Accuracy of hepatobiliary scintigraphy and added value of SPECT/CT versus planar imaging for diagnosing biliary atresia

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Abstract

Objective: Hepatobiliary scintigraphy (HBS) is an important tool in diagnosing biliary atresia in infants. There is limited evidence on the use of single photon emission computed tomography/computed tomography (SPECT/CT) as an additional imaging method to planar imaging. We evaluated the value of SPECT/CT in unclear cases of planar HBS. **Subjects and Methods:** Consecutive patients with suspected biliary atresia who underwent guideline-compliant HBS from January 2010 until March 2020 were reviewed, and cases with single photon emission computed tomography/computed tomography (SPECT/CT) were identified. Each step within the imaging procedure (dynamic, static [early and late], and SPECT/CT) was blindly reread in consensus by two observers and categorized based on a 5-point scale: 0, definitely no bowel excretion (i.e., atresia confirmed); 1, probably positive; 2,equivocal; 3, probably negative; and 4, definite negative (i.e., atresia not confirmed). In this analysis, categories were dichotomized as negative for biliary atresia (scores 3-4) or positive (scores 0-2, including equivocal scans). Available follow-up information constituted the standard of truth (SoT). **Results:** Twenty-three infants had HBS, among which ten (4 boys and 6 girls; mean age 36 days; range 8-108) underwent SPECT/CT. Single photon emission computed tomography/CT was performed as early examination (<8h) in 3 subjects and late (8 to 24h) in 7 infants. Reread SPECT/CT was categorized as positive for atresia in three infants and negative in seven infants. The SoT showed biliary atresia in one of ten patients. Single photon emission computed tomography/CT was true positive in one case, false positive in two, and true negative in seven. No false negative cases were noted. The diagnostic performance of SPECT/CT showed a sensitivity of 100%, specificity of 78%, positive predictive value (PPV) of 33%, negative predictive value (NPV) of 100%, and accuracy of 90%. For comparison, the diagnostic performance of planar HBS showed a sensitivity of 100%, specificity of 67%, PPV of 25%, NPV of 100%, and accuracy of 70%. In summary, the addition of SPECT/CT to planar HBS improved specificity and accuracy and marginally improved PPV. Single photon emission computed tomography/CT provided more confidence in the final conclusion in 8/10 patients. In the remaining two cases, SPECT/CT did not improve the level of confidence (one remained equivocal, and one changed from probably no excretion to equivocal). **Conclusions:** These preliminary data demonstrated increased accuracy of add-on SPECT to planar HBS predominantly due to improved specificity. This finding is consistent with the existing but limited literature and supports the recommendation of routine use of SPECT/CT or SPECT.

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Introduction

Biliary atresia is a progressive sclerosis of the external and internal bile ducts that develops pre- or perinatally and progresses within the first months of living [1]. If left untreated, the bile ducts may obliterate, causing irreversible liver failure and death. It is of utmost importance that this disorder is diagnosed within the first weeks of life to surgically re-establish biliary flow [1]. However, hepatocellular dysfunction covers a wide variety of conditions that cause jaundice and/or cholestasis in infancy but may not require surgery [1]. Hepatobiliary scintigraphy (HBS) is an important imaging modality in the differentiation of biliary atresia and other causes of conjugated hyperbilirubinemia, which do not require surgery [2, 3]. Most studies showed very good sensitivity of HBS, but the specificity was modest. The pooled sensitivity was 96%-99% and specificity 70%-73% in two meta-analyses [2, 3]. Factors that have been shown to increase the specificity of the investigation include premedication [4, 5], the type of radiopharmaceutical [6, 7], and the imaging procedure. Delayed imaging has been shown to decrease the number of false positive results [6, 8]. Preliminary data indicate improved specificity with single photon emission computed tomography (SPECT) [4, 6, 9]. No studies have investigated the use of SPECT/computed tomography (CT). To contribute to the limited evidence on the use of SPECT or SPECT/CT in the investigation of biliary atresia, we retrospectively evaluated

the value of these procedures in cases of equivocal or negative (no excretion) planar HBS.

Subjects and Methods

Patients

This retrospective study included consecutive patients with suspected biliary atresia who underwent guideline-compliant HBS from January 2010 until March 2020. Cases with SPECT/CT were identified for review. No patients were excluded from the study. Premedication with phenobarbitone or ursodeoxycholic acid according to local practice was recommended. The referring physician decided whether HBS should be performed with or without premedication.

Hepatobiliary scintigraphy with low-dose CT

Technetium (^{99m}Tc) mebrofenin (N-(3-bromo-2,4,6-trimethylphenylcarbamoyl methyl)-iminodiacetic acid) was injected at the start of the dynamic study. The European Association of Nuclear Medicine (EANM) Dosage Calculator [10] was used to calculate the injected dose according to body weight with a minimum dose of 20MBq. Image acquisition was performed on a Symbia T16 (Siemens Healthcare, Erlangen, Germany) equipped with a dual-head gamma camera with a zoom factor of 2.29 in a 256x256 matrix. The two-phase dynamic study was performed with 120 one-minute frames. After the first 1-hour phase, the infants were given oral feed. Static images were stopped manually when sufficient counts were detected (at the discretion of the nuclear medicine physician in charge). Late (20 h or more) static images were counted for 30-45 minutes. For the SPECT, thirty-two 30-second projections were acquired over 360° with a zoom factor of 2.29 in a 128x128 matrix. The SPECT data were reconstructed with a 3 dimension (3D) iterative reconstruction technique. Immediately after SPECT acquisition, a CT topogram was acquired. The nuclear medicine physician adjusted the field of view to include only the abdomen to reduce the radiation dose from the CT. Eventually, a low-dose helical CT was performed with the following settings: 15mA (Siemens CARE Dose), 110 peak keV, a scan time of approximately 10sec (depending on patient size), slice thickness of 5.0mm, and collimation of 16x1.2mm. The effective dose from both the topogram and the CT scan was typically 0.2-0.3mSv. Sedation was not required for any patients.

Image interpretation

The scans were analyzed using Siemens software (e.soft, Siemens Medical Solutions, Erlangen, Germany) that provided cine mode of dynamic imaging, windowing of static images, maximal intention projection (MIP) images, and transaxial, sagittal, and coronal reconstructions of SPECT, CT and fused SPECT/CT data. Each step within the imaging procedure (dynamic, static [early and late], and SPECT/CT) was blindly reread in consensus by two experienced board-certified nuclear medicine physicians who did not have access to clinical information or the final diagnosis. The results were categorized on a 5-point Likert scale for bowel excretion: 0 = Definitely not; 1 = Probably not; 2 = Equivocal; 3 = Probably; 4 = Definitely. The categories were furthermore dichotomized as negative for biliary atresia (i.e., excretion to the bowel) if the score was 3-4 or positive (no excretion to the bowel) when the score was 0-2, including equivocal scans.

Approvals

Ethical approval was waived since the national legislation in Denmark does not require the approval of retrospective trials. The study was approved by the Danish Data Protection Agency that provided a waiver for informed consent.

Statistics

Descriptive statistics were reported as the range and mean or median values depending on the distribution of the data. All available follow-up information (biopsy, direct cholangiography, biochemistry, and clinical) constituted the standard of truth (SoT). Based on all available imaging results, an imaging result was considered true positive for biliary atresia if there was no excretion on the HBS, and biopsy/direct cholangiography confirmed the diagnosis. An imaging result was considered true negative if there was excretion on the HBS or if there was no excretion on the HBS and the patient was diagnosed with another hepatobiliary condition not requiring surgical intervention or recovered completely without diagnosis or intervention. Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and accuracy were calculated.

Results

Patients

In total, HBS was performed in 23 subjects, among which ten infants (4 boys and six girls; mean age 36 days; range 8-108) underwent SPECT/CT (the final study population). Single photon emission computed tomography/CT was performed as an early examination (<8h) in three subjects and late (8 to 24h) in seven infants. Single photon emission computed tomography/CT was categorized as positive for atresia in three infants and negative in seven infants. Only two of the infants were pretreated with phenobarbitone, which was administered at 5mg/kg per day, prior to initiation of HBS. However, only two doses were administered prior to the investigation. The final diagnoses of the infants (SoT) are listed in Table 1. Biliary atresia was the confirmed diagnosis in only one subject who underwent a Kasai portoenterostomy surgical procedure.

SPECT and SPECT/CT

Ten infants underwent SPECT/CT, of whom three had an early scan, five had a late scan, and two had both an early (SPECT only) and a late scan (Table 2). No infants had two CT performed, and seven patients had static images performed at the same time point as the SPECT/CT(Table 2).

Table 1. *Patient's characteristics and final diagnoses.*

Gender	Boys=4; girls=6
Age at investigation (days)	36 (8-108)
Gestation age (weeks)	39+2 (36+3 to 41+5)
S-bilirubin (μmol/L)	158 (47-210)
Conjugated s-bilirubin (μmol/L)	90 (35-161)
Final diagnosis	
Biliary atresia	1
Cytomegalovirus	3
Alpha-1-antitrypsin deficiency	2
Galactosemia	1
Inspissated bile syndrome	1
Cholestasis, other	2

Table 2. *Number and timing of static images and SPECT and SPECT/CT with scoring.*

Patient	Static 1 hours (score)	Static 2 hours (score)	Static 3 hours (score)	Early SPECT/CT hours (score)	Late SPECT/CT hours (score)	SPECT only hours (score)	Score difference*	Final diagnosis
1	3 (3)				24 (4)	6 (4)	+1	CMV
2	3 (0)	6 (0)	24 (1)		24 (0)		-1	Giant cell hepatitis
3	2 (3)				20 (4)		+1	Cholestasis, other
4	3 (2)	5 (3)		5 (4)			+1	Inspissated bile syndrome
5	3 (0)	6 (0)	24 (0)		24 (2)	6 (1)	+2	Biliary atresia
6	4 (2)	22 (3)			22 (4)		+1	CMV
7	4 (0)	20 (2)			20 (4)		+2	CMV
8	na**			2** (4)			+1	Galactosemia
9	3.5 (1)	7.5 (2)	24 (2)	7.5 (2)			0	Alpha-1-antitrypsin
10	3.5 (0)	22 (1)			22 (4)		+3	Alpha-1-antitrypsin deficiency

**Difference=SPECT/CT or SPECT score minus score from latest planar image; **No static images - SPECT/CT directly after dynamic. 0=Definitely no excretion to bowel; 1=Probably no excretion to bowel; 2=Equivocal; 3=Probably excretion to bowel; 4=Definitely excretion to bowel*
Abbreciations: CMV, Cytomegalovirus.

The dynamic scan or latest planar image was positive (0-1) or equivocal (score 2) for biliary atresia in five patients. The result was probably excretion (score 3) in the remaining five infants before the SPECT or SPECT/CT. In eight patients, the SPECT/CT changed the score in the right direction towards the correct diagnosis (the one patient with the largest score changed from probably no excretion to definitely excretion (Figure 1)). In one patient (final diagnosis of alpha-1-antitrypsin deficiency) both the SPECT/CT at 7.5 hours and all other images, including 24-hour planar images, were equivocal. In the last patient, the scan went from definitely no excretion to equivocal at the 24-hour SPECT/CT due to some background activity that could not be definitely located outside the bowel. This infant was referred to a tertiary pediatric center, which confirmed cystic bile atresia.

Finally, one patient had a false positive SPECT/CT at 24 hours with definitely no excretion to the bowel (Figure 2). Although one of the differential diagnoses of the pathologists was biliary atresia due to a reduced number of bile ducts and very few normal ducts, the child recovered without surgery.

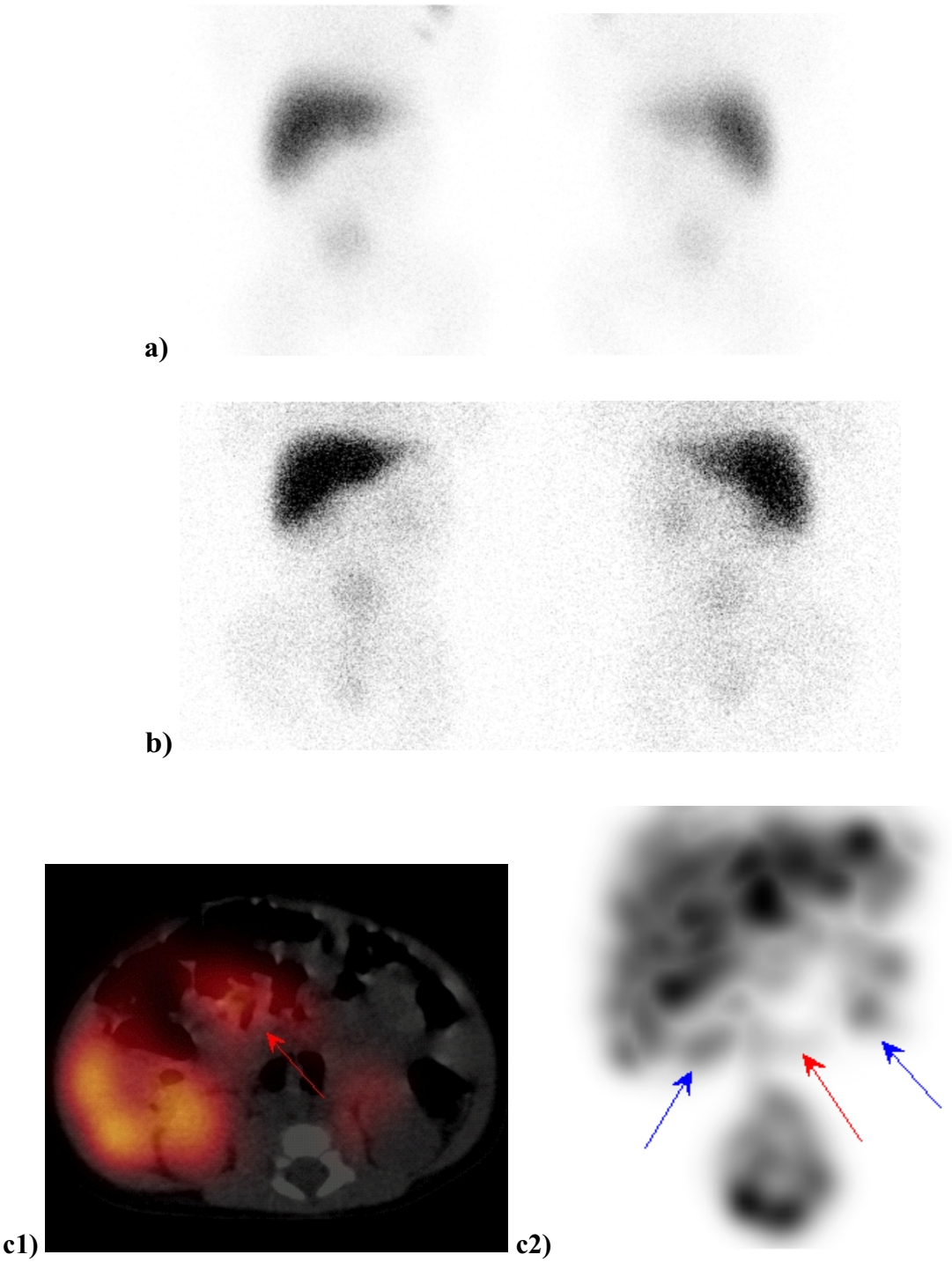

Figure 1. Four-week-old infant with negative static images in anterior and posterior projections after 3 hours (a) and 21 hours (b). However, excretion to the bowel (red arrows) was demonstrated on SPECT/CT after 22 hours on the fused images (c1) and the maximal intensity projection (c2) (blue arrows = kidneys).

Diagnostic performance

The overall diagnostic performance of SPECT/CT (n=10) showed a sensitivity of 100%, specificity of 78%, PPV of 33%, NPV of 100%, and an overall accuracy of 90%.

For comparison, the diagnostic performance of planar HBS in the same ten patients resulted in a sensitivity of 100%, specificity of 67%, PPV of 25%, NPV of 100%, and accuracy of 70%. In summary, the addition of SPECT/CT to planar HBS improved specificity and accuracy and marginally improved PPV.

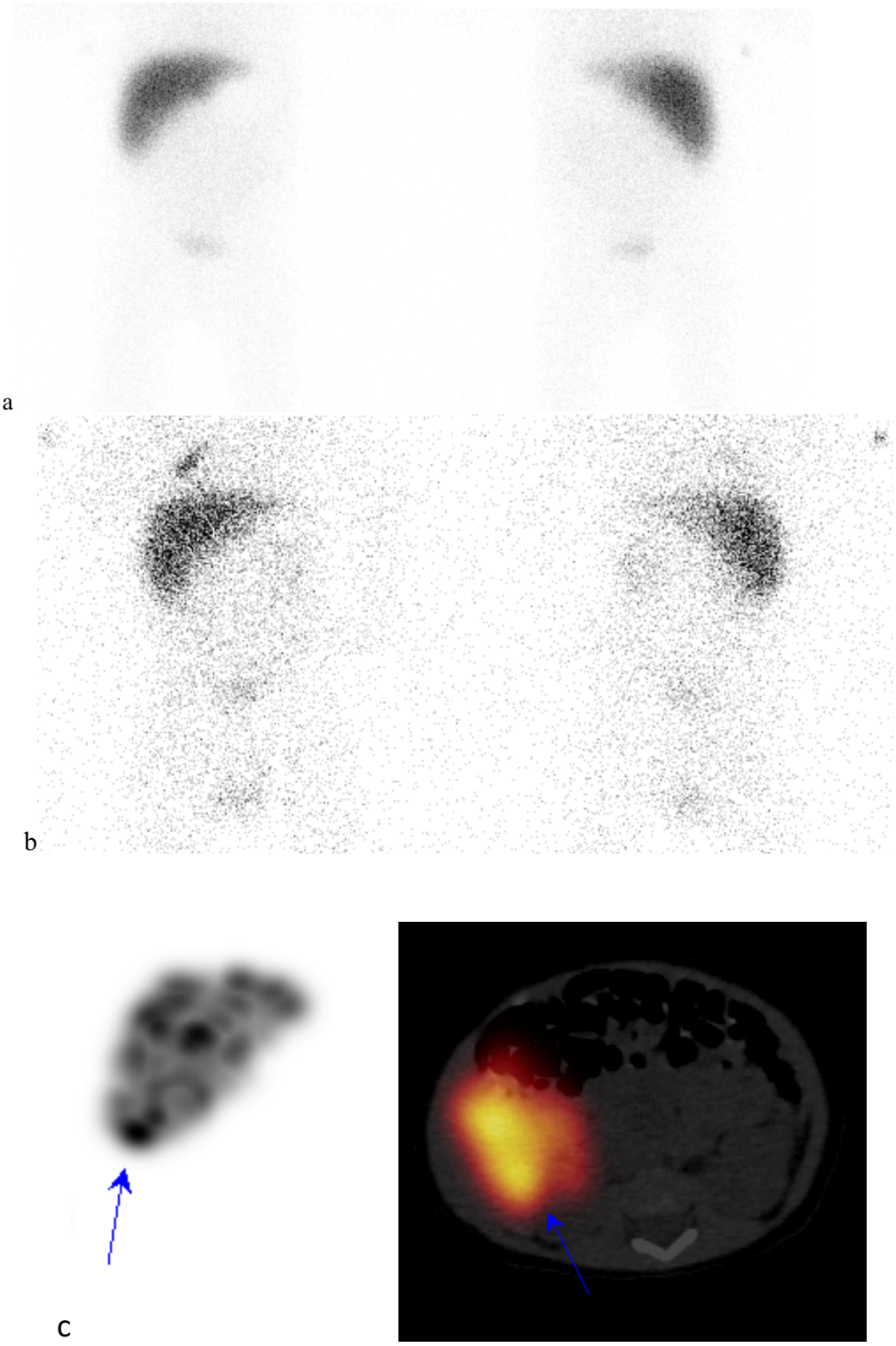

Figure 2. No bowel activity on static images in anterior and posterior projections at 6 hours (a), 24 hours (b), and at SPECT/CT at 24 hours (c) in either the maximal intensity projection or the fused images (axial displayed). Blue arrow=liver activity. The infant was diagnosed with giant cell hepatitis with severe chronic cholestasis and a reduced number of bile ducts in biopsy (differential diagnoses by pathologist: biliary atresia, Alagilles syndrome, alpha-1-antitrypsin deficiency).

Discussion

Hepatobiliary scintigraphy is an important tool in the evaluation of potential biliary atresia in infants with prolonged conjugated hyperbilirubinemia. The sensitivity is generally high but with a modest specificity depending on patient preparation, radiotracer, and imaging methods, including the use of SPECT or SPECT/CT. The data on the diagnostic value of SPECT in this population are limited [4, 6, 9], and no data on the use of SPECT/CT are available. This retrospective study found a high sensitivity (100%) of both planar imaging and SPECT/CT and a higher specificity of SPECT/CT (78%) than planar imaging (67%). Furthermore, the addition of SPECT/CT increased the reader's confidence.

Two studies have investigated the added value of SPECT at 4-6 hours and found a highly improved specificity of SPECT (90% and 89%) compared to planar imaging (planar 67% and 46%) [4, 9]. These results are not directly comparable to our findings as we did not perform SPECT/CT at a predefined time interval and often did not perform SPECT until 24 hours, which is a limitation of our study. Furthermore, Sevilla et al. (2007) found that the use of premedication increased specificity [4]. Premedication was generally not used by the clinicians in our study. This notion may partially explain the lower specificity in our study. Moreover, only the study by Sevilla et al. (2007) stated how equivocal scans were handled in the studies. Consistent with our approach, Sevilla et al. (2007) regarded equivocal scans as positive for biliary atresia. This seems to be the most logical approach as the clinical consequence of an equivocal scan would be further investigation with either a repeat study with premedication or diagnostic procedures with cholangiography and/or biopsy.

The addition of SPECT/CT resulted in a positive score change from probably no excretion, equivocal, or probably excretion to definitive excretion in 7 of the 10 cases, which were all true negative. This strongly indicates a positive effect of SPECT/CT on reaching a correct and confident diagnosis when planar HBS shows delayed excretion of the tracer.

Two infants had a SPECT/CT that was classified as equivocal. One patient was eventually diagnosed with biliary atresia and underwent a Kasai procedure with good results. The other had SPECT/CT at 8 hours only and a 24 hours static image - both were classified as equivocal. It remains uncertain whether late SPECT/CT would have provided additional information. The final diagnosis was alpha-1-antitrypsin deficiency.

Finally, there are a few limitations to the study that need to be addressed. Given that the study was not prospective but a reflection of daily routine practice, there were wide variations in both the timing and the number of all images performed. This variation is of course suboptimal for research purposes. The very limited number of enrolled patients is also a major limitation. Furthermore, no patients in this study received adequate premedication. Premedication is known to improve the specificity of HBS with or without SPECT [4, 5], and it is possible that the beneficial value of SPECT/CT would have been diminished if all infants had been properly premedicated.

In conclusion, our preliminary data suggest an added clinical value of SPECT/CT when the preceding planar images have shown indeterminate excretion of the tracer. These findings are consistent with the existing but limited literature on the role of SPECT without CT after planar HBS and support a recommendation of routine use of SPECT/CT or SPECT in HBS. However, due to the limited number of included patients, it is not possible to conclude whether the addition of CT to SPECT changed the outcome. Further extensive studies are warranted.

Conflicts of interest and source of funding

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