Review Article

Current Status in the Surgical Management of Adult Polycystic Liver Disease

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Abstract

Introduction*: In patients with adult polycystic liver disease (APLD), there is considerable debate surrounding the most effective way of managing symptomatic cysts. Conservative approaches like percutaneous aspiration or cyst fenestration are associated with low morbidity but high recurrence rates. Conversely, liver resection and hepatectomy with orthotopic liver transplantation is drastic and associated with high morbidity and mortality rates. Our aim is to review the current understanding of liver cystogenesis in these patients and the therapeutic options available in order to provide a rationale guide to management of this intriguing condition. *Methods*: This article summarises the findings of published papers in major international journals indexed on MEDLINE on APLD using the key words – adult polycystic liver disease, liver cysts, fenestration, liver resection, liver transplantation and polycystic kidney disease. The period of search includes papers between 1965 and 2000. *Results*: Published studies have suggested a 'two-hit' hypothesis to explain the development of liver cysts in patients with APLD. This will provide the rationale for future management. Meanwhile, the indications, pitfalls and results of the various therapeutic options are reviewed. Management of symptoms has to be tailored to the underlying severity of the liver cystic disease, co-morbidity and procedural risks and recurrence rates. *Conclusion*: Good long-term relief of symptoms can be achieved with the correct procedure at acceptable morbidity and mortality rates. We have provided guidelines on the various options available to enable a structured approach to the management of APLD.

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Key words: Adult polycystic kidney disease, Fenestration, Liver cysts, Liver resection

Introduction

Adult polycystic liver disease (APLD) is a rare benign condition that is characterised by the growth of multiple cystic lesions in the liver. More commonly, it occurs in close association with autosomal dominant polycystic kidney disease (ADPKD), where the prevalence increases from 25% in the third to 80% in the sixth decade of life.[1,2] Occasionally, polycystic liver occurs as an isolated disease[3] that may be sporadic or dominantly inherited,[4] but the prevalence is not known. These cysts have a random, diffuse growth pattern that tends to be progressive. Recently, advances in understanding of molecular changes in ADPKD and the development of relevant animal models have provided an insight into liver cystogenesis.

Despite documenting progression of liver cyst formation, most patients are asymptomatic and liver failure rarely occurs. Some patients experience chronic and troublesome symptoms that may be debilitating. In addition, others may develop acute complications like cyst infection or rupture that is potentially life threatening.[1,5] To cope with this subset of patients, a host of surgical procedures may be offered to combat the symptoms but controversy surrounds the 'optimum' procedure. This is because of high morbidity and poor long-term palliation associated with some of these interventions. In this review, we focus on the current state of knowledge regarding the pathogenesis and review the published results of the various surgical options so that physicians and surgeons might better understand what to offer patients with this unique affliction.

An Insight Into Liver Cystogenesis

An understanding of the development of liver cyst will provide a rationale approach for their management. In the general population, up to 5% of individuals have one or more cysts.[6] These tend to increase with age and a similar pattern is seen in patients with ADPKD. These cysts

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reportedly develop later than renal cyst and age is an independent predictor of prevalence and number of cysts. This suggests that genetic and environmental conditions may exert a cumulative effect on the growth of hepatic cysts.[7]

Epidemiological evidence points to an oestrogenic influence on the development of hepatic cysts. Polycystic livers are more common in females with ADPKD.[8] In addition, those who have had pregnancies or previously been on exogenous hormones were more likely to develop a larger cyst load. To evaluate the role of oestrogen, Sherstha et al[9] administered premarin in a study group of 20 patients with ADPKD and found that there was a selective increase in liver cyst size of 7% over 1 year compared to a control group. Another risk factor for cystogenesis is the severity of the renal failure. Patients with the most severe renal cystic disease and the greatest reduction in renal function had the most extensive hepatic cyst disease.[7,10] This suggests a parallel expression of molecular factors in the liver and kidney.

The growth of cysts in the liver is thought to arise from three elements: 1) increased cell proliferation, 2) secretion of solute and fluid into cysts and 3) abnormal cell matrix. The ability to culture liver cyst derived epithelial cell lines has conclusively demonstrated that these are of biliary origin,[11] consistent with previous hypothesis.[12] Morphological studies suggest that these liver cysts arise from two different structures. Peripheral cysts originate from biliary microharmatomas that are disconnected from the bile ducts and subsequently enlarge, and centrally located cysts arise from dilatation of peribiliary glands in the liver,[13] but what is the trigger for cyst formation?

The discovery of the PKD1[14] and PKD2[15] genes responsible for ADPKD has cast light into the underlying genetic mechanisms of cyst formation. A common feature of cyst formation in the organs of polycystic kidney patients is that it involves only a focal subset of cells. Moreover, cyst formation appears to be age related. This suggests that there is a second rate-limiting step other than the acquired genetic mutation to PKD1 or PKD2 for a pathogenic change to occur. It seems likely that cyst by cyst, a 'two-hit' model where a somatic mutation to the normal allele coupled with a germline mutation is critical for cystogenesis,[16,17] making it recessive at a molecular level. Evidence for this is mounting. These liver cysts are of clonal origin and a high percentage of hepatic cysts have somatic mutations to the normal allele with loss of heterozygosity.[18,19] In addition, murine models have shown a lack of cyst formation in heterozygotes pkd1+/- and pkd2+/- knockout mice, whereas severe cystic disease is seen in homozygotes and compound heterozygotes that are targeted with a hypermutable allele.[20,21] The next important step would be to identify the factors that control the somatic mutation rate as well as define a function for the PKD1 and PKD2 gene products. These will pave the way for therapeutic intervention and management of cystic liver disease.

Clinical Manifestations of APLD

Despite the gross cystic change seen within the liver parenchyma, the majority of patients are asymptomatic. The description of a 'huge, silent and durable liver' is the hallmark of this disease.[1] As such, most patients with APLD can be managed on a conservative basis. Symptoms, when they manifest, are caused by (a) the mass effect of the cyst or (b) the development of complications. This subset of highly symptomatic patients will benefit from timely surgical intervention.

The enlargement of the liver tends to lead to chronic symptoms that include abdominal distension, pain, early satiety, nausea and vomiting, bilateral pedal oedema, dyspnoea and the development of abdominal hernias. The long-term outcome may be one of a poor quality of life from disability, malnutrition and physical exhaustion.

Complications that arise in APLD are rare and occur in less than 5% of patients.[22] These include infection, haemorrhage, rupture of individual cysts, portal hypertension with bleeding oesophageal varices and ascites,[23] and hepatic venous outflow obstruction secondary to mechanical compression from the cyst.[24] Rarely, the cysts may undergo malignant change.[25] Despite the spectrum of complications, liver failure has never been described.

Classification of APLD

The spectrum of liver involvement by cystic change varies greatly between patients with APLD. The literature is studded with several therapeutic options but no consensus. Part of the reason for this is that there is no objective means of comparison between patients and between techniques in the long term. Gigot et al[26] attempted to classify APLD according to number and size of cysts and the amount of remaining liver parenchyma.

Type 1: Limited number (<10) of large cysts (>10 cm) with large areas of non-cystic parenchyma on preoperative computed tomography (CT).

Type 2: Diffuse involvement of liver parenchyma by multiple medium-sized cysts with remaining large areas of non-cystic parenchyma on preoperative CT.

Type 3: Massive, diffuse involvement of liver parenchyma by small and medium-sized liver cysts and only a few areas of normal liver parenchyma between cysts.

This forms a good platform for comparison of morphological disease between patients.

Therapeutic Options for APLD

We believe that the aims in surgical therapy should first be to reduce significantly the size of the severe polycystic hepatomegaly and secondly to provide long-term relief of symptoms. However, no clear consensus regarding the optimum timing or optimum procedure. On the one hand, it is technically feasible and appealing to perform resection of affected liver for highly symptomatic patients but this carries a significant morbidity and mortality. This must be balanced against less risky procedures like aspiration or cyst fenestration where the recurrence rate for symptoms is higher. As such, all patients should be carefully evaluated for symptoms and degree of disability and physical status, and amount of renal and liver dysfunction before any procedure is considered. In addition, patients should also be made aware of the risks and limitations of the surgery considered before embarking on the course of management.

Percutaneous Aspiration and Sclerosis

Cyst aspiration coupled with instillation of a sclerosant like ethanol has been proposed as a feasible initial option in high-risk APLD patients and those where a large dominant cyst is clearly the cause of the symptoms.[27-30] Recurrence is prevented by the effect of the alcohol on the lining of the cyst wall. Although it appears to be technically feasible in certain centres, the success rate (70% after a single treatment and an additional 20% after repeated treatment) is related to the size of the cyst.[31] Others have reported recurrence rates of 100% after a follow-up of 24 months.[32] Limitations include 1) the ability to only treat a limited number of cyst per session, 2) the potential complication of bleeding, 3) alcohol extravasation and 4) the inability to treat cysts containing bile. However, no long-term results are available and it seems unlikely that it will provide definitive therapy from progression of disease or cyst recurrence.

Fenestration

This technique allows for de-roofing of the cyst by dividing tissue at the common cyst-liver boundary for as many cysts as possible. This will allow cyst contents to be drained to reduce overall bulk of the liver. After fenestration, the cyst contents can drain freely into the peritoneal cavity for resorption. It may be advantageous to destroy the fluid-producing lining with diathermy or argon beam coagulation at surgery to ablate the secretory epithelium and reduce postoperative fluid loss.[33] The original transhepatic fenestration was described by Lin et al[34] on 3 patients as an open procedure with excellent symptom-free results. Since 1991, this procedure has been performed via the laparoscopic approach with some success.[35,36] The 11 published series in the literature are summarised in Table I.

This procedure is most useful for superficial and large cyst of limited numbers. Those classified as type 1 APLD are amenable. Farges and Bismuth,[43] in their series of 13 patients, reported successful long-term treatment in those with type 1 APLD during a follow-up period of 14 to 140 months. It was safely carried out and provided lasting relief of symptoms because of a significant reduction in the size of the liver and cyst. Failures in their group were those with type 2 and type 3 APDL where the cysts were smaller, more diffuse and deep-seated. Gigot et al[26] concured in their study with these findings; although they were more aggressive and performed 'extensive fenestration' in type 2 patients. Although short-term symptom relief was obtained, they conceded that it is associated with higher morbidity and does not preclude recurrence with progres-

TABLE I: RESULTS OF OPEN AND LAPAROSCOPIC FENESTRATION FOR POLYCYSTIC LIVER DISEASE

Reference	No. of patients	Technique	Mortality n (%)	Morbidity n (%)	Mean follow-up (mo)	Symptom free (%)	Re-operation (%)
Lin et al (1968)[34]	3	Open	0	0	32	100	0
Van Erpecum et al (1987)[37]	9	Open	1 (11%)	0	48	100	0
Turnage et al (1988)[38]	5	Open	1 (20%)	1 (20%)	10	60	0
Sanchez et al (1991)[32]	7	Open	0	NS	18	43	0
Farges et al (1995)[39]	13	Open	0	9 (69%)	84	77	8
Gigot et al (1997)[26]	10	9 Open	0	6 (60%)	73	89	11
		1 Lap	0	0	73	100	0
Koperna et al (1997)[40]	39	34 Open	0	NS	75	79	21
		5 Lap	0	NS	75	100	0
Morino et al (1994)[41]	9	9 Lap (2 Conv)	0	4 (44%)	NS	40	NS
Kabbej et al (1996)[42]	13	13 Lap	0	7 (54%)	26	28	23
Martin et al (1998)[36]	13	6 Open	0	2 (33%)	96	80	20
		7 Lap	0	2 (29%)	37	29	71
Katkhouda et al (1999)[43]	9	9 Lap (1 Conv)	0	3 (33%)	30	89	11

Conv: conversion; Lap:laparoscopic; NS: not stated

sion of disease. More recently, the use of a laparoscopic technique for type 1 patients has been advocated by Morino et al.[41] Advantages include a rapid recovery and less postoperative adhesions. The recurrence rate in the series was high and quoted at 60% at 6 months. A closer look at their data shows that all patients with type 1 APLD cysts remained asymptomatic and recurrence of symptoms was associated with type 2 and type 3 APLD. A similar situation is seen in the study by Kabbej et al[42] who reported a high recurrence rate of 72%, but 8 of 13 patients in the series had type 2 and type 3 APLD. The best example of this is described in the series by Katkhouda et al[43] where patient selection included only type 1 APLD livers and the recurrence rate after 30 months was only 11%.

The commonest complication postoperatively is the formation of ascites.[12,37] This is because the peritoneum cannot clear fluid in excess of 900 mL/day.[44] It is necessary to ensure that wounds and trocar sites are well closed. Peritoneal drains may be left to cope with the ascites but the Bismuth experience[39] has advised against this, citing ascending superinfection as a potential problem. Moreover, in those with renal failure, the ascites may follow a protracted course. Repeated paracentesis and diuretics are effective and the role of cimetidine or somatostatin analogues have been anecdotally useful in reducing postoperative ascites.[12] Other precautions taken at surgery include the use of a cholangiogram or dye test to ensure the absence of bile leakage and careful perioperative fluid management to prevent acute dehydration.

The choice between a laparoscopic or an open approach thus depends on three main factors. Firstly, the anatomical location of the main cysts. Certain segments, especially those in the right posterior segments, Couinauds segment VI, VII and VIII, are difficult to access in hepatomegaly. Secondly, deeply situated cysts that may communicate with superficial cysts through a thin parenchyma may be difficult to reach and differentiate from vascular structures. Thirdly, the personal expertise with performing fenestration laparoscopically will also determine the modality chosen. The main technical difficulty is avoidance of injury to the intrahepatic veins and portal radicles during fenestration. This trend towards laparoscopic fenestration as a safe and effective procedure with less morbidity and hospital stay is reasonable if the pitfalls are kept in mind.

Resection with Fenestration

A combination of partial hepatic resection and fenestration appears to be valuable for patients with symptomatic APLD. The results of 9 published series are reviewed in Table II. The largest experience is reported by Que et al[33] in a long-term follow-up of 31 patients. Patients that were included in this series had type 2 and type 3 APLD with more severe parenchymal involvement. Fenestration in this group is difficult because the liver tends to be more rigid as a consequence of fibrosis[49] around the cyst. As a result, the skeletal architecture remains stable and cysts do not collapse well. Combined fenestration resection allows for removal of multiple segments that are grossly affected segments and achieves excellent reduction in liver mass. Deep-seated cysts and large superficial cysts within segments that have normal liver parenchyma can undergo fenestration. The recurrence rate is extremely low in this series with 30 out of 31 patients remaining symptom free at a median follow-up of 28 months. Most patients experience an improvement in the quality of life, functional status and nutritional status without deterioration in liver or renal function.

Even in the hands of liver surgeons, resection of polycystic livers is not without risks. The morbidity is higher than with fenestration alone ranging from 37.5% to 100%. Bleeding, postoperative ascites and biliary leaks are the commonest complications. These will be more evident in those with prior renal failure. Selection of patients is important to gain the maximal benefit and at present this appears to be with those having type 2 and type 3 APLD livers. For patients with renal failure, major hepatic resection may represent a prohibitive risk.

TABLE II: RESULTS OF COMBINED FENESTRATION AND RESECTION FOR POLYCYSTIC LIVER DISEASE

Reference	No. of patients	Technique	Mortality n (%)	Morbidity n (%)	Mean follow-up (mo)	Symptom free (%)	Re-operation (%)
Turnage et al (1997)[38]	3	F+R	2 (67)	2 (67)	9.6	0	0
Newman et al (1990)[45]	9	F+R	1 (11)	5 (55)	17	89	0
Vauthey et al (1991)[12]	5	F+R	0	5 (100)	14	100	0
Henne-Bruns et al (1993)[46]	8	F+R	0	3 (38)	15	50	0
Soravia et al (1995)[47]	10	F+R	1 (10)	2 (20)	68	67	11
Que et al (1995)[33]	31	F+R	1 (3)	18 (58)	28	97	0
Koperna et al (1997)[40]	5	F+R	0	NS	NS	100	0
Iwatsuki et al (1989)[48]	6	R	0	0	NS	NS	NS
Martin et al (1998)[36]	9	R	0	6 (67)	9	67	0

F+R: combined fenestration and resection; NS: not stated; R: resection only

TABLE III: RESULTS OF LIVER TRANSPLANTATION FOR POLYCYSTIC LIVER DISEASE

Reference	No. of patients	Previous surgical palliation	Combined L/K Tx (n)	Mortality (n)	Mean follow-up (mo)	Symptom free (%)
Starzl et al (1990)[50]	4	2	2	1	8 to 60	100
Washburn et al (1996)[51]	5	4	1	1	38	80
Jeyarajah et al (1998)[52]	6	4	3	0	50	100
Kwok et al (1988)[53]	1	1	1	1	–	–
Lang et al (1997)[54]	17	6	8	5	12	71
Swenson et al (1998)[55]	9	4	3	1	2 to 46	100

L/K Tx: combined liver and kidney transplant

Transplantation

It seems a drastic solution to use orthotopic liver transplantation (OLT) to treat benign liver disease that typically has normal liver function. Despite this, consideration has to be given in several scenarios. Firstly, to those with severe type 3 APLD that has no spared segments. Secondly, those that have failed previous operative intervention for palliation and have 'reached the end of their functional lives because they can no longer carry the weight of their slowly enlarging livers'. Finally, patients with severe co-morbidities like concomitant renal failure.

Excluding anecdotal case reports, there have been 6 published series (Table III) documenting experience with liver transplantation for APLD. This offers long-term palliation and possibly cures. The largest series reported by Lang et al[54] confirms that patients can achieve excellent symptomatic relief in the long term and a good quality of life; however, the mortality rate in their series was 29%. This was due to immune suppression and overwhelming sepsis.

Consideration at the time of transplant should be given to a joint renal and liver transplant from the same living donor. The rationale for this is that administration of FK 506 or cyclosporine could hasten the renal failure because of its nephrotoxicity.[50] Secondly, the liver allograft can provide an immunological advantage for the renal allograft by neutralising and removing donor-specific antibodies. Renal graft acute rejection rates are reduced and graft survival rates are improved.[56] However, this should only be carried out for those with concomitant advanced renal failure.

Conclusion

Treatment of APLD remains a fascinating but formidable clinical and therapeutic challenge. With recent discoveries, we are now able to gain an insight into the clinical picture of liver cystogenesis. In molecular terms, autosomal dominant PKD is actually a recessive for phenotypic expression of cysts. The next interesting question is what factors determine this 'second-hit'. This will enable us to identify those that are at risk of developing liver cysts and possibly control the progression of liver cysts. Meanwhile, we have a wide range of options available to surgeons and physicians to cope with those that are symptomatic. All the options have been considered in terms of their indications and pitfalls and the authors hope that this will serve as a rational guide to management of this intriguing condition.

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