ANNALS OF GASTROENTEROLOGY 2006, 19(3):265-269

Review

Hepatic hydrothorax

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SUMMARY

Hepatic hydrothorax is an infrequent complication of cirrhosis and symptoms are mainly related to shortness of breath, cough and chest discomfort. A number of different pathogenetic mechanisms have been postulated for the development of pleural effusions in cirrhotic patients. Spontaneous infection of the pleural fluid, defined as spontaneous bacterial empyema, is a serious complication characterized by high mortality rate. Diagnosis is based on high clinical suspicion and initial therapy of hepatic hydrothorax is aimed at suppressing the production of ascites with administration of diuretics and restriction of sodium intake. When these fail (10% of cases) and thoracentesis is required every 2-3 weeks, the hydrothorax is defined as refractory and alternative more aggressive therapeutic strategies, such as thoracoscopic repair of diaphragmatic defects with pleural sclerosis, transjugular percutaneous intrahepatic porto-systemic shunt placement (TIPSS) and liver transplantation, must be considered.

Key words: Hepatic Hydrothorax, spontaneous bacterial empyema, hepatic cirrhosis, TIPSS

INTRODUCTION

Hepatic hydrothorax (HH) is defined as the accumulation of significant pleural effusion (>500ml) in patients with decompensated liver disease without primary pulmonary or cardiac disease.[1] Often overlooked, it is an infrequent complication of cirrhosis occurring in 5-10% of cirrhotic patients. The transudate is mostly unilateral and right-sided (85% of cases) although it may be bilateral (2%) or left-sided (13%).[2-4] Some times it is not even associated with clinically evident ascites.[5] The aim of this review is to examine the pathogenesis, to document the clinical features and complications of hepatic hydrothorax as well as to cite the available treatment options based on up-to-date literature.

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PATHOGENESIS

A number of different pathogenetic mechanisms have been postulated for the development of pleural effusions in patients with cirrhosis; the prevailing theory suggests that peritoneal fluid passes into the pleural space directly, along a pressure gradient through congenital or acquired fenestrations connecting the peritoneal and pleural space.[6,7,8] Autopsy studies on patients with hepatic hydrothorax confirmed the presence of microscopic (0.03–1.2mm) defects predominantly in the tendinous portion of the right diaphragm. On the left side they appear less frequently because it is thicker and more muscular.[9] These micro- and macroscopic holes are initially covered by pleura and peritoneum. Negative intra-thoracic pressure during breathing, along with the increasing intra-abdominal pressure of accumulating ascites, ultimately forces them to rupture allowing the transfer of fluid across the diaphragm. Hence, these patients usually have mild ascites and hydrothorax occurs when the transudate accumulation in pleural space surpasses the absorptive capacity of the pleura. This mechanism of peritoneo-pleural fluid movement was corroborated by studies which used dye, [^{99}Tcm]-human albumin or [^{99}Tcm]-sulphur colloid[10]. Although present in up to 20% of the population, these diaphragmatic fenestrations rarely lead to pneumothorax after laparoscopic operation.

Other mechanisms mentioned include azygous vein pressure increase with resulting plasma leakage, generalized hypoproteinaemia with secondary decrease of intravascular osmotic pressure, leakage of thoracic duct and direct fluid traverse from the abdominal cavity to pleural space through lymphatics of the diaphragm. These however seem to play only a minor role and are of less importance. Also they don't explain why hydrothorax is mostly right-sided.[11,12]

CLINICAL FEATURES, DIAGNOSIS AND COMPLICATIONS

In contrast to what happens in the abdominal cavity where large amounts of fluid (5–8 L) accumulate with the patient experiencing only mild symptoms, in the thoracic cavity smaller amounts of fluid (1–2 L) can cause severe symptoms usually related to shortness of breath, cough, hypoxaemia and chest discomfort. Ascites is not always present. On rare occasions patients present with acute tension hydrothorax, manifests as severe dyspnoea and hypotension.

Chest CT scan and other modalities such as nuclear scintigraphy, magnetic resonance imaging and surgical exploration for diaphragmatic defects could be performed for confirmation and exclusion of alternate diagnoses. Communication between the peritoneal and pleural space can be demonstrated by intraperitoneal injection of air or contrast agents ([^{99}Tcm]-human albumin or [^{99}Tcm]-sulphur colloid). The last has 71% sensitivity and 100% specificity in identifying hepatic hydrothorax.[10]

After diagnostic thoracentesis, pleuritic fluid should be sent for cell count, Gram stain, culture, polymerase chain reaction (PCR) for mycobacterium and cytology. In addition, determination of serum and pleural fluid protein, albumin, LDH, amylase, triglycerides and bilirubin should be performed to exclude other conditions such as tuberculosis, empyema, pancreatitis, chylothorax and malignancy. On analysis, the transudate composition should be similar but not identical to that seen in cirrhotic ascites. In uncomplicated hepatic hydrothorax the cell count is <500 cells/mm^3, total protein concentration <2.5 g/dL and although not studied, the serum/pleural albumin gradient (SAAG) should be >1.1 g/dL. Due to different hydrostatic pressure and absorption rate the total protein contentration could be slightly higher in a pleural transude compared to ascitic fluid (approximately 1g/dL).[4,6]

Spontaneous infection of hepatic hydrothorax is known as spontaneous bacterial empyema (SBEM) and defined as pleural fluid with polymorphonuclear (PMN) cell count >500 cells/mm^3 or positive culture with PMN cell count >250 cells/mm^3 with exclusion of a parapneumonic effusion. Most cases are usually due to Escherichia coli, Enterococcus, Pseudomonas, Klebsiella and Streptococcus spp. Infection of the pleural fluid must be considered in any patient with hydrothorax who develops fever, pleuritic pain, encephalopathy or unexplained deterioration of renal function. Xiol et al. studied the clinical course of 120 cirrhotics with hydrothorax and reported the presence of SBEM in as many as 13% on admission with an associated mortality of 20% during treatment. Although the route of infection is thought to be from the peritoneal cavity to pleural space, 43% of SBEM were not associated with spontaneous bacterial peritonitis (SBP).[13] As in SBP, patients with high Child-Pugh score, pleural effusions of lower opsonic activity therefore with lower total protein and C3 complement levels, have increased risk of developing SBEM.[14]

THERAPY

Initial therapy of hepatic hydrothorax is aimed at suppressing the production of ascites with administration of diuretics and restriction of sodium intake. A low sodium diet of 70–90 mmol/day is generally well-tolerated. This restriction, causes a negative sodium balance and loss of ascites and oedema in those patients with high urinary sodium excretion (>100 mmol/day as measured by a 24-h urine collection). In patients with marked sodium retention (urinary sodium excretion <10 mmol/day), such restriction is not sufficient by itself to achieve negative sodium balance but, it may slow further accumulation of fluid. These patients need diuretic therapy. As in ascites management, the best initial regimen is the combination of furosemide 40 mg/day and spironolactone 100 mg/day. If there is no response, compliance with diet and medications should be addressed, and then diuretics may be increased in a stepwise fashion every 3–5 days by doubling the doses up to 400 mg/day of spironolactone and 160 mg/day of furosemide. The goal is to achieve an average weight loss of 0.5 kg/day in patients without oedema and 1 kg/ day in those with peripheral oedema[4,6]. Ocassioally, therapeutic thoracentesis is an effective way of reducing an initial large effusion. Patients who develop SBEM should be treated with a third generation cephalosporin such as ceftriaxone (1g/24h for 7–10 days) intravenously. Albumin infusion, although not specifically studied in hepatic hydrothorax, seems to have a beneficial effect on the high mortality rate of SBEM.[15]

When these treatments fail (10% of cases) and thoracentesis is required every 2-3 weeks, the hydrothorax is defined as refractory and alternative more aggressive therapeutic strategies must be considered. Minocycline or talc-induced pleural symphysis (chemical pleurodesis), nasal continuous positive airway treatment pressure (n-CPAP), high-dose octreotide administration, primary thoracoscopic repair of diaphragmatic defects with pleural sclerosis and transjugular percutaneous intrahepatic porto-systemic shunt (TIPSS) are some of the applied therapeutic modalities.[6,16,17]

Successful chemical pleurodesis through a chest drain, despite its limitations, was described in some cases of hepatic hydrothorax. However this approach often fails, presumably because of insufficient apposition of the pleural surfaces as a result of rapid pleural fluid accumulation. Lung, spleen, liver and stomach rupture, haemothorax resulting from intercostal artery laceration, pulmonary oedema from rapid fluid removal, erroneous placement of the tube into the abdominal cavity and subcutaneous emphysema are some of the complications that may occur. Furthermore prolonged drainage through a chest drain causes massive electrolytes and protein depletion with secondary renal failure and impaired immunological function. Iatrogenic infection of the pleural space may further complicate treatment. Therefore, available data and physiological considerations present a strong argument against placing a chest drain in patients with hepatic hydrothorax.[17,18]

Nasal continuous positive airway pressure (n-CPAP) seems to be an alternative therapeutic approach. The limited data available propose the positive intrathoracic pressure during sleep to act by diminishing or reversing the pressure gradient from abdomen to thorax. Perhaps combination with other treatment options could offer more efficient approach in transudate reabsorption.[19]

There are few case reports of refractory hepatic hydrothorax treatment with octreotide administration. Most of presented cases are of patients in poor health who otherwise wouldn't tolerate surgical intervention. Octreotide acts as TIPSS reducing the portosystemic pressure gradient. This effect seems to be dose dependent since higher doses lead to greater reduction of drainage volume.[6,16]

When TIPSS is contraindicated thoracoscopy and video-assisted thoracoscopy (VATS) with pleurodesis are therapeutic alternative. Pleural symphysis is accomplished through administration of minocycline, talc poudrage, argon beam coagulation or fibrin glue. This procedure is operator-dependent and has increased morbidity and mortality. Reported complications include fever with leukocytosis, chest pain, empyema, incomplete pulmonal re-expansion, pneumonia, pneumothorax, haemothorax, wound infection and pleurocutaneous fistula. Unfortunately, up to now, only limited number of patients were treated with this modality in uncontrolled pilot studies and this is a serious drawback for adequate assessment of response (table 1).[20-23]

TIPSS seem to be effective in up to 75% of cases with refractory hydrothorax. However, the experience with this procedure derives from relatively small case series and results are difficult to interpret. Most of the studies did not have control groups and not all patients had been followed up over a longer period of time.[24-29] Effectiveness of TIPSS-placement is complicated by shunt dysfunction or occlusion, the risk of encephalopathy, congestive heart failure, haemolytic anaemia and worsening liver function while at the same time limited effect on prolonging survival is observed. Serious adverse outcomes occur particularly in those who are most debilitated and mortality rate of 20–25% can be expected in the first 45 days. Prognosis of patients receiving TIPS is related to the severity of the

Table 1. Studies of hepatic hydrothorax treated with thoracoscopy and pleurodesis

Study	Procedure	Number of patients	Effective treated	Mean follow-up (months)	Comments
Moroux et al[20] (1996)	VATS + pd + sr	8	6	7-36	
Milanez de Campos et al[21] (2000)	TS + pd (talk) + sr	18	10	3	57,1% morbidity 38,9% mortality
Ferrante et al[22] (2002)	VATS+pd (talk)	15	8	5,5	
Takayama et al[23] (2004)	TS+pd (afm)	9	7		Two recurrences after 1 and 4 months

(VATS = video assisted thoracoscopy, TS = thoracoscopy, pd = pleurodesis, sr = surgical repair, afm = argon beam coagulation + fibrin glue + minocycline)

underlying liver disease irrespective of the procedure indication.[6] Developed prognostic models for determining which cirrhotic patients are at risk of doing poorly after a TIPS have not been specifically validated for patients with refractory hepatic hydrothorax.[30,31] Therefore patients should be selected with care avoiding those over the age of 60, patients with hepatic encephalopathy and those with Child C cirrhosis.

TIPSS could also be used as a bridge to hepatic transplantation. Despite the lacking data for indication and long term outcome of patients with HH after liver transplantation (OLT), Xiol et al[32] reported an increase of mean survival in 25 patients with uncomplicated hydrothorax (90% at 1 year and 80% at 5 years), refractory hydrothorax (with 82% survival at 1 year and 70% at 5 years) and SBEM, all treated with OLT. Regardless of these results, more studies are needed to define the role of OLT in patients with hepatic hydrothorax.

CONCLUSION

Hepatic hydrothorax is an infrequent complication of hepatic cirrhosis and patients might experience dyspnoeic symptoms even with small amounts of pleuritic fluid. Diagnosis often depends on high clinical suspision. Initial treatment consists of salt intake restriction and diuretics. If refractory hydrothorax develop, additional more aggressive therapeutic modalities must be applied. Thoracoscopy with pleurodesis and TIPSS placement are operator dependent procedures with increased morbidity and mortality. The small number of case studies reported is a drawback in extrapolating definite indications and conclusions. Liver transplantation, as in most cirrhotic conditions, seems to be the ultimate therapeutic step.

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