Medical Expertise*

"Development of the European Network in Orphan Cardiovascular Diseases"
„Rozszerzenie Europejskiej Sieci Współpracy ds Sierocych Chorób Kardiologicznych"

EXPERT: Prof. Andrzej Rudziński, pediatric cardiologist

Affiliation: *Department of Cardiology, Pediatric Institute, Jagiellonian University Medical College, Krakow, Poland*

CASE SUMMARY

The authors present a case of 23 year old male (weight 47 kg, height 163 cm) with complex congenital heart disease: TGA, VSD, left atrioventricular valve atresia and hypoplasia of the right ventricle, after the Fontan procedure. In October 1989 (at the age of 6 weeks), he underwent the widening of intraatrial communication and banding of pulmonary artery. At the age of 3, hemi-Fontan procedure was done, and 6 years later (November 1998) modified Fontan procedure with 3,5 mm wide fenestration was performed. At admission patient was diagnosed with hepatic cirrhosis, ascites, hypoptoteinemia with hypoalbuminemia suggesting exudative enteropathy, and microcytic anaemia. Moreover right-side paresis was present. In October 2013 patient was readmitted to the hospital because of progressive exercise intolerance of few months duration, oedema of the abdominal wall and peripheral oedema (NYHA functional class III). In physical examination systolic murmur over the pulmonary artery and in Erb's point was heard, moreover hepatomegaly, ascites, lower limbs oedema, dental caries and umbilical hernia were found. In ECG sinus rhythm 90 bpm was present with PQ prolongation (0,22 sec), periodically second degree atrioventicular block and episodes of nodal rhythm 60 bpm were observed. In 24-hour Holter monitoring sinus rhythm 90 bpm prevailed with first degree atrioventricular block (PQ – 0,24 sec.). Also episodes of advanced second degree atrioventricular block type Mobitz II and nodal rhythm 56 bpm were present. In the cardiac echo portal vein (12 mm) and inferior vena cava (17 mm) were extended, ejection fraction of left ventricle was reduced (45-50%), there were also present mild mitral regurgitation (mitral anulus 47 mm). E/A proportion was 0,56/0,41 m/sec (1,35), E/E' proportion – 4,5. In the tunnel connecting IVC and RPA there were additional echoes suggesting thrombi. In both pleural cavities small amount of fluid was present (20-30 mm). In laboratory testing: reduction of total protein level (42,9 g/l), albumin (24,5 g/l), K^{+} (3,5 mmol/L), Fe^{+++} (6,9 – normal level 12,5-26 umol/L); D-dimer level was elevated (2998, normal level <500 μg/l) were noticed. Blood count, CRP level, hepatic enzymes including GGTP and Alcaic phosphatase were normal. NT-pro BNP level was increased (421 – norlam

level for men <55 years - 64 pg/ml) (1). Antithrombotic treatment included: Enoxaparine (40 mg twice a day). Due to reduction of volume overload of the heart, transudation into body cavities and peripheral oedema, Furosemid (once daily) and Spironol (50 mg daily) were used. In treatment of the exudative enteropathy Prednison (2,5 mg daily) was administered beside diuretics. Anticonvulsant therapy included Valproic acid (500 mg daily) and Vigabatrin (500 mg twice a day). During hospitalization intravenous albumin infusions and diet rich in proteins (1,5-3 g/kg of body weight) with the medium-chain fatty acids supplements (MCT oil) were given. According to the authors, outside the hospital patient didn't follow the physician's instructions, including diet and prescribed medications.

DISCUSSION

Heart catheterization and angiography done before Fontan procedurę revealed slightly different morphology of the heart defect than described in the presentation. Correct veno-atrial connections and correct position of atria were demonstrated (*situs solitus*), while the discordance of right atrioventricular ostium was proven – i.e. right atrium was connected via mitral valve with anatomically left ventricle located on the right side (L-loop of ventricles). Also atresia of the left atrioventricular ostium were present. Flow from the left to right atrium was made possible by atrial septum defect. In subaortic area the large ventricular septum defect was observed. It connected right-sided, well developed, anatomically left chamber with hypoplastic, outlet part of left-sided, anatomically right chamber. Both main arteries located "side by side" originated from this chamber, the pulmonary artery was slightly in the front and to the left of the aorta. Apart from those differences, this case belongs to the group of complex congenital heart defects with one well developed ventricle and hypoplastic or aplastic second chamber. Anderson used a term "functionally single ventricle" (FSV) to emphasize the role of one fully developed ventricle apart from its anatomical type (anatomically right, left or undefined) (2). The occurrence of FSV is estimated at the level of 2-10% of congenital heart defects. Differences in this estimation are caused by lack of uniform terminology and classification (3). This group, besides variations in heart chambers morphology, is characterized by significant diversity in accompanying changes of circulatory system, for example anomalies of systemic and/or pulmonary veins, defects of the heart septums, atrioventricular valves and artery valves, discordance of atrio-ventricular and ventriculo-arterious communications, abnormal location of the heart in the chest (malposition of the heart) (3,4,5). This diversity of accompanying defects determines the initial treatment. Next steps; hemi-Fontan or Glenn procedure, final – modified Fontan procedure, are the same in all cases (3,4,5). The aim of this initial treatment is to ensure undisturbed flow from systemic and pulmonary veins, eliminate difficulties in systemic flow and optimize pulmonary flow (which requires reduction in case of excess blood flow and increase in defects with diminish pulmonary blood flow). According to excess pulmonary blood flow in this case, pulmonary artery banding was initially performed to reduce the volume of flow and pulmonary pressure; because of the atresia of tricuspid valve, at the same time the intraatria communication was expanded to improve systemic venous flow to functionally single ventricle (anatomically left chamber). Initial procedures, which aim is to balance the systemic and pulmonary blood flow and reduce the preload of functionally single ventricle, are performed in neonatal period, risk ranges from 5 to 25%, depending of the type of defect and type of procedure. The pulmonary artery banding is usually done at the age of 3 weeks and

does not carry significant risk (4,5). In second step (usually performed at the age of 6-7 months), two equivalent methods are used: creation of anastomosis of the end of superior vena cava to the side of unilateral branch of pulmonary artery – called bidirectional Glenn anastomosis, or enlarged anastomosis of superior vena cava in its outlet to right ventricle with right branch of pulmonary artery (side to side) with closure of communication with right atrium by Gore-tex patch – called hemi-Fontan procedure. In this particular case hemi-Fontan procedure was performed quite late – at the age of 3 years. This method is very extensive, but at the same time, it is an introduction to creating a lateral tunnel in right atrium while final Fontan procedure is performed, the tunnel directs blood flow from inferior vena cava to right branch of pulmonary artery. This procedure separates pulmonary and systemic circulation and restores serial characteristic of circulatory system. Fontan procedure is performed at the age of 2,5-3 years. In this case it was done much later due to unclear reasons. Earlier treatment prevents the effects of chronic hypoxia and aftermatch, cyanosis, creation of veno-venous anastomosis and systemic-pulmonary anastomosis. To prevent the excessive increase of central venous pressure and to improve the filling of FSV and its output (especially during perioperative period), small fenestration in the tunnel's wall is created (about 4 mm). The cost of this procedure is desaturation and increase risk of embolism. The fenestration prevents the effects of increase central venous pressure – e.g. transudations into body cavities: pericardium, pleural cavities, peritoneal cavity. In discussed case during follow up no fenestration was found, most likely because of its spontaneous closure. Essential conditions in final procedure's effectiveness are: normal resistance and pressure in pulmonary circulation, sufficient systolic and diastolic function of FSV, laminar blood flow from systemic veins to the branch of pulmonary artery and laminar, even blood flow in its branches. Risk factors are: hypertrophy of FSV because of volume or pressure overload, impaired systolic or diastolic function of FSV, elevated end diastolic pressure of FSV, increase pulmonary resistance, deformations, stenosis of the branch of pulmonary artery causing increased flow resistance (impedance), loss of kinetic energy and increase of pressure in preceding circulatory system, significant atrioventricular valve regurgitation (3,4,5). Even the best results of modified Fontan procedure do not change the fact that it is a palliative operation. There is only one ventricle in circulatory system without advantages of additional pulse amplification of pulmonary circulation. The consequence of this anatomy is constantly increased venous pressure (mean 10-15 mmHg) and elevated resistance, against which the FSV is working – it's the sum of systemic, Fontan configuration and pulmonary resistance. Elevated central venous pressure is accompanied by relatively low pulmonary artery pressure, which is called paradox of the circulation's physiology after Fontan procedure (5). Among patients who survived perioperative period, life free of all events causing death and necessity of heart transplantation is estimated at the level of 90% during 10-years observation, after 20 years – 83% and after 25 years – 70% (6). Complications after this treatment are caused by all steps of operative corrections and the "physiology" of Fontan's circulation. Their number is increasing with time of survival because of the phenomena called "atrition" of Fontan's circulation. The most common complications are: various forms of supraventricular arrhythmias, including dysfunction of sinus node and conduction abnormalities, thromboembolic complications, impaired liver function leading to cirrhosis, exudative enteropathy, progressive dysfunction of chronic volume- undefilled FSV, formation of various anastomosis, part of which causes the increase of volumetric load of FSV, part

John Paul II Hospital in Kraków
Jagiellonian University, Institute of Cardiology
80 Prądnicka Str., 31-202 Kraków;
tel. +48 (12) 614 33 99; 614 34 88; fax. +48 (12) 614 34 88
e-mail: rarediseases@szpitaljp2.krakow.pl
www.crcd.eu

bypasses the pulmonary circulation favoring desaturation, polyglobulia, polycythemia and cyanosis. It must be emphasized that this type of circulation limits exercise capacity and neurodevelopment (4,5,7). Those are caused by repeated operation using extracorporeal circulation, emboli in central nervous system, chronic hypoxia and neurological deficits often present at birth. Most of listed above are present in described case, causing significant reduction in circulatory efficiency. Survival of the patients with atresia of the tricuspid valve after Fontan procedure is promising, especially after it's modification was applied. In Mair and co. observations of 215 patients with this type of defect (including 34 with transposition of great arteries) operated in 1973-1998; 45 died, including only 3 patients from 58 operated on in 1988-1997. Causes of 26 late deaths (4 months to 18 years after operation) were: arrhythmias (7), progressive heart failure (4), complications after re-operations (3), thromboembolic complications (3), exudative enteropathy (3), pulmonary issues (2), accidents (2), unknown causes (2). In general 171 patients were observed in the period of time ranged from 1 to 24 years, mean 13 years (8). Applied treatment in this case was adequate. Unsatisfactory effect was connected with lack of compliance and hepatitis C virus infection. In this situation, there is no option for more advanced treatment or heart transplantation in this patient.

It should be mentioned, that heart transplantation is the only alternative treatment in patients with FSV and the only option for patients with aggravating circulation's function after Fontan procedure. The most important limitation for this treatment is lack of donors and other potential recipients, with far less advanced changes in circulatory system and other organs. It has major prognostic significance and causes serious ethical and moral dilemma during decision process.

Hepatitis C virus infection is one of the most common cause of chronic hepatitis, and one of the most common causes of liver transplantation. It's also major risk factor of liver cancer. Transmission of the infection is parenteral – with infected medical equipment, blood transfusion (nowadays very rare cause). It may be also transmitted by drug addicts who do not use disposable needles, by sexual intercourse, also from mother to child. The majority (85%) of newly infected patients is unable to eliminate the virus and infection passes to chronic state. The infectious agent is RNA-virus. This group includes at least 6 subtypes with different genetic profiles. This is crucial to the therapy (best results of treatment in genotype 1) and to the difficulties in vaccine production. Initially the infection is asymptomatic. The stage of the disease is determined by the liver biopsy, which shows the steatosis and fibrosis of hepatocytes. Currently used treatment – interferon, ribavirin (Rebetol) in combination with direct antiviral agent – telaprevir (Incivek) or boceprevir (Victrelis), significantly improves prognosis (50-60%), especially in patients with genotype 1 HCV. This treatment eliminates infection and fibrosis of the liver in majority of patients. Nevertheless effect of therapy is unsatisfactory in part of them (9).

This complication in patients with chronic venous stasis – like patients with FSV after Fontan procedure, is a great therapeutic challenge and has indubitable impact on prognosis.

EXPERT'S OPINION

Presented case illustrates important issues in diagnostic procedures and therapy of

John Paul II Hospital in Kraków
Jagiellonian University, Institute of Cardiology
80 Prądnicka Str., 31-202 Kraków;
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e-mail: rarediseases@szpitaljp2.krakow.pl
www.crcd.eu

patient with complex heart defect: single, anatomically left ventricle located on the right side, with atresia of left atrioventricular ostium, VSD, ASD and both main arteries originating from hypoplastic, left-sided, anatomically right ventricle. Patient underwent staged treatment including hemi-Fontan procedure at the age of 3 years and final Fontan procedure at the age of 9 years, which is much later than recommended. The reasons of this delay are unclear. In years after procedure almost all serious complications after this type of treatment have occurred. In part, their occurrence may be connected with treatment delay. Additionally patient was diagnosed with epilepsy and hepatitis C of unknown origin (after blood transfusion?). All circulatory complications that occur (exudative enteropathy, thromboembolic complications with paresis, systolic dysfunction of systemic – left ventricle, arrhythmias and conduction abnormalities), are often observed in different periods of time after Fontan procedure (e.g. exudative enteropathy occurs in 3,7-24% of patients and usually appears 2-3 years after the operation) and are significant risk factors of death. Treatment of exudative enteropathy includes careful diuretics administration, protein supplements infusions, proper diet and steroids. Improvement in those cases is observed after pulmonary vasodilators administration, like Sildenafil or Bozentan, which are also responsible for reduction of the formation of arterial-venous anastomosis and improvement of function of the systemic ventricle (10). Where possible, after careful angiographic and hemodynamic evaluation, interventional or operational elimination of all flow obstacles in Fontan circulation and branches of pulmonary artery is necessary. It must be pointed out, that nor pharmacological, nor interventional and/or operational therapy doesn't guarantee full recovery (10). Among all serious rhythm disturbances, only atrial arrhythmias didn't occur in this patient. He was also diagnosed with moderate diastolic and systolic dysfunction of systemic ventricle, which is also common among this patients and causes significant therapeutic issues.

CONCLUSION

Presented case of the complex heart defect illustrates therapy options for patients with single ventricle, in this case systemic left ventricle. It also presents types of complications which may occur after final modified Fontan procedure. It must be pointed out that during follow up, majority of those complications occurred in the patient, except for atrial arrhythmias and fibrous bronchitis. It is possible that unclear delay in performance of the final Fontan procedure may contribute to earlier appearance of described complications. Applied therapy was adequate for the diagnosed issues. Lack of patient's compliance and probably too little pressure of his family may contribute to possible unfavorable prognosis.

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John Paul II Hospital in Kraków
Jagiellonian University, Institute of Cardiology
80 Prądnicka Str., 31-202 Kraków;
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