Investigation of Cardiomyopathy in Children With Cirrhotic and Noncirrhotic Portal Hypertension

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ABSTRACT

Background: Cirrhotic cardiomyopathy (CCMP) is a functional disorder characterized by electrophysiological disturbances, and diastolic and/or systolic dysfunction in patients with liver disease. This disorder is a well-defined entity in adults, but pediatric data are limited. The aim of the study was to determine the incidence, features, and risk factors of CCMP in children with portal hypertension (PHT).

Methods: This study included 50 children with cirrhotic PHT (40/50) and noncirrhotic PHT (10/50). Fifty healthy children were also selected for the control group. Electrocardiography and echocardiography were used to evaluate cardiac functions. Corrected QT (QTc) $\geq$ 0.45 was accepted as prolonged on electrocardiography. The study group was divided into 3 groups: cirrhotic, noncirrhotic, and control. Then, the CCMP group was created according to the diagnostic criteria. Latent CCMP was diagnosed in the presence of prolonged-QTc along with a minor criterion (tachycardia). Manifest CCMP was diagnosed in the presence of at least 2 major criteria (prolonged-QTc along with abnormal echocardiographic findings). Moreover, in this study, the risk factors for CCMP were investigated.

Results: The CCMP group included 10 cases (20%). Nine of these cases had latent CCMP (18%), and the remaining one (2%) had manifest CCMP. All of the cases with CCMP had cirrhosis and ascites. None of the patients with CCMP had severe cardiac symptoms, but they were already using some cardioprotective drugs such as propanolol and spironolactone. As risk factors for CCMP, pediatric end-stage liver disease scores, Child-Pugh scores, and ascites grades were found to be significant for the determination of CCMP. The most important risk factor was ascites severity ($P = 0.001$, odds ratio 9.4).

Conclusions: Approximately 20% of children with PHT have CCMP. A detailed cardiac examination should be carried out periodically in children with cirrhotic PHT, especially in the presence of ascites and high Child-Pugh score.

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Portal hypertension (PHT) and its complications increase the rates of morbidity and mortality in childhood (1–3). Cirrhotic cardiomyopathy (CCMP) is a hemodynamic complication of PHT, and this disease is defined as a functional disorder characterized by electrophysiological disturbances and diastolic and/or systolic dysfunction in patients with liver diseases (4–10). CCMP is usually latent and patients often exhibit asymptomatic progress, unless it is provoked by some stress factors such as exercise, excessive eating, infections, and medical interventional procedures (eg, massive ascite-fluid drainage, shunt operation, transplantation) (4–6,11–16). It usually develops in cirrhotic patients and has not been reported in any patient with noncirrhotic PHT.

Although CCMP is a well-defined entity in adults, pediatric data are limited (7–13). In children, the diagnostic criteria for CCMP is yet to be defined, and the diagnostic criteria for adults are also used in childhood (5); especially in children with cirrhosis, the prolongation of corrected QT (QTc) interval without some membrane potential disruptive causes such as electrolyte imbalances and cardioeffective drugs is accepted as an important diagnostic criterion for pediatric CCMP, even without the presence of any echocardiographic abnormality (15–18).

Generally, patients with latent CCMP treated with cardioprotective drugs do not exhibit any cardiac problems, such as arrhythmia or heart failure, until transplantation. The available data on the impact of liver transplantation on the prognosis of CCMP are controversial. Some researchers propose that CCMP may constitute some problems in the early postoperative period, but long-term prognosis is better after liver transplantation (12–16).

The aim of this study was to determine the incidence and features of CCMP and identify the risk factors for CCMP in children with cirrhotic PHT compared with those with noncirrhotic PHT.

METHODS

This study was retrospectively carried out at the Department of Pediatric Gastroenterology, Hepatology and Nutrition, Istanbul University Faculty of Medicine, between 1998 and 2008, in cases with PHT. PHT was diagnosed using both clinical findings (splenomegaly, esophageal varices, and thrombocytopenia) and hepatovascular imaging techniques such as Doppler ultrasound and computerized tomography/magnetic resonance imaging. The study included 50 children (40 cirrhotic/10 noncirrhotic) with PHT whose file reports were complete in terms of clinical, laboratory, and cardiologic investigations. Fifty healthy age- and sex-matched children were included as the control group. The study was approved by the local ethics committee.

Study and Control Groups

Exclusion criteria in this study were the presence of electrolyte disturbances, intake of cardiac medication affecting membrane potential, and presence of chronic diseases such as congenital heart disorders, congenital metabolic diseases, muscle diseases, malignancy, severe anemia, and endocrine disorders. In each of the cases, the most recent physical examination, laboratory tests, chest radiographs, electrocardiography (ECG), and 2-dimensional echocardiography results were recorded. Cardiac effective medications were stopped 3 days before the echocardiographic examination and ECG.

The cases were divided into 3 groups: I—cirrhotic group, II—noncirrhotic group, and III—control group. The CCMP group was formed according to the diagnostic criteria. The status of the ascites and the Child-Pugh (19) or pediatric end-stage liver disease/model for end-stage liver disease (PELD/MELD) (20) scores were also recorded. The presence of cirrhosis was confirmed by liver histology.

The QTc was calculated using the Bazzet formula ($QTc = QT/\sqrt{RR}$) (21,22). A value of $QTc \geq 0.45$ was accepted as prolonged (7,23,24). Standard techniques were used for the measurements of PR, RR, QT, and QRS intervals in the ECG.

The diagnosis of latent and manifest CCMP was based on modified criteria of Moller and Henriksen (5) (Table 1). Major diagnostic criteria were the presence of prolonged-QTc, and systolic and diastolic dysfunction indicators. Minor diagnostic criteria were the presence of tachycardia, abnormal chronotropic response, electromechanical uncoupling, enlarged left atrium, increased myocardial mass, and increased cardiac enzymes. Latent CCMP was diagnosed in the presence of prolonged-QTc along with a minor criterion. Manifest CCMP was diagnosed in the presence of 2 major criteria.

Echocardiographic examination included morphologic (linear) sizes of the left ventricle indexed according to the body surface, left ventricular mass (LVM) index using the Devereux formula, and evaluation of both diastolic functions (mitral valve velocity [E], mitral valve A velocity [A], E wave/A wave ratio [E/A], myocardial tissue E velocity [Em], myocardial tissue A velocity [Am], Em/Am ratio [Em/Am], and deceleration time [DECT]), and systolic functions (ejection fraction [EF] and fractional shortening [FS]). In the Devereux formula, some echocardiographic morphologic parameters such as interventricular septal thickness at end diastole (IVSD), left ventricular dimension at end diastole (LVDD), and left ventricular posterior wall thickness at end diastole (LVPWD) were used. This formula is $[LVM = 1.05 \times [(LVDD + LVPWD + IVSD)^3 - (LVDD)^3]/13.6]$, and the left ventricle mass index (LVMi) is calculated using another formula [LVMi = LVM (g)/BSA (m^2)] (25–28).

Ascite grades were determined according to the response of diuretic therapy and classified as mild, moderate, and severe/refractory.

Statistical Analysis

All of the values were presented either as mean ± standard deviation or as percentages. Among the groups, the χ^2 test was used to compare proportions; analysis of variance or Kruskal-Wallis test and post-hoc tests were used for the multiple comparisons of the mean values according to parametric or nonparametric disruption. A $P < 0.05$ value was considered statistically significant. Some variables such as age, sex, disease duration (time after the diagnosis), ascites grades, and Child-Pugh and PELD/MELD scores were investigated as risk factors of CCMP using the multiple logistic regression analysis and are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS

The age and sex distributions of the study group (age 8.4 ± 4.8 years, 54% boys) compared with the control group (age 8.8 ± 4.6 years, 54% boys) did not show any statistically significant differences. The mean values of weight, height, and body surface area in the cirrhotic group were significantly lower compared with those in the control group ($P < 0.01$). The demographic data of the studied groups are shown in Table 2.

The cirrhotic group included 40 and the noncirrhotic group 10 patients. The underlying diagnoses of the cirrhotic group were cryptogenic (16 cases, 40%), biliary atresia (6 cases, 15%), idiopathic neonatal hepatitis (5 cases, 12.5%), Wilson disease (4 cases, 10%), Byler disease (3 cases, 7.5%), cirrhosis as a result of chronic hepatitis B (2 cases, 5%), sclerosing cholangitis (2 cases, 5%), congenital hepatic fibrosis (mixed form with cholestasis; 1 case, 2.5%), and Budd-Chiari syndrome (1 case, 2.5%). The underlying diagnoses of the noncirrhotic group were portal vein thrombosis (6 cases, 60%), congenital hepatic fibrosis (3 cases, 30%), and splenic vein thrombosis (1 case, 10%).

The most common findings of the physical examination in the study group were tachycardia, relatively low blood pressure (BP), and systolic murmur (56%). Only 1 case with hepatopulmonary syndrome had cyanosis and clubbing fingers.

Twelve cases in the cirrhotic group had ascites, whereas there were none in the noncirrhotic group. Ascites grades were mild in

TABLE 1. Diagnostic criteria for CCMP in children

Criteria	Electrophysiological disturbance	Systolic dysfunction	Diastolic dysfunction
Major			
	Prolonged-QTc interval (after exclusion of other causes*)	Resting LV EF <55%	E/A ratio <1.0 or >2 (in restrictive pattern) Prolonged DECT (>200 ms) Prolonged isovolumetric relaxation time (>80 ms)
Minor			
	Elevated heart rate (tachycardia) (>top value according to age) Abnormal chronotropic response Electromechanical uncoupling Enlarged left atrium Increased myocardial mass		

Diagnostic criteria were modified from Moller and Henriksen (5). For diagnosis of latent CCMP: 1 major criterion (without echocardiographic abnormality) along with at least 1 minor criterion. For diagnosis of manifest CCMP: at least 2 major criteria. CCMP = cirrhotic cardiomyopathy; DECT = deceleration time; E/A ratio = E wave-to-A wave ratio; EF = ejection fraction; LV = left ventricular; QTc = corrected QT.

* Other causes such as electrolyte disturbances, cardiac drugs, chronic diseases.

TABLE 2. Demographic data

Group	Cirrhotic[a] (n = 40)	Noncirrhotic[b] (n = 10)	Control[c] (n = 50)	P
Sex (male)	20 (50.0)	7 (70.0)	27 (54.0)	NS
Age, y	7.8 ± 4.9	10.8 ± 3.7	8.8 ± 4.6	NS
Weight, kg	24.5 ± 13.9	30.5 ± 12.5	35.3 ± 18.5	$P^{a-c} < 0.01$
Height, m	1.20 ± 0.3	1.3 ± 0.2	1.3 ± 0.3	$P^{a-c} < 0.05$
BSA, m^2	0.9 ± 0.4	1.0 ± 0.3	1.1 ± 0.4	$P^{a-c} < 0.01$

BSA = body surface area; NS = not significant. (The values are given as number [percentage] or mean ± SD.)

6 cases (50%), moderate in 4 cases (33%), and severe/refractory in 2 cases (17%).

Child-Pugh A was defined in 23 cases (57.5%; score 5.0 ± 0.5 [5–6]), Child-Pugh B in 7 cases (17.5%; score 8.0 ± 0.8 [7–9]), and Child-Pugh C in 10 cases (25%; score 11.0 ± 0.9 [10–12]). The PELD score of the cirrhotic group was 10.0 ± 12.0 (−9 to 37).

Evaluation of Cardiologic Findings in the Groups

The mean heart rates of the cirrhotic and noncirrhotic and control groups were 103 ± 23 (65–150), 94 ± 21 (65–136), and 90 ± 18 (61–125), respectively. The mean heart rate in the cirrhotic group was higher compared with that in the noncirrhotic and control groups ($P < 0.05$).

The mean systolic/diastolic BPs of the groups were 99 ± 11 (80–120)/61 ± 8 (50–80), 105 ± 8 (95–120)/63 ± 6 (55–75), and 109 ± 10 (90–128)/66 ± 8 (50–83), respectively. In the cirrhotic group, the mean systolic and diastolic BPs were also lower compared with those in the control group ($P < 0.001$ for systolic BP, $P < 0.05$ for diastolic BP).

Cardiothoracic ratio (cirrhotic group: 0.44 ± 0.02 [0.40–0.50], noncirrhotic group: 0.44 ± 0.01 [0.43–0.46], and control group: 0.43 ± 0.01 [0.40–0.50]) and telecardiography findings in all of the cases were normal ($P > 0.05$ among the groups). Moreover, no case had arrhythmia or cardiac hypertrophy on ECG.

Mean QTc value of the cirrhotic group was 0.42 ± 0.04 (0.35–0.50), whereas those of the noncirrhotic and control groups were 0.41 ± 0.02 (0.36–0.44) and 0.38 ± 0.03 (0.32–0.43), respectively. There was no statistical difference between the mean QTc values of the cirrhotic and the noncirrhotic groups; however, those values were statistically higher compared with that of the control group ($P < 0.001$ and $P < 0.01$, respectively) (Table 3).

In addition, in the echocardiographic parameters, the values of LVMi, EF, FS, and E in the cirrhotic group were statistically higher than those of the control group ($P < 0.05$, $P < 0.001$, $P < 0.001$, and $P < 0.05$, respectively); the mean values of DECT and Am in the cirrhotic group were lower than those in the control group ($P < 0.05$). The other echocardiographic values were not different among the groups ($P > 0.05$) (Table 3).

Incidence of CCMP

In children with PHT, CCMP was defined in 10 cases (20%). Nine cases (18%) were described as latent CCMP, and another case (2%) was manifest CCMP. All of the cases of CCMP were cirrhotic. None of the cases in the noncirrhotic group had the features of CCMP.

Features of the Cases With Cardiomyopathy

In cases with CCMP, sex distribution was 5 male and 5 female patients. All of them were cirrhotic with prolonged-QTc on ECG. Child-Pugh scores of these cases were B in 1 case and C in 9 cases. The mean PELD score was found to be 24.6 ± 9.3 (4–35) in the cases with CCMP versus 5.7 ± 8.7 (−9 to 37) in the cases with normal-QTc ($P < 0.001$).

Abdominal ascites was present in 9 cases (90%) with CCMP (mild in 4 cases, moderate in 4 cases, and severe in 1 case) and in 3 cases (7.5%) with normal QTc on ECG (mild in 2 cases and severe in 1 case) ($P < 0.001$). Although the mean duration of the disease was 3.7 ± 2.8 (0.6–9) years in the group with CCMP, this value was 6.1 ± 3.3 (0.6–14) years in patients with normal QTc ($P < 0.05$).

The mean QTc value of CCMP group was 0.48 ± 0.02 (0.45–0.50) in ECG. In this group, according to results of classic echocardiographic investigation, the mean values of LVMi, EF, FS,

TABLE 3. Values of QTc and echocardiographic parameters in the studied groups

	Cirrhotic[a] (n = 40)	Noncirrhotic[b] (n = 10)	Control[c] (n = 50)	Significant P
QTc, s	0.42 ± 0.04 (0.35–0.50)	0.41 ± 0.02 (0.36–0.44)	0.38 ± 0.03 (0.32–0.43)	$P^{a-c} < 0.001$; $P^{b-c} < 0.01$
LVMi, g/m^2	100 ± 40 (43–251)	89 ± 36 (38–161)	75 ± 29 (12–175)	$P^{a-c} < 0.05$
EF, %	77.7 ± 5.9 (59–90)	76.9 ± 6.6 (68–87)	73.5 ± 3.8 (66–80)	$P^{a-c} < 0.001$
FS, %	39.9 ± 5.3 (26–54)	39.2 ± 5.9 (31–49)	35.9 ± 3.1 (30–42)	$P^{a-c} < 0.001$
E, m/s	0.96 ± 0.17 (0.57–1.40)	1.01 ± 0.19 (0.69–1.36)	0.87 ± 0.12 (0.53–1.06)	$P^{a-c} < 0.05$; $P^{b-c} < 0.05$
A, m/s	0.54 ± 0.13 (0.36–0.89)	0.58 ± 0.18 (0.39–0.84)	0.53 ± 0.08 (0.38–0.69)	NS
E/A ratio, m/s	1.8 ± 0.5 (1.2–2.9)	1.8 ± 0.4 (1.0–2.4)	1.7 ± 0.2 (1.4–2.0)	NS
DECT, ms	179 ± 32 (106–256)	170 ± 34 (115–231)	180.9 ± 21.4 (127–243)	$P^{a-c} < 0.001$; $P^{b-c} < 0.05$
Em, m/s	0.17 ± 0.03 (0.14–0.21)	0.17 ± 0.03 (0.14–0.22)	0.20 ± 0.03 (0.14–0.27)	NS
Am, m/s	0.09 ± 0.02 (0.04–0.14)	0.09 ± 0.01 (0.07–0.11)	0.10 ± 0.02 (0.08–0.16)	$P^{a-c} < 0.001$; $P^{b-c} < 0.05$
Em/Am, m/s	1.9 ± 0.3 (1.4–2.6)	1.9 ± 0.3 (1.3–2.4)	2.0 ± 0.2 (1.4–2.3)	NS

A = A wave; Am = myocardial tissue A velocity; CCMP = cirrhotic cardiomyopathy; DECT = deceleration time; E = E wave; E/A ratio = E wave-to-A wave ratio; ECG = electrocardiography; EF = ejection fraction; Em = myocardial tissue E velocity; FS = fractional shortening; LVMi = left ventricle mass index; NS = not significant; QTc = corrected QT interval in ECG.

E, A, E/A ratio, and DECT were 130 ± 58 (65–251), 77.8 ± 7.2 (59–87), 40.0 ± 5.9 (26–49), 0.98 ± 0.20 (0.57–1.20), 0.49 ± 0.13 (0.36–0.77), 2.1 ± 0.6 (1.2–2.9), and 182.2 ± 25.1 (155–245), respectively. In addition, in tissue Doppler echocardiography, the mean values of Em, Am, and Em/Am ratio were 0.17 ± 0.03 (0.14–0.22), 0.08 ± 0.01 (0.06–0.11), and 2.0 ± 0.3 (1.6–2.6), respectively.

None of the cases with latent CCMP had manifested echocardiographic abnormalities, but mean values of LVMi (g/m^2), EF, FS, E, E/A ratio, and DECT were significantly higher; the mean Am was lower compared with that of the control. On the contrary, systolic and diastolic dysfunction was present in only 1 case with manifest CCMP. Some echocardiographic parameters of this case were abnormal (LVMi 251 g/m^2, EF 55%, FS 26%, E/A ratio and Em/Am ratio >2, and enlarged atrium). The case with manifest CCMP had severe ascites, and the Child-Pugh and PELD scores of this case were C and 35, respectively.

No case with CCMP had any severe cardiac symptoms such as respiratory distress, cyanosis, massive edema, and angina pectoris. Only, 1 case with manifest CCMP had experienced exercise dyspnea. Heart rates of all of the cases with CCMP were, however, higher (127 ± 16 [102–150]/min) (CCMP vs control, $P < 0.001$). One case with manifest CCMP had accompanying human herpesvirus infection (type 8).

All of the cases with CCMP were included in the priority transplantation list for liver transplantation as soon as possible. All of the cases were, however, asymptomatic because of bed rest and low physical activity. Also, they were already using some cardioprotective drugs such as propanolol and spironolactone for the treatment of PHT and its complications. No case had used a specific therapy for CCMP in addition to those cardioprotective drugs.

Risk Factors for CCMP

In this study, the risk factors of CCMP were also investigated. The variables of sex, age, disease duration, ascites grade, scores of Child-Pugh, and PELD were investigated as the risk factors using the multivariate regression analysis. Three analysis steps were formed for the separation of the dependent variables (Child-Pugh scores with ascites presence and Child-Pugh with PELD scores). In the first step, the variables of sex, age, disease duration, and PELD scores were selected; in the second step, the variables of sex, age, disease duration, and Child-Pugh scores were selected; and in the third step, the variables of sex, age, disease duration, and ascites grade were selected. According to this statistical analysis, sex, age, and disease duration were not found to be the risk factors for CCMP ($P > 0.05$). The PELD score with the lower OR ($P < 0.01$, OR 1.2 [1.1–1.4]) was an unimportant risk factor, but Child-Pugh scores and ascites grades were important factors for CCMP ($P = 0.001$, OR 2.9 [1.5–5.4]) and ($P = 0.001$, OR 9.4 [2.5–35.2]).

DISCUSSION

CCMP is a disorder that develops as a result of cardiovascular disturbance owing to liver disease. Unfortunately, data on CCMP in children are limited. In this study, we investigated the incidence, features, and risk factors for CCMP in children with PHT.

There are few studies on CCMP in childhood (7–10). These studies do not include data associated with diagnostic criteria, incidence, and risk factors for CCMP in children. Among these studies, Polat et al (9) have investigated cardiac functions in children with chronic hepatitis B and determined that the mean E/A ratio of those with a higher fibrosis score was lower than in cases with normal fibrosis score and in controls. They suggested that there is a relation between cardiac dysfunction and severity of chronic hepatitis B. In other 2 different studies carried out by Özçay et al (8) and Arikan et al (10), evaluating ECG and echocardiographic findings on children with cirrhosis, the heart linear sizes increased and the QTc interval was prolonged in patients with Child-Pugh C when compared with those having Child-Pugh A and B. All of the studies have shown that cardiac functions were abnormal in relation to severity of chronic liver disease.

CCMP is a newly defined entity in children, which often exhibits latent and asymptomatic clinical progress in the absence of stress factors. Although the exact diagnosis of CCMP is difficult, the disorder may be diagnosed by periodical cardiac examinations. The diagnostic criteria for CCMP were described by Moller and Henriksen in adults (5), but these criteria are not validated in children. Some researchers have suggested that these criteria can be used after modification for children. Among these criteria, the determination of prolonged QTc is an important criterion for the diagnosis. In addition, echocardiographic abnormalities associated with diastolic and/or systolic dysfunctions further confirm the diagnosis of CCMP (4–6,18,23,29,30). In the present study, the presence of prolonged-QTc was accepted as the main diagnostic criteria for CCMP. The criteria of prolonged-QTc and tachycardia alone were accepted as diagnostic for latent CCMP; when an accompanying echocardiographic abnormality was present, manifest CCMP was diagnosed.

Some researchers have reported that some biochemical markers such as brain natriuretic peptide, pro–brain natriuretic peptide, and troponin-I may be helpful for the diagnosis (4–6). On the contrary, in a few studies in adults, some provocation tests such as dobutamine infusion, and exercise were suggested as more reliable (31). Data on these tests are, however, limited in children and the provocation tests should not be used in this setting because it is life threatening.

Echocardiographic parameters, such as the linear sizes of the heart, EF, and FS values, mitral valve E/A ratio, DECT, and isovolumetric relaxation time, may be useful in the diagnosis. Such parameters are, however, usually normal in the latent form of CCMP. In cirrhotic patients, the initial abnormality affects mainly diastolic functions, whereas systolic dysfunction (lower EF and FS) appears later (5,10,15,32–37). In this study, abnormal echocardiographic findings were found in 1 case with manifest CCMP. In contrast, the mean of EF and FS were significantly elevated in cirrhotic cases with latent CCMP compared with the controls. Moreover, mitral valve E/A ratios and the indexes of linear heart size in the cirrhotic cases were higher than those in healthy controls. This situation may be explained as a result of compensation of systolic functions in the early stage of cirrhosis.

Previously, the incidence of the rate of prolonged-QTc in cases with cirrhosis was reported to be 30% to 60% in adults and 15% to 45% in children (7,10,39). Actually, these rates reflect the incidence of latent CCMP. In our study, the incidence of CCMP in children with PHT was found to be 20% (manifest CCMP 2% and latent CCMP 18%).

In many previous studies, CCMP has been reported as a disease associated with cirrhotic PHT (5,29,40). There are no definitive data on the development of CCMP in patients with noncirrhotic PHT. In 2 different studies carried out by Trevisani et al (41) and Bernardi et al (23), it has been reported that cardiovascular functions were found to be impaired in both cirrhotic and noncirrhotic adults with PHT; however, in these studies, no evidence has been presented regarding CCMP. Similarly, in our study, the mean QTc values and heart rate in both cirrhotic and noncirrhotic portal hypertensive groups were significantly higher compared with the control group, but none of the noncirrhotic cases had diagnostic criteria for CCMP.

Most of the previous studies have suggested that the presence of ascites and the severity of cirrhosis are important risk factors for cardiac dysfunction (23,34,42–44). In accordance with the results of the previous studies, all of the cases with prolonged-QTc in this study had both ascites and cirrhosis labeled as Child-Pugh B (1 case) and C (9 cases) according to the stage of the cirrhosis.

To our knowledge and a search of the literature, this study is the first to investigate on the risk factors of CCMP in children. Although sex, age, liver disease duration, and PELD scores were not significant for the risk of CCMP, ascites and higher Child-Pugh scores were found to be the most important risk factors.

Although CCMP often shows latent progress, some stress factors such as invasive interventions or infections may aggravate the findings of CCMP and lead to a poor prognosis (4–6,11–16). CCMP is, however, not considered a contraindication for liver transplantation, provided the patients are administered cardioprotective drugs. Some researchers have reported that these patients have a good prognosis overall (13,14). Nevertheless, we believe that CCMP should be periodically investigated in children with cirrhotic PHT.

This is a preliminary study, and future confirmations on CCMP in this setting are needed. According to our results, a detailed cardiac examination should be carried out periodically in children with cirrhotic PHT, especially in patients with ascites and high Child-Pugh score.

REFERENCES

1. Brady L. Portal hypertension and ascites. In: Guandalini S, ed. *Essential Pediatric Gastroenterology, Hepatology & Nutrition.* New York: McGraw-Hill; 2005:123–31.
2. Ryckman FC, Alonso MH, Tiao G. Causes and management of portal hypertension in the pediatric population. In: Sanyal AJ, Shah VH, eds. *Portal Hypertension: Pathobiology, Evaluation, and Treatment.* Totowa, NJ: Humana Press; 2005:383–410.
3. Shneider BL, Bosch J, de Franchis R, et al. Portal hypertension in children: expert pediatric opinion on the report of the Baveno v Consensus Workshop on Methodology of Diagnosis and Therapy in Portal Hypertension. *Pediatr Transplant* 2012;16:426–37.
4. Wong F. Cirrhotic cardiomyopathy. *Hepatol Int* 2009;3:294–304.
5. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. *Gut* 2008;57:268–78.
6. Swanson KL, Krowka MJ. Pulmonary complications associated with portal hypertension. In: Sanyal AJ, Shah VH, eds. *Portal Hypertension: Pathobiology, Evaluation, and Treatment.* Totowa, NJ: Humana Press; 2005:455–68.
7. Fishberger SB, Pittman NS, Rossi AF. Prolongation of the QT interval in children with liver failure. *Clin Cardiol* 1999;22:658–60.
8. Özçay F, Tokel K, Varan B, et al. Cardiac evaluation of pediatric liver transplantation candidates. *Transplant Proc* 2002;34:2150–2.
9. Polat T, Urganci N, Yalcin Y, et al. Evaluation of cardiac function by tissue Doppler imaging in children with chronic hepatitis. *J Pediatr Gastroenterol Nutr* 2006;43:222–7.
10. Arikan C, Kilic M, Tumgor G, et al. Impact of liver transplantation on rate-corrected QT interval and myocardial function in children with chronic liver disease. *Pediatr Transplant* 2009;13:300–6.
11. Ma Z, Lee S. Cirrhotic cardiomyopathy: getting to the heart of the matter. *Hepatology* 1996;24:451–9.
12. Acosta F, De La Morena G, Villegas M, et al. Evaluation of cardiac function before and after liver transplantation. *Transplant Proc* 1999; 31:2369–70.
13. Myers R, Lee S. Cirrhotic cardiomyopathy and liver transplantation. *Liver Transpl* 2000;4(Suppl 1):44–52.
14. Liu H, Lee S. What happens to cirrhotic cardiomyopathy after liver transplantation? *Hepatology* 2005;42:1203–5.
15. Torregrosa M, Aguadé S, Dos L, et al. Cardiac alterations in cirrhosis; reversibility after liver transplantation. *J Hepatol* 2005;42:68–74.
16. Gaskari S, Honar H, Lee S. Therapy insight: cirrhotic cardiomyopathy. *Nat Clin Pract Gastroenterol Hepatol* 2006;3:329–37.
17. Alqahtani S, Fouad T, Lee S. Cirrhotic cardiomyopathy. *Semin Liver Dis* 2008;28:59–69.
18. Mandell MS, Lindenfeld J, Tsou MY, et al. Cardiac evaluation of liver transplant candidates. *World J Gastroenterol* 2008;14:3445–51.
19. University of Washington Medical Center. Criteria for Child-Pugh Classification. *http://depts.washington.edu/uwhep/calculations/childspugh.htm.* Published 2001. Accessed March 13, 2014.
20. Organ Procurement and Transplantation Network. MELD/PELD Calculator. *http://optn.transplant.hrsa.gov/resources/allocationcalculators.asp?index=97.* Accessed March 13, 2014.
21. Park MK, Guntheroth WG, eds. *How to Read Pediatric EKGs*. Philadelphia: Mosby Year Book; 1992:1–248.
22. Garson A. How to measure the QT interval—what is normal? *Am J Cardiol* 1993;72:14–6.
23. Bernardi M, Calandra S, Colantoni A, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology* 1998;27:28–34.
24. Friedman MJ, Mull CC, Sharieff GQ, et al. Prolonged QT syndrome in children: uncommon but potentially fatal entity. *J Emerg Med* 2003; 24:173–9.
25. Abhayaratna WP, Marwick TH, Smith WT, et al. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. *Heart* 2006;92:1259–64.
26. DeSimone G, Devereux RB, Daniels SR, et al. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol* 1995;25:1056–62.
27. Huwez FU, Houston AB, Watson J, et al. Age and body surface area related normal upper and lower limits of M mode echocardiographic measurements and left ventricular volume and mass from infancy to early adulthood. *Br Heart J* 1994;72:276–80.
28. Kampmann C, Wiethoff CM, Wenzel A, et al. Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe. *Heart* 2000;83:667–72.
29. Milani A, Zaccaria R, Bombardieri G, et al. Cirrhotic cardiomyopathy. *Dig Liver Dis* 2007;39:507–15.
30. Zambruni A, Trevisani F, Di Micoli A, et al. Effect of chronic beta-blockade on QT interval in patients with liver cirrhosis. *J Hepatol* 2008;48:415–21.
31. Pahl E, Duffy E, Chaudhry FA. The role of stress echocardiography in children. *Echocardiography* 2000;17:507–12.
32. Moller S, Henriksen JH. Cardiovascular dysfunction in cirrhosis. Pathophysiological evidence of a cirrhotic cardiomyopathy. *Scand J Gastroenterol* 2001;36:785–94.
33. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 2005;42:439–47.
34. Pozzi M, Carugo S, Boari G, et al. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. *Hepatology* 1997;26:1131–7.
35. Alexander J, Mishra P, Desai N, et al. Cirrhotic cardiomyopathy: Indian scenario. *J Gastroenterol Hepatol* 2007;22:395–9.
36. Piscaglia F, Valgimigli M, Rapezzi C, et al. Left ventricular volumes in liver cirrhosis. *Dig Liver Dis* 2000;32:392–7.
37. Timoh T, Protano MA, Wagman G, et al. A perspective on cirrhotic cardiomyopathy. *Transplant Proc* 2011;43:1649–53.
38. Deleted in proof.
39. Baik S, Fouad T, Lee S. Cirrhotic cardiomyopathy. *Orphanet J Rare Dis* 2007;2:15.
40. Liu H, Gaskari S, Lee S. Cardiac and vascular changes in cirrhosis; pathogenic mechanisms. *World J Gastroenterol* 2006;12:837–42.
41. Trevisani F, Merli M, Savelli F, et al. QT interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunt. *J Hepatol* 2003; 38:461–7.
42. Moller S, Henriksen JH. Cardiopulmonary complications in chronic liver disease. *World J Gastroenterol* 2006;12:526–38.
43. Valeriano V, Funaro S, Lionetti R, et al. Modification of cardiac function in cirrhotic patients with and without ascites. *Am J Gastroenterol* 2000;95:3200–5.
44. Finucci G, Desideri A, Sacerdoti D, et al. Left ventricular diastolic function in liver cirrhosis. *Scand J Gastroenterol* 1996;31:279–84.