CARDIOVASCULAR INVOLVEMENT OF KAWASAKI DISEASE IN THE WEST PART OF ROMANIA

Gabriela Doros[1,2], Ramona Stroescu[1,2], Cristina Olariu[1,2], Ardelean AM[1,2], Gafencu M[1,2]

Abstract

Introduction: Kawasaki disease is a self-limited vasculitides, that usually affects medium and small vessels, and more often is the affliction of children with ages between 0-5 years. Complications of Kawasaki disease include: coronary artery disease, left ventricle dysfunction, myocarditis, myocardial infarction. Aim: To present the cardiac involvement in patients diagnosed with Kawasaki disease, admitted into our clinic over a period of one year, despite the fact that this diagnosis is very rare in our region. Materials and Methods: Five patients were admitted into our clinic for prolonged fever, for whom clinical examination, lab tests, ECG, Echocardiography and in severe cases, Computer Tomography with Angiography and/or Coronary Angiography were performed. Results: Kawasaki disease was confirmed in all five cases. The majority of patients were females. One single case was a recurrent Kawasaki disease. 60% of our patients were found with cardiac involvement, out of which one was diagnosed with giant aneurysmal dilatation of the right and left coronary artery, of over 8 mm, later complicated with intracoronary thrombus and IIIrd grade mitral regurgitation. One case had mild left coronary artery aneurysmal dilatation with wall thickening and the third just minor aneurysmal dilatation of the left coronary artery. All patients presented thrombocytosis, but the level of the thrombocytes was extremely high in patients associating coronary affliction. Intravenous immunoglobulin (IVIG) and Aspirin was administered in all cases. Anticoagulation therapy was associated in one patient with intracoronary thrombus formation. Conclusions: Kawasaki disease incidence is increasing in the west part of the country. Coronary artery involvement was present in 60% of cases. Giant coronary artery aneurysm with intraluminal thrombus formation was the most severe complication found. High thrombocyte values were associated with coronary artery involvement. Immediate IVIG administration and Aspirin can help in preventing coronary artery complications and in reducing the coronary inflammatory process. Anticoagulant therapy was needed when thrombus was present. A regular follow-up plan is needed in all patients with Kawasaki disease and cardiac involvement, especially in patients with giant aneurysm formation.

Keywords: Kawasaki disease, coronary artery, giant aneurysm, thrombus

Background

Kawasaki disease is a relatively rare disease in our country. It is more frequently diagnosed in Asian countries, with a peak incidence in Japan, where it was for the first time described by Tomisaku Kawasaki. As of late, there are more cases, not only in Japan or China, but they have been diagnosed in the Central part of Europe. Although Kawasaki disease is a self-limiting disease, it can sometimes have severe cardiovascular complications. For a positive diagnosis, which is mainly clinical, a high grade fever for more than 5 days is needed and four or more of the following symptoms: polymorphous rash, extremity modifications with edema of the hands and feet, bilateral conjunctivitis, strawberry tongue, cracked lips, unilateral cervical lymph node enlargement. The complications consist of myocarditis, left ventricle dysfunction, valvular dysfunction, more frequently regurgitations, dilatation of the coronary arteries that can lead to aneurysm formation, intravascular thrombus formation, myocardial infarction and even sudden death. By far, the most common complication is aneurysmal dilatation of the coronary arteries.

Aim

The objective is to present the cardiovascular implications in patients admitted into our clinic for prolonged fever, that were diagnosed with Kawasaki disease, study performed over a one-year period. Proper treatment can reduce vascular inflammation in order to prevent severe cardiac complications or to stop progression of the coronary artery damage, this being the case for some patients.

Material and method

Five patients were admitted into our clinic, over the last year, with symptoms of high grade fever that would not easily respond to antipyretics, peculiar rashes, nonexudative bilateral conjunctivitis, cervical lymph node, strawberry tongue and fissured lips. All of them underwent thorough clinical examination, laboratory tests, Electrocardiograms and Echocardiography, even daily when it was necessary. Whenever Echocardiography results were not sufficient, Computer Tomography with Angiography and/or classic Coronary Angiography were performed in selected cases.

[1]"Victor Babeş" University of Medicine and Pharmacy Timişoara
[2]"Louis Ţurcanu" Emergency Hospital for Children Timişoara

E-mail: gdoros@gmail.com, ramona.giurascu@gmail.com, olariu.ioanacristina@yahoo.com, mgafencu@umft.to

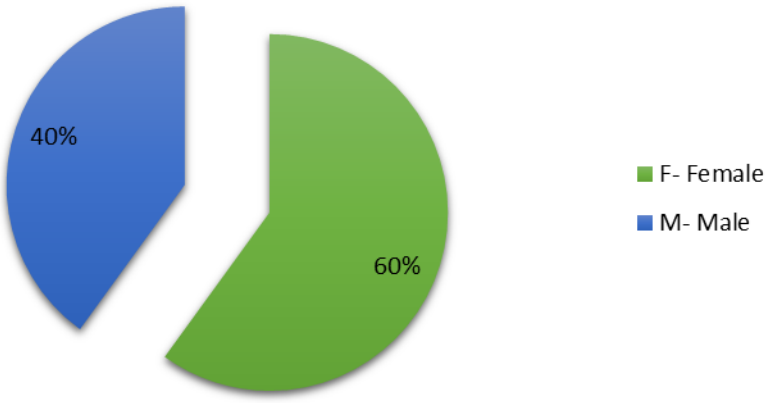

Fig.1. Case repartition according to gender.

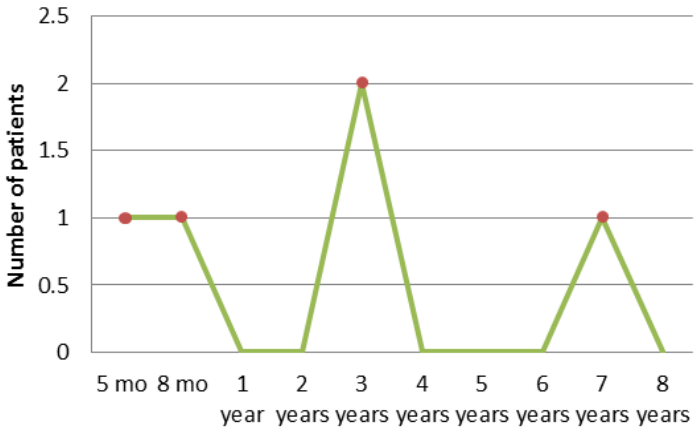

Fig.2. Case repartition by age

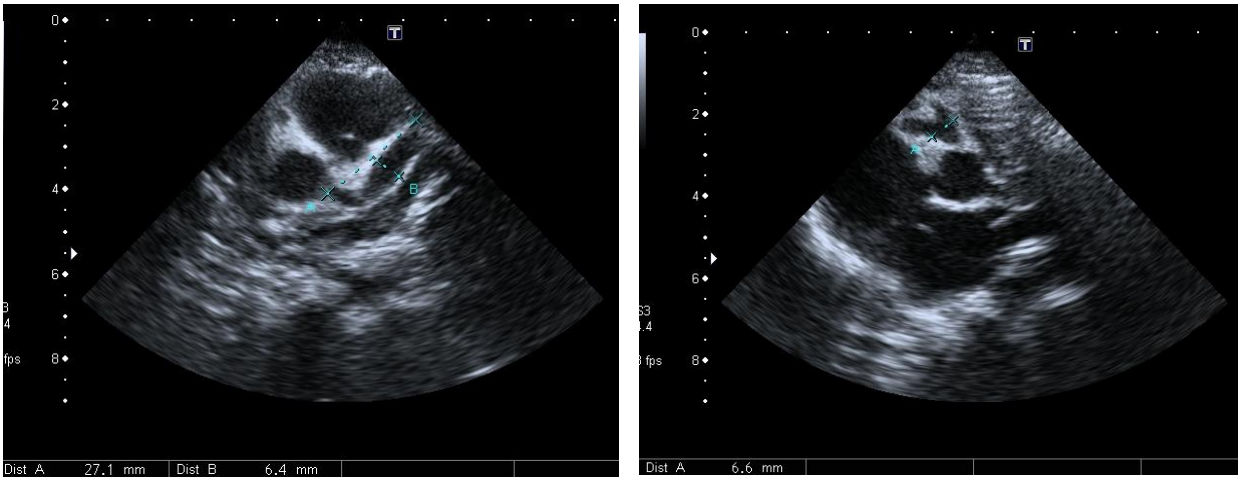

Fig.3. A. Medium dilatation of the left coronary artery (LCA-LAD) of 6.4 mm;
B. Medium dilatation of the right coronary artery (RCA) of 6.6 mm.

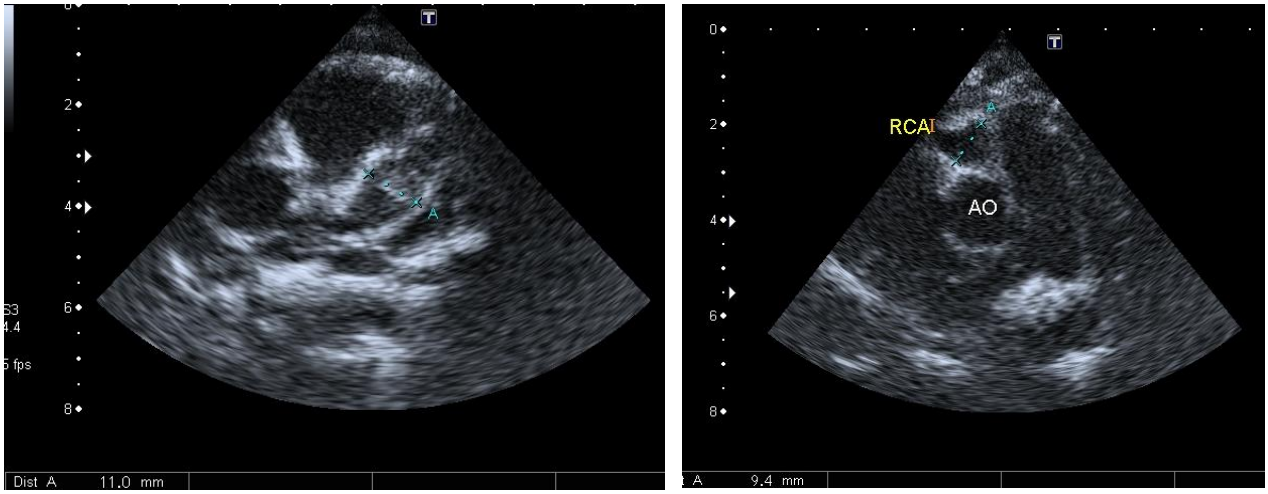

Fig.4. A. Giant aneurismal dilatation of the left coronary artery (LCA-LAD) of 11 mm with thrombus formation inside;

B. Giant aneurismal dilatation of the right coronary artery of 9.4 mm

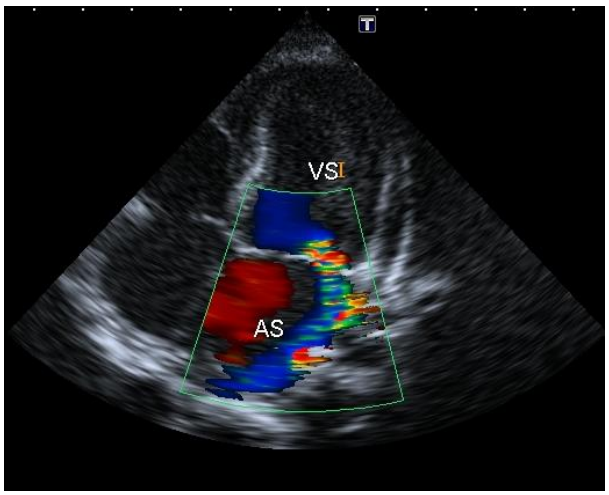

Fig.5. Third grade mitral regurgitation

Results

Over the last year, five children with Kawasaki's disease were diagnosed in our clinic. There was a predilection for the feminine gender, 3 patients, representing 60% of all patients, were females, and only 40% of the total amount of patients, were represented by males, 2 patients (Fig. 1). Regarding the age distribution, two cases were infants with ages of 5 and 8 months, two children of 3 years and one pre-school patient, of 7 years (Fig. 2). The infants were one male and one female. The children were both girls and the preschool patient was a 7-year-old girl.

After the clinical examination we classified the patients according to their clinical manifestations of the disease; if they exhibited the entire pallet of symptoms from the Kawasaki criteria, they were classified as complete Kawasaki disease, 60% of our patients were part of this group, meaning 3 cases. If they only had fever and a couple of symptoms, they were classified as incomplete Kawasaki disease, 20% of patients being repartitioned here, meaning 1 patient. The last group was recurrent Kawasaki disease, also 20% of patients, meaning one case.

Three, out of five patients, meaning 60% were discovered with cardio-vascular complications at the first cardiological examination. All of them presented aneurysmal dilatation of the coronary arteries. We classified them according to severity of aneurysmal dilatation of the coronary artery, into three classes: minor – the caliber of the coronary artery is beneath 5 mm, medium – the coronary artery caliber is between 5-8 mm and severe or giant – the coronary artery caliber is over 8 mm. There were two patients, one with small and one with medium left coronary artery aneurysm and the third patient was found with giant coronary aneurysm.

Even though there is no specific test for Kawasaki's, after the lab examination, we noticed that all patients, representing 100%, presented with thrombocytosis, out of

which 60% of patients had values slightly over the upper limit, but 40% of patients had severe thrombocytosis, with values ranging between 800.000 - 980.000/mm3.

Coronary artery dilatation is a serious complication, which is why we would like to highlight the particular case of Kawasaki disease with giant coronary dilatation. An 8 month old male presented in the emergency room with high-grade fever for almost a week, that would not cease upon administration of antipyretics. He was agitated. At clinical examination, a rash, with the aspect of perianal erythema, conjunctivitis and unilateral cervical lymph-nodes, strawberry tongue and extremity changes with edema were found. On ECG, sinus tachycardia, 153 beats/minute and an incomplete right bundle branch block was present, but with no other modifications. Echocardiography found a medium sized aneurysmal dilatation of the left coronary artery – left anterior descending coronary artery (LCA-LAD) and of the right coronary artery (RCA) and mild mitral regurgitation (Fig. 3 A.B). Laboratory tests showed severe thrombocytosis, 800.000/mm3, which is present in almost all complicated cases of Kawasaki disease.

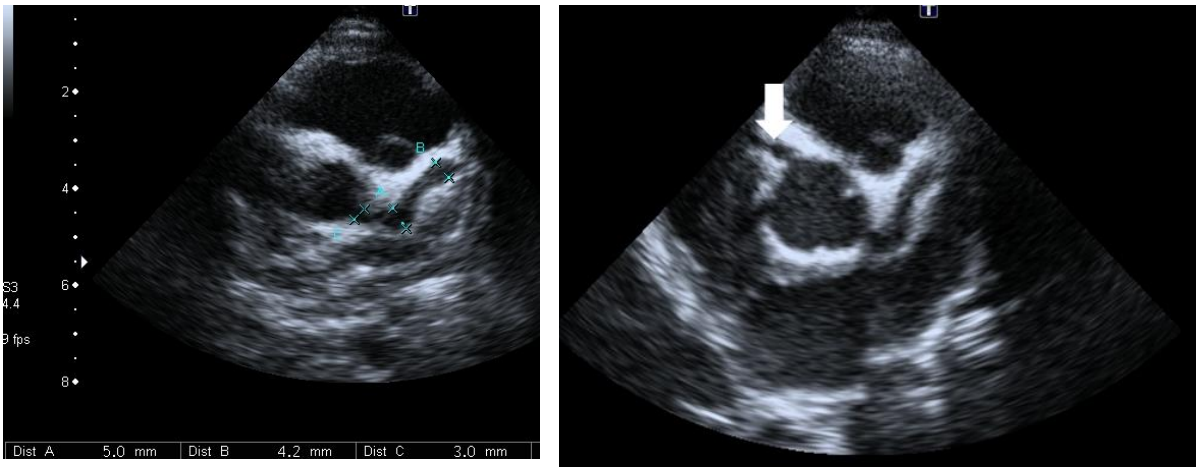

Fig.6. A. Moderate dilatation of LCA of 5 mm and the hyperechogenicity of the walls; B. minor dilatation of the RCA

After consulting the guidelines, we immediately treated the patient with IVIG 2g/kg/day and Aspirin 5 mg/kg/day. He was closely monitored, and the surprise was that, in spite of the proper treatment, he developed giant aneurismal dilatations of 11 mm of the left coronary artery – left anterior descending coronary artery (LCA-LAD) and 9.4 mm of the right coronary artery (RCA) and also associated third grade mitral regurgitation.

Returning to the guidelines, we initiate with double antiplatelet therapy: Aspirin and Clopidogrel (0.2 mg/kg/day). Under this medication, he developed an intraluminal thrombus in the left coronary artery-left anterior descending coronary artery and a third grade mitral regurgitation (Fig. 4, 5). Computed tomography of the coronary artery was performed and a clear visualization and confirmation of the thrombus was obtained. Coming back to the guidelines, anticoagulant treatment with Warfarin was started, with close INR monitoring and a follow-up schedule was established. Upon reevaluation, both coronary arteries had shrunk down, but the thrombus persisted, without obstruction, so we maintained the Warfarin and Aspirin treatment and recommended invasive catheterization with selective cardiac coronary angiography in a specialized clinic, that reconfirmed the giant left coronary artery with the thrombus inside, without obstruction.

On the 6 months' follow-up we found that the coronaries were even smaller than the previous examination and the thrombus was less intense in structure. ECG was normal, without signs of myocardial ischemia. We maintained the same treatment and recommended a second catheterization with selective cardiac coronary angiography a year after the first symptoms, as the guide underlines. The patient is doing well, with complete regression of the mitral regurgitation.

The second important case of Kawasaki disease with cardio-vascular complications was a 3-year-old female, exhibiting all necessary symptoms for a positive diagnosis and severely elevated platelet levels of 980.000/mm3. Echocardiography showed moderate aneurismal dilatation of the LCA and minor dilatation of the RCA. The particular aspect of the case was the association of moderate aneurysmal dilatation of the LCA and mild dilatation of the RCA with LCA walls thickening (Fig. 6 A.B.). Computed tomography of the coronary artery confirmed both the dilatation and the thickened walls (Fig. 7 A.B). IVIG and Aspirin were the therapy of choice.

In evolution, under treatment, the coronary artery dimensions were reduced compared with the first presentation. Platelet level reduced to normal and Aspirin therapy was stopped; now she is only on a follow-up program.

The third case presented slight enlargement of the left coronary artery with a small aneurysm that rapidly regressed under treatment.

Discussions

Although a rare disease in this part of the world, the numbers of cases seem to be growing, from a single case in years, to five cases per year, therefore the infectious hypothesis cannot be infirmed. In accord to all studies we found that the most frequent age of Kawasaki's disease diagnosis is beneath 5 years of age. Our cases were diagnosed in infancy, as usual, two cases, but also in small children, one case. However, one case was diagnosed with recurrent Kawasaki disease, which is mentioned in literature, but is relatively rare and in our female patient it occurred at the age of 7. Four years after the first episode of Kawasaki disease, the patient suddenly developed high grade fever, for more than five days, with a polymorphous rash, conjunctivitis, strawberry tongue, extremity changes and unilateral cervical lymph node enlargement. She had no cardiac involvement, except mild myocarditis with tachycardia, but because the diagnosis was recurrent Kawasaki disease, she was treated accordingly with intravenous immunoglobulin (IVIG), with a good outcome.

From the affected patients with coronary artery implication, two were females and one was male. In infant patients, one was female and one was male. The third affected patient was a three years old girl. Jane Newburger et all stipulate that the number males outnumber females in Kawasaki disease, but in our experience we claim that females are affected, rather than males, but our group was very small.

Of these five children, three had cardiovascular implications at the moment of diagnosis, such as: aneurysmal coronary artery dilatation, the left coronary artery aneurysm being more frequently involved than the right coronary artery and thickening of the coronary artery walls. One of the patients developed a severe complication such as giant coronary artery aneurysm with intraluminal thrombus formation. The rest of the patients had no coronary affliction. Under treatment with IGIV, initiated in the first 10 days of the fever onset, the evolution was good. Guidelines were not clear regarding the treatment of complex giant aneurysms, where is mentioned that "some experts recommend Aspirin and Clopidogrel". The reality was different, because under this medication, a large thrombus formed inside. It was a challenge to treat the intracoronary thrombus at such a small age, in infancy, so we had to review the literature to see the experience of different centers with severe cases of Kawasaki disease, because of the rarity of such severe complications. Finally, the patients with aneurysmal dilatation of the coronary arteries are well, with reduction of the coronary artery size, but are included in a follow up program, with special focus on the patient with thrombus, which has tendencies of reduction. This patient will remain on anticoagulant therapy. All of them have a good clinical evolution.

There are no diagnosis criteria for laboratory test to confirm Kawasaki disease, however we argue the importance of platelet count, whereas we had 100% of patients with thrombocytosis. All patients with coronary involvement presented high levels of platelets. Furthermore the levels of platelets were correlated with the severity of coronary artery affliction. The patient with giant coronary artery aneurysm and intraluminal thrombus and the patient with medium dilated coronary artery but with coronary artery wall thickening presented the highest platelet count, ranging between 800000-1 million/mm3.

IVIG is important to be administered in the first 10 days of illness, to prevent cardiac complications or to stop the progression of the coronary artery damage. One of our cases proved that despite all the effort and properly timed treatment, severe complications can still occur. Therefore, in cases with giant coronary artery aneurysm and intracoronary thrombus, anticoagulant treatment is mandatory. Giant coronary artery aneurysms are discussed in literature as isolated cases with a "single Centre's experience", so it was difficult to choose the best treatment for the case. Each Center has its own experience. Finally we turned to Warfarin and the patient is safe. New Guidelines have to be completed with recommendations for such severe cases with stratification risk of level V.

Regarding the recurrent Kawasaki disease case, it is very rare described in literature, but in our case, the clinical features matched perfectly with the Kawasaki disease criteria, being in the first ten days from the onset of fever, we decided to treat her as Kawasaki disease, with intravenous immunoglobulin (IGIV) in order to prevent cardiac involvement. The evolution was spectacularly good, with rapid fever subsidence, and extremity peeling. The patient is well. There is no indication in literature to follow up patients with Kawasaki disease without cardiac implication, because of the rarity of the recurrence.

Conclusions

Kawasaki disease's incidence has grown over the years, spreading from Japan to America and, as of late, to Europe as well. Despite all studies, we had more females affected than males, maybe a larger cohort is needed in order to sustain this assumption. Early administration of IVIG can help in preventing and reducing cardio-vascular involvement, with rare exceptions, including giant coronary artery aneurysm with intracoronary thrombus formation. Platelet count must be taken into account when the suspicion of Kawasaki disease is raised, because it is associated with cardiac involvement. In our experience, in the West part of Romania, Kawasaki disease produced, more often than not, severe cardio-vascular complications. A thorough follow-up plan is a must in Kawasaki disease with coronary artery involvement, as in the guidelines, but new guideline indications are mandatory in severe complications with risk stratifications level V, such as giant coronary artery aneurysm with thrombus formations.

References

1. Choueiter N.F., Olson A.K., Shen D.D., Portman M.A. Prospective open-label trial of etanercept as adjunctive therapy for kawasaki disease. J Pediatr 2010; 157:960.
2. Egami K., Muta H., Ishii M., et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr 2006; 149:237.
3. Furusho K., Kamiya T., Nakano H., et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984; 2:1055.
4. Iwashima S., Seguchi M., Matubayashi T., Ohzeki T. Ulinastatin therapy in kawasaki disease. Clin Drug Investig 2007; 27:691.
5. Kanai T., Ishiwata T., Kobayashi T., et al. Ulinastatin, a urinary trypsin inhibitor, for the initial treatment of patients with Kawasaki disease: a retrospective study. Circulation 2011; 124:2822.
6. Kim T., Choi W., Woo C.W., et al.Predictive risk factors for coronary artery abnormalities in Kawasaki disease. Eur J Pediatr 2007; 166:421.
7. Kimberlin D.W., Brady M.T., Jackson M.A., Long S.S. (Eds). Kawasaki disease. In: Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. American Academy of Pediatrics, Elk Grove Village, IL 2015. p.494
8. Kobayashi T., Inoue Y., Otani T., et al.Risk stratification in the decision to include prednisolone with intravenous immunoglobulin in primary therapy of Kawasaki disease. Pediatr Infect Dis J 2009; 28:498.
9. Kobayashi T., Inoue Y., Takeuchi K., et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 2006; 113:2606.
10. Nakamura Y., Yanagawa H., Kato H., et al Mortality among patients with a history of Kawasaki disease: the third look. The Kawasaki Disease Follow-up Group. . Acta Paediatr Jpn 1998; 40:419.
11. Newburger J.W., Takahashi M., Beiser A.S., et al. N Engl J Med 1991; 324:1633.A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome.
12. Newburger J.W., Takahashi M., Gerber M.A., et al.Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young. American Heart Association. Circulation 2004; 110:2747.
13. Newburger J.W., Fulton D.R.. Kawasaki disease. Curr Opin Pediatr. 2004 Oct. 16(5):508-14.
14. Newburger J.W., Sleeper L.A., McCrindle B.W., Minich L.L., Gersony W., Vetter V.L., et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med. 2007 Feb 15. 356(7):663-75.
15. Newburger J.W., Takahashi M., Burns J.C., et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. N Engl J Med 1986; 315:341.
16. Ogata S., Ogihara Y., Honda T., et al. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. Pediatrics 2012; 129:e17.
17. Okada K., Hara J., Maki I., et al. Pulse methylprednisolone with gammaglobulin as an initial treatment for acute Kawasaki disease. Eur J Pediatr 2009; 168:181.
18. Orenstein J.M., Shulman S.T., Fox L.M., et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. PLoS One 2012; 7:e38998.
19. Son M.B., Gauvreau K., Ma L., et al. Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. Pediatrics 2009; 124:1.
20. Tremoulet A.H., Jain S., Jaggi P., et al.Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet 2014; 383:1731.
21. Wang W., Gong F., Zhu W., et al. Macrophage activation syndrome in Kawasaki disease: more common than we thought? Semin Arthritis Rheum 2015; 44:405.
22. Yellen E.S., Gauvreau K., Takahashi M., et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. Pediatrics 2010; 125:e234.

Correspondence to:

Stroescu Ramona
"Louis Turcanu" Emergency Hospital for Children Timisoara,
IIIrd Pediatric Clinic
Iosif Nemoianu 2 Timisoara 300011
Mobile: 0040 742 288 868
Fax: 0040 256 201 975
Mail to: ramona.giurescu@gmail.com