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Macrophage Activation Syndrome in Children with Systemic Juvenile Idiopathic Arthritis Successfully Treated with Megadose Methyl Prednisolone Therapy

Sistemik Juvenil İdiopatik Artritli Çocuklarda Makrofaj Aktivasyon Sendromunun Megadoz Metil Prednizolon ile Başarılı Tedavisi

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ABSTRACT
Macrophage activation syndrome (MAS) is the most common serious and fatal complication of systemic juvenile idiopathic arthritis (SJIA). MAS is most commonly seen in SJIA and there are no true estimates of its incidence. Although it has been considered a rare complication, it is probably more common than it is thought. In the last sixteen years, 240 patients were diagnosed with JIA in our institute. Out of the 240 patients, 16 were diagnosed with SJIA; and four of these 16 SJIA patients had MAS. There is no consensus on the treatment of MAS. Four cases of MAS diagnosed in our institution were administered intravenous mega-dose methylprednisolone (MDMP) as induction therapy successfully without any serious adverse effects. To the best of authors' knowledge, MDMP as a treatment modality in MAS therapy is reported for the first time. Herein, we report the clinical and laboratory data of our cases who received MDMP and evaluate our clinical experience reviewing the literature. *The Journal of Pediatric Research 2015;2(2):92-5*
Key words: Methyl prednisolone, macrophage activation syndrome, treatment

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ÖZET
Makrofaj aktivasyon sendromu (MAS), sistemik juvenil idiopatik artritin (SJIA) en sık görülen ciddi ve ölümcül bir komplikasyonudur. MAS, en çok SJIA'da görülmekle birlikte gerçek sıklığı bilinmemektedir. Nadir görülen bir komplikasyon olduğu düşünülmekle beraber, muhtemelen düşünüldüğünden daha yaygındır. Son on altı yılda, kliniğimizde JIA tanısı alan 240 hastanın 16'sı SJIA olup, bu olguların 4'ünde MAS gelişmiştir. MAS tedavisi hakkında görüş birliği yoktur. Kliniğimizde MAS tanısı alan dört olguya, herhangi bir ciddi yan etkisi olmaksızın intravenöz mega doz metilprednizolon (MDMP) tedavisi uygulanmıştır. Bilindiği kadarıyla, MDMP, MAS tedavisinde bir tedavi yöntemi olarak ilk kez bildirilmektedir. Bu makalede, MDMP tedavisi alan olguların klinik, laboratuvar verileri ve prognozları literatür eşliğinde tartışılarak klinik deneyimimiz paylaşılmıştır. *The Journal of Pediatric Research 2015;2(2):92-5*
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Introduction

Macrophage activations syndrome (MAS) is a life-threatening complication of chronic rheumatic diseases in childhood, which is seen most commonly in systemic juvenile idiopathic arthritis (SJIA) (1). The clinical presentation of MAS is generally acute and occasionally dramatic, requiring the admission of the patient to the intensive care unit. Characteristic features of MAS are fever, hepatosplenomegaly, lymphadenopathy, profound depression of three blood cell lines, deranged liver function, intravascular coagulation, and central nervous system dysfunction, and is thought to be caused by the activation and uncontrolled proliferation of T lymphocytes and macrophages, resulting in an unrestricted release of inflammatory cytokines (2). The diagnostic hallmark of MAS is found in bone marrow aspiration, by which numerous well-differentiated macrophages actively phagocytosing haematopoietic cells are revealed (3).

There is no consensus of the treatment of MAS. Several treatment modalities such as high-dose systemic steroids, intravenous immunoglobulin and immunosuppressive agents are currently in use of the treatment of MAS (1,4). Other treatment strategies include etanercept, etoposide, cyclophosphamide, plasma-exchange and anakinra, although clinical evidence favoring these strategies is based on anecdotal experiences (5). Four cases of MAS followed up in our institution for 16 years were administered intravenous mega-dose methylprednisolone (MDMP) as induction therapy and oral cyclosporin as maintenance therapy successfully without any serious adverse effect and a relapse. The aim of our report is to present the clinical and laboratory data of our cases who received MDMP and to evaluate our clinical experience reviewing the literature.

Case Reports

Patients

In the last sixteen years, 240 patients were diagnosed as JIA in our institute. Out of 240 patients, 16 were diagnosed as SJIA. And four of these 16 SJIA patients were diagnosed as MAS. All patients' clinical and laboratory findings were fulfilling the clinical criteria of MAS (2). Clinical and laboratory findings of the patients are summarized in Table I. Bone marrow aspirations revealed hemophagocytosis in 3 patients. All four patients were female, and the mean age of diagnosis was 22 months (13-43 months). Disease duration between SJIA diagnosis and onset of MAS symptoms was 3 months. The fever pattern during SJIA was in quotidian character, whereas it turned into unremitting fever after the onset of MAS. Hepatosplenomegaly was found in all cases; however, lymphadenomegaly was present in 3 patients. Patient No. 3 was followed up for 5 years, but later on the patient was moved to a distant town. Other 3 patients have been being followed-up in our out-patient clinic without a relapse of MAS.

Treatment Protocol

Induction therapy of MDMP was administered to all cases. MDMP was administered within 5 to 10 minutes, once a day (30 mg/kg daily for 3 days, 20 mg/kg for 4 days and subsequently tapered to 10, 5 and 2 mg/kg, for 2 days intravenously) before 9 A.M. During the MDMP treatment, the patients were given gastro protective agents and had a salt-free diet. On the 14^{th} day of the treatment, MDMP was discontinued and switched to 2 mg/kg prednisone and administered orally twice a day until acute-phase reactants returned to normal. When acute phase reactants returned to normal levels, steroid doses were reduced to 1 mg/kg a day. Afterwards the total dose of prednisone was reduced by about 10% every week and finally discontinued. None of the patients developed hypertension, digestive system complaints, hyperglycemia and symptoms of Cushing's syndrome during MDMP.

The patient No. 2 was given intra-venous immunoglobulin G (IVIG) 1 g/kg on two successive days for the initial treatment. Because unremitting fever did not drop, and clinical and laboratory findings deteriorated, he was administered MDMP after IVIG treatment for 2 days. MDMP therapy led to complete remission of all cases. After the induction therapy, the first patient was administered methotrexate (MTX, 15 mg/m^2 a week) in addition to 2 mg/kg prednisone. Cyclosporine A (CsA, 3-5 mg/kg a day) was added to the treatment of 2 mg/kg prednisone for the rest of the cases. Patient No. 2 and No. 3 received CsA for one year and Patient No. 4 received for 2 years. There was no relapse in any of the cases during the entire treatment and follow-up period.

Discussion

Macrophage activation syndrome (MAS) is overt in 10% of children with sJIA but occurs subclinically in another 30-40%. It is difficult to distinguish SJIA disease flare from MAS (6). The onset of the syndrome is usually heralded by the sudden occurrence of unremitting high fever, profound drop in all three blood cell lines (leukopenia, anemia and thrombocytopenia), liver enlargement, generalized lymphadenopathy and increase in serum liver enzymes. There is often an abnormal coagulation profile, with prolongation of prothrombin and partial thromboplastin times, hypofibrinogenemia, detectable fibrin degradation products and increase in D-dimer. The acute phase of MAS is usually marked by a sharp rise of ferritin (6). All of our cases fulfilled the diagnostic laboratory and clinical criteria of MAS (Table I).

The patients may show a paradoxical improvement of the underlying inflammatory disease at the onset of MAS, such as an amelioration of erythrocyte sedimentation rate (ESR). This phenomenon is mainly related to the hypofibrinogenemia due to liver dysfunction and fibrinogen consumption (3). The pathognomonic feature of the syndrome is seen on bone marrow examination, which reveals numerous morphologically benign macrophages exhibiting hemaphagocytic activity. Such cells may infiltrate the lymph nodes and spleen as well as many other organs in the body and may be responsible of several clinical manifestations of the syndrome (3). However, in patients with MAS, the bone marrow aspirate does not

Table I. Clinical and laboratory characteristics of the patients with systemic juvenile idiopathic arthritis at the time of diagnosis of Macrophage activations syndrome

Patient	1	2	3	4
Age (months)	43	19	21	13
Sex	Female	Female	Female	Female
Disease duration (months)	5	2	2	3
Fever patern	U	U	U	U
Hepatosplenomegaly	+	+	+	+
Lymphadenopathy	+	-	+	+
WBC (mm3)	6 200	750	3330	20 000
Haemoglobin (g/dl)	6.1	5.6	4.1	7.9
Platelets (mm^3)	80000	48000	29000	97000
ESR (mm/h)	12	20	24	35
ALT (IU/L)	358	270	307	119
AST (IU/L)	1478	154	462	406
LDH (IU/L)	5037	698	3155	634
Ferritin (ng/ml)	13440	17 000	5490	8690
Fibrinogen (mg/dl)	not clotting	181	154	115
Bone marrow-hemophagocytosis	-	+	+	+
Induction therapy	MMDM	IVIG, MMDM	MMDM	MMDM
Maintenance therapy	Methotrexate	CsA	CsA	CsA

U: Unremitting, WBC: white blood cell, ESR: erythrocyte sedimentation rate, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, MMDM: Modified megadose methylprednisolone, IVIG: intravenous immunoglobulin, CsA: Cyclosporine A

always show hemophagocytosis. Moreover, failure to reveal hemophagocytosis does not exclude the diagnosis of MAS. There was a decline of ESR and hepatosplenomegaly at physical examination in all of the cases at the onset of MAS. Lymphadenomegaly and hemaphagocytosis in bone marrow examination were present in 3 of 4 cases (Table I).

It is suggested that the pathogenesis of MAS may be closely related to familial hemophagocytic lymphohistiocytosis (FHLH), which is a group of rare autosomal recessive immune disorders resulting from homozygous deficiency in cytolytic pathway proteins (5). The imbalance between pro- and anti-inflammatory cytokines is one of the most accurate theories reflecting MAS pathology proposed recently (5). The results of recent pathogenetic studies point towards a key role of IFN-gama and IL-10 in the physiopathology of HLH/MAS and provide the rationale for the modulation of the axes of these cytokines to treat disease (3).

MAS is a life-threatening condition associated with high mortality rates. Therefore, early recognition and immediate therapeutic intervention to produce a rapid response are critical (7). There is no single treatment guideline for MAS which is widely approved. The mainstay of the therapy of MAS complicating SJIA is traditionally based on the parenterally administration of high doses of corticosteroids (3). We reported the use of MDMP with success as a treatment option in four patients with MAS. In the mid-90s, the use of CsA was considered, based on its proven benefit in the management of MAS (8). The administration of high-dose IVIG, cyclophosphamide, plasma-exchange and etoposide has provided conflicting results (5). The utility of biologic drugs in MAS treatment remains unclear (7).

Although high dose methylprednisolon therapy has been used for several hematologic, oncologic and immunologic disorders for years, MDMP is a treatment modality emerged in the recent years. It has been shown by Ozsoylu that MDMP is an effective treatment for chronic as well as acute idiopathic thrombocytopenia purpura (ITP), moreover for non-hematologic disorders (9,10). Three out of 4 patients were administered MDMP as induction therapy at the onset of MAS. Patient No. 3 was given high dose IVIG for two consecutive days. The fact that there was no response to IVIG, the therapy was switched to MDMP therapy on day 3. MDMP therapy led to complete clinical and laboratory remission of all cases.

The corticosteroids are membrane stabilizers and their effects of mechanisms are diverse. Corticosteroids inhibit the expression of cytokins such as IL-1 and IL-6 on the antigen presenting cell membrane surface. In addition, they suppress T cell proliferation by inhibiting IL-2 production. They also have an impact on nuclear factor kappa B, which plays a role in the synthesis of several cytokins. The side effects of high dose steroids in short treatment protocols are well tolerated (4,7,10). Ozsoylu, the pioneer of MDMP treatment modality, reported that the side effects of this modality was very subtle (9,10). None of our cases experienced MDMP side effects during the therapy and long-term follow up. It is reasonable that MDMP treatment modality is successful as it impedes increased cytokin production, which has a pivotal role in MAS pathogenesis. The amelioration of clinical picture of MAS without relapse during the follow up supports our opinion.

After induction therapy, oral CsA treatment was administered to 3 cases as maintenance therapy as stated in the literature. Cyclosporin, a commonly used immunosuppressive agent in various disorders, is a cyclic peptide, which prevents calcium-dependent IL-2 secretion (11,12).

In conclusion, MDMP is an effective, safe and cost-effective induction treatment modality for MAS, which is a fatal complication in children with sJIA, and maintenance therapy with immunosupressive agents can lead to a successful cure of MAS. But a larger sample size is needed to suggest the use of MDMP as an alternative therapy for MAS.

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