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ABSTRACT

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DIFFERENTIAL DIAGNOSIS BETWEEN KAWASAKI DISEASE AND ACUTE INFECTIOUS DISEASES – A CASE REPORT

Introduction. Kawasaki disease is a relatively rare but severe acute febrile disease characterized by vasculitis. It represents a unique challenge in pediatrics due to its potential for coronary artery complications and the necessity for prompt recognition and treatment.

Materials and methods. The study was conducted at the Ivano-Frankivsk Regional Children Clinical Hospital of the Ivano-Frankivsk Regional Council. A clinical case of Kawasaki disease in a child was analyzed. The research was carried out in accordance with the principles of the Helsinki Declaration. The research protocol was approved by the Local Ethics Committee of the institution. Informed consent of the child's parents was obtained for the research.

Case presentation. We are presenting a clinical case of Kawasaki disease in a 5-year-old Ukrainian girl who was diagnosed with acute respiratory disease, tonsillopharyngitis. After the antibacterial therapy, a spotted-papular rash appeared, and the doctor suspected infectious mononucleosis. On the 7th day of the illness, signs of conjunctivitis and pain in the lower extremities appeared, and on the 8th day of the disease, the child was referred to a hospital. Based on the clinical signs and test results, the final diagnosis of Kawasaki disease was established. Upon admission, mild anemia (hemoglobin – 100 g/L), leukocytosis (16.86×10^9/L), thrombocytosis (1147×10^9/L), and an elevated erythrocyte sedimentation rate (105 mm/h) were detected. Biochemical blood tests revealed hypoalbuminemia (34.9–10.8 g/L), a decreased A/G index (0.12), and significantly increased D-dimer (6051.3 μg/ml) and C-reactive protein (185.1 mg/l) levels. Echocardiographic examination revealed expansion of the coronary arteries and regurgitation of the tricuspid valve. The patient received intravenous human immunoglobulin 10% at a dosage of 2 g/kg IV for 3 days, acetylsalicylic acid, 10 mg/kg ibuprofen, infusion therapy with glucose-salt solutions, and oral rehydration. Against the background of treatment, the child's

condition stabilized, and on the 10th day after admission, with improvement, she was discharged from the hospital.

Conclusion. The present case demonstrates that patients with Kawasaki disease need a multidisciplinary approach for timely diagnosis and treatment. Disease manifestations are nonspecific, and doctors often consider them to be signs of more common conditions, such as acute respiratory infections, tonsillitis, and infectious mononucleosis.

Keywords: Kawasaki disease, acute respiratory viral infection, tonsillitis, children.

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ДИФЕРЕНЦІЙНА ДІАГНОСТИКА МІЖ ХВОРОБОЮ КАВАСАКІ ТА ГОСТРИМИ ІНФЕКЦІЙНИМИ ЗАХВОРЮВАННЯМИ – ВИПАДОК ІЗ ПРАКТИКИ

Вступ. Хвороба Кавасакі - відносно рідкісне, але важке гостре гарячкове захворювання, що характеризується васкулітом. Вона являє собою унікальний виклик у педіатрії через потенційну можливість розвитку ускладнень з боку коронарних артерій та необхідність швидкої діагностики і лікування.

Матеріали та методи. Дослідження проведено на базі Івано-Франківської обласної дитячої клінічної лікарні Івано-Франківської обласної ради. Проаналізовано клінічний випадок хвороби Кавасакі у дитини. Дослідження проводилося відповідно до принципів Гельсінської декларації. Протокол дослідження був схвалений локальною комісією з питань етики установи. На проведення дослідження була отримана інформована згода батьків дитини.

Опис клінічного випадку. Наводимо клінічний випадок хвороби Кавасакі у 5-річної української дівчинки, якій було встановлено діагноз: гостре респіраторне захворювання, тонзилофарингіт. Після призначення антибактеріальної терапії з'явився плямисто-папульозний висип, і лікар запідозрив інфекційний мононуклеоз. На 7-й день хвороби з'явилися ознаки кон'юнктивіту та біль у нижніх кінцівках, на 8-й день хвороби дитину скерували до стаціонару. На підставі клінічних ознак та результатів аналізів був встановлений остаточний діагноз - хвороба Кавасакі. При госпіталізації виявлено легку анемію (гемоглобін - 100 г/л), лейкоцитоз ($16,86\times10^9$/л), тромбоцитоз (1147×10^9/л), підвищення швидкості осідання еритроцитів (105 мм/год). В біохімічному аналізі крові виявлено гіпоальбумінемію (34,9 - 10,8 г/л), зниження А/Г індексу (0,12), значно підвищений рівень D-димеру (6051,3 мкг/мл) та С-реактивного білка (185,1 мг/л). При ехокардіографічному дослідженні виявлено розширення коронарних артерій та регургітацію трикуспідального клапана. Пацієнтка отримувала внутрішньовенно людський імуноглобулін 10% у дозі 2 г/кг в/в протягом 3 днів, ацетилсаліцилову кислоту, ібупрофен в дозі 10 мг/кг, інфузійну терапію глюкозо-сольовими розчинами, пероральну регідратаційну терапію. На фоні проведеного лікування стан дитини стабілізувався, і на 10-й день після госпіталізації, з покращенням, вона була виписана зі стаціонару.

Висновок. Цей випадок демонструє, що пацієнти з хворобою Кавасакі потребують мультидисциплінарного підходу для своєчасної діагностики та лікування. Прояви хвороби неспецифічні, і лікарі часто вважають їх ознаками більш поширених станів, таких як гострі респіраторні інфекції, тонзиліт, інфекційний мононуклеоз.

Ключові слова: хвороба Кавасакі, гостра респіраторна вірусна інфекція, тонзиліт, діти.

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ABBREVIATIONS

KD – Kawasaki disease
TSS – toxic shock syndrome
ESR – erythrocyte sedimentation rate
CRP – C-reactive protein
IVIG – intravenous immunoglobulin
ASA – acetylsalicylic acid
TNF – tumor necrosis factor
IM – infectious mononucleosis
PCR – polymerase chain reaction
DNA – deoxyribonucleic acid
EBV – Epstein-Barr virus
CMV – cytomegalovirus
HR – heart rate
BR – breathing rate
CBC – complete blood count
RBC – red blood cells
WBC – white blood cells
HDL – high-density lipoproteins
LDL – low-density lipoproteins
INR – international normalised ratio
APTT – activated partial thromboplastin time
ASL-O – Anti-streptolysin O
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
ELISA – enzyme-linked immunosorbent assay
EF – ejection fraction
RV – right ventricle
LV – left ventricle
ECG – electrocardiography

INTRODUCTION / ВСТУП

Kawasaki disease (KD) ("systemic Kawasaki vasculitis", "Kawasaki syndrome", "mucocutaneous nodular syndrome") is an acute systemic disease of childhood characterized by damage to medium- and small-caliber arteries, the development of destructive-proliferative vasculitis, and possible damage to coronary and other visceral arteries, leading to an aneurysm [1].

In total, 90–95% of children under the age of 10 are affected, and 85–90% of patients under the age of 5 are affected. The peak incidence occurs in the winter-spring period [1, 2]. In the United States, approximately 5000 children are affected each year, with an incidence of 24.7 cases per 100000; in the United Kingdom, there are 4.5 cases per 100000 children under the age of 5. KD has been described in all ethnic groups, with the highest incidence in patients from Northeast Asia, especially Japan and Korea, indicating a significant role of genetics in the pathogenesis of this disease [3, 4]. Currently, the real incidence of KD in Ukraine is unknown due to the complexity of diagnosing the disease and the low awareness of doctors [1].

The etiology of KD remains unknown and controversial. Various speculations and evidence indicate that infections play a central role in its triggering. Some studies point to the role of numerous viral agents, including seasonal coronaviruses, as a trigger in some children with a genetic predisposition. Bacteria (staphylococci, streptococci) with tropism to the endothelium of coronary vessels may also trigger vasculitis [1, 3, 4].

Similar disease phenotypes – fever, mucosal lesions, and scaly skin – resulting from toxin-mediated effects (including staphylococcal and streptococcal toxic shock syndrome (TSS) and scarlet fever) indicate that these bacteria are likely triggers of KD. In a patient with KD, toxin-secreting *Staphylococcus aureus* was isolated, which led to TSS and the development of a coronary aneurysm. It is assumed that infection is the trigger leading to an immune-mediated reaction and promoting the development of the disease in an immunogenetically susceptible host [3, 5, 6]. KDs and TSSs are thought to be caused by viral or bacterial toxins that act as superantigens. The superantigen theory of KD continues to be studied, but substantial evidence is currently lacking [4]. Currently, it has not been proven that a certain infectious factor is the main cause of KD, and no infectious agent of KD has been identified, as no association with parvovirus B19, Epstein–Barr virus (EBV), herpes viruses, measles virus, or human coronavirus has been identified [4, 5].

The course of KD is characterized by high fever and a complex of acute inflammatory manifestations that last around 12 days. In most cases, KD results in recovery, even if no guideline treatment is used. There are no specific tests for KD. The diagnosis is based on a combination of clinical criteria and laboratory test results. For the diagnosis of the disease, the criteria of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery were used, among which 5 out of 6 were used. For KD diagnosis, the following criteria were used: fever for more than 5 days and 4 of the 5 main symptoms: 1) bilateral nonpurulent conjunctivitis or scleritis; 2) oral mucosal changes (erythema of lips or oropharynx, strawberry tongue, or drying or fissuring of the lips); 3) Peripheral extremity changes (edema, erythema, or generalized or periungual desquamation); 4) polymorphic rash; and 5) cervical lymphadenitis with lymph node enlargement more than 1.5 cm in diameter [1, 2, 3]. Disease can be diagnosed even on the fourth day of fever if 4 or more key symptoms are present, especially palmar erythema or swelling of the hands/feet. Clinicians with extensive experience can diagnose KD even on the third day in some cases [6, 7].

Damage to coronary vessels, myocarditis, pericarditis, valvular regurgitation, and aortic root dilation are common in KD patients. Possible manifestations in patients with KD may also be related to different systems and organs: interstitial infiltrative changes in the lungs, arthritis, vomiting, diarrhea, abdominal pain, hepatitis, aseptic meningitis, sensorineural deafness, and paralysis of the facial nerve [4, 5, 6].

The following laboratory changes are characteristic of KD: neutrophilia with a shift of the leukocyte formula to the left, increased erythrocyte sedimentation rate (ESR), increased C-reactive protein (CRP), anemia, dyslipidemia, hypoalbuminemia, hyponatremia, thrombocytosis after the first week of the disease, and increased levels of transaminases and gamma-glutamyl transpeptidase [7].

Early diagnosis of the disease is crucial for achieving optimal treatment results. The standard treatment for KD includes the administration of intravenous immunoglobulin (IVGG) at an immunosuppressive dose 1–2 g/kg and acetylsalicylic acid (ASA), as well as, depending on the clinical situation, glucocorticosteroids and tumor necrosis factor (TNF) blockers. However, 10–20% of patients with KD are resistant to immunoglobulin therapy and are at increased risk of developing coronary vasculitis [4, 8, 9].

We present a clinical case of Kawasaki disease in a Ukrainian girl who was receiving inpatient treatment at the Ivano-Frankivsk Regional Children Clinical Hospital. This case highlights the challenge posed by nonspecific signs at the beginning of the disease, which are misleading and delay disease diagnosis and treatment.

Objective: on the example of a clinical case, to acquaint general practitioners, family medicine doctors, pediatricians, and infectious disease specialists with the diagnosis and treatment of Kawasaki disease.

MATERIALS AND METHODS

The study was conducted at the Ivano-Frankivsk Regional Children Clinical Hospital of the Ivano-Frankivsk Regional Council. A clinical case of KD in a child was analyzed. The research was carried out in accordance with the principles of the Helsinki Declaration. The research protocol was approved by the Local Ethics Committee of the institution. Informed consent of the child's parents was obtained for the research.

Case presentation. A 5-year-old female child fell ill acutely when her temperature rose to 39.6°C. She was examined by a family doctor, and white exudates on the tonsils and enlargement of the cervical lymph node on the left side were detected. Two weeks before the disease, the girl contacted patients with catarrhal symptoms. The child was diagnosed with “acute respiratory disease: tonsillopharyngitis” based on her clinical symptoms, and antibacterial therapy (amoxicillin with 45 mg/kg/day clavulanic acid) and ibuprofen (10 mg/kg body weight 3 times a day) were prescribed. After 2 days, a maculous-papulous rash appeared on the skin, which was considered to be an allergic reaction; amoxicillin with clavulanic acid was discontinued, azithromycin was administered orally at a dosage of 10 mg/kg once per day, and symptomatic treatment (oral rehydration, antipyretic drugs, local antiseptics for the oral cavity) was prescribed. The rash disappeared after 2 days. The doctor suspected infectious mononucleosis (IM), tests for anti-EBV and anti-CMV antibodies, and polymerase chain reaction (PCR) for EBV and cytomegalovirus (CMV) DNA detection in blood were performed, and the results were negative.

On day 7, signs of conjunctivitis and pain in the lower extremities appeared, and her body temperature remained within 38–39–40°C. On day 8, the patient was urgently hospitalized, and her mother reported an increased body temperature of up to 40.0°C; pain in her lower limbs; rash on her lower limbs and right hand; swelling of her face, feet and hands; enlargement of her cervical lymph node on her left side; redness of her eyes, lips and tongue; decreased appetite; and lethargy.

Upon admission to the hospital, the general condition of the child was severe. Her body temperature was 39.0°C. The child was alert but restless, passive,

and lethargic during the examination. The appetite decreased. The skin on the lower limbs was pale, and on the right hand, there was a maculous-papulous rash. The lips were hyperemic, dry, and cracked. The mucous membrane of the oral cavity and the tonsils were hyperemic, without exudates, and the tongue was a "raspberry". The sclera was injected, and the conjunctiva of both eyes was hyperemic, without pathological secretions. The pastiness of the face, legs, hands and feet was noted. Cervical and mandibular lymph nodes were up to 1.5 cm in size, not painful, not joined, and mobile. After the lungs exhibited vesicular breathing, they were auscultated, and the breathing rate was 22/min. Her heart sounds were rhythmic and sonorous, and tachycardia was detected (HR-128/min). The abdomen was accessible for deep palpation and soft and painless, and peristalsis was preserved. The liver and spleen were not enlarged. The stool was liquid, 2 times a day, without pathological impurities. The patient's diuresis was normal.

Laboratory test results.

Complete blood count (CBC) was performed repeatedly (see Table 1). Biochemical blood tests (day 8) revealed the following: alpha-1 globulin, 5.9%; alpha-2 globulin, 20.3%; beta-globulin, 19.0%; gamma-globulin, 19.9%; albumin, 34.9%; globulins, 65.1%; A/G-0.53 (normal 1.2–2.0); potassium, 3.89 mmol/L calcium, 2.04 mmol/L; sodium, 138.7 mmol/L; high-density lipoproteins (HDL) 0.73 mmol/L; low-density lipoproteins (LDL), 2.66 mmol/L; atherogenicity index, 4.79; triglycerides, 1.37 mmol/L; and cholesterol 4.23 mmol/L.

Table 1 – Results of complete blood count

Day of the illness	Hemoglobin (g/L)	RBC (*10^{12}/L)	WBC (*10^{9}/L)	Platelet count 10^{9}/L	Hematocrit	Basophils, %	Eosinophils, %	Band neutrophils, %	Segmented neutrophils, %	Lymphocytes, %	Monocytes, %	ESR, mm/hour
8 (admission)	100	3.56	16.72	557	27.9	0	3	13	55	22	7	71
11	104	3.8	16.86	608	30.5	0.1	2.3	10.26	60.9	31.1	5.6	25
14	103	3.79	12.04	1147	30.1	0	1	6	52	33	8	95
16	107	3.85	10.10	1229	31.6	1.5	1.7	3.59	35.5	53.6	7.7	105
18	104	3.73	9.91	1044	30.4	1	1	5	30	55	8	40

Biochemical blood tests (day 14) revealed the following: alanine transaminase (ALT)-19 IU; aspartate transaminase (AST)-40 IU; alpha-1 globulin (8.9%); alpha-2 globulin (12.5%); beta-globulin (17.4%); gamma-globulin (50.4%); albumin (10.8%); globulins (89.2%); and A/G-0,12 (normal 1.2–2.0).

Coagulogram (day 8): prothrombin time – 12.7 seconds; prothrombin index – 98.4%; international normalised ratio (INR) – 1.06; fibrinogen, 4.62 g/l; activated partial thromboplastin time (APTT) 20.9.

Immunogram (day 8): IgG – 9.9 (N 6.5–18.0), IgA – 2.3 (N 0.8–2.2), and IgM – 3.0 (N 0.55–2.2).

Biochemical blood tests (day 16) revealed the following: D-dimer – 6051.3–950.3 ng/ml; CRP – 185.1–23.6–5.2 ml/l; procalcitonin – 0.05 ng/ml; rheumatoid factor, 1.5 IU/ml; Anti-streptolysin O (ASL-O) – 6 IU/ml; antinuclear antibodies – 0.66 (negative); creatine phosphokinase total – 28 U/l; and ferritin – 188.0 ng/ml.

Urine analysis on days 8 and 14 was normal.

A bacteriological test of the oropharyngeal smear (day 8) revealed no pathogenic microorganisms.

Blood culture (day 8) was negative.

For differential diagnosis and detection of the probable etiologic factor of the disease, the child was tested for parvovirus B19, CMV, EBV, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by PCR, and the results were negative. Antibodies against Yersinia were tested by ELISA, and the results were negative.

Instrumental methods of examination were used. Ultrasound examination of the abdominal cavity on day 8 revealed slight perivascular infiltration of the liver parenchyma and severe flatulence. Ultrasound examination of the lymph nodes on day 8 revealed signs of cervical lymphadenitis.

The results of echocardiographic examination on day 9 were as follows: ejection fraction (EF) – 65%;

tricuspid valve regurgitation; pulmonary artery valve pressure 7 mmHg; descending aorta pressure gradient 12 mmHg; systolic pressure in the right ventricle (RV) 27 mmHg; pericardial layers without pathological changes; cardiac chambers not dilated; myocardial walls not thickened; the left coronary artery at the exit point of 3.5 mm can be traced for 20 mm (z score + 2.59); right coronary artery – 3.2 mm (z score+2.45); moderate trabeculation of the posterior wall of the LV, apical part; conclusion: slight dilation of the coronary arteries; the sites of origin are typical; no evidence of pulmonary hypertension; and good contractility.

Electrocardiography (ECG) results on day 8 revealed a sinus rhythm, a heart rate of 105–111 beats/minute, impaired repolarization processes in the left ventricle, shortened PQ, and decreased ECG voltage in the standard and limb leads.

Ultrasound examination of the knee and hip joints on day 8 revealed signs of bilateral coxitis.

Results of echocardiographic examination on day 16: EF– 65%; tricuspid valve regurgitation+; pulmonary artery valve pressure gradient 7 mm Hg; descending aorta pressure gradient 12 mm Hg; systolic pressure in the RV – 27 mm Hg; heart chambers are not dilated; myocardial walls are not thickened; the branch of the left coronary artery is 7 mm below the division of the common artery and is locally dilated to 4.2 mm (length of the dilated part is 7 mm); the left coronary artery at the point of origin is 3.2 mm and at a distance of 17 mm from the site of division is locally dilated to 3.8 mm (z score + 5.0); and the right coronary artery at the site of origin is 3.7 mm (z score+3.63). Moderate trabecularity of the apical part of the posterior wall of the left ventricle (LV). The coronary sinus was compacted and 7x4 mm in size. Conclusion: Dilation of the coronary arteries. The places of origin are typical. No evidence of pulmonary hypertension was found. Contractility is good.

Chest X-ray (day 9) – the lung fields are evenly pneumatized. The sinuses were normal. The borders of the heart are within normal limits.

Electrocardiography (ECG) (Day 15) The rhythm was sinus, HR – 91–97 b/min. The phenomenon of a shortened PQ.

The girl was examined by a hematologist, an infectious disease specialist, an alergologist, and a cardiologist. The patient was diagnosed with Kawasaki disease.

The child was prescribed 10% IVGG in the dosage 2 g/kg (IV for 3 days), antiplatelet therapy (ASA 250 mg 2 p.d. IV), nonsteroidal anti-inflammatory drugs, infusion therapy with glucose-salt solutions, and oral rehydration.

The child's condition stabilized, and on the 10th day after hospitalization, she was discharged from the hospital, and the supervision of a cardiologist was recommended. Since thrombocytosis remained in the CBC, 100 mg ASA per day was prescribed for another 3 months. Monthly monitoring via echocardiographic examination for the following 6 months was recommended, as were CBC and ECG. Noninvasive coronary angiography should be performed within 1–2 years.

DISCUSSION

Due to the variability of clinical manifestations and the absence of pathognomonic manifestations, the diagnosis of KD is difficult. Symptoms of KD require differential diagnosis from symptoms of infectious diseases, particularly streptococcal infection (scarlet fever, toxic shock syndrome), pseudotuberculosis, and viral infections (measles, rubella, infectious mononucleosis, adenovirus infection). As a rule, at the outpatient stage, the most common preliminary diagnoses are infectious diseases, which do not always justify the prescription of antibiotic therapy. In the present case, the child’s preliminary diagnosis at the outpatient stage was upper respiratory viral infection and tonsillopharyngitis, and antibiotic therapy was prescribed.

Exanthema in KD is usually polymorphic, often maculous-papulous, and localized on different parts of the skin; it is preceded by fever and accompanied by cervical lymphadenitis, so the disease needs to be differentiated from infectious mononucleosis. To confirm this diagnosis, ELISA and PCR were performed on the child, and the results were negative.

A "raspberry tongue" is one of the diagnostic criteria for KD, and it is a typical symptom of scarlet fever and pseudotuberculosis. The need for differential diagnosis of KD with these diseases is also evidenced by erythema and edema of the hands and feet, followed by peeling, which most often appears in the second week of the disease [6, 7]. An enzyme-linked immunosorbent assay was also performed to detect antibodies against Yersinia, which were negative.

The patient was diagnosed with mild anemia, neutrophilia with a left shift in the leukocyte count, increased ESR and CRP, hypoalbuminemia, and thrombocytosis after the first week of the disease. These laboratory changes are among the main laboratory criteria for KD [1, 2].

One of the most informative methods for diagnosing KD is cardiac echocardiography with coronary vessel assessment. The patient was diagnosed with dilation of the coronary arteries, which was the main reason for this diagnosis.

In patients with KD, lesions of other organs and systems, particularly the musculoskeletal system (arthritis), are described. Accordingly, the patient was diagnosed with bilateral coxitis.

It should be noted that signs that are diagnostic criteria for KD may emerge gradually, so an "incomplete" KD will become "complete" over time. At the same time, a "wait-and-see" treatment strategy would be incorrect since the optimal time for the introduction of IVGG is up to the 10th day after the onset of fever [1]. After the administration of IVGG on the 8th day after disease onset, her symptoms decreased, and on the 10th day, her condition improved. She was discharged from the hospital and will continue to be followed up by a cardiologist.

Each patient with KD is unique, and the path to diagnosis is often difficult, but the success of timely treatment is high.

CONCLUSION

KD is an interdisciplinary problem because it requires careful differential diagnosis from other diseases, particularly infectious diseases. This clinical case demonstrates the need for prompt analysis of clinical and epidemiological data for diagnosing the disease. The diagnosis of KD should be suspected in children with a fever for more than 5 days in combination with nonpurulent conjunctivitis, "raspberry tongue", cheilitis, cracked lips, swelling of the hands and feet and/or peeling, polymorphic rash, and cervical lymphadenitis. Other diagnostic criteria for this disease include laboratory data (mild anemia, neutrophilia with a shift of the leukocyte formula to the left, increased ESR and C-reactive protein levels, hypoalbuminemia, thrombocytosis), and ultrasound examination of the heart and coronary vessels.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

Pyliuk Iryna - acquisition, analysis, or interpretation of data for the work, drafting the manuscript.
Matvisiv Mariana, Horbal Nataliia: data collection, sorting and analysis, manuscript writing.
Mateiko Halyna – formulated the the conception and design of the work, reviewed the manuscript.
Berezna Tamara - reviewed and revised the manuscript.

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None.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

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