Small Vessel Vasculitis , recent advances in Pathogenesis , diagnosis and management

Essay Submitted For
Complete Fulfillment Of M.Sc. degree In Pediatric .

Present by
Ahmed Saeed Mohammed Ahmed Thabit
(M.B.B.CH)

Supervised by
Prof.Dr. Samia Salah Eldin Mahmoud
Professor Of Pediatrics
Faculty Of Medicine – Cairo University.

Lecurer Dr.Hala Mohammed Lotfy
Lecturer Of Pediatrics
Faculty Of Medicine – Cairo University.

Lecturer.Dr.Samar Mohammed Sabri.
Lecturer Of Pediatrics
Faculty Of Medicine – Cairo University.

Faculty Of Medicine
Cairo University
2007

بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

صدق الله العظيم

سورة البقرة أيه (٣٢)

Abstract

icult of alThe small vessel vasculitis are the most diffl rheumatic diseases to classify, the classification of small vessel vasculitis has markedly changed over the past decades with the discovery of the antineutrophil cytoplasmic antibodies which change a lot in understanding of pathogensis and management.

Small vessel vasculitis has been classified to ANCA associated and non-ANCA .

Key Words :

Small Vessel Vasculitis – Diagnosis .

INDEX

Introduction

Vasculitis implies a straightforward process, inflammation of blood vessels. The conditions included in this category are anything but straightforward, however, becauses of the variability of vessels that may be involved and the multitude of ways in which they may be affected. Thus, damage to mural structures can lead to anything from numbness to pain, thrombosis to bleeding, aneurysm formation to necrosis***(Fatma et al, 2005*)**.

Classification of vasculitis has long been based in part on the type and distribution of the involved blood vessel, and the nature of the vascular inflammation. Further classification has depended upon the presence or absence of immunoglobulin in vessel walls and the specific characteristics of these immune deposits. More knowledge of the etiology and pathogenesis of various forms of vasculitis will certainly lead to refinements in our nosologic schemes***(Falk et al, 2004*)**.

Primary vasculitis may be classified according to their clinical manifestations, the size of blood vessels involved, the histology of the vascular damage, or the presumed disease pathogensis. An etiologic classification system would be ideal,

especially because it could potentially shed light on anticipated responsiveness to treatment ***(Hoffman et al , 2004*)**.

Most current classification system are based on a combination of histologic and clinical features of vaculitis***(Jennette et al , 2000*)**.

The classification of small vessel vasculitis has markedly changed over the past 150 year with the discovery of anti-neutrophilic cytoplasmic antibodies (ANCA), renewed interest in the field has spawned investigations into the immunopathogenesis of small vessel vasculitis***(Falk et al, 2004*)**.

Small vessel vasculitis may be further classified as ANCA-associated or non-ANCA-associated small vessel vasculitis. Better definition criteria and advancement in the technologies make the diagnosis increasingly common. Features that may aid in defining the specific type of vasculitic disorder include the type of organ involvement, presence the type of ANCA (myeloperoxidaseANCA or proteinase3 ANCA), presence of serum cryoglobulins, and the presence of evidence for granulomatous inflammation***(Ishak et al, 2002*)**.

The potential clinical manifestations of ANCA associated small-vessel vasculitis that is generally shared by most types of small-vessel vasculitis. Small-vessel vasculitis should be suspected in any patient who presents with a mulitsystem disease that is not caused by an infectious or malignant process (e.g., renal dysfunction, skin rashes, pulmonary manifestations, or neurologic manifestation). The frequency an combination of various system involvement vary among individual disease entities***(Guillevin et al,1999).***

Anti-neutrophil cytoplasmic antibodies (ANCA) are important serologic marker for primary systemic small vessel vasculitis (PSVV) including Wegener's granulomatosis, microscopic poly angiitis, renal limited disease (pauci-immune glomerulonephritis) and Churg-Strauss disease, where they are thought to play a role in activation of vasculitic process***(Peter et al, 2000)*** .

Pathogensis of small vessel vasculitis is based on the realization that ANCA are more than serologic markers of disease. Rather, these autoantibodies play a critical role in pathogenic mechanisms***(Kallenberg et al, 2002*****)**.

Aim of the work

The aim of the work is to describe the pathogensis, the different clinical presentations, together with the new advances in the etiology, which will be definitely reflected on the advancement of new lines of management that will help to avoid life threatening injury to organs which develops quickly and respond dramatically.

To facilitate the diagnosis and management of small vessel vasculitis which is challenging because of it is syndromatic nature, frequency and combination of various system involvement.

Rapid diagnosis of small vessel vasculitis is critically important, because life-threatening injury to organs often develops quickly and is respond dramatically to immunosuppressive therapy**.**

New considerations in the classification of small vessel vasculitis

A- Definition:-

The term ***vasculitis*** encompasses a number of distinct clinicopathologic disease entities, each of which is characterized pathologically by cellular inflammation and destruction of the blood vessel wall, and clinically by the types and locations of the affected vessels. While multiple classification schemes have been proposed to categorize and simplify the approach to these diseases, ultimately their diagnosis rests on the identification of particular patterns of clinical, radiologic, laboratory, and pathologic features ***(Stephen K etal 2006).***

The vasculitides are the most difficult of all rheumatic diseases to classify. None of studies specifically addressed vasculitis in childhood ***(James et al 2001).***

Because the etiologies of most forms of vasculitis remain unknown, the most valid basis for classifying the vasculitides is the size of the predominant blood vessels involved under such classification schemes, the vasculitides are categorized initially by whether the vessels affected are large, medium, or small. Large generally denotes the aorta and its major branches (as

well as the corresponding vessels in the venous circulation in some forms of vasculitis, e.g., Behcet's disease). Medium refers to vessels that are smaller than the major aortic branches yet still large enough to contain four elements: 1)an intima; 2) a continuous internal elastic lamina ;3)a muscular media; and 4)an adventitia.In clinical terms, medium-vessel vasculitis, is generally macrovascular involoves vessels large enough to be observed in gross pathologic specimens. Small-vessel vasculitits, which incorporates all vessels below macroscopic disease, includes capillaries, postcapillary venules, and arterioles. Such vessels are all typically less than 500 microns in outer diameter.Because glomeruli may be viewed simply as differentiated capillaries, forms of vasculitis that cause glomerulonephritis are considered to be small-vessel vasculitides ***(Jone et al, 2005).***

B- Classification :-

All discussions of vasculitis classification schemes involving vessel size must acknowledge the frequent occurrence of overlap.For example, although PAN primarily involves medium-sized arteries, palpable purpura a manifestation of small vessel vasculitis disease clearly is observed in some cases. Despite the possibility of vessel size overlap within individual cases, the categorization of a patient's vasculitis as primarily large, medium, or small vessel in nature remains enormously

useful in focusing the differential diagnosis, and is the first step in planning the approach to treatment.

Many other considerations are important in the classification of vasculitis, **1)** The patient's demographic profile , **2)** The disease's tropism for particular organs , **3)** The presence or absence of granulomatous inflammation , **4)** The participation of immune complexes in disease pathoghysiology , **5)** The finding of characteristic autoantibodies in the patient's serum (e.g., ANCA or anti-gbm antibodies); and , **6)** The detection of certain infections known to cause specific forms of vasculitis . The organ tropisms of these disorders illustrated as , Wegener's granulomatosis classically involves the kidneys, upper airways, and lungs. In contrast, Henoch-Schonlein purpura often affects the kidneys but never the nose or sinuses and almost never the lungs. In contrast to both of these forms of vasculitis, Cogan's syndrome is defined by the simultaneous occurrence of ocular inflammation (most often intersititial keratitis) and sensorineural hearing loss (and, in 10% of cases, a large-vessel vasculitis). The histopathologic findings in these three disorders are equally distinctive, ranging from granulomatous inflammation of small-to medium-sized vessels (Wegener's granulomatosis), immunoglobulin A (IgA) deposition in small vessels (Henoch-Schonlein purpura) , to large-vessel vasculitis centered on the adventitia (cogan's syndrome)***(Jone et al,2005)***.

Immune complexes are essential to the pathophysiology of some small- and medium-vessel vasculitides. Immune complex-mediated tissue injury does not produce a single clinical syndrome, but rather applies to many forms of vasculitis and overlaps with injuries caused by other immune mechanisms. Anti-GBM disease (Goodpasture's disease) is a unique form of immune complex form in situ rather than in circulation ***(Salama etal, 2002).***

Vasculitis with IgA-dominant immune deposits, affecting small vessels (i.e., capillaries or venules, or arterioles), typically involves skin, gut, and glomeruli. Necrotizing vasculitis, with few or no immune deposits, affecting small vessels like microscopic polyangiitis, may present with necrotizing glomerulonephritis is very common , Pulmonary capillaritis ofen occurs ***(Jennette etal 2004)***.

In contrast, other small- and medium-vessel vasculitis, such as Wegener's granulomatosis, microscopic polyangiitis, and the churg-strauss syndrome, are pauci-immune diseases.Pauci-immune refers to the absence of significant IgA or complement deposition within diseased tissues ***(Jone et al, 2005).***

ANCA are specific antibodies for antigens in cytoplasmic granules of neutrophils and monocytes lysosomes .Two major patterns of staining are present: cytoplasmic (cANCA) and peri-nuclear (pANCA). Specific immunochemical assays demonstrate ANCA is mainly antibodies to proteinase 3, and pANCA is antibodies to myeloperoxidase. Some major classifications of vasculitis illustrate the position of antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis among others ***(Ishak etal 2002)***.

ANCA are closely associated with pauci-immune necrotizing small vessel vasculitis. Both proteinase3 ANCA and myeloperoxidase ANCA occurred in patients with a spectrum of pauci-immune small vessel vasculitis that include microscopic polyangiitis, wegener's granulomatosis, as well as necrotizing vascular injury confined to kidney (e.g. necrotizing glomerulonephritis or renal limited vasculitis) ***(Falk etal, 2004)***.

The granulomatous features of some forms of vasculitis resemble chronic infections (e.g.those caused by fungi or myobacteria) or the inflammation induced by the presence of a foreign body. Granulomatous inflammation is more likely to be found in some organs-for example, the lung –than in others (the kidney or the skin). Some patient without evidence of

granulomatous inflammation at early points in their courses later demonstrate such features as their diseases unfold. Thus, patients initially diagnosed with cutaneous leukocytoclastic angiitis or microscopic poly angiitis may be reclassified as having Wegener's granulomatosis if disease manifestations appear in new organs and granulomatous inflammation is found on biopsy. Forms of vasculitis associated with granulomatous inflammation are 1), Giant-cell arteritis 2), Takayasu's arteritis 3), Cogan's syndrome 4), Wegener's granulomatosis 5), Churg-strauss syndrome 6), Primary angiitis of the central nervous system ***(Jone et al, 2005).***

C- Pathophysiology of small vessel vasculitis :-

Despite extensive research, mechanism underlying the onset and perpetuation of vascular inflammation are generally not understood. Epidemiology, animal models, basic experiments, and responses to directed therapy are shedding light on the processes involved in a variety of vasculitides ***(Robert et al 2005)***.

Theories of pathogensis:-

Humoral factors: Vascular damage secondary to specific antibodies is best demonstrated in the ANCA-associated vasculitides ***(Hugen et al, 2004)***.

These antibodies may activate neutrophils, causing vascular inflammation, although the lack of direct correlation between antibody titers and disease activity suggests that additional factors are important in mediating a vessel damage. Antiendothelial antibodies are present in a variety of vasculitides, but whether they are markers or mediators of vascular pathology remains unclear ***(Praprotnik et al, 2000)***.

Immune complexes: The size, charge, and immunoreactivity of immune complexes help explain aspects of the pathogenesis of Henoch-schonlein purpura and cryoglobulinemic vasculitis ***(Yoshinoya et al, 2004*)**

Similarly, polyarterites nodosa associated with hepatitis B or C seems to be triggered by inflammation incited by immune complexes deposited upon vessel walls***(Ozen et al, 2004)***.

T lymphocytes attracted to damaged or infected endothelium may contribute to vascular inflammation through direct cytotoxicity or release of inflammatory cytokines. Evidence of restricted expression of T-cell receptors a role for selection of antigen-specific lymphocytes in some types of vasculitis ***(Brogan et al, 2003)***.