

Serum Sodium Levels and Cardiac Complications in Patients with Kawasaki Disease

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ABSTRACT

BACKGROUND AND OBJECTIVE: Kawasaki disease is an acute vasculitis of childhood and can be associated with complications such as hyponatremia. The present study was conducted to evaluate the serum sodium levels and its association with cardiac complications in children with Kawasaki disease.

METHODS: In this cross-sectional study, all Kawasaki patients (according to AHA criteria) referred to Amirkola Children's Hospital in Babol in 2017-2018 were evaluated. Patients underwent serum sodium assessment and echocardiography and the relationship between serum sodium levels and cardiac complications including ectasia and coronary aneurysm, myocarditis, pericarditis and coronary artery occlusion was investigated.

FINDINGS: Of the 60 patients with Kawasaki disease, 27 (45%) were male and 33 (55%) were female. Their mean age was 32±8 months. 28 patients (47%) had serum sodium levels lower than 135 mEq/L while normal serum sodium level (135-150 mEq/L) was reported in 53% of patients. Cardiac complications including coronary ectasia and myocarditis were reported in 16 and 32 patients, respectively. There was no significant difference between serum sodium levels and cardiac complications. There was no difference in the incidence of cardiac complications and hyponatremia in males and females.

CONCLUSION: According to the results of the present study, serum sodium levels cannot be a good criterion for cardiac prognosis.

KEY WORDS: *Kawasaki Disease, Coronary Aneurysm, Hyponatremia, Myocarditis, Pericarditis, Coronary Artery Disease.*

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Introduction

Kawasaki disease is a vasculitis of unknown cause that is associated with small to medium-sized vascular involvement (1-3). Classical criteria for diagnosing Kawasaki disease include five-day fever with at least four clinical manifestations, non-exudative conjunctivitis, erythematous mucosa, strawberry tongue, atypical rash, edema or erythema of the hands and feet, and cervical lymphadenopathy (4, 5). Since Kawasaki disease is a systemic vasculitis, it can affect the arteries of any part of the body. Among these, cardiovascular disease is of great importance and can determine the final prognosis of the disease (6, 7).

Arterial inflammation in the coronary arteries is necrotic and may start from the endothelium within the first 2 weeks of the disease and penetrate into the coronary wall, and eventually lead to saccular aneurysm. Subacute or chronic vasculitis may also be caused by lymphocytes, plasma cells, and eosinophils that persist for weeks or years, leading to fusiform aneurysm. Then, in arteries with subacute or chronic vasculitis, myofibroblast smooth muscle cells expand and cause progressive coronary stenosis (8, 9).

Hyponatremia is the most common electrolyte disorder in hospitalized patients in general and can be seen in various inflammatory diseases including vasculopathies and Kawasaki (10). Hyponatremia reduces the osmolality of the extracellular space. Since intracellular space has a higher osmolality, water moves from extracellular space to intracellular space to maintain osmotic balance. Increased intracellular water causes the cells to swell. Hyponatremia can lead to muscle cramps and weakness (3, 5, 10).

Several etiologies have been suggested for Kawasaki and hyponatremia. Different mechanisms have been mentioned to cause hyponatremia. The first mechanism is the abnormal secretion of antidiuretic hormone (ADH) caused by cytokines such as IL-6, IL1 β , TNF (Tumor Necrotizing Factor), Interleukin β , and Interleukin 6, which reduces the formation and function of sodium channels as well as sodium-potassium pump. The second mechanism of dysfunction is due to severe inflammation in the proximal tubule and collecting duct system. The third mechanism is the formation of Pseudohypoaldosteronism (PHA) caused by tubular unresponsiveness to aldosterone (11-14). In a case report, cerebral salt-wasting syndrome (CSWS) along with Kawasaki syndrome were reported as the cause of hyponatremia (15). It has recently been suggested that low serum sodium levels may be

associated with the development of inflammatory reactions (2).

Published studies have shown an association between serum sodium levels and especially hyponatremia with the prognosis of Kawasaki disease. Watanabe et al. showed that decreased serum sodium levels in patients with Kawasaki significantly worsened the prognosis of patients (16). In a study by Muta et al., approximately 30% of patients with Kawasaki had serum sodium levels of 133 mEq/L or lower, with a small percentage of cases of hyponatremia seen in incomplete forms of Kawasaki (15). In the study of Schuster, mean serum sodium levels were significantly lower in the studied patients and hyponatremia occurred in 10 patients (91%) out of 11 patients with Kawasaki and 7 patients (33%) out of 21 patients in the control group. Other laboratory values were not significantly different between the two groups (17).

In another study, patients' serum sodium was evaluated in 78 children, of which 27 were associated with hyponatremia. However, no association was found between coronary lesions and sodium levels (14, 18). In a study by Park et al., hyponatremia was seen in 48 (52.7%) patients with Kawasaki disease. Kawasaki patients with hyponatremia showed severe inflammatory symptoms, including higher fever, higher WBC count, higher neutrophil and lymphocyte count, higher total bilirubin, ESR, and CRP with lower concentrations of hemoglobin, hematocrit, and serum cholesterol. In addition, CRP levels were significantly correlated with serum sodium levels (19).

Due to disagreements in the reports and different results presented in this regard, this study was conducted to investigate the prevalence of hyponatremia in patients with Kawasaki disease and its association with cardiac complications.

Methods

This cross-sectional study was approved by the ethics committee of Babol University of Medical Sciences with the ethics code IR.MUBABOL.HRI.REC.1397.214 and was conducted among all patients under 18 years of age with Kawasaki disease admitted to Amirkola Children's Hospital in Babol during the years 2017-2018. Patients with classical and atypical Kawasaki criteria were enrolled according to the American Heart Association criteria (20) approved by infectious disease specialist and cardiologist. Patients who did not meet Kawasaki

criteria or had kidney or brain disorder, underlying heart or liver disease, metabolic and immunodeficiency problems based on patients' history as well as inpatient tests that may affect serum sodium levels were excluded from the study.

Patients who were admitted with a diagnosis of Kawasaki disease had classical criteria for diagnosis, including a five-day fever and at least 4 out of 5 clinical manifestations. Atypical criteria for Kawasaki disease included 5-day fever and at least 2 out of 5 clinical manifestations including non-exudative conjunctivitis, edema and erythema of the hands and feet, erythema of the oral mucosa and strawberry tongue, atypical rash and cervical lymphadenopathy. Complementary laboratory findings were: $ESR \geq 40$ mm/hr and $CRP \geq 30$ mg/dl, age-related anemia, thrombocytosis more than 450,000, white blood cells greater than or equal to 15,000, increase in ALT, albumin less than or equal to 3 g/dl, and pyuria in urine test (white blood cells greater than or equal to 10).

These patients were also evaluated for levels of sodium and potassium and echocardiography was performed for them and the relationship between serum sodium levels and cardiac complications was examined. Normal sodium levels were considered 135-150 mEq/L and less than this range was defined as hyponatremia. Normal potassium levels were considered 3.5-5.5 mEq/L, more than 5.5 was considered hyperkalemic and less than 3.5 mEq/L was considered hypokalemia (15).

Echocardiography in the acute phase of the disease was performed by a pediatric cardiologist with an ACCU VIX echocardiograph. Diagnosis of cardiac complications including ectasia, aneurysm, myocarditis, pericarditis, and coronary artery occlusion was made at the time of diagnosis of Kawasaki disease and was repeated 6-8 weeks later if necessary for follow-up. Furthermore, if heart involvement was confirmed in the third and sixth months and one year later, the patient was re-examined by echocardiography.

Serum sodium and potassium of patients were also measured by ion - selective electrode autoanalyzer. Patients were divided into three groups based on the degree of fever: 37.5-38 °C, 38.1-39 °C and above 39 °C. Patients were divided into two groups based on the rate of hyponatremia: moderate hyponatremia with serum sodium level between 125-130 mEq/L and mild hyponatremia with serum level between 131-135 mEq/L. Blood samples were collected to measure sodium and potassium before starting treatment. Serum

sodium and potassium levels were analyzed and entered into SPSS 18 statistical software and analyzed by Chi-square test, and $p < 0.05$ was considered significant.

Results

Overall, out of 60 patients, 27 (45%) were male and 33 (55%) were female and the age of patients was from 5 months to 11 years with a mean age of 32 ± 8 months. Fever was present in all patients and the mean was 38.4 ± 0.6 °C. Among 60 children with Kawasaki disease, 28 (47%) had sodium less than 135 mEq/L and normal serum sodium level (135-150 mEq/L) was observed in 53% of patients. In 27 boys with Kawasaki disease, 13 (48%) patients had hyponatremia and among 33 girls, 15 (45.5%) patients had hyponatremia. No significant relationship was observed between serum sodium level and gender ($p < 0.05$).

Among 60 children with Kawasaki disease, 3 (5%) patients had potassium less than 5.3 mEq/L and normal serum potassium levels (3.5-5.5 mEq/L) were reported in 57 (95%) patients. The 27 boys with Kawasaki disease all had normal potassium and out of 33 girls with Kawasaki disease, only 3 (9%) patients had hypokalemia ($p < 0.05$). Of the 28 patients with Kawasaki disease who had hyponatremia, 20 had sodium levels 131-135 mEq/L and 8 had sodium levels 125-130 mEq/L.

Patients with Kawasaki fever were divided into three groups according to the degree of fever. Of the 20 patients with sodium 131-135 mEq/L, 9 patients were in the first group, 10 patients were in the second group and one patient was in the third group based on the degree of fever. In the second group of fever, 7 patients had a sodium level of 125-130 mEq/L and 10 patients 131-135 mEq/L. Among the patients in the third group of fever, one had sodium 125-130 mEq/L and one had sodium 131-135 mEq/L (Table 1).

The most common heart disorder in children with Kawasaki disease was brightness of coronary arteries, with 19 cases in children without serum sodium disorders and 17 cases in children with hyponatremia. Overall, cardiac disorders in children with Kawasaki with and without hyponatremia were not significantly different (Table 2). Kawasaki complications included brightness, myocarditis, coronary artery ectasia, and lack of tapering in 10, 14, 9, and 7 cases in boys and 22, 12, 19, and 7 cases in girls, respectively. Overall, cardiac complications in children with Kawasaki disease, although more common in girls, were not statistically significant between the two groups.

Table 1. Frequency and relative frequency of hyponatremia in Kawasaki patients by degree of fever

Serum sodium mEq/L	Fever 37.5-38 °C	First group 37.5-38 °C	Second group 38.1-39 °C	Third group Above 39 °C	Total	p-value
125-130	-	-	7	1	8	>0.05
131-134.9	9	9	10	1	20	>0.05
135-150	9	9	20	3	32	>0.05
Total	18	18	37	5	60	-

Table 2. Frequency and relative frequency of cardiac complications in Kawasaki patients in terms of presence and absence of hyponatremia

Sodium	Brightness	Myocarditis	Lack of Tapering	Coronary artery ectasia	Irregularity of internal lumen	Total
With hyponatremia	17	14	6	9	2	48
Without hyponatremia	19	18	11	7	6	61

Discussion

Based on the present study, it was found that out of 60 patients with Kawasaki, about 47% of them had hyponatremia. Although hyponatremia in febrile and inflammatory diseases has been shown in several studies, there are few studies about the association between Kawasaki disease and hyponatremia (14, 16, 21, 22). Park suggested that sodium levels may reflect the progression of inflammation in patients with Kawasaki disease (19). Hyponatremia is the most common electrolyte disorder and can be seen in a variety of inflammatory diseases and vasculopathy. Laxer et al. first described it in 1982. They reported that six out of 11 patients (54.5%) had hyponatremia (23).

In a study conducted in Japan, the relationship between increased levels of antidiuretic hormone, sodium loss, and this mechanism was shown, although the number of patients was 17 (23). A study in 2017 found that the severity of vascular inflammation in acute Kawasaki with hyponatremia may worsen the prognosis of coronary arteries. Although no statistically significant relationship was found between baseline serum sodium and coronary arteriopathy in patients with Kawasaki disease, a long-term follow-up study with a larger number of patients should be performed in the future to clarify the association (19).

In the study of Schuster et al., the mean baseline sodium level in the studied patients was significantly low and hyponatremia occurred in 10 patients (91%) out of 11 patients with Kawasaki and 7 patients (33%) out of 21 controls. Other laboratory values were not significantly different between the two groups (17). In a study by Watanabe et al., 51 patients (44.7%) had hyponatremia (16). In a case-control study by

Schuther et al. to investigate the relationship between hyponatremia and Kawasaki shock syndrome, it was found that low sodium levels were associated with disease severity (17). In a study by Lim et al., of 50 Kawasaki patients with electrolyte disturbances at the time of diagnosis, 13 had serum sodium levels below 135 mEq/L (14). In the study by Muta et al., approximately 30% of patients had serum sodium levels of 133 mEq/L or lower, and a small percentage of cases of hyponatremia were seen in incomplete forms of Kawasaki (15). According to the above studies, although the incidence of hyponatremia in patients with Kawasaki disease has been different, but it shows that a large percentage of patients develop hyponatremia, which may be a threat to the health of patients.

Most cases of hyponatremia have been reported within 3 to 5 days after disease onset (15). Suzuki et al. reported that serum sodium levels were lowest in the first week (24). It is noteworthy that 25% of patients had a serum sodium level of 133 mEq/L or lower and about 5% of patients had a serum sodium level of 130 mEq/L or lower on the first day of illness. Similar results were observed for serum alanine aminotransferase, CRP and ESR (18). These results lead to speculation about systematic changes before the onset of symptoms (22).

In the present study, serum sodium levels at the time of diagnosis were mainly measured in the first week of illness. In future studies, it is better to measure serum sodium at consecutive and different times in the course of the disease so that the relative decrease in serum sodium can be used as a diagnostic marker. While the exact pathogenesis of hyponatremia in Kawasaki is still unknown, several mechanisms have been proposed,

including the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and hyponatremic dehydration, or due to the consumption of hypo-osmolar solution (14). In the study of Miura et al., the most important cause of hyponatremia in patients with Kawasaki disease was reported to be abnormal secretion of ADH with renal excretion of sodium with increased blood volume or normal blood volume (22).

However, more studies are needed to determine the mechanisms that contribute to shock and hyponatremia and the relationship between them. Many inflammatory cytokines, vascular endothelial growth factors, TNF- α , IL-2, and IL-6 can lead to increased vascular permeability and vascular leakage, which can cause hyponatremia as well as hypoalbuminemia (19). Studies on the role of sodium in Kawasaki disease are limited and there is no complete information on its association with cardiac complications.

Overall, 55 patients had cardiac complications after Kawasaki, and in the evaluations of these patients, the risk of heart disease was not significantly associated with hyponatremia. The results of multivariate analysis in the study of Muta showed that serum sodium levels are an independent risk factor for cardiovascular complications (15). However, Suzuki et al. reported that there was no significant difference in serum sodium levels between patients with and without coronary artery disease in the first week of illness. Sodium levels in patients with coronary artery disease in the second week were significantly lower than those without coronary artery disease. The group with coronary artery lesions was younger (24).

In this study, cardiac complications including coronary ectasia and myocarditis were reported in 16 and 32 patients, respectively. Pericarditis and aneurysm were not seen in any of the patients. Irregularity of Internal Lumen was reported in 8 patients. There was no significant difference between serum sodium and potassium levels and cardiac complications. However, in the study of Watanabe et al., coronary artery lesions and dehydration were significantly more common in patients with hyponatremia. In the present study, there was no significant difference in the incidence of cardiac complications between males and females. Moreover, no significant relationship was observed between serum sodium and potassium levels and gender (16). Different types of heart involvement reported in a study using echocardiography in patients

with Kawasaki disease between 2000 and 2005 were as follows: 23 cases (71.8%) of pericardial effusion, 10 cases (31.2%) of mitral regurgitation, 10 cases (31.2%) of tricuspid valve regurgitation, 5 cases (15.6%) of regurgitation, 2 cases (6.2%) of aortic stenosis and 20 cases (62%) of coronary artery dilatation (25). Furthermore, in the study of Behmadi et al., different types of heart involvement in children with Kawasaki were as follows: perivascular brightness (27.8%), valvular lesions (22.7%) and coronary metastasis (13.6%), respectively (26). In the present study, 16 cases (27%) of coronary artery ectasia, 36 cases (55%) of brightness, 17 cases (29%) of lack of tapering, 8 cases (13%) of irregularity of internal lumen, and 32 cases (53%) of myocarditis were reported, and none of the patients had coronary artery aneurysm and pericarditis.

In the study of Watanabe et al., the duration of fever was significantly longer in patients with hyponatremia (16). In the study by Park et al., out of 91 patients with Kawasaki disease, 48 (52.7%) had hyponatremia. Fever, white blood cell count, neutrophil percentage, lymphocyte percentage, total bilirubin, natriuretic brain protein level, erythrocyte sedimentation rate and CRP were higher in patients with hyponatremia (19). Similar to the present study, no statistically significant relationship was found between serum sodium levels and coronary artery arthropathy in patients with Kawasaki in their study.

According to the present study, although the risk of hyponatremia was high in patients with Kawasaki, the chance of developing cardiac complications after Kawasaki disease was not associated with hyponatremia. There was also no relationship between age and gender in the incidence of hyponatremia and cardiac complications. Due to the high risk of hyponatremia in children with Kawasaki disease, we must be more careful about the treatment and prevention of complications of hyponatremia.

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