Collagen Vascular Diseases in Pediatric Age Group

Dr. SmithaPrabhu
Associate Professor
Kasturba Medical College, Manipal
Manipal University

Abstract:
Collagen Vascular Diseases are a relatively uncommon subset of chronic progressive systemic disorders which occur due to auto antibody production against various tissue and organs. There are several diseases in this subset, the common ones being systemic lupus erythematosus, progressive systemic sclerosis, dermatomyositis, juvenile rheumatoid arthritis and Sjogren’s syndrome. These are relatively rare in children, as compared to adults, but if present lead to long term morbidity and sequelae. Here I discuss the usually encountered collagen vascular diseases of childhood, with an emphasis on the advances in this field.

Key Words:
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Pediatric
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Introduction:
Collagen Vascular diseases are a diverse group of multisystem diseases which share the common feature of inflammation and damage of blood vessel and other tissue due to the production of antibodies directed against various cells and tissue. Skin and joints bear the brunt of the disease. These mainly manifest in adulthood, though childhood manifestation is not very uncommon.

The common collagen vascular diseases include Systemic Lupus Erythematosus (SLE), Dermatomyositis(DMy), Progressive Systemic Sclerosis (PSS), Sjogren’s syndrome and Rheumatoid arthritis. Mixed Connective Tissue disease and Undifferentiated Connective Tissue disease are also seen.

In the pediatric age group, SLE, Dermatomyositis, Neonatal LE, Scleroderma and Juvenile Rheumatoid Arthritis (JRA) predominate with an incidence of 150-200 children/ million.

My discussion would be mainly limited to the above four.

Pathogenesis:
The central mechanism is development of autoantibodies towards specific or all tissue and body organs. Recently, it has been seen that the formation of autoantigens can be precipitated in susceptible cases by T cell recognition of specific infectious agents that have genetic similarity to human proteins. This is called ‘molecular mimicry’. The course of the disease may vary from person to person depending upon their genetic polymorphisms and MHC Cl linkage.

Ultraviolet light is well known to exacerbate CVD, due to induction of cytokine release which trigger disease expression. UVB induces antigen translocation in cell membrane and induces autoantibody formation.

Lupus Erythematosus (LE):
This is seen in three forms depending upon the severity, systemic involvement and chronicity. The most chronic form with least systemic involvement is Discoid Lupus Erythematosus (DLE), sub acute chronic lupus erythematosus (SCLE) and the acute severe form with systemic involvement, systemic lupus erythematosus(SLE). In children, SLE predominates and DLE is rarely seen. There is a 4th subset called as neonatal lupus erythematosus in newborns born out of mothers with collagen vascular disease having Ro positive serology.

SLE is seen in 0.36-4 child/100000. Females outnumber males at a ratio of 2:4:1, which considerably lower than in adults. In more than 80% children, the initial presentation includes cutaneous symptoms like malar rash, arthralgia, malaise and presence of antibodies.

Immune markers in children: more than 90% have ANA positivity, whereas specific antigens are seen less frequently, i.e., anti-Smith(30%), anti ds-DNA(25%).

Rising anti ds-DNA titres and fall in C4 levels are sensitive markers of early disease activity and may be used in monitoring the disease progression.
The other common systems to be involved in children are renal (64-80%) and haematological (76-90%). Chronic renal failure is frequently seen and is associated with persistent hypertension, anaemia, granular casts and crystals in urine and elevated serum creatinine.

DLE is very rare in children. Although SCLE is also rare in children, unlike adults, more than 60% have a positive ANA and may progress to SLE. SCLE may also be associated with anti Ro antibody and C2,4 deficiencies. Bullous LE is very rare in children.

Neonatal Lupus is seen at a frequency of 1/2500-25000 live births. These children are born to mothers who tend to be HLA-DR3 positive and have anti-Ro, anti-La or anti-U1RNP antibodies. They are generally asymptomatic except for cutaneous rash which later subsides, but many may go on to develop SLE or Sjogrens disease in future. Congenital heart block is a dread complication in children with anti-Ro antibodies only, and has a mortality rate of 15-35%. Cardiac involvement begins in utero with atrioventricular inflammation and fibrosis, which begins during the tenth week of gestation. 1-10% of SLE women give birth to a child with neonatal LE, and 10-40% of these may give birth to a second child with the same. Hence ultrasound should be done at 24th week of gestation in all suspected cases, and if cardiac involvement is detected, maternal steroid therapy should be started.

Hepatic and haematological involvement may occur in 10-15% of neonatal LE cases.

**Juvenile Dermatomyositis:**

This mainly involves the skin and muscle though rarely cardiac and pulmonary systems are also affected. There is a characteristic heliotrope rash with or without periorbital oedema, symmetrical proximal muscle weakness with elevated muscle enzymes, and electromyogram and histopathology of muscles demonstrating changes consistent with inflammatory myopathy. Cutaneous rash is seen in more than 75% of children and is characterized by the heliotrope rash which is a periorbital violaceous induration, along with lichenoid erythematous papules over knuckles and dorsae, periungual telangiectasias and poikilodermia of sunexposed skin. Other changes include alopecia, periorbital oedema, vasculitis, Raynaud’s phenomenon, palmoplantokeratoderma. Calcinosis is more common in children than in adults. Nail fold capillary loop alterations and tortuosity and vessel dropout are sensitive indicators of disease activity. Current advances in pathogenesis state that there is molecular mimicry of muscle antigens with infectious agents like streptococci and coxsackie viruses.

Antibody profile includes ANA in more than 60%, anti Mi-2 muscle antibody in 10% and anti Jo-1 antibody in 0.5%, which is associated with pulmonary fibrosis. Other helpful markers include elevation of von Willebrand factor antigen in 50%, neopterin, a macrophage activation marker in 60% and increase in B cell counts in more than 80%.

As it is a relatively relentless disease, aggressive treatment is advocated with combination steroids, physical therapy, IVIG, hydroxychloroquine, methotrexate and cyclosporine, especially in resistant cases. Photoprotection is a must to prevent disease flares.

**Scleroderma:**

Scleroderma is a condition where there is thickness and restricted flexibility of skin, GIT, pulmonary tract etc. Pathogenesis involves increased production of TGF beta causing sclerosis.

Scleroderma can be localized or generalized. Localized scleroderma is otherwise known as morphea and generalized involvement usually occurs in systemic sclerosis, which can be progressive systemic sclerosis or limited systemic sclerosis. 7% of scleroderma patients have the disease onset in childhood. The disease is similar to that of adults with scleroderma, Raynaud’s syndrome, dysphagia and renal involvement being more common. Nail fold capillary changes, digital pits, sclerodactyly, calcinosis and telangiectasia may also be seen, especially in the limited variant, CREST syndrome (Calcinosis, Raynaud’s, esophageal dysmotility, sclerosis and telangiectasia).
Pulmonary disease is common in children and should be aggressively treated. There is a case report of neonatal scleroderma with pulmonary hypertension.

Among localized scleroderma variants, linear and plaque type occur more frequently. Despite ANA positivity, localized scleroderma progressing to systemic scleroderma is rare in children (less than 1%).

Treatment involves systemic steroids, calcium channel blockers and vasodilators depending on the symptomatology. Methotrexate and D penicillamine have also been tried in severe cases. Calcipotriene topically helps in localized scleroderma and may be used systemically in linear scleroderma.

**Juvenile Rheumatoid Arthritis (Still’s disease):**

This is the most common rheumatic disorder of childhood and is seen in children less than 16. There is persistent arthritis of more than 6 weeks which may be pauciarticular (involving 4 or less joints), polyarticular (5 or more joint involvement), or with systemic involvement (fever, lymphadenopathy, hepatosplenomegaly, evanescent skin rash, amyloidosis, anemia, pericarditis). These may be either Rheumatoid Factor (RF) positive or RF negative. RF positive patients have a more chronic course.

The etiology is still unknown with genetics, cellular immunity, humeral immunity leading to autoantibody formation and infectious agents being incriminated.

First-line therapy continues to be the use of NSAIDS, with methotrexate being second line therapy, in patients who do not respond within 3 months. If one NSAID does not work, either its dosage is to be increased to the maximum or changed to another. Combination of NSAIDS can lead to increased toxicity without increased efficacy.

D-penicillamine (10 mg/kg/d) and hydroxychloroquine (5 mg/kg/d) were previously used, but trials proved them to be ineffective. Chrysotherapy was the first effective second-line treatment earlier, but now Methotrexate is becoming the drug of choice for second-line therapy of JRA. It is relatively safe at a dosage of 10 mg/m² /wk. Sulfasalazine, IVIG have also been successfully tried. Systemic steroids are tried only in severe cases of pericarditis, iridocyclitis and refractory anemia.

**Sjogren’s disease:**

This is relatively rare, compared to the above conditions. The symptom complex consists of xerostomia which leads to difficulty in swallowing and speech, dry eyes and nasal cavity. Primary Sjogren’s arises de novo whereas secondary Sjogren’s is seen on a background of other autoimmune diseases like JRA, SLE, MCTD etc.

There is no association of childhood Sjogren’s syndrome with lymphomas, unlike in the adults. Recurrent parotitis misdiagnosed as mumps is very common in childhood cases.

Secretory sialography, biopsy of salivary glands, a positive Schirmer test (there is less than 5 mm of wetness of a strip of filter paper placed in the conjunctival fold for over 5 minutes) or positive Saxon test (the oral equivalent of Schirmer test) may help in diagnosis of Sjogren’s disease.

RF, ANA, SS-A (60-100%), SS-B antibodies may be positive. A child with positive ANA shows extraglandular manifestations (leukopenia, fever, arthralgia, renal complications, CNS involvement, uveitis, organomegaly, lymphoma, and monoclonal gammopathy). Cutaneous findings include erythema nodosum, annular erythema, alopecia, dryness and scaling of skin with decreased sweating.

Management of Sjogren's is conservative with artificial tears, maintenance of oral hygiene with special toothpastes and artificial saliva. Renal and CNS complications may be treated with low dosage steroids, immunosuppressives, or a combination.

**Chronic sequelae in children:**

Limitation of functions, osteopenia and nutritional deficiencies leading to growth retardation, chronic pain and disability and psychological distress are chronic sequelae in children, well known to affect their studies and social and occupational prospects. These have to be addressed at the earliest.

**Care to be taken in the pediatric age group:**
Regular monitoring of haematological parameters, growth chart, weight gain, bone mineral density, visual acuity, liver and renal function tests is a must in children with long term steroids and other immunosuppressants. Pain in hip or knee should prompt investigations to rule out fracture bones or avascular necrosis. Psychosocial support and counselling is essential for overall development of the child. Physiotherapy for optimal joint mobility and prevention of deformities is as important as medical treatment. Nutritional supplementation should ensure adequate growth of the child. Pulmonary function capacity should be periodically assessed in selected cases.

Recent Trends in Therapeutics:
Care of a child with collagen vascular disease needs an integrated approach addressing the disease as well as the chronic sequelae and psychosocial disabilities. From the 1950’s till recent, collagen vascular diseases were predominantly managed using systemic steroids in varying doses depending upon the severity of the condition. Now the trend is to combine various immunosuppressives including corticosteroids and biologicals, immunomodulators like intravenous immunoglobulins (IVIG) and anti-inflammatory drugs which has led to a better quality of life and increases the survival rate of the children. Better facilities for early detection of particular diseases has allowed for more early intervention, thus preventing long term sequelae. Photoprotection has become a crucial part of therapy as the deleterious effect of UV rays have become well known to induce auto antibodies and production of harmful cytokines. A need for aggressive nutritional intervention also has improved the overall long term prospects of such children. Advances in physiotherapy and psychological evaluation and methods to combat physical and psychological distress also has helped a lot. Future scopes include a better understanding of the minutiae of molecular pathogenesis of autoimmunity, development of genes and chemicals that help to fine-tune the immunity, thereby providing better control, or perhaps even amelioration of the diseases.

Oral prednisolone is still the first line of therapy. But children on prolonged high dose steroids should be monitored for infections, cataract, osteoporosis and aseptic necrosis of femoral head.

Combination with other immunosuppressants and immunomodulators like hydroxychloroquine, methotrexate, IVIG, cyclosporine etc. help in decreasing the steroid dose, as well as in steroid resistant cases. Severe renal disease may warrant the use of cyclophosphamide as well as hemodialysis.

Children with DLE and SCLE benefit from potent topical steroids or hydroxychloroquine, without resorting to systemic steroids, though severe SCLE warrants treatment similar to SLE.

Recombinant erythropoietin is a viable option in refractory anemia of chronic disease.

Adjuant physical and occupational therapy, pain management, behavioral therapy (biofeedback, relaxation) and looking after the psychosocial well-being is equally important.

Summary:
Collagen Vascular Diseases of childhood, though rare, are a challenging subset of conditions to the paediatrician as well as dermatologist in view of the chronic nature, possibility of life long sequelae like growth retardation, psychosocial inhibitions, restrictions posed in sexual and social life and a limited choice of occupation. These children should be managed comprehensively to the best of the physician’s ability, with a holistic approach so as to maximise the life expectancy and quality of life.

References:

Author Biography:
DR. SMITHA PRABHU S
MBBS, MD, DVD
ASSOCIATE PROFESSOR
Dr. Smitha Prabhu is working as an associate professor in the Department of Dermatology, Kasturba Medical College, Manipal University since 2003. Her main fields of interest are clinical dermatology, psychodermatology and dermatopathology. She is the recipient of south zone best student scholarship issued by Fulford in 2001, as well as travel award grantee in Int. Conference on Contact and Occupational Dermatology, Kyoto, Japan in 2009. She has co-authored chapters in National Dermatology, Trichology, and Pigmentary disorder Text books and has been co-editor for Psycho dermatology Issue in Indian Journal of Dermatology. She has published 65 articles in national and international Dermatology journals, is a reviewer for articles in various international and national journals and is a contributor of articles for local newspapers and channels.

Areas of interest: clinical dermatology, dermatopathology, psychodermatology