PAIN IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder affecting 1 in 1,000 people and is responsible for 10% of cases of end-stage renal disease. Apart from renal manifestations, changes in other organs may be present, including arterial hypertension, intracranial aneurysms, liver cysts, and others. Pain is a common complaint in ADPKD, afflicting as many as two-thirds of patients. It begins relatively early in the course of the disease, and may be associated with polycystic kidneys, extrarenal manifestations of the disease, or may be of the origin which is unspecific for ADPKD. The aim of the paper is to review the subject of pain in ADPKD patients, with its possible sources, diagnostics, and management.

Keywords: Autosomal dominant polycystic kidney disease, complications, pain, polycystic liver disease.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder affecting 1 in 1,000 people and responsible for 10% of cases of the end-stage renal disease (ESRD). Apart from renal manifestations, changes in other organs may be present, including arterial hypertension (AH), intracranial aneurysms (ICANs), liver cysts, and others. In 85% of cases, ADPKD is caused by a mutation in the PKD1 gene, encoding polycystin 1 (Type 1 ADPKD), and the remaining 15% are connected to the mutated PKD2 gene, encoding polycystin 2 (Type 2 ADPKD). The type of the mutation has a prognostic significance, as the average age of ESRD amounts to 53 years in Type 1, and 69 years in Type 2.[1]

Pain is commonly observed in ADPKD, afflicting as many as two-thirds of patients.[2] It begins relatively early in the course of the disease,[3,4] and may be associated with polycystic kidneys, extrarenal manifestations of the disease, and, of course, may be of the origin which is unspecific for ADPKD. The aim of the paper is to review the subject of pain in ADPKD patients, with its possible sources, diagnostics, and management.

LUMBALGIA AND ABDOMINAL PAIN

Lower back pain is observed in 71-77%, and abdominal pain in 61-66% of ADPKD cases.[2,3] The pain related to the polycystic kidney may be both acute or chronic. The most common reasons of acute pain include cyst infection, cyst rupture, and nephrolithiasis.

The cyst infection may lead to acute pain with accompanying elevated body temperature. The pain may be unilateral or bilateral. If there is no communication between the lumen of the infected cyst and the urinary tract, the result of urinalysis is normal and the urine culture is negative. Thus, the diagnosis may be difficult.[5] In 2012, Suwabe et al.[6] proposed the diagnostic criteria for kidney or liver cyst infection. According to them, for the diagnosis of infection, the patient must have: A) no other source of fever detectable and no evidence for acute cyst haemorrhage; B) at least 2 items from: maximum body temperature >38°C, maximum

white blood cell (WBC) count >10,000/µl, or maximum serum C-reactive protein (CRP) >15 mg/dl; C) at least 1 item from: gas inside the cyst, high density of the cyst on magnetic resonance imaging (MRI) (diffusion-weighted imaging [DWI]), fluid-fluid level in the cyst on MRI, or cyst wall thickening on MRI or computed tomography (CT); and D): at least 1 item from: abdominal pain or tenderness, or sequential changes of the cyst on imaging. In diagnostic difficulties, ^{18}fluorodeoxyglucose (^{18}FDG) positron-emission computed tomography (PET/CT) may help to confirm and locate the infection of the cyst.[7,8] *Escherichia coli* accounts for almost three-quarters of cases.[8] In the therapy of cyst infection, the antibiotics of good penetration to the cyst lumen are recommended, including fluoroquinolones, co-trimoxazole, clindamycin, metronidazole, vancomycin, and chloramphenicol.[5,8] Combination of antibiotics seems superior compared to monotherapy.[8] A 6-week course of antibiotics is recommended.[9] However, invasive approach with drainage of the infected cysts may be required, especially when their diameter exceeds 5 cm.[5,8,10]

The cyst rupture accompanied by haemorrhage causes acute pain, with gross haematuria (when there is a communication between the involved cyst and the urinary tract) or without haematuria (when there is no such communication).[5] Except for intracystic bleeding, retroperitoneal haematoma, or, in extremely rare cases, haemoperitoneum, may complicate the cyst rupture in the latter case.[11] If haematuria is present, it is usually self-limited after a few days. In more serious cases, the bleeding may be complicated with formation of clots that may cause the obstruction of the urinary tract.[5] In patients with persistent or recurrent symptoms, imaging with CT or MRI is indicated.[12] According to the criteria of Suwabe et al.,[6] acute cystic haemorrhage may be diagnosed when: A) there is abdominal pain and/or gross haematuria; B) the maximum body temperature does not exceed 38°C, the maximum WBC count does not exceed 10,000/µl, and the maximum serum CRP is <15 mg/dl; and C) CT reveals irregular high-density mass inside the cyst, or the cyst density on CT exceeds 25 Hounsfield units (HU). In most cases, conservative management with bedrest, hydration, and analgesics, is sufficient. In severe haematuria, transfusion may be required, and, in the most severe cases, nephrectomy or embolisation of the renal artery should be considered.[5]

It is also possible that the ADPKD patient suffers from combined cyst haemorrhage and infection. It may be diagnosed when the patient: A) is pyrexial, and complains of abdominal pain and/or gross haematuria; B) the patient has at least two items from: maximum body temperature >38°C, maximum WBC count >10,000/µl, or maximum serum CRP >15 mg/dl; and C) the CT scans correspond to cyst haemorrhage.[6]

The incidence of nephrolithiasis is higher in ADPKD compared to the general population. It is complicated with renal colic in 20% of ADPKD patients. In such cases, the use of non-steroidal anti-inflammatory drugs (NSAIDs) for up to 3 days seems reasonable. Opioids may be also required. The impaired anatomy in ADPKD may cause difficulties in diagnostics and treatment of renal stones.[5] CT, preferably with contrast administration, seems to be the most informative.[12] The invasive procedures including ureteroscopy, extracorporeal shock wave lithotripsy (ESWL), and nephrolithotomy are challenging.[5] However, the safety and efficacy of flexible ureteroscopy with holmium laser lithotripsy,[13] and percutaneous nephrolithotomy,[14] were proven.

Rarely, the enlarged kidney may cause the occlusion of the mesenteric vein leading to strangulation necrosis of the intestine.[15] A very rare case of sudden-onset pain localised in hypogastrium was also reported, in which the compression of enlarged kidneys and liver on the bony pelvis led to the insufficiency-type fracture of the pelvis.[16]

Compression of cysts on the surrounding tissues, traction on the pedicle of the kidney, and distention of the renal capsule may cause chronic pain,[5] defined as daily pain lasting more than 4 weeks.[12] The cyst-related pain is described as a steady discomfort, exacerbated in vertical position and during walking.[5] In general, pain correlates with the kidney size;[4,5,17] however, there are numerous exceptions from this rule. In effect, patients with mild or moderate cystic changes may complain of severe pain.[5,12,17] Additionally, the pain is unrelated with renal function. Early satiety may be the additional complaint.[5] A rare case of intestinal obstruction caused by compression of cystic kidney, successfully treated with percutaneous aspiration of the largest cysts, was also reported.[18] In general, in patients with chronic kidney pain, the goal of treatment is adaptation of the patient to the pain, because curing the pain is not always achievable.[5] Bajwa et al.[5] proposed a sequential approach

to the pain management in ADPKD, in which, at the beginning, non-invasive methods are used, with slow progress towards more complex and invasive measures.

Non-pharmacologic therapy with physical measures should be sequentially followed by acetaminophen, NSAIDs, tramadol, adjuvant analgesics (clonidine, gabapentin, or pregabalin), and opioids. Transcutaneous electrical nerve stimulation (TENS), acupuncture, and autonomic plexus blockade may be used. Invasive procedures include spinal cord stimulation, neuraxial opioids, and local anaesthetics. A case was reported[19] in which satisfactory analgaesia was achieved with sequential celiac plexus blockade, and intercostal nerve radiofrequency ablations, followed by dorsal column neurostimulation. Surgical approaches include cyst aspiration in cases of only one or a few large cysts, and surgical cyst decompression. While cyst aspiration relieves pain only temporarily,[5] cyst ablation may be used for long-lasting effect using absolute ethanol[20] or a mixture of N-butyl cyanoacrylate (NBCA) and iodised oil.[21] Surgical cyst decortication, including laparoscopic cyst decortication, is effective in the management of chronic pain associated with ADPKD.[22-25] Also, renal denervation, both via a laparoscopic[26] or thoracoscopic[27] approach, may be considered. A new method is the catheter-based renal denervation; successful treatment with this method in an ADPKD patient was recently reported.[28] Ultimately, nephrectomy may be the last option. In patients with chronic pain, ESRD, and contraindications for nephrectomy, transcathether arterial embolisation (TAE) may be considered.[5,12] TAE may be performed using either intravascular coils or ethanol.[29,30]

The common extrarenal manifestation of ADPKD is polycystic liver disease (PLD), which affects up to 94% of ADPKD subjects.[12] PLD is more common in females,[5] due to the fact that oestrogen stimulates the growth of liver cysts.[31] PLD is usually of low clinical significance; however, in some cases it may manifest with a pain which is often more severe than the pain caused by renal cysts. The pain connected to PLD is exacerbated by the standing position, and is accompanied by early satiety.[5] In patients with pain associated with PLD, invasive procedures may be considered when medical therapy is ineffective, including cyst drainage or fenestration, liver resection with fenestration, or TAE.[5,12,32-34]

The rupture of a hepatic cyst may present as an acute abdomen.[35-37] Additionally, acute episodes of pain may be caused by cyst haemorrhage, torsion, or infection.[12] In the analysis of Suwabe et al.,[6] liver cyst infections were more common compared to renal cyst infections; however, in another report[8] the prevalence of renal cyst infections was higher. In case of abdominal pain combined with a fever in an ADPKD patient, liver cyst infection should be included into the differential diagnosis. It is a potentially lethal condition in which antibiotics may be ineffective.[38] In such infections, antibiotics combined with drainage are superior to antibiotics alone. Additionally, when the diameter of the infected cyst is >5 cm, drainage is mandatory.[8,12]

Pancreatic cysts are observed in almost 20% of ADPKD patients. In very rare cases, they cause pancreatitis due to obstruction of the pancreatic duct.[12] An anatomical defect may lead to the recurrence of pancreatitis.[39] Additionally, Naitoh et al.[40] reported a case of adenocarcinoma of the pancreas leading to acute pancreatitis, and suggested a possible association between ADPKD and pancreatic carcinogenesis.

Colonic diverticula were thought to be associated with ADPKD, especially in the fifth stage of the chronic kidney disease. However, data on the frequency of diverticular disease and diverticulitis in ADPKD remain conflicting. An additional problem connected to ADPKD is increased frequency of hernias. Therefore, complications of abdominal hernias should be considered in patients with ADPKD and acute abdomen.[41]

As described below, vascular manifestations belong to the clinical picture of ADPKD. A rare case of acute abdominal pain with concomitant haemorrhagic shock, due to the rupture of a gastroepiploic artery aneurysm, was reported.[42] It should not be forgotten that there are also other possible sources of lower back pain in ADPKD. The most severe cases of chronic lumbalgia in my practice were due to the spine disease. The disorders of the spine in ADPKD are presented below.

CHEST PAIN

The prevalence of chest pain in ADPKD is estimated at 4-30%.[2,3] Vascular manifestations of the disease are due to the fact that both polycystins are expressed within arterial smooth muscle cells.[43-45] A systemic vascular defect was observed already at the oligosymptomatic stage of the disease.[46-47]

As a consequence, the most common extrarenal manifestation of the disease is AH, which often precedes impairment of kidney function,[48,49] and is complicated with left ventricular hypertrophy (LVH).[50] Both AH and LVH are well-known risk factors for ischaemic heart disease (IHD).[51] Therefore, patients with ADPKD and chest pain should be diagnosed for IHD.

Additionally, there are some disease-specific sources of chest pain in ADPKD, which should be included into the differential diagnosis. A rare cause of myocardial ischaemia and infarction may be spontaneous coronary artery dissection.[52,53] Furthermore, an association between ADPKD and non-atherosclerotic coronary aneurysm was suggested, and the latter may be - in very rare cases - connected to myocardial infarction.[54] Also, several case reports on the coexistence of ADPKD with aortic dissection, both acute[55-58] and chronic,[59] were published. They may manifest with pain localised either in the front of the chest, or in the interscapular region.[55,56]

Another disease-specific source of chest pain may be the polycystic liver. A case of ADPKD patient with chest pain caused by infected liver cyst with compression of the right atrium was reported.[60] Then, accurate imaging of the thorax is of a great value in ADPKD patients suffering from the chest pain.

HEADACHE

Headache is observed in 15-49% of ADPKD patients.[2,3] The two most common ADPKD-specific reasons of it are AH and ICAN. It is believed that up to 60% of young ADPKD patients with normal renal function have AH,[48] and its overall prevalence may exceed 80%.[49] Therefore, at the beginning, patients with headache should be examined for elevated blood pressure and treated when it is observed. Due to the fact that the non-dipping pattern is associated with ADPKD,[48,61] the special role of ambulatory blood pressure monitoring (ABPM) in the diagnosis of AH in ADPKD needs to be underlined.

ADPKD is connected to increased frequency of ICANs compared to the general population.[62] According to the literature data, the overall prevalence of ICANs in the ADPKD population ranges from 4%[63] to 22.5%.[64] In our recent study,[65] the prevalence of ICANs in ADPKD patients was 16.9%, and the only risk factor for ICANs was age; after 45 years-of-age the frequency of ICANs reached 22.4%. However, the subarachnoid haemorrhage (SAH) due to a rupture of an ICAN in ADPKD patients often occurs in relatively young subjects, with mean age below 40 years. Additionally, SAH is often observed in normotensive patients with preserved renal function.[66] Despite these facts, the universal screening for ICANs remains controversial, and only selected indications for screening are widely accepted in the clinical practice.[67] According to my unpublished, retrospective analysis of a series of ADPKD patients with nonfatal rupture of an ICAN in their medical history, more than half of them had neurological symptoms for at least a few months preceding SAH, with headache as the most common one. Therefore, in my opinion, each normotensive ADPKD patient with a new onset or chronic headache should be examined for an ICAN. Some other authors share my point of view.[41] On the other hand, according to Bajwa et al.,[3] the only indication for screening for ICANs in ADPKD is a family history of aneurysm formation, and patients with a negative family history for an ICAN should not be screened, even in case of chronic headache.[3] Due to safety reasons, MR-angiography is a method of choice in detecting ICANs in ADPKD patients, as there is no X-ray exposure or need for contrast media administration. The positive result of MR-angiography should be verified with CT-angiography, and when confirmed, the patient should be referred to the specialist in neurosurgery.[65]

Additionally to arachnoid haemorrhage, carotid artery dissection may occur in an ADPKD subject.[68] In very rare cases, headache may be a manifestation of an arachnoid cyst. Arachnoid cysts are found in fewer than 10% of ADPKD patients, compared to fewer than 1% in the general population, and are usually asymptomatic. They may be found on MRI scans performed as a screening for ICANs.[69]

OTHER LOCALISATIONS OF PAIN

Radicular pain, defined as a back pain radiating to the hips or lower extremities, is observed in 27% of patients with ADPKD.[3] Enlargement of cysts causes increased abdominal girth and leads to increased lumbar lordosis. In effect, degenerative changes of the spine appear, which manifest with pain. Bajwa et al.[5] suggested hypertrophy of the lumbodorsal muscle group in ADPKD patients as a basis of the spine 'imbalance'.

Additionally, asymmetry in renal cyst enlargement leads to chronic postural alteration, and results in the disc disease in the lumbosacral region. The diagnostic method of choice is MRI of the spine and postural muscles. Additionally, the sacroiliac joint is thought to be a common source of pain in ADPKD. Physical therapy techniques, together with local anaesthesia, can be used in such situations.[5]

CONCLUSIONS

In summary, ADPKD is a common and multi-organ disease. Therefore, the awareness of its manifestations, and possible sources of pain in ADPKD, is important not only for nephrologists but also for general practitioners and specialists in other areas of medicine. The proper and quick diagnosis may improve not only the patients' health and quality of life, but, in some cases, may save their life. Additionally, current treatment modalities enable the provision of optimal therapy for a substantial group of patients.

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