Contrast Enhanced MR Imaging of Liver Tumors in HBV Transgenic Mice

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Purpose

Hepatocellular carcinoma (HCC) is one of the most prevalent cancer. One of primary risk factors for the development of HCC is the chronic infection with hepatitis B virus. It is known that HBV transgenic mice that express the HBV X protein (HBx) develop a progressive hepatocyte damage due to intracellular accumulation of such a protein. In the first month of life, this chronic insult induces degenerative alterations, followed by an active inflammatory damage which became clearly neoplastic after 12 month. The aim of the present study was to evaluate the potentialities of contrast-enhanced MRI to detect primary tumor formation in liver of HBV transgenic mice. A new blood pool agent B22956/1 (Gadocoletic acid trisodium salt), currently under evaluation as potential imaging for liver cancer detection, tumor neovascularization characterization and biliary tree, has been tested to detect parenchyma degeneration and HCC formation in liver of HBV transgenic mice.

Materials and Methods

Transgenic mice expressing HBV genes were developed at the animal facilities of CEINGE (Napoli, Italy). MR imaging experiments were performed at 2 Tesla (MR Research Systems Ltd, Surrey UK, Oxford Magnet, bore= 45 cm i.d.) over a total of 52 animals (30 +/- pathological, 22 +/+ control) from 3 to 15 month old. For all animals, pre and post contrast images were acquired successively (up to 40 min) after intravenous (tail vein, 6 mL/min) administration of B22956/1 (0.025 mmol/kg), and 24 h after, with MultiHance® (0.05 mmol/kg) as reference contrast agent. Animals were anaesthetized with 0.4 mL/kg of Zoletil® and 0.25 mL/kg of Rompun® i.m. Coronal and axial T1 and T2-weighted images were acquired with gradient echo and/or spin echo sequences with optimized parameters for high resolution images with a good contrast to detect tumors in the liver. Signal fat saturation and respiratory gating were also used in spin-echo sequences. Signal intensity was calibrated by a standard reference (NiCl2 solution 3.75 mM) placed close to the animal during imaging acquisition. From these serial images, it was possible to distinguish the dynamic distribution of the contrast agents in aortic, portal vein and delayed phases. For each MRI exam, the kinetic of signal enhancement post contrast was measured in the abdominal aorta, vein cava, portal vein and in the liver.

Results and discussion

In control mice (+/+), no difference of signal enhancement in liver was measured with the age of the animals after with MultiHance, whereas with B22956/1, in animals of 15 month old, the signal enhancement was lower than in younger animals.

In pathological mice (+/-), the signal enhancement in vessels (vein cava and portal vein) and also in the liver was higher with B22956/1 compared to MultiHance. Furthermore, with B22956/1, the signal enhancement from the liver was lower in mice from 9 to 15 month old respect to younger ones (3 and 6 month) as compared to animals treated with MultiHance, where no differences with the age were observed. From 6 month-old, lesions were distinguished in pathological mice (+/-). Abnormalities have been seen after administration of B22956/1 or MultiHance®. Lesions, detectable as well-defined foci of signal hypointensity, have been seen in 12 month old pathological mice. Lesions were better defined after administration of B22956/1 respect to MultiHance. An example of multifocal lesions highlighted during portal phase in 15 month old pathological mouse ,T22 in figure 1, after administration of B22956/1. The measured signal intensity showed different trends for the 3 lesions after administration of B22956/1. Nodular-shaped lesions have been seen in an other 15 month pathological mouse , T39 in figure1, in post contrast images. Different uptake of the contrast, confirmed by measured signal, was found post administration of B22956/1.

Conclusions

B22956/1-enhanced MRI experiments allowed :

- the evaluation of the degenerative processes and alterations of the liver parenchyma progressing with the animal age;
- the detection of neoplastic lesions in chronically altered liver parenchyma of HBV transgenic mice;
- the characterization of lesions on the basis of their different vascularization.

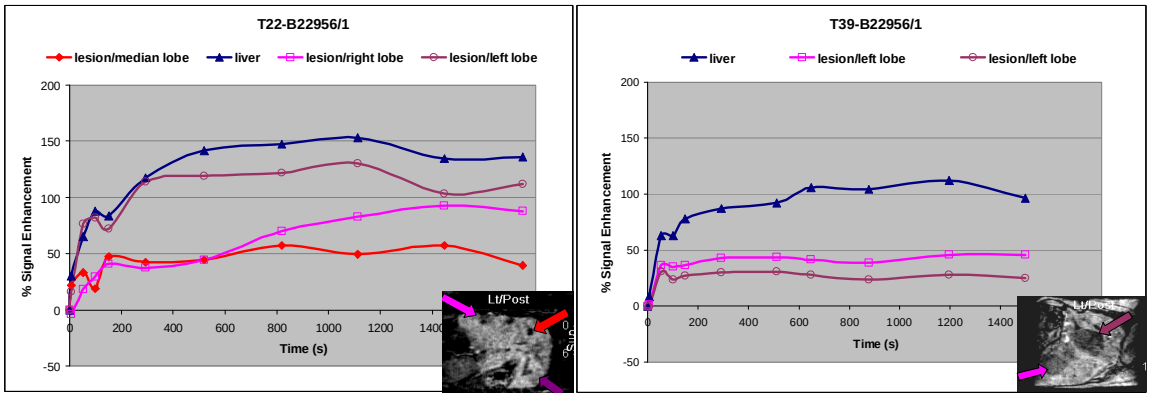

Figure1
In pathological mice of 15 month old, two type of lesions were distinguished with 2956/1: multifocal (T22) and nodular lesions (T39).