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EDUCATIONAL REVIEW

The "other" vasculitis syndromes and kidney involvement

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Abstract There are a number of vasculitides that are not confined to a specific vessel size, do not have characteristic features, and/or are not secondary to another disease. Most of these vasculitides are rare in childhood. Behçet disease is representative of this group as it involves vessels of any size on both the arterial and venous side. In addition to renal vascular involvement, Behçet disease may involve the kidney through glomerulonephritis, secondary amyloidosis and, rarely, tubulointerstital involvement. Vasculitis secondary to infections, malignancy, and drugs are not common among children. However, vasculitis may be associated with a number of rheumatic diseases in childhood and the auto-inflammatory syndromes (periodic fever syndromes). Auto-inflammatory syndromes are diseases characterized by periodic attacks of clinical and laboratory inflammation. Studies carried out during the past decade have provided valuable information on the mechanism of inflammation and innate immunity in general. This group of vasculitides is associated with secondary amyloidosis of the kidney if not treated. Hypocomplementemic urticarial vasculitis is an interesting vasculitic disease with frequent kidney involvement. Here, we introduce the reader to the wide scope of these diseases; although rare, such diseases represent a challenge to the nephrologist.

Keywords Auto-inflammatory syndromes · Behcet disease · Child · Familial Mediterranean Fever · Vasculitis

Introduction

The primary vasculitis syndromes tend to involve a specific vessel size only and to present with a constellation of clinical symptoms. Indeed, the primary vasculitides have been classified both by internists and pediatricians according to the vessel size they affect [1, 2]. However, there are a number of vasculitides that are not classifiable within this context. In 2006, a group of pediatricians developed a working classification for childhood vasculitides in which they included a group of "other vasculitides". This group represents those vasculitides that do not affect one size of vessel only, are not secondary to another disease or factor, and/or do not have exceptional features [2]. This paper will review these vasculitides and the vasculitis associated with Familial Mediterranean Fever as the prototype of autoinflammatory diseases (Table 1).

Cogan syndrome is a rare syndrome of interstitial keratitis and vestibuloauditory symptoms [3]. Isolated vasculitis of the central nervous system (CNS) is characterized by the involvement of the CNS vessels only. Diagnosis is based on the demonstration of brain vessel inflammation by angiography or, in rare cases, brain biopsy [4]. Isolated cutaneous vasculitis is seen in patients whose vasculitis is confined to the skin. These three diseases do not affect the kidney—at least not as a primary target—and will not be discussed in this paper.

Behçet Disease

Behçet Disease (BD) is a vasculitis with characteristic features affecting both the skin and mucosa [5, 6]. It is the only primary vasculitis that can affect vessels of all sizes and both the arteries and veins. The vasculitis and CNS involvement of BD are associated with considerable morbidity and even mortality, and they need to be managed judiciously. Behçet Disease is characterized by periods of exacerbations and remissions [5, 6]. The presence of these inflammatory episodes and the lack of significant autoanti-

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Table 1 The "other" vasculitides

1. Behçet disease
2. Vasculitis secondary to infection, malignancies, and drugs
3. Vasculitis associated with connective tissue diseases and with Familial Mediterranean Fever and other periodic fever syndromes (autoinflammatory diseases)
4. Hypocomplementemic urticarial vasculitis
5. Cogan syndrome:
6. Isolated vasculitis of the central nervous system (CNS)
7. Isolated cutaneous vasculitis (hypersensitivity vasculitis)

bodies has led to its possible classification as an "auto-inflammatory disease".

Epidemiology

Behçet Disease is a disease that is common in specific geographic regions although a considerable number of patients have been defined in many ethnic groups and geographic locations. In a recent analysis from France, BD (prevalence 7.1/100,000) was more frequent than polyarteritis nodosa (PAN; 3/100,000), microscopic polyangiitis (MPA; 2.5/100 000), and Wegner's granulomatosis (WG; 2.4/100 000) [7].

Classification

The disease is classified according to criteria proposed in 1990 [8]. These criteria require the presence of recurrent oral ulcers and the presence of at least two of the following: genital ulcers, eye involvement (often panuveitis), skin lesions, and a positive pathergy test.

Clinical features

Recurrent oral ulcers have been described in all patients. Genital ulcers, panuveitis, and skin lesions are also common findings in children. Along with these skin and mucosal findings, children also display the features of vasculitis, and CNS involvement is also common [6]. Venous lesions are characterized by thrombosis, whereas arterial lesions occur in the form of aneurysms and stenosis [5]. Behçet Disease may also affect the vasculature of the kidney. Based on an extensive review of renal involvement in BD, renal involvement in BD is more frequent than has been recognized, although it is most often mild in nature [9]. In this review renal problems have been summarized in five groups [9]: glomerulonephritis (glomerular involvement), amyloidosis, renal vascular involvement, tubulointerstitial involvement, and other problems, such as side effects of drugs. Renal amyloidosis is secondary to uncontrolled inflammation in BD, but whether there is a causal relationship with BD and other renal lesions is not so evident.

A metanalysis by Akpolat et al. in 2002 on kidney involvement in BD revealed an abundance of clinical and demographic information. The age range of patients with glomerulonephritis was found to be 13–70 years, and the mean interval between the time of diagnosis of BD and the development of glomerulonephritis was 8 years (2 months to 22 years). The glomerular disease can be silent and detected incidentally [9]. Any type of histopathological lesion can develop, but crescentic glomerulonephritis and immunoglobulin (Ig)A nephropathy are probably the most common types [10, 11].

Secondary amyloidosis has been an important complication in the past, even in childhood onset patients. AA-type amyloid fibrils were found in all cases studied [9]. The incidence of secondary amyloidosis has decreased with better management of the disease. The reactive amyloidosis may be regarded as yet another feature supporting the view that BD is an autoinflammatory disease. Renal vascular disease is a rare but important event in BD. The most common renal vascular disease is renal artery aneurysm [9]. Intrarenal aneurysms, renal artery stenosis, and renal venous thrombosis has also been described. Hypertension is common among patients with renal artery aneurysm or stenosis [9]. A renal disease [amyloidosis or glomerulonephritis (GN)] or other major vascular involvement were present in all cases with renal vein thrombosis. Thus, especially BD patients with nephrotic syndrome should be screened for renal venous thrombosis. It is noteworthy that patients with vascular involvement carried a high risk for amyloidosis, which may reflect the association between both of these features and significant inflammation in the body. Finally, tubulointerstitial lesions have been descried in BD, although they are rare [9]. Other causes, such as infections, need to be considered in these lesions.

Treatment and management

The reader is referred to recent guidelines on the management of BD and vascular involvement [12]. The treatment of glomerular disease has been similar to those of the primary kind of lesions. Steroids are indicated for the glomerulonephritides of BD. Additional immunosuppressives, such as

cyclophosphamide or azathioprine, are indicated in Behçet vasculitis; however, Level I evidence is lacking for the best treatment in children. In patients with renal venous thrombosis, most centers would use anticoagulation during the acute phase [12]. Anticoagulation is contraindicated in the presence of pulmonary aneurysms.

Vasculitis secondary to infection, malignancies, and drugs

There are a substantial number of published and probably many unpublished cases of vasculitic syndromes developing in association with various infections, malignancies, and drugs [13, 14]. In most of these cases, vasculitis is limited to the skin, and renal involvement is rare [14]. In our pediatric practice, infection-associated vasculitis has been more common than vasculitis associated with malignancies and drugs in children. PAN associated with hepatitis B antigen also falls into this category since it is an immune complex-mediated disease [15]. A few cases have been reported in a multicenter study involving the analysis of children with PAN [16]. Pediatric patients with hepatitis B surface antigen (HBsAg)-associated PAN have had renal artery aneurysms and present with hypertension [16, 17]. Other features of systemic PAN may also be present. These patients should be treated with lamivudine as antiviral treatment plus steroid therapy, similar to that suggested in large adult series [15]. The prognosis for patients treated in this way is good. HBsAg-associated PAN is becoming extinct in children, thanks to the vaccination programs. In comparison, hepatitis C-associated cryoglobulinemic vasculitis has not been reported in children.

The association of vasculitis with drugs is based on the temporal relationship between clinically evident vasculitis and the administration of the offending drugs [18]. A typical example would be the association of propylthiouracil with the development of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The treatment of the associated disease or drug elimination will usually result in regression of the vasculitis. In ANCA-associated vasculitis due to drugs, the duration of immunosuppressive therapy should be much shorter than that in primary ANCA-associated vasculitis (AAV), and long-term maintenance therapy may not be necessary [18].

Vasculitis associated with other diseases

Vasculitis associated with connective tissue diseases

Many rheumatic diseases are associated with vasculitis. In adults, rheumatoid vasculitis is probably the most common vasculitis, whereas this disease is extremely rare in childhood. In childhood, systemic lupus erythematosus (SLE) is the most common rheumatic disease associated with vasculitis and kidney involvement. It is an autoimmune disease affecting the vessels with immune complexes. A number of renal vascular lesions can be seen in adult patients with SLE, such as those associated with vascular immune complex deposits and non-inflammatory necrotizing vasculopathy [19]. The kidney may also be involved through thrombotic microangiopathy [20], and the latter condition is an interesting feature of SLE that is associated with dramatic consequences. The microangiopathic lesions result in clinical features similar to those of hemolytic uremic syndrome [20]. Plasmapheresis is beneficial in such cases, although controlled studies are not available on this rare association. There has been much progress in the treatment of SLE, especially with the introduction of biologics, that would apply to vascular and glomerular involvement as well.

Vasculitides associated with periodic fever syndromes

During the past decade, the autoinflammatory diseases (AIDs) have emerged as a new chapter in the medical field. These are a group of diseases characterized by unprovoked inflammatory episodes and the lack of autoantibodies [21]. Most of the well-defined diseases in this group are monogenic diseases where there is interleukin (IL)-1 overproduction [22, 23]. These diseases are of general medical interest since they can be used to obtain information on the mechanism of inflammation [21, 22]. They are of interest to nephrologists since they are associated with a dramatic kidney disease, secondary amyloidosis, that can be prevented by suppressing the inflammation. The prototype of autoinflammatory diseases is Familial Mediterranean Fever.

Familial Mediterranean Fever

Familial Mediterranean Fever (FMF) is an autoinflammatory disease caused by mutations in the Mediterranean Fever (*MEFV*) gene [21, 22] that lead to a defect in pyrin. such mutations are associated with increased IL-1β production and an enhanced innate immune system response [23]. Clinically, FMF is characterized by short attacks of fever and serositis along with high acute phase reactants. The serositis may manifest itself as abdominal pain (peritonitis), chest pain (pleuritis), or arthritis. Pediatric FMF is usually diagnosed based on criteria established for adult patients [24]. A recently proposed set of criteria for children has been suggested but awaits validation in multi-ethnic populations [25].

Many researchers have focused on identifying the clinical implications of the inflammation associated with mutations in the *MEFV* gene. FMF is an autosomal

recessive disease, and FMF patients have high acute phase inflammatory markers and attacks of manifest clinical inflammation [22]. In fact, the mean erythrocyte sedimentation rate and C-reactive protein levels are higher than normal even in between attacks [26, 27]. Kidney involvement in FMF may fall into one of three categories: in the form of secondary amyloidosis, the occurrence of other glomerulonephritides (incidental), and the association with vasculitic lesions.

Secondary amyloidosis may occur in untreated patients. The use of colchicine prevents the occurrence of secondary amyloidosis and thus represents the only kidney disease that can be prevented by an inexpensive drug [28–30]. Patients present with proteinuria only or with full-blown nephrotic syndrome [28]. Hematuria and hypertension almost never occur. In a multicenter study from Turkey in which patients, both adult and pediatric, with amyloidosis were analyzed, 32% presented with proteinuria, 40% with nephrotic syndrome, and 28% with renal failure (n = 88) [31]. For the patients who developed end stage renal failure, 58 were on hemodialysis, 17 were on peritoneal dialysis, and 14 were transplanted [31]. Transplantation is the preferred mode of treatment in patients developing end stage renal failure. However, colchicine must be continued at effective doses after renal transplantation otherwise reactive amyloidosis will recur in the transplanted kidney and other organs, including the heart [28, 31].

An increased rate of inflammatory diseases, including vasculitides, has been noted in recent years among the patients and carriers of *MEFV* mutations [27, 31]. We initially observed in small series that certain vasculitides had increased among these patients [27]. In a multicenter study in Turkey involving almost 3000 patients, the highest frequency of inflammatory diseases were PAN (0.9%), Henoch-Schonlein purpura (HSP) (2.7%), and rheumatoid arthritis, all higher than expected in the general population [31].

On the other hand, we and others have reported that among patients with certain vasculitides there is an increased carrier rate for mutations in the *MEFV* gene. In a pediatric cohort, the mutated MEFV allele frequency among pediatric patients with rheumatic diseases, including HSP and PAN, was significantly higher than those in controls [27]. Gershoni-Baruch et al. [32] showed increased *MEFV* mutations among children with HSP. We subsequently showed a high carrier rate of *MEFV* mutations among childhood PAN patients in Turkey [33]. All of these values reached statistical significance. It should be noted that these reports were from two countries with a very high carrier rate for MEFV mutations.

Based on the results of a collaborative study with Israel, we also suggested that patients with FMF and PAN had a number of specific characteristic features [34]. They had younger age of onset, with a significant number of childhood cases. Half of the patients (8/17) reported in this study had perirenal hematoma [34]. A striking result was that five of the 17 patients had overlapping features of both classic PAN affecting the mid-size artery and microscopic PAN. All were treated with immunosuppressives in addition to colchicine, and overall the prognosis of these patients was good [34]. The association of vasculitis and FMF may be simply explained by the increased inflammatory milieu in patients with *MEFV* mutations. However, the *MEFV* mutation may be acting as a susceptibility gene for vasculitis in these multi-factorial diseases [35]. The effect of these polymorphisms are probably mediated through the upregulation of the innate immune system, which serves as the initial response to the environmental trigger [35]. The answer to the question of whether polymorphisms in the autoinflammatory disease genes will serve as susceptibility factors in other populations awaits more studies. These data suggest that one needs to be aware of the possible occurrence of these vasculitides in FMF and ensure that proper management of the disease occurs. The other common AIDs have been rarely associated with vasculitic features; however, their general characteristics and kidney involvement will also be summarized here.

Tumor necrosis factor receptor-associated periodic syndrome

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is associated with attacks of longer duration. The attacks of fever are associated with abdominal pain, myalgia, migratory erythematous skin rash, conjunctivitis, and/or periorbital edema [21, 22, 36]. Amyloidosis has also been reported in these patients; 14% of whom have developed amyloidosis to date [21]. Thus, urinalysis needs to be checked at each visit. Amyloidosis has been associated with cysteine substitutions in the protein [21, 36]. Anti-TNF treatment is used to suppress the inflammation. Etanercept is the preferred treatment since caution has been suggested for the use of infliximab in TRAPS patients [37].

Hyperimmunoglobulinemia D with periodic fever syndrome

Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) is an autosomal recessively inherited periodic fever syndrome caused by mutations in the *MVK* gene, which codes for the enzyme mevalonate kinase [38, 39]. The majority of the patients reported to date are from The Netherlands and France. However, cases have been reported worldwide. The fever is commonly accompanied by abdominal pain, diarrhea, vomiting, and cervical lymphadenopathy [38, 39]. There has been only one case of amyloidosis. Although the risk of

amyloidosis seems to be low, the patients suffer from a poor quality of life in their early years. Crescentic GN has been reported in a patient with HIDS; however, the causal association was unclear [40].

There is currently a lack of solid evidence for the treatment of HIDS. Anti-TNF and anti-IL-1 treatment has been reported to be effective in recent studies [39].

CIAS-1-pathies—the cryopyrin-associated periodic fever syndromes

These include:

Familial cold autoinflammatory syndrome (FCAS);
Muckle-Wells syndrome (MWS);
Neonatal-onset multi-system inflammatory disease [NOMID, also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome].

These three syndromes are associated with mutations in cryopyrin [41–43]. All are characterized by fevers and a nonpruritic, urticarial rash that usually presents in infancy (later in MWS). They may have some of the overlapping features described above [41–43]. FCAS presents with attacks precipitated by cold, as suggested in the name [42]. The main differentiating feature of MWS is the hearing defect [41]. NOMID/CINCA represents the most severe form of the three and is associated with neurological defects and more persistent features [43]. All are associated with the development of secondary amyloidosis mainly affecting the kidney, if inflammation is not suppressed. Anti-IL1 treatment is the mainstay of treatment, and it is hoped that this treatment will prevent the reactive amyloidosis.

Hypocomplementemic urticarial vasculitis syndrome

Hypocomplementemic urticarial vasculitis syndrome (HUVS), first described in the early 1970s, is very rare in the pediatric population. However, it must be considered in the differential diagnosis for patients with glomerulonephritis, urticarial rash, arthralgias/arthritis, and pulmonary disease [44]. HUVS is a rare autoimmune disease characterized by recurrent urticaria and low complement levels. In 1982, these two features were designated as the major criteria, with the suggestion that at least two minor criteria are also required for the diagnosis of HUVS [45]. These minor criteria are venulitis on skin biopsy, arthritis, ocular inflammation, abdominal pain, positive C1q antibodies, and glomerulonephritis. The binding of C1q antibodies to immune complexes is thought to be important in the pathogenesis of renal disease in HUVS [44]. Indeed, C1q antibodies are probably present in all patients. Half of the patients develop glomerulonephritis. Various types of renal lesions may be observed: mesangial proliferative lesions, focal proliferative, membranoproliferative, and membranous lesions have been reported [46]. No specific therapy is currently available for HUVS. Patients have been treated with steroids and various immunosuppressives [46]. It is the experience of the author and others that crescentic glomerulonephritis is particularly aggressive and difficult to treat in patients with HUVS. The presence of high levels of ANA and positivity of anti-double stranded DNA Ab are exclusion factors for the disease [44]. However, a portion of patients may progress to full-blown SLE. The patients should be thus screened appropriately.

Conclusion

The vasculitides reported here are relatively rare diseases in the common practice of pediatric nephrologists. However, they have remarkable features that are of interest. They also shed light on our understanding of other common diseases. Awareness of the features of these vasculitides will allow for an earlier diagnosis of the problem and better management.

Questions

(Answers appear following the reference list)

1. Which is true for Behçet disease?
   a. It is never seen in children
   b. It is a short lasting mucositis
   c. Only mid-size arteries are affected
   d. Both the veins and arteries may be affected
   e. CNS is not involved
2. What kind of kidney involvement is seen in Behçet disease?
   a. Glomerulopathies
   b. Secondary amyloidosis
   c. Tubulointerstitial disease
   d. Renal artery aneurysm
   e. All of the above
3. Autoinflammatory diseases lack autoantibodies. Is this statement:
   a. True
   b. False
4. In FMF patients who are not sufficiently treated what kind of kidney disease develops?
   a. Tubulointerstitial nephritis due to colchicine
   b. Microscopic polyarteritis/polyangiitis
   c. Secondary amyloidosis
   d. An immune complex nephritis
   e. IgA nephropathy

5. In hypocomplementemic urticarial vasculitis syndrome which is false?
   a. There is hypocomplementemia
   b. There is persistent urticaria
   c. Anti C1q antibodies are detected
   d. Half develop glomerulonephritis
   e. Patients have cryoglobulins

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Answers

1. d
2. e
3. a
4. c
5. e