Anemia in Kawasaki Disease

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Abstract

Kawasaki disease (KD) is the most common acute coronary vasculitis syndrome that mainly affects genetically susceptible kids under 5 years of age. Aside from the standard diagnostic five criteria, patients with KD may also experience a variety of nonspecific clinical symptoms and signs. Anemia is the most common clinical feature in KD patients. In 2001, the scientists have the discovery of a liver-derived peptide hormone named as hepcidin began revolutionizing the understanding of anemia's relation to a number of inflammatory diseases, including KD. This chapter focuses on hepcidin-induced iron deficiency's relation to transient hyposideremia, anemia, and disease outcomes in KD patients, and goes on to suggest possible routes of KD study.

Keywords

Kawasaki disease · Anemia · Hepcidin
HAMP · Iron

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Kawasaki Disease Is the Most Common Vasculitis of the Coronary Arteries in Children

Kawasaki disease (KD) is an acute multisystem vasculitis syndrome that mainly affects genetically susceptible infants and kids under 5 years of age. Although the cause of KD is not clearly known, it is temporarily defined as an infection–immune–genetic pathogenesis for this mysterious disease [1]. Tomisaku Kawasaki is the first doctor to publish 50 cases of KD in English in 1974 [2]. KD shows signs and symptoms such as high fever for several days, conjunctivitis, diffuse mucosal inflammation, polymorphous skin rashes, peeling of the skin on the hands and feet (especially on their tips), and nonsuppurative lymphadenopathy [1]. Inflammation in small- and medium-sized blood vessels, particularly the coronary arteries, may be also manifested in KD patients. The most serious complication in KD is coronary artery lesions (CAL), including myocardial infarction and coronary artery aneurysm. If left untreated, 20% of the affected kids may suffer from a sequelae of vasculitis with coronary aneurysms [3]. Currently, a single dose of 2 mg/Kg intravenous immunoglobulin (IVIG) is the main treatment for coronary artery lesions (CAL) in KD patients [4]. The global prevalence of KD among children is the highest in Japan ($218/10^5$) and the lowest (4.7/105) in kids of European descent, while the incidence in Taiwan

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is 66/10^5 [1]. During our recent study period, the incidence of KD in Taiwan more than doubled from 28.58 to 60.08 per 100,000 [5]. Therefore, the prevalence of KD in Asia is nearly 10 times higher than in Europe and the USA. However, for clinicians in the pediatric emergency department, the biggest challenge is to identify KD itself in the early stage, because KD shares many of the same clinical signs with other childhood diseases with high fever [6]. Even worse, 20–30% of KD patients do not fully meet the diagnostic criteria and are considered to suffer an incomplete KD, making the diagnosis even more challenging for inexperienced pediatricians [7, 8].

Anemia in Patients with Kawasaki Disease

Aside from the standard diagnostic criteria, patients with KD may also experience a variety of nonspecific clinical symptoms, such as uveitis, aseptic meningitis, abdominal pain, hydrocystic gallbladder, skin rash at the site of BCG-Carinella inoculation, impaired liver function, hypoalbuminemia, and anemia [9–12]. Among them, anemia is the most common clinical feature in KD patients and is considered to have a longer duration of active inflammation [13–16]. A study involving 783 people including 441 KD patients and 342 febrile controls showed that hemoglobin level is one of the seven variables with the largest absolute value of the diagnostic coefficient [17]. In addition, Lin et al. observed that hemoglobin is a useful marker for telling KD shock syndrome from toxic shock syndrome in pediatric intensive care units [18]. Although severe hemolytic anemia that requires blood transfusion is rare, it may be related to IVIG infusion [14, 15, 19]. The main cause of hemolysis is usually related to anti-A and anti-B IgM antibodies and anti-Rh IgG antibodies [20]. In fact, the IVIG products used today are generally safe and effective. They consist of at least 98% IgG and very low anti-A (1:8) and anti-B (1:4) IgM antibodies, but no anti-D IgG antibodies [22, 31]. In addition, Rh-negative blood types are much less common in the Asian populations (0.3%) than in the Caucasian populations (15%). The phenomena and literature concerning hemolysis after IVIG in KD patients may thus be more commonly reported in European ancestry than Asian ancestry. We also found that there were no significant differences in total bilirubin and haptoglobin levels between KD patients before and after IVIG treatment [11]. Therefore, we believe that the key etiological link can explain the relationship between KD and anemia.

Anemia associated with inflammation represents a serious, highly common clinical problem [21]. Anemia of chronic disease is usually observed in various inflammatory states, such as infections, inflammatory diseases, and certain cancers [22–25]. In 2000, Krause et al. described a peptide that was first called liver-expressed antimicrobial peptide-1 or LEAP-1 but later named "hepcidin" due to its liver expression and antibacterial activity [26]. It is understood that hepcidin plays a vital role in preventing the subsequent iron influx into the plasma: duodenal absorption, macrophage release, mobilization of iron stored in liver cells, and inflammatory anemia [21, 27]. In anemia associated with inflammatory diseases such as infections [39, 40], autoimmune diseases [41, 42], severe diseases [43, 44], obesity [28], and acute myocardial infarction [29], abnormally elevated levels of hepcidin have also been observed.

Hepcidin Expression Is Associated with the Prognosis of Kawasaki Disease

We have previously reported that before receiving IVIG treatment, the plasma hepcidin and IL-6 levels of KD patients were higher than those of febrile controls [30]. After IVIG treatment, the levels of hepcidin and IL-6 decreased significantly. Interestingly, changes in hepcidin levels are related to the resistance to IVIG treatment and the formation of CAL, which supports the theory that inflammation markers and increased IVIG anergy may be related to the development of CAL in KD patients [30].

It is proven that IVIG can effectively reduce the incidence of CAL [4], but it is still unclear what role aspirin plays and how much aspirin should be administered on KD patients. In the

past few decades, even before IVIG was used, aspirin-related practices have been administered in KD treatment [3]. Moreover, anemia and significant bleeding are associated with the use of aspirin [31]. In a study of 851 patients with KD, we have reported that high-dose aspirin in acute-phase KD does not benefit the disease outcomes but may be harmful in reducing disease inflammation [32]. In addition, this is the first study to show that high-dose aspirin can lower hemoglobin levels and hinder the ability to lower hepcidin levels after IVIG treatment. Therefore, high-dose aspirin may not be an essential part of acute-phase KD treatment. Nevertheless, more randomized placebo-controlled studies are needed to clarify the function of high-dose aspirin in KD.

Iron Deficiency Caused by Hepcidin Is Related to Transient Hypoferremia and Anemia in KD Patients

Hepcidin is essential in coordinating iron metabolism and the pathogenesis of inflammatory anemia [33, 34]. After hepcidin interacts with ferroportin, the ferroportin is internalized and degraded, which ultimately leads to a decrease in iron chelation and iron absorption in the cells [35]. Currently, ferroportin is the only known exporter of mammalian iron and is essential for transporting iron from one cell type to another [35]. Hepcidin not only controls the absorption of iron, but also has a direct inhibitory effect on erythropoiesis [36]. Moreover, it is also proved that hepcidin can directly affect the proliferation and survival of erythroid precursors, because the formation of erythrocyte colony [37] is consistent with the observation of transient erythrocytopenia in bone marrow aspiration in patients with KD [38]. In our previous study, hemoglobin levels kept on decreasing significantly after IVIG treatment, showing that myelosuppression in KD patients does not quickly reverse after IVIG treatment. In our age-matched 27 health controls and 117 KD patients, the hemoglobin level increased 3 weeks after IVIG treatment, and the hemoglobin level was completely restored during the 6-month follow-up (Fig. 1). Thus, we recommend that patients with KD do not need to supplement iron.

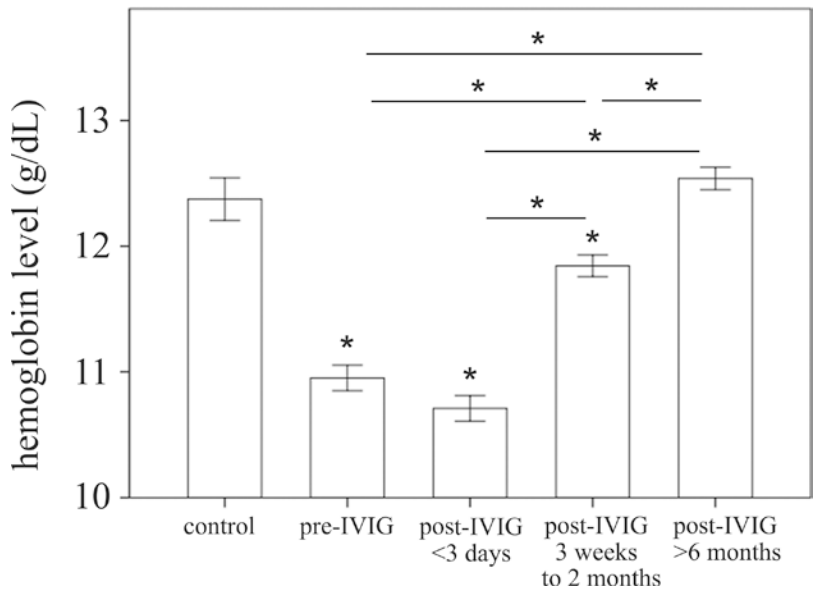

Fig. 1 Comparison of hemoglobin levels in age-matched healthy controls ($N = 27$) with Kawasaki disease (KD) ($N = 117$) patients before and after receiving intravenous immunoglobulin therapy. The data are expressed as mean ± standard error. * indicates $p < 0.05$ between groups (reproduced with permission from https://encyclopedia.pub/3623)

HAMP Promoter Hypomethylation and Elevated Hepcidin Levels Are Biomarkers of Kawasaki Disease

The genome-wide DNA methylation method shows that DNA methylation occurs in the epigenetic regulation mechanism, which is used for the transcriptional inhibition of HAMP in alcohol-related hepatocellular carcinoma [39]. In our previous study, univariate analysis showed that the methylation status of the HAMP promoter was significantly and negatively correlated with plasma hepcidin levels in KD patients and controls [40]. Since DNA methylation is the most famous control mechanism of gene expression, our in vitro research results also show that promoter DNA methylation under epigenetic regulation can be used as a regulatory mechanism for the transcription regulation of HAMP genes. In addition, these findings highlight the epigenetic hypomethylation of the HAMP promoter and the upregulation of hepcidin expression. These results establish a new significance for the epigenetic hypomethylation of HAMP in KD patients and indicate that a significant increase in the level of hepcidin can be used as a biomarker for KD. In 2021, we further demonstrated a novel scoring system, which has good ability to distinguish children with Kawasaki disease from other kids with high fever and highlights the importance of eosinophils in Kawasaki disease. Using this novel scoring system to evaluate factors, including hemoglobin, average red blood cell hemoglobin, and average red blood cell hemoglobin concentration level, can help first-line doctors diagnose and treat Kawasaki disease as soon as possible [41].

Other Studies on Hepcidin in Kawasaki Disease

Macrophages play a vital role in regulating iron homeostasis, which is closely related to polarization during innate immunity. The iron homeostasis of macrophages is related to the functional polarization and plasticity of these cells and plays an extreme role in the process of inflammation, immune regulation, and inflammation regression [42]. According to the Mosser and Edwards model, macrophages are grouped by their functional characteristics into three populations, including host defense (M1), wound healing (M2a), and immune regulation (M2b/c). Under a conceptual framework these three basic macrophage populations can be blended into a large number of different macrophage subpopulations [43]. Polarization characteristics usually refer to the cytokine profile that has been extensively studied in KD patients. However, no studies have yet been made to resolve the exact macrophage polarization in KD. Since iron is an essential growth factor for most bacteria and parasites, they have developed various mechanisms to separate iron from the host. Doing so makes M1-macrophages a major iron storage site under inflammatory conditions [42]. In contrast, M2-macrophages increase ferroportin to promote iron release [44]. However, little is known about whether iron homeostasis affects the ability of the macrophage polarization program and molecular mechanisms involved in the KD disease process.

Conclusion

Inflammation-induced hepcidin can bring about transient hypoironemia, anemia, and disease outcomes in acute-phase KD (Fig. 2, published Int J Mol Sci. 2017 Apr 12; 18 (4): 820. doi: 10.3390/ijms18040820, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5412404/). However, further research is needed to better clarify the role of hepcidin in the pathogenesis of KD.

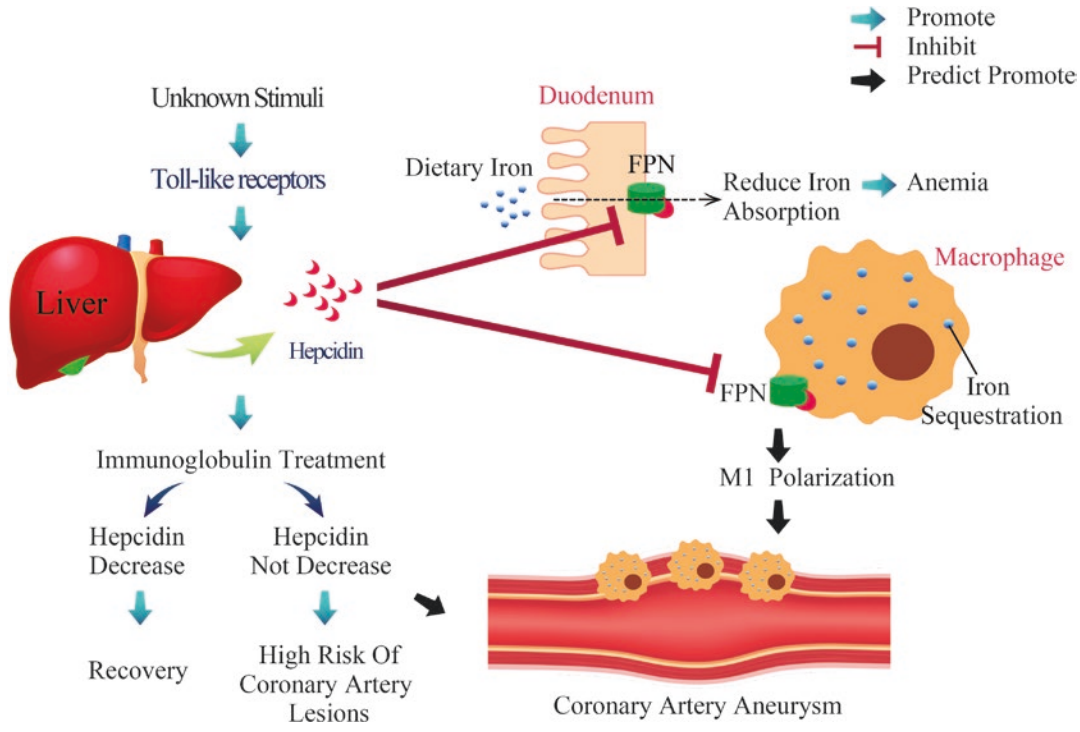

Fig. 2 Proposed mechanism of transient anemia and coronary artery lesions caused by hepcidin in patients with Kawasaki disease. Although the exact cause of Kawasaki disease (KD) is still uncertain, we have reported that KD stimulates the abnormal upregulation of most TLRs, and these TLR arteries upregulate the expression of Hepcidin. After hepcidin interacts with ferroportin, the ferroportin is internalized and degraded, which ultimately leads to the reduction of intracellular iron chelation and duodenal iron absorption. Hepcidin not only controls the absorption of iron, but also has a direct inhibitory effect on erythropoiesis, which can cause transient hypoironemia and anemia in patients with KD. The iron homeostasis of macrophages is related to the functional polarization and plasticity of these cells and makes M1-macrophages a major iron storage site under inflammatory conditions. However, little is known about whether iron homeostasis affects the macrophage polarization program and the ability of the molecular mechanisms involved in the KD disease process. (Reproduced with permission from Int J Mol Sci. 2017 Apr 12; 18 (4): 820. doi: 10.3390/ijms18040820)

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