European Journal of Radiology 116 (2019) 41–46

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Imaging liver nodules in tyrosinemia type-1: A retrospective review of 16 cases in a tertiary pediatric hospital

H. Nursun Ozcan[a,*], Musturay Karcaaltincaba[a], Emine Pektas[b], H. Serap Sivri[c], Berna Oguz[a], Ali Dursun[c], Aysegul Tokatli[c], Turgay Coskun[c], Mithat Haliloglu[a]

[a] Department of Radiology, Hacettepe University School of Medicine Ankara, Turkey
[b] Department of Pediatrics, Division of Pediatric Metabolic Diseases, Cengiz Gokcek Children Hospital Gaziantep, Turkey
[c] Department of Pediatrics, Division of Pediatric Metabolic Diseases, Hacettepe University School of Medicine Ankara, Turkey

ARTICLE INFO

Keywords:
Liver
Tyrosinemia type 1
Magnetic resonance imaging

ABSTRACT

Objective: To describe the liver imaging findings of Hereditary tyrosinemia type-1 (HT1) patients.
Materials and methods: We report 16 patients (8 Female and 8 Male) with HT-1. Their demographic features, imaging findings and alpha feto protein (AFP) levels were recorded. Imaging features on CT and MR were evaluated for the following characteristics: contour of the liver and liver nodules. Liver nodules were categorized as; regenerative, dysplastic, fatty and malignant nodules (HCC).
Results: Thirteen (81%) patients had multiple liver nodules (> 20) on imaging studies. Five patients (31%) had regenerative nodules, six (38%) had dysplastic nodules and ten (63%) had fatty nodules. Dysplastic nodules were encountered in two patients with HCC and in four patients without a tumor. Four patients (25%) had HCC nodule on imaging studies. Those four patients had biopsy and all of them had HCC nodule on histopathology. In the follow-up period, in one patient fatty nodules had increased in size, in one patient regenerative nodules had disappeared and in one patient dysplastic nodules had disappeared.
Conclusions: Multiple fatty nodules can be seen in HT1 patients and in some patients, the regenerative and dysplastic nodules can disappear during the follow-up period.

1. Introduction

Hereditary tyrosinemia type-1 (HT1) is a severe, autosomal recessive inherent error of metabolism caused by the deficiency of fumarylacetoacetate hydrolase (FAH), a metabolic enzyme that catalyzes the last step of tyrosine metabolism [1]. Metabolic block of the step of FAH induces accumulation of toxic metabolites-i.e. maleylacetoacetate, fumarylacetoacetate (FAA), and succinylacetone (SA)- which are responsible for the hepatic and renal manifestations of the disease [1].

Infants with HT1 present with acute liver failure as early as few weeks of age. Spectrum of disease ranges from hepatic dysfunction/failure within the first months of life to a chronic illness with hepatic cirrhosis, which is directly associated with the ongoing hepatic/renal damage. FAA accumulation appears to directly damage the hepatocytes and renal proximal tubules [2,3]. To prevent the development of such complications, patients are treated with a low tyrosine diet and 2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione (NTBC). This drug blocks the second step in the tyrosine degradation pathway and prevents the accumulation of FAA and its conversion into SA as well. This combined treatment has led to a greater than 90% survival rate [2,3]; however, it cannot prevent HCC development.

Alpha-fetoprotein (AFP) values and liver imaging should be carried out periodically for early detection of HCC. However, normal AFP values do not rule out HCC. Imaging modalities especially magnetic resonance (MR) imaging play an important role on the evaluation of liver lesions in HT1 patients. In the radiology literature, to the best of our knowledge, there is only one study that demonstrates the liver findings of five HT1 patients [4]. In that old study, liver was evaluated by only computed tomography (CT) and regenerative nodules were noted as the main finding [4]. In our practice, fatty nodules drew our attention during the follow up of these patients. There are only two case reports in the literature whereby such nodules have also been mentioned [5,6]. In this study, we aimed to review the liver imaging findings of HT1 patients together with their clinical follow-up and histopathological

Abbreviations: HT1, hereditary tyrosinemia type-1; AFP, alpha feto protein; FAH, fumarylacetoacetate hydrolase; SA, succinylacetone; NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione; HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging

* Corresponding author at: Department of Radiology/Subdivision of Pediatric Radiology, Hacettepe University School of Medicine, Sıhhiye 06100, Ankara, Turkey.
E-mail address: drhnozcan@yahoo.com (H.N. Ozcan).

https://doi.org/10.1016/j.ejrad.2019.04.016
Received 5 January 2019; Received in revised form 7 March 2019; Accepted 23 April 2019

Table 1
Demographic findings of the patients.

Patient	Sex	Age at diagnosis (months)	Tyrosine level at diagnosis (mg/dl) (N: < 2 mg/dl)	Age at NTBC onset (months)	Duration of NTBC treatment (months)	Age at diet onset (months)	Biopsy	Age at initial radiological evaluation	AFP level when the liver lesion was diagnosed(IU/ml) (reference ranges:8.5 ± 5.5)	The last AFP level (IU/ml) (reference ranges: 8.5 ± 5.5)	Clinical follow-up (years)	Radiological follow-up (years)	Transplantation
1	M	7.5	7.9	7.5	2	7.5	No	7.5 months	109761 ↑	250 ↑	4	4	Yes
2	M	6	10.3	6	24	6	Yes	7 months	43958 ↑	1.94	2	2	Yes
3	M	5	7.2	6	96	6	No	12 months	5.02 ↑	3.22 ↑	8	5	No
4	F	10	6.94	11	36	10	Yes	14 months	2192 ↑	720 ↑	3	3	Yes
5	F	6.5	11.9	6.5	6	6.5	No	6 months	107000 ↑	4803 ↑	1	1	Yes
6	F	12	12.6	12	5	12	Yes	12 months	132689 ↑	871 ↑	1	1	Yes
7	F	24	4	24	108	24	Yes	24 months	74.07 ↑	16.4 ↑	9	9	No
8	F	10	8.9	10	3	10	Yes	10 months	178588 ↑	178588 ↑	1	1	Yes (Died)
9	M	1	9.4	1	114	1	No	11 months	4.18 ↑	4.95 ↑	10	9	No
10	F	26	8.4	26	84	26	Yes	36 months	7.41 ↑	2.65	7	7	No
11	M	24	6.4	24	120	24	Yes	36 months	27.46 ↑	18.5 ↑	10	10 y	No
12	M	9	7.4	168	144	9	Yes	12 years	4.96 ↑	4.16 ↑	26	14	Yes
13	M	36	7	36	1	36	No	42 months	6987 ↑	52.63 ↑	1	1	Yes
14	F	60	7.3	180	72	60	Yes	5 years	225 ↑	14773 ↑	16	16	No (Died)
15	F	5	9.17	6	132	5	Yes	6 months	50.65 ↑	30.62 ↑	11	11	No
16	M	3	10.06	16	120	16	No	16 months	761.5 ↑	5.35 ↑	10	10	No

NTBC: 2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione.

examinations.

2. Materials and methods

A retrospective study was performed after approval of our institutional review board. The archives in the pediatric metabolism unit were reviewed for HT1 patients documented between 1991–2017. The search yielded 27 patients, 11 of 27, did not have imaging studies available. Eleven patients' imaging modalities were not registered in our hospital PACS system and CT and/or MRI of these patients were from different centers and we could not reach those images. The remaining 16 patients (8 Female, 8 Male; age of diagnosis ranging between 1 month-60 month; median value 5.5 months) were enrolled in this study. 13 patient had MR examination and 3 patient had CT. None of the patients had both MRI and CT. Their demographic features, imaging findings, metabolic tests (blood tyrosine levels and the presence of SA in urine) and alpha fetoprotein (AFP) levels were recorded.

2.1. Image technique

2.1.1. MRI technique

All MRI examinations were performed on 1.5-T imaging unit (Symphony TIM; Siemens, Erlangen, Germany), equipped with eight-channel phased-array body coil. The patients were examined in the supine position, and the receiver coil was placed to cover the upper abdomen. 13 patients underwent a routine imaging protocol including breath-hold coronal TRUE-FISP, axial T2-weighted half-Fourier acquisition single-shot turbo spin echo, axial in-phase (TR/TE, 190/4.2) and opposed phase (TR/TE, 190/2.4) chemical shift imaging, breath-hold T2-weighted fast spin echo with fat suppression and dynamic 3D T1-weighted gradient-recalled echo fat-suppressed (VIBE) sequence (TR/TE, 3.9/1.7) before and after injection of the contrast agent. Gadoxetate disodium (Gd-EOB-DTPA) (Primovist, Bayer HealthCare Pharmaceuticals) was administered to 2 patients and gadoterate meglumine (Dotarem, Guebert) was administered to 11 patients. Delayed hepatobiliary imaging was performed at 20 min after for gadoxetate disodium injection. An IV bolus of contrast agents (Gd-EOB-DTPA, 0.0025 mmol/kg; gadoterate meglumine, 0.1 mmol/kg) were administered at a rate of 1 mL/sec.

2.1.2. CT technique

All CT examinations in three patients were performed with a 64-MDCT scanner (Somatom Definiton 64; Dual Source, Siemens Medical Solutions, Erlanger, Germany). Parameters were detector collimation, 64 × 0.625 mm; total z-axis coverage, 40 mm per rotation; gantry rotation speed, 0.4 s; tube voltage, 120–140 kV; and tube current with automatic dose modulation ranging from 150 to 320 mA. 2.0 ml/kg of nonionic IV contrast material Iohexol Omnipaque [300 mg of iodine permilliliter]; GE Healthcare) was administered. Contrast medium was injected using a power injector at an injection rate of 2 mL/s, followed by 15–20 mL of saline flush. The volumes of contrast medium used for CT was adjusted according to the weight of the patients. A slice thickness of 5 mm is used with a pitch of 1 to 1.5, depending on patient size, and 3-mm reconstructions. For dual-phase imaging, the arterial phase of liver enhancement was obtained 10 to 15 s after the start of the contrast bolus. The portal venous phase was initiated 20–40 seconds after completion of the arterial phase image acquisition.

2.1.3. Image analyses

Images were reviewed by one pediatric radiologist with 5 years of experience in pediatric radiology and an abdominal radiologist with 18 years of experience in abdominal radiology and the diagnoses were established by their consensus. Imaging features on CT and MR were evaluated for the following characteristics: contour of the liver and liver nodules. Liver nodules were categorized as; regenerative, dysplastic, fatty and malignant nodules (HCC). Regenerative nodules were defined

Table 2
Imaging findings of the patients.

Patient	Radiologic Imaging	Number of nodules	Largest nodule (mm)	HCC	Regenerative Nodule	Displastic Nodule	Fatty Nodule	Biopsy
1	CT	> 20	16	–	–	–	+	
2	MRI	> 20	4	–	–	–	+	+
3	MRI	> 20	10	–	+	–	+	
4	MRI	> 20	23	+	–	+	+	+
5	MRI	> 20	17	–	–	–	+	
6	MRI	> 20	14	–	+	–	+	+
7	MRI	> 20	9	–	+	–	–	+
8	CT	> 20	10	–	–	–	+	+
9	MRI	–	–	–	–	–	–	
10	MRI	> 20	9	–	–	+	–	+
11	MRI	> 20	16	–	–	+	+	+
12	MRI	1	8	+	–	–	–	+
13	MRI	> 20	7	–	+	+	+	
14	CT	5	80	+	–	–	–	+
15	MRI	> 20	16	+	+	+	+	+
16	MRI	> 20	20	–	–	+	–	

HCC: Hepatocellular carcinoma.

when they displayed similar enhancement to the normal liver parenchyma on post-contrast CT and MR images, in both portal venous and hepatocellular/delayed phases; without arterial phase enhancement [7]. Dysplastic nodules were defined when there was early contrast enhancement without washout on delayed phase. Fatty nodules were defined as the liver signal intensity loss on out-of-phase images in comparison with in-phase gradient echo MR images and decreased attenuation on post contrast CT images compared with normal liver parenchyma at CT, with a range of −10 to −100 HU. HCC were diagnosed when typical hypervascularity in the arterial-phase followed by washout in the delayed-phase was observed [7].

All nodules were reviewed for their number, size, signal intensity on T1- and T2-weighted images, arterial, portal and equilibrium phase enhancement (evaluated by visual comparison with the signal intensity of the adjacent hepatic parenchyma), hepatobiliary phase enhancement and presence of steatosis in the nodule. Follow up MR and CT images were assessed for change in the size, number and appearance of the nodule(s).

3. Results

Patient demographics are presented in Table 1. All received NTBC treatment and low tyrosine diet. In nine patients, NTBC treatment had been started at the time of diagnosis. In three patients, NTBC treatment was started late despite recommendation. Two of them (patients number 12 and 14) were unable to obtain medication because NTBC became available in our drug market after their diagnosis. Parents of the 3rd patient (patient number 16) refused the treatment and NTBC was started after the development of metabolic crisis. Ten patients had liver biopsy whereby the histopathology showed cirrhosis in all of them.

Imaging findings of the patients are summarized in Table 2. In 9 patients, liver contours were irregular. Thirteen (81%) patients had multiple liver nodules (> 20) on imaging studies (range: 4–23 mm). Five patients (31%) had regenerative nodules, six (38%) had dysplastic nodules and ten (63%) had fatty nodules on imaging studies (Figs. 1 and 2). Dysplastic nodules were encountered in two patients with HCC and in four patients without a tumor (Fig. 3a, b). Four patients (25%) (patient number 4, 12, 14, 15) had HCC nodule on imaging studies and were confirmed by histopathology (Fig. 3c, d). In all patients with HCC, the liver parenchyma's were consisted with cirrhosis. In 3 of 4 patients the HCC nodules were progressed from dysplastic nodules and only in 1 patient the HCC was present in the initial imaging. All HCC nodules were operated after the diagnosis. In the follow-up period, in one patient (patient number 5), fatty nodules had increased in size (in four months, growth of maximum diameter is from 5 mm to 17 mm) (Fig. 4), in one patients' (patient number 7) regenerative nodules had disappeared (in seven years) (Fig. 5) and in one patients' (patient number 16) dysplastic nodules had disappeared (in six years). In remaining patients, nodules did not change in the follow-up period. None of the patients presented distant metastasis, vascular or lymphatic invasion. Eight patients underwent liver transplantation and one patient died soon after the transplantation. The remaining seven patients had successful liver transplantation and there was no recurrence of HCC in the follow-up.

4. Discussion

Our study has two major findings; multiple fatty nodules can be seen in HT1 patients and some of the regenerative and dysplastic nodules can be disappear in the follow-up period.

Multiple regenerative nodules are the most frequent liver lesions in HT1 patients [4]. They show similar enhancement with the normal liver parenchyma in both portal venous and hepatocellular/delayed phases on post-contrast CT and MR images without arterial phase enhancement. In our patients, five (31%) of them had multiple regenerative nodules. Interestingly, we observed multiple fatty nodules in 10 (63%) patients. In the pertinent literature, Shteyer et al. [5] and Tazawa et al. [6] presented two different cases with fatty liver changes. Both of cases received low tyrosine diet after the diagnosis. They illustrated the implications of nutrition on the liver. In our 10 patients (with multiple fatty liver nodules), all received NTBC treatment and low tyrosine - protein diet. Adequate calorie is supplemented with increased fatty and carbohydrate ratio in the diet. In this sense, we suggest that low tyrosine - protein, high fatty-carbohydrate diet could be a predisposing factor for the development of fatty nodules in HT1 patients with damaged liver tissue.

In our study, during the follow-up, we observed disappearance of the nodules in two patients. One of them had regenerative nodules, which disappeared in 7 years and the other had dysplastic nodules, which disappeared in 6 years. Both of them had received NTBC treatment. In the relevant literature, regenerative nodules were reported to disappear with NTBC treatment [8]. Additionally, it has also been mentioned that appropriate NTBC treatment is associated with reduction in AFP levels, regression of regenerative nodules and decrease in the incidence of liver cancer especially when administered early in the course of the disease [9]. Herewith, although the treatment can decrease the risk of HCC prevalence, it cannot prevent HCC development.

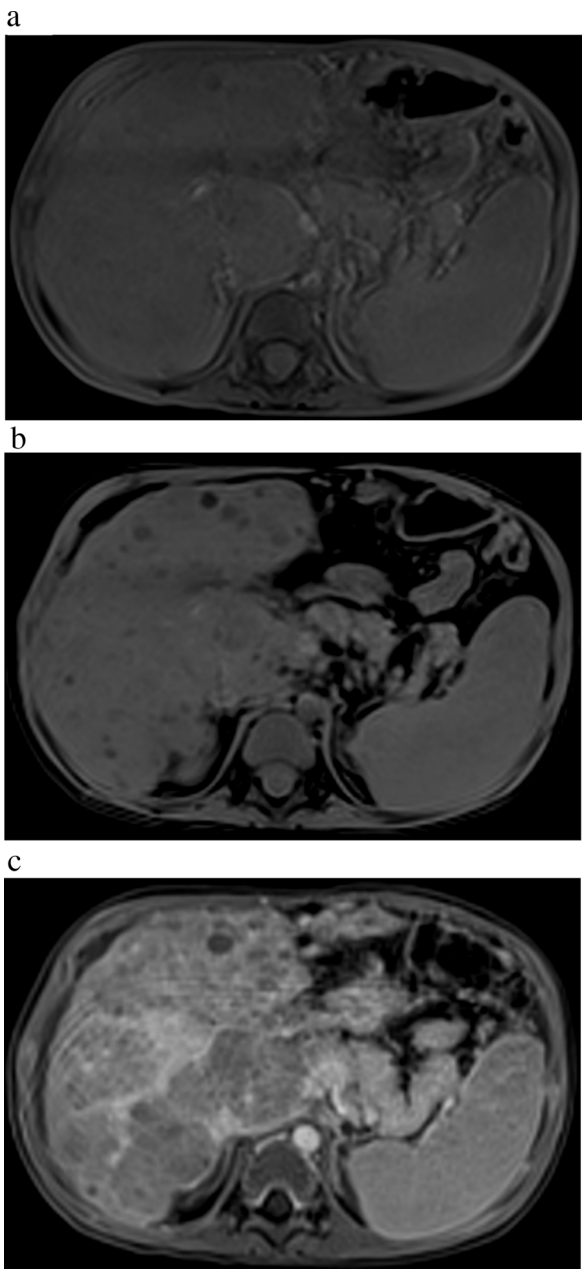

Fig. 1. A–C: One-year-old girl with tyrosinemia type 1. **(A)** In-phase and **(B)** out-of-phase MR images show multifocal fat containing lesions. Out-of-phase MR image shows multiple lesions with signal drop compared with in-phase image consistent with multifocal fat containing lesions. **(C)** Post-contrast axial MR image shows no retention of contrast medium in lesions.

Moreover, although AFP is almost always elevated in cases with HCC, some cases might also show minimally elevated or normal AFP levels [1]. In HT1 patients, the measurement of AFP levels is not reliable for ruling out HCC [9]. In one of our patients with HCC, AFP level was normal and the other three patients had high AFP levels. Of note, the patients with HT1 having elevated serum AFP levels should be closely monitored for developing HCC and physicians should be alert in oscillations of AFP levels. However, if the AFP levels are stable for a long period, radiological changes are the most important tools for the detection of HCC. The optimal follow-up program is unclear, similar with many groups we suggest screening with both measurements of AFP levels and radiologic imaging being performed every 3–6 months and instantly if AFP increases.

Magnetic resonance (MR) imaging is more helpful than CT for detecting and characterization of the sub centimeter liver nodules [10]. The diagnosis of HCC can be difficult in HT1 patients due to cirrhotic, heterogeneous nodular liver parenchyma. The small tumors can have similar imaging findings with regeneration or dysplastic nodules. Hepatocyte specific agents can be helpful for these difficult cases. MR imaging with dual echo is very useful for demonstrating fatty changes with signal drop in out-of-phase images. The Liver Imaging Reporting and Data System (LI-RADS) is a reporting system for the standardized interpretation of liver imaging findings in patients who are at risk for HCC; however, pediatric patients are excluded from the LI-RADS diagnostic population because the performance of LI-RADS has not been approved in this age group.

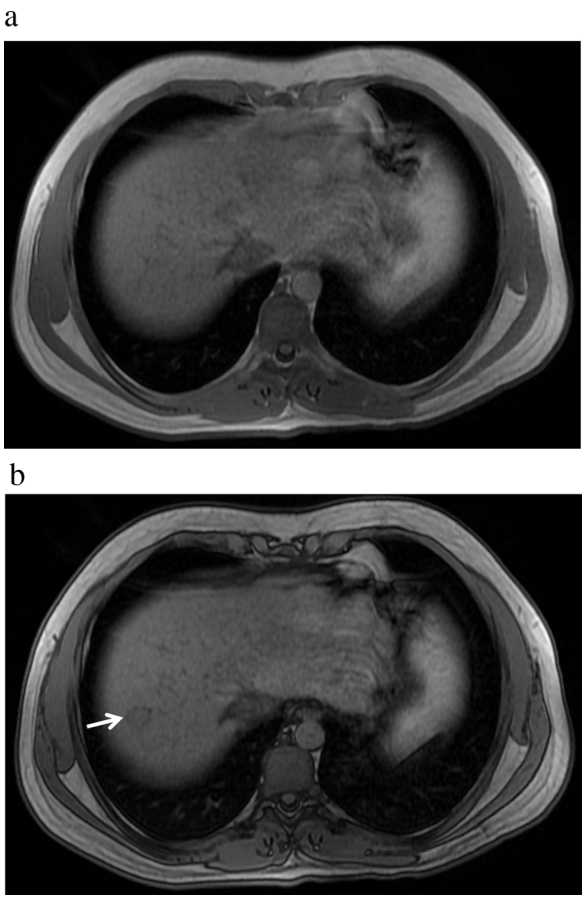

Fig. 2. A, B: 16-year-old boy with tyrosinemia type 1. **(A)** In-phase and **(B)** out-of-phase MR images show fat containing lesion. Out-of-phase MR image shows the lesion with signal drop compared with in-phase image consistent with fat containing lesion (arrow).

Our study has some limitations. First, due to the retrospective design of the study, patient follow-up intervals were variable. Second, only 10 patients had histopathological evaluations and in the remaining six patients, biopsy was not performed due to benign appearance of the lesions and clinical/radiological stability during follow-up.

In conclusion, our findings showed that fatty liver nodules might be observed in HT1 patients and regenerative/dysplastic nodules can disappear during the follow-up. As such, while calling attention of radiologists to the fact that each and every liver nodule might not always/necessarily be HCC. MR imaging can be performed for the characterization and follow-up of nodules in HT1 patients.

Declarations of interest

None.

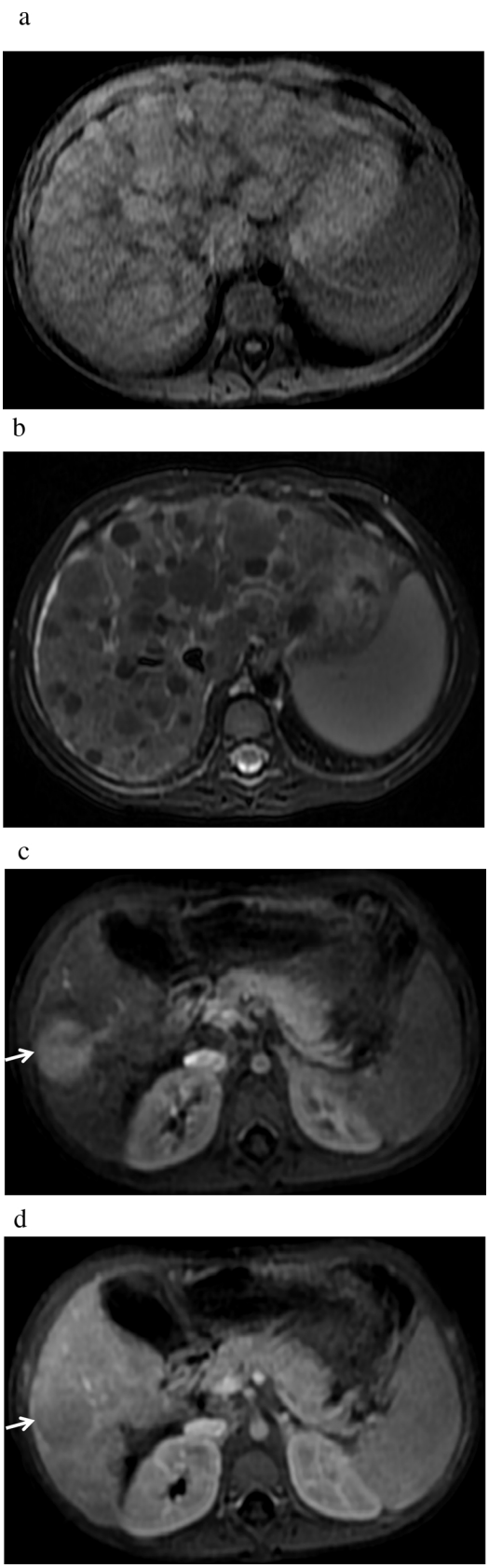

Fig. 3. A-D: Four-year-old girl with tyrosinemia type 1. **(A)** Axial T1-weighted and **(B)** T2-weighted images show multiple dysplastic nodules. **(C)** Axial arterial phase GRE T1-weighted MR image shows heterogeneous enhancement of the nodule in segment VI (arrow). **(D)** On an axial delayed phase GRE T1-weighted MR image, the nodule shows washout of contrast material, becomes hypointense adjacent to the liver parenchyma (arrow), findings that are consistent with HCC.

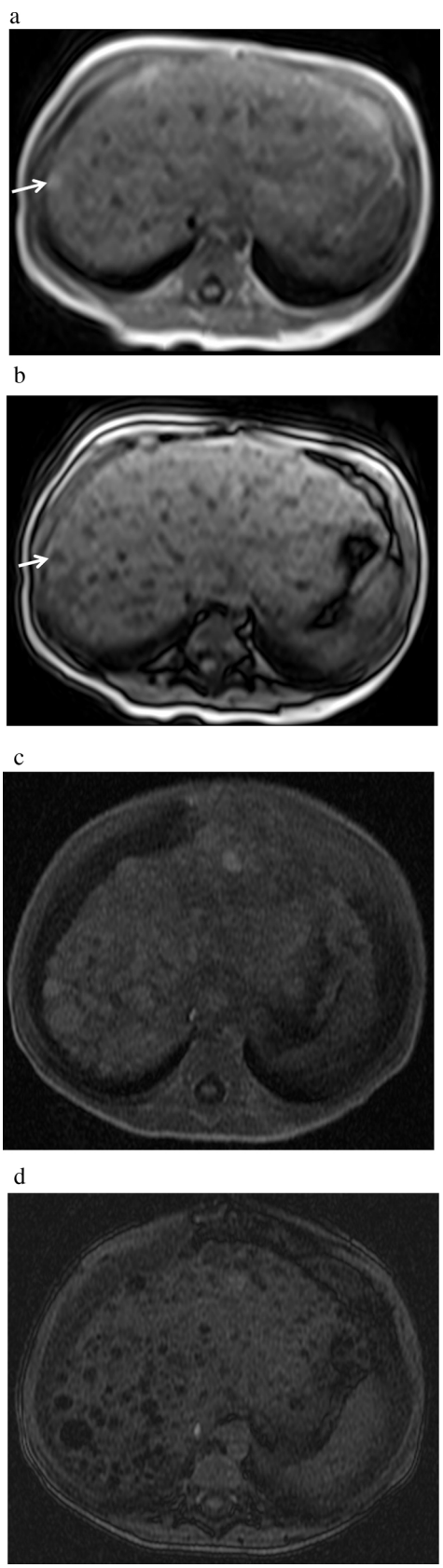

Fig. 4. A-D: Seven-month-old girl with tyrosinemia type 1. **(A)** In-phase and **(B)** out-of-phase MR images show multifocal fat containing lesions (arrow). Out-of-phase MR image shows multiple lesions with signal drop compared with in-phase image consistent with multifocal fat containing lesions. During the follow-up, after 4 months, **(C)** in-phase and **(D)** out-of-phase MR images show that lesions sizes were increased.

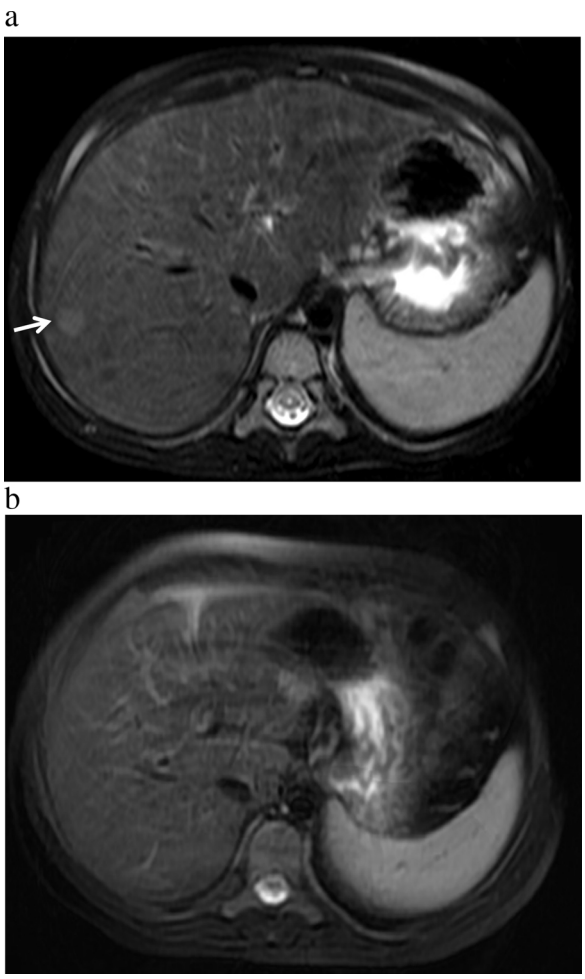

Fig. 5. A, B: Two-year-old girl with tyrosinemia type 1. **(A)** Axial fat-saturated T2-weighted image shows hyperintense lesion in the right liver lobe diagnosed as regenerative nodule (arrow). **(B)** During the follow-up, after seven years, axial fat-saturated T2-weighted image shows that the lesion disappeared.

Funding

This work received no funding or grants.

References

[1] P.A. Russo, G.A. Mitchell, R.M. Tanguay, Tyrosinemia: a review, Pediatr. Dev. Pathol. 4 (2001) 212–221.
[2] P. McKiernan, Nitisinone in the treatment of hereditary tyrosinaemia type 1, Drugs 66 (2006) 743–750.
[3] A. Masurel-Paulet, J. Poggi-Bach, M.-O. Rolland, et al., NTBC treatment in-tyrosinaemia type I: long-term outcome in French patients, J. Inherit. Metab. Dis. 31 (2008) 81–87.
[4] D.L. Day, J.G. Letourneau, B.T. Allan, H.L. Sharp, N. Ascher, L.P. Dehner, W.M. Thompson, Hepatic regenerating nodules in hereditary tyrosinemia, AJR Am. J. Roentgenol. 149 (1987) 391–393.
[5] E. Shteyer, N. Simanovsky, B. Koplewitz, S.H. Korman, Multiple hepatic lesions in a girl with tyrosinemia: not always hepatocellular carcinoma, J. Pediatr. 158 (2011) 513.
[6] Y. Tazawa, M. Kikuchi, I. Kurobane, A. Watanabe, H. Nakai, K. Narisawa, K. Tada, An acute form of tyrosinemia type I with multiple intrahepatic mass lesions, J. Pediatr. Gastroenterol. Nutr. 10 (1990) 536–539.
[7] S.M. Hussain, P.E. Zondervan, J.N. IJzermans, S.W. Schalm, R.A. de Man, G.P. Krestin, Benign versus malignant hepatic nodules: MR imaging findings with pathologic correlation, Radiographics 22 (2002) 1023–1036 discussion 1037-9.
[8] J. Crone, D. Möslinger, O.A. Bodamer, W. Schima, W.D. Huber, E. Holme, S. Stöckler Ipsiroglu, Reversibility of cirrhotic regenerative liver nodules upon NTBC treatment in a child with tyrosinaemia type I, Acta Paediatr. 92 (2003) 625–628.
[9] J. Seda Neto, K.M. Leite, A. Porta, et al., HCC prevalence and histopathological findings in liver explants of patients with hereditary tyrosinemia type 1, Pediatr. Blood Cancer 61 (2014) 1584–1589.
[10] G.C. Mueller, H.K. Hussain, R.C. Carlos, H.V. Nghiem, I.R. Francis, Effectiveness of MR imaging in characterizing small hepatic lesions: routine versus expert interpretation, AJR Am. J. Roentgenol. 180 (2003) 673–680.