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Original Article

Hypergalactosemia in early infancy: Diagnostic strategy with an emphasis on imaging

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Abstract ***Background***: Portosystemic shunt is one of the main causes of persistent hypergalactosemia without enzyme deficiency, but the diagnostic imaging strategy has not yet been established. The purpose of the present study was to establish a diagnostic imaging strategy.
Methods: A retrospective investigation of the clinical and imaging findings of 10 children with persistent hypergalactosemia without enzyme deficiency detected by screening was undertaken.
Results: Abnormal ultrasonography (US) findings were detected in all eight patients with liver disorders. In three patients with citrin deficiency, the combination of fatty liver on US and laboratory evidence of cholestasis led to the diagnosis. In three patients with portosystemic shunt, US on sedation clearly depicted the shunt vessels. The extent was more easily understood on contrast computed tomography (CT). Per-rectal portal scintigraphy with *N*-isopropyl-p-I-123 iodoamphetamine and lung perfusion scintigraphy with ^{99m}Tc macroaggregated albumin were useful for evaluation of portal shunt index and assessment of pulmonary arteriovenous shunt. One patient underwent transarterial coil embolization. In two patients with hepatic tumor, the lesions and its vascularity were clearly demonstrated on US and dynamic CT. In one patient, small shunt index on per-rectal portal scintigraphy suggested no need for treatment. The other patient was treated with a combination of steroid, radiation, and interventional radiology. The etiology remained unknown in two children.
Conclusions: In the assessment of hypergalactosemia, US is the modality of choice. CT is a useful tool for more detailed evaluation of the abnormalities found on US. Per-rectal portal scintigraphy and pulmonary perfusion scintigraphy play an important role in the evaluation of portosystemic shunt. Interventional radiology is sometimes effective.

Key words citrullinemia, galactosemia, hemangioendothelioma, intervention, portosystemic shunt.

Hypergalactosemia detected on newborn screening may be commonly transient and rarely persistent.[1–3] Most newborns with hypergalactosemia need no treatment and show spontaneous resolution without any complications, and it is considered to be transient hypergalactosemia of unknown etiology. The remaining transient hypergalactosemia patients are mainly caused by delayed closure of the ductus venosus and heterozygous enzyme deficiency.[4] In contrast, patients with persistent hypergalactosemia are divided into two groups: patients with and without enzyme deficiency, as shown in Table 1.[5–13] The causes of persistent hypergalactosemia in patients without enzyme deficiency are varied. Among the major causes, intra- or extra-hepatic portosystemic shunt (PSS) is clinically important. Recent clinical investigations demonstrated that evaluation of patients with hypergalactosemia should not be limited to enzymatic analysis, but should also include hepatic imaging.[4] The diagnostic imaging strategy, however, has not yet been established because of its rarity.

We investigated clinical and imaging findings of 10 children with persistent hypergalactosemia without enzyme deficiency to establish a diagnostic imaging strategy in the evaluation in early infancy.

Methods

The subjects consisted of 10 children with persistent hypergalactosemia >3.0 mg/dL galactose concentration on Paigen's method obtained from dried filter-paper blood samples collected for newborn screening. Abnormal values obtained from samples at both 4–8 days and after 9 days of age were defined as persistent. Galactose-1-phosphate (Gal-1-P) uridyltransferase, galactokinase, and uridine diphosphate-galactose (UDP-Gal)-4-epimerase deficiencies were excluded on enzymatic and biochemical analysis.

Initial ultrasonography (US) was done in every patient. Some patients underwent additional imaging evaluations using computed tomography (CT), magnetic resonance imaging (MRI), radioisotope scintigraphy (RI) or X-ray angiography (XA) based on US findings. CT was performed using a multislice CT scanner (Sensation 40/64, Siemens, Munich, Germany) with the following parameters: 120 kV, reference 120 mAs with automated dose

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Table 1 Causes of persistent hypergalactosemia

Enzyme deficiencies (hemozygous/heterozygous)
Galactose-1-phosphate uridyltransferase (type 1)
Galactokinase (type 2)
Uridine diphosphate galactose-4-epimerase (type 3)
Normal enzyme activity
Portosystemic shunt
Intrahepatic
Extrahepatic
Portal hypoplasia/absence
Patent ductus venosus
Liver tumors (hemangioendothelioma, etc.)
Hemangiomatosis
Hepatitis
Citrin deficiency

reduction technique, helical beam pitch 1.0, and collimation 1.25 mm. Multi-phased images were obtained with the dynamic technique. A total of 600 mgI/kg of contrast medium was manually injected with an injection speed of 600 mgI/kg per 15 s (patients 4–6) or 600 mgI/kg per 30 s (patients 7,8) via peripherally inserted i.v. line in the upper extremity. Portal (50 s) and venous (80 s) phase images were obtained for patients 4–6, whereas pre-contrast, arterial (30 s), hepatocyte (60 s), and equivalent (120 s after the beginning of injection) phase images were obtained in patients 7,8. Per-rectal portal scintigraphy and lung perfusion scintigraphy were performed with *N*-isopropyl-p-I-123 iodoamphetamine (I-123 IMP) and ^{99m}Tc macroaggregated albumin (MAA), respectively. MRI was performed using a 1.5 T superconductive unit (Magnetom, Siemens, Munich, Germany).

Clinical manifestations, imaging findings, and the role of diagnostic imaging in clinical decision making were retrospectively analyzed.

Diagnoses

The diagnosis was citrin deficiency (newborn-onset adult-type citrullinemia type 2: CTLN2), PSS, and hepatic arteriovenous malformation (AVM)/hemangioendothelioma (HEM) in three, three and two patients, respectively. The etiology remained unknown in two children. US was the primary modality of choice in every patient. At least one abnormal US finding was detected in eight patients who had an aforementioned liver disorder. Clinical patient profiles are summarized in Table 2.

Patients 1–3

In three children (patients 1–3), homogeneous bright liver with mild hepatomegaly was identified on US (Fig. 1a). These patients also had laboratory evidence of cholestasis such as elevated serum gamma glutamyl transpeptidase (G-GTP) or total bile acid. The combination of fatty liver and cholestasis led us to the tentative diagnosis of CTLN2. Abdominal plain CT was performed to enhance the reliability of the presence of fatty liver (Fig. 1b). Diffuse parenchymal low attenuation supported the presence of severe fatty infiltration of the liver. No further imaging evaluation was done in these patients. Genetic analysis of the mutations of the *SLC25A13* gene encoding citrin confirmed the diagnosis of CTLN2 in these three patients.

Table 2 Clinical and imaging findings of children with persistent hypergalactosemia

No	Gender	Initial Gal (mg/dL)	Diagnosis	US	CT	Per-rectal scintigraphy	Pulmonary perfusion scintigraphy	IVR	Surgery
1	F	10.0	Citrin deficiency	Bright liver	Fatty infiltration	ND	ND	ND	ND
2	M	10.3	Citrin deficiency	Bright liver	Fatty infiltration	ND	ND	ND	ND
3	M	4.8	Citrin deficiency	Bright liver	Fatty infiltration	ND	ND	ND	ND
4	M	5.0	Intrahepatic PSS	Intrahepatic PSS	Intrahepatic PSS	SI = 75%	No shunt	Diagnostic	Ligation
5	F	17.0	Portal hypoplasia	PSS + portal hypoplasia	PSS + portal hypoplasia	SI = 69%	No shunt → (+)	Diagnostic	Liver transplantation
6	M	3.8	Extrahepatic PSS	Anomalous vessels	Extrahepatic PSS	SI = 74%	No shunt → (+)	Coil TAE (B-RTO)	ND
7	M	17.0	HEM	Heterogeneous tumor	A ring-enhanced tumor	SI = 8%	No shunt	ND	ND
8	M	21.8	HEM + AVM?	Large tumor + vessels	Hypervascular tumor	ND	ND	Coil TAE	Ligation
9	M	5.5	Unknown	Normal	ND	ND	ND	ND	ND
10	F	3.3	Unknown	Normal	ND	ND	ND	ND	ND

AVM, arteriovenous malformation; B-RTO, balloon-occluded retrograde transvenous obliteration; CT, computed tomography; Gal, galactose; HEM, hemangioendothelioma; IVR, interventional radiology; ND, not done; PSS, portosystemic shunt; SI, portal shunt index; TAE, transarterial embolization; US, ultrasonography.

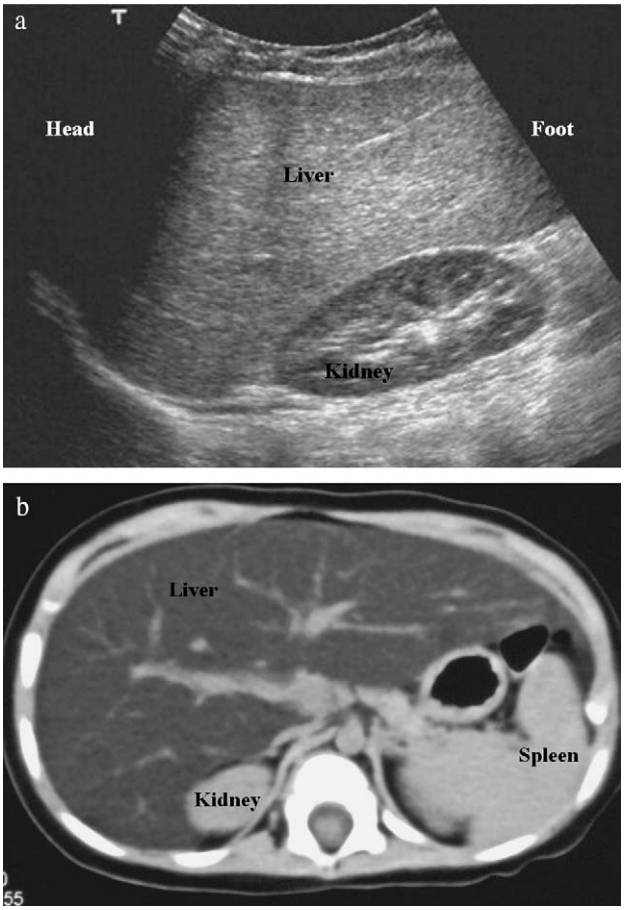

Fig. 1 Citrin deficiency (newborn-onset adult-type citrullinemia type 2: CTLN2). (a) Homogeneous bright liver with mild hepatomegaly identified on ultrasonography. Liver/kidney contrast ratio was exaggerated. (b) Plain computed tomography indicated diffuse fatty infiltration.

Patients 4–6

Portosystemic shunt was identified on US in three children. The type of the shunt was intrahepatic portal vein–inferior vena cava (IVC) shunt in one patient (patient 4) and extra-hepatic portal vein–IVC shunt in two patients (patients 5,6). Portal vein was hypoplastic in one patient (patient 5). US could clearly depict the shunt vessels in every patient (Figs 2a,3a), although the initial US examination without sedation failed to detect any abnormal findings in one patient (patient 6). In the other patients we performed the initial US examination with sedation to avoid motion artifacts on color/power Doppler images. To confirm the diagnosis of PSS and to demonstrate the extent of the anomalous vessels, contrast-enhanced CT was performed. CT clearly depicted the anomalous shunt vessels as good as on CT (Figs 2b,3b). The extent of the anomalous vessels was more easily understood on multiplane and 3-D reconstructions. MRI and contrast-enhanced magnetic resonance angiography (MRA) could depict the anomalous shunt vessels as well, but no additional information to the CT results was obtained.

For the evaluation of the degree of PSS, per-rectal portal scintigraphy with I-123 IMP was done. The per-rectal portal shunt index was calculated as 75% (Fig. 2c), 69%, and 74% in patients 4, 5, 6, respectively. These three children also underwent lung perfusion scintigraphy with ^{99m}Tc MAA for the evaluation of pulmonary arteriovenous (AV) shunt, which is the most important complication of PSS. No evidence of pulmonary AV shunt was identified in the neonatal period. Sequential lung perfusion scintigraphy in patient with hypoplastic portal vein (patient 5) indicated pulmonary AV shunt at 1 year of age (Fig. 4c). Orthotopic liver transplantation was performed to avoid further progress of pulmonary AV shunt.

Although diagnostic necessity was questionable, XA was also performed with general anesthesia for the purpose of evaluation of the possibility of therapeutic intervention. The passage of an i.v. inserted catheter from the IVC to the portal vein confirmed the diagnosis (Figs 2d,3c,4d). In patient 4, because the intrahepatic PSS was very thick and short, we abandoned interventional radiology (IVR) and adopted a surgical treatment (Fig. 2d). In patient 6 the extrahepatic PSS vessels were evaluated to be long enough, curved, and balloon-occludable (Fig. 3d). He underwent balloon-occluded retrograde transvenous obliteration (B-RTO) of the anomalous vessels with metallic microcoils and had a favorable outcome without any serious complications.

Patients 7,8

Hepatic tumor was identified in two patients on US. One of them (patient 7) had a well-defined heterogeneous parenchymal tumor (Fig. 5a). Contrast-enhanced CT was performed to make a diagnosis of the tumor. A ring-enhanced hypervascular tumor was depicted on arterial, portal, and venous phases with minimal feeding and drainage vessels (Fig. 5b). A diagnosis of hepatic HEM was made. Per-rectal portal scintigraphy indicated an 8% of portal shunt index. No pulmonary AV shunt was identified with on ^{99m}Tc MAA scintigraphy. This patient underwent no further diagnostic procedure and required no treatment except careful US observations.

Another (patient 8) had a large heterogeneously high-echoic parenchymal tumor with development of feeding and drainage vessels. Contrast-enhanced CT indicated a hypervascular tumor with neovascular formation (Fig. 6). A diagnosis of hepatic HEM with predominance of AV malformation/fistula was made. Because this patient developed heart failure probably associated with the large intrahepatic AV shunt, per-rectal portal scintigraphy or pulmonary perfusion scintigraphy could not be done. This patient was treated with a combination of steroid, radiation, and IVR with a favorable outcome.

Patients 9,10

No abnormal finding could be found on US in two patients (patients 9,10). Repeated US with sedation were also negative. No further diagnostic imaging evaluation was performed in these patients. Serum galactose concentration remained high only in the first 2–3 months of age, and then normalized before 12 months of age. The etiology remained unknown.

Discussion

Although diagnostic imaging strategy has not yet been established in patients with persistent hypergalactosemia without enzyme deficiency, imaging plays an important role in addition

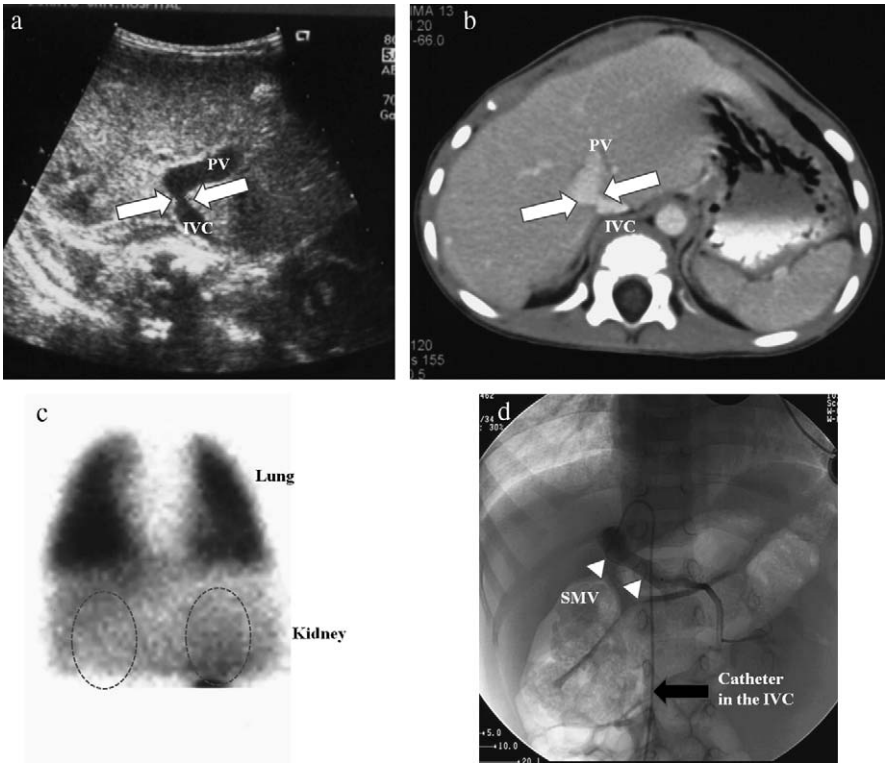

Fig. 2 Intrahepatic portosystemic shunt. (a) Intrahepatic portal vein (PV)–inferior vena cava (IVC) shunt was identified on ultrasonography and (b) contrast-enhanced computed tomography. The direction of blood flow was from the portal vein to the IVC on color Doppler (not shown). (c) Per-rectal portal scintigraphy with *N*-isopropyl-p-I-123 iodoamphetamine demonstrated accumulation in the lung and portal shunt index was calculated as 75%. (d) Diagnostic angiography demonstrated passage of an i.v. inserted catheter from the IVC to the portal vein. SMV, superior mesenteric vein.

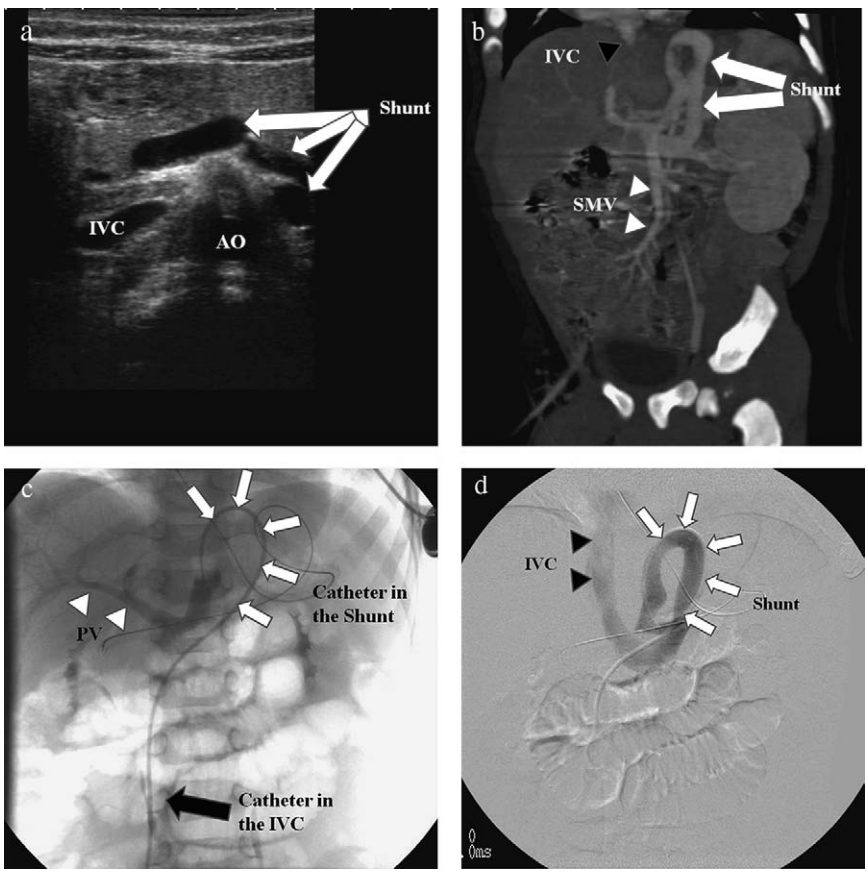

Fig. 3 Extrahepatic portosystemic shunt. (a) Extrahepatic portal vein (PV)–inferior vena cava (IVC) shunt demonstrated on ultrasonography was more easily recognized on (b) multiplane reconstruction of contrast-enhanced CT. (c,d) The shunt vessels were long enough, curved, and balloon-occludable. This patient underwent balloon-occluded retrograde transvenous obliteration with metallic coils. AO, aorta.

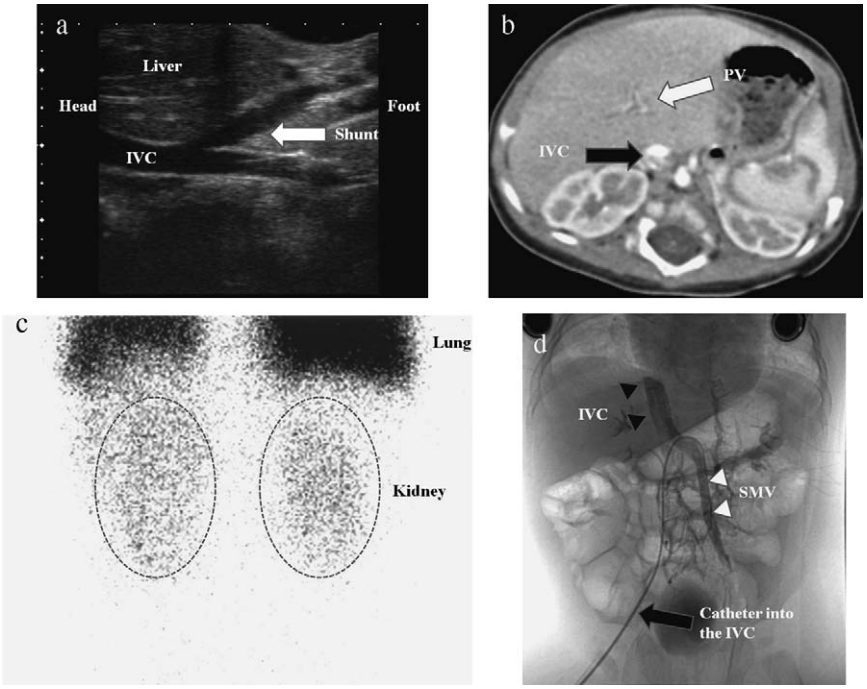

Fig. 4 Extrahepatic portosystemic shunt with portal vein hypoplasia. (a) Extrahepatic portal vein (PV)–inferior vena cava (IVC) shunt was clearly demonstrated on sagittal view on ultrasonography. (b) Contrast-enhanced computed tomography also demonstrated the lesion. (c) Lung perfusion scintigraphy with ^{99m}Tc macroaggregated albumin demonstrated pulmonary arteriovenous shunt at 1 year of age. (d) Angiography confirmed the diagnosis of portosystemic shunt. Also note hypoplastic portal vein. SMV, superior mesenteric vein.

to physical and laboratory examinations because some disorders causing hypergalactosemia are demonstrable on imaging.

Ultrasonography

Undoubtedly, US is the primary modality of choice in every patient because it is easy, useful, non-invasive, and it needs no radiation exposure. The only disadvantage of US is the relatively poor objectivity because it depends on the operator's clinical skills. In the present eight patients out of 10, experienced pediatric radiologists performed the examinations and could detect the abnormalities. In general, routine abdominal US requires no sedation.[14] Authors recommend sedation, however, for patients with persistent hypergalactosemia because color/power Doppler evaluation is very important in US diagnosis of such patients and motion-related artifact may disturb an exact evaluation. Indications for US are detection of tumors, abnormal vessels including patent ductus venosus, and fatty liver, and evaluation of portal vein development.[8,11,12]

Computed tomography

When no abnormality can be found on US with sedation by an experienced operator, no further invasive diagnostic imaging is recommended. Only follow-up US is necessary. If any abnormality is found on US, CT is recommended as the following modality of choice. In patients with US evidence of fatty liver, even several slices with reduced radiation dose (e.g. 40 mAs) can objectively confirm the diagnosis of fatty liver. Contrast enhancement is not necessary. In patients with abnormal vessels or liver tumor, contrast CT is recommended. A total of 600 mgI/kg (2 mL/kg in use of most common 300 mgI/mL media) of contrast medium is usually injected manually with an injection duration of 15–30 s in combination with a following saline injection (dual shot). If available, use of mechanical injector is a good option. Because detection of abnormal vessels or abnormally enhanced tumor is important in such patients, dynamic CT is almost always required. In adults, various methods have been proposed for dynamic CT of the liver and 3-phase scan obtained at around 40 s, 70 s, and 150 s for arterial, portal, and venous phases, respectively, is accepted as one of the optimal methods.[15] Because infants have more rapid blood circulation than adults, we have to adopt earlier exposure times although the method has not yet been established. We recommend 50 s and 80 s for PSS and 0 s, 25–30 s, 50–60 s, and 120 s for liver tumors.

Magnetic resonance imaging

Magnetic resonance imaging and MRA with/without contrast enhancement may depict the abnormalities detected on CT, but no additional information could be obtained in the present patients. We regard MR as an optional modality.

Scintigraphy

The degree of PSS can be evaluated on per-rectal portal scintigraphy. Currently this modality is the only method to assess portal shunt index or fraction. A solution containing I-123 IMP or ^{99m}Tc pertechnetate was instilled into the rectosigmoid colon using a thin multi-purpose tube, and serial scintigrams were taken. The shunt index was determined by liver : lung (I-123 IMP) or liver : heart count ratio (^{99m}Tc pertechnetate).[16–18] The mechanism of this method is simple. Per-rectally injected I-123 IMP or ^{99m}Tc pertechnetate is absorbed through colonic and rectal mucosae, and then returned to the portal vein via superior

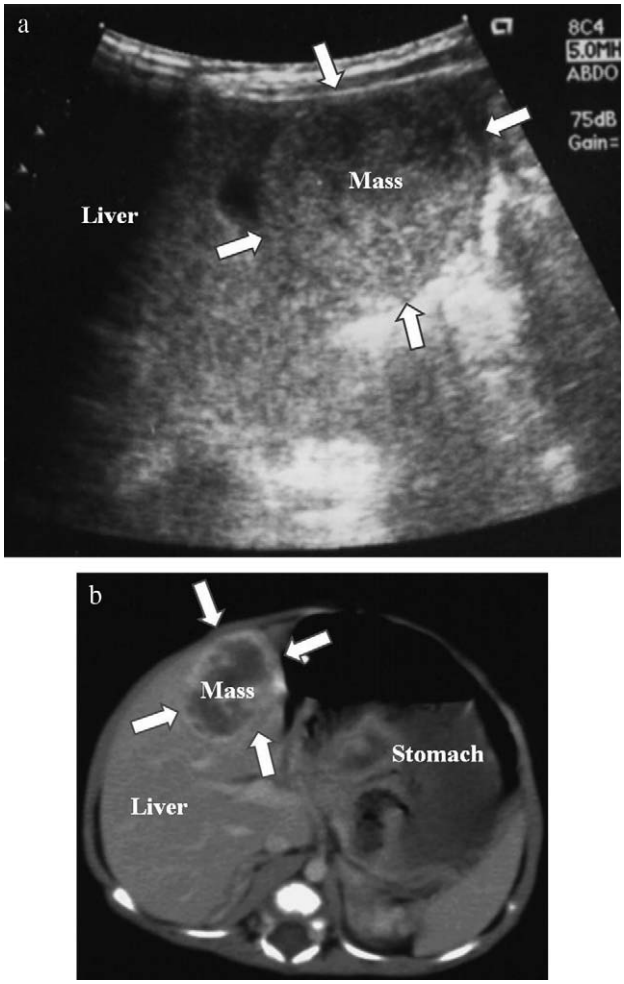

Fig. 5 Hepatic hemangioendothelioma. (a) A well-defined heterogeneous parenchymal tumor was identified on ultrasonography. (b) The tumor was a ring-enhanced hypervascular tumor with minimal feeding and drainage vessels. A diagnosis of hepatic hemangioendothelioma was made.

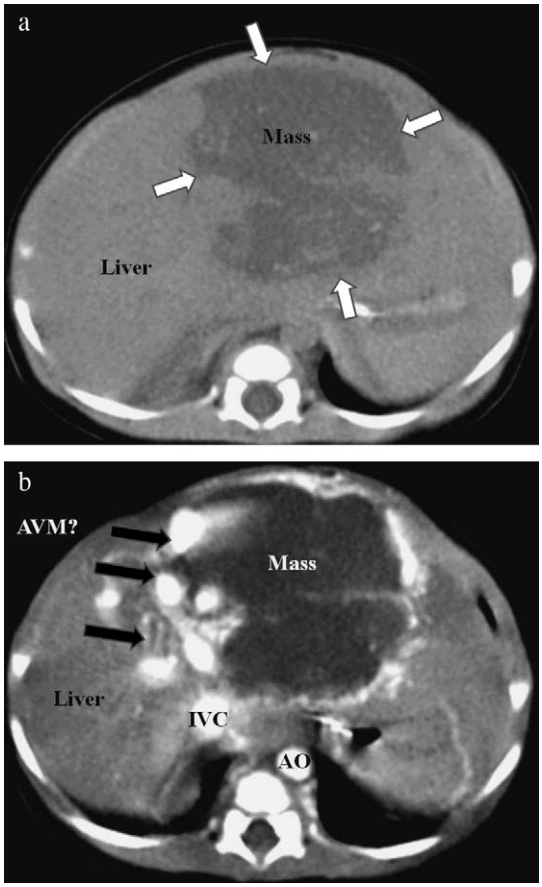

Fig. 6 Hepatic hemangioendothelioma with arteriovenous malformation? (a,b) Plain and contrast-enhanced computed tomography indicated a hypervascular tumor with neovascular formation. This patient was treated with the combination of steroid, radiation, and interventional radiology with a favorable outcome.

and inferior mesenteric veins. If there is no PSS, most of the radioisotopic tracer accumulates in the liver. In patients with PSS a part of the radioisotopic tracer passes through the liver and accumulates directly in the lung (I-123 IMP) or heart (^{99m}Tc pertechnetate). Thus, liver : lung or liver : heart count ratio indicates portal to systemic venous shunt fraction (portal shunt index) despite normal extravascular distribution. We think this non-invasive examination with little radiation exposure should be performed in every patient with PSS.

Complications associated with PSS are not obvious at birth and will progress after birth. They include pulmonary AV shunt, hepatopulmonary syndrome, heart failure, varix, failure to thrive, and hyperammonemia.[19,20] The complications that require the highest attention are pulmonary AV shunt/fistula and pulmonary hypertension because they are irreversible and life-threatening. In patients with PSS a vasoconstrictive agent or a substance toxic to the small pulmonary arterial walls, which is destroyed by the liver in normal subjects without PSS, reaches the pulmonary arteries through PSS and may cause pulmonary arterial wall injury.[21] The presence or absence of pulmonary AV shunt can be approximately demonstrated on transvenous right heart angiography, but pulmonary perfusion scintigraphy with ^{99m}Tc MAA is less invasive and more useful. Intravenously injected ^{99m}Tc MAA usually accumulates exclusively in the lung because MAA does not pass through pulmonary capillaries. If there is a pulmonary AV shunt/fistula, ^{99m}Tc MAA in the pulmonary arteries reaches directly to the pulmonary vein and accumulates in the kidney.[22] Thus, accumulation in the kidney indicates the presence of pulmonary AV shunt. This examination usually requires sedation because a cry of the newborn patient may induce right-to-left shunt via foramen ovale in the interatrial septum and may result in a false positive. US cardiography is also required to exclude congenital heart diseases with right-to-left shunt. We regard pulmonary perfusion scintigraphy with ^{99m}Tc MAA as essential for the evaluation of patients with PSS.

Interventional radiology

In patients with hepatic HEM, surgical resection of the tumor is the best and the most reliable treatment if the lesions are small in size and few in number. If the lesions are large or multiple in more

Table 3 Recommended diagnostic imaging strategy for persistent hypergalactosemia

US with sedation	
Bright liver	Plain CT
Anomalous vessels	Dynamic CT (50, 80 s)
Liver tumor	Dynamic CT (0, 25–30, 50–60, 120 s)
Normal	Repeat US
CT	
Fatty infiltration	Check citrin gene
Hypervascular tumor	Consider surgery or IVR
Anomalous vessels	Per-rectal scintigraphy pulmonary perfusion scintigraphy (^{99m}Tc MAA)
MRI: optional	
Per-rectal scintigraphy	
Shunt index high	Early intervention
Shunt index low	Close observation
Pulmonary perfusion scintigraphy (needs sedation)	
Accumulation in the kidney	Early intervention
Angiography	
Anomalous shunt vessels	
Short, thick, intrahepatic	Surgery
Long, thin, balloon-occludable	B-RTO

B-RTO, balloon-occluded retrograde transvenous obliteration; CT, computed tomography; IVR, interventional radiology; MAA, macroaggregated albumin; MRI, magnetic resonance imaging; US, ultrasonography.

than two or three segments, IVR may be considered. For the treatment of the patients who manifest signs and symptoms of heart failure associated with intrahepatic AV or PV shunt, transarterial coil embolization is the most useful method. In patients with PSS the size and the extent of the anomalous vessels affect the indication of IVR. If the anomalous vessels are short and thick, surgical ligation is recommended. When the anomalous vessels are long, thin, balloon-occludable, and accessible from IVC, IVR may be a safe, least invasive, and most effective method. During the procedure, balloon-occluded method, for example B-RTO, is recommended to avoid coil migration.

In the diagnostic process of patients with persistent hypergalactosemia, a comprehensive knowledge of diagnostic imaging modalities and clinical skill in US to detect abnormalities in the setting of differential diagnosis is required. We propose a diagnostic imaging strategy for the evaluation of patients with persistent hypergalactosemia involving US as the primary modality of choice, as shown in Table 3. Pediatric radiologists should be aware of their responsibility to assess children with persistent hypergalactosemia. In conclusion, in the assessment of patients with persistent hypergalactosemia, US is the primary modality of choice. CT is a useful tool for more detailed evaluation of the abnormalities found on US. Per-rectal portal scintigraphy and pulmonary perfusion scintigraphy play an important role in the evaluation of patients with portosystemic shunt. IVR is sometimes an effective therapeutic option.

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