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Alkaptonuria: a 60-yr follow-up

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In 1901, Sir Archibald Edward Garrod made the seminal observation on the inheritance of the inborn errors of metabolism [1, 2]. He described a newborn infant whose urine darkened in its napkin on exposure to air and contained homogentisic acid [2]. The infant was born to apparently normal consanguineous (first cousins) parents and was their fifth child. An older sibling (Thomas P) had previously been shown by Garrod to have alkaptonuria. At that time the inheritance of alkaptonuria and other metabolic conditions was not understood. Garrod was aware that the mother of Thomas P was pregnant and made arrangements to carefully observe all the napkins. The infant was born on 1 March 1901 and the typical dark staining was not observed until the third day, when breast feeding and therefore protein intake had been established. Garrod deduced that the occurrence of two siblings with alkaptonuria and consanguineous parents suggested an inherited cause. He was aware of one similar family and that there were no recorded instances of alkaptonuria occurring in two generations of the same family. In 1901, Garrod was not fully aware of Mendel's work on the genetics of peas. However, by the end of 1902 following correspondence with the botanist and geneticist William Bateson he was able to conclude that ‘...there seems to be little room for doubt that the peculiarities of the incidence of alkaptonuria and of conditions which appear in a similar way are best explained by supposing that, leaving aside exceptional cases in which the character usually recessive assumes dominance, a peculiarity of the gametes of both parents is necessary for its production’ [3]. The occurrence of a normally recessive disorder in successive generations would now be termed pseudodominance due to one parent being a homozygote and the other being a heterozygote and therefore clinically silent.

Alkaptonuria (Mendelian Inheritance in Man number 203500) is an inherited disorder of aromatic amino acid metabolism in which homogentisic acid (2,5-dihydroxyphenalacetic acid) accumulates behind the metabolic block [deficiency of homogentisate 1,2-dioxygenase (HGO)] and is excreted in the urine. The urine is of normal colour when passed but rapidly darkens to jet black on exposure to atmospheric oxygen or other oxidative conditions. The abnormality may be noticed when a child’s napkins are noted to darken when urine gets stained, but occasionally passes unnoticed until the patient presents in middle or late life with back pain due to spinal ochronotic spondylosis and the characteristically densely calcified intervertebral discs with relatively few other symptoms of degenerative arthritis.

Only a small proportion of the homogentisic acid formed endogenously is retained in the body because of its high renal clearance; that which gets retained is oxidized to benzoquinone acetic acid under the influence of polyphenol oxidase, and polymerizes to form a macromolecule that damages and blackens connective tissues including cartilage. The black inelastic cartilage is visible in the auricles (Figs 1 and 2). The pigmentation is called ochronosis because although grey-black grossly, it is ochre microscopically. Generally the pigmentation does not appear until 20–30 yrs of age [4]. The typical radiographic appearances of ochronotic spondyloarthropathy are typical wafer like calcifications in the intervertebral discs, with narrowing of disc spaces and osteoporotic rarefraction of the vertebral bodies [4] as shown in Fig. 3. The term alkapton and hence alkaptonuria contains Greek and Arabic roots and is intended to denote the substance’s rapid absorption of oxygen when exposed to either alkali or room air.

In 1958, one of us saw a Mr AP with alkaptonuria and the story circulated that he was the same infant described in Garrod’s seminal paper in 1901. This is confirmed by a search of the 1901 census in which a family with the surname P and with a structure corresponding to that described by Garrod resided in Bethnal Green. Figures 1 and 2 show the characteristic pigmentation in the conjunctiva and auricular of AP taken in 1958 and 1960, respectively. Figure 3 shows the typical ochronotic spondylosis we believe that was taken in the early 1960s. These images are we feel of historic interest and show that Garrod’s historic infant did indeed progress to demonstrate the typical features of the condition, which in its later stages is of interest to rheumatologists and spinal surgeons.

Archibald Edward Garrod (1857–1936) was the son of Alfred Baring Garrod (1819–1907). Both father and son were prominent physicians in London with a particular interest in rheumatic disease, especially gout and were elected to fellowships of the Royal Society (FRS). Archibald obtained a first class honours degree in chemistry from Oxford University in 1880 and then studied medicine at St Bartholomew’s Hospital, London qualifying in 1884. Except for military service as a colonel in the RAMC during the First World War he remained at St Bartholomew’s Hospital for the rest of his career until he was invited to become Regius Professor of Medicine at Oxford University in 1920. Archibald was one of the staff of the Hospital for Sick Children, Great Ormond Street, London as well as at St Bartholomew’s Hospital.

Archibald continued to work actively as a chemist throughout his career often combining the roles of chemical pathologist and physician. His research field was the identification and chemical characterization of urinary pigments, hence his interest in ‘black urine disease’ as alkaptonuria was then known. It was also known that alkaptonuric patients’ urine could reduce Fehling’s solution suggesting glycosuria and leading to diagnostic problems,
although such confusion could be avoided by using appropriate chemical investigations that were then available.

By the time that Archibald published his seminal paper in 1901, which led to his establishing that alkaptonuria is inherited as a Mendelian autosomal recessive, 2,5-dihydroxyphenylacetic acid had been isolated from alkaptonuric patient’s urine. His contribution on the chemical front was to recognize that this could arise from failure to open the benzene ring of tyrosine and phenylalanine and this was reported in his 1908 Croonian lecture to the Royal College of Physicians and the term ‘inborn error of metabolism’ coined [5]. This has now been fully confirmed, the whole metabolic pathway is known and the deficient enzyme was identified by La Du et al. in 1958 [6]. The mutant gene HGO has been identified and more that 60 mutations have been identified [7].

It was this combination of what we would now call General Internal Medicine and Paediatrics and collaboration with the botanist and geneticist William Bateson that enabled him to recognize that four rare diseases, the first of which was alkaptonuria were inherited in accordance with Mendel’s laws, thus laying the foundation for modern human biochemical genetics.

He continued to develop these ideas, and that there is a dual component, genetic as well as environmental, to the aetiology of diseases that are not inherited along simple Mendelian lines, and ultimately to his final classic monograph ‘The inborn factors in disease: an essay’ in 1931 [8]. The concept of this duality of disease aetiology, inherited by environmental factors is now fully recognized and is the basis of current molecular and proteomic research.

References