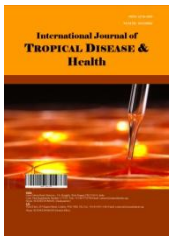

International Journal of TROPICAL DISEASE & Health

Volume 43, Issue 24, Page 44-50, 2022; Article no.IJTDH.93478
ISSN: 2278–1005, NLM ID: 101632866

Kawasaki Disease Complicated with Hemophagocytic Syndrome: A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2022/v43i241378

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/93478

Review Article

Received: 29/09/2022
Accepted: 18/11/2022
Published: 26/12/2022

ABSTRACT

Kawasaki Disease with Hemophagocytic syndrome (KD-HPS) is a rare disease that threatens the health of children around the world. Though it has low incidence rate, it progresses rapidly with atypical clinical symptoms which leads to misdiagnosis, posing serious threat to children's life with high mortality. This article presents the review on Kawasaki Disease (KD) with hemophagocytic syndrome pathogenesis, clinical symptoms, characteristics, diagnosis, and treatment.

Keywords: Kawasaki disease; hemophagocytic syndrome; lymphohistocytosis.

1. INTRODUCTION

Formally called mucocutaneous lymphnode syndrome (MCLS) [1] KD is an acute systemic vasculitic disease that occurs mostly in infants under the age of 5 years. The clinical features are mainly recurrent fever, varying degrees of oral mucositis, binocular conjunctival hyperemia, non-suppurative lymphadenitis, hard swelling of the extremities with fingertip desquamation, and systemic pleomorphic rash [2]. At present, the pathogenesis of the disease is still unclear in the

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global clinic but more and more experimental studies have proved that KD is related to infections caused by bacteria, viruses and mycoplasma [3]. The disease can cause coronary artery injury, coronary arteritis, coronary artery stenosis, coronary aneurysm, and in severe cases, it can result in acute myocardial infarction and sudden death due to coronary artery rupture.

Hemophagocytic lymphohistocytosis (HPS) which was first reported by Risdall in the United States in 1979 [4] is a rare and potentially fatal complication of KD. Its clinical features include persistent high fever, anemia, hepatosplenomegaly, abnormal liver function, and coagulopathy. Bone marrow smear can reveal large blood cells, and the phagocytic cells are often morphologically intact white blood cells, nucleated red blood cells or mature red blood cells and platelets. The incidence of KD complicated with HPS (KD-HPS) is low, the clinical progress is rapid, has a high mortality rate, and has received insufficient clinical attention, which seriously threatens the life and safety of children. The mechanism of KD-HPS is not clear, and there is no corresponding diagnosis and treatment guideline. With the deepening of HPS research, the literature reports on KD-HPS are gradually increasing. The research progress of pathogenesis, clinical symptoms and characteristics, diagnosis and treatment, summarized in this literature aims to improve the understanding of KD-HPS.

2. ETIOLOGY AND PATHOGENESIS

A large number of epidemiological and clinical observations have shown that KD is caused by pathogens. KD is a self-limiting disease that has high incidence rate in infant but rare in adults. KD pathogens are prevalent in the natural environment and also caused by microorganisms that can cause most individuals asymptomatic infections which has acquired immunity in adulthood. However, in the past 20 years, many researchers have not found pathogens through serology and advanced culture techniques. The fever and major clinical manifestations of KD overlap with some diseases that are clearly caused by bacterial toxins, such as toxic shock syndrome and scarlet fever. KD has the characteristics of abnormal activation of the immune system that is not found in most fever and rash diseases. Therefore, many researchers believe that the abnormal immune system activation of KD is caused by the super antigen-mediated mechanism of bacterial or viral toxins [4]. Toxic shock syndrome toxin (TSST), exfoliative toxin (ET), streptococcal pyrogenic exotoxins (SPE), microbial toxins, super antigen pathogenic bacteria, heat shock protein (HSP) mimics the pathogenic role of the host's own antigens and may play an important role in its pathogenesis of KD [5]. High activation of the immune system and immune-damage vasculitis are prominent features of KD. The T cell-mediated abnormal immune response and the cascade effect of cytokines are the basis of KD vasculitis injury.

At present, the pathogenesis of HPS is not completely clear. It is generally believed that HPS is based on various causes or primary diseases, and the immune regulation function of the child is abnormal which causes the immune active cells in the body to proliferate excessively. Among them, T cells are the main participants in the onset of HPS, which is expressed as CD8+T cells were significantly elevated, CD4+T cells were significantly decreased, and CD4+/CD8+ was decreased [6]. These immunocompetent cells can produce a large number of inflammatory cytokines, such as tumor necrotic factor-α, interleukin-1, interleukin-6 and α-interferon, which stimulate the proliferation, activation and the release of macrophages. A large number of inflammatory cytokines cause inflammatory cytokines to form a waterfall. These inflammatory cytokines can cause various pathological damages and produce a variety of clinical symptoms.

It is worth noting that both KD and HPS are a series of pathophysiological changes caused by abnormalities in immune regulation induced by infection, and the inflammatory cytokines are similar in the blood samples of patients with KD and HPS. Increased levels of inflammatory cytokines such as tumor necrotic factor-α, interleukin-1, and interleukin-6 can also be detected in blood samples from patients with KD complicated with HPS [7], maybe suggesting that there is a common path for pathogenesis of KD and HPS. However, the pathogenesis of KD-HPS still needs further study to be fully understood.

3. CLINICAL SYMPTOMS AND CHARACTERISTICS

Though there are no published guidelines for the clinical symptoms and characteristics of KD-HPS, it is generally believed that the typical clinical manifestations of KD-HPS are high fever, which

may be intermittent fever, continued fever or irregular fever, progressive hepatosplenomegaly, nervous system disorders, and some with lymphadenopathy and rash. Other symptoms include chills, general malaise, fatigue, digestive and respiratory symptoms. The disease progresses rapidly, and the prognosis is poor if it is not diagnosed and treated in time.

KD-HPS has the following clinical features: more in males, the average age of onset is 5 years, KD-HSP occurs mostly after 2 weeks of KD, long lasting fever, rash, the splenomegaly is obvious. When the HPS is complicated, the liver is palpated to the right clavicle. The mid line rib is 3cm, and it increases sharply in a short period of time. The incidence of coronary complication is not significantly increased compared with the normal KD. Children with KD who have echocardiographic coronary artery or coronary dilatation or who do not respond to IVIG therapy are prone to HPS [8]. KD-HPS laboratory examination features: On the basis of KD high platelet count, sudden onset of platelet sharp decrease with or without WBC and HB reduction, the average PLT count in HPS is 82.9×10^{9}/L; increase LDH and ALT is the most prominent; the incidence of hemophagocytic cells is high, and hematopoietic tissue cells are found in liver puncture.

4. DIAGNOSIS

Currently, there is no recognized KD-HPS diagnosis and treatment guide. KD and HPS have common clinical manifestations such as fever, rash, hepatosplenomegaly, abnormal liver function, and others especially in the early stage, it is difficult to specifically distinguish the clinical manifestations of HPS from KD. Therefore, the diagnosis of KD-HPS in the clinic is based on the KD diagnostic criteria, and further combined with the comprehensive diagnosis of HPS corresponding symptoms. KD can be divided into typical and atypical types. Typical KD: In 2002, the Japanese KD research team proposed a typical KD diagnostic criteria, which was published in Pediatrics International (2005) after the 7th International KD Conference [9]. The American Heart Association (AHA) also proposes a typical KD diagnostic criteria and publishes it in Pediatrics (2004) [10] and Circulation (2004) [11]. The AHA lists fever as an essential diagnostic condition; if there are 4 major clinical manifestations other than fever, echocardiography found coronary aneurysm or coronary dilatation, the typical KD diagnosis can be confirmed when the fever is 4 days. However, the proportion of children with KD who have no fever is extremely low. Only 0.3% of children with KD epidemiological findings in Beijing have no fever. Therefore, the typical KD diagnosis in China [12]: fever for 5 days or more (some cases are treated with fever Less than 5 days) with 4 of the following 5 items: bilateral conjunctival hyperemia, redness of the lips and oral mucosa, changes in the extremities (swelling in the acute phase, scaling in the recovery period), rash and non-suppurative cervical lymphadenopathy can be diagnosed as KD. A typical KD can also be diagnosed if there are 3 manifestations other than fever and a confirmed coronary aneurysm or coronary dilatation. It must be emphasized that KD diagnostic criteria are not specific and must be excluded from other diseases that cause various clinical manifestations. It should also be noted that the clinical manifestations do not occur at the same time and should be observed dynamically to aid in diagnosis.

Incomplete KD: About 10% of children (especially infants) present with incomplete KD. The name of the model is confusing, with atypical KD, incomplete KD, and delayed diagnostic KD. Atypical KD, especially those with rare clinical manifestations (such as aseptic meningitis, kidney involvement, etc.), delayed diagnostic KD means that the diagnostic indicators have been shown in about 10d, thus delaying the diagnosis. China adopt the unified name “incomplete KD” [13] and is not the same as mild KD. The risk of coronary artery involvement and laboratory findings are similar to those of typical KD. It is important to note that erythema, induration, anterior uveitis, gallbladder enlargement, and perianal peeling during recovery are important indicators to aid in diagnosis. The rise of brain natriuretic peptide can be used as a reference for the diagnosis of KD [14]. For infants younger than 6 months, KD performance is more atypical. According to the AHA standard, if the fever continues to subside, other diseases are excluded, and laboratory evidence has evidence of inflammation (erythrocyte sedimentation rate and C-reactive protein increase) High), although there is no clinical manifestation of KD, echocardiography should be repeated to understand the presence or absence of coronary artery injury. Once a clear coronary lesion is found, an incomplete KD can be diagnosed and a standard treatment regimen is used. However, for children older than 6 months, fever for 5 days or more, it is necessary to have several major clinical manifestations of KD before the

suspected KD is still controversial. Recommendation: In addition to fever for 5 d or more, there should be at least 2 major clinical manifestations of KD, and the inflammatory response index is significantly increased. In addition to other diseases, if incomplete KD is suspected echocardiography should be reviewed to monitor coronary and other cardiac changes. If coronary artery lesions occur, and standard treatment options such as coronary artery disease are not available, it is recommended that gamma globulin (IVIG) should not be used. If the fever persists and does not meet the echo-cardiogram and experimental indicators, similar clinical manifestations caused by other diseases should be excluded, including viral infection, scarlet fever, staphylococcal scalded syndrome, toxic shock syndrome, bacterial neck lymphadenitis, drug allergy, Stevens-Johnson syndrome and systemic juvenile idiopathic arthritis.

Because some clinical manifestations of HPS are similar to some primary diseases (sepsis, systemic inflammatory response syndrome, etc.), and the lack of specific laboratory tests for the disease, it will mask the performance of the primary disease, interfere with the diagnosis, and lead to misdiagnosis and missed diagnosis. Even with early diagnosis and timely treatment, there is still a high mortality rate. Therefore, the diagnosis of the disease should be comprehensive diagnosis from clinical manifestations, laboratory, imaging and other aspects [15].

In 2009, the American Society of Hematology developed new diagnostic criteria [16] and while confirming that molecular/biological defects are known to be the basis for independent diagnosis of HPS, the following adjustments have been made to clinical diagnostic indicators:

(1) 1. Fever (most common, the incidence is almost 100%), 2. splenomegaly; 3. blood cell reduction (peripheral blood at least two or more reduction), 4. Hepatitis. At least 3 of the above 4 indicators are met.
(2) 1. Bone marrow, spleen or lymph node cytology found in the phenomenon of hemorrhage, 2. Elevated ferritin. 3. sCD25 level (related to age), 4. NK cell activity decreased or absent. At least one of the above four indicators are met.

Other indicators that support HPS diagnosis: 1. Hypertriglyceridemia, 2. Hyperfibrinogenemia, 3. Hyponatremia.

In combination with the diagnostic criteria, long-term fever, especially the peak temperature of the body above 38.5□ combined with hematocytopenia, hepatosplenomegaly are the joint symptoms of HPS, and for patients with these joint symptoms be alert for HPS [17]. Combined with other laboratory indicators, the disease can be determined or eliminated relatively quickly. Patients with unexplained fever, hepatosplenomegaly, and hematocytopenia should be alert to this disease. The central nervous system damage caused by the disease is mostly irreversible and the mortality rate is extremely high. It is also necessary to perform imaging examination of the skull in patients with suspected patients or patients with central nervous system involvement. If necessary, cerebrospinal fluid examination can be performed to early control of the disease or reduce death of patients due to central nervous system involvement.

5. TREATMENT AND PROGNOSIS

Similarly, there is no published guideline for the treatment of KD-HPS. At present, the mainstream treatment plan still refers to systemic juvenile idiopathic arthritis complicated by giant cell activation syndrome (So-JIA-MAS).

5.1 Treatment

If a general treatment can find a suspected trigger that triggers KD-HPS, it can be targeted for anti-infective, anti-viral, and suspicious drug withdrawal. According to the patient's organ damage, the corresponding breathing, circulation support and other treatments are given. Early and timely intravenous and topical application of glucocorticoids, high-dose gamma globulin and immunosuppressive agents such as cyclosporine A, cyclophosphamide, etoposide, vincristine, etc., yields positive prognosis. Studies have shown that in the early stages of HPS, only a timely application of intravenous glucocorticoids can achieve a cure rate of 50% [18]. At the same time, infusion of specific inflammatory cytokine antibodies (such as γ-interferon monoclonal antibody, tumor necrotic factor alpha monoclonal antibody) and its receptor antibodies (such as monoclonal antibodies to interleukin receptor) and plasma exchange. Therapeutic methods for clearing inflammatory cytokines such as white blood cell classification are also being carried out [19-22]. While treating HPS, attention should be paid to the impact of primary KD treatment on HPS treatment. For example, in the KD standard

treatment, anticoagulant therapy is of great importance, and most patients with HPS have thrombocytopenia. At this time, whether anticoagulant therapy needs to be continued, how to grasp the anticoagulant dose and application timing particularly is very important. And this is one of the issues that needs further study.

5.2 Prognosis

According to the literatures, the prognosis of KD-HPS is relatively good [22-23]. As mentioned earlier, the incidence rate was 1.10%~2.10%, which was significantly lower than the incidence of So-JIA-MAS (10.00%); the case fatality rate was 5.00%, which was also slightly lower than the So-JIA-HPS mortality rate (8.00%) [24-26]. It should be noted that IVIG treatment is the preferred treatment for patients with KD, and intravenous glucocorticoid is the first choice for patients with IVIG non-responsive KD. It can be seen that KD and HPS have obvious commonality in treatment. This may be the reason why clinicians are concerned about the small number of patients with KD-HPS, low complications and mortality, and relatively good prognosis. It is also suggested that a significant proportion of KD-HPS patients have not been correctly recognized.

6. CONCLUSION

KD-HPS is not an independent disease, it is a high-inflammation clinical syndrome with many causes, rapid progression, and life-threatening. Its clinical features are similar to other diseases and the lack of specificity of symptoms and signs makes it to be easily misdiagnosed and missed diagnosed. There is currently no standardized treatment for KD-HPS, and it is still controversial whether KD-HPS patients need to receive chemotherapy. But whether it is pure HPS or KD-HPS, controlling infection is crucial. For patients with long-term fever, hepatosplenomegaly, and thrombocytopenia, the possibility of this disease should be considered in time. Although HPS is not uncommon in clinical practice, it can be complicated by life-threatening complications such as septic shock, multiple organ failure, intracranial and visceral hemorrhage due to the danger of the disease itself, and the mortality rate is high. As a result, clinicians need to be highly vigilant about the disease, early identification and diagnosis can yield good prognosis and reduce mortality. At the same time, as the center of this paper, doctors have a certain understanding of KD-HPS, both in diagnosis and treatment. Undoubtedly, there are still problems, such as the inability to accurately identify patients early, the poor understanding of the cause of the disease, the inability to block KD-HPS from the source, and the small number of cases that cannot accumulate sufficient clinical experience and do not get accurate epidemiological data. These problems pose a huge challenge to clinicians, but also guide the next research direction.

FUNDING

(1) Shaanxi Province Key Research and Development Program in 2020 (International Cooperation).
(Project No. 2020KW-052);
(2) Program of Shaanxi Province (International Cooperation Project. No.2022KW-13).

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/93478