The Spectrum of Vasculitis in Pediatric Rheumatic Disease

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Introduction and Overview

Although it was recognized as early as 1545 that children had joint disease, it was not appreciated until the late 1700s that children could present with a range of musculoskeletal and connective tissue diseases. It took another 100 years to establish that children were not "little adults", and the field of Pediatric Rheumatology in the United States became "of age" in 1992, when the first Sub-speciality Credentialing Boards were established for this discipline. The pathophysiology of inflammation involving blood vessels is only partially described for some pediatric illnesses, and most publications have been directed toward identifying the clinical presentation of these diseases. This discussion will focus on the relationship of inflammation of blood vessels in selected types of pediatric rheumatic disease and review the symptoms and signs that result from this involvement as well as the impact of vasculitis in children on effectiveness of therapy.

One commonly used classification system for the vasculitic syndromes is based on the size of the primary vessel involved, often in conjunction with a description of the type of cellular response that predominates. For example, Takayasu Arteritis is an example of larger vessel disease in which the primary targets are large elastic arteries, while in Behçet's disease in children, intravascular thrombosis is present in which a venous>arterial location is seen. Kawasaki Disease is an example of involvement of medium sized arteries, while Henoch-Sch Henoch-Schönlein Purpura (HSP) serves as the most common example of leukoclastic vasculitis, in which capillaries and, rarely, arterioles are eroded by degenerating polymorphonuclear cells. In contrast, in juvenile dermatomyositis, mononuclear cells are the almost exclusively seen participating in occlusion of capillaries and arterioles. It is not yet known which factors determine the size of the vessels and/or specific target organ in children with vasculitic syndromes.

Potential Mechanisms of Vascular Damage in Pediatric Vasculitis

One general hypothesis for disease susceptibility centers about the response of the host to a possible infectious agent and/or environmental antigen. Viral infections that have been associated with vasculitis in children include Hepatitis A & B, Cytomegalovirus, Parvovirus, Herpes Zoster, HIV and human T-cell leukemia/lymphoma Virus 1 or 3. In this scenario, the likelihood of contracting a particular vasculitic disease, is enhanced if the child has a specific genetic background. Data has accumulated for some of the pediatric diseases, such as juvenile dermatomyositis, which will be discussed later, and there are clues that genetic susceptibility may play a role in some of the other conditions as well. The humoral response can be either a specific increase in one of the immunoglobulins (IgM or IgA, followed by IgG) or as in systemic lupus, a polyclonal B cell activation, in which all of the immunoglobulins are elevated. The primary mechanism that has been implicated in many of the pediatric vasculitic syndromes involves immune complex formation: the presumed antigen combines with an immunoglobulin to form immune complexes, which then activate complement–C3a and C5a to elicit a cellular immigration to the area. The cellular response observed in the histologic studies may vary not only with the size of the vessel, but with the stage of the disease (interval between onset and biopsy) at the time of observation. For example, in the most common of the pediatric vasculitic syndromes, HSP,

the first cellular response is of PMNs with the observed "nuclear dust", followed by mononuclear cells —macrophages and then T cells, presumed with clonal expansion of a particular subset of antigen specific lymphocytes.

General clinical aspects of vasculitis in children

Common presenting symptoms in children with vasculitic syndromes include those that are constitutional, such as weight loss, fatigue and fever, as well as musculoskeletal complaints such as myalgia, arthralgia and arthritis. Cutaneous signs range from a localized rash that comes in crops as in HSP, to one in which there is more generalized involvement as in SLE. Cardiovascular signs can range from pericarditis and myocarditis seen frequently in systemic onset juvenile rheumatoid arthritis, to conduction abnormalities seen frequently in untreated juvenile dermatomyositis. Neurologic compromise can be both central and peripheral and range from a specific localization of cerebral vasculitis demonstrated by angiogram or MRA, or a mono-neuritis (which may be multiplex in character).

In many of the vasculitic syndromes, the pattern of the child's growth is disturbed, so that the disease onset may be mapped to when the child "fell off their growth curve". A decrease in bone density in active disease may be compounded by decreased absorption of calcium if oral corticosteroids are administered. The metabolic rate of drug pharmakokinetics is often increased in children, and absorption of drug from the gastrointestinal tract may be impaired by local vasculitis. Finally, drugs that alter the body shape, as well as linear growth, such as corticosteroids may precipitate depression and non-compliance.

Takayasu Arteritis "pulseless disease". This disease is the third most common form of childhood vasculitis in the world with increased incidence in Asian and Indian populations. The gender ratio is 2.5 female: 1 male, while 1/3 of cases are identified between 10-20 years of age. *Clinical signs* include night sweats, weight loss and fatigue, erythema nodosum, a malar rash in the early stages. Later, a bruit can be heard over the carotid or subclavian arteries with the characteristic decreased radial pulses. Little is known about the specific *pathogenesis* of this diseas, but it is thought that an HLA predisposition (DRB1*1602, *1001) may be associated with immune complex formation and complement activation. *Target damage*: Chronic inflammatory and obliterative disease of large vessels, the aorta and its major branches, with renal lesions that include crescentic glomerulonephritis. *Laboratory data* includes an elevated ESR and WBC, polyclonal hypergammaglobulinemia, circulating immune complexes, increased factor V Leiden, and restricted T cell receptor usage. An angiogram is diagnostic. *Therapy* is a combination of surgical excision of lesions with patching of affected areas and immuno- suppressive agents, methotrexate, prednisone, cyclophosphamide; some of the newer agents remain to be proven effective. Hypertension may be controlled by ACE inhibitors. *Prognosis* is guarded: 5 year mortality is as high as 35%, but the process may become "inactive".

Behçet's Disease (BD) in Children: The *Clinical Definition* of the disease includes recurrent buccal aphtosis, three times in 12 months, lips>cheeks>tongue>gingiva> pharynx. Genital ulcers, vulva>scrotuom>penis>perianal area are more common after puberty, uveitis with hypopion and/or positive pathergy test consists of: skin trauma by needle prick followed at 48 hours by a papule/pustule, with surrounding erythema. Erythema nodosum occurs in 40%. Blindness in 10%. *Epidemiology.* The incidence is 1:600,000 children and new cases follow the former silk route: Japan, Turkey, Iran and Mediterranean countries. 12% of pediatric cases have a positive family history vs 2% sporadic cases; females=males, and mortality is 3%.HLA-B51 increased (Middle East). *Target damage* includes venous thrombosis located in the lower extremities, diarrhea and colitis, headache and depression and aneurysms of the pulmonary arteries with hemoptysis and chest pain. *Therapy* for mild cases include corticosteroids; some children become refractory and thalidomide may be required.

Kawasaki Disease (mucocutaneous lymph node syndrome, infantile polyarteritis nodosa). The *Clinical Signs* of this disease includes remittent, spiking fever to 104º or higher, unresponsive to antibiotics, lasting as long as 3-4 weeks (usually 1-2 weeks); bilateral bulbar conjunctival injection; mucosal changes; rash, primarily truncal; edema

or erythema of hands or feet (arthritis ↑ in girls), lymph node enlargement and cardiac involvement: tachycardia, and decreased ventricular function, pericardial effusion with coronary dilation occurring in 2-3rd week of illness. *Epidemiology.* This disease is worldwide, but Asians are at highest risk. There is a male predominance; 80% of children are under the age of 5 years; 20% of untreated cases develop coronary thrombosis, stenosis, myocardial infarction and sudden death. *Laboratory Data* includes increased acute phase reactants, ESR, CRP; platelet count may exceed 1 million/mm^2 . Two-D Echo most useful test. *Therapy* centers on IVIG and high dose ASA as soon as possible, *delay immunization* with MMR and rubella vaccines. Recurrent illness occurs in 1-3% cases with mortality in Japan at 0.1%.

Henoch-Schönlein Purpura (HSP) (anaphylactoid purpura). *Clinical signs:* low grade fever, rash in crops lasting 3-10 days that evolve from red to purple to rusty brown before they fade and which recur as long as three years after initial event. Arthritis reported in 2/3 of children primarily in lower extremities with associated edema. Abdominal pain: may be complicated by intussusception (current jelly stools), GI: complete bowel obstruction, infarction and perforation, 50% have heme-positive stools. Renal involvement is seen in 25-50% of cases. There also may be testicular torsion or CNS involvement with seizures and coma. *Epidemiology /pathogenesis.* This vasculitis which may follow an upper respiratory infection, often group A β hemolytic streptococcal, is the most common vasculitis in childhood, 0.06% of in-patient hospital admissions and affects children 2-8 years of age. *Laboratory data.* Nonspecific anemia, acute phase reactants with IgA in immune complexes associated with C3 deposition in mesangial and GI tissue. *Therapy* reduction of intussusception, hydration, bland diet, relief of torsion, oral or IV corticosteroids for GI or CNS symptoms. Less than 1% persistent renal disease.

Systemic Onset Juvenile Rheumatoid Arthritis (S-JRA) *Diagnostic Criteria:* inflammation (swelling, tenderness, effusion), pain on motion, heat in one or more joints with duration of symptoms: 6 weeks or longer. *Classification:* Pattern of disease *onset* (first 6 months) and then by disease *course:* a) Systemic onset; b) Pauciarticular onset (4 joints or less); c) Polyarticular onset (5 joints or more) and d) exclusion of other rheumatic diseases such as SLE, Juvenile dermatomyositis, scleroderma, and in USA, other forms of chronic arthritis also excluded, such as psoriatic, bowel related, or reactive arthritis. *Clinical Signs of S-JRA*: Cutaneous: evanescent, maculopapular salmon pink rash, palms and soles, associated with spiking fever returning to the base-line, pericardial effusion and myocarditis, anemia (often Coombs positive), reticuloendothelial activation (hepatosplenomegaly); arthritis is seen in 95% cases by one year after onset with evolution into polyarticular disease. *Pathogenesis* viral "trigger" speculated. Evolution into polyarticular disease course associated with HLA-DR 4 alleles (DRB1* 0401); vasculopathy with intravascular thrombosis, complement activation, macrophage and T-cell activation, T cell clonal expansion with increased levels of IL-6 and TNFα. *Laboratory data:* Leukocytosis, thrombocytosis, anemia and increased ESR, increased immune complexes, activation of coagulation pathway: PT; vWF:Ag and decreased osteocalcin, bone mineral density. *Therapy:* Corticosteroids, methotrexate PO and IV with non-steroidal anti-inflammatory drugs; other immuno suppressive agents: Cyclophosphamide, Etanercept, protection of bone with adequate Ca++ diet and oral vitamin D.

Suggested Evaluation for Children with Possible Vasculitis: CBC, differential, ESR, platelet count; UA, BUN, creatinine; Immunoglobulins (IgG, IgA, IgM), ANA, RF, Coombs, C1q, Raji (for immune complexes) ; C3, C4, CH50, PT/PTT, von Willebrand factor antigen, SGPT; organ angiography, pulmonary evaluation, skin/muscle/renal biopsy. If immunosuppression to be used, consider: DEXA: nailfold capillary studies, D-xylose to evaluate absorption, OT/PT.

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