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Mini Review

A Review on Childhood-onset Systemic Lupus Erythematosus

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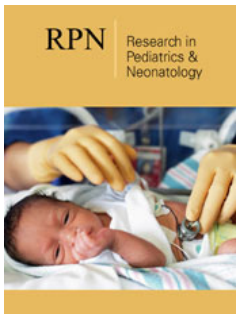

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Abstract

Systemic Lupus Erythematosus is a serious disease in children. Despite its shares many similarities with the adult patients, it has its distinct clinical features and management issues, including growth, puberty, fertility, psychosocial impact, treatment adherence and compliance issues that post extra difficulties and concerns for pediatricians who take care of these children. Increase the awareness of the disease and understand its complexity will enhance the care and support to this group of patients.

Introduction

Systemic Lupus Erythematosus is a prototype of an autoimmune disease affecting any organ in the body. It is a disease in which chronic inflammation, antibody production and complement immune-complex deposition cause tissue damage and organ failure. Childhood-onset system lupus erythematosus (CSLE) is fundamentally the same disease as the adult counterpart (ASLE); however, they differ in several aspects, including the severity of the disease and long-term prognosis.

Epidemiology

Ten to twenty per cent of all SLE patients developed the disease during childhood [1]. The peak age of childhood presentation is 12-13 years. It is rare before five years old. Worldwide the prevalence is around 1.9-25.7 per 100,000 children, and the incidence varies between 0.36-2.5 per 100,000 children-years [2]. Asian, African, indigenous North American and Hispanic ancestry are more frequently affected than European ones.

Pathogenesis

The etiology of SLE remains unknown. Like many other autoimmune diseases, the interactions of genetic, immunologic and environmental factors play pivotal roles in the pathogenesis. With the advances in Genome-Wide Association Studies (GWAS), several common alleles which may increase the risk of lupus development were identified in adult patients. More than 30 genes causing a monogenic form of childhood-onset SLE were described. These genetic defects are rare. They mainly involved the complement systems, interferon pathway, and abnormal B cell development [3].

Clinical Presentation

The presentations of CSLE are diverse. Systemic features are common, including pyrexia of unknown origin with nonspecific symptoms like weight loss and fatigue. The typical malar rash may not be present at the initial presentation, and the dermatological features may be subtle. Hematologic disease, neuropsychiatric SLE (NPSLE), nephritis, seizures and lymphadenopathy are more common in CSLE than in ASLE [4,5]. Childhood-onset SLE tends to be more severe at presentation and more likely to involve the kidneys and central nervous system. They are more likely to have an abrupt onset with an aggressive clinical course

[6,7]. Hematologic abnormalities are common, including anemia, leucopenia, lymphopenia and thrombocytopenia. These patients may present as isolated immune-mediated thrombocytopenia (ITP) or autoimmune hemolytic anemia (AIHA) months to years before the disease evolves into flank lupus. Regularly monitoring the serological markers, complements, and other organ involvement helps reveal the ultimate diagnosis.

Lupus nephritis and NPSLE may be the first clinical presentations in CSLE without any musculocutaneous hint. Lupus nephritis is classified as its adult counterpart. The severe forms of Lupus nephritis, ISN/ RPS (2004) class III or IV, are common in renal histology and usually present clinically as nephrotic syndrome [8]. Recurrent relapse of lupus nephritis is one of the significant risk factors for progressive renal failure in lupus patients. Neuropsychiatric symptoms in CSLE are diverse and more challenging to diagnose. The prevalence of NPSLE may be underestimated as features like mood changes, headache, and cognitive impairment may be too subtle to diagnose and differentiate from the drug effect. It was estimated that around 10% of CSLE presented with non-classical manifestations, mainly affecting the pulmonary, gastrointestinal and cardiac systems. These presentations can be life-threatening. These patients may not fulfil the diagnostic criteria of ACR at its presentation, and appropriate treatment may be delayed if clinicians fail to be aware of the diagnosis [9].

Diagnosis

There are three diagnostic criteria for systemic lupus erythematosus. The first one was established by the American College of Rheumatology (ACR), which was last revised in 1997, followed by the Systemic Lupus International Collaborating Clinic (SLICC) group classification criteria which were published in 2012 and the most recent European League Against Rheumatism (EULAR) criteria established in 2019 for ASLE. These criteria help to make the diagnosis; however, in children, a single manifestation may predominate in the early course of the disease before additional features that met the diagnostic criteria were revealed. The SLICC criteria were validated for CSLE and has a higher sensitivity and lower specificity than the ACR criteria [10].

Treatment

Studies in CSLE were generally non-Randomized. Most recommendations were extrapolated from the results of clinical trials in the adult populations and consensus from experts. In general, corticosteroid is the mainstay of treatment. In severe disease, pulse methylprednisolone at 10-30mg/kg (maximum of 1000mg/dose) intravenous daily for 3-5 doses then, followed by oral prednisolone at 1-2mg/kg/day (maximum 60mg daily) according to the severity of organ involvement. An equivalent dose of alternative preparation of corticosteroids like dexamethasone, which has better oral absorption and CNS penetration than prednisolone can be considered in some patients. Some authors preferred to use weekly pulse methylprednisolone while keeping a medium-to-low dose oral prednisolone at 10-20mg daily during the acute phase [11,12] as pulse methylprednisolone, but not the usual-dose prednisolone was shown to eliminate the interferon-alpha gene expression signature in SLE [13]. However, it is uncertain whether this practice will improve patient outcomes. There is no absolute rule on steroid tapering. Based on clinical improvement, one can generally reduce 10-20% of the dose in 1-2 weekly intervals. Steroid complications are well-known. The cushingoid appearance and striae are significant concerns to teenage girls.

Cyclophosphamide, given either as an infusion or oral form, has been used as adjuvant therapy in severe lupus for decades. Before the NIH IV cyclophosphamide protocol, oral cyclophosphamide at 2-3mg/kg (maximum 100mg) daily for 12 weeks was a common regime for treating lupus nephritis in children [8]. The NIH infusion protocol using a high dose at 500mg-1000mg/m2 monthly for six doses as induction [11,12] has its advantage in providing better hydration. It allows the use of Mesna to minimize cyclophosphamide-induced haemorrhage cystitis. The infusion route may help to ensure drug compliance. In the recent decade, the Euro-Lupus Nephritis trial using a lower standard dose of cyclophosphamide at 500mg infusion once every two weeks for six doses showed equal effectiveness and less serious complication [14]. Gonad toxicity of cyclophosphamide is a major concern in young patients. GnRH analogue, like triptorelin, can be given before or after the dose of IV cyclophosphamide as an ovarian protection agent [15]. Sperm cryopreservation for future assisted reproductive technologies in post-pubertal males could be considered before cyclophosphamide therapy. However, in life or organ-threatening scenarios, the window for intervention is narrow.

Mycophenolic acid (MPA), a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), is an alternative to cyclophosphamide to treat moderate to severe lupus disease in pediatrics. It is a favorable option when there are concerns about future malignancies, fertility and other severe complications of cyclophosphamide. Studies in adults showed that Mycophenolate Mofetil (MMF) showed a non-inferior efficacy compared with cyclophosphamide in controlling severe lupus nephritis [16]. MMF is usually given at a dose of 600mg/m2 per oral twice daily, and the usual dose is not to exceed 1gm/dose in most Asian patients [11,12,17]. Side effects include gastrointestinal symptoms, cytopenia, hypogammaglobulinemia, opportunistic infection and teratogenicity. Mycophenolate sodium is the enteric-coated salt form of MPA and may have fewer gastrointestinal side effects. Clinicians have to be aware of the dosage difference between these two preparations. Most active lupus patients are female at reproductive ages, so advice on contraception and possible teratogenicity of MPA should be provided. Rituximab (RTX) is an anti-CD 20 monoclonal antibody targeting B-cells but not plasma cells. It is licensed for adult rheumatoid arthritis, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Despite that, it is commonly used as rescue therapy in patients resistant to usual treatment. A recent systemic review on the efficacy and safety of Rituximab in Pediatric SLE showed that most literature data available are reports

on case series [18]. There was acceptable evidence suggesting that Rituximab may improve the renal, neuropsychiatric and hematological disease of CSLE and had a steroid-sparing effect. The overall safety profile was acceptable in children [18]. The doses and duration of Rituximab varied. The most common regime was RTX at 375mg/m2/ week. The number of doses per course varied from 2 to 4, and the number of courses ranged from 1 to 12. RTX at 750 mg/m2 (maximum 1gm) given as two doses 14 days apart is also a common practice. Rituximab administration may result in severe infusion reactions and hepatitis B reactivation; hence a careful selection of patients, screening of hepatitis status, and IGRA for latent tuberculosis should be performed before its use [18].

After the initial induction phase, either azathioprine at 2-3/kg (maximum 150mg) or MMF is the drug of choice for maintenance therapy. Given the long-term gonad toxicity of cyclophosphamide, the original NIH protocol of intravenous cyclophosphamide every three months is seldom used nowadays. Azathioprine is a purine antimetabolite. It is metabolized to 6-mercaptopurine (6-MP) after ingestion. Both Thiopurine Methyltransferase (TMPT) and Nudix Hydrolase (NUDT15) are enzymes that metabolize azathioprine. Genotyping of TMPT and NUDT 15 helps predict the potential toxicity of thiopurine drugs and allows dose adjustment individually. Short-term outcomes may improve with intensive immunosuppressive agents. The long-term prognosis is affected by a number of disease relapses. Nephritic relapses can occur in 35% of initial responder and is a significant factor in developing the end-stage renal disease in lupus patients. Combination of therapy with calcineurin inhibitors (CNI) like Cyclosporine A or Tacrolimus with MPA are options to induce remission and to prevent frequent relapses. However, the long-term nephrotoxicity of CNI is another concern [19].

Belimumab, a fully humanized monoclonal antibody which inhabits B Lymphocytes stimulator (BLYS), was approved by the FDA and European Medicines Agency for treating SLE in adults with moderate disease activity. The FDA recently approved its use in CSLE between 5-17 years. A recent phase 2 randomized placebo-controlled double-blinded study evaluating the safety of Belimumab at 10mg/kg showed that Belimumab had a benefit-risk profile in CSLE consistent with adult studies [20]. However, patients with active and severe lupus nephritis, CNS lupus or using systemic prednisolone >1.5mg/kg/day were excluded from this study. More data is coming out to support the efficacy and safety of Belimumab in adults and children [21]. As in the adult patient, hydroxychloroquine at a 5mg/kg dose with regular ophthalmological assessment is also recommended for children with SLE. Other adjuvant therapies, including oral aspirin to avoid thrombotic phenomenon, calcium and vitamin D supplements to prevent osteoporosis, appropriate vaccinations, and advice on contraception, are all essential management issues.

Long term prognosis

Childhood-onset SLE tends to be more aggressive. The risk of organ damage is related to the number of relapses, organ involvement and the side effect of drugs, especially steroid-induced cataract, avascular necrosis of hips and growth failure [22]. Depression can be a manifestation of active NPSLE, the side effect of medications or the impact of lupus itself [23]. Negative emotions can affect patients' daily activity, school performances, peer relationships and treatment adherence. They should not be overlooked in long-term management.

Conclusion

Childhood-onset SLE is a severe disease. Although there are many similarities to adult patients, it has many different features in its clinical presentation, treatment and prognosis in children.

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