ORIGINS OF RENAL DISEASES

Tear drops of kidney: a historical overview of Polycystic Kidney Disease

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Abstract

Polycystic kidney disease (PKD) is one of the most common inherited kidney diseases causing end stage renal disease. Although it has been in existence with humanity, it was defined in 18th century.

The most detailed observations on PKD have been written after the disease of Stephen Bathory, the King of Poland. He had fatigue and chest pain accompanied by unconsciousness within a few days after a hunting trip, and died within 9 days, at the age of 53 years in 1586. Surgeon Jan Zigulitz described the cysts in his kidneys as " large like those of a bull, with an uneven and bumpy surface" during the mummification. Based on available information, 347 years later, a group of physicians and historians in Krakow concluded that the probable cause of King's death was "PKD and uremia".

Unfortunately, PKD did not attracted the interest of physicians until the 18th century. In late 18th century, Matthew Baillie noted that these vesicular cysts in kidney were different from hydatid cysts, and described them as "false hydatids of kidney".

In 1888, Félix Lejars used the term of "polycystic kidney" for the first time, and stressed that these cysts were bilateral, and causing clinically identifiable symptoms.

At the end of 19th century, the basic clinical signs, and genetic basis of the disease have been better defined. However, the inheritance pattern could only be understood long years later.

In this study, the history of PKD, i.e., the tear drops (cysts) of kidney will try to be explained by the light of old and current knowledge.

Key words: cystic disease, history, King Stephen Bathory, polycystic kidney disease

Introduction

Polycystic kidney disease (PKD) is one of the most common systemic inherited kidney diseases causing end stage renal disease (ESRD). It has been described in all racial and ethnic groups, and there are 13 million autosomal dominant PKD (ADPKD) individuals worldwide [1]. ADPKD is thought to be responsible for one in every twenty cases of ESRD requiring renal replacement therapy in USA [2]. This article will mainly address the possible answers of following questions in light of old and current knowledge;

a) When did we notice this disease?

b) Did we show enough interest to PKD?

c) Does it have the deserved place in the literature?

History of polycystic kidney disease

PKD has been in existence with humanity. It is a natural process to be observed firstly in the animals' internal organs, since they have been used for nutrition and/or sacrificed for God. Although forbidden meats described very well in several religions, there is no enough information about the abnormalities of kidneys in literature. Nevertheless, hydatid cysts were recognised in animals and humans from very early times [3]. Examination of dead human body to help the living ones is a revolution in understanding of the diseases.

Recognition of PKD begins with the death of King Stephen Bathory. He was born on 27 September 1533, and became the third elected king of Poland in 1576. He reigned for 10 years (1 May 1576-12 December 1586). Within a decade, he was one of the most successful kings in Polish history, particularly in the realm of military history, and the reform of judicial system. He had no children. His father and two brothers had gout, and his brothers died before the age of 50 years. In his personal life, hunting and reading were his favorite activities. Symptoms of the king had began after his last hunting trip, and caused the death within 9 days, at the age of 53 on December 12, 1586 [4] [4] [5] (full text) [6]. King's symptoms and progress of the disease have been well documented in the article written by Torres and Watson [5] (full text), and summarized in Table 1.

The death of king in a short time caused serious and unpleasant discussions about the diagnosis among his two doctors, Dr. Simon Simonius and Dr. Nicholas Buccella. In fact, both of his doctors had great background. Dr. Simon Simonius was an Italian philosopher and physician educated in Geneva and Heidelberg. Dr. Nicholas Buccella mainly educated in Padua, and also had experience in general surgery. Dr. Simonius was believing in the "humoral theory of diseases" in accordance to his education, as proposed by the ancient Greeks. His diagnosis was "discrasia frigata" caused by overexposure to cold during hunting. Therefore, his suggestion was "the steady warming of the King" [4] [5] (full text) [6]. Dr. Buccella believed that the basis of diseases was of "organic nature", and the King could be suffering from "meningeal abscess". He recommended "cooling agents" to treat the King's symptoms, and accused

Dr. Simonius regarding of wrong treatment application. Their suggestions were completely opposite to each other, and led to rumor between royal doctors over many years.The autopsy during mummification in Grodna put an end to these discussions. During the extraction of internal organs, surgeon Jan Zigulitz, assisted by Dr.Buccella, described the cysts in kidneys as; "*large like those of a bull, with an uneven and bumpy surface*". They noted that there was a stone in gall bladder, and heart, lungs, liver, stomach, spleen were all normal [4] [5] (full text) [6]. However, the head was not dissected.

The renal findings were not considered to be related to the cause of King's death at that time. In 1933, 347 years later of this gross definition, Hungary and Poland celebrated the "400th anniversary of King's birth". On this occasion, Prof. Franciszek Walter, at the Krakow Medical School, invited a group of medical specialists and historians to review in detail the description of the disease and autopsy findings of King Bathory. After this meeting, they concluded that the most likely cause of King's death was " *PKD and uraemia*" [5] (full text) [7].

Discussion

It has been well known that uremic patients have high morbidity and mortality rates. Compared to the age adjusted cardiovascular disease mortality in the general population, mortality is approximately 15 to 30 times higher in dialysis patients [8] [9] (full text). Uraemia-specific risk factors, hypertension, left ventricular hypertrophy (LVH), uremic cardiomyopathy and heart failure, increase in prevalence as kidney function declines, and especially LVH is an independent risk factor for cardiac death [8] [9] (full text). Anemia, hyperhomocysteinemia, and increased phosphate (P) level (P> 6.5 mg/dL) are other contributing factors causing increased mortality risk in these patients [8] [9] (full text).

If we re-evaluate the symptoms of King Stephen Bathory in the light of current knowledge, one of the first questions may be *whether the King had uremia due to PKD*.

There is no enough information about his urinary problems, urinary output, symptoms regarding hypertension, exercise intolerance (he was an active king), no fatigue, shortness of breath and/or chest pain until the date of his death. In fact, there may be some clues that he had PKD before his death. He wore slack suits in his all portraits, suggesting he might have enlarged kidneys (Figure 1).

His father and his brothers had gout, and his brothers died before the age of 50 years. Considering the genetic basis and high uric asid levels in PKD, it is possible that they might have some forms of PKD [10] (full text). It has been noted that he had no children. However, it is hard to say that he had infertility, common in males with PKD, or it was only because of the age of his wife, Anna Jagielleonka. She was 53 years old when married, a late age for childbirth.

The second question to be asked is *whether the real cause of King's death could be anything else*.

Two possible scenarios may be written in this regard. One is subarachnoid hemorrhage (SAH) due to vascular aneurysm in brain. Almost 10% of asymptomatic PKD patients have intracranial aneurysms during screening, while it increases up to 25% in patients with a family history of subarachnoid or intracranial haemorrhage [11]. The rupture of these aneurysms may be induced by exercise or trauma. Possible cause-effect relationship is described in detail in Figure 2.

The key question in this scenario may be why he had severe chest pain. Although it is difficult to explain severe chest pain in a patient with SAH with the old knowledge, recent knowledge demonstrates that acute lung injury or the acute respiratory distress syndrome [12] and neurocardiogenic injury [13] can be seen in patients with SAH. Therefore, severe chest pain of the King may be explained by this way.

The second scenario may be written on aortic dissection. Progression of this dissection to aortic arch may explain the following complaints of the King after the first day (Figure 3).

Although the physicians noted his heart as normal (accepting also the examination of the vessels) during the mummification, it does not imply that he did not have aortic dissection. Probably, it might not be recognized since aortic dissection has been firstly described by Frank Nicholls in 1760 [14].

Unfortunately, PKD did not attract the interest of physicians until the 18th century. In late 18th century, Dr. Matthew Baillie noted that these vesicular cysts in kidney were different from hydatid cysts, and described them as "false hydatids of kidney" in his anatomy book [15]. Rayer quoted the descriptions of PKD in newborns and infants in 18th century, and "cystic degeneration " was noted as a "cause of kidney failure" in his book [16]. He also stressed severe functional alterations of other systems, par-

Table 1. Symptoms of King Stephen Bathory and progress of the disease

Date - 1586	Symptoms
December 3	Fatigue and a severe chest pain
December 5	Continuation of same symptoms
December 7	Falling down after getting up and transiently loss of consciousness
December 8	General weakness, chattering teeth, difficulty in breathing, and uncontrollable twitches in facial muscles
December 9	Loss of consciousness, general shivering, very pale facial colour, heavy sweating with weak and irregular heartbeats
December 12	Death of the King

ticularly the central nervous system, causing the death of the patient in PKD [16]. This description referring "*the relation between structural changes in an organ and the disease*" attracted the attention of firstly pathologists. Such a comprehensive approach to the clinical problems of nephrology described as "Pierre Rayer's innovative method of clinical investigation" by Professor Gabriel Richet in 1991 [17].

With the increase in number of autopsies during the early 19th century, renal cysts began to be defined in more detail, that is "*teardrops of the kidney began to be noticed by investigators*".

In 1888, Félix Lejars used the term of "polycystic kidney" for the first time in his doctoral thesis, and stressed that these cysts were bilateral [18]. He also underlined that this disease is not an only anatomopathological condition, but also causing clinically identifiable symptoms [18]. Then, in 1899, genetic basis of the PKD was firstly recognised by Steiner (313 years after the King's death) [19]. However, the researches to understand the mode of inheritance and other genetic abnormalities have taken more than 90 years.

In 1902, W. Osler described two patients having bilateral tumours in the flanks together with cardiovascular changes and differences in the urine content [20]. In parallel to developments in radiology, renal pathologies were identified better and radiological attempts began to be used in treatment of these patients. T. Rovsing shared the results of multiple punctures in 3 PKD patients [21]. Microscopic analysis of specimens obtained during surgery or autopsy has enabled the further identification of cellular pathology in PKD. It has been stated that the reasons of cysts may be "*obstruction, neoplasia or developmental abnormality*" [5] (full text) [21]. These theories regarding cyst pathogenesis during 19th century explained with details in article of Torres and Watson [5] (full text). They have been summarized in Figure 4.

Significant research breakthroughs into PKD occurred in the 1990s. Cyst formation in this disease began to be better understood at the molecular level. It has been shown that abnormalities of expression and function of the epidermal growth factor – axis, decreased intracellular calcium with aberrant intracellular cAMP signaling, abnormal structure and/or function of the primary cilia and alterations in cell-cell, and cell-matrix interactions resulting in tubular cell hyperplasia, tubular fluid secretion, abnormalities in tubular extracellular matrix, structure, and/or function [1].

PKD-1 gene on chromosome 16, present in approximately 85% of ADPKD patients, has been discovered in 1994 [22] (full text). Subsequently, detailed genetic studies have been achieved regarding PKHD1 gene, causing autosomal recessive PKD (ARPKD) [23] (full text). After the researches in PKD animal models showing the effectiveness of vasopressin V2

Figure 1.
Different portraits of King Stephen Bathory. Slack suits in his all portraits may be a clue for enlarged kidneys.

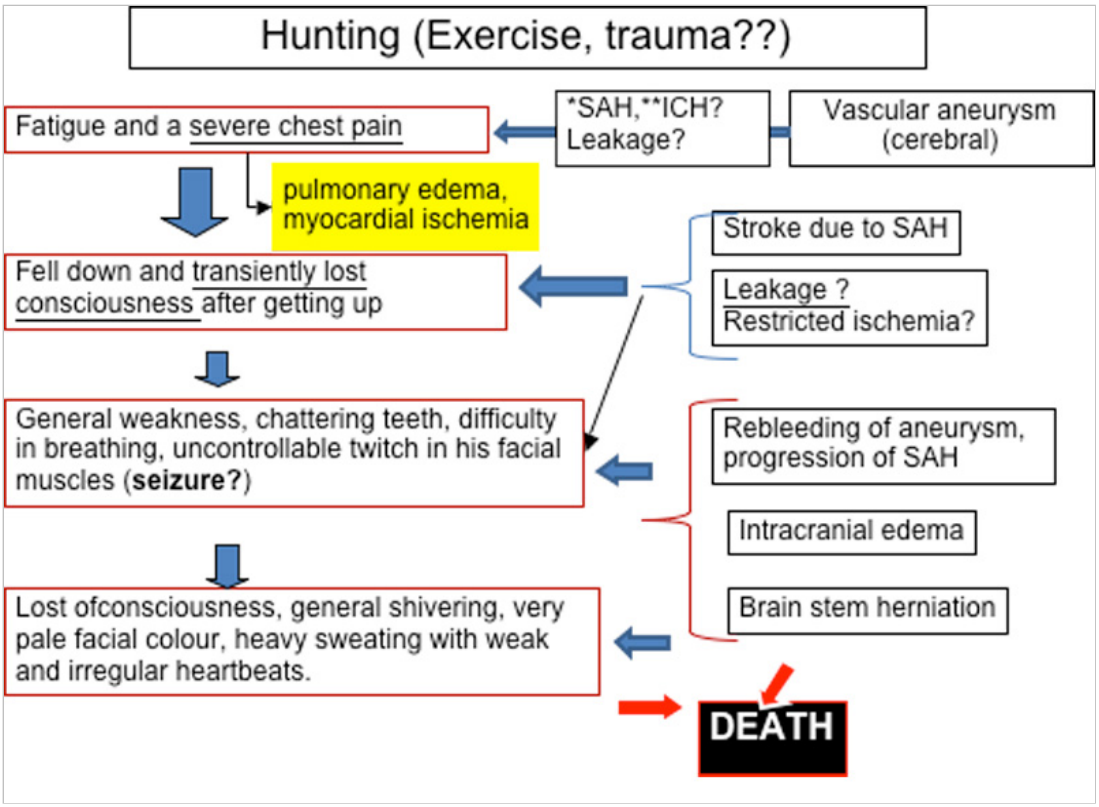

Figure 2.
*Scenario 1; Possible cause-effect relationship regarding the death of Stephen Bathory due to intracranial haemorrhage (*SAH; Subarachnoid haemorrhage, **ICH; Intracranial haemorrhage)*

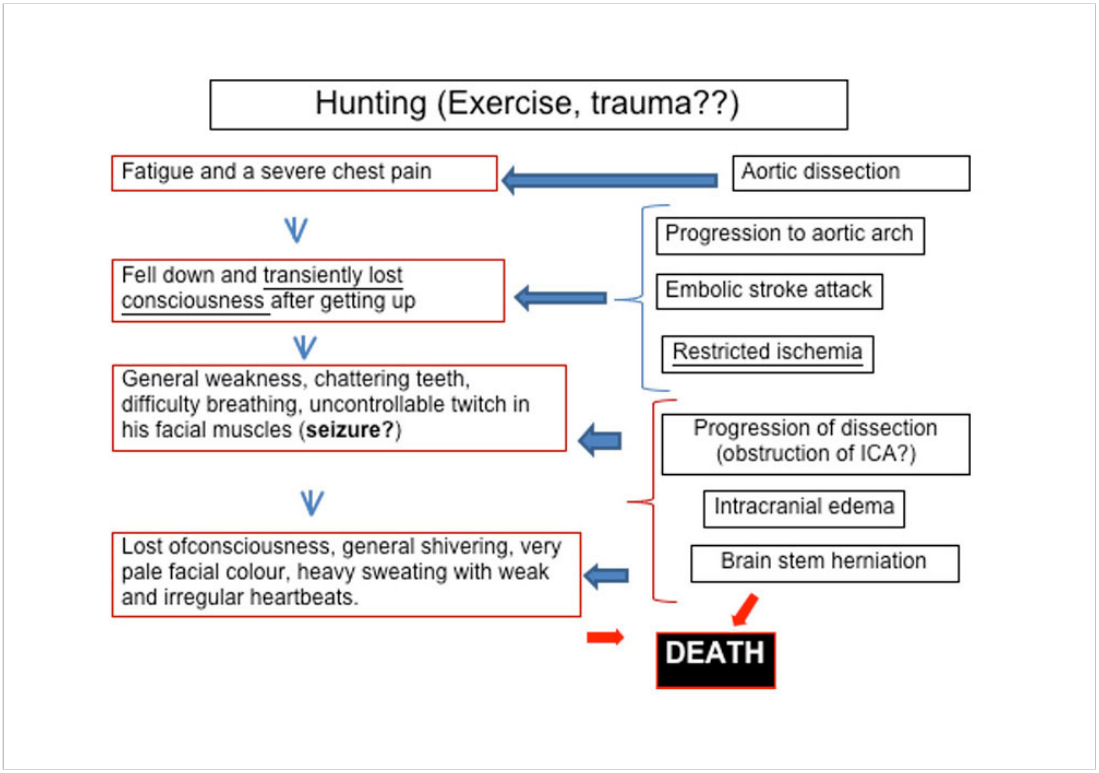

Figure 3.
*Scenario 2; Possible cause-effect relationship regarding the death of Stephen Bathory due to aortic dissection (*ICA; Internal carotid artery)*

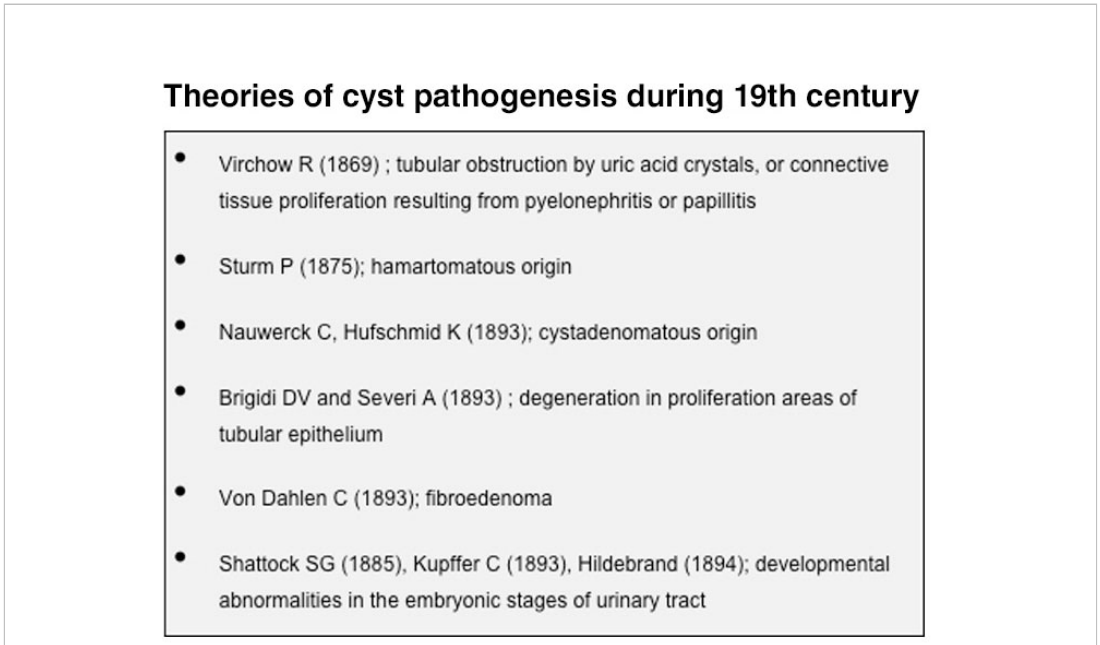

Figure 4.
Main theories of cyst pathogenesis in polycystic kidney disease during 19th century.

receptor antagonist (Tolvaptan) in prevention of kidney enlargement, clinical trials was initiated [24]. The UK ADPKD and ARPKD Study Groups are formed under the Renal Association/Renal Registry in 2012, to increase the attention that this disease deserved.

Conclusion

The reason of the present article titled as "*tear drops of kidney*" was; PKD has been like an invisible reality until the 18th century. At the end of 19th century, the basic clinical signs, and genetic basis of the disease have been better defined. After the recognition of genetic basis, the inheritance pattern was understood almost within a 100 years. Although more than 300 different mutations in the PKHD1 gene have been described in nowadays, further studies are still needed at molecular level regarding the pathogenesis of PKD.

We finally see the teardrops of kidney; cysts, measured by magnetic resonance imaging as total kidney volume, are being accepted as "*the best available biomarker of disease progression*" [25] (full text).

I believe, further researches will wipe away the teardrops of kidney in the near future.

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