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ORIGINAL ARTICLE

Feasibility and reproducibility of shear wave elastography in pediatric cranial ultrasound

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Abstract

Background Head ultrasound (US) is commonly used to evaluate the neonatal brain but may be limited by its lack of sensitivity and specificity. Ultrasound shear wave elastography (SWE) might provide additional information to conventional gray-scale imaging.

Objective To assess whether SWE of brain parenchyma can be (1) successfully performed at a large academic medical center where US technologists perform the majority of examinations and (2) used to detect intracranial pathology.

Materials and methods Pediatric patients undergoing head ultrasound underwent simultaneous SWE examination. We included normal examinations (n=70) and those with intracranial pathology (n=8) for analysis. We analyzed inter-reader variability and examination success rates and assessed the stiffness of white matter and deep gray nuclei in normal and pathological states across multiple gestational age groups.

Results Average gestational age of the term, pre-term and extreme pre-term groups were 38.4±1.2 weeks, 29.0±3.7 weeks and 28.3 ±3.1 weeks, respectively. Overall examination success rate was 79.5%. We observed a decrease in the SWE examination time from the first month (5.9±3.7 min) to the second month (4.1±1.7 min; P=0.01). Forty-one repeat examinations were performed on 14 children by different technologists, with an intraclass correlation coefficient (ICC) of 0.91. Mean stiffness in the periventricular white matter was lower than in the deep gray nuclei in all gestational age groups: term group (1.3 m/s vs. 1.5 m/s, P<0.001), pre-term (1.3 m/s vs. 1.4 m/s P=0.12), and extremely preterm group (1.2 m/s vs. 1.4 m/s, P=0.001). Mean stiffness for the deep gray nuclei differed between the term (1.5±0.3 m/s) and pre-term (1.4±0.2 m/s) groups (P<0.01). No significant differences in white matter stiffness were seen in relation to gestational age. Infants with large intraparenchymal hemorrhage had increased white matter stiffness (1.3±0.1 m/s) and deep gray nuclei stiffness (1.6±0.2 m/s) compared to full-term infants with normal head ultrasounds. These differences approached statistical significance with P=0.09 and P=0.06, respectively.

Conclusion We demonstrated that SWE performed by pediatric sonography technologists is reproducible. We found differences in stiffness between deep gray nuclei and periventricular white matter across multiple age groups.

Keywords Brain · Cranial ultrasonography · Infant · Neonate · Shear wave elastography · Stroke · Ultrasound

Introduction

Conventional cranial ultrasonography (US) of the pediatric brain is inexpensive, portable and high-resolution, and it does not use ionizing radiation. Similar to US imaging of other organ systems, however, gray-scale and color Doppler imaging of brain parenchyma have lower diagnostic sensitivity and specificity compared to CT and MRI [1]. Elastography has been shown to improve US sensitivity and specificity for detecting pathology in multiple organ systems, most notably cirrhosis [2–5]. Brain MR elastography has demonstrated changes in parenchymal stiffness in the setting of various intracranial pathologies, and intraoperative US elastography has demonstrated that brain masses have increased stiffness [6].

Ultrasound shear wave elastography (SWE) is a relatively new technique that utilizes an acoustic radiation force impulse (ARFI) to measure tissue stiffness. Because the ARFI induces internal tissue deformation (shear waves), the technique is inherently less operator-dependent than other ultrasound-based elastography techniques such as strain elastography. SWE allows for simultaneous

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correlation with gray-scale images and quantitative stiffness measurement [7]. In the pediatric population, SWE has proved to be a promising and safe modality to evaluate pathologies affecting a variety of organ systems including the gastrointestinal system (primarily liver disease), musculoskeletal system and central nervous system [8].

In pediatric brain imaging, two reports have explored the feasibility of ultrasound elastography performed by experienced pediatric radiologists; however, many questions remain [9, 10]. The generalizability of the technique has not been explored. In many countries, sonography technologists — not experienced pediatric radiologists — routinely perform most pediatric ultrasound examinations. Additionally, the aforementioned studies only evaluated normal brain parenchyma. To date, no published reports have described SWE findings in pediatric patients with intracranial pathology.

The purpose of this study was to describe the implementation of an SWE protocol for pediatric transcranial ultrasound for normal infants and those with intracranial pathology at an academic medical center in North America where scanning is primarily performed by sonography technologists. We measured brain parenchymal stiffness in the normal and pathological states.

Materials and methods

Study population and recruitment

Our institutional review board approved this study. We enrolled infants over a 2-month period in late 2018. The sole inclusion criterion was that a technically adequate head ultrasound via an anterior fontanelle was possible. Exclusion criteria included any condition that would preclude head ultrasonography, including a soft-tissue abnormality overlying the anterior fontanelle and a very small anterior fontanelle through which SWE could not be obtained reliably. An additional exclusion criterion was lack of sufficient brain parenchyma for SWE evaluation (<2-cm thickness of brain parenchyma).

We collected relevant clinical information from the electronic medical record including age at imaging (days) and gestational age at delivery (weeks). We categorized infants according to gestational age: term (>37 weeks) and pre-term (<37 weeks); a subset of preterm infants, those born at <33 weeks, we categorized as "extreme preterm." This categorization was selected to maintain consistency with prior literature on brain elastography by Albayrak and Kasap [10]. We also calculated corrected gestational age (cGA) for preterm infants by adding the child's chronological age to their estimated gestational age at delivery. For example, an infant born at 32 weeks of gestation with a chronological age of 2 weeks would have a cGA of 34 weeks.

Ultrasound shear wave elastography examination

Shear wave elastography was performed on Logiq E9 ultrasound machine (GE Healthcare, Waukesha, WI) using a C1–6 curved transducer (GE Healthcare). The SWE examination was added to the end of our routine institutional head ultrasound protocol. Infants were imaged in the standard supine position when feasible. Occasionally critically ill, nonmobile infants were imaged in the semi-upright position. All elastography measurements were obtained via an anterior fontanelle approach. Elastography was performed using the standard SWE presets of the ultrasound equipment. Mechanical index (MI) was 1.4, thermal index (TI) ranged from 0.4 to 0.7 and power output was 100%.

All examinations were performed by pediatric sonography technologists with occasional assistance from pediatric radiologists. As part of this study protocol, the ultrasound technologists received educational material and a classroom session on optimal SWE technique and relevant brain anatomy. The pediatric radiologists involved with the study protocol (S.S. and J.H.S.) have 10 years of combined experience in transcranial ultrasound.

Each US examination began with diagnostic gray-scale and Doppler imaging of the brain and note was made of whether concurrent intracranial pathology existed at this time. After this, two separate areas of brain parenchyma were evaluated with SWE: periventricular white matter in the parietooccipital region and deep gray nuclei. Three regions of interest (ROI) were attempted in each location. In cases with definite intracranial pathology, care was taken to avoid measuring nonparenchymal pathology. For example, if the child had an intraparenchymal hemorrhage, care was taken to avoid measuring the hematoma itself. Figure 1 outlines adequate measurement technique in various brain regions and includes several examples of technically limited studies. We recorded the length of each SWE examination in minutes from the timestamp of the last conventional US image to the timestamp on the last frame with SWE. During this period, intermittent elastography was performed with periods of rest taken for patient and probe repositioning.

Ultrasound shear wave elastography analysis

Infants with successful brain SWE examinations were assigned to two groups. The first group, hereafter termed normal exams, did not contain any significant abnormality on US or any follow-up brain imaging that might impact elastography analysis. Examinations in this category either had (1) no sonographic abnormality; (2) normal variant anatomy (e.g., connatal cysts, mega cisterna magna, or prominence of the extra-axial spaces that did not meet criteria for benign enlargement of the extra-axial spaces); or (3) pathology that was unlikely to affect brain stiffness. Examples of such pathology includes grade 1 germinal matrix hemorrhage and

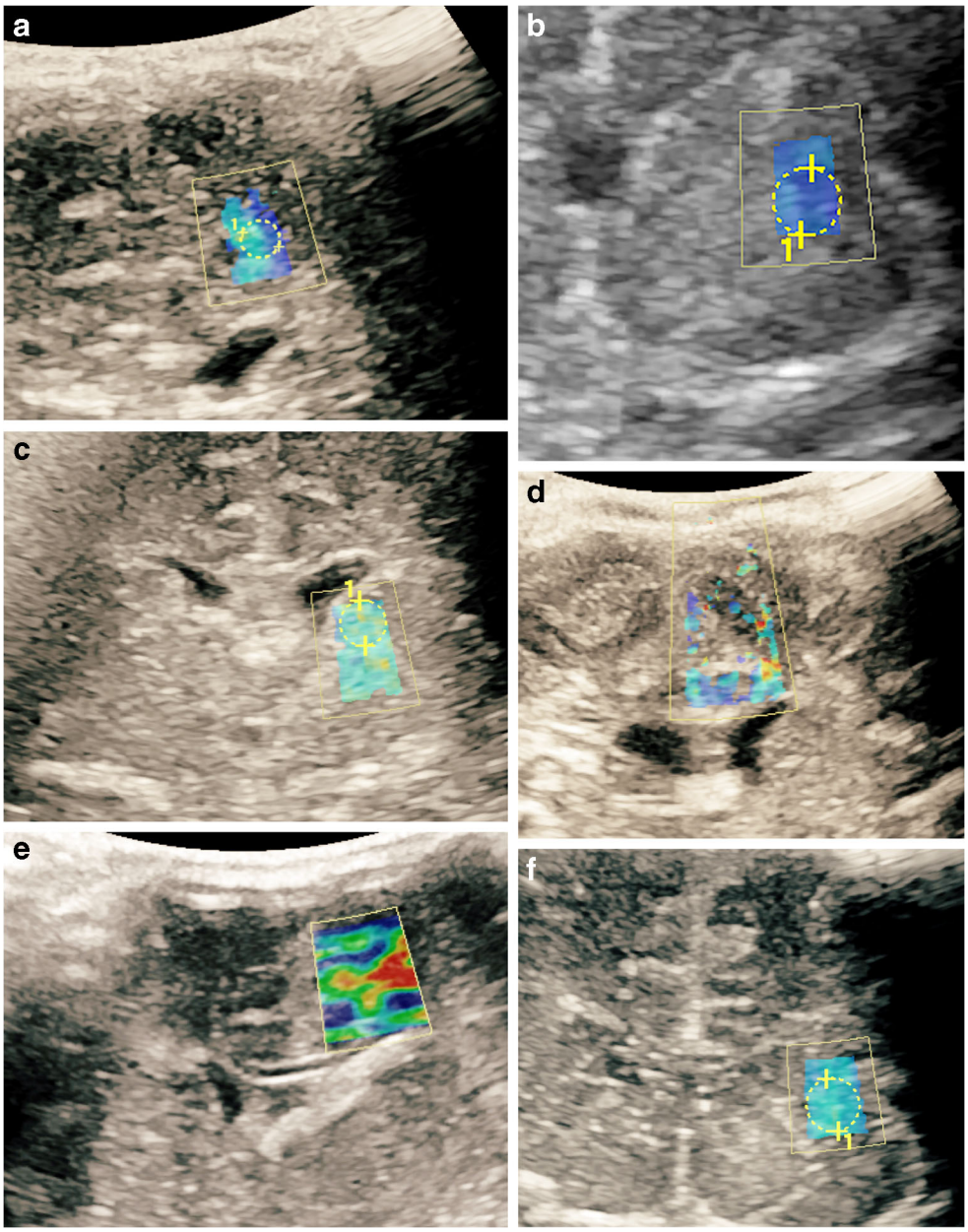

Fig. 1 Several examples of wave elastography imaging are provided in the coronal imaging plane. **a–c** Diagnostic measurements in the (**a**) white matter of a 3-month-old girl, (**b**) thalamus of a 1-month-old boy and (**c**) caudate of a 2-month-old boy. **d–f** Failed imaging from (**d**) poor color fill-in in a 2-week-old boy, (**e**) sharp color transitions in a 2-month-boy and (**f**) non-target sampling in a 3-day-old boy

small (<1 cm) spatially distant hemorrhage without mass effect. The second group included all infants with intracranial pathology including intracranial hemorrhage, sinus venous thrombosis with infarction, and periventricular leukomalacia.

The SWE measures of the deep gray nuclei (thalamus and caudate) were pooled for final analysis. We considered the SWE imaging adequate when there was: (1) at least 50% color fill-in of the sampling volume, (2) smooth color fill-in and (3) absence of significant artifacts or poor B mode contact resulting in suboptimal gray-scale image. Imaging deeper than 1.5 cm from the cortex was preferred to avoid potential reverberation artifacts from the calvarium, a technique commonly employed in SWE of the liver [11]. Finally, we used the mean of the three ROIs as the measurement of stiffness.

Statistical analysis

We performed statistical analysis using the R software package (Vienna, Austria). When comparing means of continuous variables from two groups, such as stiffness and age, we performed an independent samples two-tailed Student's *t*-test. When comparing means of continuous variables from multiple groups, we used one-way analysis of variance (ANOVA). A *P*-value of <0.05 was considered significant. Standard deviations are indicated alongside mean values by "±" wherever appropriate.

We assessed inter-reader reliability using a one-way random effects, agreement, average-measures intraclass correlation coefficient (ICC) to assess the degree that separate

technologists agreed in their elastography measurements. Two examinations were considered a pair for reliability measurement when the scans had no sonographic abnormality and were repeated by different technologists [12].

Results

Examination feasibility and inter-rater reliability

Of the 98 attempted ultrasound examinations during the study period, 78 scans yielded diagnostic elastography values — a success rate of 79.6%. The 78 scans were obtained on a cohort of 51 infants, with 14 infants undergoing repeat examination during the study period. Infants in the pre-term group were given the sub-label of *extreme pre-term* if <33 weeks of gestation for consistency with prior literature.

Over the study period, elastography examinations took an average of 5.3±3.2 min. We observed a decrease in the SWE examination time from the first month (5.9±3.7 min) to the second month (4.1±1.7 min; P=0.01). Examination success rate was not significantly different between the first and second months after implementation (85% vs. 79%, P=0.60).

Forty-one repeat examinations were performed on 14 children by different technologists. The mean interval between repeat imaging was 8.8±9.7 days. The ICC was in the excellent range, ICC=0.91 (Fig. 2) [13]. The high ICC suggests that a minimal amount of measurement error was introduced by the independent measurements, and therefore statistical power for subsequent analyses is not substantially reduced [14].

Normal elastography examinations

Of the 78 successfully performed examinations, 70 studies did not demonstrate any discernable abnormality and were termed normal. Fifty of these examinations were performed on term infants and 20 examinations on pre-term infants. Average age at imaging for the normal exams from all gestational age groups was 40.3 days (range: 0–201 days). The average gestational ages of the term, pre-term and extremely pre-term groups were 38.4–1.2 weeks, 29.0±3.7 weeks and 28.3±3.1 weeks, respectively. Normal head ultrasound demographic information and stiffness values are provided in Table 1.

The most common indications for normal head US examinations were infants with congenital heart disease undergoing screening examination in the cardiac intensive care unit (41.4%), follow-up evaluation of small (Grade 1) germinal matrix hemorrhage in the neonatal intensive care unit (32.5%), and evaluation of macrocephaly (12.0%). A breakdown of recruitment and reasons for examination failure can be found in Fig. 3.

Mean stiffness in the periventricular white matter was lower than in the deep gray nuclei in all gestational age groups. This difference was statistically significant in the term group (1.3 m/s vs. 1.5 m/s, P<0.001) and extreme preterm group (1.2 m/s vs. 1.4 m/s, P=0.001). However, when including all pre-term babies, this difference did not meet the significance threshold (1.3 m/s vs. 1.4 m/s P=0.12; Fig. 4).

There were significant differences in mean deep gray stiffness across groups (ANOVA, P<0.01). Furthermore, the mean stiffness for the deep gray nuclei differed between the term (1.5±0.3 m/s) and pre-term (1.4±0.2 m/s) groups (P<0.01). No significant differences in white matter stiffness were seen in relation to gestational age.

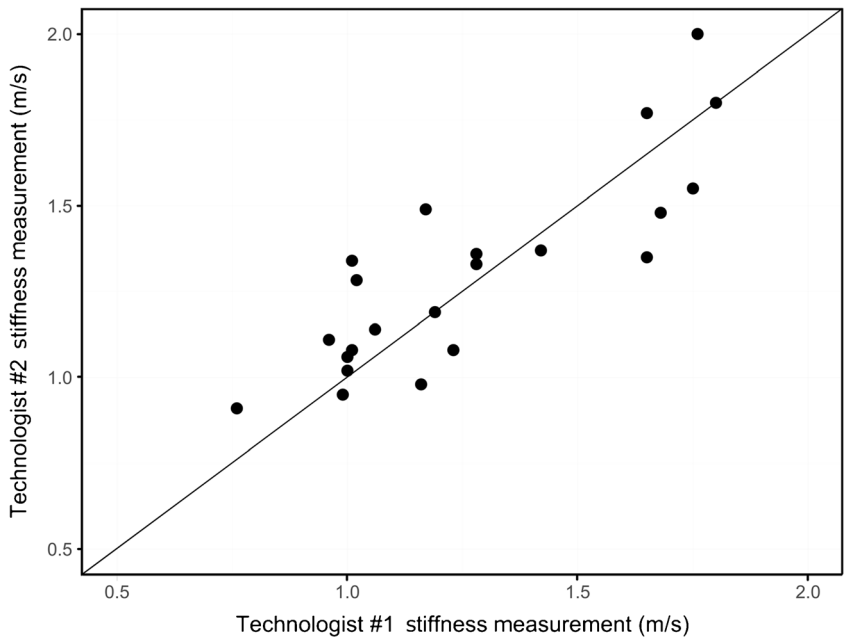

Fig. 2 Graph shows pairwise matching of elastography measurements obtained by different technologists on the same child

Table 1 Summary of normal head ultrasound stiffness for term (>37 weeks), pre-term (<37 weeks) and extremely pre-term (<33 weeks) infants

Normal patients	Term	SD	Pre-term	SD	*P*-value[a]	Extremely pre-term	SD	*P*-value[a]
Normal exams (*n*=70)	50		20			18		
Mean gest age (weeks)	38.4	1.2	29.0	3.7	<0.01	28.3	3.1	<0.01
Mean age at scan (days)	39.7	57.7	41.4	52.2	0.91			
Mean cGA at scan (weeks)	n/a	n/a	36.1	6.4		35.2	7.4	
White matter (*n*)	46		19			17		
Mean white matter	1.3	0.4	1.3	0.4	0.86	1.2	0.4	0.90
IQR/median	0.1		0.1			0.1		
Deep gray (*n*)	39		17			15		
Mean deep gray	1.5	0.3	1.4	0.2	<0.01	1.4	0.2	<0.01
IQR/median	0.1		0.1			0.1		

cGA corrected gestational age, *gest* gestational, *IQR* interquartile ratio, *n/a* not applicable, *SD* standard deviation

[a] A *P*-value of <0.05 was considered significant

We performed a subgroup analysis comparing pre-term infants based on corrected gestational age. No difference in brain stiffness was seen between cGA<37 weeks (*n*=12, white matter = 1.3 ±0.3 m/s, deep gray nuclei = 1.4±0.4) versus cGA>37 weeks (*n*=8, white matter = 1.2±0.4, deep gray nuclei = 1.5±0.3 m/s) (white matter *P*-value = 0.40, deep gray nuclei *P*-value = 0.59).

Children with large intraparenchymal hemorrhage had increased white matter stiffness (1.3±0.1 m/s) and deep gray nuclei stiffness (1.6±0.2 m/s) compared to full-term infants with normal head ultrasounds. These differences approached statistical significance, with *P*=0.09 and *P*=0.06, respectively (Fig. 5).

Shear wave elastography in the setting of parenchymal disease

Of the 78 successfully performed examinations, 8 infants with intracranial pathology were imaged. All 8 cases had confirmatory imaging with CT or MRI. Five infants had intraparenchymal hemorrhage with intraventricular extension, two had dural venous sinus thrombosis with venous infarction and one had periventricular leukomalacia. Average age at imaging for infants with intracranial pathology was 48.6 days (range: 0–123 days) and average gestational age of these infants was 38.9 weeks (range: 37.0–40.0 weeks).

Discussion

Our study sought to determine the feasibility of performing shear wave elastography in a large North American academic medical center and explore its use in detecting intracranial pathology.

Previous studies of transcranial US elastography in neonates were performed by single pediatric radiologists with significant ultrasound experience (14 years and 6 years, respectively), which raises questions about reproducibility of the technique [9, 10]. We found excellent agreement (ICC=0.91) among our ultrasound technologists in measuring

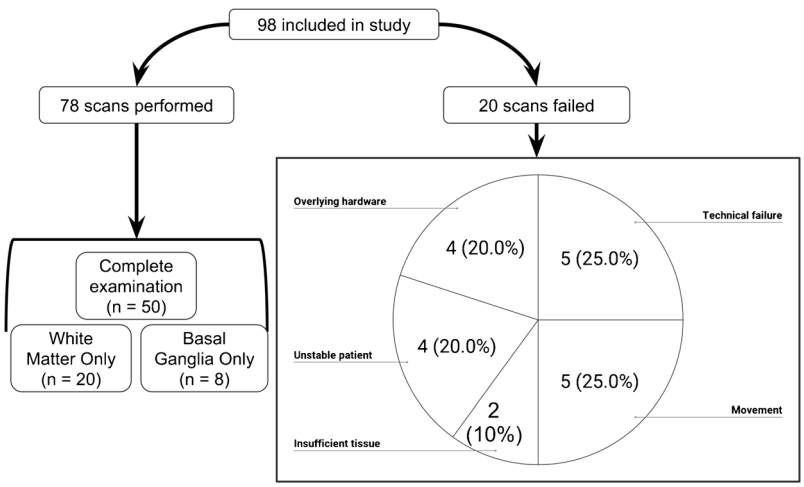

Fig. 3 Schematic representation of patient recruitment including reason for examination failure

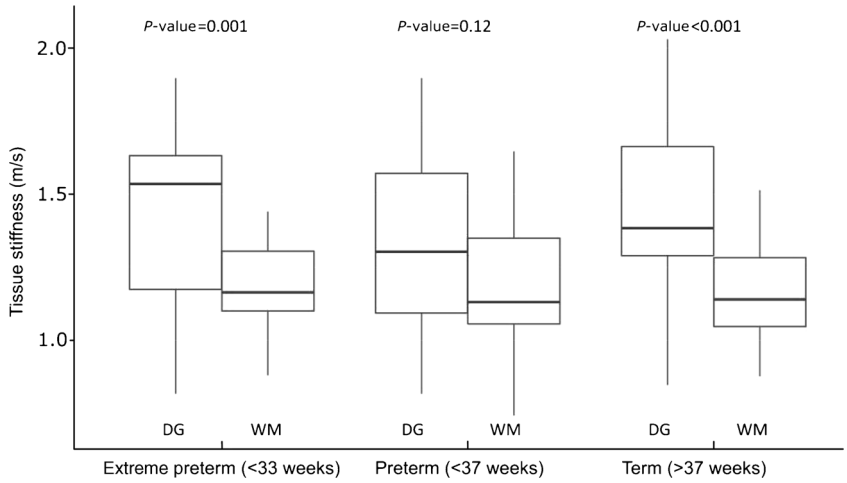

Fig. 4 Box plot demonstrates the deep gray nuclei (*DG*) and white matter (*WM*) stiffness

brain stiffness, suggesting that the examination is reproducible. Additionally, we found that pediatric sonographers quickly overcame the learning curve associated with this new technique. By the second month of implementation the average examination time dropped below 5 min (4.1 ±1.7 min), with no SWE examination taking more than 9 min.

The ability to rapidly perform elastography of the brain is essential for fast throughput in a busy quaternary referral center ultrasound department. More important, however, this ensures that any potential bioeffects related to performance of head ultrasound and elastography are minimized. During any brain ultrasound, possible heating and mechanical impact on brain tissue should be minimized to ensure no disruption to neuronal migration or neurotransmitter level and function. In a mouse model, no histological changes within the brain were seen after exposure to elastography for extended periods from thermal or mechanical effects. However, alterations in signaling pathways of the brain can be seen with as little as 10 min of exposure to a continuous elastography pulse, although these effects appear to normalize by 3 months after elastography exposure [15].

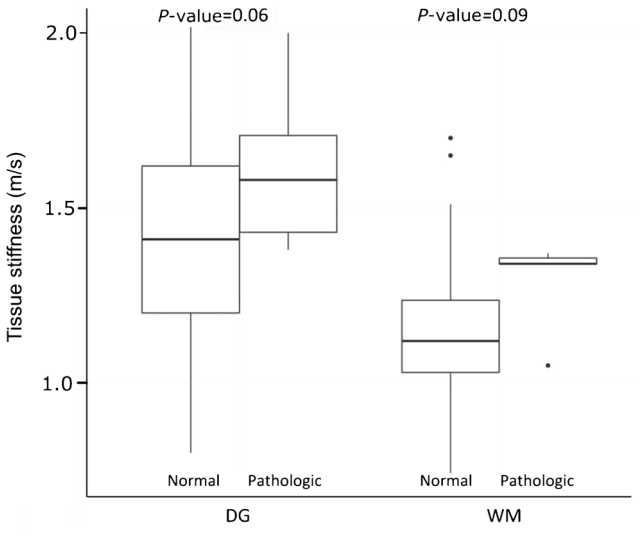

Fig. 5 Box plot demonstrates the difference between pathological and normal stiffness values in deep gray nuclei (*DG*) and white matter (*WM*). Outlier values are indicated by black dots and signify values outside of the third and first quartile ±1.5 interquartile range. The box for pathologic under white matter appears small because there is a narrow interquartile range, likely due to the small sample size

As described in the literature, we also found that the deep gray nuclei were consistently stiffer than white matter [9, 10]. Stiffness value differences were statistically significant in the term (>37 weeks, $P<0.01$) and extremely preterm (<33 weeks, $P=0.01$) groups and approached significance in the preterm group (<37 weeks, $P=0.12$).

Interestingly, we did not find differences in white matter stiffness based on gestational age as described by Albayrak and Kasap [10]. Differences in chronological age of the child at imaging might, in part, account for this discrepancy. The average age at imaging of our population was 39.7±57.7 days for term infants and 41.4±52.2 days for preterm babies compared to 7.2 ±5.7 days for term infants and 7.3±7.4 days for preterm infants in their study. Because our imaging was obtained at approximately 5–6 weeks after birth, any differences in stiffness at birth related to gestational age were likely masked by the normal myelination process in the postnatal brain, which is the likely etiology of increasing neonatal brain stiffness in animal models [16].

A unique aspect of our study is that we assessed brain stiffness in cases with intracranial pathology. We found that average brain stiffness was higher in the white matter and deep gray nuclei of infants with intracranial hemorrhage, with *P*-values approaching significance ($P=0.09$ and $P=0.06$, respectively). The mechanism for brain stiffening in the setting of intracranial hematoma might be related to increased intracranial pressure and changes in local microvasculature.

Although our findings are analogous to the work of Chauvet et al. [6], who demonstrated that adult brain tumors have abnormally increased stiffness on intraoperative SWE, our study differs in two important ways. First, we measured stiffness of parenchyma adjacent to pathology, whereas they measured the brain tumors themselves [6]. Second, Chauvet et al. performed elastography on tumors intraoperatively using transdural and transpial approaches, not a transcutaneous, transfontanelle approach described herein.

A potential criticism of our study is that all infants with a normal brain ultrasound were considered part of the control cohort. Because the sensitivity of conventional brain ultrasonography is lower than that of CT/MRI, it could be argued that we inadvertently labeled a child with disease as a control. However, no child had any abnormal follow-up brain imaging. Furthermore, many of our control patients had serial ultrasound examinations (47%) performed without any sonographically detectable disease. Indeed, serial cranial ultrasound has been shown to have greater than expected sensitivity compared to single ultrasound examinations [17]. Despite these reassuring trends, the authors acknowledge that conventional imaging with US, CT and MRI are unable to detect abnormalities in brain physiology in children with several commonly encountered conditions in the neonatal intensive care setting including sepsis, congenital heart disease, and other systemic conditions [18–20].

Although our study provides preliminary evidence of abnormal stiffness in infants with intracranial hemorrhage, it is limited by sample size (n=8). Further research is required to determine whether intracranial hemorrhage, or other pathologies, affect brain stiffness and, importantly, whether elastography has a role in the detection of pathology that would otherwise be missed by conventional ultrasound.

Conclusion

We demonstrated that SWE is feasible in a large North American medical center where scanning is performed by pediatric sonography technologists. We found reliable differences in stiffness between deep gray nuclei and periventricular white matter. Finally, we uncovered a trend toward abnormally increased stiffness in infants with intracranial hemorrhage.

Compliance with ethical standards

Conflicts of interest None

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