Early myocardial functional abnormalities in primary dyslipidemia: clinical and echocardiographic observations in young children from a highly consanguineous population

Nehal M. El-koofy, MD¹, Aya M. Fattouh, MD¹, Areef Ramadan, MSc¹, Mohamed A. Elmonem, MD, PhD², Dina H. Hamed, MD¹
¹Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo, Egypt; ²Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt

Background: Dyslipidemia is a major health problem among children and adolescents worldwide due to its significant association with cardiovascular disease. Primary dyslipidemias are commonly familial syndromes that can be completely asymptomatic.

Purpose: Apart from the risk of coronary artery disease (CAD), limited data are currently available on the direct effects of dyslipidemia on myocardial function in children.

Methods: We recruited 25 children with primary dyslipidemia (14 with isolated hypercholesterolemia, 4 with isolated hypertriglyceridemia, and 7 with combined dyslipidemia). Relevant clinical manifestations and laboratory and radiological investigations were evaluated. Pulsed-wave Doppler and tissue Doppler imaging echocardiography were performed for all recruited patients and the results were compared with those of 15 age- and sex-matched healthy children.

Results: The median age of the dyslipidemic children was 8 years (range, 1.5–16 years). A family history was documented in 13 cases (52%), while 18 (72%) had consanguineous parents. None of the dyslipidemic children had a personal history or clinical manifestations of CAD. In contrast, echocardiographic findings differed in several diastolic function parameters of both right and left ventricles in dyslipidemic children compared to controls. Based on normalized z scores, aortic valve narrowing was detected in 7 patients (28%), while narrowing of the aortic sinus (sinus of Valsalva) was detected in 15 patients (60%).

Conclusion: Different types of primary dyslipidemia produce functional myocardial abnormalities early in childhood. Biochemical and echocardiographic screening of high-risk children is advised to minimize the incidence of serious cardiovascular complications.

Key words: Primary dyslipidemia, Cardiovascular complications, Pulsed-wave Doppler, Tissue Doppler echocardiography, Child

Key message
In children with primary dyslipidemia, functional myocardial abnormalities can occur at young age, including diastolic functional impairment of both ventricles and narrowing of the aortic valve and the sinus of Valsalva. Echocardiographic evaluations of high-risk children may be as important as biochemical evaluations.

Introduction
Dyslipidaemia is currently a major health problem among children and adolescents, as it predisposes to significant cardiovascular disease. It is defined as the elevation of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides or lipoprotein(a) levels or decreased high-density lipoprotein cholesterol (HDL-C) level. Dyslipidemias are classified into primary and secondary types. Primary dyslipidemias are either due to well-defined genetic causes or due to polygenic hyperlipidemia, in which environmental influences play a role superimposed on a genetic predisposition. Well-defined genetic hyperlipidemias are either autosomal dominant, such as familial hypercholesterolemia with various degrees of penetrance or autosomal recessive, such as in familial hypertriglyceridemia and combined dyslipidemias. Clinical manifestations of primary dyslipidemia include xanthomas, xanthelasmas, arcus cornae, and rarely lipemia retinalis, but dyslipidemia could be also asymptomatic. Complications include cardiovascular disease and acute pancreatitis in cases of hypertriglyceridemia. Treatment includes diet therapy, statins for hypercholesterolemia and fibrates for hypertriglyceridemia. Screening in high-risk individuals is very important to detect silent cases and prevent future complications.

Data are currently scarce on the direct effects of dyslipidemia on myocardial function in children and adolescents. The current study aims to assess the clinical, laboratory, sonographic,
and particularly echocardiographic features in children and adolescents with primary dyslipidemia before the appearance of coronary artery disease (CAD) manifestations.

**Methods**

1. **Patients**
   This is a cross-sectional study including 25 patients aged less than 18 years (median, 8 years; range, 1.5–16 years; 14 males) with strong clinico-laboratory evidence of primary dyslipidemia and 15 age and sex matched healthy children (median, 7.5 years; range, 2–16 years; 8 males), who served as control group. The study was conducted in accordance with the declaration of Helsinki for experiments involving humans and approved by the institutional ethics committee at Cairo University Children’s Hospital. Written informed consents were obtained from all study participants and/or their legal guardians before recruitment.

2. **Clinical evaluation**
   All recruited patients underwent complete history taking with special emphasis on the age of onset of symptoms if any, age of laboratory diagnosis and the presence of abdominal pain or chest pain. Dyslipidemic children were recruited based on a clearly abnormal lipid profile in the affected child (TC ≥ 200 mg/dL, LDL-C ≥ 130 mg/dL, triglycerides ≥ 100 mg/dL from 0–9 years and ≥ 130 mg/dL from 9–18 years and/or HDL-C ≤ 40 mg/dL), together with suspicious family history (positive consanguinity, family history of similar conditions, previous sudden death, or premature ischemic heart disease in the family), clinical signs of hyperlipidemia, such as xanthomas and xanthelasma and the absence of secondary causes of dyslipidemia, such as diabetes mellitus, nephrotic syndrome, chronic renal failure, systemic lupus, Kawasaki disease or human immunodeficiency virus infection. Healthy controls were selected based on normal laboratory data and absence of any suspicious family history.

   Thorough clinical examination was performed stressing on the age of patient. It was performed by a single experienced operator who was blinded to the assigned group of each child. The electrocardiographic cable was connected to the ultrasonography machine to define and to time cardiac cycle events. The examination consisted of M mode, 2-dimensional, pulsed-wave, and color Doppler blood flow velocity measurements of the heart valves. Left ventricular fractional shortening and ejection fraction (EF) were calculated.

3. **Ophthalmological examination**
   Slit lamp and fundus examination were performed by a specialized pediatric ophthalmologist to detect the presence of lipemia retinalis and/or corneal arcus.

4. **Nutritional assessment**
   Full nutritional history was obtained to reveal dietary habits. After proper diagnosis patients were referred to the clinical nutrition clinic for counseling and medical therapy. Patients were instructed to start diet (skimmed milk, excess fibers, vegetables and low-fat diet stressing on the use of omega 3 rich oils like flaxseed oil) and pharmacological therapy according to the type of lipid profile abnormality.

5. **Laboratory parameters**
   Serum levels of TC, total triglycerides, LDL-C, and HDL-C were assayed after a 12-hour fasting for all patients and their relatives. The lipid profile was measured using direct enzymatic colorimetric methods on Roche Integra Biochemical analyzer with commercially available kits (Roche Diagnostics GmbH, Mannheim, Germany). Other assayed laboratory parameters included complete blood count, random blood glucose, and liver enzymes.

6. **Abdominal ultrasonography**
   All hyperlipidemic children underwent abdominal ultrasonography using a 3.5-MHz probe of the device FF sonic (UF-4000) to detect the presence of hepatic echogenicity indicating the probability of a fatty liver, gall bladder stones, or biliary mud.

7. **Echocardiography**
   Echocardiographic assessment was performed for all cases with primary dyslipidemia and healthy controls in the supine and left lateral positions using GE, Vivid-7 system having tissue velocity imaging capabilities, with 3 or 5 MHz probes according to the age of patient. It was performed by a single experienced operator who was blinded to the assigned group of each child. The electrocardiographic cable was connected to the ultrasonography machine to define and to time cardiac cycle events. The examination consisted of M mode, 2-dimensional, pulsed-wave, and color Doppler blood flow velocity measurements of the heart valves. Left ventricular fractional shortening and ejection fraction (EF) were calculated.

   Tissue Doppler imaging was obtained from the 4 chambers apical view, and tissue velocities were calculated. Using pulsed tissue velocity indices, the sample volumes were placed in the lateral sides of the mitral and tricuspid annuli and the base of the interventricular septum. The peak systolic and early and late diastolic velocities (S, E, and A, respectively) at these points were measured, and the E/E ratio was calculated. The isovolumic relaxation time and isovolumic contraction time (IVCT) were both measured for both left ventricular and right ventricular lateral walls.

   Calculation of global myocardial performance index (MPI) was performed by pulsed tissue velocity imaging. For tissue Doppler, all interval measurements were performed within one cardiac cycle. The MPI was calculated as\((a′−b')/b′\) where \(a′\) is the time interval from the end of \(A\) wave to the onset of \(E\) wave and \(b′\) the time from the onset to the end of the \(S\) wave. Z scores for the various Doppler parameters were also calculated.
8. Statistical analysis

SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA) and WinPepi statistical software package (ver. 11.65) were used for data analysis. Quantitative data were summarized as means and standard deviations or medians and percentiles for quantitative values, while categorical data were presented as numbers and ratios. Student t test or Mann–Whitney U test were used for the comparison of quantitative data sets as appropriate. Pearson chi-square test was performed for the comparison of categorical data. Numerical correlations were performed using the Pearson correlation coefficient. P values was considered significant if <0.05.

Results

Twenty-five children with primary dyslipidemia from unrelated families were recruited in this study with median age of 8 years (1.5–16 years). The majority of cases were either accidentally discovered (40%), or detected during screening of siblings of a previous case (32%). The remaining cases (28%) were diagnosed after showing characteristic skin manifestations of hyperlipidemia. Males were a little more predominant (56%). Fifty-two percent of families (13 of 25) had a history of similar condition, while 72% of children were born to consanguineous parents. Dyslipidemic children were mostly lean (92%) in accordance with a primary etiology. Arcus cornea was the most common dyslipidemia related clinical finding detected in 10 children (40%), while xanthomas were detected in 8 (32%) and xanthelasma in 6 (24%).

Table 1. Demographic and clinical characteristics of children with primary dyslipidemia versus healthy controls

| Characteristic                        | Patients (N=25) | Controls (N=15) | P value |
|--------------------------------------|----------------|----------------|---------|
| Sex                                  |                |                | 0.870   |
| Male                                 | 14 (56)        | 8 (53)         |         |
| Female                               | 11 (44)        | 6 (40)         |         |
| Age (yr)                             | 7.6±4.6        | 8.1±4.1        | 0.757   |
| Residence                            |                |                | 0.744   |
| Rural                                | 13 (52)        | 7 (47)         |         |
| Urban                                | 12 (48)        | 8 (53)         |         |
| Consanguinity                        | 18 (72)        | 6 (40)         | 0.046   |
| Similar condition in the family      | 13 (52)        | 0 (0)          | 0.001   |
| Symptoms                             |                |                |         |
| Chest pain                           | 5 (20)         |                |         |
| Abdominal pain                       | 12 (48)        |                |         |
| Signs                                |                |                |         |
| Cardiac murmur                       | 0 (0)          |                |         |
| Hepatomegaly                         | 1 (4)          |                |         |
| Arcus cornea                         | 10 (40)        |                |         |
| Lipemia retinalis                    | 0 (0)          |                |         |
| Xanthoma                             | 8 (32)         |                |         |
| Xanthelasma                          | 6 (24)         |                |         |
| Blood pressure (BP)                  |                |                |         |
| Systolic BP percentile               | 71.9±19.5      | 65.8±18.3      | 0.333   |
| Diastolic BP percentile              | 66.3±19.7      | 63.2±16.8      | 0.614   |
| Anthropometric measures              |                |                |         |
| Weight percentile                    | 56.5±21.1      | 46.1±24.1      | 0.160   |
| Height percentile                    | 39.2±26.4      | 44.4±31.1      | 0.577   |
| BMI percentile                       | 49.7±25.8      | 45.3±21.3      | 0.582   |
| Triceps skin fold thickness percentile| 61.9±14.6     |                |         |
| Overweight above 85th percentile     | 2 (8)          | 1 (6.7)        | 0.834   |

Values are presented as number (%) or mean±standard deviation. BMI, body mass index.

Table 2. Laboratory investigations of dyslipidemic patients (N=25)

| Laboratory parameter                  | Familial hypercholesterolemia (N=14) | Familial hypertriglyceridemia (N=4) | Combined hyperlipidemia (N=7) | P value |
|---------------------------------------|--------------------------------------|-------------------------------------|--------------------------------|---------|
| Total cholesterol (mg/dL)             | 594.4±181.2                          | 169.2±30.7                          | 383.9±170.7                    | <0.001  |
| LDL-cholesterol (mg/dL)               | 351.2±203.1                          | 117.6±15.8                          | 271.3±125.8                    | 0.069   |
| HDL-cholesterol (mg/dL)               | 88±34.4                              | 96.8±13.6                           | 75.1±25.4                      | 0.466   |
| TG                                    | 157.7±28.6                           | 696±231.2                           | 1346.1±1102.4                  | 0.001   |
| Hemoglobin (g/dL)                     | 10.7±0.86                            | 11.2±0.82                           | 11.1±0.7                       | 0.419   |
| ALT (μL)                              | 26.4±6.6                             | 23.5±4.8                            | 39.2±26.2                      | 0.146   |
| AST (μL)                              | 29.9±6.1                             | 35.1±15                             | 37.1±12.3                      | 0.261   |
| RBG (mg/dL)                           | 99.8±10.9                            | 94.8±5.1                            | 100±10                         | 0.657   |

Values are presented as mean±standard deviation. LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; ALT, alanine transaminase; AST, aspartate transaminase; RBG, random blood glucose. P values were calculated based on analysis of variance using the WinPepi statistical software package. Boldface indicates a statistically significant difference with P<0.05.
biliary mud, while none were suffering from gall bladder stones.

For echocardiographic assessment we calculated the \( z \) scores of various parameters and we further recruited 15 age and sex-matched healthy children to compare their various measurements and \( z \) scores with those of the dyslipidemic children.

We measured aortic root dimensions during echocardiographic assessment of children with primary dyslipidemia. They were plotted as \( z \) scores normalized for age and sex using the equations provided by Campens et al.\(^\text{16}^\) Dyslipidemic children in our study showed aortic ring diameter ranging from 1 cm to 1.8 cm, diameter of supravalvular ring ranged from 1.3 cm to 2.3 cm and diameter of aortic sinus (sinus of Valsalva) ranged from 1.1 cm to 2.4 cm. After normalization, 7 children showed a narrowed aortic ring (below -2 \( z \) score) (3/14 hypercholesterolemia, 2/4 hypertriglyceridemia and 2/7 combined dyslipidemia), 15 children showed narrowing in the sinus of Valsalva (7/14 hypercholesterolemia, 2/4 hypertriglyceridemia, and 6/7 combined dyslipidemia), while none had narrowing of the supravalvular aortic ring (Table 3). None of the dyslipidemic children with narrowing of the aortic ring or the sinus of valsalva

### Table 3. Aortic root dimensions of dyslipidemic children

| Aortic root dimensions | Diameter (cm) | Diameter (\( z \) score) | Children with narrowing, n (%) |
|------------------------|--------------|--------------------------|-------------------------------|
| Aortic ring            | 1.6 (-1.0–1.8) | 0.29 (-3.1 to 4.7)    | 7 (28)                       |
| Supravalvular aortic ring | 1.8 (1.3–2.5) | 1.4 (-0.05 to 4.3)    | 0 (0)                        |
| Sinus of Valsalva      | 1.7 (1.1–2.4) | -2.5 (-4.7 to 2.8)    | 15 (60)                      |

A \( z \) score below -2 indicated a narrowed ring.

### Table 4. Right and left ventricular tissue Doppler findings of patients versus controls

| Variable           | Doppler value | z score | \( P \) value |
|--------------------|---------------|---------|--------------|
|                    | Patients (N=25) | Controls (N=15) | Patients (N=25) | Controls (N=15) |
| **Left ventricle tissue Doppler** |               |          |              |
| \( E \) (cm/sec)   | 20 (18–22) | 16.5 (14.5–18.3) | 0.76 (0.24–1.15) | -0.19 (-0.73 to 0.34) | 0.003 |
| \( A \) (cm/sec)   | 6 (5.5–7.5) | 6 (5–6.6) | -0.22 (-0.5 to 0.53) | -0.37 (-0.79 to -0.01) | 0.127 |
| \( S \) (cm/sec)   | 9 (7.6–9.5) | 7.6 (6.2–8.5) | -0.24 (-0.9 to 0.07) | -0.81 (-1.02 to -0.43) | 0.034 |
| \( E/A \)          | 2.7 (2.4–4) | 2.8 (2.5–3.4) | - | - | 0.675 |
| IVRT (msec)        | 43 (39–46) | 47 (37–50) | - | - | 0.401 |
| IVCT (msec)        | 39 (36–41) | 53 (44–56) | - | - | <0.001 |
| MPI                | 0.3 (0.25–0.34) | 0.26 (0.18–0.33) | - | - | 0.263 |
| **Right ventricle tissue Doppler** |               |          |              |
| \( E \) (cm/sec)   | 18 (15–20.5) | 17 (14.6–19.8) | 0.45 (-0.5 to 1.1) | 0.17 (-0.66 to 0.87) | 0.769 |
| \( A \) (cm/sec)   | 9 (6–11) | 9.5 (7.1–10.5) | -0.38 (-1.41 to 0.41) | -0.23 (-1.06 to 0.12) | 0.867 |
| \( S \) (cm/sec)   | 12 (9.5–13) | 14 (12.8–15.5) | -0.7 (-1.9 to 0.1) | -0.1 (-0.5 to 1.1) | 0.043 |
| \( E/A \)          | 1.9 (1.76–2.3) | 1.83 (1.66–2.28) | - | - | 0.876 |
| IVRT (msec)        | 40 (38–49) | 36 (34–47) | - | - | 0.052 |
| IVCT (msec)        | 41 (38–52) | 49 (47–63) | - | - | 0.031 |
| MPI                | 0.32 (0.28–0.34) | 0.32 (0.12–0.37) | - | - | 0.933 |
| **Septum tissue Doppler** |               |          |              |
| \( E \) (cm/sec)   | 15.5 (13.5–16) | 14 (12.8–15.2) | 0.58 (-0.38 to 1.35) | 0.32 (-0.3 to 0.65) | 0.184 |
| \( A \) (cm/sec)   | 6.5 (5.5–7.5) | 6 (5–7.5) | 0.17 (-0.31 to 0.87) | 0.39 (-0.37 to 1.04) | 0.769 |
| \( S \) (cm/sec)   | 8 (7.5–9) | 8 (7.3–9) | 0 (-0.07 to 0.61) | 0.13 (-0.19 to 0.85) | 0.726 |
| \( E/A \)          | 2.3 (2–2.9) | 2.5 (1.8–2.6) | - | - | 0.695 |
| **M mode**         |               |          |              |
| AO (cm)            | 2.1 (1.6–2.2) | 2.1 (1.7–2.3) | 1.33 (0.43–2.04) | 0.77 (-0.03 to 2.14) | 0.608 |
| LA (cm)            | 2.1 (1.9–2.6) | 2.3 (2.1–2.55) | -0.89 (-1.84 to 1.06) | 0.23 (-0.5 to 0.69) | 0.299 |
| RV (cm)            | 1 (0.8–1.3) | 1.7 (1.2–1.95) | -1.99 (-2.73 to -1.12) | 0.73 (-1.12 to 2.15) | <0.001 |
| IVS (cm)           | 0.8 (0.7–0.9) | 0.6 (0.5–0.65) | 0.42 (-0.51 to 1.14) | -0.44 (-0.82 to 0.84) | 0.209 |
| PW (cm)            | 0.9 (0.7–1.1) | 0.5 (0.4–0.6) | 1.9 (1–1.34) | -0.25 (-1.48 to 0.01) | <0.001 |
| LVEDD (cm)         | 4 (3.2–4.2) | 3.7 (3.1–4.1) | -0.72 (-2.53 to 1.56) | -0.04 (-0.74 to 0.42) | 0.655 |
| LVESD (cm)         | 2.4 (2.1–2.6) | 2.2 (1.95–2.55) | -0.51 (-2.23 to 1.18) | -0.43 (-0.73 to 0.49) | 0.586 |
| FS %               | 38 (36–43) | 43 (36–45) | - | - | 0.565 |
| EF %               | 69 (66–75) | 74 (67–77) | - | - | 0.356 |

Values are presented as median (interquartile range). IVRT, isovolumic relaxation time; IVCT, isovolumic contraction time; MPI, myocardial performance index; AO, aortic root dimension; LA, left atrial dimension; RV, right ventricular dimension; IVS, interventricular septal thickness at end-systole; PW, left ventricular posterior wall thickness at end-systole; LVEDD, left ventricular internal dimension at end-diastole; LVESD, left ventricular internal dimension at end-systole; FS, fractional shortening; EF, ejection fraction.

\( P \) values were calculated through a 2-tailed Mann-Whitney \( U \) test analysis based on the comparison of \( z \) scores if calculated and the raw data for ratios if \( z \) scores could not be obtained.

Boldface indicates a statistically significant difference with \( P<0.05 \).
had significant pressure gradient across the left ventricular outflow tract.

Regarding Doppler findings in the M mode, we detected a significant difference concerning the left ventricular posterior wall thickness at end-systole ($P<0.001$), which indicates left ventricular hypertrophy. On the other hand, the most noticeable observation in the tissue Doppler of both ventricles was the significant shortening of the IVCT in both left and right ventricles ($P<0.001$ and $P=0.031$, respectively) (Table 4).

We further correlated major clinical manifestations with positive echocardiographic findings. The presence of xanthoma correlated significantly with IVCT in right ventricular tissue Doppler ($R=0.531$, $P=0.006$). Furthermore, the presence of xanthelasma correlated significantly with the E wave in left ventricular tissue Doppler ($R=0.486$, $P=0.014$), IVCT in right ventricular tissue Doppler ($R=0.585$, $P=0.002$), and IVS in M mode ($R=0.488$, $P=0.013$). Finally, the presence of arcus cornea correlated significantly with E wave in left ventricular tissue Doppler ($R=0.455$, $P=0.022$) and IVCT in right ventricular tissue Doppler ($R=0.647$, $P<0.001$). We also correlated aortic root dimension measurements with various clinical findings; however, there were no detected significant correlations with the presence of xanthomas, xanthelasma or arcus cornea or with the lipid profile parameters.

### Discussion

Seventy-two percent of our patients were born to consanguineous parents. Consanguinity is a major problem in Egypt, where it's estimated that 40% of marriages are consanguineous. This clearly indicates that familial dyslipidemias, especially the autosomal recessive, are more prevalent in Egypt.Positive family history of primary dyslipidemia, early sudden death, and/or premature coronary heart disease was observed in 52% of families.

Forty percent of our patients were completely asymptomatic at recruitment. This observation emphasizes the importance of predictive screening of family members of hereditary dyslipidemia patients even if they are asymptomatic and also to screen relatives of patients who died from myocardial infarction at young age without reasonable cause. Schellack et al. stated that dyslipidemia poses a significant challenge in the pediatric population, mostly due to the fact that serum lipid abnormalities in children are often missed. It has been proposed that the lack of routine screening in children with inherited or acquired dyslipidemias may account for as many as half of them being missed during childhood.

Hyperlipidemia is a major risk factor for CAD and only limited data are available regarding its direct effects on myocardial function apart from CAD. We assessed left ventricular function by pulsed-wave Doppler and tissue Doppler echocardiography in recruited patients and compared the findings with established z scores for many of evaluated parameters and a matched healthy control group. Evidence of left ventricular diastolic dysfunction was detected as tissue Doppler showed that E/E' ratio and IVCT were significantly lower in patients than controls. Di Salvo et al. suggested that reductions in longitudinal and circumferential deformation are compensated for by increasing radial strain in children with familial hypercholesterolemia with normal left ventricular EFs in a study conducted on 45 children with hypercholesterolemia.

Assessment of right ventricular function by tissue Doppler of dyslipidemic children showed evidence of impairment of both systolic and diastolic functions. In tissue Doppler, $S$ and IVCT were lower in patients than controls. Similarly, studies conducted on adult patients with metabolic syndrome detected right ventricular remodeling.

The systolic function as assessed by EF in M mode in our patients was normal. The only morphological changes detected by M mode were septal and left ventricular hypertrophy with significant difference between patients and controls, which came in agreement with the results of the study conducted on children aged 7–18 years with hypercholesterolemia and demonstrated that left ventricular hypertrophy can be also seen at younger ages.

In our study, we detected aortic valve narrowing in almost 30% of studied patients from all 3 categories of dyslipidemia. Several studies demonstrated previously that hypercholesterolemia is related to increased risk of aortic valve calcification and that preventive treatment of hypercholesterolemia could play an important role to decrease or inhibit development of aortic valve calcification, thus, it is expected that early preventive measures during childhood could minimize aortic valve involvement.

In contrast to adult studies of dyslipidemia, we did not detect supravalvular aortic stenosis in our dyslipidemic children. This, may be attributed to the young age of our patients. On the other hand, we detected narrowing of the sinus of Valsalva in the majority of our dyslipidemic patients (60%), which came in agreement with previous results obtained also in familial hypercholesterolemia. We further detected that the majority of cases with combined dyslipidemia in our cohort showed narrowing of the sinus of Valsalva (86%) compared to only 50% in children with isolated hypercholesterolemia and 50% of children with isolated hypertriglyceridemia.

The study has some limitations, mainly the low number of recruited children with primary dyslipidemias; however, being rare disorders, it was extremely difficult to recruit a higher number of patients within a reasonable time frame. Another limitation is the cross-sectional nature of the study, which limits the follow-up of the progression of the subtle echocardiographic functional defects detected in children into symptomatic cardiovascular disease later in life. Finally, the inconclusiveness in some of the parameters measured may require more advanced echocardiographic technologies, such as the 4-dimensional speckle tracking to get more evidence on the early development of the diastolic dysfunction in dyslipidemic children.
In conclusion, data available about myocardial defects of primary dyslipidemia are mostly obtained from studies in adults and inpatients with familial hypercholesterolemia, thus, there are limited data about the effects of different types of dyslipidaemias particularly in children. Here, we show that these complications exist in all types of primary dyslipidemias, particularly impaired diastolic functions of both ventricles, and narrowing of aortic valve and sinus of Valsalva. Thus, early echocardiographic screening of dyslipidemic children and their family members should be as essential as biochemical screening.

See the commentary on “Early echocardiographic screening for subclinical myocardial dysfunction in children and adolescents with dyslipidemia: why and when?” via https://doi.org/10.3345/cep.2022.00031.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study was funded by Cairo University

Acknowledgments: We sincerely thank all our patients and control subjects and their families for their participation.

ORCID:
Mohamed A. Elmonem https://orcid.org/0000-0002-3154-1948
Nehal M. El-koofy https://orcid.org/0000-0002-7464-6715

References

1. Hedayatnia M, Asadi Z, Zare-Feyzabadi R, Yaghoobti-Khorasani M, Ghazizadeh H, Ghaffarian-Zirak R, et al. Dyslipidemia and cardiovascular disease risk among the MASHAD study population. Lipids Health Dis 2020;19:42.
2. Lozano P, Henrikson NB, Morrison CC, Dunn J, Nguyen M, Blasi PR, et al. Lipid screening in childhood and adolescence for detection of multifactorial dyslipidemia: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2016;316:6344.
3. Castro Cabezas M, Burggraaf B, Klopf B. Dyslipidemias in clinical practice. Clin Chim Acta 2018;487:117-25.
4. Ruiz LD, Zuech ML, Dimitratos SM, Scherr RE. Adolescent obesity: diet quality, psychosocial health, and cardiometabolic risk factors. Nutrients 2019;11:42-43.
5. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128 Suppl 5(Suppl 5):S213-56.
6. Lim JS, Kim EY, Kim JH, Yoo JH, Yi KH, Chae HW, et al. 2017 Clinical practice guidelines for dyslipidemia of Korean children and adolescents. Clin Exp Pediatr 2020;63:4546.
7. Blackett PR, Wilson DP, McNeal CJ. Secondary hypertriglyceridemia in children and adolescents. J Clin Lipidol 2015;9(Suppl 5):S29-40.
8. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva (Switzerland): World Health Organization, 2006.
9. El-Koofy N, El-Karayek H, El-Akel W, Helmy H, Anwar G, El-Sayed R, et al. Ultrasonography as a non-invasive tool for detection of nonalcoholic fatty liver disease in overweight/obese Egyptian children. Eur J Radiol 2012;81:3120-3.
10. Uhlay A, Tati E. Myocardial performance index. Anadolu Kardiyol Derg 2008;8:143-8.
11. Etem DM, McMahon CJ, Cohen RR, Wu J, Finkelshtein I, Kovalchik JP, et al. Impact of cardiac growth on Doppler tissue imaging velocities: a study in healthy children. J Am Soc Echocardiogr 2004;17:212-21.
12. Dallaire F, Sborach C, Hui W, Sarkola T, Friedberg MK, Bradley TJ, et al. Reference values for pulse wave Doppler and tissue Doppler imaging in pediatric echocardiography. Circ Cardiovasc Imaging 2015;8:e002167.
13. Jain A, Mohamed A, El-Khuffash A, Connelly KA, Dallaire F, Jankov RP, et al. A comprehensive echocardiographic protocol for assessing neonatal right ventricular dimensions and function in the transitional period: normative data and z scores. J Am Soc Echocardiogr 2014;27:1293-304.
14. Neilan TG, Pradhana AD, King ME, Weyman AE. Derivation of a size-independent variable for scaling of cardiac dimensions in a normal paediatric population. Eur J Echocardiogr 2009;10:50-5.
15. Cantinotti M, Scalese M, Murzi B, Assanta N, Spadoni I, Festa P, et al. Echocardiographic nomograms for ventricular, valvular and arterial dimensions in Caucasian children with a special focus on neonates, infants and toddlers. J Am Soc Echocardiogr 2014;27:179-91.
16. Campens L, Demulier L, De Groote K, Vandekerckhove K, De Wolf D, Roman MJ, et al. Reference values for echocardiographic assessment of the diameter of the aortic root and ascending aorta spanning all age categories. Am J Cardiol 2014;114:914-20.
17. Hafez M, El-Tahan H, Awadalla M, El-Khayat H, Abdel-Gafar A, Ghoneim M. Consanguineous matings in the Egyptian population. J Med Genet 1983;20:58-60.
18. Schellack G, Schellack N, Malan L. An overview of childhood dyslipidaemia: review. SA Pharmaceutical J 2016;83:38-42.
19. Di Salvo G, D’Aiello AF, Castaldi B, Fadel B, Limongelli G, D’Andrea A, et al. Early left ventricular abnormalities in children with heterozygous familial hypercholesterolemia. J Am Soc Echocardiogr 2012;25:1075-82.
20. Tadic M, Ivanovic B, Cupсиди C. Metabolic syndrome and right ventricle: an updated review. Eur J Intern Med 2013;24:608-16.
21. Hosseini SM, Kelshidi R, Lotfi N, Sabri MR, Mansouri S. Factors influencing left ventricular hypertrophy in children and adolescents with or without family history of premature myocardial infarction. Adv Biomed Res 2014;3:60.
22. Rabya SB, Kayalar N, Sareeyuacho B, Erklin A, Kirali K, Yakut C. Hypercholesterolemia association with aortic stenosis of various etiologies. J Card Surg 2009;24:146-30.
23. Kawaguchi A, Miyatake Y, Yutani C, Beppu S, Tsuchima M, Yamamura T, et al. Characteristic cardiovascular manifestation in homozygous and heterozygous familial hypercholesterolemia. J Am Heart J 1999;137:410-8.
24. Labib D, Soliman H, Said K, Sorour K. Early severe coronary artery disease and aortic coarctation in a child with familial hypercholesterolemia. BMJ Case Rep 2016;2016:bcr2016216147.
25. Smith JG, Luk K, Schulz CA, Engert JC, Do R, Hindy G, et al. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. JAMA 2014;312:1764-71.
26. Beppu S, Minura Y, Sakakibara H, Nagata S, Park YD, Nambu S, et al. Supravalvular aortic stenosis and coronary ostial stenosis in familial hypercholesterolemia: two-dimensional echocardiographic assessment. Circulation 1983;67:878-84.
How to cite this article: El-koofy NM, Fattouh AM, Ramadan A, Elmonem MA, Hamed DH. Early myocardial functional abnormalities in primary dyslipidemia: clinical and echocardiographic observations in young children from a highly consanguineous population. Clin Exp Pediatr 2022;65:410-6. https://doi.org/10.3345/cep.2021.00598