Aims and objectives

Benign hypervascular liver tumors (BHLT) represent a rather diverse group of diseases. Understanding of vascular tumors in children is much more difficult because of the wide range of terminology used. In the literature often any benign hypervascular liver formation called hemangioma. However, it is necessary to understand that morphologically and clinically hemangiomas in children and adults are different lesions. It is extremely important to make a thorough differential diagnosis of these entities, as they differ not only clinically, but also by medical tactics. To date, there is no uniform classification of benign hypervascular liver formations. Mulliken and Glowacki [2] divided vascular neoplasms in children into two categories: high-flow and low-flow lesions. The high-flow group includes arteriovenous malformations and true neoplasm - infantile hemangioma. Low-speed lesions includes venous, lymphatic and capillary malformations.

Mo and colleagues in the study of 19 types of liver tumors in children have identified two groups of lesions based on their immunoreactivity for GLUT-1. The first group consisted of GLUT-1 positive education. Multiple tumors were usually without necrosis and large vessels were subjected to involution. The authors call these formations infantile hemangiomas of the liver and their peers think of infantile hemangiomas of the skin [3]. The second group consisted of GLUT-1 negative lesions, which were mostly solitary with central necrosis and large peripheral vessels. These formations are not regressed and did not respond to therapy. The authors identified this group as vascular malformations of the liver with capillary proliferation [3]. Other authors identify further GLUT-1 negative lesions that undergo involution [4]. Thus GLUT-1 negative lesions are a heterogeneous group.

For differentiation BHLT we developed a working classification, which is based on the classification of the International Society for the Study of Vascular Anomalies (ISSVA) 1992 [5]. This classification is made clear separation of all vascular anomalies on 2 large groups: tumors and malformations. This classification was developed for skin tumors. We applied it to a benign hypervascular liver formations. (Fig.1) The group of vascular tumors included infantile hemangioma and hepatic adenoma. In group of vascular malformations were arteriovenous fistula, arteriovenous malformations, arterial venous malformations and malformations, capillary malformations. According to many authors, FNG development occurs in the area of vascular malformations, that is why it is in the group of vascular malformations.

The incidence of hemangiomas in newborns is about 2% [6]. However, by the age of 1 year it reaches 12% [7]. Infantile hemangioendothelioma, or infantile hemangioma of the liver, is a vascular tumor and is the most common benign tumor of the liver in children. (Fig. 2) About half of the cases presented solitary formations and half multifocal. Despite the fact that the biological behavior of the tumor is benign, there is potential for serious complications.
About 90% of infantile gemangioendoteliomas are diagnosed in the first 6 months of life, of which one third in the first month [8.9]. Lesions are more common in women. There is no racial predisposition. There is a high propensity for patients with hemihypertrophy and BWS [10]. In most cases, hemangioendothelioma manifest as asymptomatic abdominal mass lesion, but may develop life-threatening complications [8]. Hemangioma affecting other organs, skin, trachea, adrenal glands, dura, according to the literature to occur in 68% of patients with multiple hemangiomas of the liver, but major studies indicate a lower number of 10 - 15% [8].

Infantile hemangiomas have rapid growth phase, which can last up to 1 year age, the plateau phase, which lasts for several months and involution phase up to several years. Clinically, infantile hemangiomas are divided into capillary, cavernous and mixed, containing in itself the first two signs. This division is merely a clinical value, since all 3 type are morphologically identical and are represent one process steps. As often in clinical practice initially the child has a capillary hemangioma, which over time develops into cavernous or mixed. Apparently this is due to stretching of capillary cavities and their transformation into the cavity. [11]

In our opinion it is possible to use the term infantile hemangioma exclusively for GLUT + tumors in young children. For GLUT - tumors and tumors of adults term hemangioma is used.

The second in frequency BHLT in children is focal nodular hyperplasia. FNG is benign epithelial lesion of the liver with a polyclonal proliferation of hepatocytes, Kupffer cells, vascular structures and the biliary tract. Complex structure of the tumor with well differentiated hepatocytes forming nodes separated by fibrous septa, which forms central stellate scar[13]. (Fig. 3)

FNG is 2% of all primary liver tumors in children from birth to 20 years of age [14]. The tumor usually is diagnosed in age of 2 - 5 years [15]. Although it is believed that the tumor develops at the site of vascular malformation, FNG is not reported in infants and young children. There ia a prevalence of FNG in women [13]. Symptomatic cases occurs in 20% [13]. The most frequent symptom of FNG is abdominal pain. Rarely occurs rupture of lesion and bleeding[13]. a-fetoprotein level remains normal [13].

Hepatocellular adenoma, or hepatic adenoma, is rare benign neoplasm of the liver, which is associated with steroid use, particularly oral contraceptives. Morphologically adenoma represented hepatocyte sheets with inclusions of fat and glycogen.

In most cases, hepatocellular adenoma is common in women of reproductive age (mean age 30 years). In children, education is mostly found in girls older than 10 years, most of which took oral contraceptives[16,17]. Adenoma also common in children with Fanconi anemia, which is associated with androgen therapy [18]. There are reports of hepatocellular adenomas in association with certain diseases, such as glycogen storage disease type 1 and 3, galactosemia, diabetes. In addition there is a link with vascular anomalies of liver, such as the absence or occlusion of the portal vein and other hypervascular liver tumors [19,20].

In most cases, benign liver hypervascular lesions are asymptomatic and are incidental findings. However, in certain sizes and localizations they may be symptomatic. Symptoms of various BHLT are nonspecific, so we should consider the entire clinical
picture of the whole group. The most common complaint is pain, occurring usually in subcapsular location of the tumor or due to stretching of the capsule of the liver [12]. Intratumoral bleeding is common for adenomas, which occurs in 10% of patients, or in rare cases, tumor rupture with the development of intraabdominal hemorrhage and hypovolemic shock [19]. Furthermore cholestasis syndrome often occur. There are cases of compression of vascular structures and bile ducts up to the development of portal hypertension and obstructive jaundice [21,22,23]. Extremely rare tumors with extensive compression occurs with the development of adjacent organs or gastro duodenostasis [24, 25]. Changes in the biochemical analysis of blood are non-specific and the most frequent of them are cholestasis syndrome and thrombocytopenia. Development of liver failure in total haemangiomatosis is possible but occurs extremely rare [26]. In children, most often we are faced with the absence of any complaints. Lesions are detected incidentally during diagnostics for other diseases.

For the child with liver masses it is necessary to provide complete physical, laboratory and instrumental examination. At the first place it is necessary to make a differential diagnosis with malignant tumors. As the first line tests biochemical analysis of blood, a-fetoprotein test and abdomen ultrasound with duplex scanning is performed.

Ultrasoundography often possible to establish the nature of lesion, parenchyma, presence or absence of a capsule, topical location, relationship with intrahepatic vessels. (Fig. 4, 5) Ultrasound examination is highly subjective and depends on the doctor performing this study, therefore the published data about the objectivity and accurate survey of the method is quite different.

In the literature there is a large number of publications about the advantages and disadvantages of methods for diagnosis of liver mass lesions. We believe that currently the clinic should be guided by the presence in them of a diagnostic equipment. However, in most cases, the "gold standard" in the diagnosis of liver lesions is an MRI. (Fig. 6,7) For a long time recognized the key role in the diagnosis BHL for angiographic study, but now we consider it necessary to conduct angiographic examination after CT or MRI. Since the latter methods are less invasive and to rule out the need for angiography to a group of patients who did not require endovascular occlusion of the lesion.

The indications for angiographic examination should consider hypervascular liver formation, which requires endovascular treatment, failure to perform a CT scan or MRI or emergency situations that arise at lesion rupture with the development of bleeding. (Fig. 8,9,10)

Question of diagnostic biopsy is disputable. In our practice, we rarely use this method as ultrasound, MRI and laboratory tests allow us a high accuracy in differential diagnosis of lesions. Also needle biopsy of hypervascular liver lesions can lead to bleeding. However, we believe it possible to use the method in difficult cases.
**Fig. 1:** Classification of benign hypervascular liver lesions (how we see it)
Fig. 2: Histology. Infantile hemangioma.
Fig. 3: Histology. Focal nodular hyperplasia.
Fig. 4: Ultrasound. Liver hemangiomatosis.
Fig. 5: Ultrasound. Liver hemangiomatosis.

Fig. 7: CT. FNG.
Fig. 8: Angiography. Liver hemangiomatosis.
Fig. 9: Liver hemangiomatosis.
Fig. 10: Angiography. FNG.
Fig. 6: CT Liver hemangioma.
Methods and materials

Between 2005 and 2012 at the department of endovascular diagnostic and treatment methods of the Russian Children’s Clinical Hospital we have observed 68 children with hypervascular liver formations. (Fig. 11) Of these, 52 with benign tumors. The complex study of children included: blood biochemical test, ultrasonography, angiography, MRI. All lesions were divided: infantile hemangiomas (10), hemangiomas (9), nodular hyperplasias (20), adenomas (7), dysplasias (6). All patients older than 2 years with hemangiomas, dysplasias and FNG endovascular occlusion by hydrogel cylinders (0.5 - 0.6 mm) or occlusive coils was made. (Fig. 12, 13) The postoperative period was uneventful in all cases. As a follow-up was performed ultrasonography at 1, 7, 30 days, 6 and 12 months. Children with a diagnosis of hepatic adenoma, due to the possibility of malignancy undergo surgical resection. Patients with infantile hemangiomas of the liver received medical therapy by propranolol for 6 months under the supervision of a cardiologist and a pediatric surgeon, to control heart rate, blood pressure and conductivity.

Images for this section:
Fig. 11: Range of children with benign hypervascular liver lesions in our clinic 2005 — 2012 y.
Fig. 12: Angiography. Liver hemangioma. Before embolisation.
Fig. 13: Angiography. Liver hemangioma. After embolisation.
Results

In the group of children with hemangiomas, dysplasias and nodular hyperplasia of the liver after endovascular occlusion accumulation of radiopaque drug was not mentioned, or was highly reduced. During ultrasonography for more than 7 days in 30% of cases there was a little blood flow in the periphery of lesion. In the period from 6 months to 1 year active growth of lesion was not mentioned in any observation. In children treated with propranolol we had very good result in regression of hemangiomas during therapy and absence of growth at follow-up 6 months after discontinuation of the drug.

Conclusion

The endovascular occlusion can be successfully used as an alternative to surgical treatment in children with malformation of the liver and patients with nodular hyperplasia of the liver. In our study, the method proved to be an effective, low-impact and safe. Patients with infantile hemangiomas of the liver is a promising application of the drug propranolol, because it allows to achieve good therapeutic effect with good tolerability and the almost complete lack of serious side effects.

Personal information

References