History

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Content

AKU is an ancient disease; scientists have found evidence of alkaptonuria in the Egyptian mummy Harwa dated 1500 B.C. However, the term alkaptonuria (AKU) was used for the first time in 1859 in a female patient who had a reducing compound detected in urine. Later on, this compound was identified as homogentisic acid. In 1890, the English physician Archibald Garrod examined the urine of a 3-month-old boy – it was yellow brownish and Dr. Garrod diagnosed alkaptonuria. At that time, it was assumed that alkaptonuria was induced by a bowel bacterial infection. However, Garrod also examined the parents of the boy, and he found out that they had a close family relationship (cousins). After examining several patients and their families, he concluded that the answer to his questions was provided in the work of Mendel on inheritance that had appeared in England at that time. In 1902, Garrod proposed the hypothesis that alkaptonuria is an inherited metabolic disease, and the lack of the enzyme which degrades homogentisic acid is the result of a defective gene. Later on, this conception proved to be true. His article on alkaptonuria was published in the Lancet (Garrod 1908). At that time, it was a daring statement when we realise how little was known of enzymes, human genetics

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and intermediary metabolism. His knowledge was summarised in the book called 'Inborn Errors of Metabolism' (Garrod 1909). For his scientific work, he became a member of the Royal Society, and he was knighted in 1918. Almost half a century later in 1958, La Du published biochemical proof of the defect in AKU (La Du et al. 1958). He demonstrated the absence of activity of 1,2-dioxygenase of homogentisic acid in liver homogenates from a patient with AKU, and he found out that the defect was associated with one enzyme. He assumed that affected persons do not synthesise this enzyme. The gene responsible for AKU was localised in 1993 by Pollak et al. in chromosome 3 (3q2) (Pollak et al. 1993). Siťaj, Červeňanský, Urbánek, Hüttl and other co-workers significantly contributed to the knowledge of clinical manifestations of alkaptonuria and ochronosis (Siťaj 1947, 1977; Urbánek and Siťaj 1955; Siťaj et al. 1956; Hüttl et al. 1966). In 1947, Siťaj diagnosed and described the first case of alkaptonuria (Siťaj 1947), and by 1953, he and his co-workers had collected a set of 102 patients, while there were only about 100 predominantly sporadic cases described worldwide at that time. Slovakia and the Dominican Republic were presented in the world literature as the countries with the highest incidence of alkaptonuria (1:19,000 people). One case per 250,000 to 1 million people is given worldwide (Phornphutkul et al. 2002). Siťaj, Červeňanský and Urbánek dealt with the description of ochronosis and its development in patients with AKU as well as with its detailed clinical manifestations in joints. The results were published in the monograph *Alkaptonuria and ochronosis* (1956) – the first one in the international literature. Their pioneering works are still quoted. In 1968, Sršeň and his co-workers (Sršeň and Neuwirth 1974; Sršeň 1984; Sršeň and Sršňová 1996; Sršeň et al. 1996, 2002) from the Research Laboratory of Clinical Genetics in Martin continued their epidemiological and genetic studies in patients suffering from AKU in Slovakia. The following institutions participated in the molecular characterisation of mutations in the Slovak population: the Institute of Molecular Physiology and Genetics of Slovak Academy of Sciences in Bratislava and Faculty of Natural Sciences of Comenius University in Bratislava (Zaťková et al. 2000a, b, c). The majority of the followed families came from the locations in Slovakia that were studied by Siťaj et al. and later on by Rovenský with his co-workers. Genetic aspects were studied by Bošák in cooperation with institutions in Bratislava (Rovenský and Urbánek 2000, 2003; Rovenský et al. 2000; Zaťková et al. 2000a, b, c). Current diagnostic innovations contributed to the characterisation of alkaptonuria as a separate diagnostic entity. Magnetic resonance imaging can display a thickening of the Achilles tendon; CT scans and echocardiography can reveal coronary arterial calcification or injury of the heart valve. Prostate stones in ochronosis can be visualised by X-ray, and kidney stones can be detected by ultrasonography. Biochemical analysis of urine shows increased excretion of telopeptide fragments of collagen (NTx) suggesting increased bone resorption. The results of molecular genetics enable DNA diagnostics of AKU which is considered the definitive diagnosis of the disease and represents qualitatively the highest degree of diagnostics.

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