Original Article Role of Renal Elastography for the Early Detection of ChildhoodGlomerulonephritis.

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ABSTRACT

Introduction: Glomerulonephritis is a frequent childhood renal disease, that has diverse underlying etiologies. It has an underlying immunologic mechanism in most cases.

Aim of the study: To evaluate renal elastography performance as a diagnostic tool for the early detection of acute childhood glomerulonephritis (AGN) and to determine its role in differentiation of different subtypes of AGN.

Methods: This prospective research performed on eighty children separated into 2 groups: **Group I:** forty cases with clinical and laboratory evidence of glomerulonephritis and **Group II**: 40 healthy volunteers of comparable age and sex as controls at our University Children Hospital, Paediatric Nephrology Unit from January 2021 to December 2022. Acoustic radiation force impulse (ARFI) elastography was performed to analyse both kidneys in all participants

Results: The comparison of cases &control groups revealed a significant elevation in acoustic radiation force impulse elastography (ARFI-e) measurement values (p<0.001). By using Receiver operating characteristic (ROC) curve analysis, renal elastography can differentiate acute glomerulonephritis from normal at cut off 3.98 with sensitivity, specificity, PPV & NPV were 100%, 92.5%, 93% & 100% respectively (p<0.001). However, no significant difference in ARFI-e measurement values was found between different types of glomerulonephritis in case group (p>0.05).

Conclusion: As a bedside easily applicable, non-invasive method for the early detection of acute glomerulonephritis in children, the ARFI-e technique showed promising results that needs further investigation on larger number of different types of AGN.

Key words: ARFI-e, Glomerulonephritis, SWS, Elastography

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INTRODUCTION

Acute glomerulonephritis (AGN) is a prevalent childhood kidney disease. Acute post-streptococcal glomerulonephritis (APSGN) is the most prevalent one, characterized typically by gross haematuria. mild oedema, oliguria, hypertension, &varying degrees of kidney impairment. It has excellent prognosis [1]. However, lupus nephritis, ANCA related GN and rapidly progressive GN (RPGN) can occur in children with variable prognosis. Such types are marked by fibrosis of the tubulo-interstitial lining of the renal cells & basement membranes of capillaries, mesangial cells, and tubules. This fibrosis is caused by glomerular inflammation & proliferation of these which structures, are induced bv immunologic mechanisms [2].

underlying The pathological alterations are partially irreversible in these types; therefore, it is critical to establish treatment as soon as possible following a prompt diagnosis. This is especially important for cases with RPGN. The diagnosis is established through the of evaluation clinical. laboratory, findings. & conventional US For а definitive diagnosis, a renal biopsy is regarded as the standard. However, this invasive microsurgery carries the risk of severe haemorrhage complications; so, it is longitudinal recommended for not monitoring or critically ill patients. [3,4].

Shear wave elastography (SWE) is a quantitative method that uses highintensity pulses that generate shear waves in the different tissues. The tissue shear wave speed (SWS) correlates with tissue stiffness. Performing this method in a stiffer tissue leads to a higher SWS thereby providing quantitative information about tissue elasticity [5]. It gained significant importance in evaluation of liver conditions, as chronic hepatitis, alcoholic liver illnesses, & non-alcoholic fatty liver illnesses [6]. In addition, it has been utilised to assess the rigidity or elasticity of renal allografts. Nonetheless, the application of SWE to native renal diseases is still limited [7].

The purpose of the present work is to assess the diagnostic efficacy of renal elastography in early detection of acute childhood glomerulonephritis (AGN) and to determine its role in differentiation of different subtypes of AGN.

METHODS

This prospective research performed on eighty children separated into 2 groups: **Group I:** forty cases with clinical and laboratory evidence of glomerulonephritis and **Group II:** 40 healthy volunteers of comparable age and sex as controls at our University Children Hospital, Paediatric Nephrology Unit from January 2021 to December 2022

Inclusion criteria: Age one year up to 16 years' subjects with clinical and laboratory evidence acute glomerulonephritis (acute onset of gross haematuria, proteinuria, oliguria, and oedema with or without raised renal function).

Exclusion criteria: Patients with chronic kidney disease.

Methods: Full history taking, clinical examination, and routine laboratory evaluation were done for all patients. Laboratory evaluation included serum creatinine, ESR, CRP, ASOT, C3, C4 for all cases on 1st to 4th day of presentation. ANA, anti-DNA, and ANCA were done in selected cases (which don't fulfill criteria of APSGN). Renal biopsy was done in non-postinfectious cases. Histopathological diagnosis was done as a

part of routine patient care for such indicated cases to reach final cause of AGN.

Radiological Procedures

Acoustic radiation force impulse (ARFI) elastography was performed to analyse both kidneys in all participants, using ultrasound system software (LOGIQ P9, GE ultrasound Korea Ltd.), with 2.5-MHz convex transducer (C1–5/60) probe

Acoustic radiation force impulse

subtype shear ARFI is of wave elastography that generates shear waves inside the organ due to focused acoustic radiation force pushing pulses. The system is integrated into an ultrasound machine, and the ultrasound image is used to guide the site of elastography measurements. generation, the After shear waves propagate through the soft tissue, their speed represents the tissue shear wave speed (SWS). It is expressed in m/s and correlates with tissue stiffness. The region of interest (ROI) appears as a color-coded map mosaic inside which the measurement is performed [8].

Radiological evaluation was done on 1st to 4th day of presentation. The evaluation of renal elastography's diagnostic efficacy is conducted by analysing the ROC curve. Although the examiner was informed of

that all participants have a recent history of glomerulonephritis, he was not privy to the conclusive diagnosis, the group of children involved, or any other clinical, radiological, or laboratory data. Findings of renal elastography were compared with clinical, laboratory, conventional radiological findings and histopathological data if present.

Examination protocol

The patient was positioned in a mild lateral decubitus position with maximum The kidney abduction of the arm. morphology was evaluated first with Bmode US imaging and then ARFI mode was initiated. Measurements of the kidney were taken in the longitudinal plane. The ARFI excitation pulse axis was almost perpendicular to the middle zone of the renal cortex, while the pulses sent to the upper and lower polar cortices were from different angles. The elastography values were obtained from the upper, middle, and lower zones of the kidney. For each kidney, a total of nine SWE measurements were made, three from each zone. The mean ARFI-e values were used as representative values. Using the same technique, the SWV of the healthy control group was measured and compared with the data of the AGN patients.



Figure 1: Measurement of SWS with ARFI e using a Logiq E9- General Electric ultrasound system [9]

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In order to evaluate the diagnostic performance of ARFI in the early diagnosis GN. of childhood its specificity, sensitivity, & accuracy were evaluated. In addition, to evaluate its role differentiation in between different subtypes of AGN

This carries great importance especially as regard early immunosuppressive treatment in patients with RPGN even before results of renal biopsy become available. This will save much time in those patients and allow early proper intervention in those critical patients.

Ethical Considerations

Ethical considerations, both procedural or substantial, were present in this research. A written consent from one of the parents of the patient was obtained to perform the examination. To the greatest extent feasible, the confidentiality of all participants admitted to this study was maintained. A statement describing the research procedure was provided to the participants.

Statistical Analysis Computer software

SPSS version 20 was utilized.

Statistical tests

Descriptive statistics such as (percentage, mean, standard variations, ...etc) were performed. For quantitative variables test of normality was performed by Shapiro-Wilkes test then students' T-test is used for normal distribution. data of nonparametric tests was used for non-normally distributed data. Differences between qualitative variables were evaluated by chi-square test. Receiver operating characteristic curve (ROC) was used to identify sensitivity, specificity and

determine optimal cut-off points. Sensitivity = true positive / (true positive + false negative). Specificity = true negative / (true negative + false positive).

RESULTS

This work included 40 children with AGN: 31 patients with APSGN, 5 cases with lupus nephritis, & 4 cases with clinical and pathological features of RPGN. The control group included 40 healthy children of comparable age and significant variances sex. No were observed among cases & control groups as regard gender & age in years (p>0.05). The mean age in group of cases is 8.20 ± 3.52 years, ranged from 2 years to 16 years with men to female ratio of ~1.4: 1. Data are demonstrated within Table 1.

Regarding laboratory data, we found significant decreases in hemoglobin concentration, and significant increases of serum creatinine, CRP, ASOT and ESR values in the patient group when compared to their levels in the control one as shown in **Table 2**. As regard, serum level of C3 and C4 among the studied cases: there was decrease in C3& C4 levels in 38 cases (95%) and in 5 cases (12.5%) of the studied cases respectively. Decreased C3 only without corresponding decrease in C4 levels was detected in (82.5) % of the studied cases.

As regard ARFI-e, **Table 3** showed significant elevation in ARFI-e measurement values when comparing case group to control one,

By utilizing ROC curve, renal elastography can differentiate acute glomerulonephritis from normal at cut off 3.98 with sensitivity, specificity, PPV and NPV were 100%, 92.5%, 93% and 100% respectively as shown in **Table 4.** While

Table 5 showed no significant relation wasfound in ARFI-e measurement values

between diagnosed subtypes of glomerulonephritis in case group (p>0.05).

Table 1: Demogr	aphic data c	of the investigated	groups (age in	years & gender).
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	(0 (No. = 40)	Control gro	up (No. = 40) Test value		P-value
		No.	%	No.	%		
Gender	Male	23	57.5%	20	50.0%	$X^2 = 0.453$	0.501
	Female	17	42.5%	20	50.0%		
Age	Mean± SD	8.20± 3.52		$8.38\pm$	8.38 ± 3.53		0.790
(years)	Median	7.5		7.5			
	Range	3.0-16.0		3.0-1	6.0		

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation, ZMWU: Mann-Whitney U Test, X²: Pearson Chi-Square test

Table 2: Laboratory data of cases on admission and control group

					Mean Paire		ed T Test		
		Mean	± SD	Median	Ra	nge	difference	Т	P- value
Hb.	Studied	10.43	±1.70	10.85	6.20	14.00	3.07	6.98	≤0.001
(gm/dL)	cases on								
	admission						-		
	control	13.5	±2.2	13	11	15			
TLC	Studied	9.49	±4.07	9.50	3.30	20.00	1.65	2.38	0.019
(×10 ³ /µL)	cases on								
	admission						_		
	control	7.84	±1.61	7.5	4	11			
BUN	Studied	74.40	±45.32	67.50	15.00	159.00	61.17	8.51	≤0.001
(mg/dL)	cases on								
	admission						-		
	control	13.23	±3.5	13	6	20			
S. creatinine	Studied	1.45	±1.34	0.90	0.10	4.70	0.89	3.342	≤0.001
(mg/dL)	cases on								
	admission						-		
	control	0.56	±0.1	0.5	0.1	0.7			
S. Albumin	Studied	3.15	±0.45	3.0	2.0	4.4	0.24	1.735	0.086
(g/dL)	cases on								
	admission						-		
	control	3.39	±0.75	4.4	3.4	5.4			
CRP (mg/L)	Studied	51.34	±35.51	42.0	11.0	201.0	48.59	8.65	≤ 0.001
	cases on								
	admission				_	_	-		
	control	2.75	±1	2.5	0	5			
ESR	Studied	67.82	±30.64	62.0	30.0	160.0	60.37	12.43	≤0.001
(mm/hr)	cases on								
	admission						-		
	control	7.45	± 1.80	7.5	4	11			
ASOT	Studied	411.85	±304.6	400.0	150.0	1479.0	295.18	6.1016	≤0.001
	cases on								
	admission						4		
	control	116.67	±28.87	35	50	190			

P value< 0.05 is significant, P value< 0.01 is highly significant, SD: Standard deviation,

Table 3: ARFI e measurement values of cases & control groups.

		Cases group	Control group	Mann-Whitne	y U Test
		(No. = 40)	(No. = 40)	Test value	P-value
ARFI-e	Mean± SD	10.64 ± 3.69	2.80 ± 1.27	$Z_{MWU} = 7.58$	<0.001
measurement	Median	10.18	2.65		
values (m/s)	Range	4.01 - 17.4	1.06 - 7.20		

Table 4: Validity of Renal elastography in prediction of acute glomerulonephritis.

Parameters	Cut off value	AUC	Sensitivity	Specificity	PPV	NPV	P value
Renal	3.98	0.992	100%	92.5%	93%	100%	<0.001
elastography							

PPV= Positive Predictive Value, NPV= Negative Predictive Value, AUC= Area Under Curve

Table 5: Relation between ARFI-e measurement values in the diagnosed types of glomerulonephritis in cases group

		ARFI-e meas					
	Mean	± SD	Median	Min.	Max.	Test value	P-value
PSGN	10.44	±4.14	9.80	4.01	17.40	1.306	0.520
RPGN	10.05	± 2.84	9.85	6.05	14.00		
Lupus Nephritis	12.03	±2.76	14.00	8.30	14.20		





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Figure 3: (A) and (B) showed right and left renal shear wave speed as evaluated using a 2D SWE. GE on a LOGIQ P9-General Electric ultrasound system.

DISCUSSION

This study included 40 children with acute GN due to different causes. Most of them are due to post-infectious cause, while smaller number are due to lupus nephritis and RPGN. All of cases have variable degree of proteinuria and hematuria. In addition. there were significant decreased hemoglobin concentration, and increased CRP, ASOT and ESR values in the patient group when compared to their levels in the control one. This is due to the acute inflammatory nature of AGN in the studied case. As regard, serum level of C3 and C4 among the studied cases: there was decrease in C3& C4 levels in (95%) and (12.5%) of cases respectively. Glomerulonephritis is singular illness; a rather. its not manifestation is depended upon the specific illness entity. It can manifest as a nephritic syndrome, isolated haematuria, or proteinuria [10].

C3 and C4 are the most commonly measured complement components in childhood AGN. Occasionally, a pattern of C3/C4 levels may provide insight into the

precise diagnosis. In MPGN and postinfectious glomerulonephritis, C3 levels drop but C4 levels stay the same. This shows that the alternative pathway is more often activated than the classical pathway. Activation of the classical pathway typically results in a decrease in both C3 and C4; thus, lupus nephritis & cryoglobulinemia are conditions in which both C3 and C4 are diminished. These indicators have the potential to provide a hint into the inflammatory mechanism underlying different types of acute GN [11].

In the present work, there was significant variance among the two groups regarding echogenicity of both right and left kidneys using US B-mode image with no significant differences between them regarding renal span, transverse diameter and cortical thickness. Regarding ARFI-e measurement values; Case group showed a elevation ARFI-e significant in measurement values compared to control Renal elastography group. can differentiate cases from control at cut off 3.98 with reasonable sensitivity and specificity. Gray-scale ultrasound (US)

utilized evaluate imaging is to parenchymal echogenicity thickness, alters, &kidney size. While diffuse kidney parenchymal disorders can demonstrate enhanced echogenicity &a rise or decline in corticomedullary differentiation, the interpretation of these results can be subjective. Recently, the shear wave velocity (SWV) is found to be directly proportional to the elasticity of the tissue, as determined by ultrasound elastography. The principle that underlies SWV is that the propagation velocity of ultrasound is faster in hard tissue than in soft one [12].

UE is becoming more essential in the assessment of thyroid nodules, liver fibrosis, prostate lesions, splenic stiffness, breast lesions, &lymph nodes [5]. Nevertheless, the kidney parenchyma demonstrates greater anisotropy than the liver as a result of its double compartment structure. composed of the cortex &medulla. as well as its extensive vascularization. Consequently, the elastography utilization of the in assessment of kidney disorders isn't widespread. There are a few UE studies that have assessed kidney parenchymal diseases; with lack of pediatric studies [13].

The elevated acoustic radiation force impulse elastography measurement values in the case group are in accordance with Yoğurtçuoğlu & Damar, who studied the average ARFI in 30 children with GN and similar number of comparable age children as controls. The researchers discovered that the values of children with glomerular disorders are greater than those of controls Nevertheless, [10]. this result isn't definitely generalizable, as all of the participants had already initiated steroid therapy at the time of the examination. In addition, their studied cases included

mainly minimal change disease (MCD) & segmental glomerulosclerosis focal (FSGS) cases. FSGS cases have variable degree of fibrosis, while MCD has no definite gross pathology. So, the nature of their cases doesn't represent typical acute inflammatory nature of AGN. In contrast the present work included only cases that have acute inflammatory state of the kidney as evidenced by clinical and laboratory data (all patients have proteinuria, hematuria. raised inflammatory markers, and consumed C3 +/- C4).

Proliferation capillary of &endothelial cells &invasion of inflammatory cells result in the constricting of the glomerular capillary wall during the acute phase of glomerulonephritis. The loss of function in certain glomeruli is caused by blood stagnation [14]. These changes can explain elevated ARFI in the case group.

In this aspect, ONO et al found increased SWV in APSGN, with significant correlation with disease activity. However, he studied only one case of APSGN [15]. Actually, no study has yet measured SWV in a substantial number of children with acute glomerulonephritis, to the greatest of our current knowledge.

Most of the previous studies included chronic cases of GN for adult patients not children. For example, SWV may have role in detection of renal fibrosis in chronic cases as approved by Cui et al., who studied cases with nephropathy and classified them into 4 categories based on the results of kidney biopsy. Using the ARFI-e method, groups exhibiting fibrosis exhibited statistically significant greater SWV values in comparison to those with no fibrosis. Nevertheless, no statistically significant variance was observed in the SWV values among the fibrosis-affected groups [16].

In the same way, Leonget et al. parenchymal stiffness assessed in individuals with CKD using SWE & found that the patient group had higher SWV values than the control group [17]. Maralescu FM found similar results, in addition they correlate it with the renal function and inflammation and recommend them to be utilized in clinical practice routinely [18]. Conversely to the mentioned investigations Bob et al. documented that the ARFI measurements of the adult cases with Glomerulonephritis were lower than control one [19]. Also, Grossmann et al. demonstrated that US elastography's diagnostic efficacy for identifying glomerulonephritis was superior to that of B-mode parameters, However, they included adult patients with many stages of GN including chronic stages of CKD which is not similar to our studied cases [20].

In the current research, there was no significant variances ARFI-e in measurements between different subtypes of acute glomerulonephritis in patient group. This can be attributed to the similar inflammatory nature of all subtypes. All subtypes of AGN have the same gross pathology of kidney with capillary & endothelial proliferation cell & invasion inflammatory cell causing vascular narrowing which mav be responsible for such changes of SWV. ABBREVIATIONS

LIMITATIONS OF THE STUDY

The total number of cases is small. In addition, our results about ability of elastography diagnose to different subtypes was insignificant. It may be due to the small number of different subtypes or may be actual finding. So. futures studies including larger groups of different subtypes of AGN are needed to confirm the results of the present work. No follow up of cases was done by renal elastography after resolution of the acute attack. Follow up is important here to compare each patient with himself after regaining normal renal morphology.

RECOMMENDATIONS

Further studies with larger sample size and longer follow-up are needed to assess the diagnostic performance of US elastography for the early detection of different subtypes of glomerulonephritis in children.

CONCLUSION

As a bedside easily applicable, noninvasive method for the early detection of AGN, the ARFI-e technique showed promising results. However, it cannot differentiate between among different types of AGN. Further studies on larger number of AGN in children is need.

ADDREVIA	nons			
AGN	Acute glomerulonephritis.			
SWS	tissue shear wave speed			
ARFI-e	Acoustic radiation force impulse elastography (ARFI-e) measurement			
ROC	Receiver operating characteristic			
APSGN	Acute post-streptococcal glomerulonephritis			
LN	lupus nephritis			
RPGN	Rapidly progressive GN			
UE	Ultrasound elastography			
MRE	Magnetic resonance elastography.			
FSGS	focal segmental glomerulosclerosis			
MCD	minimal change disease			

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STATEMENTS

Ethics approval and consent to participate:

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of the Faculty of Medicine, Assiut University, Assiut, Egypt with ethical N 3357841. And informed written consent was obtained in every case from their legal guardians.

Consent for publication: The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

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