Segmental liver hyperintensity in malignant biliary obstruction on diffusion weighted MRI: associated MRI findings and relationship with serum alanine aminotransferase levels

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Objectives: Segmental liver hyperintensity can be observed in malignant biliary obstruction on diffusion weighted MRI (DW-MRI). We describe MRI findings associated with this sign and evaluate whether DW-MRI segmental hyperintensity has any relationship with serum alanine aminotransferase (ALT) levels.

Methods: The DW-MRI T_1 weighted, T_2 weighted and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced T_1 weighted images obtained in 21 patients with hepatic malignancy, who demonstrated biliary obstruction and segmental hyperintensity on DW-MRI ($b=0-750 \text{ s mm}^{-2}$), were retrospectively reviewed by 2 readers blinded to clinical results. DW-MRI hyperintense liver segments were recorded as hypointense, isointense or hyperintense relative to normal liver on T_1/T_2 weighted imaging. It was also noted whether contrast enhancement was similar to that observed in normal liver or diminished in the hepatocellular phase. The mean apparent diffusion coefficient (ADC) value ($\times 10^{-3} \text{ s mm}^{-2}$) of DW-MRI hyperintense segments, normal liver and tumour were compared using Student's *t*-test. The frequency of MRI findings was corroborated with serum ALT levels, which reflect hepatocyte injury.

Results: DW-MRI hyperintense segments frequently showed T_1 hyperintensity (10/21), T_2 hyperintensity (19/21) and/or diminished contrast enhancement (15/21). Tumours showed significantly lower mean ADC values than liver (1.23 ± 0.08 vs 1.43 ± 0.05 ; $p=0.013$). Segments showing concomitant T_1 hyperintensity had lower mean ADC values than liver (1.30 ± 0.05 vs 1.43 ± 0.05 ; $p=0.023$). The patients (8/10) with concomitant T_1 and DW-MRI segmental hyperintensity showed elevated ALT levels ($p=0.030$, Fisher's exact test).

Conclusion: Concomitantly high T_1 weighted and DW-MRI signal in liver segments was associated with lower ADC values and abnormal liver function tests, which could reflect underlying cellular swelling and damage.

Received 23 February 2010
Revised 14 April 2010
Accepted 23 April 2010

DOI: 10.1259/bjr/24852804

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Hepatic malignancies, both primary tumours and metastases, are known to cause biliary obstruction. Although a tumour at the porta hepatis might obstruct bile ducts to both hepatic lobes, smaller tumours arising in the periphery of the liver can also cause localised segmental or subsegmental biliary obstruction. Such obstruction can lead to intrahepatic biliary dilatation demonstrable by ultrasound [1] or CT [2]. Significant biliary obstruction can result in hepatocellular injury, which can be reflected by an increase in serum alanine aminotransferase (ALT) [3]. ALT is a cytosolic enzyme highly specific for hepatocytes that is released when cell membrane integrity is compromised during cell injury or cell death [4, 5].

MRI has been used to evaluate the effects of biliary obstruction on the liver parenchyma. The liver segment associated with intrahepatic biliary obstruction has been

reported to show high T_2 signal intensity but more variable hypointense to hyperintense signal intensity on T_1 weighted imaging [6, 7], reflecting a probable change in tissue composition. However, morphological imaging does not necessarily reflect biochemical or histological changes that occur as a consequence of obstruction. Diffusion weighted MRI (DW-MRI) informs us of the mobility of water molecules in the microenvironment [8], which can be inferred from the higher b -value images ($b>500 \text{ s mm}^{-2}$) and quantified by the apparent diffusion coefficient (ADC). In areas of impeded water diffusion (e.g. owing to increased cellularity and/or cellular swelling) b -value images ($b>500 \text{ s mm}^{-2}$) return high signal intensity and low ADC values. This technique has been used in the liver for the characterisation of tumours, cancer treatment response assessment and for the evaluation of liver fibrosis [9, 10].

At our institution it has been observed that some patients with intrahepatic duct dilatation secondary to a hepatic tumour show hyperintensity of involved liver

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Figure 1. A 79-year-old male with metastatic colorectal cancer to liver. Diffusion weighted images acquired at (a) a b -value of 0 s mm^{-2} and (b) a b -value of 750 s mm^{-2} show segmental hyperintensity (arrows) of the obstructed liver segment resulting from a metastasis (arrowheads) located at the apex of the segment. Note small dilated biliary ducts within the segment are signal-suppressed on the high b -value image (b).

segments on DW-MRI (Figure 1). Given that biliary obstruction causes increased hepatocyte volume [11] and ALT derangement [3], we hypothesise that segmental hyperintensity in the liver parenchyma associated with biliary obstruction on DW-MRI might indicate underlying hepatocellular swelling and damage that could be related to serum ALT levels. Thus, DW-MRI could enable the identification of obstructed liver segments with functional damage for which urgent intervention is needed (*e.g.* by selective biliary drainage/stenting) to prevent further deterioration [12]; DW-MRI might also provide a means to assess the effectiveness of stenting or treatment by resolution of this appearance.

As far as we are aware, the application of DW-MRI for the assessment of biliary obstruction has not been previously described. The association of DW-MRI findings to other conventional MRI findings has not been established. Furthermore, the relationship between DW-MRI findings and serum ALT derangement is also unknown. Hence, the aim of this study was to explore the conventional MRI findings associated with DW-MRI hyperintensity in patients with malignant biliary tree obstruction and to evaluate whether DW-MRI segmental hyperintensity has any relationship with serum ALT levels.

Methods and materials

The study was approved by the institution research review board and ethics committee.

Patient population

In our specialist oncological institution, patients with hepatic malignancies are referred for MRI using unenhanced T_1/T_2 weighted sequences, dynamic gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI sequences and DW-MRI as

part of standard diagnostic work-up. A magnetic resonance cholangiopancreatography (MRCP) examination is not performed as part of this imaging protocol. Over the period 1/1/2007 to 31/4/2009, 184 patients underwent such MRI studies, of whom 22 fitted our inclusion and exclusion criteria.

There were two inclusion criteria: newly diagnosed hepatic malignancy with associated segmental or sub-segmental biliary obstruction (*i.e.* a dilated bile duct could be observed on conventional T_2 weighted MRI) and segmental hyperintensity on high b -value DW-MRI ($b=750 \text{ s mm}^{-2}$) in the liver segment showing biliary dilatation distal to the obstructing tumour. Patients who received arterial embolisation of the hepatic artery or who had evidence of portal vein, hepatic vein or hepatic artery thrombosis on prior imaging were excluded. Patients were also excluded if they demonstrated significant fatty changes in the liver segment (signal drop of $>50\%$ on in/out of phase T_1 weighted imaging), as this could make ADC quantification less accurate.

MR technique

Images were acquired on two 1.5 T MR systems (Siemens Avanto, Erlangen, Germany, and Philips Intera, Best, the Netherlands) employing a phased-array body coil. Unenhanced T_1 weighted in-phase and oppose-phase [gradient echo (GE), repetition time/echo time (TR/TE) 264/4.6 and 2.3 ms, field-of-view (FOV) 380 mm, $\alpha=70^\circ$, 256×256 matrix, GRAPPA/SENSE=2, section thickness 5–7 mm] and unenhanced dual echo-times T_2 weighted [turbo spin echo (TSE), TR/TE 4160/80 ms, $\alpha=90^\circ$, FOV 380 mm, 256×256 matrix, GRAPPA/SENSE=2, section thickness 5–7 mm, with or without SPAIR fat suppression; HASTE, 1000/240 ms, $\alpha=150^\circ$, FOV 380 mm, 256×256 matrix, GRAPPA/SENSE=2, section thickness 5–7 mm] imaging was initially performed.

Free-breathing, multiple averaging echoplanar imaging DW-MRI was performed prior to contrast administration

using 4 gradient factors ($b=0, 100, 500$ and 750 s mm^{-2}) and a 3-scan trace simultaneous gradient application scheme (spin-echo TR/TE $>2500/60\text{--}72 \text{ ms}$, FOV 380 mm , 128×128 matrix, GRAPPA/SENSE=2, section thickness $6\text{--}7 \text{ mm}$, SPAIR fat suppression, bandwidth 1850 Hz , averages=4–6).

Following intravenous administration of Gd-EOB-DTPA (0.1 ml per kilogram of body weight), axial T_1 VIBE/THRIVE (TR/TE $5.7/2.6 \text{ ms}$, FOV 380 mm , $\alpha=10^\circ$, 256×256 matrix, GRAPPA/SENSE=2, section thickness 3 mm , SPAIR fat suppression) and axial and coronal breath-hold GE T_1 weighted imaging (TR/TE $264/4.6$, FOV 380 mm , $\alpha=70^\circ$, 256×256 matrix, GRAPPA/SENSE=2, section thickness $5\text{--}7 \text{ mm}$) were performed in the arterial, portovenous and interstitial phases of contrast enhancement. Delayed imaging in the hepatocellular phase of liver parenchymal enhancement was performed at 20 min to 1 h after contrast administration.

Image interpretation and analysis

Images were reviewed on the workstation (Philips PACS system) by an expert body MRI radiologist (DMK) with more than 15 years' experience in consensus with a clinical scientist (DJC) with more than 20 years' experience with regions of interest (ROI) analysis and clinical trials. Qualitative and quantitative analyses were performed as detailed below.

Qualitative analysis

For each hyperintense liver segment identified on the $b=750 \text{ s mm}^{-2}$ DW-MRI, 3 features were recorded:

- (1) The appearance on unenhanced T_1 weighted imaging: the segment was recorded as being hyperintense, isointense or hypointense compared with surrounding liver parenchyma.
- (2) The appearance on unenhanced short (TE=80 ms) and long (240 ms) echo time T_2 weighted imaging: the segment was recorded as being hyperintense, isointense or hypointense compared with surrounding liver parenchyma.
- (3) The appearance on contrast-enhanced imaging: the same segment was also assessed on the hepatocellular phase of contrast-enhanced images and graded as showing similar enhancement or diminished enhancement compared with the surrounding liver parenchyma.

Quantitative analysis

Two types of quantitative analysis were performed: ADC analysis and estimation of the volume of hyperintense liver segment.

For the ADC analysis, ROIs were manually drawn around the tumour, the hyperintense liver segment and the normal liver parenchyma on every section of the $b=750 \text{ s mm}^{-2}$ images. These ROIs were then copied to the ADC maps and the averaged mean ADC value and the area (in square millimetres) of these recorded.

To estimate the volume of the hyperintense liver segment, the volumes of the hyperintense liver segment,

normal liver parenchyma and tumour were calculated using the formula: $\Sigma (\text{areas} \times \text{thickness} \times \text{number of image sections})$. The volume of tumour or hyperintense segment was expressed as a percentage of the whole liver.

Blood biochemical results

Serum ALT levels obtained within 2 weeks of the MRI scan as part of the patients' diagnostic work-up were recorded.

Statistical considerations

All statistical analyses were performed with SPSS software (version 17, SPSS Inc., Chicago, IL). The mean ADC values of tumours, DW-MRI hyperintense segments and normal liver parenchyma were compared using paired t -tests. The serum ALT levels were categorised as normal or abnormal according to the laboratory reference values of normal ranges. The potential relationship between abnormal serum ALT and the appearance of the liver segments on MRI were evaluated using Fisher's exact test. The serum ALT was correlated with ADC measurements by Spearman's correlation coefficient. The percentage of liver volume occupied by tumour and the percentage of liver volume occupied by the DW-MRI hyperintense segment were correlated with serum ALT derangement by Spearman's correlation coefficient. Two-sided tests were used and $p<0.05$ was considered significant.

Results

A total of 22 patients were identified; 1 was excluded as the diffusion weighted image of the liver lesion (which was situated in the left lobe) was degraded by cardiac motion. The resulting data set comprised 21 patients (14 males, 7 females; mean age 66.0 years; range 51–86 years); the underlying diagnoses were 2 cholangiocarcinomas and 19 metastases.

Qualitative analysis

Of the 21 patients, 10 had hyperintense liver segments on T_1 weighted imaging and 19 on T_2 weighted imaging; 15 patients had isointense segments on long TE T_2 weighted imaging. Following Gd-EOB-DTPA contrast, 15/21 patients demonstrated reduced segmental enhancement in the hepatocellular phase; 6/21 showed similar enhancement compared with the rest of the liver. The frequency of the different signal intensities on T_1 , T_2 and long TE T_2 weighted sequences is illustrated in Table 1. The imaging appearances are demonstrated in Figures 2 and 3.

Quantitative analysis

The ADC value of tumour was significantly lower than that of normal-appearing liver parenchyma (tumour $1.23 \pm 0.08 \times 10^{-3} \text{ s mm}^{-2}$; liver $1.43 \pm 0.05 \times 10^{-3} \text{ s mm}^{-2}$; $p=0.013$). The mean ADC value of DW-MRI hyperintense segments ($1.32 \pm 0.06 \times 10^{-3} \text{ s mm}^{-2}$) was not different from

Table 1. Frequency of different signal intensities of diffusion weighted MRI hyperintense segments on other MRI sequences

Signal intensity	T ₁ weighted imaging	T ₂ weighted imaging (TE=80 ms)	T ₂ weighted imaging (TE=241 ms)
Hypointense	2	0	0
Isointense	9	2	15
Hyperintense	10	19	6

TE, echo time.

that of the surrounding normal liver parenchyma ($p=0.091$) (Figure 4). However, the mean ADC value of hyperintense DW-MRI liver segments that were also hyperintense on T₁ weighted imaging segments ($1.30 \pm 0.05 \times 10^{-3} \text{ s mm}^{-2}$) was significantly lower than that of the liver parenchyma ($p=0.023$) (Figure 5).

Relationship with biochemical liver function test

Of the 10 patients demonstrated to have concomitant T₁ and DW-MRI segmental hyperintensity, 8 showed an elevated ALT level ($p=0.030$, Fisher's exact test). The

mean percentage of liver volume occupied by tumours was 1.48% (range 0.06–6.77%), whereas the mean percentage of liver volume occupied by DW-MRI hyperintense liver segment was 2.95% (range 0.06–2.26%). The percentage volume of liver occupied by the DW-MRI hyperintense segments showed no correlation with serum ALT levels ($\rho=-0.03$, $p=0.961$).

Discussion

There has been no prior description of using DW-MRI to assess the potential effects of biliary obstruction on the

Figure 2. A 58-year-old male with metastatic colorectal cancer to liver. (a) T₁ weighted in-phase and (b) T₁ weighted oppose-phase imaging shows two T₁ hyperintense liver segments (arrows) located distal to metastasis (asterisk). Note there is no appreciable signal loss on oppose-phase imaging to suggest fatty infiltration. (c) Turbo spin echo T₂ weighted image (TE=80 ms) shows mild hyperintensity of liver segments (arrows). High signal dilated biliary ductules (arrowheads) are visible within segments. (d) Diffusion weighted MRI (DW-MRI) obtained at a b -value of 0 s mm^{-2} and (e) DW-MRI at a b -value of 750 s mm^{-2} show hyperintensity (arrows) corresponding to segments observed on T₁ weighted imaging. (f) Apparent diffusion coefficient maps show reduced tissue diffusivity (arrows) within T₁ and DW-MRI hyperintense liver segments.

Figure 3. An 83-year-old male with metastatic prostate cancer to liver (tumour not shown). (a) Fat-suppressed turbo spin echo T_2 weighted image ($TE=80$ ms) shows segmental hyperintensity in the posterior right lobe of the liver (arrow). Note the high signal intensity dilated bile duct (arrowhead) within the segment. (b) The segment also appears hyperintense on T_1 weighted imaging (arrow). (c) Diffusion weighted MRI at a b -value of 750 s mm^{-2} demonstrates segmental hyperintensity (arrow). (d) The segment shows diminished contrast enhancement on a delayed phase T_1 weighted fat-suppressed image acquired at 20 min following gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid contrast administration, suggesting impaired liver excretory function (arrow).

liver in the literature. To our knowledge, this is the first case series describing a DW-MRI feature associated with malignant biliary tree obstruction and the related morphological findings on conventional MRI. We also explored the potential relationship of the MRI findings with the results of serum ALT.

Of all patients who showed segmental DW-MRI hyperintensity in our study, the majority showed concomitant T_1 hyperintensity; a smaller proportion showed either segmental T_1 hypointensity or isointensity. This is in line with previous observations in the literature. Muramatsu et al [13] reported wedge-shaped areas of increased T_1 signal intensity surrounding benign or malignant lesions. The affected areas were shown to have intraductal tumour extension, liver cell atrophy and sinusoidal dilatation with inflammation of the perivascular fibrous area. Lipofuscin deposition in the hepatocyte was offered as an explanation for the T_1 hyperintensity. In another study of 16 patients [6], the appearance of segmental high T_1 signal intensity and biliary dilatation was attributed to intrahepatic cholestasis with ductular proliferation and bile pigment deposition in the hepatocytes. However, Soong et al [7] showed that, in nine patients with intrahepatic biliary duct dilatation secondary to hepatolithiasis, the affected segments were either isointense or hypointense

on T_1 weighted imaging and all showed contrast enhancement in all three phases (arterial predominant, portal and delayed) using non-specific extracellular gadolinium chelates.

In our study, we found that in liver segments affected by biliary obstruction concomitant high signal intensity on DW-MRI and on T_1 weighted imaging was associated with lower ADC and raised ALT levels. These imaging findings reflect a change in the local microenvironment. We hypothesise that sustained biliary obstruction might lead to hepatocellular oedema and hepatocyte dysfunction associated with intraductal infiltration/ductular proliferation [6, 13], which could account for the lower ADC and increased serum ALT levels. In addition, ADC might be decreased by the presence or accumulation of paramagnetic materials [14] that are normally excreted via the biliary system. Paramagnetic materials (e.g. iron, copper and manganese ions that can be deposited in hepatocytes during cholestasis) might accumulate as a consequence of biliary obstruction and can also shorten T_1 . Such accumulation could account for or contribute to the triad of imaging findings: high T_1 signal, DW-MRI hyperintensity and low ADC values. In our study, the serum ALT levels appeared to be independent of the percentage volume of metastatic disease or segmental

Figure 4. Box and whisker plots comparing apparent diffusion coefficient (ADC) values of tumour, normal liver parenchyma and diffusion weighted MRI (DW-MRI) hyperintense segments. Circles on plots represent mean values; bars indicate the 5th and 95th confidence intervals. When compared with normal liver parenchyma, the mean ADC value of tumour was significantly lower, whereas that of DW-MRI hyperintense segments was not different from that of surrounding normal liver parenchyma.

changes within the liver. This poor correlation between transaminase levels and the degree of liver injury has been described in the literature [5, 15].

There has been no report in the literature describing hepatic contrast enhancement patterns in biliary obstruction in humans. In an animal study using selective intrahepatic biliary branch ligation in rats [16], a delayed clearance of Gd-EOB-DTPA contrast from the ligated segment was observed in the early post-operative period; however, no differential enhancement or decay pattern after Gd-EOB-DTPA injection was seen between the ligated segment and normal liver at 1–4 weeks after ligation. This enhancement/decay pattern differs from those observed in our study where we found impaired enhancement of the affected liver segments compared with the surrounding liver parenchyma. A possible explanation of this discrepancy is that patients with intrahepatic biliary obstruction tend to present later than 4 weeks. At the time of presentation, sustained hepatocellular injury with or without local hepatic atrophy [17] could result in diminished contrast uptake/secretion.

It would appear from the current study that the imaging appearance of intrahepatic biliary obstruction, confirmed by DW-MRI, could be categorised into two groups: one with T_1 segmental hyperintensity and associated raised ALT, suggesting underlying hepatocyte dysfunction with possible deposition of paramagnetic substances, and

Figure 5. Box and whisker plots comparing mean apparent diffusion coefficient (ADC) values of normal-appearing liver parenchyma and diffusion weighted MRI (DW-MRI) hyperintense segments showing concomitant T_1 hyperintensity. Circles on plots represent mean values; bars indicate the 5th and 95th confidence intervals. Mean ADC values of concomitant T_1 and DW-MRI hyperintense segments were significantly lower than that of liver parenchyma.

another group without T_1 hyperintensity, which might represent less severe or an earlier stage of biliary obstruction. Thus, concomitant T_1 and DW-MRI hyperintensity might indicate the functional sequelae of biliary obstruction and could be useful in identifying and localising liver parenchyma at risk of dysfunction; however, the clinical impact of this observation will need to be tested in future prospective studies.

There are limitations to our study. Firstly, our study was a retrospective study of oncological patients. Although this patient population frequently poses management dilemmas and would benefit from further evaluation of their liver lesions, the findings derived from this population might not necessarily apply to patients with other pathologies (e.g. hepatolithiasis). Hence, there is a need for our findings to be further validated by other authors and also in other clinical contexts to determine whether the constellation of findings would indeed be robust and clinically meaningful. A further issue arising from the retrospective design of this study is that the serum biochemical tests were not necessarily performed on the same day as the imaging study. Indeed, an abnormality in the serum liver function tests was often the trigger for initiating imaging studies. Thus, serum biochemical tests obtained within 2 weeks of the MRI scan was felt to be a

reasonable compromise in this study. Secondly, it was unclear what proportion of patients with intrahepatic biliary duct dilatation in a wider, non-neoplastic population also display segmental hyperintensity on DW-MRI. Thirdly, we have not been able to correlate histopathological data with imaging findings in this study, because the patients included had relatively advanced disease that was not suitable for surgery; however, we could corroborate our present findings with data gathered from published pre-clinical studies.

In conclusion, segmental hyperintensity on T_1 weighted imaging and DW-MRI might be useful for identifying patients at risk of hepatocellular impairment from biliary obstruction. Further studies would be valuable in establishing the utility and robustness of our imaging findings.

Acknowledgments

CRUK and ESRC Cancer Imaging Centre and NHS funding to the NIHR Biomedical Research Centre C1060/A10334.

References

1. Foley WD, Quiroz FA. The role of sonography in imaging of the biliary tract. *Ultrasound Q* 2007;23:123–35.
2. Pedrosa CS, Casanova R, Rodriguez R. Computed tomography in obstructive jaundice. Part I: The level of obstruction. *Radiology* 1981;139:627–34.
3. Georgiev P, Jochum W, Heinrich S, Jang JH, Nocito A, Dahm F, et al. Characterization of time-related changes after experimental bile duct ligation. *Br J Surg* 2008;95: 646–56.
4. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology* 2002;123: 1367–84.
5. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000;342: 1266–71.
6. Hashimoto M, Akabane Y, Heianna J, Iwama T, Tate E, Nishii T, et al. Segmental high intensity on T_1 -weighted hepatic MR images. *Abdom Imaging* 2005;30:60–4.
7. Soong TC, Lee RC, Cheng HC, Chiang JH, Tseng HS, Lin CW, et al. Dynamic MR imaging of hepatolithiasis. *Abdom Imaging* 1998;23:515–19.
8. Le Bihan D. Molecular diffusion nuclear magnetic resonance imaging. *Magn Reson Q* 1991;7:1–30.
9. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. *AJR Am J Roentgenol* 2007;188:1622–35.
10. Koinuma M, Ohashi I, Hanafusa K, Shibuya H. Apparent diffusion coefficient measurements with diffusion-weighted magnetic resonance imaging for evaluation of hepatic fibrosis. *J Magn Reson Imaging* 2005;22:80–5.
11. Gall JA, Bhathal PS. A quantitative analysis of the liver following ligation of the common bile duct. *Liver* 1990;10: 116–25.
12. Freeman ML, Overby C. Selective MRCP and CT-targeted drainage of malignant hilar biliary obstruction with self-expanding metallic stents. *Gastrointest Endosc* 2003;58: 41–9.
13. Muramatsu Y, Takayasu K, Furukawa Y, Miyakawa K, Iwata R, Ushio K, et al. Hepatic tumour invasion of bile ducts: wedge-shaped sign on MR images. *Radiology* 1997; 205:81–5.
14. Firat AK, Sanli B, Karakas HM, Erdem G. The effect of intravenous gadolinium-DTPA on diffusion-weighted imaging. *Neuroradiology* 2006;48:465–70.
15. Fauci AS, Harrison TR. *Harrison's principles of internal medicine*. 17th edn. New York, NY: McGraw-Hill Medical, 2008.
16. Ni Y, Lukito G, Marchal G, Cresens E, Yu J, Petre C, et al. Potential role of bile duct collaterals in the recovery of the biliary obstruction: experimental study in rats using microcholangiography, histology, serology and magnetic resonance imaging. *Hepatology* 1994;20:1557–66.
17. Kusano T, Isa T, Ohtsubo M, Yasaka T, Furukawa M. Natural progression of untreated hepatolithiasis that shows no clinical signs at its initial presentation. *J Clin Gastroenterol* 2001;33:114–17.