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Original article

Prevalence of congenital heart defects among 54 Egyptian children with Maple syrup urine disease

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1. Introduction

Maple syrup urine disease (MSUD) is an autosomal recessive disorder caused by a defect in any of the subunits of the mitochondrial branched-chain alfa ketoacid dehydrogenase (BCKAD). The metabolic defect results in accumulation of branched-chain amino acids (BCAAs) (leucine, isoleucine and valine) and their keto acids [1].

Amino acids are key nutrient molecules essential for cell growth, survival, and normal function. In addition to providing building blocks for protein synthesis, many amino acids are essential ingredients for biosynthesis of other molecules as the source of nitrogen and carbon [2]. Some amino acids, including branched-chain amino acids, also have been shown to possess a potent signaling function to regulate global growth and metabolism [3]. Therefore, the impact of amino acid metabolism on embryonic development and human congenital diseases has long been recognized [4].

The clinical manifestations of classical MSUD are mostly neuropathic, including seizures and mental retardation [5]. However, recent studies from animal models of MSUD raise concerns about the potential adverse impact of branched –chain amino acid metabolic defects on cardiac development and function [4].

2. Subjects and methods

This cross-sectional descriptive study involved 54 children with MSUD who were recruited from the Genetics clinic, Pediatric Hospital, Ain Shams University. Their ages ranged from 1 month to 7.5 years with a mean of (26.7 months ± 21.5). Informed consent was obtained from guardians of all examined cases before participation in the study which was approved by the Institutional Ethical Review Board.

The diagnosis of MSUD was confirmed in all patients by high serum levels of leucine, isoleucine, valine, elevated leucine/alanine ratio and leucine/phenylalanine ratio by Tandem mass spectrometry (LC-MS/MS). All patients were subjected to history taking and clinical evaluation for cardiac symptoms and signs. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments in humans.

A standard two-dimensional (2D), M-mode, color flow (CF), continuous wave (CW) and pulsed wave (PW) Doppler echocardiography was performed for patients using the segmental sequential approach [6]. Views included subcostal view (short axis, four chamber and coronal), parasternal view (long axis and short axis),

Abbreviations: MSUD, Maple syrup urine Disease; CHD, Congenital heart defects; ASD, Atrial septal defect; BCAA, Branched chain amino acids; BCKA, Branched chain keto acids; LC-MS/MS, Liquid chromatography-Tandem mass spectrometry.

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Table 1
Echocardiographic findings in MSUD patients.

		Frequency	Percentage (%)
Normal		29	53.7
Abnormal			
	Thickened fenestrated interatrial septum	17	31.4
	Secundum atrial septal defect	4	7.4
	Mitral valve prolapsed and regurgitation	2	3.7
	Pulmonary valve stenosis	1	1.9
	Bilateral branch pulmonary stenosis	1	1.9
	Total	25	46.3
Total		54	100

apical view (four chambers and five chambers) and suprasternal view (short axis and long axis). Echocardiography was done using the Vivid E9 machine (GE Vingmed Ultrasound, Horton, Norway) and pediatric multiplane ultrasound probe with a frequency ranging from 1.5 to 4.5 MHz and a 120- degree field of view (M5S-D,S/N 000002891,Portugal).

The anatomy was described in details including the situs of the heart, atrio-ventricular concordance, and relation of the great vessels, interatrial and interventricular septae, pulmonary and systemic venous drainage, morphology and excursion of cardiac valves, cardiac chamber sizes and ventricular function. The study included the description of the aortic arch anatomy, anatomy of the great vessels, the presence of PDA and measurement of the pulmonary artery pressure. The presence of patent foramen ovale (PFO) was considered normal finding.

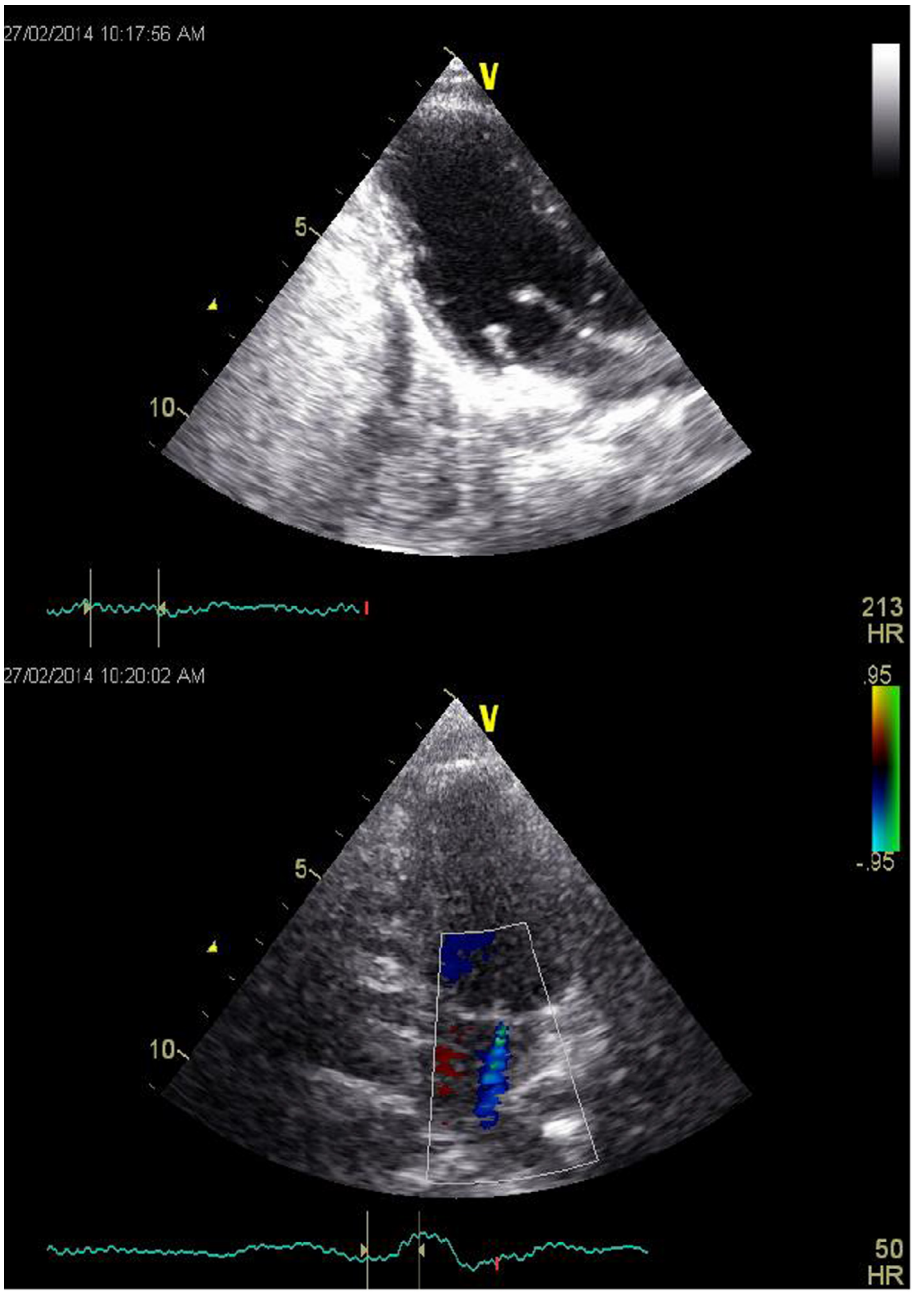

Fig. 1. 2D and color flow Doppler echocardiography showing thickened prolapsed regurgitating mitral valve in patient No. 41.

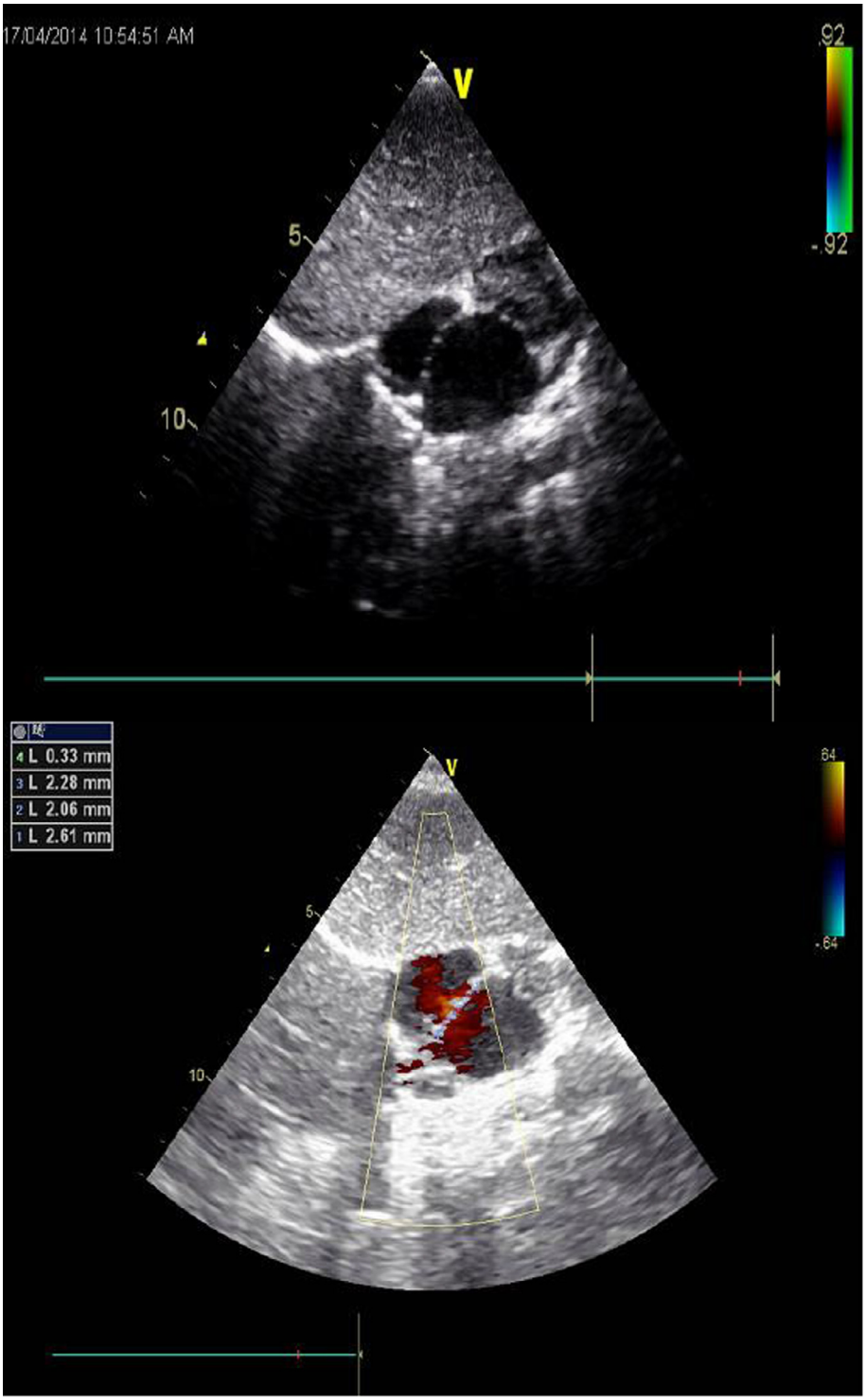

Fig. 2. 2D and color flow Doppler echocardiography showing fenestrated interatrial septum in patient No. 22.

3. Statistical analysis

Statistical analysis was done using SPSS program version 17. Qualitative data is presented as number and percentage and quantitative data is presented as mean ± standard deviation.

4. Results

Twenty-five (46.3%) MSUD patients had cardiac affection. Twenty-one of the affected patients (84%) had defects related to the interatrial septum in the form of fenestrated thickened interatrial septum (17,68%) and secundum type atrial septal defect (ASD) (4, 16%). Abnormal echocardiographic findings among MSUD patients are shown in Table 1 and Figs. 1 and 2.

5. Discussion

Due to the overwhelming neurological manifestations of MSUD, little emphasis has been given to the prenatal or postnatal involvement of other organs that are involved in the metabolism of BCAA

despite the fact that most of the BCAAs are transaminated outside the nervous system in the liver, muscles, and heart [7]. It has been shown that skeletal muscles of newborn patients with MSUD show focal diffuse destruction of myofibrils with evidence that the increased levels of amino acids were not the cause [8]. Recent studies have shown that the impaired branched-chain alpha keto acid-dehydrogenase complex (BCKD) function can be pathologic to the heart[9].

The prenatal occurrence of such early anomalies denotes that the pathological effect of the disease on the growing embryonic cardiac muscle cells could not be compensated by the maternal degradation of excess BCAA/BCKA. It is known that BCAA/BCKA can inhibit pyruvate and fatty acid transport and utilization [10]. The BCKD complex is genetically linked with the pyruvate dehydrogenase complex (PDH) because they share extensive homology in their subunit composition and regulation [4].

The underlying mechanisms for the clinical manifestations of MSUD are still not well established, but the adverse impact on glutamine transport and the induction of reactive –oxygen species (ROS) have been implicated [11]. Recently, Sun et al., 2011 [4] have established that a mitochondrial targeted 2C-type ser/thr protein phosphatase, PP2Cm, is the endogenous phosphatase of the (BCKD) and functions as a key regulator in branched-chain amino acid catabolism and homeostasis. They found that genetic inactivation of PP2Cm in mice leads to significant elevation in plasma concentrations of BCAAs and BCKAs at levels similar to those associated with intermediate mild forms of MSUD. In addition to neuronal tissues, PP2Cm was found to be highly expressed in the cardiac muscle and its expression is diminished in hearts under pathologic stresses and thus, defects in PP2Cm-mediated catabolism of branched –chain amino acids can be a potential novel mechanism not only for MSUD but also for CHD and heart failure.

Furthermore, it has also been found that fibroblasts from patients with MSUD tend to accumulate damage in mitochondrial DNA (mtDNA) as well as nuclear DNA with a corresponding reduction in mitochondrial transcription, mtDNA copy number and pyruvate dehydrogenase[12]. Recent studies have shown that CHDs are commonly associated with a mutation in mtDNA in 9 out of 22 patients with CHD undergoing cardiac surgery [13]. The above studies point to the possibility of derangement of mitochondrial metabolism during cardiac muscle development leading to the higher frequency of CHD among MSUD patients.

To the best of our knowledge, there has been no information regarding the prevalence of CHD among patients with MSUD. However, few reports of autopsies of deceased patients with MSUD showed cardiac enlargement or congestion [14–16]. Also, a case report of CHD in a patient with MSUD was reported by Fukutomi et al., 1993 [17] in a 2-year old Japanese girl with tetralogy of Fallot who had undergone intracardiac repair in 1989.

In this study, (46.3%) of the MSUD patients had cardiac involvement. Among the affected children, defects related to the interatrial septum were the commonest (84%) in the form of fenestrated thickened interatrial septum (68%) and secundum type ASD (16%). The remaining encountered findings included prolapsed mitral valve leaflets with valve regurgitation (8%), branch pulmonary artery stenosis (4%), and pulmonary valve stenosis (4%).

Unfortunately, there is no reliable data on the prevalence of CHD among Egyptian children due to lack of computer records in most of the hospitals, lack of congenital malformation registry, defective registration of the cause of death, poor coordination between cardiac outpatient clinics at ministry hospitals and pediatric clinics at the private sector; in addition to the absence of autopsy procedures to detect the incidence of CHD among the stillborn [18].

Atrial septal defects constitute 8–13% of all CHDs. These types of defects probably occur as a result of programmed cell death in particular areas of the septum primum during embryogenesis [19] Pathologically, there is deficiency of the septal tissue in the region of fossa ovalis. Most of the time, these are single defects, although, occasionally multiple defects and fenestrated defects can also be seen in a frequency around 7% [19,20]. In this study, defects related to the interatrial septum were the commonest encountered cardiac abnormality as they were detected in 84% of the affected children. This is in contrast to an Egyptian study done by Bassili et al., 2000 [18] who detected ASDs in 13.6% of 881 school children in Alexandria with a prevalence of (1.4/10,000). This difference could be attributed to the differences in the ages and the nature of the studied population in both studies as they included older aged school children who were not suffering from any underlying genetic diseases. We believe that it would be more accurate to compare our results with other studies that include children belonging to the same or closer geographical distribution as the relative frequencies of CHD categories differ significantly among different regions [21]. Up to our knowledge there were no previous studies done to screen CHD among MSUD patients of any nationality, so we were not able to compare our results with similar studies and this supports the novelty of our study.

Although none of our patients show any signs of cardiac decompensation, those defects may worsen the outcome during the frequent metabolic crises that occur in the course of the disease. We suggest that echocardiographic screening of neonates and patients with MSUD should be done to detect possible CHD and anticipate cardiac complications during severe illness.

6. Study limitations

This study is a pilot study that only highlights the importance of screening patients with MSUD for cardiac defects; yet whether the presence of cardiac involvement is a sequelae of the genetic disease or only a concomitant association still needs to be thoroughly investigated by studying the risk factors known to increase the incidence of CHD and by comparing findings among different types of MSUD.

7. Conclusion

Interatrial defects among other congenital heart defects have been found to be a frequent finding in patients with MSUD. Therefore, routine screening of MSUD patients by echocardiography is recommended in all cases with MSUD to detect silent cardiac anomalies that may worsen the clinical outcome.

Contributions

A-Alyaa Amal Kotby: Conceived of the presented idea, supervised the findings and revised the work.

B-Marwa Moustapha Al-Fahham: Designed the model of the study, performed the echocardiographic examinations, wrote the paper in addition of being the corresponding author.

C-Heba Salah A Elabd: Conceived the presented idea, designed the model of the study, collected and analyzed the data.

D- Osama Kamal Zaki: Conceived the presented idea, helped Author B in writing the manuscript.

Conflict of interest

All authors declare that there was no conflict of interest in this study.

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