Overview of Polycystic Liver Disease

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Abstract

Polycystic liver disease is a hereditary liver disorder which may present independently or as a consequent symptom of autosomal dominant polysystic kidney disease or autosomal recessive polycystic kidney disease. The pathophysiology remains complicated and yet to be understood completely which makes it difficult to standardize diagnostic and management protocols. Gigot classification and Schnelldorfer classification are used to determine severity in PLD. Clinical presentation of PLD in most patients remain ill defined and only a few patients present with complications and need theatments. However various imaging studies such as magnetic resonance imaging and computed tomography makes it possible to identify and diagnose PLD at ease. The management stratergies include somatostatin analogues, ursodeoxycholeic acid and vasopressin 2 receptor antagonists are potentially effective while fenestration, cyst aspiration and sclerosis, hepatic resection and liver transplantation are other incasive therapeutic options. This review focuses on briefing the classificaition, diagnostic techniques, and various management stratergies to optain potential directions for future researches.

Keywords:

Polycystic liver disease, Autosomal dominant polycystic kidney disease, Autosomal recessive polycystic kidney disease, Isolated polycystic liver disease, Diagnosis, Treatment.

Introduction:

Polycystic liver disease (PLD) is a rare hereditary disease and is often defined as multiple diffuse cysts of the liver(1). Initially, it was thought that PLD could develop only in the context of Autosomal Dominant Polycystic Kidney Disease(ADPKD). The notion that isolated PLD might be a separate condition was proposed in the 1950s. In 2003, a linkage analysis of eight Finnish families confirmed that PLD is genetically distinct from ADPKD(2). Asymptomatic patients usually do not require any intervention(3). In some patients, massive hepatomegaly can cause pain or compression of the adjacent gastrointestinal organs, vasculature, and diaphragm. This can have a significant effect on patients' quality of life and performance status(3)(4). For these patients, the main aim is to reduce their symptoms by decreasing liver volume(5)(6). Current surgical options include open or laparoscopic cyst fenestration with or without hepatic resection and liver transplantation (LT). Significant advances in surgical techniques have improved the outcomes of PLD patients. However, the selection of the appropriate approach remains a clinical challenge, and there is no consensus on the optimal timing and what represents the best therapeutic modality.

Epidemiology:

Polycystic liver disease affects around one in 100,000 people(7). Males and females are affected in equal numbers, but most patients with symptoms and with severe disease are women(8). The suggested cause of this difference is that, female sex hormones such as estrogen contribute to growth of liver cysts(9)(10).Oral contraceptives and estrogen replacement therapy are also associated with more severe disease. Cysts can begin to grow at any age, but are rare in childhood and more common with age. The age at which symptoms begin to occur varies with individuals, but is usually around 50 years old.

Causes:

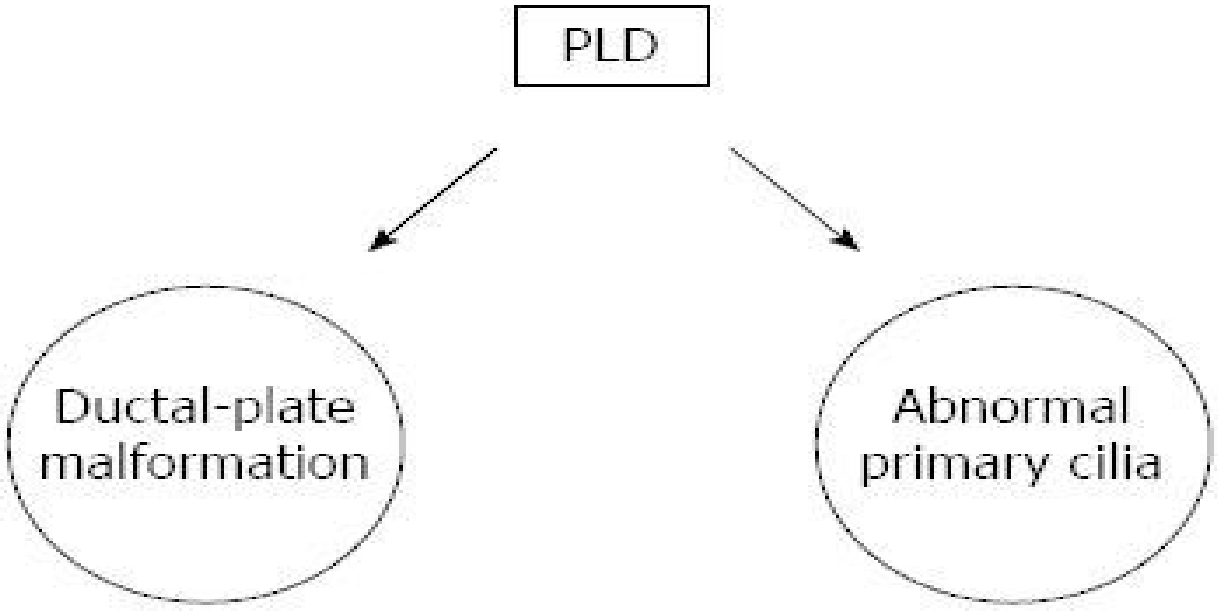
Changes (mutations) in three genes, *PRKCSH, LRP5* , and *SEC63*, are linked to polycystic liver disease(11). These genes are not associated with AD-PKD. Individuals with mutations in *SEC63* or *PRKCSH* tend to have more severe symptoms compared to individuals with the polycystic liver disease without mutations in one of these two genes(11). However, less than 50% of individuals with polycystic liver disease have a mutation in one of these genes, so other genes may be involved in this condition(12). *GANAB, ALG8*, and *SEC61B* are three genes potentially involved in polycystic liver disease and are being investigated as possible causes of the disease(13).

Disease-causing (pathogenic) mutations in *SEC63* and *PRKCSH* lead to defects in processing, folding, and translocation of newly synthesized glycoproteins. This is associated with embryological malformations which causes the formation of fluid-filled cysts throughout the liver(10)(12).

Most cases of polycystic liver disease are inherited in an autosomal dominant pattern. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary to cause a particular disease. The abnormal gene can be inherited from either parent or can be the result of a mutated (changed) gene in the affected individual. The risk of passing the abnormal gene from an affected parent to an offspring is 50% for each pregnancy. The risk is the same for males and females.

Pathophysiology:

Malformation of the hepatic ductal plate and cilia of cholangiocytes is the main characteristic linked to the pathophysiology of PLD(9).



Ductal- Plate Malformation: Ductal plate malformations (DPMs), also known as fibropolycystic liver diseases, represent a unique spectrum of pathological abnormalities that are caused by an insult to the embryonic ductal plate development at various stages. This results in the formation of congenital cystic lesions of the biliary tract that involve the intra as well as extrahepatic bile ducts. The importance of detecting these DPMs at an early stage is their predisposition for pancreatitis, cholangitis, lithiasis, and malignancy. The purpose of this pictorial essay is to acquaint the readers with imaging features in DPMs(14).

Abnormal Primary Cilia: In the past decade, a class of disorders known as ciliopathies has become recognized, comprising a unique spectrum of genetic syndromes. These disorders are caused by dysfunction of primary cilia—small non-motile, hair-like organelles that are found to protrude from the surface of nearly all vertebrate cell types, at a frequency of one per cell, and are highly conserved throughout evolution. The cilium comprises a microtubule-based core, the axoneme, which extends from a specialized centriole at the base of the cilium, termed the basal body, and a region between the axoneme and the basal body known as the transition zone(15). The specialized structure of the primary cilia offers a unique opportunity for the partitioning of sensory and signaling proteins away from the main body of the cell in a different cytoplasmic environment to enable fine-tuning of biological responses to various stimuli, such as mechanical stimuli and light. For instance, flow-induced passive bending of cilia present on kidney tubular epithelial cells mediates the mechanosensation of extracellular urine flow, while in retinal photoreceptors, a specialized primary cilium connects the inner segment, which contains the cellular nucleus, with the outer segment, which contains the photopigment. Furthermore, many receptors expressed on the primary cilium surface are necessary to bind specific hormones (for example, somatostatin), growth factors (for example, platelet-derived growth factor), or morphogens (for example, sonic hedgehog [SHH] and Wnt), which have essential roles especially during embryonic development. Indeed, primary cilia sense and transduce many extracellular signals to influence a wide variety of processes, such as cell proliferation and polarity, developmental processes, and neuronal growth(16).

Defects in the primary cilia can lead to a wide array of clinical phenotypes, and in fact, ciliopathies can affect nearly every major body system, including the brain, eyes, liver, kidneys, skeleton, and limbs. Advances in our understanding of the biology of primary cilia have provided important insights into the unifying features of these distinct disorders. In turn, elucidation of the genetic basis of many ciliopathies has informed our understanding of ciliary biology and helped identify many of the key molecular components that underlie cilium formation and function(16).

Signs & Symptoms:

Polycystic liver disease is characterized by the growth of more than 10 cysts in the liver, ranging in size from a few millimeters to over 15 cm in diameter. Symptoms usually begin to show in people around 50 years old, as cysts grow in size and number with age(7). Some people begin to have symptoms in early adulthood and many affected individuals do not have symptoms.

The growth and accumulation of cysts can cause enlargement of the liver (hepatomegaly) and compression of adjacent anatomical structures.

Leading to abdominal pain and discomfort.

Shortness of breath (dyspnea).

Indigestion (dyspepsia).

Gastro-esophageal reflux and limited mobility(9). More rarely, liver cysts can also compress the bile duct and lead to yellowing of the skin (jaundice). Compression of the blood vessels of the liver by cysts can lead to accumulation of fluid in the abdomen (ascites), bleeding, and high blood pressure in the blood flow from intestines to the liver (portal hypertension)(17). In rare cases, patients can suffer from cyst bleeding (hepatic cyst hemorrhage), or a cyst can be infected by bacteria (hepatic cyst infection), causing pain and fever. Infrequently, large liver cysts may rupture, causing severe abdominal pain. Even with the presence of many cysts, the liver of individuals with polycystic liver disease functions normally. (10)

Diagnosis:

Most patients with polycystic liver disease (PLD) are asymptomatic with simple cysts found following routine investigations. After confirming the presence of cysts in the liver, Magnetic resonance

imaging (MRI), computed tomography (CT) scan, and ultrasound (US) are used to take pictures of the liver to see if cysts are present. The images are used for diagnosis and monitoring of cysts growth laboratory tests may be ordered to check for liver function including bilirubin, alkaline phosphatase, alanine aminotransferase, and prothrombin time.

It is also possible to test for blood levels of two markers of liver and bile duct disease: gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP). These two markers might be elevated in patients with severe polycystic liver disease.

The diagnosis of PLD is usually made when the number of hepatic cysts is more than 20. However, a patient with a family history of PCLD can be diagnosed when the number of cysts more than 4. However, the type of PLD can be hard to distinguish. Because PCLD patients may have renal cysts while ADPKD or ARPKD patients may have hepatic cysts as the main clinical manifestations, the identification between them without family history may be difficult and requires genetic analysis.

Currently, there are mainly two clinical classifications on PLD: Gigot classification and Schnelldorfer classification. Both of them include the number and size of cysts and the remaining liver parenchyma volume as the criteria for typing, while the latter also considers the inflow and outflow of pre-retained liver segments, which is more conducive to the choice of treatment. There was a Qian classification relying on the number of cysts and the presence of symptomatic hepatomegaly however it is seldom used now because of oversimplification and, more importantly, having no contribution to the selection of treatments.

ADPKD: Autosomal dominant polycystic kidney disease; ARPKD: Autosomal recessive polycystic kidney disease; PCLD: Isolated polycystic liver disease. (1)

Gigot classification:

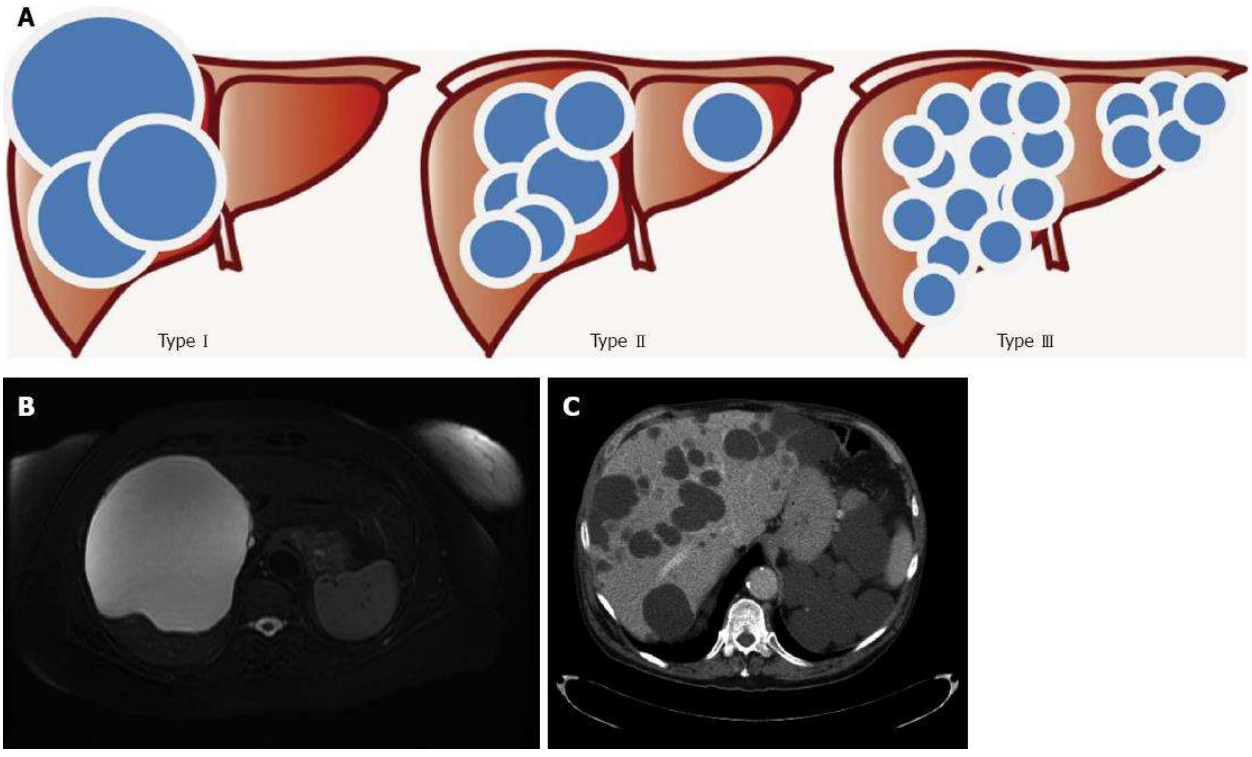


Figure 1 Gigot's classification for polycystic liver diseases. A: Graphical representation; B: Abdominal magnetic resonance imaging of a patient affected by Gigot I cystic liver disease; C: Abdominal computerized tomography of a patient affected by Gigot II cystic liver disease. (9)

Table 1: Gigot classification:

Gigot classification:	
Type I	Patients with a limited Number (<10) of Large cysts (>10cm)
Type II	Patients with Diffuse involvement of liver parenchyma by multiple medium-sized cysts, with remaining large areas of noncystic liver parenchyma on preoperative CT
Type III	Massive, diffuse involvement of liver parenchyma by small and medium-sized liver cysts and only a few areas of normal liver parenchyma between cysts

Schnelldorfer classification:

Schnelldorfer's classification aims at differentiating patients who could benefit from resection or transplantation as summarized in Table

Figure 2: Schnelldorfer classification:

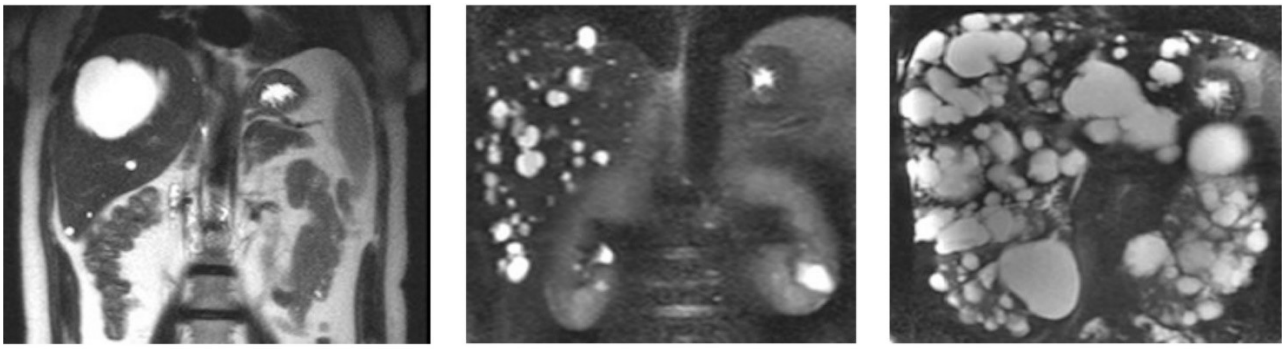


Table 2(9)**: Schnelldorfer classification**

Schnelldorfer classification				
Symptoms	Type A Absent or Mild	Type B Moderate or Severe	Type C Severe (or Moderate)	Type D Severe (or Moderate)
Cyst Charact	Any	Limited no. Large Cysts	Any	Any
Normal Liver	Any	≥2 Sector	≥1 Sector	≥1 Sector

Treatment	Observation or Medical Treatment	Cyst Fenestration	Hepatectomy + Cyst Fenestration	Liver Transplantation

Treatment:

Treatment may not be necessary in many cases of polycystic liver disease and is only indicated in severely affected or symptomatic patients. Medication to slow down cyst growth and fluid secretion in the liver (somatostatin analogs, namely octreotide, and lanreotide) is also useful in reducing liver volume(10)(18).

Ursodeoxycholic acid (UDCA), which is a Ca^{2+} agonist in hepatocytes and biliary epithelial cells, has been shown to delay the growth of hepatic cysts in PLD animal model experiments. The mechanism is to inhibit cystic hyperplasia of biliary epithelial cells by inhibiting the proliferation of cystic bile duct epithelium and decreasing cytotoxic bile acid levels in the liver without affecting apoptosis by the PI3K/AKT/MEK/ERK1/2 pathway(19). Because they are very expensive, these medications are typically reserved for patients with moderate to severe disease with reduced quality of life. Large cysts (>5 cm) can be treated with aspiration sclerotherapy, which includes puncture of the cyst, removal of the fluid, and treatment of the cyst wall with a chemical allowing tissues to harden, (sclerosing agent) such as ethanol(20). When multiple large cysts are causing symptoms, keyhole surgery can be a treatment option. The surgeon punctures and then removes the 'roof' of the cysts. This procedure is called laparoscopic fenestration(6). It is also possible to remove parts of the liver (hepatic resection) to reduce symptoms related to hepatomegaly(10). The only definitive treatment of PLD, used in only the most severe cases, is liver transplant (8)(21).

Liver transplantation is currently the only cure for PLD, which is mainly applied in Gigot type III patients with severe symptoms that seriously affect the quality of life of patients, as well as untreated complications such as portal hypertension and malnutrition(6). In the PLD classification designed by Schnelldorfer et al(21), liver transplantation is suitable for patients with type D. Meanwhile, most patients have a significant improvement in health-related quality of life assessment after transplantation(22). Even liver transplantation performs comparatively well in PLD, however, due to the lack of liver donors, relatively low urgency, and low mortality rate, it is difficult to extensive performance and necessary to carefully evaluate the indications of liver transplantation.

Referral to a specialized center is recommended. As estrogen promotes cysts' growth, it is recommended for women diagnosed with polycystic liver disease to stop hormonal contraceptives or estrogen replacement therapy(9)(10)(23).

Genetic counseling is recommended for patients and their families

Discussion:

PLD is a rare hereditary disease, with age, only in a small number of patients mostly in Female patients. They have symptoms that require treatment. The Treatment of PLD is mainly somatostatin analogs, Ursodeoxycholic acid this is the oral medication treatment for the PLD. Surgical Procedures are sclerotherapy, cyst punctures and Liver transplantation (LP) is the only cure for PLD.

Conclusion:

PLD is a hereditary genetic disease. Although the manifestation and progression of the disese intensifies with age only a small population require medical intervention. At present the diagnosis and management of PLD are still on the road to perfection. The current treatment stratergies for PLD revolves around drugs intervention, cyst puncture and sclerotherapy, fenestration, transcatheter arterial embolization,

liver resection, liver transplantation. Pharmacological drug therapy for PLD is focused on vasopression 2 receptor antagonists, ursodeoxycholeic acid somatostatin analogues, while many other drug targets are being developed as more and more clinical trials are validating their effectiveness. At present, Liver transplantation is probably the only cure for PLD, but it cannot be done to all the patient due to a wide variety of complications. Except liver transplantation, the other four surgical and interventional treatments can be widely used for PLD patients with different conditions. But considering the high recurrence rate, serious complications and mortality, it is necessary to carefully consider the indications. Besides, various combination therapies should be investigated in future researches for better effectiveness.

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