

Review Article

Current status and progress in the treatment of congenital liver cyst

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ABSTRACT

Liver cyst is a relatively common benign liver disease. According to the cause of the disease, it can be divided into two types: non-parasitic liver cyst and parasitic liver cyst. Congenital liver cyst is the most common non-parasitic liver cyst in clinical practice, also known as true cyst, which mainly include simple liver cyst and polycystic liver diseases (PLD). In recent years, with the popularization of ultrasound and other examinations, the detection rate of liver cyst has increased year by year, but there is no unified consensus on the treatment of liver cysts. This article reviews the conservative treatment, puncture drainage, aspiration sclerotherapy, surgical treatment and other treatment options for congenital liver cysts, as well as the technological progress in recent years.

Keywords: Congenital liver cyst, Treatment, Progress, Review

INTRODUCTION

Congenital liver cysts mainly include simple liver cysts and polycystic liver disease, which are more common in women. Its pathogenesis is not yet clear. At present, the mainstream believes that simple liver cysts may be caused by non-hereditary congenital bile duct malformations. Polycystic liver disease is a genetic disease characterized by the presence of a large number of liver cysts (usually >20).¹ With the popularization of imaging examinations and health examinations, the detection rate of congenital liver cysts is increasing year by year. Treatment methods such as fenestration, puncture drainage and aspiration sclerotherapy can be adopted in simple liver cyst which required intervention. For symptomatic polycystic liver disease can take fenestration, aspiration sclerotherapy, resection, liver transplantation, targeted inhibitors and other treatment methods.² With recent studies on the pathogenesis of congenital liver cysts and a large number of clinical cases, there has been a new consensus and progress in the treatment of congenital liver cysts.

Simple liver cyst

The pathogenesis of simple liver cyst is not clear at present, and there is no unified consensus on the treatment of simple liver cyst. But the mainstream thought that canceration doesn't occur in simple liver cysts, so the patients with diameter less than 4 cm and no symptoms can be followed up and observed. For large cyst or patients with oppression symptoms or with complications such as bleeding, infection, can take the puncture drainage, aspiration sclerotherapy, laparotomy, laparoscopic surgery and other treatments.

Fenestration

Fenestration can be accomplished in laparotomy or laparoscope, and laparoscopic fenestration has gradually replaced laparotomy as the preferred surgical method because of its advantages such as less trauma, stable efficacy, low recurrence rate and quick recovery with the development of minimally invasive surgery in recent years. Laparoscopic fenestration is best for patients who have not undergone abdominal surgery. Fenestration is

usually used in the large cysts on the surface of the liver without intracystic hemorrhage and the cyst cavity is not connected to the bile duct. The postoperative recurrence rate is about 0-20%. Common postoperative complications include biliary fistula, bleeding and so on. And the incidence is about 0-25%.³ In recent years, studies have shown that removing the cyst wall as completely as possible during the operation or cauterizing the cyst wall as thoroughly as possible with an argon-helium knife or bipolar electrocoagulation can effectively prevent cyst recurrence, but its safety and long-term efficacy need to be further studied.⁴ Covering the residual cyst with omentum can significantly reduce the recurrence rate of liver cysts after fenestration, but increase the incidence of mild gastrointestinal dysfunction due to extensive adhesions. For single hepatic cysts located in liver segments IV, VII, and VIII that are difficult to cover with omentum, the use of sclerosing agents such as lauromacrogol to inject into the cavity can also significantly reduce the recurrence rate.⁵

Aspiration sclerotherapy

Aspiration sclerotherapy is currently controversial as the first-line treatment for simple liver cysts, mainly because of its relatively high postoperative recurrence rate, and its advantage is that it is less traumatic and can be repeated many times. Aspiration sclerotherapy mainly includes ultrasound-guided percutaneous puncture and endoscopic ultrasound (EUS) puncture. For giant cysts of the right liver, ultrasound-guided percutaneous puncture is preferred, for multiple liver cysts with relatively small volumes in the left liver and hepatic caudate lobe, endoscopic ultrasound puncture is preferred.⁶ Commonly used sclerotizing agent include ethanol, polidocanol, minocycline hydrochloride, tetracycline and so on. Among them, ethanol is the most commonly used, which has the advantages of low price and obvious therapeutic effect. However, studies have shown that polidocanol has the same efficacy as ethanol and more reliable safety.⁷ Minocycline hydrochloride is also a safe and effective hardener and is widely used.⁸ For aspiration sclerotherapy, the reduction of cyst diameter does not reflect the success of aspiration sclerotherapy, while the symptoms measured by the polycystic liver disease questionnaire (PLD-Q) can be used as a reliable measure of outcome.⁹ The hepatic cyst accompanied by intracystic hemorrhage often indicates poor efficacy of aspiration sclerotherapy, so the dose of sclerosing agent can be appropriately increased to achieve the desired therapeutic effect.¹⁰ Studies have shown that aspiration sclerotherapy has the same therapeutic effect as fenestration surgery, and the incidence of postoperative complications is low, but still need a lot of research data and long-term follow-up to prove its long-term efficacy.^{11,12}

Hepatic cystectomy

Hepatic cystectomy can also be divided into two methods: open surgery and laparoscopic surgery. It has a very low

postoperative recurrence rate, but not as a conventional treatment for simple liver cysts because hepatic cyst resection is often accompanied by partial hepatic tissue resection, which is more traumatic and more serious postoperative complications and simple liver cysts are considered to be benign liver diseases without malignant tendency.³ When the imaging studies do not rule out the possibility of malignant lesions such as cystadenoma or cystadenocarcinoma of the biliary tract or the hepatic cyst is combined with intracystic hemorrhage or bile duct communication can be explored by laparoscopy. And determine the specific operation method according to the results of intraoperative medical examination and the nature of the fluid in the capsule.^{13,14}

Puncture and drainage

Liver cyst puncture and drainage can only temporarily relieve the symptoms of compression caused by giant cysts, cysts usually recur shortly after drainage has ended.¹¹ Not as a recommended treatment for congenital liver cysts. Temporary puncture and drainage can be used to relieve symptoms only at the advanced age and the general condition is very poor that cannot tolerate the above multiple treatment options or when acute infection in the cyst is combined. Follow-up treatment will be performed after the above conditions are improved.

Polycystic liver disease

Polycystic liver disease (PLD) is an autosomal dominant genetic disease that can exist alone or as an accompanying symptom of polycystic kidney disease, (94% of patients with polycystic kidney disease have polycystic liver disease).¹⁵ PLD is a liver cyst characterized by the presence of a large number of cysts, although there is no clear definition of PLD, the previous literature generally believes that the number of cysts greater than 20 is called PLD. The recently formed International PLD registration steering committee reached a consensus to redefine the number of polycystic liver disease cysts greater than 10.¹⁶ Studies have shown that age, estrogen, female, pregnancy, taking birth control pills are risk factors for the progression of polycystic liver disease.¹⁷ At present, Gigot classification and Schnelldorfer classification are commonly used to define the severity of PLD, which has guiding significance for the treatment of PLD. The commonly used treatment methods for PLD include percutaneous puncture, aspiration sclerotherapy, surgical treatment, liver transplantation, targeted drug therapy, etc. With the deepening of understanding of the pathogenesis of PLD in recent years, targeted drug therapy has become a new hot spot for treatment.¹⁸

Percutaneous aspiration sclerotherapy

Percutaneous aspiration sclerotherapy is mainly suitable for Gigot type I PLD with a single giant cyst, not suitable for PLD treatment of multiple small cysts. Same as the above simple liver cyst treatment, sclerotizing agents

include ethanol, polyol, minocycline, tetracycline, etc. The current controversy regarding the efficacy and safety of this treatment, some studies believe that when aspiration sclerotherapy is used to treat larger cysts, the growth of other small cysts may be accelerated due to the decrease in pressure, and that PLD is mostly multiple cysts. Therefore, this treatment method is rarely used in the actual treatment of PLD.¹⁸

Fenestration

Fenestration therapy for liver cysts is often used for Gigot I-II PLD patients, and it is also suitable for patients who have failed in percutaneous aspiration sclerotherapy. With the development of laparoscopic surgery and studies have shown that laparoscopic surgery and open surgery have considerable curative effects and the probability of complications, so fenestration of liver cysts is performed under laparoscopy. Same as the fenestration of the above simple liver cyst, as many fenestrations and cyst walls can be removed during the operation to reduce the short-term recurrence rate. Omentum can also be used to fill the residual cyst wall and intraoperative sclerosing agent injection to prevent short-term recurrence. However, unlike simple liver cysts with laparoscopic fenestration, PLD patients have a higher recurrence rate and complication rate after surgery. The postoperative recurrence rate of simple liver cysts was 9.6%, and the incidence of complications was 10.8%, and the recurrence rate after PLD was 33.7%, and the complication rate was 29.3%.¹⁹

Hepatic resection

Hepatic resection is suitable for patients with Gigot type II PLD who have at least one liver segment with normal function. The location and extent of the resection depends on the size and distribution of the cyst. However, due to cysts in PLD patients, the Glisson system and anatomical structure changes, which increases the difficulty of surgery. Fenestration is often used for cysts that cannot be resected. Studies have shown that the volume of liver cysts after hepatic resection is reduced by about 60%, the incidence of postoperative complications is about 20%, and the postoperative mortality rate is about 2%.²⁰ For most patients, hepatic resection combined with liver cyst fenestration can be used, partial hepatic resection and cyst fenestration can significantly improve the symptom burden and quality of life of patients with severe polycystic liver disease, and have acceptable safety.²¹ However, due to its high complication rate and mortality rate, and possibly due to the adhesion of the surgical area, the later liver transplantation treatment cannot be implemented. Therefore, it is not recommended as a first-line treatment.

Transarterial embolization

Current studies believe that liver cysts are mainly supplied by the hepatic artery, so transcatheter hepatic artery embolization uses embolic agents to selectively embolize

the branches of the hepatic artery of the liver cyst to destroy the cyst cells and control the progress of the liver cyst. For patients with Gigot type III PLD and PLD patients who do not have any liver segments with normal liver function who are not suitable for hepatic cyst fenestration and hepatectomy, transarterial embolization (TAE) can be considered. TAE is a reproducible, minimally invasive, and effective treatment for PLD.²² Moreover, recent studies have shown that the addition of bleomycin, n-butyl-2-cyanoacrylate and other drugs on the basis of traditionally applicable coils and lipiodol embolization materials has better curative effect and will not cause more serious complications.^{23,24} At present, TAE treatment of PLD still lacks a large number of clinical studies to prove its long-term efficacy and safety, but from the current research, it appears that it has great potential as an adjuvant treatment of PLD in the future.

Liver transplantation

Liver transplantation is the only method that can cure PLD at present, and it is mainly suitable for Gigot type III patients with severe PLD. Liver transplantation is safe and feasible for such patients, and studies have shown that the 5-year survival rate after PLD liver transplantation is greater than 90%, and the symptoms of patients have been significantly improved.^{25,26} Compared with patients undergoing liver transplantation for other reasons, such as chronic liver failure and liver cancer, PLD patients have a higher survival rate after liver transplantation, so in the case of liver source, priority can be given to PLD patients for liver transplantation.²⁷ For patients with polycystic liver disease and polycystic kidney disease, combined liver and kidney transplantation can be considered. The 5-year survival rate is greater than 90%. Moreover, the survival rate of patients with polycystic liver and kidney disease who underwent liver and kidney transplantation is higher than that of patients who underwent combined liver and kidney transplantation for other reasons and those who underwent only liver transplantation.²⁸ Although the effect of liver transplantation in PLD patients is good, only a few severe PLD patients can be cured due to the scarcity of liver sources and high cost. Further evaluation of PLD liver transplant indications is needed to make full use of each donor liver.

Targeted drug therapy

With the research on the mechanism of PLD in recent years, targeted drug therapy for PLD has become a new hot spot for treatment. Studies have shown that elevated cAMP in PLD patients is related to the progression of PLD.²⁹ Somatostatin analogs can bind to somatostatin receptors to reduce cAMP levels. It is currently the only targeted drug that has been clinically proven to have a reliable effect. It mainly includes octreotide, lanreotide, and pasireotide. A number of studies have shown that it can significantly delay the progression of PLD, reduce the volume of liver cysts, and relieve symptoms.³⁰ But long-term application will lead to drug resistance (usually the

effect will be reduced after 6 months of use). Discontinuation of the drug can lead to disappearance of the efficacy and even a rebound of the disease. Re-use after a period of discontinuation will still have the same efficacy as the initial use.³¹ The efficacy of lanreotide is related to the dosage, and studies have shown that it still has a considerable efficacy 4 months after stopping the drug.³² Compared with octreotide, pasirotide has better stability and a wider spectrum of somatostatin receptors, and has better curative effect. It also has a good curative effect for patients with PLD and polycystic kidney disease.³³

More clinical data is needed for the research of somatostatin analogues. In addition to somatostatin analogues, mammalian target of rapamycin (mTOR), including sirolimus, everolimus and other drugs still lack sufficient clinical data to prove their effectiveness, and long-term use can increase infection and the incidence of malignant tumors. Drugs such as ursodeoxycholic acid are still in the stage of animal experiments, and further studies are needed to prove their clinical safety and effectiveness. At present, with the gradual deepening of the pathogenesis of PLD, the follicle-stimulating hormone receptor and secretin receptor, bile acid receptor TGR5, cAMP downstream effectors (PKA, RAS, RAF, MEK and ERK1/2) may become new targets for PLD treatment.^{34,35}

CONCLUSION

At present, there is a lack of standardized treatment guidance for congenital liver cysts. The indications for conservative, aspiration sclerotherapy, and surgical treatment mainly rely on the subjective judgment of doctors, and the efficacy and safety of various treatment methods are still controversial, and a lot of them support of clinical data. The treatment of congenital liver cysts in the future can be improved from the following aspects: 1) study the pathogenesis and risk factors of congenital liver cysts, and reduce the incidence from the root cause; 2) the above-mentioned treatment methods for congenital liver cysts lack a large number of multi-center clinical trials to verify their safety and effectiveness; 3) a more detailed classification of congenital liver cysts and a model for evaluating the curative effect after treatment to formulate indications and contraindications for different treatment methods to avoid overtreatment and delay in treatment; 4) at present, most of the targeted drug treatments for PLD stay in the animal experiment stage, and there is a lack of strong evidence to prove its efficacy and safety. As research progresses, the treatment of congenital liver cysts will definitely be further standardized and improved in the future.

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