémica, também se manifesta ao nível do trato genito-urinário, afetando mais comumente os homens e principalmente a próstata.\textsuperscript{8}

A presença de cálculos prostáticos e de cálculos renais, surge habitualmente na quinta e sexta décadas de vida (figura IV).\textsuperscript{24} Apesar dos cálculos poderem resultar em obstrução e infeção, a maioria dos doentes é assintomática e os cálculos são achados incidentais.\textsuperscript{4,46}

A deposição do pigmento ocronótico no parênquima renal, por si só, não costuma causar doença renal clinicamente evidente, sendo necessária uma doença renal adicional e não associada para que haja diminuição da taxa de filtração com consequente aumento da deposição do ácido e agravamento da patologia.\textsuperscript{8,28,34,48}

Diagnóstico

Atualmente, o diagnóstico de alcaptonúria é feito através da quantificação do ácido homogentísico presente numa amostra de urina de 24h usando técnicas de cromatografia gás-liquido ou de camada fina.\textsuperscript{6,30,38}

A determinação da quantidade de ácido homogentísico presente numa amostra de urina é suficiente para estabelecer o diagnóstico da doença.\textsuperscript{6} Contudo, a quantificação da atividade residual da enzima em défice através de espectrofotometria, seguida de teste genético são também importantes na avaliação adicional da doença.
O rastreio neonatal não está ainda preconizado em nenhum país a nível mundial.²

**Tratamento**

Até ao momento, várias foram as tentativas de tratar a alcaptonúria e as complicações associadas. Contudo este objetivo ainda não foi atingido e a terapêutica mais promissora atualmente em investigação é a nitisinona, um fármaco inibidor da enzima 4-hidroxifenilpiruvato dioxidase responsável pela produção de ácido homogentísico. A nitisinona é já utilizada para tratar outras doenças metabólicas como a tirosinemia tipo I. Ao inibir a enzima 4-hidroxifenilpiruvato dioxidase e a produção de ácido homogentísico, provoca hipertirosinemia.⁵² Até à data foram poucos os ensaios realizados envolvendo esta hipótese de tratamento, sendo que estes demonstraram uma redução da quantidade excretada de ácido homogentísico, com melhoria subjetiva dos sintomas manifestados pelos doentes e sem alterações significativas nos parâmetros clínicos e objetivos.⁵²⁵⁴

Tendo em conta que a alcaptonúria é uma doença metabólica envolvendo o metabolismo dos aminoácidos fenilalanina e tirosina, um dos primeiros tratamentos sugeridos foi a ingestão de uma dieta pobre em proteínas. Apesar desta ser uma das opções mais lógicas, na prática pensa-se que não seja útil e que, a longo prazo, os doentes apresentem baixa adesão.⁵¹

Outra das alternativas de tratamento da alcaptonúria consiste na utilização de antioxidantes, uma vez que as manifestações clínicas resultam da acumulação de pigmento ocronótico produzido a partir de um processo de oxidação. Nesta categoria são considerados o ácido ascórbico, conhecido como vitamina D, e a N-acetil-cisteína. Os estudos realizados não conseguiram demonstrar a diminuição da quantidade excretada na urina de ácido homogentísico, com alguns ensaios a evidenciarem até um aumento da mesma, pelo que são necessários mais ensaios para aferir o papel destes fármacos no controlo da doença.⁶⁵⁰⁵¹⁵⁸

A abordagem atual mais importante compreende o controlo dos sintomas, especialmente tendo em conta que a alcaptonúria tem um grande impacto na qualidade de vida dos doentes. Este objetivo pode ser conseguido através de orientações sobre o estilo de vida, controlo da dor, fisioterapia, cirurgia paliativa, terapia ablativa com laser, terapêutica de substituição renal e vigilância.

Foi ainda considerada a possibilidade de cura da alcaptonúria após transplante hepático.⁶⁴ Contudo, dado o facto da doença não afetar a sobrevida dos doentes, esta hipótese parece pouco justificável.²
O tratamento ideal seria a terapêutica de substituição gênica ou enzimática, mas esta ainda não está disponível e é necessária investigação adicional antes que se possa considerar esta opção.

Prognóstico

Sabe-se hoje que a alcaptonúria não afeta a sobrevida, mas antes a qualidade de vida dos doentes, principalmente devido às repercussões osteoarticulares da doença.¹²¹³

Sendo uma doença progressiva e sem tratamento eficaz, a morbilidade associada é elevada.⁶⁵

Conclusão

A alcaptonúria é uma doença metabólica rara de transmissão autossômica recessiva e que apresenta uma tríade característica de manifestações clínicas: acidúria homogentísica, ocronose e osteoartropatia ocronótica. É uma doença sistémica, com atingimento preferencial da orelha, olho, pele, coração, próstata e rim.

A alcaptonúria é mais exuberante durante a idade adulta, o que a distingue da maioria das doenças metabólicas hereditárias e que condiciona atraso no reconhecimento.

Assim, esta é uma entidade clinicamente particular, de fácil diagnóstico e seguramente subdiagnosticada. Dado o seu caráter sistémico e morbilidade significativa com subsequente má qualidade de vida dos doentes, sobretudo pela osteoartropatia, é essencial um diagnóstico precoce de forma a permitir uma monitorização adequada dos doentes e prevenção do dano irreversível.

Nas últimas décadas, existiram poucas descobertas sobre a doença, sendo a área do tratamento a mais problemática. Atualmente existe uma variedade de potenciais opções terapêuticas, mas os estudos publicados até à data relatam resultados pouco consistentes e remetem para a necessidade de mais ensaios. A terapêutica mais promissora para a alcaptonúria é a nitisinona, mas a sua utilização ainda não está aprovada e mais estudos são necessários antes que se possam estabelecer conclusões sobre os benefícios deste fármaco na progressão da doença.

O objetivo, ainda longínquo, é a terapêutica de substituição gênica ou enzimática.
REFERÊNCIAS BIBLIOGRÁFICAS


