KAWASAKI DISEASE IN KAZAKHSTAN: AN UNMET CLINICAL AND PUBLIC HEALTH ISSUE?

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Abstract
Kawasaki disease (KD) is a systemic vasculitis targeting medium-sized and small arteries. It manifests in young children. If not appropriately treated, KD leads to the development of coronary artery aneurysms in about 20% of patients. No local evidence-based clinical and epidemiological data on KD are currently available in Kazakhstan. The awareness of KD among physicians is inadequate, resulting in underdiagnosis of the disease in the country. Given the high priority of cardiovascular morbidity and mortality in Central Asian countries, clinical and epidemiological studies on KD along with measures for early diagnosis and management of the patients with cardiovascular affections are warranted.

Keywords: Kawasaki disease, Mucocutaneous lymph node syndrome, Coronary aneurysm, Intravenous immunoglobulin, Kazakhstan, Central Asia, Hypothesis


INTRODUCTION
Kawasaki disease (KD) is a systemic vasculitis affecting medium-sized and small arteries. It manifests in early childhood with systemic inflammatory syndrome characterized by high and prolonged fever along with multi-system organ affections. KD often manifests with acquired cardiopathy due to vasculitis of the coronary arteries, leading to the formation of aneurysms in about 20% of patients failing to receive appropriate and timely intravenous immunoglobulin (IVIG) therapy [1].
The etiology of Kawasaki disease is unknown. However, as any other immune-mediated disease, it may develop and evolve in predisposed children due to the interaction of multiple etiopathogenic factors, such as infectious and other environmental agents and HLA- and non-HLA-related genes. The importance of the genetic background is emphasized by variable incidence of KD across different ethnicities; KD is much more common in Japan and Asia than elsewhere in the world. The epidemiological data in 2010 pointed to KD annual incidence rate of 239.6 per 100,000 children aged below 4 years in Japan. Children of Japanese descent residing outside Japan are also at high risk of KD. In North America and Europe, KD incidence is as low as 15-30 per 100,000 children aged below 5 years. KD is rarely described in infants below 4 months, and it is uncommon in adolescents and adults. This disease is prevalent in males, with 1.5:1 male-to-female ratio [2].

No specific laboratory test is available to confirm KD. Although the clinical picture can vary widely, the diagnosis relies on the description of specific “core” symptoms and signs. KD should be suspected in infants and children with high and/or unremitting fever persisting more than 5 days. Fever is the only pertinent feature in KD patients. Other common features of the disease include bilateral nonexudative conjunctivitis, characteristic affections of the lips, tongue and oral mucosa (e.g., injection, drying, cracking), skin (edema, erythema, desquamation of palms and soles), polymorphic and diffuse exanthema, nonsuppurative cervical lymphadenopathy (at least 1 node more than 1.5 cm in diameter). The presence of at least 4 of these signs defines the “typical” form of KD. However, the diagnosis should be made even in patients with less than 4 typical criteria (“incomplete” KD) and/or different organ-related clinical manifestations (“atypical” KD). The timely diagnosis with administration of IVIG therapy significantly reduces the occurrence of the coronary artery aneurysms [3,4].

At the onset, laboratory exams reveal significant nonspecific inflammatory shifts, such as C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), leukocyte and neutrophil counts increase, in a febrile clinical setting without signs of bacteremia or sepsis. The patients may also present with thrombocytosis after the initial 2 weeks of the disease. Cardiac ultrasound is informative in the complex differential diagnostic process, especially in incomplete and/or atypical cases of KD. The evidence of coronary alterations according to the international criteria and Z-score classification may prompt timely and appropriate diagnosis in children with prolonged fever and supportive laboratory tests [5,6].

**CURRENT EVIDENCE**

Although there is an approved clinical protocol for diagnosis and treatment of KD in Kazakhstan [7], no local evidence-based documents are available to describe clinical and epidemiological features of the disease. The MEDLINE/PubMed search employing “Kawasaki Disease” and “Kazakhstan” as keywords retrieves no any relevant article. The search with “Central Asia”, “Uzbekistan”, “Turkmenistan”, “Tajikistan” and “Kyrgyzstan” also ends up with no relevant results. There is, however, one intriguing article titled “Association of Kawasaki disease with tropospheric wind patterns” by Rodó X et al. that suggests an association of KD epidemics in Japan with wind-borne environmental triggers originating from Central Asia [8].

Although KD is spread around the world, its incidence is strongly associated with certain ethnicities and geographical areas, and it is increasing over the time [2]. Although it is possible to explain high prevalence of KD in some areas in association with factors beyond the immunogenetic predisposition, precise mechanisms of such an association remain unclear.

The highest incidence of KD is recorded in Japan. There are also incidence data from Korea (134.4 per...
100,000 children younger than 5 years in 2011), Taiwan (69/100,000 for children younger than 5 years in 2003-2006), China (46-50/100,000 for children younger than 5 years in 2000-2007). Lower incidence rates are recorded in India and Thailand [9]. No related epidemiological data are available in Kazakhstan and other Central Asian countries. Lyskina G at al. pointed that KD diagnosis is complicated due to the poor awareness of the disease among physicians in Russia [10]. The same issue may affect timely diagnosis of KD in Kazakhstan and Central Asia.

Historically, three largest epidemics of KD have been described in Japan in 1979, 1982 and 1986. Interestingly, these events were preceded with a shift from the typical south-blowing winds to northwesterly winds. Similar tropospheric phenomena have been described in relation to major interannual peaks of incidence in Japan in 1987-2005. Likewise, all major interannual peaks of KD cases in San Diego in 1994–2008 can be linked with interannual tropospheric anomalies caused by winds from Central Asia. A chronological analysis of KD case series from Japan, San Diego and Hawaii showed a “synchronization” of KD disease activity from November to March, which was again associated with northwesterly winds and Pacific winds from Central Asia for Japan and Hawaii/San Diego, respectively. It is, therefore, hypothesized that the environmental trigger for KD is wind-borne [8,11].

HYPOTHESIS
KD can be a cause of coronary artery aneurysms. Around 7% of patients develop KD shock syndrome (KDSS) [3]. The main cause of KD mortality relates to the coronary alterations. Indeed, one-quarter of untreated or inappropriately treated KD children develop coronary aneurysms. A recent study in Japan showed that the standardized mortality ratio beyond the acute illness was statistically elevated (SMR, 1.86; 95% confidence interval, 1.02–3.13) for all patients with cardiac sequelae. Even though the mortality peak occurs in the first 2 months after the onset of fever, when coronary vasculitis evolves alongside marked elevation of platelet count, sudden death from myocardial infarction due to the rupture of coronary aneurysms can occur many years later [3,12]. In fact, numerous cases of fatal and nonfatal myocardial infarction in young adults below 40 years have been attributed to “missed” KD in childhood. A U.S. (San Diego)-based study in revealed that at least 5% of young adults undergoing coronary angiography for myocardial ischemia had lesions consistent with late sequelae of KD [13].

Cardiovascular diseases are the major noncommunicable disorders that contribute to mortality in the developed nations. Globally, a large proportion of the cardiovascular mortality (above 40%) is due to coronary artery diseases with myocardial ischemia. Cardiovascular diseases are also the leading cause of death in low- and middle-income countries. It is well known that cardiovascular mortality is higher in Central Asia than in Europe. In most developed European countries, cardiovascular mortality accounts for around 40% of all deaths. This figure is more than 50% in Kazakhstan, with acute myocardial infarction being the main cardiovascular event [14,15].

Although the incidence of myocardial infarction increases in Kazakhstan, no age-distributed data about cardiovascular morbidity and mortality is available. Therefore, the proportion of early cardiovascular diseases remains unknown.

FURTHER RESEARCH
Along with measures to improve early detection, management and follow-up of patients with cardiovascular disorders in Kazakhstan [16], there is an urgent need to better characterize the epidemiology of this public health issue. Particularly, it is necessary to examine cardiovascular morbidity and mortality across all age groups in Kazakhstan. To start with, it would be useful to obtain a cross-sectional picture of the age of patients affected with cardiovascular diseases in Kazakhstan. Currently, it is impossible to retrieve related data from the publicly available resources, such as MED inform (http://www.medinfo.kz) and its Data Presentation System Kazakhstan [17].
Country-based comparative epidemiological data on early cardiovascular morbidity and mortality due to myocardial ischemia may pave the way for targeted preventive measures aimed to early diagnosis and proper management of children with cardiovascular diseases, including KD.

The detection of cardiovascular disorders in some target groups is low in Kazakhstan. The age-related analysis of cardiovascular diseases may describe the structure of early morbidity and mortality and reveal potential risk factors. In this regard, focus on expanded spectrum of cardiovascular risk factors in childhood is warranted. An improved awareness of some childhood diseases, particularly KD, may change the structure of cardiovascular diagnosis in Kazakhstan.

To sum up, a greater attention to the epidemiology of KD in Kazakhstan, and related studies, are warranted. An initial estimation of the national consumption of IVIG therapy and analysis of its therapeutic indications is also advisable for improving diagnosis of KD in Kazakhstan.

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**CONFLICTS OF INTEREST**
DP and BA declare that they have no conflict of interest.

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**REFERENCES**


Болезнь Кавасаки в Казахстане: малоизученная проблема клинической медицины и общественного здравоохранения?

Резюме
Болезнь Кавасаки (БК) представляет собой системный васкулит, поражающий средние и мелкие артерии. Проявляется в раннем детском возрасте. В 20% случаев при неправильном лечении БК ведет к аневризматоне коронарной артерии. На данный момент в Казахстане нет научно-обоснованных клинических и эпидемиологических данных относительно БК. Осведомленность врачей о БК низкая, как результат, качество диагностики заболевания остается низким. Сегодня необходимы меры для проведения ранней диагностики и эффективного лечения пациентов с сердечно-сосудистыми заболеваниями, а также необходимы клинические и эпидемиологические исследования. Это обусловлено высокими показателями заболеваемости и смертности от сердечно-сосудистых заболеваний в странах Центральной Азии.

Ключевые слова: Болезнь Кавасаки, Синдром слизисто-кожных лимфатических узлов, Коронарная аневризма, Внутривенный иммуноглобулин, Казахстан, Центральная Азия, Гипотеза