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Hepatomegaly as the first symptom of malignant solid tumors in children

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Abstract:

Introduction: Hepatomegaly is a physical symptom that may suggest primary liver disease, or it may be present as a component of the generalized disorder. One of uncommon reasons of hepatomegaly, which occur in children of all ages, but most common in infants and toodlers, are primary and metastatic neoplasms, such as hepatoblastoma (HB) and neuroblastoma (NB).

The aim of this work is to prove how significant implementation of appropriate diagnostics after detecting hepatomegaly in a child is by presenting an example of two patients' medical history.

Cases report: A 3-month-old girl and a 2-year-old boy were admitted to the Department of Pediatric Hematooncology because of the tumors, which were detected in abdominal ultasound examinations. The examinations were performed in order to find the causes of growing abdominal circumferences observed by the parents and significant hepatomegaly, which were shown in physical examination of both children. A tumor of the right adrenal gland with numerous metastatic changes in the liver was detected in the girl and a single tumor coming out most likely from the liver was revealed in the boy. Laboratory tests have shown a significant increase in the levels of tumor markers: NSE in the girl (51 μg/l) and AFP (327 830 U/ml) in the boy. On the basis of the performed tests' results, the girl was suspected to have NB with liver metastases and the boy appeared to have HB with lung metastases, inferior vena cava and right hepatic vein invasion.

Conclusions: Attention should be paid to palpation and percussion examination of the abdomen in order to detect hepatomegaly at the earliest possible stage. It is important to implement appropriate diagnostics after detecting the enlargement of the liver in a child, because this symptom may be a sign of developing dangerous tumor process.

Keywords: hepatomegaly, children, hepatoblastoma, neuroblastoma

Introduction

Hepatomegaly is a physical symptom that may suggest primary liver disease, it may be also present as a component of the generalized disorder [1, 2]. The liver edge that is palpable 3.5 cm below the costal margin in newborns or 2 cm in older children should raise the suspicion of hepatomegaly [1]. However, conditions that cause pushing the liver down and thereby only imitate hepatomegaly (such as accumulation of fluid or air in the thorax, bronchiolitis, bronchial asthma, retroperitoneal mass, choledochal cyst, or perihepatic abscess, narrow chest walls or pectus excavatum) should be excluded [1, 3, 4].

The mechanisms involved in the onset of liver enlargement are varied and complex, and include inflammation, excessive storage, cellular infiltration, congestion and obstruction of biliary flow [1, 2]. The inflammation may occure due to toxins, radiation, autoimmune disease, Kupffer cell

hyperplasia, infections from viruses, bacteria, fungi, and parasites. Products that can accumulate in the liver and cause its enlargement in the storage mechanism are: glycogen, fats, metals and abnormal proteins. The cellular infiltration may appear as a result of primary tumors of the liver or metastatic disease, parasitic cysts, extramedullary hematopoiesis and hemophagocytic. Congestive heart failure, restrictive pericardial disease and hepatic vein thrombosis (Budd-Chiari) are the causes of hepatomegaly in the mechanism of congestion. Obstruction of biliary flow may occure due to tumors outside the liver or problems of the biliary system such as biliary atresia, choledochal cysts, and cholelithiasis [1].

The most frequent causes of hepatomegaly in children regardless of their age are: biliary tract obstruction, congestive heart failure, drugs, sepsis, systemic infections and viral hepatitis (they are most commonly caused by TORCH infections in newborns). Maternal diabetes, malnutrition, metabolic disorders, parenteral nutrition, pseudohepatomegaly and storage diseases can also be considered as the most common causes of liver enlargement in newborns, such as anemias, cystic fibrosis, leukemia, lymphoma, obesity, parasitic infections and parenteral nutrition in older children and adolescents [1].

One of uncommon reason of hepatomegaly, which occur in children of all ages, but most common in infants and toodlers, are primary and metastatic neoplasms [1, 5, 6]. International consensus classification for pediatric liver tumors includes following categories: epithelial tumors (e.g. epithelial variant of hepatoblastoma), mixed epithelial and mesenchymal tumors (e.g. mixed variant of hepatoblastoma), mesenchymal tumors, germ cell tumors and metastatic or secondary tumors (eg. neuroblastoma) [7].

Hepatoblastoma (HB) is the most common primary hepatic tumor in children (it accounts for about 37% of this group) and represents a little over 1% of cases of cancer in the pediatric population [6, 8]. The disease usually appears in the fourth year of life [5, 6]. Boys develop this neoplasm more often than girls – the men: female ratio is around 2: 1 [9]. HB is an embryonic tumor that is probably formed from hepatoblasts present in the liver during embryonic life [10]. Some conditions, such as familial adenomatous polyposis, Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome, Prader-Willi syndrome, fetal alcohol syndrome, hemihyperplasia, total parenteral nutrition related cholestasis, type 1 glycogen storage disease, Gardner's syndrome, very low birth weight (VLBW - defined as <1500 g), may predispose to the development of HB [6, 10].

Neuroblastoma (NB) is the most common extracranial solid tumor in childhood [11]. It accounts for 8–10% of all pediatric cancers and 15% of all cancer-related deaths in the pediatric population [6, 12]. The average age at the time of diagnosis is 19 months [11]. NBs are

embryonal tumors which are formed from cells of the sympathetic nervous system. The most common place of their development are adrenal glands, but they can also appear in the neck, chest and pelvis [6]. Familial NB syndrome occurs in 1-2% of children with NB and is caused most commonly by mutations in the ALK, PHOXB2 and GALNT14 genes. The Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome, Sotos syndrome, neurofibromatosis type 1, Costello syndrome, Noonan syndrome are other known risk factors for developing NB [6, 11]. In children, especially infants, hepatic metastasis is sometimes detected in NB. Patients with NB younger than 18 months of age with metastases limited to skin, liver, and bone marrow without cortical bone involvement, but with no limitation on the size of the primary tumor, belong to the group called a stage MS and have better outcomes than infants with metastases to other organs [13]. The MS stage accounts for about 5.3% of all NB cases and can undergo spontaneous regression without any treatment [11, 14, 15].

The purpose of this work is to present, on the example of medical history of two patients, how significant implementation of appropriate diagnostics after detecting hepatomegaly in a child is, because it may be a sign of development of a malignant neoplasm.

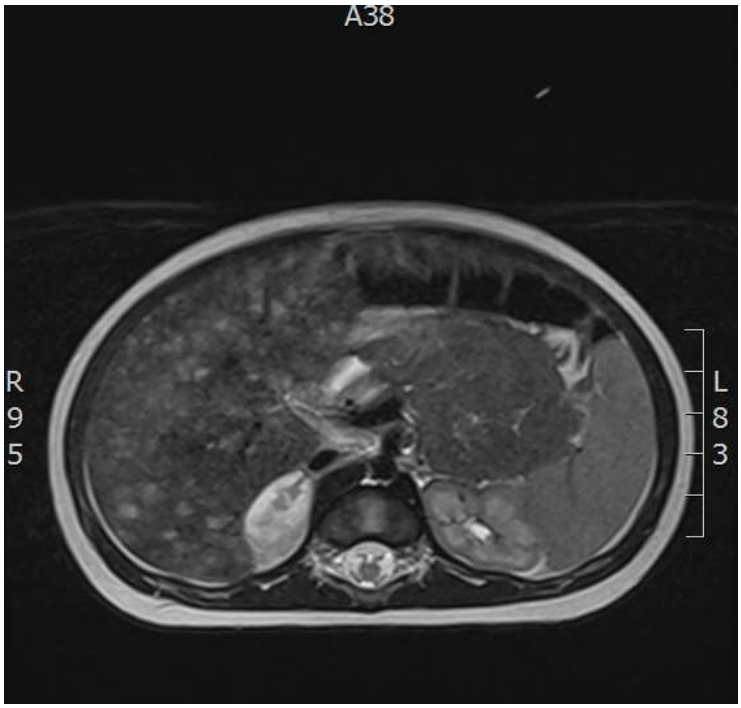
Cases report

Parents, who were concerned about the growing abdominal circumference of their 3-month-old daughter, came to the family doctor with their child. Parents of a 2-year-old boy arrived to the hospital emergency department with the same problem. The boy also complained about the pain of the right lower limb. Physical examination showed significant hepatomegaly in both children and thickening of the right thigh and swelling of the right foot in the boy. The abdominal ultrasound examination was performed in both children. A tumor of the right adrenal gland with numerous metastatic changes in the liver was detected in the girl and a single tumor coming out most likely from the liver was revealed in the boy. The children were admitted to the Department of Pediatric Hematooncology. Laboratory tests showed a significant increase in the levels of tumor markers: in the girl NSE level was 51 μg /l (norm - 18 μg /l) and in the boy AFP level was 327 830 U/ml (norm - 8 U/ml). The MRI with cotrast agent administration was performed in the girl and demonstrated tumor with size 21 x 13 x 24 mm and smooth borders, which was hypointense on T1-weighted images and hyperintense on T2-weighted images in the right adrenal gland. After administration of the contrast agent, quite intensive heterogeneous amplification of the tumor's signal could be observed. Numerous metastatic lesions in the liver with diameters up to approximately 7 - 8 mm have been revealed in the study (Pic. 1). The right kidney was compressed and dislocated by enlarged adrenal gland. No pathological changes

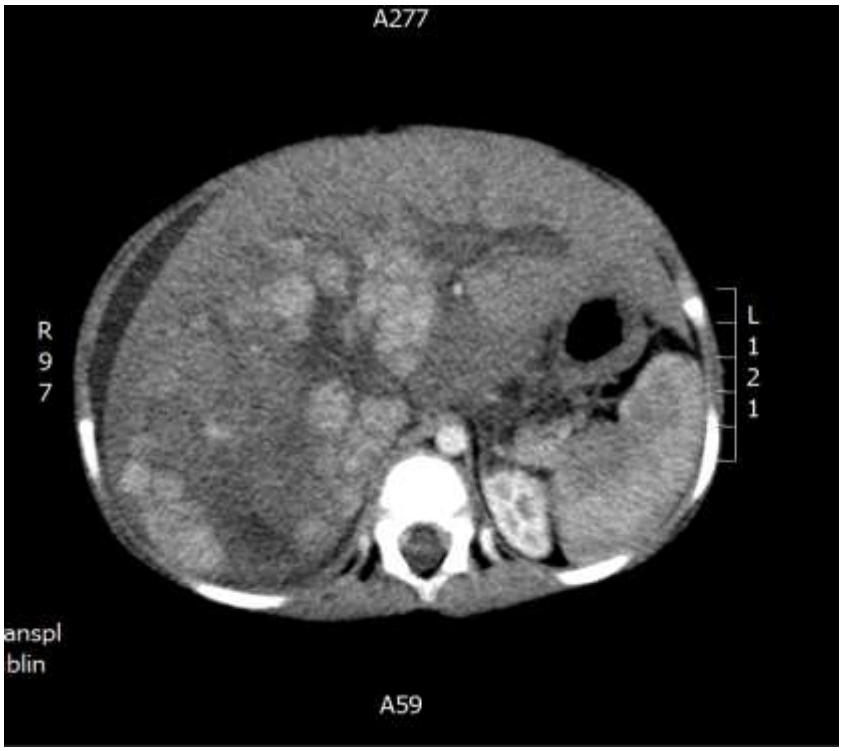
were shown in the left adrenal gland. The CT scan, which was performed in the boy, showed lobulated and heterogeneus tumor in the right lobe of the liver (Pic. 2). The described tumor with dimensions of 92 x 105 x 160 mm was characterized by the presence of numerous small calcifications and fluid areas and its signal was strengthened after the administration of the contrast agent. The right kidney was dislocated in the caudal direction, the aorta has been moved to the left and the head of the pancreas was compressed under the pressure of the tumor. At the site of hepatic venous drainage, the tissue masses occupying the right hepatic vein and the inferior vena cava were visualized. The entire liver was significantly enlarged and surrounded by a layer of fluid about 11 mm thick. Numerous metastatic changes were demonstrated in both lungs. On the basis of the performed tests' results, the girl was suspected to have neuroblastoma with liver metastases and the boy appeared to have hepatoblastoma with lung metastases, inferior vena cava occupation and right hepatic vein invasion.

Histopathological examinations of hepatic sections taken during the surgery of removing the right adrenal gland confirmed previous diagnoses in the girl. No amplification of the N-myc gene or structural chromosomal aberrations were found in the performed cytogenetic tests. Based on the clinical picture, the child was classified as low-risk (MS group) and adjuvant chemotherapy with etoposide and carboplatin was initiated. The abdominal MRI scan revealed regression of metastatic changes in the liver. Serum NSE level gradually decreased and eventually reached the norm.

The boy was diagnosed with hepatoblastoma and neoadjuvant chemotherapy according to the SIOPEL 4 scheme was introduced. A control CT scan performed between chemotherapy cycles showed regression of tumor size, the dimensions of which were about 65 x 62 x 98 mm. Tumor morphology remained similar as in the previous study. There was no more compression of the tumor on neighboring structures - the right kidney, the head of the pancreas and the aorta. Changes in the inferior vena cava were still visible. The liver was surrounded by a layer of fluid about 6 mm thick. In the lungs, regression of metastatic lesions was noted. The remaining two lesions were located at the top of the left lung (2 mm in diameter) and subpleurally in the sixth segment of the left lung (3 mm in diameter). The boy is still in the middle of chemotherapy.



Pic. 1 Tumor of the right adrenal gland with hepatic metastasis in MRI examination (the girl).



Pic. 2 Tumor in the right lobe of the liver in CT scan (the boy).

Discussion

Hepatomegaly is a pretty disquieting symptom in infants and toddlers, because it is more likely than in adults to indicate the development of tumors, although the neoplasms still remain one of the rarer reasons for liver enlargement in pediatric population [1, 5, 6]. Therefore it is highly significant to estimate the liver span by palpation-percussion method during a physical examination. This method is reasonably accurate diagnostic tool in majority of children because it can detect hepatomegaly with ultrasound-like sensitivity - the size of the liver measured by the palpation and percussion method is about 0,5 cm lower than obtained in ultrasonography [4].

Many causes of the liver enlargement should be taken under consideration after detection of this condition in a child, that is why more precise imaging examinations and laboratory tests need to be performed [1]. Ultrasound examination of the abdomen is the first step for identification of etiology of hepatomegaly, because it is able to distinguish the presence of a liver tumor from generalized liver enlargement [16]. The mere presence of a tumor without an already established diagnosis should form the basis for further imaging with computed tomography (CT) or magnetic resonance imaging (MRI) [10, 16]. The triphasic contrast-enhanced abdominal CT and the MR with hepatocyte specific contrast administration are gold standards of hepatic imaging [10]. HB presents as a sharply circumscribed mass that is slightly hypoattenuating in relation to the adjacent liver parenchyma on both CT and MR. On MR, it is hypointense on T1-weighted images and hyperintense on T2-weighted images relative to adjacent liver parenchyma [17]. NB may be of variable size, but in most cases it is present as large, particularly those in the abdomen and pelvis. On CT image tumors are often lobulated, heterogeneus with areas of haemorrhage and necrosis between areas of anhancing tumor tissue and without an identifiable capsule. More than 90% of them demonstrate calcifications on CT examination. On MR, it is characteristic for NB to have prolonged T1 and T2 relaxation times with low signal on T1 and high signal on T2. The CT and MR examinations usually show a displacement of other organs and vessels caused by NB growth, however invasion *per se* of blood vessels is rare [18].

Tumor markers such as α-fetoprotein (AFP), neuron-specific enolase (NSE), lactate dehydrogenase (LDH), iron-binding protein – ferritin, may be also helpful in diagnosis after the detection of pathological mass in the liver [19-22]. AFP is produced by HB and secreted into the bloodstream. Elevated levels of AFP (>10 ng/ml) in younger children with hepatomegaly may be indicative for developing HB. Changes in AFP levels are a reliable predictor of outcome and may be used to identify poor treatment responders, who should be qualified for alternative

therapies. In some medical centers the assessment of serum AFP levels is routinely performed every 3 months in children suffering from Beckwith-Wiedemann syndrome and hemihyperplasia to screen for HB [19]. However, AFP is not particularly specific and it should be remembered that its level may also be increased in hepatocellular carcinoma, some subtypes of germ cell tumors as well as in uncomplicated chronic liver disease, after hepatic surgery or in certain conditions such as hereditary ataxia telangiectasia. A physiologically elevated level of AFP can be observed in infants up the age of 6 months [19, 22]. There are no specific markers for NB, but increased serum levels of NSE (>100 ng/ml), LDH (>1500 U/ml), ferritin (>142 ng/ml) have been shown to significantly correlate with advanced stage of NBs and poor patient survival rates. Increased levels of catecholamine metabolites including dopamine (DA), vanillylmandelic acid (VMA) and homovanillic acid (HVA) in the collected urine is also valuable in diagnostics when NB is suspected [20, 21].

Imaging examinations and laboratory tests may facilitate the identifications of liver tumors, but usually biopsy or resection for histological diagnosis becomes necessary. Many research prove that biopsy in HB is safe and reliable. Currently a closed needle biopsy under ultrasonographic or laparoscopic guidance is recommended in such cases. When HB occurs in just one or two liver sections, laparotomy and resection at diagnosis are preferred [10, 22]. It is not required to perform a tumor biopsy in children aged from 6 months to 3 years with a very high AFP serum level and diagnostic imaging results characteristic for HB [23]. Tumor biopsy allows to perform histopathological and cytogenetic examination, the results of which affect further treatment and prognosis. Histological examination of HB may distinguish its subtypes, which affect different prognosis. For example, pure fetal histology of the tumor herald a favorable prognosis because of very little mitotic activity whereas small cell undifferentiated subtype may portend a poor outcomes [10]. Cytogenetic examination is particularly important in the diagnosis of NB - it detects the presence of N-myc proto-oncogene amplification, which is a very important prognostic factor. N-myc amplification, which means more than 10 copies of the gene per cell, is associated with advanced stages of the disease, rapid tumor progression and poor results. Other structural chromosomal aberrations (such as deletion of the short arm of chromosome 1 and deletion of the long arm of chromosome 11), which affect the prognosis, may be detected in cytogenetic examination [15].

In conclusion, such serious symptom as hepatomegaly should not be neglected in children. Attention should be paid to scrupulous palpation and percussion examination of the abdomen in order to detect hepatomegaly at the earliest possible stage. It is important to implement

appropriate diagnostics after detecting the enlargement of the liver in a child, because this symptom may be a sign of a developing dangerous tumor process.

References

[1] Wolf AD, Lavine JE. Hepatomegaly in Neonates and Children. Pediatrics in Review 2000; 21(9):303-310.

[2] Walker WA, Mathis RK. Hepatomegaly: An Approach to Differential Diagnosis. Pediatric Clinics of North America 1975; 22(4):929-942.

[3] Carpenterei U, Gustavson LP, Leach TM, Bunce H. Liver size in normal infants and children. South Med J. 1977; 70:1096–1097.

[4] Amatya P, Shah D, Gupta N, Bhatta NK. Clinical and Ultrasonographic Measurement of Liver Size in Normal Children. Indian J Pediatr 2014; 81(5):441–445.

[5] Meyers RL. Tumors of the liver in children. Surgical Oncology 2007; 16:195–203.

[6] Scollon S, Knoth-Anglin A, Thomas M, Turner JT, Wolfe Schneider K. A Comprehensive Review of Pediatric Tumors and Associated Cancer Predisposition Syndromes. J Genet Counsel 2017; 26:387–434.

[7] Lopez-Terrada D, Alaggio R, DeDavila MT et al. Towards an international pediatric liver tumor consensus classification: Proceedings of the Los Angeles COG International Pathology Pediatric Liver Tumors Symposium. Mod Pathol. 2014; 26:19–28.

[8] Rozell JM, Catanzano T, Polansky SM, Rakita B, Fox L. Primary Liver Tumors in Pediatric Patients: Proper Imaging Technique for Diagnosis and Staging. Seminars in Ultrasound, CT and MRI 2014; 35(4):382–393.

[9] Spector LG, Birch J. The epidemiology of hepatoblastoma. Pediatr Blood Cancer 2012; 59:776–779.

[10] Rebecka L. Meyers , Piotr Czauderna , Beate Häberle and Eiso Hiyama. Liver Tumors in Children. [in:] Robert Carachi, Jay L. Grosfeld. The Surgery of Childhood Tumors. London: Springer-Verlag Berlin Heidelberg; 2016.

[11] Irwin MS, Park JR. Neuroblastoma Paradigm for Precision Medicine. Pediatr Clin N Am 2015; 62:225–256.

[12] Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis and treatment. Pediatric Clinics of North America 2010; 55:97–120.

[13] Pinto NR, Applebaum MA, Volchenboum SL et al. Advances in Risk Classification and Treatment Strategies for Neuroblastoma. Journal of Clinical Oncology 2015; 33(27):3008-3017.

[14] van Noesel MM, Hählen K, Hakvoort-Cammel FG, Egeler RM. Neuroblastoma 4S - A Heterogeneous Disease with Variable Risk Factors and Treatment Strategies. Cancer 1997; 80(5):834-43.

[15] Davidoff AM. Neuroblastoma. Seminars in Pediatric Surgery 2012; 21:2-14.
[16] Shelmerdine SC, Roebuck DJ, Towbin AJ, McHugh K. MRI of paediatric liver tumours: How we review and report. Cancer Imaging 2016; 16(1):21.
[17] Chung EM, Cube R, Lewis RB et al. From the archives of the AFIP: Pediatric liver masses: radiologic-pathologic correlation, benign tumors. Radiographics 2010; 30:801–826.
[18] Hiorns MP, Owens CM. Radiology of neuroblastoma in children, Eur Radiol 2001; 11:2071-2081.
[19] Murray MJ, Nicholson JC. α-Fetoprotein. Arch Dis Child Educ Pract Ed 2011; 96:141–147.
[20] Ishola TA, Chung DH. Neuroblastoma. Surgical Oncology 2007; 16:149–156.
[21] Mullassery D, Losty PD. Neuroblastoma. Paediatrics and Child Health 2016; 26(2):68-72.
[22] Fernandez-Pineda I, Cabello-Laureano R. Differential diagnosis and management of liver tumors in infants. World J Hepatol 2014; 6(7):486-495.
[23] Czauderna P, Otte JB, Aronson DC et al. Guidelines for surgical treatment of hepatoblastoma in the modern era – recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). Eur J Cancer 2005; 41:1031-1036.