REVIEWS

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Ultrasound Elastography – Review of Techniques and Its Clinical Applications in Pediatrics – Part 2

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Sonoelastography is a novel technique that uses ultrasound waves to assess the elasticity of tissues noninvasively. It provides an ultrasound-based method to detect and display the relative stiffness of tissue. The main principle of sonoelastography is the measurement of tissue distortion in response to external compression. Changes in elasticity and tissues deformation elicited by compression are measured, processed and then shown in real time presentation with color-coded elastograms. Most of the elastography applications are well known and have been described in detail in adults, e.g. evaluation of liver fibrosis or thyroid nodules. Similarly, most of sonoelastographic studies are based on groups of adults. The purpose of this review article is to bring this technology closer to pediatric clinicians and to summarize some of its current clinical applications that are being pursued. In this part we take into consideration utility of elastography in evaluation pathologies of musculoskeletal system, lymphatic nodes, thyroid, kidneys in pediatric patients and also elastography of placenta (**Adv Clin Exp Med 2015, 24, 4, 725–730**).

Key words: sonoelastography, muscles, thyroid.

Muscles represent a soft tissue, which make them a very appropriate structure for elastography examination. Although the assessment of the muscle elasticity can be used in such conditions as e.g. muscles injuries (including intramuscular haemorrhages), some myopathies, myositis, spastic disorders [1], more studies are focused on adult patients and only a few researches concern children. Berko et al. applied a strain elastography in order to establish muscle elasticity in children at rest and after exercise. Examination was performed on biceps brachii and rectus femoris muscles at rest and after exercise in a group of 42 healthy children (23 males, 19 females; age range: 2–18 years). They assigned elasticity scores to the 5-point color scale: a score of 1 (predominantly red) was equal to the greatest elasticity (soft muscle) and a score of 5 (predominantly blue) indicated the lowest elasticity (hard muscle). This study determined the normal elasticity values of muscles in healthy children at rest and after exercise, taking into consideration also the children's age, gender, height, weight, BMI, dominant arm and history of musculoskeletal injuries. The results of this study might be valuable as a baseline in investigating children with various muscle pathologies. [2]. Kwon et al. presented the usefulness of semi-quantitative elastography in an assessment of muscle stiffness in children with spastic cerebral palsy, which, combined with clinical evaluation of spasticity, can be helpful in treating, planning and evaluating therapy effectiveness (therapy monitoring) in these patients. The study was based on the elasticity assessment of the medial gastrocnemius muscle (GCM). Measurements were performed in a group of 28 children, including 15 children with cerebral palsy (27 examined legs because of 3 children with hemiplegia) and 13 children without any neurological

or musculoskeletal disabilities (26 examined legs). Three different elastography applications were used. Authors estimated the elasticity of medial GCM, using a histogram to define the intensity of color pixels and DS score. The authors also measured the strain ratio by putting ROI gate in medial GCM and soleus muscle and calculated relative strain ratio medial GCM to soleus muscle (semi-quantitative elastography) and used ARFI to measure the velocity of shear waves in these muscles. Apart from the elastography, researchers also assessed muscle spasticity of the ankle using a modified Ashworth scale score, measuring the thickness of the medial GCM and calculating GCM ratio using ultrasonography. The study revealed significant differences in elasticity of medial GCM in DS score, ARFI value and also a significant difference in strain ratio between the 2 groups. What is more, the authors noticed a significant correlation between stiffness parameters obtained by elastography and the degree of ankle spasticity assessed by modified Ashworth scale scores in children with spastic cerebral palsy. [3] The same authors made an attempt to establish a diagnostic value of strain elastography in infants with congenital muscular torticollis. The study was performed in 50 children and the main group was divided in 2 subgroups, taking into consideration such parameters as sternocleidomastoid muscle (SCM) thickness, sonoelastographic score and the extent of longitudinal involvement in the muscle. Group 1 included 29 children with SCM thickness greater than 10 mm, sonoelastographic score of 4 and involvement of the entire length of the muscle, whereas group 2 was related to infants with a SCM muscle thickness less than 10 mm, a sonoelastographic score of 3 and involvement of only part of the muscle. B-mode ultrasonography and sonoelastography were performed during the same examination, the thickness of the SCM was measured and the cross-sectional area of the muscle involvement was evaluated. The sonoelastographic score of the SCM was graded from 1 (soft) to 4 (stiff) by using a color scale. The study revealed greater thickness and larger cross-sectional area of the SCM in group 1 than in group 2, as well as a greater stiffness of SCM in group 1. Research findings showed at the final outcome that residual mass entirely disappeared in all children in group 2; however, it was still detected in 20% of children in group 1. Based on these findings, it can be assumed that elastography might serve as an additional diagnostic tool to conventional ultrasonography in predicting treatment results of congenital muscular torticollis. As authors pointed out, some further investigation is needed, because of the small number of infants included in this study [4]. Another study concerning congenital torticollis was recently published by Lee et al. Twenty seven children with diagnosis of congenital torticollis and 17 healthy controls were examined by using conventional US and color-coded strain elastography. The authors concluded that elastography could be helpful for the diagnosis of congenital muscular torticollis, especially in patients with isoechogenic SCM [5]. Drakonaki and Allen performed the research, which actually is a case report of a 15-years-old boy affected by Bethlem myopathy, a congenital muscle dystrophy, related to muscle weakness and contractures. They used strain elastography to evaluate elastic properties of the muscle by using color maps and in effect proved greater stiffness of abnormal muscle areas in comparison with normal-appearing areas. These findings are suitable with MR and US pattern of muscle involvement and suggest that elastography can be useful as an ancillary technique in assessing the pattern of muscle changes in congenital myopathies. [6]. All studies mentioned above show that elastography can become a significant examination method in the diagnosis and monitoring of musculoskeletal disorders; however, further studies on its utility need to be performed.

Lymphatic Nodes

Lymphadenopathy is one of the commonest clinical problems in children. In most cases it is caused by benign conditions such as inflammation, although enlarged lymph nodes might be also the first sign of the malignant diseases, including Hodgkin disease, acute leukemia or non-Hodgkin lymphoma. [7]

The majority of the clinical studies on the utility of elastography in superficial lymph nodes assessment is related to adult patients and very often concerns metastatic nodules. Furukawa et al. used RTE to establish its usefulness in the diagnosis of cervical lymph nodes metastasis and monitoring the treatment results in adult patients with head and neck cancer. The elasticity of the examined lymph nodes was estimated qualitatively and classified into 4 patterns: in pattern 1, 80% or more of the cross-sectional area of the lymph node was revealed as red or green, i.e. soft; in pattern 2, 50% or more and less than 80% was showed in red or green; in pattern 3, 50% or more and less than 80% was shown in blue and in pattern 4, 80% or more was revealed in blue, i.e. hard. Research outcomes allowed the authors to claim that RTE might be a useful technique in lymph node metastasis detection in patients with head and neck malignancies [8]. Zhang et al. carried out the study on a value of

the RTE in distinguishing benign and malignant superficial lymph nodes. A total of 112 adult patients (82 with lymphadenopathy and 30 healthy volunteers) with 155 lymph nodes were examined with B-mode ultrasonography, power Doppler US and RTE. Most of them were histopathologicaly diagnosed by FNAC and some of them had the diagnosis confirmed by clinical data considered together with follow-up findings. The elasticity of the lymph nodes was measured semi-quantitatively and determined as a stiffness value. The elastographic outcome was referred to the findings by Furukawa et al. [8] and classified into 4 patterns. In both researches most of malignant lymph nodes were rated as patterns 3 and 4, whereas most of the benign ones as pattern 1 and 2. In conclusion, the authors assumed that RTE could potentially serve as a valuable technique for evaluating the nature of the superficial lymph nodes in clinical practice [9]. There are also studies on quantitative assessments of the lymph nodes elasticity using shear-wave ultrasound elastography (SWE). One of them, performed by Bhatia et al., included 46 patients with cervical lymphadenopathy – 55 lymph nodes were examined by conventional US, underwent US-guided FNAC and were followed by real-time SWE. Outcomes of elasticity measurement were displayed on color-coded elastograms and correlated with cytology findings. This study showed that although SWE is technically feasible for cervical lymph nodes examination, it seems to be unsuitable screening tool for neck nodal malignancies. However, it could serve as an ancillary technique in identifying the most likely malignant nodes with indication to FNAC [10]. The other study carried out by Choi et al. was focused on patients with head and neck carcinoma. Authors compared the diagnostic performance of SWE and grey-scale ultrasound to distinguish metastatic from benign lymph nodes. Histopathological examinations of surgical specimens served as a reference standard. This study included 15 patients (total number of 67 lymph nodes were examined) with pathologically confirmed diagnosis of head and neck malignancy. All of those patients underwent surgery and received final diagnosis based on surgical specimen examination. This study showed higher sensitivity, specificity and accuracy of SWE than grey-scale ultrasound in differentiation between benign and malignant cervical lymph nodes, which suggests that SWE can be a valuable technique in reaching the decision about the necessity to perform an invasive biopsy [11]. Although all presented research, including different types of elastography, were performed in groups of adult patients, their results let us suppose that it can be also a useful tool in the examination of children, especially important for the differentiation of benign and malignant lymphadenopathy. Up to now there are some symposium abstracts which seems to confirm the usefulness and advantages of this method in children lymph nodes examination [12] (Fig. 1). However, further multicenter trials focused on children need to be performed.

Thyroid

The prevalence of thyroid nodules in children has been estimated to range from 0.9% to 5.1% [13, 14, 59, 60]. However, even 25% of these nodules are malignant [13, 15]. Fine-needle aspiration cytology (FNAC) is the main tool to define the character of the nodule due to its high accuracy and

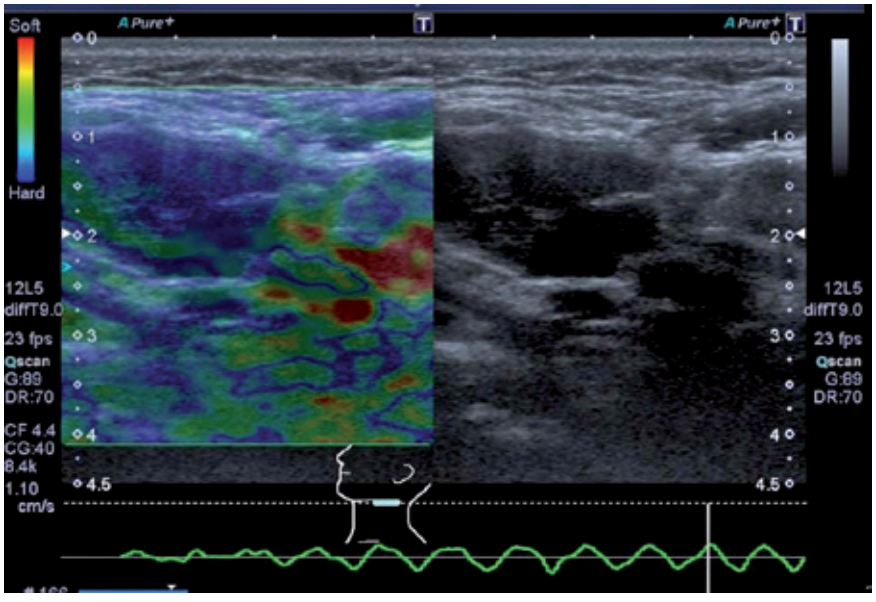

Fig. 1. A 14-year-old patient with HL (nodular sclerosis), clinical stage: IIIs. Enlarged (2.6 × 1.4 cm) lymph node in the left IIA neck region. Picture of Tsukuba 4 lymph node during maximum tissue compression. Increased FDG uptake in PET-CT was observed in this lymph node. After the first course of chemotherapy, the lymph node size decreased to 1.5 × 1.0 cm

reproducibility [16]. However, FNAC is characterized by a grey diagnostic area – Thy3 in the British Thyroid Association guidelines [17, 18]. The consequence of this fact is that about 80% of patients with Thy3 undergo unnecessary thyroidectomy [16, 17]. A meta-analysis published in 2010 could be an example of a study suggesting the usefulness of elastography in the dilemma mentioned above. It showed that qualitative real-time ultrasound elastography had a sensitivity of 92%, specificity of 95% in differentiating malignant from benign nodules and it could reduce the rate of unnecessary surgical interventions after FNAC [19]. However, later research did not confirm the usefulness of strain elastography in the pre-surgical selection of nodules and their authors suggest the need for a quantitative or semi-quantitative elastography [20, 21]. Such research was made by Cantisani et al. Authors reported high sensitivity, specificity, negative and positive predictive values of semi-quantitative elastography in the differential diagnosis of thyroid nodules with indeterminate cytology [16]. However, probably the largest study in the last years gave unsatisfied results. Bhatia et al. compared SWE results with US guided FNAC also to assess discriminatory capability of SWE. Authors reported a sensitivity of 76.9% and specificity of 71.1% by using the cut-off value of 34.5 kPa, which was the threshold of highest accuracy [22]. That study showed SWE is probably more operator-dependent than it was considered to be. Despite this, results of Corrias et al. in their review suggest a follow-up in negative for malignancies elastography in case a suspicions of FNAC in children [23].

Kidneys

Very interesting preliminary results were presented by Bruno et al. Twenty-eight children (age range 9–16 years) with primary or secondary vesicoureteral reflux (≥ grade III) underwent scintigraphy and ultrasound with ARFI. ARFI examination was also performed on 16 age – matched healthy controls. After scintigraphy, the kidneys had been divided in two groups: "affected" and "contralaterals". Kidneys of controls were described as "healthy". The mean ARFI values obtained in the "affected" kidneys (5.70 ± 1.71 m/s) were significantly higher than those measured in both "contralateral" (4.09 ± 0.97, $p < 0.0001$) and "healthy" kidneys (3.13 ± 0.09, $p < 0.0001$). Authors noticed decreasing ARFI values from kidneys with secondary vesicoureteral reflux to kidneys with primary reflux, than to unaffected kidneys contralateral to reflux and then finally to normal kidneys [24]. These preliminary results are very encouraging and show the possibility to include elastography in renal diagnostic imaging protocols. A study by Lee et al., where age-related normal ARFI values for kidneys, liver and spleen were measured, was mentioned above [25].

Placenta

Tissue rebuilding is a process that need some time; therefore, there is a small possibility that elastography will take a leading place in neonatal diagnostic imaging. However, there are some cases when it could be useful. Sugitani et al. from Fukuoka analyzed *ex vivo*, after delivery, velocity of shear wave propagation in placentas by using ARFI technique. The study group included 115 patients divided in 3 subgroups: normal, fetal grow restriction (FGR) and pregnancy-induced hypertension (PIH). Results revealed a significant difference in shear wave velocity between FGR and normal group – higher in FGR group (1.94 ± 0.74 vs. ± 1.31 0.35, $p < 0.05$), and no significant difference between normal and PIH group. Moreover, authors noticed a correlation between increased velocity and decreased birth weight Z-score [26].

Despite that the authors did not observe any histological damage to the placental tissue after ARFI examination and some researches confirm that temperature increase caused by pulse burst might still be within the safe limits determined by Food and Drug Administration [26–28], safety of ARFI or other similar techniques on pregnant should be carefully investigated.

Conclusion

Pediatric elastography studies are visibly less numerous, often less structured and more equivocal than those based on adults. In the last years, however, more and more research based on children was published and it seems that tendency will last. Some pediatric pathological conditions are either rarely or not seen at all in older patients and, therefore, are at risk of being inadequately diagnosed with the use of conventional methods. It is very likely that sonoelastography will fill the gap and help to clear many diagnosing doubts as relatively accurate, non-traumatic and non-expensive method. However, it is rather not possible to say that elastography is commonly acclaimed as a basic diagnostic tool in pediatrics groups of patients. To summarize, sonoelastography still requires many well-designed studies to confirm its value in pediatric diseases. Hopefully, actually available research is rather encouraging. Probably in next couple of years this method will be more and more popular and therefore widely accepted.

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