Journal of Advances in Medicine and Medical Research

Volume 34, Issue 24, Page 222-229, 2022; Article no.JAMMR.94948
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Early Prediction of Asymptomatic Cardiac Insult in Pediatric Patients with Lysosomal Storage Diseases

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2022/v34i244920

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/94948

Original Research Article

Received: 12/10/2022
Accepted: 20/12/2022
Published: 28/12/2022

ABSTRACT

Introduction: An essential separate and curable cause of cardiomyopathy, lysosomal storage disorders are defined by the increasing buildup of undigested material within lysosomes, which causes cellular dysfunction in a variety of organs, including the heart. Due to the function of oxidative stress in many inborn errors of metabolism, many studies are evaluating oxidative stress and hence the role of antioxidants in patients with LSDs.
The Aim of This Study: Was to perform a comprehensive evaluation of cardiac function in patients with a lysosomal storage disease and measure a biomarker that could be associated with impaired cardiac function and correlate this biomarker with echo findings.

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Patients and Methods: This were a prospective case-control study including 30 patients with LSDs and an equal number of healthy individuals of matched age and sex who served as the control group. The study was conducted at the Pediatric Department of Tanta University Hospital's Medical Genetics and IEM Unit. All participants were subjected to a comprehensive history and physical examination, serum NT-proBNP, and comprehensive cardiac evaluation was done using tissue Doppler imaging and speckling tracking echo.
Results: There was evidence of subclinical diastolic and systolic dysfunction in patients who had no symptoms with LSDs assessed by STE and TDI in comparison with the healthy controls. Patients with LSDs had significantly higher levels of serum NT-proBNP than controls.
Conclusion: These findings suggest that patients with LSDs have a subclinical cardiomyopathy as compared to healthy controls.

Keywords: LSDs; NT-proBNP; cardiomyopathy; lysosomes.

1. INTRODUCTION

A category of more than 50 disorders known as lysosomal storage disorders (LSDs) are brought on by a lack of membrane transporters, lysosomal enzymes, or other proteins essential to lysosomal function. The prevalence of LSDs is 1 in 5,000 live births, and they can be divided into several categories based on the kind of material they store, such as lipid storage diseases, mucopolysaccharidosis, and glycoproteins [1-4].

The majority of LSDs have a progressive course that often leads to severe clinical manifestations and may end by death. The resulting phenotype usually associated with LSDs results from the abnormal accumulation of undegraded substrates causing cellular malfunction in several organs, including the heart, brain, bone, muscle, skin, and spleen [5].

Approximately 5% of juvenile cardiomyopathies are caused by LSDs, which may have a significant effect on the heart and are a considerable, unique, and curable causes of cardiomyopathy in children. Cardiac symptoms are a frequent finding in many LSDs and may vary from apparent morphological abnormalities (such as cardiomegaly, cardiomyopathy, coronary artery diseases, and cardiac valve anomalies) to more quietly functional problems including conduction anomalies and arrhythmias.

Cardiovascular involvement a major source of death and morbidity among MPS patients as well as other LSDs. There is an increasing need to develop novel noninvasive means of early prediction of potential cardiac involvement in patients with LSDs [4-8].

In an effort to contain the increasing quantity of macromolecules that have not been digested, metabolites that collect in LSDs drive a growth in the size and number of lysosomes. These activities may set off a number of pathogenic intracellular processes, including oxidative stress, inflammation, altered lipid trafficking, and autophagy, which lead to malfunction in cells and tissues. As a result, biomolecules (proteins, lipids, and DNA). are damaged due to the excessive generation of reactive species and/or the depletion of the tissue's antioxidant properties.

2. METHODS

2.1 Study Population and Design

This randomized controlled trial was conducted at the unit of Medical Genetics and Inborn Errors of Metabolism at the Pediatric Department of Tanta University Hospital (TUH) for a period of 2 years starting from August 2019 to August 2021. This study was conducted on thirty patients diagnosed and followed with an LSD at the Medical Genetics and IEM Unit at the Pediatric Department of TUH during the period of the study and an equal number of healthy children of matched age and sex without any known chronic disorder served as a control group.

2.2 Inclusion Criteria

Pediatric patients with a lysosomal storage disease aged from 1 to 18 years were diagnosed by enzyme assay for LSDs.

2.3 Exclusion Criteria

Patients with congenital heart diseases, symptomatic cardiac complications, and associated systemic diseases like diabetes mellitus, cancer, and bronchial asthma were

excluded as these diseases may cause cardiac diseases, alter the patient's response to the used drug, and may affect the level of the studied biomarkers.

2.4 Measures

Using several echocardiographic modalities, echocardiography was used to evaluate heart function. Systolic and diastolic mitral annulus velocities, as well as the left ventricular myocardial performance index, were assessed using traditional echocardiography techniques like M mode and Tissue Doppler imaging. The left ventricular myocardial performance index was determined by the formula Tei index = a 0 - b'/b', where a' is the time between the end of the A'-wave and the beginning of the E'-wave and b' is the time from the start to the end of the S'-wave. Global radial, global area, global circumferential, and global longitudinal strains were measured using three-dimensional speckle-tracking echocardiogram. Apical 2-, 3-, and 4-chamber viewpoints were used to determine longitudinal strain. Short-axis parasternal views were used to evaluate the radial and circumferential strain. The left ventricular entire volume in three dimensions was then measured during a breath hold in order to determine the left ventricular ejection fraction. Using an area of interest identified at end systole as a starting point, three-dimensional strain tracking is carried out. The area of interest's three-dimensional strain is constructed from an endocardial and an epicardial mesh and is automatically created in the end-systolic frame. For a clearer view, the user may manually adjust the area of interest.

2.5 Endpoints

The primary outcome was to perform a comprehensive evaluation of cardiac function in asymptomatic patients with a lysosomal storage disease. The second aim was to measure a biomarker that could be associated with impaired cardiac function in those patients and correlate this biomarker with echo findings.

2.6 Statistical Analysis

Version 20.0 of the IBM SPSS software program was used to analyse the data (Armonk, NY: IBM Corp). Chi-square test was used to compare qualitative variables that were provided as numbers and percentages. If they were normally distributed, quantitative variables were shown as means and standard deviation. Shapiro-Wilk test was used to determine whether the data had a normal distribution or not. To compare normally distributed numeric values across groups, one-way analysis of variance was utilised. Quantitative factors in the same group were compared prior to and after the therapy using a paired t-test. The Kruskal-Wallis test was used to assess quantitative variables with non-normal distributions; additional analysis, using the Mann-Whitney (U) test to compare each two groups, was then carried out. The p-Value of less than 0.05 was regarded as significant. It was done using the correlation coefficient (r). To eliminate recollection bias, the echocardiographic examination was done by the same observer (O.E.) twice within a week in order to measure intra-observer variability. The echocardiographic exams were carried out by a second observer (D.E.), who was blind to the first observer's findings in order to measure inter-observer variability.

3. RESULTS

This table shows that 22 (73.3%) of the s tudied patients were diagnosed with mucopolysaccharidosis, 7 (23.3%) of the studied patients were diagnosed with sphingolipidosis and 1 (3.3%) was diagnosed with free sialic acid storage disease.

The mean value of serum NT-proBNP was significantly higher in patients than in controls, (P-value < 0.001) Table 3.

Regarding MPS patients, all patients with MPS type 1, MPS type 2, and MPS type 4 are receiving their specific enzyme replacement therapy. There is no enzyme replacement therapy available yet for MPS type 3 (Sanfilippo), Neiman-Pick disease, Farber disease, and free sialic acid storage disease.

3.1 Echocardiographic Data in the Included Children

Regarding the echocardiographic evaluation of the study individuals, the median mitral É/Á ratio and the mean left ventricular systolic mitral annulus velocity (S) were both considerably lower in the examined patients as compared to the healthy controls. Furthermore, when comparing the diseased group to the healthy control group, there was a statistically significant rise in doppler imaging's measurement of left ventricular myocardial function. Additionally, the average value of the 2D longitudinal strain, the

3D global longitudinal strain, the 3D global radial strain, the 3D global circumferential strain, and the 3D global area strain decreased statistically significantly in the diseased group in comparison to the healthy control group (p-value<0.001) Tables 5 & 6.

4. DISCUSSION

Purpose of this research was to conduct a thorough examination of heart function in individuals with a lysosomal storage disease, measure a biomarker (N-terminal proBNP) that could be associated with impaired cardiac function and correlate this biomarker with echocardiographic findings in those patients.

Despite the fact that numerous studies have shown the importance of NT-proBNP as a diagnostic markers for cardiac dysfunction, its assessment is not typically used in routine screening in children with heart disease because there is little information about its accuracy, validity, and function in this age group [9].

Table 1. Demographic data of the studied subjects

	Cases (n = 30)		Control (n = 30)		p
	No.	**%**	**No.**	**%**	
Sex					
Male	23	76.7	24	80.0	0.754
Female	7	23.3	6	20.0	
Age (years)					
Min. – Max.	1.0 – 18.0		1.0 – 14.0		0.630
Median (IQR)	4.50 (2.50 – 10.0)		5.50 (3.0 – 10.0)		
Consanguinity					
Negative	4	13.3	27	90.0	<0.001*
Positive	26	86.7	3	10.0	
Family history of similar condition					
Negative	13	43.3	30	100.0	<0.001*
Positive	17	56.7	0	0.0	

Table 2. Distribution of the studied patients according to their type of lysosomal storage disease (n = 30)

	No.	**%**
MPS	**22**	**73.3**
-Type 1 MPS	**4**	**13.3**
-Type 2 MPS	3	10.0
-Type 3 MPS	6	20.0
-Type 4 MPS	9	30.0
Sphingolipidosis	**7**	**23.3**
-Gaucher disease	5	16.6
-Nieman Pick disease	1	3.3
-Farber disease	1	3.3
Free Sialic acid storage disease	**1**	**3.3**

Table 3. Comparison between the studied patients and controls according to serum NT-proBNP

Basal laboratory markers NT- proBNP (pg/ml)	**Cases (n = 30)**	**Control (n = 30)**	**t**	**p**
Min. – Max.	313.0 – 506.0	170.0 – 288.0	16.902*	<0.001*
Mean ± SD.	433.63 ± 51.74	231.17 ± 40.34		

NT-proBNP: N-terminal pro-brain natriuretic peptide

Table 4. Summary of enzyme replacement therapy among LSDs patients in this study

Disease	Total Number	ERT
MPS		
Type 1	4	4
Type 2	3	3
Type 3	6	0
Type 4	9	9
Sphingolipidosis		
Gaucher disease	5	5
Neiman Pick disease	1	0
Farber disease	1	0
Free sialic acid storage disease	1	0

MPS; mucopolysaccharidosis

Table 5.Tissue Doppler imaging parameters of the studied patients and controls

	Cases (n = 30)	Control (n = 30)	Test of Sig.	p
LV S (cm)				
Min. – Max.	3.0 – 9.0	6.0 – 8.0	t=	0.002*
Mean ± SD.	5.77 ± 1.55	6.80 ± 0.66	3.362*	
Mitral E'/A'				
Min. – Max.	0.53 – 1.30	1.10 – 1.90	U=	<0.001*
Median (IQR)	0.78(0.66 – 0.88)	1.50 (1.40 – 1.70)	16.0*	
MPI				
Min. – Max.	0.30 – 0.95	0.30 – 0.50	U=	0.017*
Median (IQR)	0.40 (0.40 –0.50)	0.40 (0.30 – 0.40)	297.0*	

(LV S= mitral annulus peak velocity during ventricular systole, È=peak velocity during early ventricular diastole, À= Peak velocity during atrial contraction; MPI= myocardial performance index)

Table 6. Speckle tracking echocardiography parameters of the studied patients and controls

	Cases (n = 30)	Control (n = 30)	Test of Sig.	p
2D LS				
Min. – Max.	-25.0 – -4.0	-27.0 – -20.0	t=	<0.001*
Mean ± SD.	-16.10 ± 5.27	-23.30 ± 1.84	7.067*	
3D-GLS%				
Min. – Max.	-25.0 – -4.0	-25.0 – -17.0	t=	<0.001*
Median (IQR)	-16.10 ± 5.27	-20.63 ± 2.27	4.330*	
3D-GCS%				
Min. – Max.	-25.0 – -7.0	-23.0 – -15.0	U=	<0.001*
Median (IQR)	-12.0(-16.0 – -8.0)	-18.0(-21.0 – -16.0)	154.0*	
3D-GAS%				
Min. – Max.	-33.0 –- 10.0	-29.0 – -20.0	t=	<0.001*
Median (IQR)	-18.80 ± 5.30	-23.97 ± 2.93	4.672*	
3D-GRS%				
Min. – Max.	18.0 – 50.0	30.0 – 45.0	U=	<0.001*
Median (IQR)	25.0 (22.0 – 35.0)	38.0 (33.0 – 40.0)	170.50*	

2D LS = two-dimensional longitudinal strain, GLS: global longitudinal strain, GCS: global circumferential strain, GRS: global radial strain, GAS: global area strain

In this study, there was a statistically significant rise in serum NT-proBNP in LSDs patients in comparison to healthy controls. This agrees with results obtained by Coats, et al. who reported that NT-proBNP values were higher in Fabry disease patients in their study performed on 117 patients in comparison to healthy controls [10].

Table 7. Correlation between NT- proBNP (pg/ml) and different parameters

	NT-proBNP (pg/ml)	
	r	**p**
Mitral E/A	-0.813	<0.001*
MPI	0.306	0.017*
2D LS	-0.711	<0.001*
3D-GLS%	-0.534	<0.001*
3D-GCS%	-0.549	<0.001*
3D-GAS%	-0.537	<0.001*
3D-GRS%	-0.548	<0.001*

È=peak velocity during early ventricular diastole, À= Peak velocity during atrial contraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; MPI= myocardial performance index; 2D LS = two-dimensional longitudinal strain; GAS: global area strain; GCS: global circumferential strain; GLS: global longitudinal strain; GRS: global radial strain.

In this study, regarding our echocardiographic results, there was a substantial decrease in left ventricular diastolic functions (mitral E '/A ') in LSDs' patients compared to the group of healthy controls as detected by TDI. Also, left ventricular myocardial performance index was significantly increased in patients with LSDs in comparison to healthy controls indicating both systolic and diastolic dysfunction. Moreover, STE in our study revealed that the LSDs patients had abnormal systolic function presented by a significantly lower left ventricular two-dimensional longitudinal strain, three-dimensional global area strain and global radial strain in comparison to those of the healthy control.

This result agrees with the result obtained by Nijmeijer, et al. in their case-control study performed on the cardiac evaluation of patients with MPS type III. They reported that the mitral E'/A' ratio was much lower in patients than in controls, which is indicative of LV diastolic dysfunction. Also, Nijmeijer, et al. reported that left ventricular 2D-global longitudinal strain in pediatric and in adult patients with MPS type III was considerably less detrimental than controls. The longitudinal strain is a negative number because it reflects a myocardial shortening [11].

Also, Borgia, et al. reported similar findings. They compared Fifteen MPS patients (types I, II, III, IV, and VI) to healthy controls and assessed echocardiographic features and myocardial deformation measurements. Ten patients were receiving enzyme replacement therapy. Patients showed left ventricular diastolic dysfunction compared to healthy controls evidenced by a significantly lower E '/A 'ratio. Also, they reported that left ventricular two-dimensional global circumferential strain, and global radial strain were significantly lower in the studied MPS patients than in healthy controls (P=0.014, P=0.02, P=0.012, respectively); however, global longitudinal strain did not achieve statistical significance between the two groups [12].

Additionally, Shanks, et al. assessed myocardial strain using 2-dimensional speckle tracking in individuals with Fabry disease, a lysosomal storage disorder brought on by galactosidase, as well as left ventricular systolic performance using conventional echocardiography. A deficit that may cause complications in multiple organs and systems, including the brain, kidneys, and heart, owing to protein accumulation in the tissues. The average duration of enzyme replacement treatment for the 16 patients in the study was more than six years. All patients showed normal left ventricular systolic function as determined by EF measurement, however the research noted a lower average left ventricular global longitudinal strain measurement in this group compared to healthy controls, indicating that this measure is more sensitive to assessing systolic function in this community of patients. However, they reported normal circumferential strain among studied patients [13].

Additionally, Andrade et al. assessed myocardial deformation using the two-dimensional speckle-tracking technique and echocardiography in patients with MPS to assess the left ventricle. They assessed the global longitudinal strain value of the left ventricle and found that, of the 16 individuals studied, 56.2% exhibited abnormal GLS readings [14].

Assessment of this parameter in individuals with lysosomal storage disorders is hardly documented. The discrepancy in these results can be attributed to the type of LSD, duration of enzyme replacement therapy, sample size, and

different techniques as 2D-STE was used in the other studies however, in our study 3D-STE was performed.

Progressive GAG infiltration of valvular tissues, myocardial, coronary arteries, and the conduction system may be responsible for MPS-related cardiac problems [12].

An endomyocardial biopsy performed on a patient with MPS IIIA revealed inflated cardiomyocytes with storage vacuoles holding GAGs. This might be the reason for the initial left ventricular dysfunction that has been shown in several investigations [11].

STE enables the LV deformation's subclinical impairment to be seen. Experimental research and autopsy results may be used to understand the modification of strain components in MPS. Children with MPS had previously been discovered to have an accumulation of storage cells in the walls of their coronary arteries, affecting the whole course of the vessels and leading to decreased coronary flow. Chronic inflammation and glycosaminoglycan deposition boost cytokine release, and oxidative stress-induced formation of reactive radicals may be to blame for permanent cardiac alterations [12].

Regarding the correlation of N-terminal proBNP with various TDI and STE parameters, there was a significant negative correlation between NT-proBNP and left ventricular systolic mitral annulus velocity (S), Mitral E ‘/A, LV two-dimensional longitudinal strain, three-dimensional global longitudinal strain, three-dimensional global circumferential strain, three-dimensional global area strain and three-dimensional global radial strain. While there was a significant positive correlation between NT-proBNP and MPI.

Şimşek, et al.reported a significant negative correlation between serum levels of NT-proBNP and ventricular global longitudinal strain and circumferential strain in their study to evaluate left ventricular functions with 2D-STE and NT-proBNP in diabetic children [15].

Moreover, Nur İzgi, et al. reported a significant negative correlation between NT-proBNP and ventricular global longitudinal strain in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis [16].

On the other hand, Kato, et al. reported that no correlation was seen between NT-proBNP and LV GLS by STE, but there were significant correlations between NT-proBNP and cytokines in patients with Kawasaki disease suggesting that NT-proBNP might be a marker of inflammation in these patients [17].

The discrepancy in results can be attributed to the difference in the sample size, the nature of the primary disease, and the method of echocardiographic evaluation (2D vs 3D).

5. CONCLUSIONS

Patients with LSDs had significantly higher levels of NT-proBNP than controls denoting ongoing cardiac involvement. There is evidence of subclinical diastolic dysfunction *(significant decrease in mitral annulus E'/A')* and systolic dysfunction *(significant decrease in LV longitudinal. circumferential. area and radial strain)* in asymptomatic LSDs patients assessed by STE and TDI compared to healthy controls.

ETHICAL APPROVAL AND CONSENT

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees of Faculty of Medicine, Tanta University and obtaining written informed consent from children guardians.

ACKNOWLEDGEMENTS

Authors wish to thank all the patients who participated in the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Coutinho MF, Prata MJ, Alves S. A shortcut to the lysosome: the mannose-6-phosphate-independent pathway. Mol Genet Metab. 2012;107(3):257–66.
2. Ferreira CR, Gahl WA. Lysosomal storage diseases. Transl Sci Rare Dis. 2017;2:1–71.
3. Marques ARA, Saftig P. Lysosomal storage disorders – challenges, concepts

and avenues for therapy: Beyond rare diseases. J Cell Sci. 2019;132(2).

4. Nair V, Belanger EC, Veinot JP. Lysosomal storage disorders affecting the heart: a review. Cardiovasc Pathol [Internet]. 2019;39(2019):12–24. Available from: Available:https://doi.org/10.1016/j.carpath.2018.11.002
5. Martina JA, Raben N, Puertollano R. SnapShot: Lysosomal Storage Diseases. Cell [Internet]. 2020;180(3):602-602.e1. Available:http://dx.doi.org/10.1016/j.cell.2020.01.017
6. Mueller P, Attenhofer Jost CH, Rohrbach M, Valsangiacomo Buechel ER, Seifert B, Balmer C, et al. Cardiac disease in children and young adults with various lysosomal storage diseases: Comparison of echocardiographic and ECG changes among clinical groups. IJC Hear Vessel. 2013;2(2014):1–7.
7. Laney DA, Gupta D, Wechsler SB. Getting to the Heart of the Matter: Lysosomal Storage Diseases That Manifest a Cardiac Phenotype. Curr Genet Med Rep. 2018;6(2):28–42.
8. Canda E, Köse M, Kağnıcı M, Dondurmacı M, Uçar SK, Sözmen E, et al. Evaluation of Cardiovascular Involvement and Cytokine Levels in Patients with Mucopolysaccharidosis. J Pediatr Res. 2019;6(2):121–8.
9. Li N, Zhang Y, Fan S, Xing J, Liu H. BNP and NT-proBNP levels in patients with sepsis. Front Biosci (Landmark Ed. 2013 Jun;18:1237–43.
10. Coats CJ, Parisi V, Ramos M, Janagarajan K, O'Mahony C, Dawnay A, et al. Role of Serum N-Terminal Pro-Brain Natriuretic Peptide Measurement in Diagnosis of Cardiac Involvement in Patients With Anderson-Fabry Disease. Am J Cardiol [Internet]. 2013;111(1):111–7. Available:https://www.sciencedirect.com/science/article/pii/S0002914912020723
11. Nijmeijer SCM, de Bruin-Bon RHACM, Wijburg FA, Kuipers IM. Cardiac disease in mucopolysaccharidosis type III. J Inherit Metab Dis [Internet]. 2019;42(2):276–85. Available:https://onlinelibrary.wiley.com/doi/abs/10.1002/jimd.12015
12. Borgia F, Pezzullo E, Schiano Lomoriello V, Sorrentino R, Lo Iudice F, Cocozza S, et al. Myocardial deformation in pediatric patients with mucopolysaccharidoses: A two-dimensional speckle tracking echocardiography study. Echocardiography [Internet]. 2017;34(2):240–9. Available:https://onlinelibrary.wiley.com/doi/abs/10.1111/echo.13444
13. Shanks M, Thompson RB, Paterson ID, Putko B, Khan A, Chan A, et al. Systolic and Diastolic Function Assessment in Fabry Disease Patients Using Speckle-Tracking Imaging and Comparison with Conventional Echocardiographic Measurements. J Am Soc Echocardiogr [Internet]. 2013;26(12):1407–14. Available: https://www.sciencedirect.com/science/article/pii/S0894731713007281
14. Andrade MFA, Guimarães ICB, Acosta AX, Leão EKEA, Moreira MIG, Mendes CMC. Left ventricular assessment in patients with mucopolysaccharidosis using conventional echocardiography and myocardial deformation by two-dimensional speckle-tracking method. J Pediatr (Rio J). 2019;95(4):475–81.
15. Şimşek A, Turan Ö, Çiftel M, Kardelen F, Durmaz E, Özdem S, et al. Evaluation of left ventricular functions with two-dimensional speckle-tracking echocardiography (2D-STE) and N-terminal ProBNP in diabetic children. Turk J Pediatr. 2018;60(6).
16. Nur İzgi T, Barutcu Ataş D, Ataş H, Akaslan D, Ilgın C, Velioğlu A. Prediction of subclinical left ventricular dysfunction by speckle-tracking echocardiography in patients with anti-neutrophil cytoplasmic antibody--associated vasculitis. Arch Rheumatol. 2022;37.
17. Kato M, Ayusawa M, Watanabe H, Komori A, Abe Y, Nakamura T et al. Cardiac function on 3-D speckle tracking imaging and cytokines in Kawasaki disease. Pediatr Int. 2018;60(4):342–8.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/94948