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ALKAPTONURIA – FIRST INBORN ERROR OF METABOLISM KNOWN FOR A CENTURY AND NEW TREATMENT OPTION – PRELIMINARY REPORT

ALKAPTONURIA – PIERWSZA WRODZONA WADA METABOLIZMU ZNANA OD WIEKU I NOWA METODA LECZENIA – DONIESIENIE WSTĘPNE

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Abstract

Alkaptonuria is a rare inborn error of metabolism, identified over a century ago. But its basic pathomechanism (i.e. ochronosis) is still not completely explained. Though clinical onset of osteoarthropathy and complications from other organs (including: heart and blood vessels, skin, eyes, kidneys) occurs at adult age, the symptoms are progressive, cause severe pains and significantly limit everyday life of the patients. Until now no effective therapeutic methods have been known in alkaptonuria. Recently, thanks to an initiative of the international patient organization for alkaptonuria, a hope for a potential treatment availability, appears. So, alkaptonuria is an example of a role of multidisciplinary care, cooperation and ongoing progress in the area of rare diseases.

Key words: alkaptonuria, inborn error of metabolism, ochronosis, nitisinone

Streszczenie

Alkaptonuria jest rzadką wrodzoną wadą metabolizmu, zidentyfikowaną ponad sto lat temu. Nadal jednak podstawowy jej patomechanizm (tj. ochronoza) nie jest do końca wyjaśniony. Choć objawy kliniczne osteoartropatii i powikłań ze strony innych narządów (w tym: serca i naczyń krwionośnych, skóry, narządu wzroku, nerek) ujawniają się w wieku dorosłym, mają postępujący charakter i powodują silne dolegliwości bólowe oraz w znacznym stopniu ograniczają codzienne funkcjonowanie pacjentów. Do tej pory nie były znane skuteczne metody leczenia w alkaptonurii. Ostatnio dzięki inicjatywie międzynarodowej organizacji pacjentów z alkaptonurią, pojawiła się nadzieja dostępu do potencjalnie skutecznej terapii. Alkaptonuria jest więc przykładem znaczenia wielodyscyplinarnej opieki, współpracy oraz postępu, jaki dokonuje się w obszarze chorób rzadkich.

Słowa kluczowe: alkaptonuria, wrodzona wada metabolizmu, ochronoza, nityzynn

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Alkaptonuria (MIM #203500) was described (together with three other diseases) for the first time by Archibald Garrod in 1908 [1]. He was the first, who gave the name of these diseases, which is still in use - "inborn errors of metabolism", although only after over fifty years enzymatic

defect was revealed, as deficiency of homogentisate 1,2 dioxygenase (HGO) (EC 1.13.11.5) [2]. Crystal structure of HGO was reported in 2000 [3]. This enzyme is involved in the breakdown of tyrosine and phenylalanine. HGO acts at the third step of phenylalanine metabolic pathway,

converting homogentisic acid (HGA, known as alkapton) to maleylacetoacetic acid.

The *HGD* gene maps to chromosome 3q13.33, encompassing 14 exons [4]. By now there are more than hundred identified mutations responsible for alkaptonuria, with predominance of missense mutations [5]. It was the first human disease, which was shown by Garrod as transmitted by Mendelian trait at the beginning of the last century. The genetic trait is autosomal recessive, but interestingly male patients usually suffer from more severe clinical signs and symptoms. The metabolic effect is increased concentration of HGA in blood and urine. HGA oxidizes giving the urine a deep brown color. Therefore the disease was used to be diagnosed during infantile period by observation of darkening diapers. Nowadays, when pampers are in common use, such abnormality is easily missed, so the correct diagnosis is frequently delayed. This delay may be quite significant, because the first symptoms occurring after infantile period, generally appear at the fourth or the fifth decade of life.

Alkaptonuria (called also “black bone disease”) causes severe pain associated with progressive osteoarthritis. Chronic, severe back and joint pain is a dominant clinical symptom in patients with alkaptonuria. Such joints as: hips, knees and shoulders, but also spine are most affected. First skeletal symptoms occur usually at age of the 20s and 30s, when back pain becomes evident. The patients start suffering from knee pain in their 40s. Hip and shoulder pains typically appear later, but before age of 50 years. The clinical onset varies; dependently on individual person and/or individual disease phenotype and course. Due to arthropathy joint replacements are frequently required; by age of 55 years many patients have at least one joint already replaced. Unfortunately such management is insufficient. Bones and cartilage destruction, as other symptoms in alkaptonuria, are due to ochronosis. This term was used by Rudolf Virchow already in the 19th century. Ochronosis means pigmentation of the connective tissue caused by accumulation of HGA. It associates with collagen fibers, which is followed by non-catalytic polymerization and oxidation to benzoquinoneacetic acid (BQA). Such binding becomes irreversible and looks like melanin-like pigment deposits. As a consequence it leads to tissue dysfunction. So cartilages all over the body become black and brittle. Vertebral changes and disc calcification result in spine deformity, stiffness and severe pain. From clinical and radiological aspects the symptoms may imitate ankylosing spondylitis.

Beside cartilage alkaptonuria affects skin, sclera, but also cardiac valves and kidneys. Skin becomes dark, sweat is black and stains clothes, especially at areas of the body, which are exposed to the sun and where sweat glands are located. Hyperpigmentation is initially seen in the ear lobes, then in the nasal bridge, cheeks, hands and tendons.

Sclera becomes dark, which is visible relatively early. Changes appear at various shapes and areas, but in most cases are symmetrical [6]. Additionally some recent case reports showed progressive astigmatism, glaucoma and

anterior uveitis as possible pathological conditions in the course of alkaptonuria [7]. Corneal “oil-drops” seem to be pathognomonic to ochronosis.

Pigment deposits in the cartilage of larynx, trachea and bronchi cause respiratory problems, as well as result in formation of atherosclerotic plaques in the blood vessels. Moreover calcification of the coronary arteries leads to dysfunction of the cardiac valves (mainly mitral and aortic valves) and so called black aorta.

The presence of HGA in urine expresses high lithogenic effect [8]. So to the genitourinary symptoms belong urolithiasis and prostatolithiasis.

Interestingly, in the alkaptonuria mouse model ochronosis is not observed, what may be explained by higher murine capacity of HGA excretion, thus preventing elevated blood concentration or by protection through endogenous production of vitamin C [9].

Alkaptonuria is an ultrarare disease; less than one in 250.000 – 1 million people are affected. But the worldwide highest incidence is observed in Slovakia - 1:19.000 live births [10].

Several trials to treat patients with alkaptonuria have been performed until now. They have been based mainly on symptomatic treatment. Adequate pain control is needed, but long-acting non-steroidal anti-inflammatory agents are frequently inefficient. It is worth noticing that in alkaptonuria inflammation seems to be prevalent pathomechanism (though varies in intensity), but also pro-aggregating and pro-amyloidogenic power of HGA and BQA play a role [11, 13]. HGA and BQA promote local inflammation, production of serum amyloid and formation of amyloid fibrils.

All patients with alkaptonuria should be monitored for possible clinical complications. As in other rare diseases, due to multisystem involvement, multidisciplinary team is required to maximize the effectiveness of a management.

Chronologically therapeutic options included: high dosage of vitamin C, protein (or phenylalanine and tyrosine) restricted diet and nitisinone. Administration of high doses of ascorbic acid (as an antioxidant) was beneficial in animals, but not in humans. Some clinical reports suggested that a low-protein diet; particularly with reduced amount of phenylalanine and tyrosine (as precursors of HGA), may slow disease progression, but it was never proved. Currently vegetarian diet is preferred for the patients with alkaptonuria [14].

Recently new hope has appeared for the patients with alkaptonuria. New drug, which actually has been already known as a therapy of choice in tyrosinaemia type 1 for over twenty years, has been introduced in treatment of alkaptonuria. It is nitisinone (previously called NTBC, nowadays - Orfadin[®]), which is a herbicide by origin, but inhibits the enzyme that produces HGA. Therefore an efficacy of nitisinone in alkaptonuria is expected. So far undertaken studies on a safety and efficacy of nitisinone showed that this medication is safe and beneficial in terms of reducing endogenous HGA production by up to 95 per cent in the adult patients, during treatment with nitisinone. First trials were performed in the USA ten years ago [12]. Currently

the project „Clinical Development of Nitisinone for Alkaptonuria” (acronym DevelopAKUre) is underway in Europe with three contributing centres; in United Kingdom, France and Slovakia.

To test nitisinone as a specific therapy in alkaptonuria was an initiative of the Alkaptonuria Society. The Alkaptonuria Society, which is support organisation for the patients with alkaptonuria and their families, proactively looks for a cure for this rare severe disease. It helps patients via website www.alkaptonuria.info and through many other activities regarding information, education, contacting patients, research and both general and specific support, including setting up the National Alkaptonuria Centre.

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Conflicts of interest/Konflikt interesu

The Author declare no conflict of interest.

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