Polycystic kidney disease: antiquity to the 20th century

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History of polycystic kidney disease

Polycystic kidney disease is a common disease, the prevalence of which is not likely to have changed markedly over the centuries because of the late onset of its clinical manifestations. It has inflicted great suffering on mankind and has probably influenced human culture and history. Yet, the early descriptions of polycystic kidney disease are difficult to trace with confidence. This may be due, in part, to the theories of the origin of human disease which were prevalent in antiquity and in the Middle Ages, to the reluctance to perform autopsies for social and religious reasons and to the inability to tell the condition apart from the common cystic hydatid disease.

Ancient Greeks, whose concepts dominated medical science for nearly 18 centuries, explained disease largely through the humours [1]. According to this theory, disease resulted from disturbed proportions or qualities of the fluid components of the body. Since solid organs, their anatomical structure and their alterations were not thought to play an important role in the causation of disease, autopsy had little place in medicine [2,3]. With the exception of Alexandria, where human dissection and possibly vivisection were practised between 300 BC and 200 AD, anatomical knowledge in antiquity and in the Middle Ages derived from the study of animals as part of cult (Haruspicy and animal sacrifices), the kitchen (the Bible [15] ‘thou shalt not eat of anything that dyeth of itself’) and anatomical studies performed for the sake of knowledge rather than understanding of disease. The rarity of dissection studies in humans explains the inaccuracies in the descriptions and drawings by Aristotle, Galen, Ibn Sina, Leonardo da Vinci and Andreas Vesalius, who placed the right kidney at a position higher than the left kidney [4–6].

Despite this philosophical approach to medicine, certain anatomical aspects of disease, such as obstruction caused by renal calculi or other surgical conditions, could not be ignored. Hippocrates (460 BC) mentions diseases of the kidney in many passages of his works, and indeed he recommends incisions to be made in cases of abscess in order to furnish an outlet for pus. Calculi may well have been removed in some of these operations; given the lack of imaging techniques, it would be surprising if some patients with pain associated with polycystic kidney disease did not have the same treatment. Hippocrates describes four diseases of the kidney. The first two fit descriptions of renal calculi associated with ureteric obstruction, the third and fourth types are less easy to classify, but by a stretch of the imagination the fourth type might encompass polycystic kidney disease:

‘the fourth disease arises from the gall and mucus chiefly in summer time and also after sexual excess. The patient feels pain in the side, in the groin, and in the inguinal region and in the muscles; he cannot lie on the healthy side, suffers fearful pain, and feels as if something were torn in the side. The feet and ankles are always cold, urine is passed with difficulty on account of the mucus and if the urine is allowed to stand a sediment is left like flour. If gall predominates the urine is slightly red, and if mucus, white and thick. The symptoms may last a year, and suffering during that time becomes more acute. If a swelling appears during suppuration, it should be cut. A purgative and warm bath should be given in the treatment of the disease, and the patient should be kept warm.’

Hippocrates was unusual in promoting the use of surgical incisions, but the willingness to operate on patients with kidney problems was not widely accepted, one suspects because the results were poor. Galen, for example, describes many aspects of disease of the kidney but makes no mention of surgery as a means of treatment. Aetius of Amida (6th century after Christ) describes some of the causes of bleeding from the kidneys:

‘as it arises in those who have lifted a heavy weight, or have jumped vigorously, or have fallen from a height, or undergone some other similar violent shock’.

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How many of these patients, one wonders, would have had cysts present on an ultrasound scan?

There is little doubt that hydatid cysts were recognized in animals and humans from very early times [7,8]. Old Babylonian and Standard Babylonian cuneiform texts contain descriptions of multiple cysts with clear fluid (Bubu‘tu lesions) found in livers of animals used for divination, especially sheep, goats and cattle [9]. The Talmud contains references to ‘water bladders’ encountered in the course of the investigation of the fitness or unfitness of slaughtered animals for sacrifice or human consumption [7]. Hippocrates stated in his fifty fifth aphorism, Section VII:

‘when the liver is filled with water and bursts into the epiloon, in this case the belly is filled with water and the patient dies’

Galen, in commenting on this case, regarded it as a reference to hydatid cysts of the liver with rupture into the abdominal cavity [7]. Hydatid disease was commonly prevalent in the Middle Ages. References to hydatid disease can be found in medical works of that time and even non-medical texts such as Thorlak’s Saga from the 12th century [10]. The difficulty in making a distinction between polycystic kidney disease and hydatid disease is illustrated by the remains of a young female leper discovered at the site of a Danish Mediaeval Leprosy Hospital (Sankt Jørgens Spital) which functioned from ~1250 to 1550 [10]. The abdominal cavity of this patient contained innumerable calcified cysts and fragments of cysts located in the left renal–splenic area, both lumbar fossae and in the pelvis (Figure 1). Although this young woman probably suffered from hydatid disease, the distribution of the cysts would also be consistent with polycystic kidney disease.

The humoral theory of disease continued to influence scholars well into the 17th century, but gradually the concept that illness is directly related to changes in the structure of the solid organs developed in Italy in the late Middle Ages and began to modify the attitude of the church toward autopsies. Reports of autopsies mainly performed for forensic reasons date back to the 8th and 9th centuries [1–3]. In 1480, Pope Sixtus IV issued a bill permitting studies of human bodies by students at Bologna and Padua. In the late 15th century, Antonio Benevieni recorded a number of his clinical experiences, many of them with autopsies, under the title De abditis ac mirandis morborum et sanationum causis [11]. The rise of anatomy as the single medical discipline capable of precise investigation in the 14th and 15th centuries set the stage for the great Italian anatomists of the 16th (Eustachio, 1520–1574; Fallopius, 1523–1562), 17th (Malpighi, 1628–1694; Bellini, 1643–1704; Valsalva, 1666–1723) and 18th centuries (Morgagni, 1682–1771) [12–14].

With dissection becoming common place, it is likely that polycystic kidneys were encountered during autopsies performed in the 16th and 17th centuries. Several examples of cystic kidneys can be found in one of the great compilations of the time, the Sepulchretum Sive Anatomia Practica of Theophilus Bonetus (Théophile Bonet) (1620–1689), which was published in 1679 in three volumes and included a collection of descriptions of >3000 autopsies [15]. Other examples of cystic kidneys appear in Morgagni’s De sedibus et causis morborum per anatomen indagatis [16]. Valsalva has been given credit for first studying the chemical composition of cyst fluids by tasting the fluid from renal cysts. Nevertheless, polycystic kidney disease was not yet recognized as a clinicopathological entity. It has been claimed erroneously that Bartholomeo Eustachio, Professor of Anatomy at Rome, included a drawing of a polycystic kidney in Plate Number 4 of his Opuscula Anatomica published in 1563 (Figure 2) [17]. However, the description of this drawing by the same Eustachio indicates that the illustration in question is a bear kidney, ‘which like the bovine kidneys, is composed of numerous gland-like structures of the size of a cherry’. Eustachio indicates that in some human fetuses he had ‘observed, as did Aristotle, similar kidneys’, undoubtedly referring to what it became known as foetal lobulation.

The co-existence during the Renaissance of a longing to emulate the ancient cultures of Greece and Rome on one hand, and the yearning to develop a new science based on observation of nature on the other, created a complex situation in medicine. This is best illustrated by the controversy that surrounded the illness and death of the Polish King Stefan Bathory, possibly the first known case of polycystic kidney disease.

Stefan Bathory was born in 1533. In 1571, he was elected Prince of Transylvania. On May 1, 1576, he married Anna Jagiellonka and was anointed King of Poland. Although he was King for only 10 years, his accomplishments qualify him as the most successful monarch in Polish history [18,19]. His accomplishments included the submission of Gdansk, the reform of the judicial system and the army, the subjection of the Cossacks and nobles, the restoration of public finances, and especially the defeat of the Grand Duke of Moscow, Ivan the Terrible, in a war that lasted

Fig. 1. Abdominal cavity of a leper containing multiple cysts.
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from 1576 to 1582. The painting by Matejko (Figure 3) presents Stefan Bathory at the peak of his glory in 1581 during the siege of Pskov. The years that followed the defeat of the Russian Tsar were less successful for Stefan Bathory. He fell into a deep depression, languished in that mood and composed his last will and testament. The evidence of a chronic ailment may be evident on his face in a portrait painted by Kober in 1583 (Figure 4). On December 3, 1585, while returning from a hunting trip, he experienced severe chest pain and felt unusually tired [20–22]. On December 5, back in his palace in Grodno, his symptoms returned. On December 7 he fell down and transiently lost consciousness after getting up from his bed. On December 8, after supper, he experienced general weakness, chattering teeth and difficulty breathing. On December 8, his face muscles twitched uncontrollably. The next day, at 3 a.m., he again lost consciousness, experienced general shivering, very pale facial colour and heavy sweating. His heartbeat was weak and uneven. He died on December 12, during the day, at the age of 53 years. The illness and death of King Stefan Bathory led to a violent confrontation between his two main physicians, Simon Simonius and Nicolaus Buccella [20–22]. Simon Simonius had been born in Luccana, and received his medical education in Geneva and Heidelberg. He believed in the humoral theory of disease proposed by the ancient Greeks, consequently, he made a diagnosis of ‘discrasia frigata’ caused by overexposure to cold, and indicated that the proper treatment of the King required steady warming. On the other hand, Nicolaus had been born and educated in Padua. Faithful to the Padua medical teaching, Buccella believed that the basis of disease was of organic nature. He suggested that the King could be suffering from meningeal abscess and recommended cooling agents to treat the King’s symptoms. The orders by one physician were strongly opposed and replaced with the orders from the other physician, and eventually the King died. At the solemn exequies, which took place on May 23, 1588, the blame for the death of the King fell on the disputes among the royal physicians (‘turba medicorum perdidit caesarem’) [19].

The body of Stefan Bathory was embalmed in Grodno and later transported to Krakow where it was buried (Figure 5). During the embalming, an autopsy was performed by the surgeon Jan Zigulitz who was assisted by Buccella [19–22]. The kidneys were described as ‘large like those of a bull, with an uneven and bumpy surface, nothing like Buccella or I had ever seen’. The gall bladder contained a stone. The other organs, including the heart, lungs, liver, stomach and spleen appeared healthy. The head was not opened. The renal findings, impressive as they were, were not linked to the cause of death and did not stop the dispute between Simonius and Buccella, who for a number of years continued to publish accusations and counter-accusations, without sparing personal insults.

The most probable cause of death of King Stefan Bathory was not established until 347 years later, in Krakow in 1933 [20]. That year, Poland and Hungary celebrated the 400th anniversary of his birth. On this occasion, Franciszek Walter, Professor at the Krakow Medical School, gathered a group of medical specialists and historians to review in detail the descriptions of the illnesses and autopsy findings of King Bathory. They concluded that the most likely cause of death was polycystic kidney disease and uraemia.

Stefan Bathory belonged to one of the richest and most powerful families in Hungary [19]. It is known that his father had suffered from podagra. In addition, two of his brothers also had gout and died prematurely before reaching the age of 50 years. One can only wonder whether some of them might have had polycystic kidney disease. A niece of King Stefan Bathory...
became particularly famous and has inspired legends which have permeated popular culture [23]. This was Elizabeth Bathory who was born in 1560. She was a well-educated woman, fluent in Latin, Hungarian and German. In 1585, she married Count Ferenc Nadasdy, a Hungarian hero who spent most of his life fighting the Turks and was known by the popular nickname of the ‘Black Knight’. It is said that from childhood Elizabeth Bathory was subject to periodic fits during which she was overcome by seizures of rage and uncontrolled behaviour. In 1610, six years following the death of her husband, she was accused and tried for having murdered 650 girls, supposedly to bathe in their blood in order to maintain her youthful appearance. It is uncertain to what extent this accusation and trial were instigated by economic and religious motives and favoured by the witch craze that was dominant throughout Europe at the turn of the 17th century. Although extensive evidence was presented at the trial to support the murder of young women by Elizabeth Bathory and her accomplices, it cannot be ignored that she was a Lutheran and that the Holy Roman Emperor Matthias II, who was financially indebted to her, benefited from her downfall. She was condemned to life-long imprisonment in her castle of Cachtice where she died on August 21, 1614. The legends inspired by the history of Elizabeth Bathory undoubtedly had a strong influence on Bram Stoker’s Count Dracula. Whether she might have had polycystic kidney disease is not known.

In the 16th, 17th and 18th centuries, as illustrated by the autopsy of King Stefan Bathory, polycystic kidneys did not attract the attention of physicians. In the *Dictionnaire des Sciences Médicales par un Société de Médecins et de Chirurgiens* published in Paris in 1820, for example, the description of polycystic kidneys is reduced to the following statement under ‘dégeneraison stéatomateuse’: ‘There are examples of transformation of the kidneys and even the majority of other abdominal organs into a mass of vesicles full of a thick, sticky, and yellow fluid’ [24]. Nevertheless, towards the end of the 18th century, the distinction between renal hydatid cysts and ‘vesicular disease’ of the kidney, which Dr Matthew Baillie in his *Morbid Anatomy of Some of the Most Important Parts of the Human Body* published in 1793, termed ‘false hydatids of kidney’ began to be recognized [25]. In this work, Dr Baillie remarks:

‘these hydatids do not appear to be of the same nature with hydatids of the liver; they are not enclosed in firm cysts like those of the liver; their coats are also thinner and less pulpy; and not uncommonly they are almost as thin as any membrane of the body. I do not recollect to have seen any instance of small hydatids attached to the coats of larger hydatids in the kidney, as may be frequently observed in the liver. It is therefore probable that the hydatids of the kidney depend on a diseased alteration of the structure of this
organ and are not distinct organized simple animals.\textsuperscript{1}

The major role of autopsy in medical science became established in the early part of the 19th century. To quote Hill and Anderson ‘discovery in medicine thrived on the autopsy—discovery, synthesis, analysis—all the ways in which medical science flourished and grew so spectacularly during the period—were dependent on the autopsy’. The concept that illness is associated with changes in organ structure, and that the state of the tissues making up the organs of the body holds the key to understanding normal and diseased function became accepted [14,26].

It is within this context that a description of ‘cystic degeneration’ of the kidneys as a cause of renal failure was made by Rayer in his Traité des maladies des reins published in 1841 [27]. He wrote: ‘There are cases where both kidneys are affected by a true generalized cyst degeneration of the cortical substance, which in some cases may be of such a degree that only traces of renal substance are left; in these cases the urinary functions are interrupted or damaged and severe functional alterations of other systems, particularly the central nervous system, cause the death of the patient … These cases, noted by pathologists, have attracted little attention from physicians’. A similar description and illustration of polycystic kidneys can be found under the name of cystic transformation of the kidneys in the atlas by Cruveilhier, Anatomie pathologique de corp humain (1829–1835) [28].

Gradually, an increasing number of case reports followed, such as those from Bristowe [29] and Wilks [30] in London and others throughout Europe, in which ante-mortem clinical illness was discussed in terms of the subsequent autopsy findings. Lejars, in his doctoral thesis published in 1888, introduced the term ‘polycystic kidneys’ and emphasized the bilateral nature of the condition. He concluded that polycystic kidney disease is not only an anatomico-pathological entity, but also a defined clinical entity with characteristic symptomatology and susceptibility to being diagnosed clinically [31]. This crucial step of making use of the distinctive clinical features to make the diagnosis of cystic kidney disease during life had become established by the end of the century. The diagnosis should be suggested, as Osler indicated in his report of two cases, by the characteristic combination of symptoms and signs including the presence of bilateral tumours in the flanks, cardiovascular changes of interstitial nephritis (in essence those of hypertension), the condition of the urine (low specific gravity, trace of albumin and scanty casts) and haematuria [32].

Advances in anaesthetics and infection control made operations on the kidney viable by 1870—although not without significant risk. Surgical intervention on

\textsuperscript{1}Editor's note: See also Fogazzi GB. The description of polycystic kidneys by Domenico Gusmano Galeazzi. Iconographic Archives of European Nephrology. Nephrol Dialysis Transpl 1998; 13: 1039–1040.
the basis of a constellation of symptoms, in the absence of imaging technology, became a useful approach to treatment. By 1879, there were reports of 28 nephrectomies, of which seven were for hydronephrosis or cystic disease. There were five deaths in this series [34]. Because of the bilaterality of polycystic kidney disease, it soon became obvious that surgery had a minimal role in its treatment. In his thesis published in 1888, Lejars wrote: ‘The bilaterality of polycystic kidney disease explains the disastrous results of surgical intervention’ (i.e. nephrectomy) … ‘While nephrotomy may be indicated in the case of a large renal cyst, this is not applicable to polycystic kidney disease. An exception should be made in the case of a perinephric abscess co-existing with an infected polycystic kidney … The treatment of polycystic kidney disease should be that of Bright’s disease with diet and hygiene’ [31].

Further developments of the role of physician and surgeon were dependent on the advent of X-ray imaging. Voelcker first demonstrated the possibilities of retrograde pyelography by injecting Collargol through ureteric catheters [34]. Braasch, working at the Mayo Clinic, reported in 1911 his experience with this technique for imaging a range of renal pathology, including cystic kidney disease [35], allowing, for the first time, imaging of kidneys in vivo. The same year, Rovsing reported his results on the treatment of polycystic kidney disease by multiple punctures based on his experience in three patients [36].

Tissues obtained from polycystic kidneys at autopsy or at surgery were used for microscopic analysis and recognition of the crucial role of cellular pathology in organ dysfunction. Many theories of cyst pathogenesis evolved during the 19th century, centred around the role of obstruction, neoplasia or a developmental failure. Virchow was a powerful proponent of the theory of tubular obstruction, whether by uric acid crystals [37] or later by connective tissue proliferation resulting from pyelonephritis or papillitis [38]. A role for cell proliferation and neoplasia was always an attractive option. Early proposals were for a hamartomatous [39] or cystadenomatous origin [40]. Brigidi and Severi (1880) [41] admitted that there might be multiple causes, but proposed that cysts form as a consequence of degeneration of areas of proliferation of tubular epithelium. Others suggested that there were characteristics of a fibroedema [42]. Coincident with these observations, there were also significant developments in renal embryology. Kupffer (1865) [43] recognized the dual origin of renal tubules, and this prompted various theories on the role of developmental abnormalities. Shattuck (1885) [44] suggested that the metanephric blastema rose in intimate relationship to the mesonephros and grows into it, incorporating tubules of the latter to form cysts—the associated fibrous hyperplasia being a secondary feature. Hildebrand (1894) [45], on the other hand, proposed that the primary defect was a failure of union of the metanephric blastema and the ureteric bud. These various descriptions had by the turn of the century become more clearly defined as either a primary role of urinary retention or a key role for cell proliferation.

The increasing use of autopsy in the 18th and 19th centuries also led to the description of other forms of renal cystic disease, such as infantile polycystic kidney disease, multicystic renal dysplasia and acquired renal cystic disease. Descriptions of polycystic kidney disease in newborns and infants date back to the 18th century and are quoted by Rayer in 1841 [28]; but widened portal spaces with increased connective tissue and proliferation of bile ducts showing cystic dilation in infants with polycystic kidneys were not described until the turn of the 19th century [46,47]. The first description of multicystic renal dysplasia is probably by Littre in 1701 [49]. He described a 9 month fetus with kidneys that resembled a bunch of grapes, with ureters which had normal appearance except for the proximal one inch, where they became solid without lumen.

Early descriptions of acquired renal cystic disease also date back to the 19th century. In the paper to the London Royal Medical and Surgical Society in 1847, Simon reported that renal cysts form as a consequence of tubular obstruction caused by a variety of kidney diseases, including subacute inflammation [50]. He went on to suggest that the clear fluid in the cysts represented an attempt by cyst epithelial cells ‘to withdraw from the blood, if they cannot eliminate from the body, the materials which fill them’. In 1882, Sabourin also described the partial cystic degeneration of the kidney in the case of Bright’s disease and proposed that as a result of this process the epithelium of the convoluted tubules in the renal cortex regresses to a stage of undifferentiated cells [51].

Thus, by the end of the 19th century, the main clinical features of polycystic kidney disease were clear and the scene was therefore set for further detailed studies on its natural history. The anatomical changes were understood, and many of the pathogenetic mechanisms entertained by recent investigations were already being considered. Most importantly, recognition of the genetic basis of the disease was first made in 1899 by Steiner [46], but further clarification of the mode of inheritance was required, and understanding of the underlying genetic abnormalities was to take almost another 100 years of research.

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