European Review for Medical and Pharmacological Sciences 2017; 21: 4322-4326

Macrophage activation syndrome as a complication of juvenile rheumatoid arthritis

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Abstract. – OBJECTIVE: Juvenile rheumatoid arthritis (JRA), also known as juvenile idiopathic arthritis (JIA), is a rare autoimmune joint disorder of children. The concrete causes for the prevalence of the above pathological state are still unknown. In other words, it is an arthritis affecting mainly children and adolescents. Clinically, it has 3 different clinical subtypes. JRA patients are often noticed with some confirmed symptoms including coagulopathy, disseminated intravascular coagulation (DIC) with hepatosplenomegaly, fall in erythrocyte sedimentation rate and higher levels of liver enzymes leading to a life-threatening outcome. The above complications of JRA are recognized as a macrophage activation syndrome (MAS), which is similar to hemophagocytic lymphohistiocytosis (HLH). Pathogenesis of JRA manly involves deregulation of immunological processes with excessive and persistent activation of antigen presenting cells and T-lymphocytes. Further, abnormalities in the functioning of NK cells are often observed in JIA cases. Also, 40% of patients with these abnormalities are habitually associated with perforin gene mutations. Today, MAS remains a clinical and diagnostic challenge.

RESULTS: The diagnosis of MAS is mainly based on clinical grounds. However, laboratory evidence of macrophages in the bone marrow performing phagocytosis of variable hematopoietic cells also help in diagnosis. For confirmation of MAS, there must be present either of two clinical or laboratory criteria. Further, laboratory criteria often appear late and are unable to diagnose the complication right at the beginning stage. Important laboratory findings in macrophage activation syndrome associated with JIA include hypertriglyceridemia, anemia, low erythrocyte sedimentation rate, elevated alanine aminotransferase level, higher than normal bilirubin levels, presence of fibrin degradation products, high lactate dehydrogenase level, low sodium, low albumin, and hyperferritinemia.

CONCLUSIONS: MAS is a confirmed life threatening complication of patients with JIA. Further, an early diagnosis and treatment of MAS could be a life-saving mode for this syndrome.

Key Words:

Juvenile rheumatoid arthritis (JRA), Juvenile idiopathic arthritis (JIA), Hemophagocytic lymphohistiocytosis (HLH), Regulatory immunological processes.

Introduction

Juvenile rheumatoid arthritis (JRA) is an autoimmune joint disorder of children with ages up to 16 years[1,2]. It is also known widely as juvenile idiopathic arthritis (JIA). JIA is a rare pathological state, but both causes and genetic predisposition are still unknown. JIA often results in inflammation of the joints, fever, rash, lymphadenopathy, splenomegaly and iridocyclitis[3]. Some children have been reported to be having self-limiting form of the disease where symptoms last for only a few months. On the other hand, some patients have chronic form of the disease. The disease is confirmed mainly by clinical examination. JRA patients are associated with sensitive, painful and swollen joints with outbursts. These outbursts interfere with both growth and development of joints. There are usually three different clinical subtypes of the disease. The first one is known as Still's disease and is characterized by fever, rush, splenomegaly, lymphadenopathy, pericarditis or pleuritis. It is basically signifies onset of the arthritis and is present in 20% of the cases. The second subtype is monoarticular or pauciarticular form of the disease, which features maximum of 4 affected joints. The third subtype is polyarticular form including 5 or more joints and is reported mostly in girls. It is often reported to be associated with elevated levels of rheuma factor (RF).

In pediatric patients, JRA is usually suspected by inflammation of the joints, lymphadenopathy, splenomegaly, iridocyclitis, rush and fever that last for few days. Iridocyclitis could cause con-

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junctivitis, pain and photophobia. Iridocyclitis is often asymptomatic, but it could result in scarring and glaucoma. The diagnosis is primarily clinical, but antinuclear antibodies (ANA) and RF should also be investigated for confirmation. In this way, above immunological analyses could help in the diagnosis of JRA and differentiate subtypes. ANA and RF are not detectable in very first stage/subtype of JRA called as Still's disease. Moreover, earlier studies reported iridocyclitis more frequently in second subtype viz. monoarticular of JRA in comparison with third subtype[4,5].

MAS – Life Threatening Complication of JRA

MAS is a life threatening complication of JRA and is associated with coagulopathy, DIC with hepatosplenomegaly, fall in erythrocyte sedimentation rate and high levels of liver enzymes[6]. The characteristic feature of MAS has been confirmed to be the presence of macrophages in bone marrow showing hemophagocytosis as well as the presence of hematopoietic elements in cytoplasm[7]. Furthermore, the above process could be triggered in different infections or during treatment with anti-inflammatory drugs. Furthermore, Ravelli et al[8] described macrophage activation syndrome (MAS) as a severe, often lethal complication of systemic juvenile idiopathic arthritis (sJIA). It has been reported to be evident in 10% of children with sJIA; however, it occurs sub clinically in another 30-40%. This life-threatening complication of JRA is caused by excessive activation and proliferation of T cells along with macrophages leading to a stormy systemic inflammatory reaction. During the microscopic analysis of bone marrow aspirates, it was observed that macrophages were actively involved in the phagocytosis of hematopoietic cells[9]. Macrophage activation syndrome is characterized by an intense reaction of immune system that is self-destructive in nature. Such recognized syndrome has now become one of the leading clinical challenges responsible for high mortality rate of JRA.

Pathogenesis of MAS

MASis quite similar to hemophagocytic lymphohistiocytosis (HLH) in terms of pathogenesis. It is a rare complication with the presence of hyperactive histiocytes and lymphocytes with possible lethal outcomes. Like HLH, MAS involves deregulation of immunological processes responsible for termination of inflammatory response. As a result, there appears an excessive and persistent activation of antigen presenting cells and T lymphocytes. Moreover, abnormalities in functioning of NK cells were also reported[10]. NK cells lyses target cells, but mechanisms of their action have been unknown until recently[11]. NK cells allow normal functioning of the immune system and maintain normal immune responses levels. The normal functioning of NK cells is crucial for the prevention of autoimmune diseases. The most usual dysfunction of immune system in these patients is impairment of cytotoxic function of NK cells and the function of CD8 T cells also get affected. In approximately 40% of patients, these abnormalities are linked with the mutation of genes for perforin. Perforin is a cytolytic protein that is found in CD8 and NK cells and it participates in the formation of pores in membranes[12]. Damaged cytotoxic cells upon activation result in increased secretion of proinflammatory cytokines especially, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-10. It is believed that IL-18 is a major cytokine responsible for the above pathological state as bone marrow cells showed high levels of IL-18. So, it was considered that bone marrow was the origin of elevated levels of IL-18. So, the above observation confided that bone marrow could be a very important organ in the pathogenesis of JIA[13].

Previous studies described infiltrating cells in MAS. They showed that histiocytes were monocyte or macrophage lineage, and the lymphocytic infiltrate mostly belonged to T lymphocytes[14,15]. Henter et al[16] analyzed patients with primary HLH and found elevated levels of inflammatory cytokines IFN-γ, TNF-α, IL-6. Cytokines might have an important part in the pathogenesis of the disease. The authors also suggested that genetic defects cause the hypercytokinemia. They also find elevated soluble CD8, which suggested that cytotoxic T cells could have role in pathogenesis of the disorder. Akashi et al[17] analyzed patients with primary HLH and showed that $CD2^+$ circulating lymphocytes spontaneously excreted IFN-γ *in vitro*. They also discovered that monocytes excrete TNF-α and IL-6[18]. Billiau et al[19] showed direct evidence on the involvement of activated CD8+ cells and macrophages: IFN-γ-producing $CD8^+$ lymphocytes, and of TNF-α- and IL-6 producing macrophages. They supported the hypothesis on the immunopathogenesis of this syndrome

Table I. Laboratory and clinical criteria for diagnosing MAS complicating JIA.

Laboratory criteria	Clinical criteria
Decreased platelet count < 262 × 10*9/l Elevated aspartate aminotransferase levels > 59 U/l Leukocytes < 10*9/l Fibrinogen < 2.5 g/l	CNS Disfunction Irritability Disorientation Lethargy Headache Seizures Coma Bleeding (purpupa, hematomas that develop easily, bleeding from mucous membranes) Hepatomegalia (> 3 cm below the costal arch)

and also emphasized the view that MAS share a common effector pathway in different types of HS[18].

In patients suffering from acquired HLH, the pathways leading to cytolytic defects in immunocompetent are not yet clear. Very low or undetectable levels of cytolytic NK cell activity could be observed in patients suffering from virus-associated HLH. Nevertheless, in contrast to FHLH, this phenomenon seems to be linked to a deep shoot in the number of NK cells rather than a reduced perforin expression. Previous reports[19] revealed that NK function recovered completely in some patients after the acute phase was resolved. On the other hand, there are reports suggesting that low NK activity, with or without abnormal perforin expression, might also be implicated in the pathogenesis of SJIA-associated macrophage activation syndrome. In patients with active SJIA, the levels of perforin expression in NK cells and cytotoxic $CD8^+$ T lymphocytes were quite low than that in healthy control subjects and those who suffered from other subtypes of juvenile idiopathic arthritis[20].

Reduced NK activity was linked to very low NK cells counts. This condition slightly increased perforin expression levels in NK cells and cytotoxic $CD8^+$ T lymphocytes. This pattern to a certain extent is comparable to condition in patients with virus-associated HLH.

Most of patients with low perforin expression also had a history of multiple episodes of macrophage activation syndrome. Two features distinguish patients with SJIA from those with other forms of juvenile idiopathic arthritis: (1) a decline in NK cell counts; (2) depressed NK cell cytolytic activity[2]. However, the diagnostic potential of these abnormalities is still under review and no concrete conclusion is available.

Diagnosis of MAS

MAS still remains a clinical as well as a diagnostic challenge. Diagnosis is mostly based on clinical ground, but some laboratory findings do help in the diagnosis but are slow in nature. Ravelli et al[21,22] developed diagnostic guidelines for macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (SJIA), which include both clinical as well as laboratory criteria (Table I). The important symptoms associated with above criteria include anemia, lower erythrocyte sedimentation rate, high alanine aminotransferase, high bilirubin level, presence of fibrin degradation products, elevated lactate dehydrogenase level, hypertriglyceridemia, low sodium level, low albumin, and hyperferritinemia. Minoia et al[23] in 2014 developed the new classification criteria for MAS complicating SJIA (Table II). The above guidelines provided a highly specific and sensitive set of criteria that could help physicians in diagnosing of MAS complicating JIA. This would help to enable a prompt reaction of the physician and application of suitable therapy, which in turn could prevent lethal outcomes of this life-threatening disease.

Table II. A new set of classification criteria for MAS complicating sJIA.

Hyperferritinemia > 684 ug/ml	1. Decreased platelet count < 181 × 10*9/l 2. Elevated aspartate aminotransferase levels > 59 U/l 3. Triglycerides > 156 mg/dl 4. Fibrinogen < 360 mg/dl

Table III. Clinical discriminators in MAS diagnosis.

Clinical discriminators	MAS %	sJIA %
Skin rash	65	47
Hepatomegaly	88	20
Spenomegaly	59	29
Limphadenopaty	41	33
CNS dysfunction	53	0
Hemorrhages	23	0

Table IV. Laboratory discriminators in MAS diagnosis.

Laboratory discriminators	MAS %	sJIA %
Leukopenia < 4.0×10^9	56	0
Hb < 90 g/l	82	36
Decreased platelet count < 150×10^9	88	0
Erythrocyte sedimentation rate < 50 mm/h	60	20
Increased aspartate aminotransferase > 40 U/l	94	6
ALT > 40 U/l	81	8
Bil > 20 µmol/l	46	0
LDH > 900 U/l	87	7
Hypofibrinogenemia < 2.5 g/l	89	3
Albumin < 2.5 g/l	15	5
Triglycerides > 2.5 mmol/L	86	15
Ferritin > 10,000 µg/l	100	0

How to Distinguish JRA from MAS

Ravelli et al[20] compared patients with the index disease and patients with indistinctly manifested disease. The strongest clinical discriminators were hemorrhages, and central nervous system dysfunction (Table III). The strongest laboratory discriminators were decreased platelet count, increased aspartate aminotransferase, leukopenia, and hypofibrinogenemia (Table IV). Ravelli et al[21] identified preliminary diagnostic guidelines for MAS complicating JIA, which would be quite helpful in further diagnosis of patients with this challenging disease. MAS often occur in children of both sexes, at any age. The youngest child with MAS so far known is 12 months old.

Conclusions

MAS is a major complication of JIA and could be exploited for dialogistic purpose of JIA at quite early stage. Timely diagnosis of JIA especially, in children would defiantly help in initiation of proper treatment that would help in prevention of mortality.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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