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Retrospective Study

Classification of Hepatobiliary Scintigraphy Pattern in Segmented Gallbladder according to the Anatomical Discordance

Y.C. Lee *et al*. Interpretation of Hepatobiliary Scintigraphy

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Abstract

BACKGROUND

Hepatobiliary scintigraphy (HBS) is a useful diagnostic imaging technique that uses radiotracers to evaluate the function of the gallbladder (GB) and biliary system. In segmented GB, **s**ome HBS images reveal a discordant GB boundary compared with anatomical images.

AIM

To evaluate the characteristics of HBS in segmented GB and determine the clinical relevance according to HBS characteristics.

METHODS

A total of 268 patients with chronic cholecystitis, gallstones, or biliary colic symptoms who underwent HBS between 2011 and 2020 were enrolled. Segmented GB was defined as segmental luminal narrowing of the GB body on computed tomography (CT) or magnetic resonance (MR) images, and HBS was examined before or after one month of CT or MR. Segmented GB was classified into 3 types based on the filling and emptying patterns of the proximal and distal segments according to the characteristics of HBS images, and gallbladder ejection fraction (GBEF) was identified. Type 1 was defined as a normal filling and emptying pattern, whereas Type 2 was defined as an emptying defect on the distal segment, and Type 3 as a filling defect in the distal segment.

RESULTS

Segmented GB accounted for 63 cases (23.5%), including 36 patients (57.1%) with Type 1, 18 patients (28.6%) with Type 2, and nine patients (14.3%) with Type 3. Thus, approximately 43% of HBS images showed a discordant pattern compared to the anatomical images in segmented GB. Although there were no significant differences in clinical symptoms, rate of cholecystectomy, or pathological findings based on the type, most gallstones occurred in the distal segment. Reported GBEF was 62.50 ± 24.79% for Type 1, 75.89 ± 17.21% for Type 2, and 88.56 ± 7.20% for Type 3. Type 1 showed no difference in reported GBEF compared to the non-segmented GB group (62.50 ± 24.79% vs. 67.40 ± 21.78%). In contrast, the reported GBEF was higher in Types 2 and 3 with defective emptying and filling than in Type 1 (80.11 ± 15.70% vs. 62.57 ± 24.79%; P = 0.001).

CONCLUSION

In segmented GB, discordant patterns compared with HBS and anatomical images could lead to misinterpretation of GBEF. Clinicians should be careful when interpreting HBS results in segmented GB.

Key Words: Gallbladder; Segmented; Gallbladder emptying; Radionuclide imaging; Misdiagnosis; Cholecystitis

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Core Tip: This retrospective study aimed to evaluate the clinical relevance of discrepancies between anatomical and HBS images in a segmented gallbladder (GB). Hepatobiliary scintigraphy (HBS) images of segmented GB can be classified according to filling and emptying patterns. Type 1 was a normal pattern, Type 2 was an emptying defect on the distal segment, and Type 3 was a filling defect in the distal segment. Types 2 and 3 had higher values of the gallbladder ejection fraction (GBEF) than Type 1. Therefore, clinicians should be careful when interpreting the results of HBS for segmented GB.

INTRODUCTION

The gallbladder (GB) is a single pear-shaped chamber mainly located in a shallow depression below the right lobe of the liver. The GB can be anatomically divided into four parts: fundus, body, infundibulum, and neck. The neck is connected to the common bile duct *via* the cystic duct. The liver secretes approximately 600 mL of bile per day (0.4 mL/min),(1) a major portion of which enters the GB during fasting, and the rest bypasses the GB and enters the duodenum. In the basal state, bile moves in the GB from the long central axis toward the periphery in a lamellar fashion within approximately 30 min.(2)

A segmented GB refers to a hyperplastic condition of uncertain etiology, in which the GB is divided into two chambers by a fold or septum.(3, 4) Nevertheless, it is unknown how GB segmentation affects hepatic bile entry and exit from the two segments. Studies have demonstrated a relationship between segmented GB and cholestasis development.(4) A few studies have proposed a relationship between cholestasis and GB cancer.(4-6) Thus, it is hypothesized that segmented GB influences bile flow, which may be associated with GB-related diseases. Therefore, cholecystectomy can be considered for the treatment of a segmented GB.

Hepatobiliary scintigraphy (HBS) is a diagnostic technique used in nuclear medicine to continuously capture the pattern of radiotracers ingested by hepatocytes and secreted together with bile acid. The radiotracer is administered intravenously, bound to albumin, transported to the liver, and drained into the duodenum through the GB and bile ducts. Normal hepatobiliary findings are characterized by the presence of hepatic parenchyma and rapid clearance of cardiac hematologic activity, followed sequentially by activities in the intrahepatic and extrahepatic biliary ductal system, GB, and upper small bowel within approximately 1 h.(7) Abdominal ultrasonography (US), computed tomography (CT), or magnetic resonance cholangiopancreatography (MRCP) provides morphological information for the diagnosis of hepatobiliary disease, whereas HBS can be used to delineate hepatic and GB function and degree of cholestasis by tracking the radiotracers in the bilirubin metabolic pathway into the bile duct.(8)

HBS is used to assess the adequacy of GB contraction and calculate the GB ejection fraction (GBEF) to determine the need for surgery in patients with chronic cholecystitis and GB dyskinesia, and in symptomatic patients without gallstones.(8-11) An absolute ejection fraction cut-off for surgery has not been definitively established but has historically been suggested to be approximately 40%.(10) Because clinicians usually make the decision for surgery based on these results and patient symptoms, accurate measurement of GBEF is mandatory. However, it is generally accepted that scintigraphic findings are not always specific. Therefore, it is crucial to correlate HBS findings with clinical information and findings from other modalities to arrive at optimal decisions.(7)

In a segmented GB, changes in bile flow may affect HBS results. Some HBS images revealed discordant GB filling and emptying patterns compared to anatomical images. Changes in these patterns may influence the interpretation of HBS findings and lead to miscalculation of GBEF. However, there are no studies on the clinical significance of HBS in a segmented GB with a reasonable classification of the HBS pattern. Therefore, this study aimed to evaluate HBS image features in a segmented GB and determine their clinical impacts.

MATERIALS AND METHODS

Study population and clinical information

This was a retrospective review of patients who underwent HBS at Jeonbuk National University Hospital from 2011 to 2020. Baseline demographic and clinical characteristics on biliary colic symptoms (right upper quadrant and epigastric pain or discomfort or postprandial discomfort) and atypical abdominal symptoms (dyspepsia or abdominal discomfort in an uncertain location) were obtained. In addition, the presence of GB stones with their location, sludge, or polyp was assessed. Laboratory findings (alkaline phosphatase, gamma(γ)-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, carcinoembryonic antigen, and carbohydrate antigen 19-9) were based on tests performed close to the date of HBS. Morphological characteristics of the GB were verified by CT or MRCP. The interval between CT or MRCP and HBS was examined within one month. GBEF and scanned images of the radiotracers were validated using HBS. This study was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB No. 2021-07-005).

Definition of segmented GB

A segmented GB was defined as segmental luminal narrowing of the GB body observed in CT or MR imaging. Segmented GB contains a fold or septum that divides the GB lumen into two or more interconnected compartments: a neck proximal to the stricture and a fundus distal to the stricture, based on a review of CT or MR images. A new approach was proposed to define segmented GB (Figure 1). The segmented GB was first defined as:

$$A + B > 3C$$

where A and B denote the long axes of the outer lumen of the distal and proximal portions, respectively. C is defined as the diameter of luminal narrowing based on the outer lumen of the GB body. This definition was calculated by observing a segmented GB on CT or MR images and HBS images of an enrolled patient and measuring each GB area of that patient.

Hepatobiliary scintigraphy

After a minimum of 6 h of fasting, each patient received ^{99m}Tc-mebrofenin intravenously while lying supine underneath a dual-head gamma camera fitted with a low-energy parallel-hole collimator, with a detector centered over the abdomen covering the region between the heart and pelvis in the field of view. GB phase images were obtained 60 min after ^{99m}Tc-mebrofenin injection. Following a fatty meal, GB phase images were obtained at 30 and 60 min. GBEF was measured using immediate pre- and post-fatty meal images, and the regions of interest were drawn around the GB (considering the patient's movement) and adjacent liver (background). The GBEF is calculated as the ratio of the difference between the maximum and minimum signals to the maximum signal and corrected for the background signal.(7)

Classification of a segmented GB based on HBS

Baseline images for classification were the image obtained 60 min after ^{99m}Tc-mebrofenin injection and GB phase obtained 30 and 60 min after fatty meal intake. HBS images were compared with CT or MR images and classified into three groups according to the filling and emptying patterns according to the real anatomical morphology of the GB. Type 1 was defined as a normal filling and emptying pattern, whereas Type 2 was defined as an emptying defect on the distal segment, and Type 3 as a filling defect in the distal segment (Figure 2). Figure 3 depicts the anatomical boundaries of segmented GB as shown in typical CT images, the scanned images of HBS in normal GB, and each classified segmented GB subtype based on the filling and emptying pattern.

Statistical analysis

Results were reported as numbers (percentages) or mean ± standard deviation. Continuous variables were compared using the Student's *t*-test, and categorical data were compared using Pearson's chi-squared test and Fisher's exact test. Statistical significance was set at $P < 0.05$. Data were analyzed using SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

A total of 268 adult patients aged > 18 years underwent HBS for chronic cholecystitis, gallstones, or biliary colic. The patients' baseline characteristics are listed in Table 1. The mean age was 51.65 ± 13.10 years and men constituted 43.2% of the study population. Approximately 20% of the patients complained of biliary colic pain. Among these, 63 (23.51%) belonged to the segmented GB group. There was no difference in laboratory findings between the non-segmented and segmented GB groups. Based on radiological findings, adenomyomatosis and chronic cholecystitis were diagnosed more frequently in the segmented GB group (18/63, 28.6%; 45/63, 71.4%, respectively) than in the non-segmented GB group (12/205, 5.9%; 107/205, 52.2%, respectively) ($P < 0.001$ and $P = 0.009$, respectively). Reported GBEF was 68.01 ± 22.05%, and there was no difference between the two groups (61.70 ± 21.78% vs. 70.05 ± 22.97%; $P = 0.405$). Cholecystectomy was performed more frequently in the segmented GB group (45/63, 71.4%) than in the non-segmented GB group (73/205, 35.6%; $P < 0.001$).

Clinical characteristics of variables according to the type of segmented GB

According to the HBS pattern in a segmented GB, 36 patients (57.1%) with Type 1, 18 patients (28.6%) with Type 2, and nine patients (14.3%) with Type 3 were identified. A comparison of variables according to the type of segmented GB is presented in Table 2. Demographic, radiological, and pathological findings did not differ according to the type of segmented GB. In addition, the rates of atypical symptoms and biliary colic pain did not differ between the groups. GB stones occurred more frequently in the distal segment in both groups; however, no significant intergroup difference was found. Type 1, with normal emptying and filling patterns, showed no difference in the reported GBEF compared to the non-segmented GB group. Interestingly, the reported GBEF was higher in Types 2 and 3 with defective emptying and filling than that in Type 1 (80.11 ± 15.70% vs. 62.57 ± 24.79%; *P* = 0.001).

The reported GBEF was 62.50 ± 24.79% for Type 1, 75.89 ± 17.21% for Type 2, and 88.56 ± 7.20% for Type 3 (Figure 4). Notably, a significant difference was observed between the reported GBEF of Types 1 and 3 (*P* = 0.005). The Mean reported GBEF was higher in Type 2 than in Type 1, but the difference was not significant (*P* = 0.082).

DISCUSSION

The segmentation of the GB into two chambers by a fold or septum is a hyperplastic condition of uncertain etiology.(3, 4) GB segmentation in adults is often caused by adenomyomatosis or congenital septa.(12, 13) The term segmented GB is used in a broader concept to include segmental adenomyosis of the GB. This term is not commonly used; however, GB segmentation without adenomyomatosis is often observed in imaging studies of patients of any age. *Gerbail T. Krishnamurthy et al* reported that microscopic examination of a segmented GB revealed chronic inflammatory changes, fibrosis, and wall thickening.(14) The strictures caused by the annular thickening of the GB wall may be narrow.(2) The anatomical stricture of a segmented GB leads to difficult bile movements and causes cholestasis, which may lead to chronic inflammatory changes, cholelithiasis, and tumorigenesis.(4, 5, 13) Therefore, clinical symptoms and the patient's physiological reserve should be considered; however, surgical treatment is recommended in the segmented GB.

Gallstones are one of the most common biliary tract diseases, and its prevalence is known to be 5.9-21.9% in the West and 3.1-10.7% in Asia.(15) Diagnosis of gallstones are made incidentally in most of the people, and remain asymptomatic throughout their lives. During a follow-up period of 10–15 years, symptoms appear in approximately 15–25% of patients, and the risk of developing biliary pain due to complications is reported to be approximately 2–3% per year.(16-18) Patients with symptomatic gallstones are at high risk of gallstone-related complications, and cholecystectomy is recommended in such cases.(19) In addition, cholecystectomy is recommended if there are risk factors for gallbladder cancer (e.g., anomalous pancreatic ductal drainage, gallbladder adenoma, porcelain gallbladder, or large gallstones (especially larger than 3 cm)).(20-22) However, if a patient with gallstones has ambiguous symptoms, it is often difficult to distinguish gallstone-related symptoms; therefore, blood tests, ultrasound, HBS, and the patient's personal circumstances are considered to determine the need for surgery.

HBS is a radionuclide diagnostic imaging modality that is used to evaluate the hepatocellular function and the biliary system by tracing the synthesis and flow of bile from the liver and its passage through the biliary system into the small intestine.(7) The technique assesses the function of hepatocytes, patency, and integrity of the biliary ducts, gallbladder contractility, and sphincter of Oddi function.(23) HBS has been frequently used to investigate the physiological parameters of the GB during emptying and filling.(24) A reduced GBEF is observed in calculous and acalculous biliary diseases, such as chronic acalculous cholecystitis, biliary dyskinesia, and sphincter of Oddi dysfunction. It may also be associated with various nonbiliary diseases and conditions and the use of various medications (e.g., morphine, atropine, calcium channel blockers, octreotide, *etc.*)(7, 25) In this regard, a meta-analysis concluded that the value of a low GBEF in deciding whether to perform cholecystectomy in individuals with GB dyskinesia is still unclear.(10) However, the reduced GBEF in HBS has been advocated as a diagnostic parameter for the clinical evaluation of individuals presenting with suspected biliary pain or gallstones and altered GB morphology (such as segmented GB) in deciding whether to proceed with cholecystectomy.

The GBEF evaluated in this study did not differ between segmented and non-segmented GB. In a previous study, the GBEF measured in a segmented GB was lower than that in a non-segmented GB.(14) In this study, we observed the appearance of partial filling and emptying events in each lumen in a segmented GB using HBS images. The anatomical features of annular strictures in a segmented GB may alter the emptying of radiotracers without completely replenishing them. Defective HBS images in a segmented GB have been reported;(26) however, they have never been classified according to filling and emptying patterns on scanned images. HBS images were divided into three categories. Type 1 was defined as a normal filling and emptying pattern. Type 2 was defined as emptying defects in the distal portion, and Type 3 was characterized by filling defects in the distal portion.

Furthermore, GBEF varied across segmented GBs depending on the HBS imaging pattern. We have described GBEF as "reported GBEF" because GBEF may be incorrectly measured depending on the type. Reported GBEF of Type 1 was 62.50%, whereas the reported GBEF of Types 2 and 3 with defective filling or emptying was higher than that of Type 1 (P = 0.001). Filling or emptying defects in HBS images of a segmented GB are attributable to the undesirable effects of bile flow. However, the higher GBEF of Types 2 and 3 compared with that of Type 1 renders the results unreliable and inconsistent with those of a previous study of seven patients with segmented GB analyzed *via* HBS.(14) In a previous study, the total GBEF was determined by measuring the EF of the proximal and distal segments on HBS. Distal EF was lower in the segmented GB group than in the proximal EF. The total EF in the segmented GB group was also lower than that in the non-segmented GB group. However, in the non-segmented GB group (n = 10), distal EF was higher than proximal EF. Decreased emptying (low EF) of the distal segment indicates that the septum acts as a one-way valve, allowing normal bile entry into the distal segment, but does not allow an easy exit. However, the total GBEF of a segmented GB measured in our hospital was often good, suggesting normal GB contractility. This phenomenon indicates that the measurement of total GBEF *via* HBS in a segmented GB does not reflect the actual contractility of the GB. Total GBEF in Types 2 and 3 was primarily measured based on the contractility of the proximal part rather than the overall contractility of the GB because the GB boundary was not accurately demonstrated in the HBS images.

Changes in bile acid filling and emptying and the effect of the segmented GB on GBEF can be determined from the location of the gallstones. GB stones were located mainly in the distal part and were related to the contraction and imbalance of the bile flow between the two segments. *Nishimura A.et al.* reported an investigation of the association between segmental adenomyomatosis of the GB and gallstones.(4) In addition, the contribution of gallstones to adenomyomatosis was investigated by examining their components. According to this study, the incidence of GB stones was higher in segmental adenomyomatosis than in fundal and diffuse adenomyomatosis, and GB stones were detected in 80.6% (58/72) of the distal compartment. In our study, GB stones were found in 75.7% (28/37) of the distal segments, 10.8% (4/37) in both segments, and only 13.5% (5/37) involved the proximal segment of the segmented GB. Although the size or composition of gallstones was not investigated in our study, the narrowed passageway was considered to obstruct the flow of bile and facilitate the production of gallstones at the distal part of the segmented GB.

The total GBEF (80.11 ± 15.70%) of the groups with defective filling or emptying (Types 2 and 3) mainly suggested an overestimation of the proximal portion compared with the normal filling and emptying group (62.57 ± 24.79%). The difference between the two groups suggests the need to interpret the HBS results of segmented GB compared with other imaging modalities (US, CT, or MRCP) that are used to detect morphology. Therefore, in a segmented GB, it is important to determine the pattern of the scanned image in the total GBEF using HBS.

This study had some limitations. Our study was a relatively small, single-center cohort study. In addition, the EF of the proximal and distal parts was not investigated, which precluded the precise quantification of each EF in the proximal and distal parts affecting the total EF. The filling and emptying radiotracer volume of bile flow could not be confirmed; therefore, no quantitative results were available. However, quantitative studies require the use of Single-photon emission computed tomography. Lastly, non-specific fatty meals were used to stimulate gallbladder contraction because cholecystokinin (CCK) was unavailable for use at our institute. Although CCK would have offered a more reliable GB stimulus, a previous study did not show any significant difference between CCK and fatty meals in measuring GBEF.(27)

Despite these limitations, our findings provide a better understanding of the results of HBS in segmented GB. Clinically, a segmented GB is associated with a higher incidence of GB-related diseases than other morphological features. Therefore, cholecystectomy is often indicated for the surgical treatment of segmented GBs. In addition to symptoms, reduced contractility of segmented GBs measured in terms of GBEF using HBS is critical in determining the need for cholecystectomy. However, GBEF in a segmented GB may be misinterpreted depending on the type of HBS images. In particular, the GBEF in Type 2 and Type 3 HBS scans can be overestimated, which hinders the development of an ideal treatment plan such as cholecystectomy.

CONCLUSION

In segmented GB, discordant patterns compared to images of HBS and anatomical images could lead to inaccurate results in GBEF. Therefore, clinicians should be careful when interpreting GB contractability through HBS in a segmented GB.

ARTICLE HIGHLIGHTS

Research background

Hepatobiliary scintigraphy (HBS) is a useful diagnostic imaging technique that uses radioactive tracers to evaluate the function of the gallbladder (GB) and biliary tract. In segmented GB, some HBS images show inconsistent GB boundaries compared with anatomical images, limiting evaluation of GB contractability through HBS.

Research motivation

+ADw-html+AD4APA-p+AD4-Cholecystectomy is sometimes necessary in patients with gallstones or chronic cholecystitis. In addition, in the case of anatomically segmented GB, cholecystectomy is recommended because of the possibility of future gallbladder disease. Because there are patients who are reluctant to undergo cholecystectomy, cholecystectomy is recommended again if cholecystectomy decreases after evaluating the GB contractability using HBS. In previous studies, the gallbladder ejection fraction (GBEF) was reduced in the case of segmental GB, but GBEF was often observed as normal when tested on patients.+ADw-/p+AD4APA-/html+AD4-

Research objectives

We evaluated the characteristics of HBS in segmented GB and investigated the effect of segmented GB on the results of GBEF through HBS.

Research methods

Among patients with chronic cholecystitis, gallstones, or biliary colic, patients who underwent HBS were identified. Patients with segmented gallbladder features with segmental lumen stricture were identified using computed tomography (CT) or magnetic resonance (MR) imaging. The patient who performed HBS confirmed whether or not CT or MR images was taken one month before and after. Segmented GB was classified into 3 types based on the filling and emptying patterns of the proximal and distal segments according to the characteristics of HBS images, and gallbladder ejection fraction (GBEF) was identified. Type 1 was defined as a normal filling and emptying pattern, whereas Type 2 was defined as an emptying defect on the distal segment, and Type 3 as a filling defect in the distal segment.

Research results

Segmented GB accounted for 63 cases (23.5%), including 36 patients (57.1%) with Type 1, 18 patients (28.6%) with Type 2, and nine patients (14.3%) with Type 3. Thus, approximately 43% of HBS images showed a discordant pattern compared to the anatomical images in segmented GB. Although there were no significant differences in clinical symptoms, rate of cholecystectomy, or pathological findings based on the type, most gallstones occurred in the distal segment. Reported GBEF was 62.50 ± 24.79% for Type 1, 75.89 ± 17.21% for Type 2, and 88.56 ± 7.20% for Type 3. Type 1 showed no difference in reported GBEF compared to the non-segmented GB group (62.50 ± 24.79% vs. 67.40 ± 21.78%). In contrast, the reported GBEF was higher in Types 2 and 3 with defective emptying and filling than in Type 1 (80.11 ± 15.70% vs. 62.57 ± 24.79%; P = 0.001).

Research conclusions

In segmented GB, discordant patterns compared to images of HBS and anatomical images could lead to inaccurate results in GBEF. Therefore, clinicians should be careful when interpreting GB contractability through HBS in a segmented GB.

Research perspectives

Since the presence or absence of gallstones may affect HBS, additional studies may be conducted to examine the difference in GBEF according to the presence or absence of gallstones in patients with segmented GB. Further studies using Single-photon emission computed tomography (SPECT) to evaluate discrepancies between HBS images and anatomical boundaries are expected to help determine cholecystectomy.

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