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REVIEW ARTICLE

Vasculitis: Decade in Review

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Abstract: ***Background*:** In the last decade, we have come to better understand and manage the vasculitides. The classification of vasculitides has been revised. Genome- wide association studies and linkage analyses have been undertaken in hope of better understanding the pathogenesis of vasculitides. Comprehensive genetic studies have highlighted new pathways that may guide us in more targeted therapies. Description of the monogenic forms of vasculitis, such as deficiency of adenosine deaminase type 2 (DADA2), Haploinsufficiency of A20 (HA20), have introduced a new perspective to vasculopathies, and introduced alternative treatments for these diseases.

***Conclusion*:** In this review, the important discoveries in pathogenesis and consensus treatment recommendations from the past decade will be summarized.

Keywords: Systemic vasculitis, treatment, pathogenesis.

1. INTRODUCTION

The vasculitides are defined as inflammation of the blood vessels which may lead to end organ injury. In the last decade, there has been a lot of progress in the field of vasculitis that enlightens the pathogenesis. We have been able to better define vasculitides since we had better understood the pathogenesis. New researches have pointed out to specific pathways and cytokines that we may target in our treatment. Genetic studies have introduced us to the new concept of monogenic diseases with vasculitis mimics. Multicenter collaborations have enabled us to do treatment studies and produce recommendations. In this review, we will concentrate on the aforementioned new findings in the pathogenesis of these diseases, for the vasculitides that we encounter in childhood. We have aimed to summarize findings in pathogenesis in last decade that may lead to more targeted therapy. We will also summarize the treatment recommendations developed for adult vasculitides in the last 10 years.

2. DEFINITIONS AND CLASSIFICATIONS

During the last decade, it has been shown that adulthood classification criteria have failed to classify many pediatric vasculitides. In 2006, pediatricians have established the *Ankara* classification criteria for childhood (Table **1**) (published in 2008); these included criteria for Henoch-Schönlein purpura (HSP) (now IgA Vasculitis), childhood Polyarteritis Nodosa (PAN), Wegener Granulomatosis (WG) (Granulomatous Polyangiitis) and Takayasu Arteritis (TA). These criteria were endorsed by European League Against Rheumatism, Paediatric Rheumatology International Trials Organization and Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) [1, 2].

With the improving of knowledge in etiopathogenesis, definitions of the diseases have been updated in the Chapel Hill Consensus Conferences (CHCC) 2012 (Table **2**) [3]. A number of revisions were introduced in this new nomenclature paper: the small vessel vasculitides were divided into two pathogenetic categories. More descriptive names were substituted with the eponyms. New categories such as variable vessel vasculitis, single organ vasculitis, vasculitis associated systemic disease and vasculitis associated with probable etiology were introduced [3]. Finally, if the vasculitis was associated with a known cause it was grouped separately: as an example, Hepatitis B virus associated vasculitis was not classified as PAN anymore, it was now categorized under 'vasculitis associated with probable etiology' [3]. This category of 'vasculitis associated with probable etiology' became very appropriate for the monogenic forms of vasculitis defined in recent years (see below).

3. PREDOMINANTLY SMALL VESSEL DISEASE

3.1. Immunoglobulin A Vasculitis (IgAV)/Henoch-Schönlein Purpura (HSP)

Immunoglobulin A vasculitis (IgAV), also referred to as Henoch-Schönlein purpura (HSP), is one of the most common vasculitis of childhood. It affects predominantly small vessels with the presence of immunoglobulin A1 (IgA1) dominant immune deposits [1, 3]. The pathogenesis of IgAV contains still many unknowns. Vascular inflammation is accompanied by IgA1 deposits, complement factors and large neutrophil infiltrates. It is generally accepted that galactose-

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Table 1. Ankara 2008 criteria [1, 2].

IgA vasculitis	Purpura or petechia (mandatory) with lower limb predominance plus 1 of 4: • Abdominal pain • Histopathology (predominant IgA deposit in a biopsy) • Arthritis or arthralgia • Renal involvement
Polyarteritis nodosa	Histopathology or angiographic abnormalities (mandatory) plus 1 of 5: • Skin involvement • Myalgia/muscle tenderness • Hypertension • Peripheral neuropathy • Renal involvement
Granulomatous polyangiitis	At least 3 of 6 • Histopathology (granulomatous inflammation) • Upper airway involvement • Laryngo-tracheo-bronchial stenosis • Pulmonary involvement (chest X-ray or CT showing the • Presence of nodules, cavities, or fixed infiltrates) • ANCA positivity • Renal involvement
Takayasu arteritis	Angiography (conventional, CT or MRI) of the aorta or its major branches and pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion or thickened arterial wall (mandatory) plus 1 of 5: • Pulse deficit or claudication • Four limbs blood pressure discrepancy >10 mmHg • Bruits • Hypertension (>95 percentile for height) • Elevated acute phase reactants

*Adapted from European League Against Rheumatism, Paediatric Rheumatology International Trials Organization and Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) Ankara 2008 criteria.

deficient IgA1 (Gd-IgA1) plays a key role in the pathogenesis of renal involvement in IgAV [4]. Novak *et al.* [5] have proposed a multi-hit hypothesis to explain the role of Gd-IgA1 in IgAV and also IgAV with nephritis (IgAVN). This hypothesis introduced that Gd-IgA1 produced in increased levels in patients with IgA nephropathy (IgAN) (hit 1), is recognized in the circulation by autoantibodies produced due to molecular mimicry (hit 2) [5]. The result is the formation of Gd-IgA1- containing immune complexes which are mediated by complement factors and IgA receptors such as TFR and sCD89 (hit 3). The immune complexes deposit in the mesangium and induce renal injury (hit 4) [5]. The multi-hit model explains the role of Gd-IgA1 antibodies in IgAN and IgAVN but its role in IgA vasculitis is still controversial. Recently Heineke *et al.* [4] have proposed an alternative multi-hit hypothesis to explain the systemic symptoms of IgAV and IgAVN and they have suggested the increased serum level of IgA1 anti-endothelial cell antibodies (AECA) as the first hit. The binding of IgA1 AECA to

Table 2. Chapel Hill Consensus Conferences 2012 Classification criteria [3].

I. Large-vessel vasculitis (LVV) • Takayasu arteritis • Giant cell arteritis
II. Medium-vessel vasculitis (MVV) • Polyarteritis nodosa • Kawasaki disease
III. Small-vessel vasculitis (SVV) A. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis • Microscopic polyangiitis • Granulomatosis with polyangiitis (Wegener granulomatosis) • Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) B. Immune complex SVV • Anti-glomerular basement membrane (anti-GBM) disease • Cryoglobulinemic vasculitis • IgA vasculitis (Henoch–Schönlein) • Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
IV. Variable vessel vasculitis • Behçet's disease • Cogan's syndrome
V. Single-organ vasculitis • Cutaneous leukocytoclastic angiitis • Cutaneous arteritis • Primary central nervous system vasculitis • Isolated aortitis • Others
VI. Vasculitis associated with systemic disease • Lupus vasculitis • Rheumatoid vasculitis • Sarcoid vasculitis • Others
VII. Vasculitis associated with probable etiology • Hepatitis C virus-associated cryoglobulinemic vasculitis • Hepatitis B virus-associated vasculitis • Syphilis-associated aortitis • Drug-associated immune complex vasculitis • Drug-associated ANCA-associated vasculitis • Cancer-associated vasculitis • Others

*Adapted from Chapel Hill Consensus Conferences (CHCC) 2012 criteria.

endothelial cells, leading to the production of cytokines like IL-8 has been introduced as the second hit [6]. IL-8 is a chemoattractant for neutrophils. Finally, according to the last hit, the attracted neutrophils activate by the interaction between IgA1 and FcαRI, and the activated neutrophils cause vascular inflammation and damage in IgAV [4]. In addition, a number of published studies have focused on the role of T cells in the pathogenesis of IgAVN. Finally, our group has shown increased tissue levels of inflammatory cytokines of IFN-γ and IL-17 in renal biopsies of pediatric IgAV patients [7].

Some certain clinical differences stand out between pediatric and adult forms of vasculitides. In adulthood, IgAV/HSP tends to have a more severe course with more severe renal involvement [8-10]. Children more frequently present with abdominal pain before the appearance of purpuric rash, while diarrhea is more common in adulthood [8, 11]. However, there are no prominent differences regarding the distribution of purpura, joint involvement or laboratory findings [12].

We lack evidence-based treatment approach for IgAV/HSP management in childhood, the management approaches mainly depend on adult practice or personal experiences. For this purpose, the SHARE initiative (Single-Hub Access for pediatric Rheumatology in Europe) [13] has been set up to develop evidence-based recommendations for pediatric vasculitides (manuscript in preparation). Our pediatric practice is as follows; the management of IgAV is mainly conservative and includes rest, hydration and symptomatic relief of pain. Severe GIS manifestations and severe skin lesions may need systemic steroid treatment [14]. It has been shown in controlled studies that, early steroid treatment does not prevent renal involvement [15]. In presence of impaired glomerular filtration and severe or persistent proteinuria, patients should be referred to a nephrologist. The severity of the histologic lesions is the best indicator for treatment. In the presence of severe renal involvement, corticosteroids are the first line therapy, combined with other immunosuppressive drugs such as cyclophosphamide, azathioprine or mycophenolate mofetil [12].

3.2. Antineutrophil Cytoplasmic Antibody (ANCA)-associated Vasculitis (AAV)

Antineutrophil cytoplasmic antibody (ANCA)-associated Vasculitis (AAV) includes Granulomatosis with Polyangiitis (GPA) (formerly known as Wegener Granulomatosis), Eosinophilic Granulomatosis with Polyangiitis (EGPA) (previously known as Churg-Strauss syndrome), Microscopic Polyangiitis (MPA), and single organ disease including renal-limited vasculitis characterized with predominantly small size vessels inflammation, and commonly the presence of ANCA [3].

The main underlying pathogenesis is the interaction between genetic susceptibility and triggering environment exposures. ANCAs directly play role in the pathogenesis of small vessel vasculitis. Antibodies targeting neutrophil Proteinase-3 (PR3) and Myeloperoxidase (MPO), are named C-ANCA and P-ANCA respectively. PR3-ANCA is highly sensitive for GPA being present in 80-95% [16]. MPO-ANCA positivity is detected in 40% of EGPA cases [16]. In addition, the presence of MPO-ANCA is described up to 70% of MPA patients [17]. However, there are ANCA negative cases. In childhood, AAV has a higher frequency of morbidity, relapse and accrued damaged when compared to adult AAV patients [18]. Fever, subglottic stenosis, ischemic abdominal pain and nasal cartilage damage are more common in pediatric AAA patients while myalgia and peripheral neuropathy are less common [18]. EGPA is really rare in childhood, however pediatric patients with EGPA have more cardiopulmonary involvements and less peripheral neuropathy [19].

Genome-wide Association Studies (GWAS) studies have confirmed the role of ANCAs in pathogenesis and have highlighted the differences between PR3 and MPO ANCA positive patients. Lyons *et al.* [20] have demonstrated that anti-PR3 ANCA was associated with HLA-DP, the genes encoding alfa-1-antitrypsin (*SERPINA1*) and PR3 (*PRTN3*), whereas anti-MPO ANCA was associated with HLA-DQ. This study has thus confirmed the genetic distinctions between GPA and MPA regarding ANCA serotype [20]. In other genetic studies, *protein tyrosine phosphatase nonreceptor type 22* (*PTPN22*), and *cytotoxic T-lymphocyte antigen* (*CTLA-4*) genes have been associated with the loss of immune tolerance in patients with AAV [21].

Laboratory and clinical studies have underlined the evidence of environmental trigger in pathogenesis as well. Nasal carriage of *Staphylococcus aureus* has been found to be an increased risk for relapse in PR3-AAV patients [22, 23]. Molecular mimicry between PR3 and parts of *Staphylococcus aureus* may explain the association. Furthermore, the reduction of relapse rate with antibiotic prophylaxis supports these findings. The linkage between infections and pathogenesis has also been supported by the discovery of Lysosome-Associated Membrane Protein 2 (LAMP-2) autoantibodies, which has homology to bacterial adhesion FimH [24]. On the other hand silica exposure is found to be an increased risk factor of AAV [25]. Drug associated with AAV have been described previously.

Recently, Sangaletti *et al.* [26] have described that the formation of neutrophil extracellular traps (NETs) plays a role in inducing loss of tolerance to both MPO and PR3.

The European League Against Rheumatism (EULAR) recommendations for the management of AAV have been recently published in 2016 [27]. According to these recommendations, in case of new onset severe organ involvement or life-threating AAV, treatment with a combination of glucocorticoids and either cyclophosphamide or rituximab for the remission-induction is recommended. However, in patients with non-organ threating AAV, combination of glucocorticoids and either methotrexate or mycophenolate mofetil may be preferred for remission-induction [27]. For major organ relapse, treatment as per a new onset severe organ involvement or life-threating AAV is recommended [27]. In case of rapidly progressive glomerulonephritis or severe diffuse alveolar hemorrhage, plasma exchange is advised. Combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil is commended as remission-maintenance treatment. In refractor cases switching cyclophosphamide to rituximab or just the opposite may be an alternative [27]. However, these recom-

mendations have been designed for adult patients, pediatric approach mainly depends on adult experiences.

The conventional treatment of EGPA and MPA is basically similar to GPA treatment. However, some promising results with more targeted therapies have been reported in EGPA patients [28-30]. Recently improved remission rates with mepolizumab (a monoclonal antibody against IL-5) have been described in EGPA patients [30]. Omalizumab is an anti-IgE monoclonal antibody. EGPA patients with asthmatic and/or sinonasal manifestations may be treated with omalizumab [28, 29].

4. PREDOMINANTLY MEDIUM VESSEL DISEASE

4.1. Polyarteritis Nodosa

Polyarteritis Nodosa (PAN) is a primary systemic necrotizing vasculitis, characterized by inflammatory lesions of medium size vessels and necrosis of the vessel walls.

The pathogenesis of PAN is still not clear. Unlike the other necrotizing vasculitis patients are ANCA negative. It is suggested that both innate and adaptive immunity are operative in necrotizing inflammation. Shimojima *et al.* [31] have demonstrated that increased expression of Th1 cells, and Tregs in peripheral blood samples of PAN patients. These findings supported that T-cell mediated immunity roles in disease pathogenesis. The association between cutaneous PAN and streptococcal infection also underline the linkage between the innate immune system and pathogenesis [32].

The disease may be limited to the skin without systemic involvement, which is called cutaneous PAN. The prevalence of cutaneous PAN is probably higher in children than in adults. cutaneous PAN is associated with a better prognosis, but patients relapse more frequently. However, most of the patients with cutaneous PAN are accompanied by musculoskeletal complaints, elevated levels of acute phase reactants. The jury is still out on how to classify cutaneous [33, 34]. In childhood, PAN has a more benign course (with less renal and neurologic involvement) than adult onset PAN. Pediatric PAN patients more commonly present with arthralgia/arthritis and skin involvement, while in adulthood weight loss, renal and neurologic involvement are more frequent [35].

During the course of Hepatitis B infection, necrotizing arteritis, mimicking PAN, may be seen. However, the pathogenesis of Hepatitis B related necrotizing vasculitis differentiates from classic PAN with deposition of immune complex. It is now classified as 'associated with a probable cause' according to 2012 CHCC [3].

Some genetic predisposing factors may predispose to PAN or a PAN-like disease. An association between *Mediterranean FeVer* (*MEFV*) gene and PAN disease have been described among Turkish population [36]. The increased immune response probably triggers necrotizing vasculitis in Familial Mediterranean Fever (FMF) patients.

PAN is a multifactorial complex disease. Thus, as many of our rheumatic diseases, many SNPs with a low effect and probable environmental factors lead to the phenotype. We now have become aware that a SNP/mutation with a significant effect may lead to a similar, if not the same phenotype as the multifactorial "well-known" disease. Deficiency of adenosine deaminase 2 (DADA2)' is a monogenic disorder which leads to a PAN-like phenotype, and strongly mimics classic PAN [37, 38]. Such monogenic diseases can now be classified also as 'vasculitis with probable cause'. Although it is challenging to draw a border between the common form of PAN and this monogenic-mimic, features of an autosomal recessive disease will be helpful for the clinician to decide on a genetic test. This is important since treatment is different for DADA2.

Deficiency of Adenosine Deaminase Type 2 (DADA2) is an autosomal recessive inherited disease, characterized by early onset stroke and vasculopathy, elevated acute phase reactants, fever, peripheral neuropathy, mild immunodeficiency, fluctuating low titers of antibodies [37, 38]. Clinical, histopathological and radiological findings are compatible with PAN in many cases. It is caused by loss of function mutation in the *cat eye syndrome chromosome region candidate 1 (CECR1)* gene [37, 38]. This gene encodes Adenosine Deaminase 2 (ADA2) which roles in endothelial stability, leucocyte development and differentiation [37, 38]. However, the real role of this protein in endothelial hemostasis has not been clearly described. Deficiency of ADA2 leads to endothelial damage and decrease of anti-inflammatory macrophage [37, 38].

Definition of DADA2 has enabled us to better treat these patients as well. Conventional treatment is often not successful. Anti-Tumor Necrosis Factor (TNF) drugs have been found to be effective in disease control [37, 39]. However, duration of treatment is still a matter of debate. Hematopoietic Stem Cell Transplantation (HSCT) should be recommended only in patients with serious illness [40]. Most recently Caorsi *et al.* [41] reported complete response with thalidomide in six DADA2 patients. However, thalidomide was discontinued in three of these patients at a median of 25 (20-60) months due to neuropathy [41].

In patients with early onset, parental consequently, familial history, or PAN unresponsive to conventional treatments, genetic analyzes of *CECR1* is recommended to detect the DADA2 cases. Previous studies have demonstrated that ADA 2 enzyme activity to be significantly reduced in affected individuals compared to healthy controls [42] and should be checked.

Consensus treatment recommendations have been published for adult PAN patients as well [43]. The classic treatment of PAN is glucocorticoids and cyclophosphamide as remission induction and either azathioprine or methotrexate combination with low-dose steroid as maintenance treatment [43]. However, there are no evidence-based data for pediatric PAN treatment. With this background, researches focus to find a less toxic, alternative drug in PAN patients. Thus, 'the MYPAN trial', a multicenter, open-label, randomized controlled trial comparing myclofenate mofetil versus cyclophosphamide for the induction of remission have been designed and continued.

4.2. Kawasaki Disease

Kawasaki Disease (KD) is an acute febrile childhood vasculitis of small and medium-size arteries with an in-

creased risk of development coroner artery abnormalities [44]. Numerous studies suggested a linkage between infectious agents and KD. The seasonal cluster has been shown among different ethnical groups, such as winter/spring peak in Japan, summer/spring peak in Chine [45]. The seasonal variation in different countries may be driven by different infectious agents [45]. Most recent studies have speculated that tropospheric wind patterns and air population may trigger the immunopathological pathways in genetically susceptible children by variable inhaler agents [44].

In the last decade, in GWAS, numerous single nucleotide polymorphisms (SNPs) significantly associated with the occurrence of KD have been identified. SNPs such as *B cell lymphoid kinase* (*BLK), CD40, FCGR2A, inositol-triphosphate 3-kinase C* (*ITPKC*), and *caspase 3* (*CASP3*) have been described as an increased risk of KD [46-50]. Recently Alphonse *et al.* [51] demonstrated the linkage between calcium mobilization and inflammatory response in KD. They showed that *ITPKC* regulates NLRP3 inflammasome activation via calcium mobilization, resulting in increased IL-1β and IL-18 production. Polymorphism in *ITPKC* has been found to be associated with highest basal and stimulated calcium levels, increased NLRP3 activation and IL-1β and IL-18 production [51]. Based on these findings, IL-1 blockade treatment has emerged as an option in unresponsive KD [51].

Most recently, a new guideline for KD treatment and follow-up has been established by the American Heart Association (AHA) [44]. This guideline has underlined that the importance of the coronary arteries imaging with a quantitative assessment of luminal dimensions, normalized as Z scores adjusted for body surface [44]. According to this guideline, a single administration of 2 g/kg Intravenous Immunoglobulin (IVIG) plus Acetylsalicylic Acid (ASA) is the still standard therapy of KD. However, the standard dose of ASA at initiation is still a matter of debate [44]. A portion of patients was resistant to IVIG treatment [44]. These patients were at risk of coronary artery involvement. According to AHA guideline, high-dose pulse steroids, infliximab, cyclosporine, anakinra should be considered in patients who have failed response to standard therapy (IVIG resistance cases) [44]. Risk scoring systems have been developed to predict the IVIG resistance patients at the initiation of the treatment [52-54]. In high-risk patients administration of corticosteroids treatment concomitant with IVIG and ASA, is recommended [44]. Kobayashi score [54] is the most popular scoring system while this score did not prove as useful in western ethnicities [55, 56].

5. PREDOMINANTLY LARGE VESSEL DISEASE

5.1. Takayasu Arteritis

Takayasu Arteritis (TA) a large vessel vasculitis that affects the aorta and its main branches [3]. The arterial inflammation of vessels may lead to vascular damage, characterizing with arterial stenosis, ischemia, progressive occlusions, and/or aneurysms.

In TA genetic susceptibility loci have been identified, for example, the potential role of human leukocyte antigen (HLA) genes in the pathogenesis has been demonstrated [57]. *HLA-B*52:01* allele has been found to be associated with the disease in Japanese patients, then confirmed in other populations such as Chinese, Korean, Turkish, European-American [57]. In addition, many susceptibility loci have been identified throughout GWAS such as *RPS9/LILRB3*, *LILA3*, *IL38,* IL12B [57]. These studies have suggested that inappropriate response of the immune response may paly a role in the pathogenesis. Recently, elevated IL6 levels have been demonstrated in the vascular lesions and the serum of TA patients [58, 59]. This observation has supported the use of anti-IL6 in TA. Terao *et al.* have demonstrated that SNP in *IL12B,* encoding IL12/23p40, is strongly associated with disease activity [60, 61]. These findings have also provided targeted therapy in TA patients.

Pediatric TA is more acute disease (personal observation) and patients commonly present with arterial hypertension (82%), headache (31%), fever (29%), and dyspnea (23%) and weight loss (22%) [62-64]. Musculoskeletal involvement is more and ocular findings are less common in children [62-64] whereas bruits and claudication are more frequent among adult patients [65].

EULAR endorsed recommendations have been developed for TA for adults as well [66]. However, treatment approaches are commonly based on personal experiences in pediatric clinics. Steroids are the mainstay of therapy. Remission induction may include immune suppressive agents such as_cyclophosphamide, azathioprine or biologics and maintenance treatment may continue with lower dose steroids and methotrexate [67, 68]. With recent insights into the pathogenesis, biologic therapies are increasingly used in TA treatment. Successful control of the disease with anti-TNF has been reported [67, 69]. Promising results with anti-IL6 (tocilizumab) have also been reported in the last years as well [70]. Batu *et al.* have demonstrated an effective disease control with tocilizumab in four pediatric TA patients [71]. On the other hand, Terao *et al.* have demonstrated that ustekinumab, a monoclonal antibody against IL-12/ 23p40, may be a safe and effective treatment option for TA patients, which is supported by genetic association findings [60]. Despite the increasing use of biologic therapies in TA, there is still a lack of randomized controlled trials. In addition, surgical procedures may be required for the treatment due to the destructive effect of the disease on the large vessels. Surgery may be considered in the inactive phase of the disease [72].

6. VARIABLE VESSEL DISEASE

6.1. Behçet's Disease

Behçet's Disease (BD) is a systemic vasculitis, affecting any vessel size in both the arterial and venous systems and has thus been recently classified as variable vessel vasculitis in the CHCC 2012 [3]. Although it was originally described as a triad of aphthous stomatitis, genital ulceration, and uveitis, cutaneous, articular, gastrointestinal, and/or central nervous system inflammatory lesions may accompany the disease.

Until now more than 15 sets of diagnostic/classification criteria for BD have been developed [73]. The most commonly used one, International Study Group (ISG) criteria fail to classify most of pediatric BD patients due to its low sensi-

tivity. A new set of criteria for adult BD patients, was called the International Criteria for BD (ICBD), have been created [74-76]. Recently, an international expert consensus group (the pediatric BD [PEDBD] group) has established a new set of classification criteria for pediatric BD [77]. The performance of the new pediatric criteria was found to be 73.5% sensitive and 98.9% specific in childhood BD, by a Turkish and Israel group [78].

There are certain differences between pediatric and adult patients. Clinical findings may differentiate between gender. Uveitis is more common and more severe in boys [79-83] and genital ulcers are more frequent in girls [80-84].

A complex genetic background plays a role in pathogenesis. There is a strong association with human leukocyte antigen (HLA)-B51. Studies have demonstrated a significant effect (odds ratio [OR] 3.49-5.78) of HLA–B51/B5 on the risk of BD [85, 86]. GWAS studies have confirmed the association of BD with HLA–B51/B5 and also shown an association with *interleukin (IL)-10*, and *IL23R/IL12RB2, STAT4, endoplasmic reticulum aminopeptidase1 (ERAP1)* genes [86-91]. IL-10 is an anti-inflammatory cytokine, and IL-23 has a critical role in the inflammatory Th17 pathway. *ERAP1* gene encodes endoplasmic reticulum aminopeptidase, which trims intracellular proteasome-derived peptides and binding of HLA class I molecules in the Endoplasmic Reticulum (ER). *ERAP1* isoforms coordinate the amino terminals of intracellular proteasome-derived peptides and lead to changing peptide binding affinity which may result in disordered folding of HLA molecules, hence triggering the inflammation through the IL23/IL17 pathway [89, 92]. Recently Taeuchi *et al.* [93] have demonstrated an epistatic relation and a 10.96-fold increased risk odds in the presence of homozygosity for *ERAP1* haplotype 10 and HLA-B51. [93]. A new Immunochip study, including 1900 Turkish patients with BD and 1779 controls, has provided further perspective in the pathogenesis of BD [94]. A strong association of HLA-B51 has been confirmed, and three new risk loci including *IL1A-IL1B*, *interferon regulatory factor* (*IRF*) *8*, and *CEBPB-PTPN1* have been identified in Turkish patients [94]. In the same study, two of these loci were confirmed in the Iranian and Japanese patient cohorts [94]. This study also highlighted the *Laccase Domain Containing 1* (*LACC1*) and *fucosyltransferase 2* (*FUT2*) loci. All these loci are associated with microbial response. Thus, suggesting a linkage between innate immune response to microbes and BD susceptibility [94].

EULAR recommendation of the BD management has been updated in 2016 [95]. According to the new recommendation, anti-TNF treatment may be used in the refractory case and even the first-line therapy in severe neuro-BD. New treatment alternatives have been emerged depending on new genetic insights. Almost all patients with BD suffer from mucocutaneous involvements, especially aphthous stomatitis. However, traditional treatments such as colchicine, azathioprine are inadequate in some patients. Recently, a randomized, placebo controlled trial with apremilast has been conducted in Behçet's patients with active mucocutaneous involvements and no major organ involvement [96]. Apremilast is a phosphodiesterase 4 inhibitor. Significant reduction of oral ulcers in 12 weeks has been shown in apremilast group as compared to placebo group [96]. However, the study was insufficient in evaluating the effect of the drug on controlling genital ulcers (only including 10 patients in apremilast group and six in control group) [96]. Nausea, vomiting, and diarrhea were the most common side effects [96]. Gevokizumab is a monoclonal IL-1β blocking antibody, and its initial results are promising in resistant uveitis [97]. Recently Grayson *et al.* [98] have presented a partial response with 200 mg daily anakinra in resistant oral and genital ulcers in patients with Behçet's disease. Finally, ustekinumab (anti-IL12/23 antagonist) may be an alternative agent in refractory mucocuteneous BD [99, 100]. However, further data is needed.

We now have a monogenic disease mimicking BD as well: Haploinsufficiency of A20 (HA20). Zhou *et al.* [101] described this new autoinflammatory syndrome mimicking BD in six unrelated families. Contrary to the polygenic inheritance of BD, this disease is caused by high-penetrance heterozygous mutations in *TNF α-induced protein 3* (*TNFAIP3/ A20*) which encodes the nuclear factor kappa-B (NF-κB) regulatory protein [101]. TNFAIP3/ A20 plays a role in suppressing the NF-κB signals via deubiquitinating. In case of the loss of function, A20 leads to increased inflammatory process [101]. Anti-TNF, or anti-IL1 (anakinra), are currently used to treat HA20 patients [101, 102].

CONCLUSION

We have been able to better define and classify the vasculitides. Recent studies have improved our understanding of the pathogenesis of the disease. Well-designed, multicenter studies are hoped to guide us in more targeted therapy.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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