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SLE IN PEDIATRIC POPULATION

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Abstract

Background: *Systemic Lupus Erythematosus (SLE) is a common chronic autoimmune disorder that can attack almost all body organs leading to the development of significant complications that can be serious and fatal. The incidence of childhood-onset systemic lupus erythematosus in the United State is as low as 3 per 1,000,000 children-years with a prevalence that is less than 9 per 100,000 children. Usually, childhood systemic lupus erythematosus presents acutely with more severe clinical manifestations when compared to adulthood systemic lupus erythematosus.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: Systemic lupus erythematosus, manifestation of childhood SLE, investigation of childhood SLE, management of childhood SLE, complication of SLE, differences between adult and pediatric SLE*

Aim: *In this review, we aim to study how SLE manifests differently in pediatric population when compared to adults, the laboratory work-up for SLE, and its management.*

Conclusion: *Childhood systemic lupus erythematosus is a chronic condition that can be associated with severe outcomes due to the involvement of multiple systems in the body. Childhood systemic lupus erythematosus can be more severe than adulthood disease, with more activity of the disease, and earlier organs involvement. The most commonly found antibody is anti-nuclear antibody. Anti-dsDNA antibodies and anti-smith antibodies have higher specificity for the disease and should thus be tested before making a diagnosis. Treatment of systemic lupus in children depends mainly on corticosteroids along with immunosuppressants. The most important complication is the development of secondary infections which can be severe due to the presence of underlying immunosuppression.*

Keywords: *Systemic lupus erythematosus, pediatric auto immune disorders, pediatric rheumatology*

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INTRODUCTION:

Systemic Lupus Erythematosus (SLE) is a common chronic autoimmune disorder that can attack almost all body organs leading to the development of significant complications that can be serious and fatal. Many physicians call systemic lupus erythematosus as 'the great mimicker' due to the presence of mutual characteristics with many other autoimmune disorders. Similarity of lupus to other diseases is even more obvious in patients who do not develop the classic malar lupus rash, making the diagnosis of lupus even more challenging. Systemic lupus erythematosus mainly affects females in the child-bearing ages, with rare cases occurring in younger ages. Actually, the incidence of childhood-onset systemic lupus erythematosus (cSLE) in the United State is as low as 3 per 1,000,000 children-years with a prevalence that is less than 9 per 100,000 children [1].

When studying other populations like blacks, Asians and pacific islanders, Hispanics, and Indian Americans, higher incidence and prevalence of childhood systemic lupus erythematosus can be observed. Studies on childhood systemic lupus found that the median age of the occurrence of the disease in children is between eleven and twelve years, with extremely rare cases occurring in children younger than five years. Similar to the disease in adults, childhood systemic lupus mainly affects females with less than 20% of cases being males [2].

Usually, childhood systemic lupus erythematosus presents acutely with more severe clinical manifestations when compared to adulthood systemic lupus erythematosus. Most previous studies have concluded that involvement of renal, hematological, and neurological systems is more common and rapid in children with systemic lupus erythematosus than adults with the disease [1].

METHODOLOGY:

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: Systemic lupus erythematosus, manifestation of childhood SLE, investigation of childhood SLE, management of childhood SLE, complication of SLE, differences between adult and pediatric SLE

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

MANIFESTATION OF CSLE:

Childhood and adulthood systemic lupus erythematosus can have many similarities in clinical manifestations, with childhood disease being more common to cause lymphadenopathy and fever than adulthood disease. On the other hand, adults with systemic lupus are more likely to present with arthritis than children. Developing lupus before or after puberty can also lead to different manifestations and progression of the disease. For example, hemolytic anemia and kidney disease are more likely to occur in children who developed lupus before puberty, while cutaneous symptoms and musculoskeletal involvement are more likely to occur early in children who developed lupus following puberty [1].

Similar to adults with lupus, up to 35% of children or adolescents who develop systemic lupus erythematosus will present with early hematological conditions like anemia, lymphopenia, and/or thrombocytopenia. Leukopenia is also a common presentation with childhood systemic lupus erythematosus that can occur in up to 35% of patients (while only occur in 18% of adults with lupus). Similar to adulthood disease, about 20% of children with systemic lupus erythematosus will have positive anti-smith antibodies, anti-La antibodies, anti-Ro antibodies, and/or anti-ribonucleoprotein antibodies [3].

MUCOCUTANEOUS AND MUSCULOSKELETAL MANIFESTATIONS:

Generally, children with systemic lupus erythematosus are significantly more likely to develop rashes than adults with the disease, including the classical malar rash of lupus. On the other hand, the risk of developing painful arthritis (usually non-erosive) is similar among both adults and children with systemic lupus. Many children with systemic lupus develop overt arthritis, while adults have a higher risk of developing myalgias and arthralgias. Additionally, up to 40% of patients with childhood systemic lupus erythematosus will develop osteopenia (with a z-score that is less than -1.5), leading to the development of pathological fractures

in about 10% of cases. These rates of osteopenia and fractures are generally less than adulthood systemic lupus erythematosus, but are somewhat similar to postmenopausal systemic lupus erythematosus, where about 40% develop osteopenia and 5% develop osteoporosis [4].

CENTRAL NERVOUS SYSTEM INVOLVEMENT:

Involvement of the central nervous system is relatively common in patients with systemic lupus erythematosus. However, its involvement is usually challenging to be detected especially within the early course of the disease due to the absence of specific investigations (laboratory of imaging) that can early detect central nervous system involvement. Involvement of the central venous system in childhood systemic lupus erythematosus is clinically similar to adulthood disease. However, incidence of neuropsychiatric involvement is more common in children than adults, with up to 70% of patients with childhood systemic lupus erythematosus developing neuropsychiatric symptoms within the first year following diagnosis versus less than 30% of adults developing similar symptoms at that early course of the disease [5].

The most common psychiatric disorder in patients with childhood systemic lupus erythematosus is major depressive disorder. Other clinical manifestations of neuropsychiatric involvement in childhood lupus include seizures, pseudotumor cerebri, and transient ischemic attacks, which have similar incidence and prevalence in both children and adults with systemic lupus. Some studies have also found that about one fourth of children with lupus that involved the central nervous system can develop cerebrovascular events, which is considered a relatively high rate. Additionally, about one fifth of patients with childhood lupus involving the central nervous system can present with psychosis manifesting by visual hallucinations. In fact, encephalopathy, psychosis, and chorea are generally more common in childhood systemic lupus erythematosus than adulthood systemic lupus erythematosus [6].

The development of a cerebral venous thrombosis has been found in about one fourth of children with systemic lupus, and usually manifests as headaches in a patient with positive lupus anticoagulant. Moreover, up to 60% of patients with childhood systemic lupus erythematosus can develop cognitive dysfunctions [6].

In summary, the involvement of the central nervous system in patients with childhood systemic lupus erythematosus is not uncommon and can present with several clinical manifestations. Different studies have reported varying prevalence and incidence, which may be attributed to the differences in study designs and definitions of the diseases [7].

CARDIOPULMONARY MANIFESTATION:

The most common cardiac complication of systemic lupus erythematosus is pericarditis which can be present in up to 33% of patients, regardless of their age. Adults with systemic lupus can also develop acute coronary syndrome and myocardial ischemia. However, this is extremely rare in children with lupus [7].

On the other hand, pulmonary complications can develop in more than half patients with childhood systemic lupus erythematosus. One of the common pulmonary complications in both children and adults with systemic lupus erythematosus us the development of a restrictive lung disease that affects the diffusion capacity of the lungs. One rare pulmonary complication is ‘shrinking lung syndrome’ that is a syndrome of paralysis of the diaphragm together with the presence of a restrictive pulmonary disease. Shrinking lung syndrome is considered extremely rare with only ten cases reported in the literature among patients with childhood systemic lupus erythematosus, and 150 cases in adulthood systemic lupus erythematosus. The development of a pulmonary hemorrhage in either a child or an adult with lupus is associated with significantly high mortality [8].

HEMATOLOGICAL MANIFESTATION:

The presence of chronic systemic lupus is highly correlated with the development of anemia in both childhood and adulthood diseases. Incidence of anemia increases in younger onset of the disease, with up to 77% infants with lupus versus 35% of children with lupus. Generally, childhood lupus-associated anemia is mild or moderate and does no lead to severe manifestations. In most cases, it starts as a normocytic normochromic anemia that can later progress to a microcytic hypochromic anemia as the disease progresses [2].

Leukopenia is also considered to be relatively common in both childhood and adulthood systemic lupus erythematosus, affecting up to 75% of patients at least once throughout the course of their condition. However, infants who develop systemic lupus have relatively lower risk of developing leukopenia than

children with the disease [9].

On the other hand, neutropenia is relatively rare in adulthood systemic lupus erythematosus, but is considered more common in children with the disease affecting up to 15% of patients. The presence of neutropenia in a child or an adult with lupus has been found to increase the risk of developing thrombocytopenia or central nervous system involvement [10].

Lupus-associated thrombocytopenia is generally more prevalent among children with lupus than adults. It has been found to be present in about 65% of children with lupus, while only present in 25% of adults with the disease. In most cases with lupus-associated thrombocytopenia, antiphospholipid antibodies and antiplatelet antibodies are found positive in serum [9].

ENDOCRINAL MANIFESTATION:

Endocrinal manifestations following a diagnosis of systemic lupus erythematosus are common in both children and adults with the disease. A previous study on children with systemic lupus has found that up to 85% can develop dyslipidemia [11]. Another study has found that abnormal lipid profiles can be present in most children and adults with systemic lupus erythematosus even before the initiation of their corticosteroids therapy. Moreover, both childhood and adulthood systemic lupus erythematosus lead to the formation of smaller particles of LDL which have more atherogenicity. Metabolic syndrome and insulin insensitivity have also been observed to be higher in patients with lupus (regardless of age) when compared to the general population. The increased risk of developing diabetes mellitus among children with lupus is still debatable. Thyroid conditions can also be associated with lupus. A previous study has found that up to 20% of children and adults who have systemic lupus can develop an autoimmune thyroid condition [12].

Childhood systemic lupus erythematosus has been found to cause an average one-year delay in menarche in female patients. This delay in menarche could be due the disease itself or a side effect of corticosteroids treatment. Amenorrhea can develop in some patients and has been found in a study in about 12% of adolescent females with the disease. Amenorrhea is generally correlated with the duration and severity of the disease. The use of IV cyclophosphamide treatment in childhood systemic lupus erythematosus can lead to the development of ovarian failure. However, rates of ovarian failure are generally less common in childhood disease than adulthood disease. Female children with systemic lupus erythematosus have been found to have a 10% risk of developing premature ovarian failure. However, this number is not accurate as it was based on a single small study [13].

Similar to adulthood systemic lupus erythematosus, childhood disease can lead to abnormalities in the semen, the testes, and the levels of gonadotropic hormone. These abnormalities even increase in patients who receive cyclophosphamide therapy after puberty. Abnormalities in the functions of Sertoli cells have been found to occur in male children with systemic lupus erythematosus [14].

Immunological Manifestation

Similar to adulthood systemic lupus erythematosus, childhood disease is also marked by the presence of circulating anti-nuclear antibodies, which are present in all patients. However, the presence of circulating anti-nuclear antibodies is not considered specific for the disease up to half children with positive anti-nuclear antibodies were found to have other rheumatological diseases liked musculoskeletal pain syndrome, rather than systemic lupus erythematosus. A previous retrospective cohort that included 110 children with positive anti-nuclear antibodies and followed them for four years found that ten of them developed childhood systemic lupus erythematosus during the study period [15].

Anti-dsDNA antibodies, on the other hand, are present in about 90% of infants with systemic lupus erythematosus. Similar to adults, levels of anti-dsDNA antibodies can be used to observe the progression of the disease in children with lupus. In addition, patients with childhood systemic lupus erythematosus are more likely to have positive anti-ribosomal P antibodies and anti-histone antibodies than adults with lupus. Previous reports have found that up to 42% of children with lupus have positive circulating anti-ribosomal P antibodies while only 11% of adults have positive circulating anti-ribosomal P antibodies [15].

Other antibodies that are usually found positive in patients with childhood systemic lupus erythematosus include anti-Smith antibodies (present in about half of the patients), anti-ribonucleoprotein antibodies, (present in about 35% of the patients), anti-Ro/SSA and anti-La/SSB antibodies (which are present in about 15% of patients [9].

Rheumatoid factor can be also positive in patients with childhood systemic lupus erythematosus. Previous studies have found that up to 5% of patients

have a positive rheumatoid factor at the time of diagnosis, and 54% will develop positive results over the course of their disease, which is considered higher than the number of patients with Juvenile Idiopathic arthritis with positive rheumatoid factor [9].

Laboratory Findings

When children have clinical manifestations that lead to suspicion of systemic lupus erythematosus, laboratory investigations are generally important to confirm or exclude the presence of the disease. The most important finding in patients with systemic lupus erythematosus is the presence of multiple positive antibodies in the serum. As we mentioned earlier, Anti-nuclear is the most common antibody in patients with lupus. However, its not specific for lupus (with a specificity that is less than 36%), making it necessary to investigate for the presence of other antibodies, like anti double-stranded DNA antibodies and extractable nuclear antigens, before making a diagnosis. Investigations for other antibodies are essential as up to 10% of healthy children will have positive circulating anti-nuclear antibodies. On the contrary, the specificity of anti-dsDNA antibodies is relatively high. The best specificity for childhood systemic lupus erythematosus is with anti-smith antibodies. However, they have considerably low sensitivity [16].

Involvement of kidneys can generally be followed with levels of anti-dsDNA antibodies and anti-Smith antibodies. Females with systemic lupus erythematosus who test positive for circulating anti-Ro antibodies have been found to have a higher risk of having a child with neonatal lupus erythematosus, which can cause congenital heart block. Therefore, these females must be educated about their risks before any pregnancy [16].

Apart from positive antibodies, laboratory findings in patients with systemic lupus erythematosus can include decreased C3 complement levels, decreased C4 complement levels, anemia, leukopenia, thrombocytopenia, neutropenia, along with increased ESR (with normal C-RP) [16].

Complications of SLE

Most patients with systemic lupus erythematosus are immunosuppressed for two main reasons [17]:

1. The disease itself affects and weakens the immune system. It also leads to decreased circulating complements levels, leukopenia, and neutropenia.
2. The long-term of high doses of corticosteroids along with other immunosuppressive pharmacological agents.

Therefore, it is extremely common for these patients to develop secondary infections, making infections one of the main causes of morbidity and mortality in these patients.

Most lupus-associated infections are caused by bacterial organisms, which will lead to an elevation of C-RP, that is not usually present in lupus patients who do not have infections. Patients with systemic lupus erythematosus usually require IV antimicrobials treatment. Most lupus patients have impaired immunity especially against capsulated organism like meningococcus, pneumococcus, salmonella, and hemophilus influenza type B [17].

Viral infections, on the other hand, can cause similar clinical manifestations to those observed in a lupus flare. Levels of C-RP will be rarely elevated. CMV infection in lupus can lead to the development of a severe, and potentially fatal, systemic disease. Moreover, herpes zoster infections can occur in lupus patients, especially those who receive corticosteroids treatment, even if they had previously received varicella vaccination. Opportunistic infections like pneumocystis jiroveci can develop in lupus patients who are receiving cyclophosphamide for immunosuppression [17].

MANAGEMENT:

The management and treatment of children and adolescents with systemic lupus erythematosus usually requires a coordination between a rheumatologist, a primary health care provider, a nephrologist (for renal involvement), a psychiatrist, and a physical therapist. Aggressive pharmacological treatment is usually needed due to the severity of the disease. Most pharmacological agents used for the treatment of lupus have significant adverse events. Therefore, it is important to always balance the benefits against the harms before initiating any new agent [18].

Mild cases of lupus can be usually managed with hydroxychloroquine or chloroquine. The presence of musculoskeletal symptoms can be managed with nonsteroidal anti-inflammatory drugs. Corticosteroids (oral or intravenous) remain to be among the most important drugs in the treatment of systemic lupus. Studies suggest that almost all lupus patients will receive corticosteroids at least once during the course

of their disease [19].

The use of immunosuppressants is also essential for the treatment of systemic lupus erythematosus, mainly to decrease the use of steroids. In lupus patients with arthritis, methotrexate and azathioprine can be used. azathioprine is also effective for cases that have vasculitis or serositis. In cases with glomerulonephritis, Mycophenolate mofetil can be used to induce remission. Cyclophosphamide is generally kept for severe cases due to its significant adverse events like infertility, malignancies, and infections. It can be used in cases of severe central nervous system involvement or refractory renal involvement [20].

CONCLUSION:

Childhood systemic lupus erythematosus is a chronic condition that can be associated with severe outcomes due to the involvement of multiple systems in the body. Childhood systemic lupus erythematosus can be more severe than adulthood disease, with more activity of the disease, and earlier organs involvement. Lupus in children have many similarities to lupus in adults regarding clinical manifestations, with the presence of some differences. The most commonly found antibody is anti-nuclear antibody, which is, however, not specific for the disease and can be present in many healthy children. Anti-dsDNA antibodies and anti-smith antibodies have higher specificity for the disease and should thus be tested before making a diagnosis. treatment of systemic lupus in children depends mainly on corticosteroids along with immunosuppressants. The most important complication is the development of secondary infections which can be severe due to the presence of underlying immunosuppression.

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