Original papers

Med Ultrason 2022, Vol. 24, no. 3, 284-289
DOI: 10.11152/mu-3454

Contrast-enhanced ultrasound of adrenal hemorrhage: a helpful problem solving tool

Maciej Piskunowicz[1], Joanna Stefanowicz[2], Tomasz Batko[3], Misun Hwang[4], Dominik Świętoń[5], Arkadiusz Szarmach[5], Susan J Back[4], Wojciech Kosiak[3]

[1]Department of Radiology, Medical University of Gdansk, Poland, [2]Department of Paediatrics, Haematology, and Oncology, Medical University of Gdansk, Poland, [3]Ultrasound and Biopsy Diagnostics Lab at the Clinic of Pediatrics, Hematology and Oncology, Medical University of Gdansk, Poland, [4]Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA., Perelman School of Medicine, Philadelphia, Pennsylvania, USA, [5]2nd Department of Radiology, Faculty of Health Sciences, Medical University of Gdansk, Gdansk, Poland

Abstract

Aims: A focal lesion in the region of the adrenal gland in a newborn often requires further assessment. Ultrasound (US) is the initial imaging method of choice in young children as it does not use radiation or require sedation and it has excellent spatial resolution. In this case series, we present contrast-enhanced ultrasound (CEUS) as a problem-solving tool in the evaluation of neonatal adrenal lesions. **Material and methods:** The imaging and medical records of five patients with adrenal lesions were retrospectively reviewed. All patients underwent US as an initial examination and all had US follow-up. Additionally, two patients had MRI examinations. CEUS was performed in all patients as a follow up examination. The enhancement characteristics of the adrenal masses on CEUS were analyzed with the use of VueBox software. In addition, qualitative analysis of the cine loops for the presence of vascularization within the lesions was performed by consensus between two radiologists. **Results:** The presence of an adrenal hematoma was correctly detected and characterized by CEUS in all five cases using VueBox perfusion analysis. Adrenal hematomas had no internal perfusion and flat time intensity curves. **Conclusion:** The quantitative and qualitative CEUS assessment of the mass can distinguish hemorrhage from a malignant lesion. Based on our findings, CEUS could serve as an alternative diagnostic tool to magnetic resonance imaging in the diagnosis of slowly resolving NAH lesions.

Keywords: CEUS; adrenal gland; children; neonatal adrenal hemorrhage; neuroblastoma

Introduction

The neonatal adrenal hemorrhage (NAH) is the most frequent cause of an adrenal mass in newborns with an incidence ranging from 1.9 to 5.5 per 1000 live births [1,2]. NAH is associated with a difficult delivery, hypoxia or asphyxia, sepsis, large birth weight and infants of diabetic mothers.

It is often incidentally diagnosed as most NAH lesions are small and asymptomatic. Clinical symptoms include persistent jaundice, anemia, poor feeding, vomiting, palpable flank mass, swelling and bluish discoloration of the scrotum. Adrenal insufficiency or shock can be associated with large lesions. Ultrasound (US) with color and power Doppler is the modality of choice for the diagnosis and follow-up of adrenal hemorrhage. However, the final diagnosis of some NAH lesions cannot be established exclusively on baseline and follow-up US examination. In these instances, magnetic resonance imaging (MRI) may be performed for differential diagnosis. Given that neuroblastoma (NB) is the most common solid neoplasm

Received 02.10.2021 Accepted 23.01.2022
Med Ultrason
2022, Vol. 24, No 3, 284-289
Corresponding author: Maciej Piskunowicz
Department of Radiology,
Medical University of Gdansk,
7 Debinki Street, 80-291 Gdansk, Poland
Phone: +48583493680
Fax: +48583493690
E-mail: mpiskunowicz@wp.pl

in neonates and infants and 90% of congenital NBs are located in the adrenal glands [3,4], it is essential to distinguish between NAH and NB. Contrast-enhanced ultrasound (CEUS) with the ability to characterize the vascularity of the adrenal lesion in real-time may play an important role in the diagnostic pathway. CEUS is able to depict tiny vessels with low-velocity blood flow that are difficult to resolve using Doppler techniques. The aim of this case series was to demonstrate the role of CEUS in the characterization of NAH. Up to today, there are only a few publications describing the current experience in pediatric CEUS of the adrenal glands [5-7].

Material and methods

The imaging and medical records of six patients with adrenal lesions from the Medical University of Gdansk were retrospectively reviewed (Table I). The final diagnosis in all cases of adrenal hemorrhage (patients 1-5) was based on US follow-up and CEUS examination and in patient 6 on the surgical specimen. All patients underwent US as an initial examination and five of them had US follow-up, including CEUS. Additionally, patient 1 and patient 6 had MRI examinations. The CEUS studies were approved by the Institutional Review Board and written informed consent was obtained from the parents. The CEUS examinations were performed using Philips iU22 US unit (Philips Medical Systems, Bothell, WA, USA), convex probe (C5-1), and xMATRIX probe (X6-1) without sedation. The ultrasound contrast agent (UCA) SonoVue (Bracco, Italy) was used in all cases and the dose ranged from 0.1 ml to 0.3 ml per injection. The specific doses for each patient are presented in Table I.

The enhancement characteristics of the adrenal masses on CEUS were analyzed for the purposes of research on a separate work station with the use of VueBox software (Bracco Research, Geneva, Switzerland). Regions of interest (ROI) were manually placed inside the adrenal mass, on DICOM cine loops, in a position least affected by patient motion (i.e. respiration). The software analyzes the perfusion and presents parametric color-coded maps with a linearized time-intensity curve (TIC). In brief, the software assigns different colors as a heat map to indicate the amount of blood flow in each pixel within the region of analysis, and the time-intensity curves are created. The absolute peak enhancement (PE), which is

Table I. Demographic, clinical and imaging data of six children who underwent contrast-enhanced ultrasound (CEUS) evaluation for adrenal lesions.

Patient number	Gender	Final diagnosis	CEUS examination		Ultrasound examinations	
			Age at CEUS	UCA dose (ml); number of injections	Age at US	Lesion size length x height (mm)
1	M	Hematoma	2m2d	0.2; 1	1m7d	18x16
					1m18d	18x16
					1m28d	16x9
					3m13d	7.7x3.5
					7m6d	no lesion
2	M	Hematoma	4m1d	0.2; 1	12d	25x22
					2m20d	22x19
					3m18d	17.5x8.3
3	M	Hematoma	8m17d	0.3, 0.1; 2	1m6d	30x15
					1m15d	30x16
					3m21d	21x12
					8m6d	21x22
					1y4m18d	6x5
					1y7m26d	6x6
					2y6m25d	7x5x5
					3y24d	no lesion
4	M	Hematoma	1m	0.1; 1	4d	30x25
					23d	31x28
					3m10d	10.8x6.5
					4m28d	no lesion
5	F	Hematoma	1m9d	0.1; 1	30d	30x20
					1y2d	13x7
					1y3m25d	11x7
					1y10m5d	8.5x5
6	M	Ganglioneuroma	6y7m3d	0.3, 0.2; 2	6y6m26d	25x22

F – female; M – male; ml – milliliter; mm – millimeter; d – day; m – month; y – year; UCA – ultrasound contrast agent; US – ultrasound

an expression of echo-power signal over the time- and displayed in arbitrary units (a.u.), was calculated automatically in the ROI. In addition, qualitative analysis of the cine loops (frame-by-frame) for the presence of vascularization within the lesions was performed by consensus between two radiologists (M.P. and W.K. with 10 and 18 years of experience in CEUS, respectively). For the qualitative analysis the longest recorded cine loops, without artifacts, including all phases of enhancement were selected. The lesion enhancement in the arterial, venous, and delayed phases were recorded.

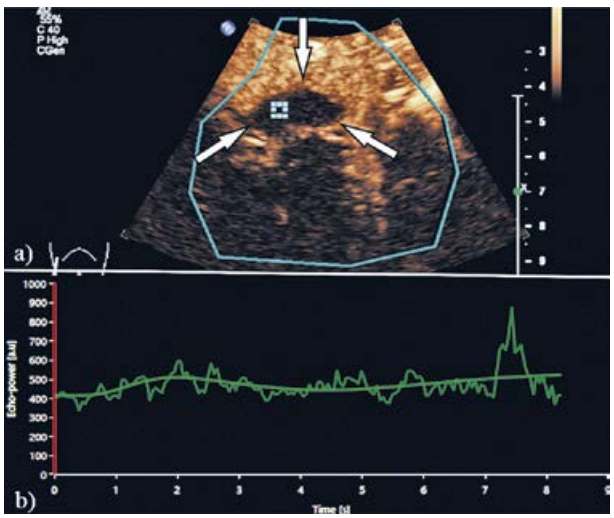

Fig 1. Results of the software perfusion analysis for patient 4 (1-month-old boy): a) CEUS of neonate with adrenal hemorrhage (white arrows) in sagittal plane, inside selected region of interest (small blue squares) surrounded by blue line of automatic motion correction; b) linearized time-intensity curve of perfusion – echo-power signal over the time-course with mean of the 414 arbitrary units.

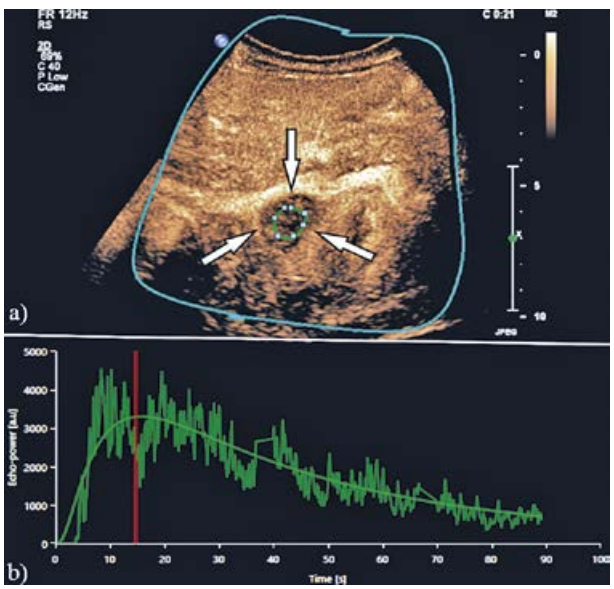

Fig 2. Results of the software perfusion analysis for patient 6 (six years and seven month old boy): a) CEUS of the ganglioneuroma (white arrows), inside selected region of interest (green circle) surrounded by blue line of automatic motion correction; b) linearized time-intensity curve of perfusion – echo-power signal over the time-course with weak homogenous enhancement of the mass and mild wash-out starting seventeen seconds after contrast administration.

Statistical analysis was carried out as the descriptive analysis.

Results

The demographics of the six patient is presented in Table I. In five cases (patients 1-5) the final diagnosis was established as NAH and one (patient 6) as ganglioneuroma. Of the five patients with NAH, three resolved between 8 to 12 weeks and two resolved between 21 and 30 months. For patient 3, three subsequent US examinations over a period of 10 weeks did not show a significant decrease in the size of the lesion which prompted a MRI examination. The MRI was inconclusive due to motion artifact despite the use of sedation. The lesion size did not change significantly and the final diagnosis was established 5 months later on a CEUS examination. Patient 6 had a CEUS one week after his initial US which showed a vascularized lesion. On MRI performed two days after CEUS a neuroblastoma tumor was suggested. The final diagnosis of ganglioneuroma was established by pathology following surgical excision.

The presence of an adrenal hematoma was correctly detected and characterized by CEUS in five cases using VueBox perfusion analysis. Adrenal hematomas had no internal perfusion and flat TICs (fig 1). In comparison, ganglioneuroma showed a gradual, increasing centrifugal complete enhancement (weaker than liver) with slow wash-out starting seventeen seconds after contrast administration (fig 2). Additionally, there is no appreciable flow identified on color Doppler images within the lesion (fig 3). The mean value of PE for hematomas ranged

Table II. Values of peak enhancement and length of cine loop of six patients who underwent CEUS evaluation for adrenal lesions.

Patient number	Region of interest mean value: Peak Enhancement (a.u.)	Cine loop length (seconds)
1	457.05	11.5
2	756.95	17.0
3	498.87	10.0
4	414.02	8.5
5	720.02	21.0
6	3295.54	90.0

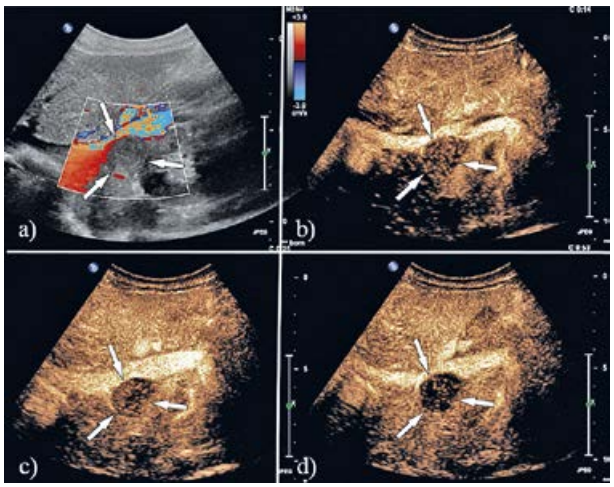

Fig 3. Images in sagittal plane of the boy with ganglioneuroma (white arrows): a) no flow is appreciable within the lesion on color Doppler. CEUS of the lesion (b) 14 seconds after contrast administration showing mild enhancement, (c) 25 seconds after contrast administration showing sustained contrast within the lesion and (d) 53 seconds after contrast administration showing mild wash-out (decrease) of contrast from the lesion.

from 414.02 to 756.95 a.u. compared to 3295.54 a.u. for the ganglioneuroma (Table II). There were higher than expected values of the PE in patients 1-5 which was attributed to motion artifact and erroneous inclusion of background signal. The background signal was captured as the ROI shifted outside of the lesion into adjacent enhanced tissues. This is depicted on the TIC as high-pointed peaks of short duration. The ganglioneuroma had weak enhancement compared to the liver and kidney and mild wash-out.

The normal adrenal gland has a strong, homogenous enhancement, within the crescent-shaped structure with arrival time of the microbubbles similar to the kidney parenchyma (fig 4).

The qualitative analysis of the lesion perfusion detected on CEUS revealed 100% agreement between both study investigators and was consistent with the quantitative assessment made by Vuebox software.

Discussion

Our results demonstrate that CEUS has the potential to discern adrenal hemorrhage from adrenal tumors based on qualitative as well as quantitative assessment. Finding a mass in the region of the adrenal gland is always worrisome because it can include congenital NB, especially if the mass remains solid over time and does not decrease in size. The presence of a hemorrhage is not a diagnostic of a benign lesion because intra-tumor bleeding can also occur and decrease in size over time.

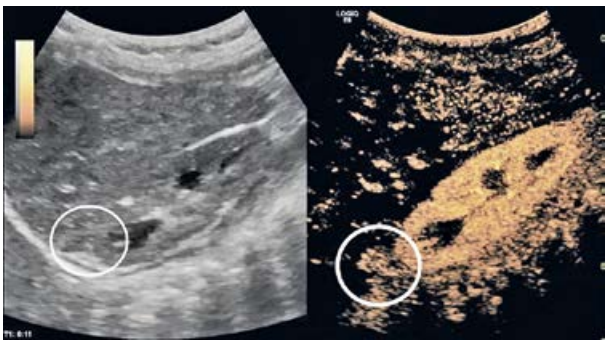

Fig 4. Sagittal plane side-by-side images, b-mode (left) and CEUS (right), of a 7-month-old girl with the healthy adrenal gland visible inside the white circle 11 seconds after contrast administration.

According to the ongoing Trial of International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) if an adrenal mass is suspicious for neuroblastoma the following studies must be carried out: the initial US has to be repeated at the referral center and complemented with abdominal MRI (within the first 9 weeks) to rule out regional or metastatic involvement; blood counts; LDH (lactate dehydrogenase); urine catecholamines and free cortisol; and MIBG (iodine-123 meta-iodobenzylguanidine) scan [8]. Due to the specific biology of NB in neonates and young infants (a tendency to regress and a benign clinical course despite malignant histology) if a suprarenal mass does not reach the midline and it measures ≤5 cm at the largest diameter without regional involvement, then SIOPEN recommends an observational approach until the age of 12 months which includes US follow-up [5]. If at month 12 (48 weeks of observation) the suprarenal mass still persists, pathological analysis is recommended [8].

On the other hand, diagnosis and follow-up of uncomplicated NAH is most commonly done by sequential US examination. Initially on US, NAH appears as a solid echogenic mass, which over time progressively becomes heterogeneous, liquefies, and decreases in size. The hematoma most commonly resolves within 4 to 16 weeks: however, some report a prolonged time to resolution of up to 36 weeks [9-13]. In our series for two patients the time to resolution was much longer. The hematoma in patient 3 took 30 months to resolve and in patient 5 it took 21 months. The prolonged time for NAH to resolve is a problem for both the physician and the child's family.

The Doppler US may be helpful in the differential diagnosis of NAH which is easy to apply but has some disadvantages. Color and power Doppler are depth-dependent and can and may not show blood flow in lesions deeper in the body or with slow blood flow [14]. Additionally, Doppler is sensitive to motion, and bowel peri-

stalsis or breathing movements may result in artifactual signal resulting in a false positive assessment of blood flow [14]. Although the Doppler settings were optimized, blood flow was not detected within the ganglioneuroma in this series. Doppler assessment can be challenging as well in congenital NB with cystic changes which may not have much solid tissue and are weakly vascularized. In one series, color Doppler US showed vascularity along the tumor walls and septum in only 9 of 18 (50%) cystic congenital NB [15].

Another diagnostic tool is MRI; however, it often requires general anesthesia and gadolinium administration for mass characterization. Moreover, imaging small adrenal lesions on MRI is difficult due to the minimal amount of surrounding visceral fat to help to define the gland and relatively low spatial resolution which can limit the assessment even in dynamic contrast-enhanced sequences.

Computed tomography (CT) can confirm the presence of an adrenal mass; however, it is burdened by ionizing radiation and the need for iodine contrast administration. Thus, it is typically not used for serial follow-up examinations. Although it can depict calcifications in the lesion, CT has low tissue resolution especially in neonates who lack visceral fat.

Less than 70% of perinatal NB are MIBG avid and urine catecholamines are negative in two-thirds of cases [15-17]. Despite this, SIOPEN recommends that these procedures be performed. MIBG should be done within the first 9 weeks of age to confirm the diagnosis of neuroblastoma and exclude metastasis [8]. An MIBG examination is mandatory in all suprarenal masses with increased catecholamines level except lesions smaller than 1 cm with negative catecholamines [8].

Considering the findings here, CEUS may be useful in differentiating NAH from adrenal mass. Only a single report in a pediatric population confirmed CEUS congruency with CT and MRI for adrenal lesions [6]. However, CEUS offers more advantages over other imaging modalities. CEUS is highly sensitive to depicting contrast signals even within the smallest vessels, and can therefore, be of assistance to differentiate between a vascularized mass and NAH. Its high temporal and spatial resolution help assess blood flow which is particularly useful in lesions without significant change in size or morphology over time. Contrary to MRI, a CEUS examination can be performed at a patient's bedside, without sedation or, in neonates, the potential risk of hypothermia while in the magnet. The final diagnosis on CEUS can be established shortly after the examination saving parents unnecessary anxiety, induced by prolonged follow-up imaging protocols. UCA have a favorable safety profile with a low incidence of adverse reactions [18,19]. As a result of the safety profile, the Food and Drug Administration in the United States approved an UCA for use in children for the assessment of liver lesions in 2016 [20].

There are several disadvantages and limitations to the use of CEUS. Although it is relatively easy to learn how to perform and interpret these examinations, they are operator dependent. Imaging of the adrenal gland is currently an off-label application of the commercially available UCA which may require informed consent depending on institutional guidelines. The problem of registration and off-label use of numerous drugs and contrast agents in the pediatric population is well known [21,22].

In the presented cases the cine loops of the NAH that were used for quantification were short and affected by the motion artifact. Thus, automatic quantitative evaluations performed with a ROI over lesions in young children who are moving, can be difficult to perform. Although this is a potential limitation, even short cine-loop (regardless of the phase during which it is obtained) provided a sufficient amount of data that can be interpreted by the radiologist or the software. Erroneous signal, attributed to motion artifact and inclusion of background tissue enhancement, was easy to identify and distinguish from the lesion vasculature. Although, the motion correction option given by software was active, it was not able to prevent against all body or breath movement.

Adrenal glands are on the extended list of future applications of CEUS in the position statement of the European Federation of Societies in Ultrasound and Medicine [18]. Our cases show that CEUS can be helpful in distinguishing between vascularized tumors and non-vascularized hemorrhages of the adrenal gland. It can serve as a problem solving tool and decrease or possibly replace MRI in the future when there are questionable or slowly resolving NAH lesions mimicking NB. Both quantitative and qualitative analyses can be used to confirm the lack of blood flow within the adrenal lesion in order to establish a final diagnosis. This series demonstratesthe first descriptive use of CEUS and the perfusion software to analyze NAH.

Conclusions

The quantitative and qualitative CEUS assessment of the mass can distinguish hemorrhage from a malignant lesion. Based on our findings, CEUS could serve as an alternative diagnostic tool to MRI in the diagnosis of slowly resolving NAH lesions. Although the results are very promising, due to the single case of a tumor, our results need to be confirmed by larger series including tumors to establish a role of CEUS in the diagnosis of NAH.

Conflict of interest: none

References

1. Felc Z. Ultrasound in screening for neonatal adrenal hemorrhage. Am J Perinatol 1995;12:363–366.
2. Lee MC, Lin LH. Ultrasound screening of neonatal adrenal hemorrhage. Acta Paediatr Taiwan 2000;41:327–330.
3. Acharya S, Jayabose S, Kogan SJ, et al. Prenatally diagnosed neuroblastoma. Cancer 1997;80:304–310.
4. Cho JY, Lee YH. Fetal tumors: Prenatal ultrasonographic findings and clinical characteristics. Ultrasonography 2014;33:240–251.
5. Rafailidis V, Deganello A, Sellars ME, Makin E, Sidhu PS. Pediatric adrenal trauma: evaluation and follow-up with contrast-enhanced ultrasound (CEUS). J Ultrasound. 2016;20:325-331.
6. Al Bunni F, Deganello A, Sellars ME, Schulte KM, Al-Adnani M, Sidhu PS. Contrast-enhanced ultrasound (CEUS) appearances of an adrenal phaeochromocytoma in a child with Von Hippel-Lindau disease. J Ultrasound 2014;17:307–311.
7. Back SJ, Acharya PT, Bellah RD, et al. Contrast-enhanced ultrasound of the kidneys and adrenals in children. Pediatr Radiol 2021;51:2198-2213.
8. ProtocolClinicalTrials.gov. European Low and Intermediate Risk Neuroblastoma Protocol (October 2019). Available from: https://clinicaltrials.gov/ct2/show/study/NCT01728155; Last accessed: 15.12.2020.
9. Toti MS, Ghirri P, Bartoli A, et al. Adrenal hemorrhage in newborn: How, when and why – from case report to literature review. Ital J Pediatr 2019;45: 58.
10. Mutlu M, Karagüzel G, Aslan Y, Cansu A, Okten A. Adrenal hemorrhage in newborns: a retrospective study. World J Pediatr 2011;7:355–357.
11. Fedakar A. Adrenal hemorrhage in the neonatal intensive care unit: a four-year experience. European Res J 2018;5:816–821.
12. Demirel N, Baş AY, Zenciroğlu A, Taşci-Yildiz Y. Adrenal bleeding in neonates: report of 37 cases. Turk J Pediatr 2011;53:43–47.
13. Postek G, Streich H, Narębski K. Assessment of diagnostic methods in adrenal gland hemorrhage in neonates on the basis of own material from the years 2007–2011. Pol J Radiol 2011;76:62-64.
14. Burns PN. Principles of Doppler and color flow. Radiol Med 1993;85:3–16.
15. Hwang SM, Yoo SY, Kim JH, Jeon TY. Congenital adrenal neuroblastoma with and without cystic change: Differentiating features with an emphasis on the of value of ultrasound. AJR Am J Roentgenol 2016;207:1105–1111.
16. Sauvat F, Sarnacki S, Brisse H, et al. Outcome of suprarenal localized masses diagnosed during the perinatal period: A retrospective multicenter study. Cancer 2002;94:2474–2480.
17. Fisher JPH, Tweddle DA. Neonatal neuroblastoma. Semin Fetal Neonatal Med 2012;17:207–215.
18. Sidhu PS, Cantisani V, Deganello A, et al. Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement. Ultraschall Med 2017;38:33-43.
19. Piskunowicz M, Kosiak W, Batko T, Piankowski A, Połczyńska K, Adamkiewicz-Drożyńska E.. Safety of intravenous application of second-generation ultrasound contrast agent in children: Prospective analysis. Ultrasound Med Biol 2015;41:1095–1099.
20. Food & Drug Administration. Approved Drug Product List (March 2016). Available from: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071120.pdf; Last accessed: 15.12.2020.
21. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005;164:552–558.
22. Sidhu PS, Cantisani V, Deganello A, et al. Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement. Ultraschall Med 2017;38:33–43.