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REVIEW ARTICLE

Cerebrovascular involvement in systemic childhood vasculitides

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Abstract

Pediatric vasculitides sometimes involve central nervous system (CNS). The manifestations are diverse, ranging from headache, seizures, vertigo, ataxia, behavioral changes, neuropsychiatric symptoms, consciousness disorders, and even cerebrovascular (CV) accidents that may lead to irreversible impairment and even death. Stroke, on the other hand despite the great progress in prevention and treatment, is still one of the leading causes of morbidity and mortality in the general population. The aim of this article was to summarize CNS manifestations and CV issues observed in primary pediatric vasculitides and the current knowledge of etiology and CV risk factors, preventive strategies, and therapeutic options in this target patient population. Pathophysiological links reveal similar immunological mechanisms involved in both pediatric vasculitides and CV events with endothelial injury and damage being the central point. From the clinical point of view, CV events in pediatric vasculitides were associated with increased morbidity and poor prognosis. If damage has already occurred, the therapeutic approach consists of good management of the vasculitis itself, antiplatelet and anticoagulation therapy, and early rehabilitation. Risk factors for acquiring cerebrovascular disease (CVD) and stroke, particularly hypertension and early atherosclerotic changes, already begin in childhood, with vessel wall inflammation contributing itself, once more emphasizing that appropriate preventive measures are certainly necessary in pediatric vasculitis population to improve their long-term outcome.

Keywords Central nervous system involvement · Cerebrovascular disorders · Pediatric vasculitis · Risk factors

Introduction

Vasculitides are a heterogeneous group of diseases of mostly unknown etiology with a common pathohistological finding of inflammation and necrosis of the blood vessel wall, which causes organ damage. They can appear secondary as a part of multisystemic inflammatory disease or as primary but, in general, occur more often in adults than children [1]. Since many organs and tissues can be affected, clinical features of primary systemic vasculitides are very diverse and depend on the localization, type, and size of the affected vessels and on the severity of associated inflammatory symptoms. This makes diagnosing challenging, especially in childhood which as a consequence can have significant morbidity. However, the final European League Against Rheumatism (EULAR)/Pediatric Rheumatology International Trials Organisation (PRINTO)/Pediatric Rheumatology European Society (PRES) classification criteria adopted in Ankara

Key Messages
- Pediatric vasculitides are rare, but possible cause of stroke in children and adolescents
- Endothelial injury plays central role in both pediatric vasculitides and cerebrovascular diseases (CVDs), including stroke
- The healthcare approach to a pediatric vasculitis patient who developed CVD includes three key steps: vasculitis specific treatment, CVD management and implementation of preventive measures

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2008 for the four pediatric vasculitides have high sensitivity and specificity making it easier to diagnose [2]. For remaining vasculitides, Revised International Chapel Hill Consensus Conference (CHCC) endorsed in 2012, which classifies individual vasculitides according to the size of the predominantly affected blood vessels, may be used [3]. Otherwise, these rare diseases through complex mechanisms result in macrovascular and microvascular damage during both the acute and chronic phases of the disease. Active vasculitis directly leads to endothelial dysfunction, intimal hyperplasia, and a low-grade procoagulant state by increased inflammatory cells recruitment and locally released cytokines. This may cause tissue ischemia and thus predispose these patients to various cardiovascular events. This particularly applies to stroke, myocardial infarction (MI), cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral arterial disease (PAD) since various evidence suggest that cardiovascular diseases are today a leading cause of morbidity and mortality among adult patients with systemic vasculitis [4–11]. The term CVD includes all disorders such as stroke, carotid, vertebral and intracranial stenosis, aneurysms, and vascular malformations, in which an area of the brain is temporarily or permanently affected by ischemia or hemorrhage. Despite great progress in prevention and acute treatment in recent decades, stroke still remains the second most common cause of death and major cause of disability affecting approximately 1.1 million inhabitants of Europe annually and due to the aging of the European population, a further increase to 1.5 million is expected by 2025 [12–14]. Approximately 5–10% of all cerebrovascular (CV) events are caused by vasculitides, with this percentage being slightly higher in the young adult population (< 45 years) [15, 16]. Central nervous system (CNS) involvement and pathological changes in the main cerebral vessels are seen in vasculitides, placing patients directly and indirectly at increased risk for developing CVD. Although CVD is mainly clinically expressed in the middle and older age, the complex synergy of traditional and non-traditional risk factors as well as the first atherosclerotic signs is present since childhood. Therefore, the objectives of this review article are to discuss the CNS manifestations and CV issues observed in primary pediatric vasculitides, to assess their prevalence, and to summarize the current knowledge of etiology and CV risk factors, preventive strategies, and therapeutic options in this patient population.

Search strategy

For this narrative review, we searched the MEDLINE database through PubMed. The selected articles were original research published in English from inception until the end of November 2022. The search strategy used the following MeSH terms "Takayasu arteritis," "Kawasaki disease," "polyarteritis nodosa," "Henoch-Schönlein purpura," "IgA vasculitis," "granulomatosis with polyangiitis," "eosinophilic granulomatosis with polyangiitis," "microscopic polyangiitis," "Behçet's disease," "cerebrovascular disorders," "stroke", "central nervous system involvement," "childhood-onset," "pediatric," "juvenile." Expert opinions, editorials, and letters to the editor were excluded. Eligible studies were those meeting the following criteria: pediatric population, disease of interest (primary vasculitis), original research, and full-length articles, although we did not limit ourselves to these. Vasculitides associated with other connective tissue diseases, infections, malignancies, and medications as well as unclassified vasculitides have been excluded from the present review, since these entities involve additional pathological mechanisms. Studies were screened by titles and abstracts for relative content. Additionally, articles were extracted from the reference list of retrieved articles if they were considered relevant. Selected articles were assessed for quality. Finally, a total of 113 articles were evaluated and included in this review, of which 27 articles directly focus on CNS involvement and CVD issues in pediatric vasculitides (Fig. 1).

Endothelial injury in pediatric vasculitis and cerebrovascular damage

Pathogenesis of pediatric vasculitides remains unclear, but it is known to involve immune complex depositions in the vessel wall probably as a response to a certain trigger, such as infection, in individuals who have a genetic predisposition. In vitro and animal models support the idea that autoantibodies have a direct pathological role in the formation of small vessel vasculitides. Autoantibodies directed to myeloperoxidase (MPO) and proteinase 3 (PR3) activate inflammatory cells, particularly neutrophils, which then adhere to the inner vessel wall and cause intramural inflammation by releasing numerous proteolytic enzymes, triggering a cascade of pro-inflammatory cytokines and activate endothelial cells (ECs) which all interfere with vascular homeostasis [17, 18]. Various adhesion molecules expressed on EC cells become upregulated [19]. Activated neutrophils form neutrophil extracellular traps (NETs) composed of neutrophil double-stranded DNA, histones, highly decondensated chromatin fibers, and neutrophil granules containing MPO, PR3, elastases, proteases, and cathepsin G. resulting in a novel type of active cell death called NETosis [20]. The enzyme peptidylarginine deiminase 4 (PAD4) is essential for NETosis, since it converts arginine residues of histones H3 and H4 into citrulline residues, thereby inducing chromatin decondensation and thus swelling of the nucleus, facilitating the expulsion of chromosomal DNA. Targeted autoantigens

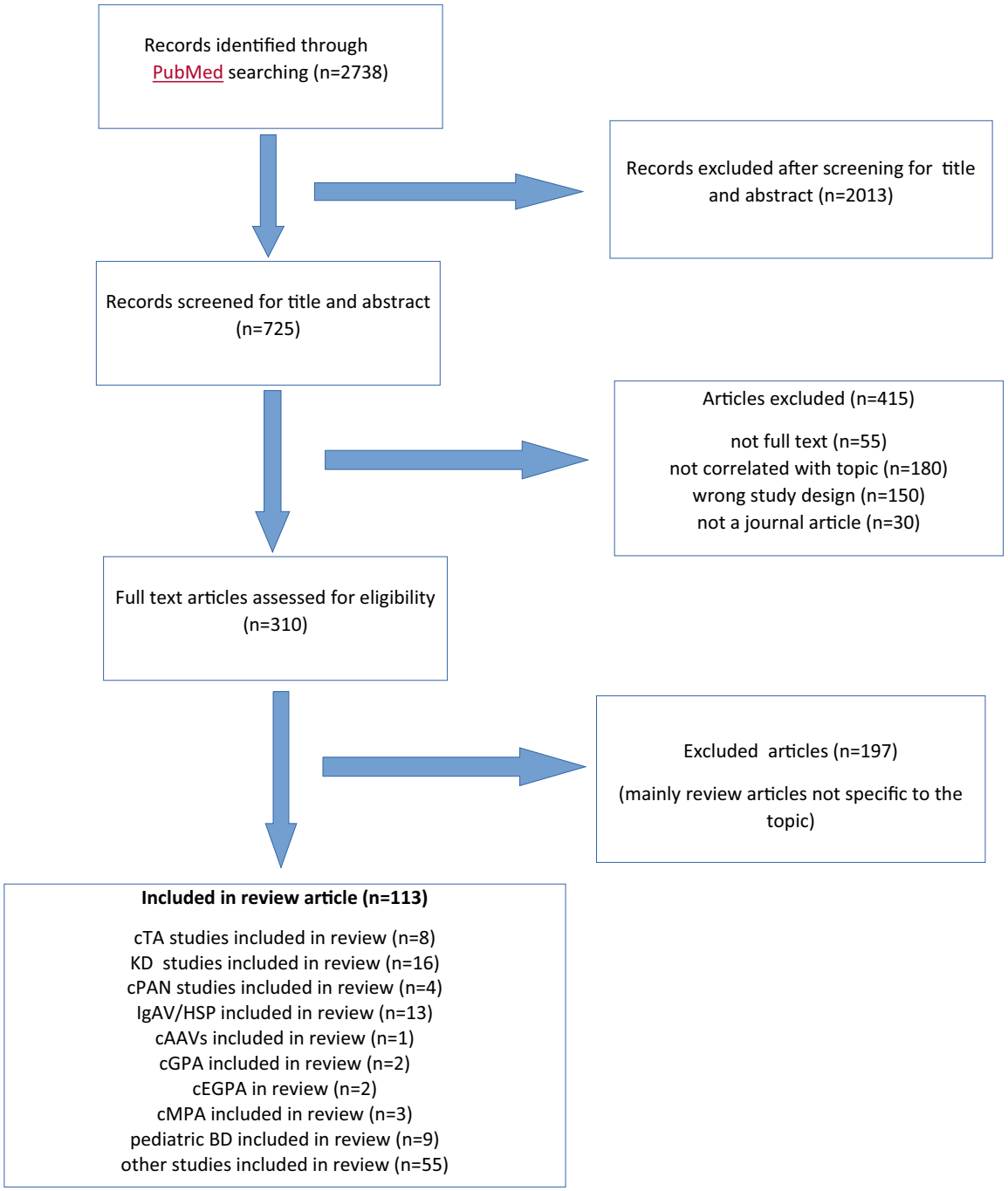

Fig. 1 Flowchart of search strategy and selection process

MPO and PR3 were found within NETs, suggesting that NET formation promotes ANCA-associated vasculitis (AAV) while it was demonstrated that patients with AAV have elevated circulating NET levels and deposits in renal biopsy specimens [21]. Several studies have indicated elevated NET levels during the acute and/or active phase of IgA vasculitis, Kawasaki disease, and Behcet's disease [22–24]. Inhibition of PAD4 may become a promising therapeutic strategy in thrombotic complications of BD as PAD4-deficient mice failed to form stable thrombi in a model of deep vein thrombosis (DVT) suggesting the importance of this enzyme in NET-thrombosis interaction [25]. In addition to hypercoagulability, NETs also cause endothelial dysfunction by decreasing cell proliferation and inducing apoptosis in vitro while NET release was inhibited by colchicine suggesting a potentially therapeutic effect [26]. In addition

to NETs, increasing researches show that many small fragments termed microparticles (MPs) that are shed into the bloodstream by activated platelets, ECs, and leukocytes are also associated with pediatric vasculitides [27–29]. There is much evidence to suggest that endothelial injury occurring in pediatric vasculitides promotes early atherosclerosis while chronic inflammation and immune dysregulation of ECs play an important role in its development and further progression [30, 31]. Oxidized low-density lipoprotein (oxLDL) represents a crucial pro-inflammatory stimulus for atherosclerosis development [32]. OxLDL activates ECs and upregulates adhesion molecule expression and chemotactic chemokine secretion leading to granulocyte and monocyte recruitment. In vitro studies showed that autoantibodies such as ANCA, antiphospholipid (aPL) antibodies, and anti-EC antibodies may further activate ECs [19, 33]. There is also evidence that MPO is implicated in atherosclerosis development [34]. Early atherosclerosis is primarily characterized by the adherence of monocytes on the endothelium with platelets aggregating on the injured area; then monocytes migrate to the subendothelial space and differentiate into tissue macrophages which locally proliferate and phagocytose oxLDL and finally turning into foam cells. Injured ECs, foam cells, platelets, and released cytokines encourage smooth muscle cell proliferation and migration from the tunica media into the intima. Injured ECs produce less nitrix oxide (NO) and prostacyclin (PGI2) resulting in less smooth muscle cell relaxation while overexpressed endothelin constricts blood vessels raising blood pressure. Reduced blood flow causes local ischemia which ultimately leads to damage and necrosis due to tissue hypoxia. In addition to all, long-term treatment and medication deleterious effects may also contribute to endothelial injury in pediatric vasculitides. Glucocorticoids affect plasma lipoproteins and may have a proatherogenic effect, promote insulin resistance, and increase body mass and sodium retention resulting in hypertension. Methotrexate may increase homocysteine levels, while immunosuppressants from the group of calcineurin inhibitors by sodium and liquid retention may promote hypertension. In brief, in pediatric vasculitides, several mechanisms are involved in endothelial injury and vascular damage: (1) local intramural vessel wall inflammation; (2) systemic inflammation response following local inflammation; (3) early atherosclerosis; and (4) treatment duration and deleterious drug effects on the vessel wall (Fig. 2).

CVD, especially stroke as its most severe event, share similar pathological mechanisms as vasculitides. NETs are recognized in the development and progression of ischemic stroke as well [35, 36]. Ducroux et al. performed histological analysis on 34 human ischemic stroke thrombi and found that NETs were abundantly present in all thrombi via triple staining positive for DNA, MPO, and citrullinated histone [35]. Interestingly, aforementioned endothelial adhesion molecules are upregulated in animal models of ischemic stroke and thrombotic conditions as well [37–40]. Furthermore, several studies reported elevated circulating levels of PMPs, EMPs, and leukocyte-derived microparticles in ischemic CVD and stroke reflecting vascular inflammation injury and correlating with the clinical disease severity, stroke volume, and outcome [41–43]. In addition to all, vascular endothelial growth factor (VEGF) is expressed in higher than normal concentrations in the penumbra after ischemic stroke suggesting that it could be involved in the repair processes [44]. It is not as simple as it appears to answer whether there is a some secret link between pediatric vasculitides and cerebrovascular damage but similar pathological pathways are included in both disorders. Family, age and gender disposition, dyslipidemia, hypertension, diabetes,

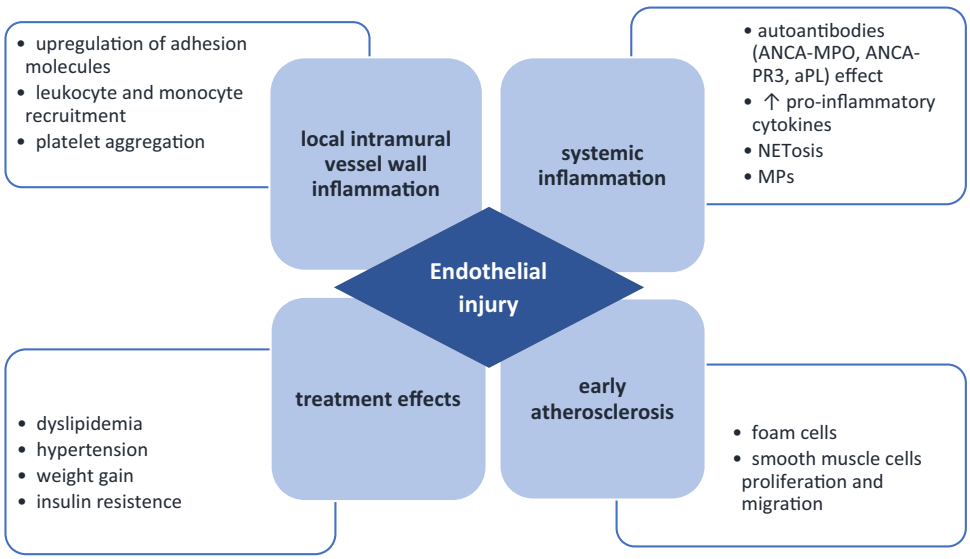

Fig. 2 A schematic overview of mechanisms involved in pediatric vasculitides

obesity, sedentary lifestyle, and tobacco smoking are well-known risk factors for CVD, of which premature atherosclerosis, hypertension, and obesity are certainly observed in pediatric vasculitides [30, 45, 46]. Impaired renal function, commonly encountered in some pediatric vasculitides, also contributes to CVD by increasing the likelihood of hypertension, one of the most significant modifiable risk factors. All of this once again intertwines CVD and pediatric vasculitides, thus although rare, vasculitides may be an important cause of CV events and should not be neglected for stroke, especially in the pediatric population in whom conventional risk factors are absent or slightly present.

Cerebrovascular issues in large vessel vasculitis

Childhood-onset Takayasu arteritis (c-TA)

Childhood-onset Takayasu arteritis (c-TA) is the only large vessel vasculitis seen in the pediatric population characterized by granulomatous inflammation that mainly involves the aorta and its major branches at their origin that may develop stenosis, occlusion, dilatation, and/or aneurysm formation in the affected arteries. The exact incidence of c-TA is unknown; it varies across different populations and geographic regions, ranging from 0.4 to 6.3 per million, with higher rates observed among Asians, estimated at 2.6/1,000,000 in all ages [1, 47]. Etiology is still not fully understood, but it is known that TA usually affects young females under the age of 40 years [1, 2]. However, in up to 30% of patients, clinical features of the disease are reported before the age of 18 years, once again emphasizing the importance of considering this diagnosis so that it does not remain unrecognized [48, 49]. c-TA is classified according to the EULAR/PRINTO/PRES (Ankara 2008) criteria [2].

c-TA initially begins with constitutional and nonspecific symptoms including fever, fatigue, weight loss, night sweats, malaise, fainting, headache, arthralgias, and cutaneous manifestations (rash, nodules) [49–51]. In the next phase of the disease, angiographic abnormalities of the characteristically affected vessels predominate, with neurological manifestations, particularly present in classification type I involving supra-aortic arteries and type IIa involving the aortic arch with common carotid, subclavian, and brachiocephalic arteries. Neurological symptoms, as shown in Table 1, are commonly observed in c-TA and may be one of the initial presentations of the disease, especially headache [48, 49, 51, 52]. The major cause of headache in c-TA is reduced blood flow to the brain due to narrowing and/or occlusion of the subclavian and common carotid artery. However, it can also appear in the acute, inflammatory phase of the disease as a constitutional symptom. A large observational Indian cohort compared children and adult patients with TA and reported headaches significantly more frequent in c-TA [53]. Common neurological manifestations occurring in 15–35% of c-TA patients also include dizziness and syncope [45, 49, 52, 54]. Other slightly less reported symptoms are blurred vision, seizures, carotidynia, and jaw pain [45, 50, 53, 54]. Angiographic findings showing narrowing of subclavian and carotid arteries are reported in 42.9–71% of c-TA patients [45, 49, 50, 53, 54]. Stenosis affecting the supra-aortic arteries impairs cerebral perfusion and heightens the risk for the most severe neurological complications seen in c-TA, and

Table 1 Central nervous system (CNS) involvement and cerebrovascular disease (CVD) in pediatric vasculitides

Neurologic manifestation	c-TA	KD	cPAN	IgAV	BD
Stroke	6–18% [45, 48, 49, 52–55]	0.9% [57]	5.8–10% [58, 59]	Rarely [case report: 91]	17% [60]
Headache	14.3–52.5% [48–55]	< 1% [61]	9.6–13.6% [59, 62]	9.8–28% [63, 64]	60–75% [60, 65]
Dizziness	4.8–29.4% [45, 49, 50, 54]	NR	NR	9.8% [63]	20% [65, 66]
Syncope	2–35.3% [45, 48–54]	NR	8.3% [67]	rarely [68]	NR
Seizures	7–9.5% [49–51]	1.1 to 3.7% [57]	0.09–7.7% [59, 62, 67]	0.7% [63]	3–20% [60, 65, 66]
Carotidynia	3–17.6% [45, 49, 50, 53, 54]	NR	NR	NR	NR
Visual disturbances	9.5–29.4% [50, 52–54]	1.7% [57]	9.6% [59]	Rarely [69]	16.7–20% [60, 65, 70]
Cranial nerve palsy	NR	0.9% [57]	6–15.4% [58, 59, 62]	Rarely [71]	20% [65]
Ataxia	NR	9.5% [57]	1.9% [59]	Rarely [71]	Not known, but possible [72]

c-TA childhood-onset Takayasu arteritis, *KD* Kawasaki disease, *cPAN* childhood-onset polyarteritis nodosa, *IgAV* IgA vasculitis, *cAAVs* childhood-onset antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, *cGPA* childhood-onset granulomatosis with polyangiitis, *cEGPA* childhood-onset eosinophilic granulomatosis with polyangiitis, *cMPA* childhood-onset microscopic polyangiitis, *BD* Behçet's disease, *NR* not reported

those are transient ischemic attack (TIA) and stroke. Prevalence of stroke according to different patient studies varies between 6 and 18% [45, 48, 49, 52–55]. Fan et al. assessed 101 c-TA patients and observed that stroke at initial presentation was an independent predictor for poor outcome increasing 7.4 times risk for further events [45]. The underlying mechanisms of stroke in c-TA remain unclear, and various causes have been suggested: vascular stenoses and occlusions, carotid aneurysm, vasospasm in hypertensive encephalopathy, etc., while in adults, it is also associated with positive lupus anticoagulant (LAC) [56].

The majority of cross-sectional and observational studies on c-TA patients reported systolic hypertension as the leading clinical feature since its frequency ranged between 60 and 82.6% [45, 48, 49, 52–55] reaching a significant difference compared to adult patients in some studies [49, 53]. When a severe increase of blood pressure occurs, hypertension in the form of crisis, it may also present with neurological symptoms such as headache, confusion, convulsions, transient cortical blindness, malaise, and loss of consciousness causing cerebral damage as reported in the case of a 20-year-old female with TA [73]. In addition to all the above mentioned, hypertension proved to be one of the most important modifiable risk factors for CV events both in general population as well as among TA patients [7, 12, 14, 16]. To conclude, neurological manifestations may be observed in c-TA and are potentially life-threatening; therefore, early recognition and adequate therapy are important to avoid persistent vessel damage with consequent ischemia of vital organs.

Cerebrovascular issues in medium vessel vasculitis

Kawasaki disease (KD)

Kawasaki disease (KD) is a medium vessel vasculitis predominantly occurring in infants and during early childhood. It is the second most common primary systemic childhood vasculitis after IgA vasculitis (IgAV) and is characterized by an acute onset with fever persisting for at least 5 days and 4 of the 5 following clinical criteria: bilateral conjunctival injection, unilateral cervical lymphadenopathy, maculopapular erythematous rash, oropharyngeal mucosal changes, and hyperemic and painful hands and feet edema that tends to desquamation from the second week of the disease [74]. It is worldwide distributed with the highest rates reported among Asian children, especially in Japan where the estimated incidence is 330/100,000 in children aged 0–4 years with boys more commonly affected than girls [1, 75]. The most important complication of KD is certainly coronary artery aneurism formation which occurs in approximately 25% of untreated children [74]. Up to 30% of patients with KD may exhibit CNS involvement [76]. Some neurological manifestations are summarized in Table 1. Although cerebral arteries are usually spared from the disease process, neurologic imaging findings in some cases reveal cerebral ischemia and infarct with or without neurological manifestations [77, 78], subdural effusion [79], cerebellar infarction and obliteration of posterior inferior cerebellar artery [80], and subarachnoidal hemorrhage caused by the rupture of middle cerebral artery aneurysm [81]. Ichiyama et al. observed transient localized cerebral hypoperfusion on SPECT (single-photon emission computed tomography) in 6 of 21 children with KD (29%) during the acute stage [82]. These reports may indicate that KD patients have silent CV lesions. Prospective clinical study conducted on 115 children with KD observed ataxia in 9.5% of patients while magnetic resonance angiography (MRA) showed lesions consistent with cerebral ischemia in one patient presented as chorea [57]. For comparison, a huge retrospective study on 1582 adult KD patients observed neurological involvement in 5% of patients with consciousness disorders, convulsions, and headache being the most frequent [61]. Carotid artery intima media thickness, evidence of endothelial dysfunction, and arterial stiffness have been well documented in children and adolescents with a history of KD, particularly those who developed coronary artery aneurysms thus suggesting an adverse cardiovascular risk profile longer after initial inflammation resolution [30, 83]. Furthermore, hypertension and hyperlipidemia, two major risk factors for CVD and stroke, are commonly reported in children and adolescents with KD [30, 83, 84]. Finally, Liu et al. in their large nationwide retrospective study assessed 8467 children with KD and reported very important findings of a 3.2-fold higher overall CVD incidence rate in KD, particularly in those younger than 5 years [85].

Childhood-onset polyarteritis nodosa (cPAN)

Childhood-onset polyarteritis nodosa (cPAN) is a systemic necrotizing medium-sized vessel vasculitis of unknown etiology that typically involves muscular arteries preferentially at bifurcations, especially renal arteries and other internal organs arteries and generally sparing the lungs' circulation. These lesions may result in microaneurysm formation, hemorrhage due to aneurysmatic rupture, thrombosis, and consequently organ ischemia or infarction. Therefore, various complications are possible, so although rare, cPAN remains a severe and life-threatening condition with a reported mortality rate between 1 and 4% [58, 59, 62]. cPAN is classified according to the previously mentioned EULAR/PRINTO/PRES (Ankara 2008) criteria [2]. In cPAN, almost any organ can be involved, but constitutional symptoms, skin, musculoskeletal, renal,

and gastrointestinal manifestations occur more frequently than CNS, cardiovascular, and pulmonary involvement [58, 59, 62, 67]. The affection of the peripheral nervous system commonly presents in the form of motor mononeuritis multiplex and sensory peripheral neuropathy, and CNS involvement often manifests as seizures, headache, cranial nerve palsy, and altered state of consciousness (Table 1) and is usually observed in up to 30% of cPAN patients [58, 59, 62, 67]. Stroke as the most severe complication has been reported in up to 10% of cPAN patients with CNS involvement [58, 59]. Perhaps even more important information is the one from a retrospective study on 52 cPAN patients by Falcini et al. where all deceased cPAN patients were those with severe CNS involvement complicated by cerebral infarction [59]. The same authors observed that CNS involvement during the disease, in particular cranial nerve palsy, was associated with a more aggressive disease course, while the occurrence of seizures correlated with the development of irreversible organ damage [59]. One of the most important risk factors for CVD and stroke is hypertension, which in cPAN is certainly an important and frequent feature, since it even forms a minor criteria for diagnosing the disease. In the largest multicentric study to date, including 110 pediatric patients with PAN, hypertension was observed in 43% of patients [62]. In a huge nationwide study of 2644 adult patients suffering from systemic necrotizing vasculitis, hypertension proved to be associated with an increased risk of stroke [86]. Being in mind that valuable information, it is noteworthy to monitor and take good care of blood pressure already in the pediatric population with PAN.

In children with PAN-like phenotype and early-onset stroke episodes, deficiency of adenosine deaminase 2 (DADA2) should be considered in the differential diagnosis. Although DADA2 is a monogenic autoinflammatory disease that can manifest with a diverse spectrum of clinical features, arterial vasculopathy is the most common and may result in neurological impairment. The frequency of stroke in children with DADA2 is very high and according to various studies ranges between 40 and 60% [87–90]. In particular, the fact that most patients suffer several strokes at once should not be neglected [88–90]. Usually, it is a series of smaller ischemic strokes that predominantly affect the basal ganglia and brain stem, and the accumulation of their effects can cause severe damage such as ataxia, palsy of one or more cranial nerves, dysarthria, cognitive impairment, or seizures. Sometimes, hemorrhagic insults are also observed. A retrospective study conducted on 31 patients with DADA2 with a median age of 15 years reported a beneficial effect of anti-TNF on reducing CV ischemic events [90].

Cerebrovascular issues in small vessel vasculitis

IgA vasculitis (IgAV) /Henoch-Schönlein purpura (HSP)

IgA vasculitis (IgAV), also known as Henoch-Schönlein purpura (HSP), is the most common systemic vasculitis in childhood characterized by non-granulomatous inflammation of small blood vessels with predominant IgA1 immune deposits. IgAV is worldwide spread with an estimated incidence rate of 3 to 55.9 cases per 100,000 children, while the prevalence varies between 6.1 and 20.4 per 100,000 children, and its most recognizable sign is certainly purpuric rash [1, 2, 91, 92]. Although IgAV usually has a favorable prognosis with symptoms lasting up to 4 weeks, various acute and chronic complications may occur. The most frequent acute complications are those related to gastrointestinal involvement and include bleeding, intussusceptions, and bowel perforation, while the most significant chronic complication of the disease and main cause of morbidity and mortality is the development of IgA vasculitis nephritis (IgAVN) reported in 20–60% of patients which can result with end-stage renal disease (ESRD) in 1–3% of cases [92–94]. CNS involvement in IgAV is rare and has been reported in up to 10% of children [63]. The most common CNS manifestations are headache, dizziness, behavioral changes, seizures, irritability, and emotional instability (Table 1) and may be a result of CNS vasculitis or associated with arterial hypertension in IgAVN and treatment [63, 64, 68, 95]. However, Ostergaard and Storm reported headache and behavioral alterations with normal neurological examination in 28% of patients in their cohort of 39 children with IgAV. Fifty-five prevent of these patients had transient electroencephalograhic abnormalities in the form of focal or diffuse slow wave activity and paroxysms, thus indicating that mild cerebral involvement is quite often found in IgAV and probably is being underestimated [64]. Rare and uncommon features including posterior reversible encephalopathy and ataxia have also been reported [69, 71]. CNS vasculitis in IgAV may present as edema, ischemia, infarction, and intracranial hemorrhage [95]. Garzoni et al. in their systematic review encompassing 37 IgAV patients described that the most frequently detected anomalies by neuroimaging were ischemic vascular lesions involving two or more vessels and intracerebral hemorrhage [95]. Furthermore, Liu and Zhang measured levels of LAC, anticardiolipin antibodies, and anti-β2 glycoprotein I antibodies in serum and cerebrospinal fluid (CSF) in 46 children with IgAV who developed CNS involvement and observed significantly

increased percentage of all aPL antibodies suggesting that aPL antibodies are related to nervous system damage in children with IgAV [63]. In addition to all the above, Sokol et al. reported a 15-year-old girl with IgAV and cerebral infarction who had a transient IgA antiphosphatidylethanolamine (aPE) antibodies in her serum and CSF presuming that aPE were associated with thrombotic cerebral event [96]. For children with IgAVN, who had or have developed hypertension, similar care management and strategies for preventing CV events should be also undertaken as in abovementioned pediatric vasculitides. Obesity has also been shown to significantly contribute to a poor prognosis in IgAVN, and thus indirectly possibly to CVD [46].

Childhood-onset antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (cAAVs)

Childhood-onset ANCA-associated vasculitides (cAAVs) include childhood-onset granulomatosis with polyangiitis (cGPA), childhood-onset eosinophilic granulomatosis with polyangiitis (cEGPA), and childhood-onset microscopic polyangiitis (cMPA). cAAVs are rare in childhood with annual incidence of 0.5/1,000,000 children and are mainly classified according to the CHCC criteria which are intended for adult patients except GPA which is classified according to the EULAR/PRINTO/PRES criteria [1–3]. CNS involvement in cAAVs is less frequent than in adult patients, and it is more common with the ANCA-positive subtype [97, 98]. In a cross-sectional retrospective study that included 85 pediatric patients with AAVs, hypertension and CNS involvement were associated with the development of both chronic kidney disease (CKD) and ESRD [98]. CNS involvement in cGPA is quite uncommon, and it is reported in up to 10% of patients mainly in the form of headache and dizziness [99, 100]. In the largest cEGPA cohort to date, CNS manifestations were observed in only one patient (7.1%) [101]. Gendelman et al. in their case series of 9 cEGPA patients reported an ischemic stroke due to thromboembolic event attributed to prior MI and subsequent atrial fibrillation [102]. According to various cohort studies, CNS involvement in cMPA may be found in up to 20% of patients usually in the form of headache, seizures, and dizziness (Table 1) [98, 100, 103]. One case report of female adolescent with cMPA presented with severe headache and sudden visual loss revealed intraparenchymal cerebral hemorrhage [104]. Hypertension, one of the most important modifiable risk factors for CV events, is highly reported in cAAVs, especially if kidneys are affected by the disease [98, 100]. In overall, increased risk of mortality due to CVD and stroke, as well as MI, is well documented among adult AAV patients [9–11].

Cerebrovascular issues in variable vessel vasculitis

Behçet's disease (BD)

Pediatric onset Behçet's disease (BD) is both an autoimmune and autoinflammatory disease that can affect any type and size vessel, but particularly involves veins and is classified according to the pediatric BD criteria [105]. In up to 20% of patients, disease begins already in childhood [105, 106]. CNS involvement is observed in up to 20% of pediatric BD patients and may be seen with various clinical findings including intracranial hypertension, hemiparesis, paraparesis, seizures, dural sinus thrombosis, vertigo, and facial nerve paralysis (Table 1) [65, 66, 106]. Generally, neuro-Behçet is classified into two major categories: parenchymal and non-parenchymal (cerebral venous thrombosis, acute meningeal syndrome, intracranial hypertension syndrome), and for definite neuro-Behçet's diagnosis are required all 3 criteria: satisfying the International Studies Group (ISG) criteria for BD, neurologic symptoms recognized to be caused by BD and supported by relevant and characteristic abnormalities seen on either or both neuroimaging and CSF findings and no better explanation for the findings [107]. Mora et al. performed a meta-analysis of pediatric patients with neuro-Behçet's disease and described the prevalence of neurologic features in 53 patients of whom 14 subjects had parenchymal, 35 had non-parenchymal while 4 subjects had mixed disease [60]. Neuro-Behçet's disease in most of these patients manifested as cerebral venous sinus thrombosis (CVST) and cranial nerve palsies [60]. Demir et al. in their case study series on 12 pediatric BD patients with CVST reported that in 50% of patients, initial features were CVST with transverse sinus being the most common site [70]. According to pediatric BD and ISG criteria, isolated headache is not scored as a neurological feature of neuro-Behçet's although is frequently observed in children even in 75% of patients [60, 65]. The most common neuroimaging findings reported are previously mentioned CVST and angiocentric brainstem lesions with or without hemorrhage and enhancement [70, 108]. Together with thrombotic events, CNS involvement is often the cause of death in BD patients, especially among men younger than 35 years [109, 110]. One meta-analysis revealed that BD patients had a significantly higher risk of stroke [110]. Considering all of that, it is of great importance to take good disease control in pediatric population in order to prevent irreversible damage. Colchicine and anti TNF-α therapy show favorable effect for neuro-BD [60, 72, 107].

Therapeutic and preventive approach to CV events in pediatric vasculitides

Management of pediatric vasculitides itself includes appropriate therapeutic and preventive measures (Fig. 3). Considering the therapeutic approach, each pediatric vasculitis patient should be treated individually with appropriate therapy according to type of vasculitis and affected organs. Following the above, as a part of project *Single-Hub Access for Pediatric Rheumatology in Europe* (SHARE) section for vasculitis performed scientifically based guidelines for treatment of pediatric vasculitis [111–113]. Since it was shown that may contribute to poor clinical outcome in every vasculitis patient with positive aPL antibodies, low anticoagulation therapy with acetylsalicylic acid should be included. If CV event occurs, emergency stroke management should be performed in the acute stage as in the recovery stage as well. Generally, the treatment of patients after admission to the hospital can, according to the guidelines of the European Society for stroke, be roughly divided into five points: (1) early application of general therapeutic measures (correction of accompanying disorders: hypoxia, hypertension, dehydration, hypoglycemia/hyperglycemia); (2) attempt to recanalize the occluded blood vessel (early systemic thrombolysis with recombinant tissue plasminogen activator (rt-PA) and/or mechanical thrombectomy); (3) resolving of emerging CNS complications (brain edema, seizures, hemorrhage); (4) introduction of medications for secondary prevention in order to prevent early recurrence of the disease (antilipemic drugs, acetylsalicylic acid, anticoagulation); and (5) early rehabilitation [12, 14–16]. A much better option for each patient is certainly appropriate risk factor management which includes good blood pressure control, physical activity, maintenance of normal body mass index, antilipemic and anticoagulant therapy if hyperlipidemia and atrial fibrillation exist, and if possible avoiding tobacco smoking in adolescents and young. In addition, it would be good that at least once a year, in all pediatric vasculitis patients, a screening program for modifiable risk factors for CVD should be implemented during regular visits in pediatric rheumatology clinics.

Conclusion

This review article provides a comprehensive view and summarizes current literature data on CNS manifestations, particularly CVD and CV events in primary pediatric vasculitides, although main limitations in searching strategy were rare occurrence of CNS involvement and CVD in pediatric vasculitides and restriction to only English articles. Also, only primary vasculitides were taken into account, not vasculitides that are currently classified as secondary or under the category of "others" or those associated with single gene defects. In some pediatric vasculitides, especially those involving large and medium vessels, like c-TA, cPAN, and BD, CNS manifestations and thus CVD are relatively frequent features of the disease. Although rare cause of stroke, pediatric vasculitides should be considered in its differential diagnosis. Complex immunologic mechanisms involving cytokines, activated inflammatory cells and ECs, and adhesion molecules dysfunction develop a chronic inflammation state in which endothelial damage takes central stage in both pediatric vasculitides and CVD and should be closely monitored. At the same time, reducing conventional risk factors for CVD, improving vasculitis-specific management, and implementing preventive measures should be a health

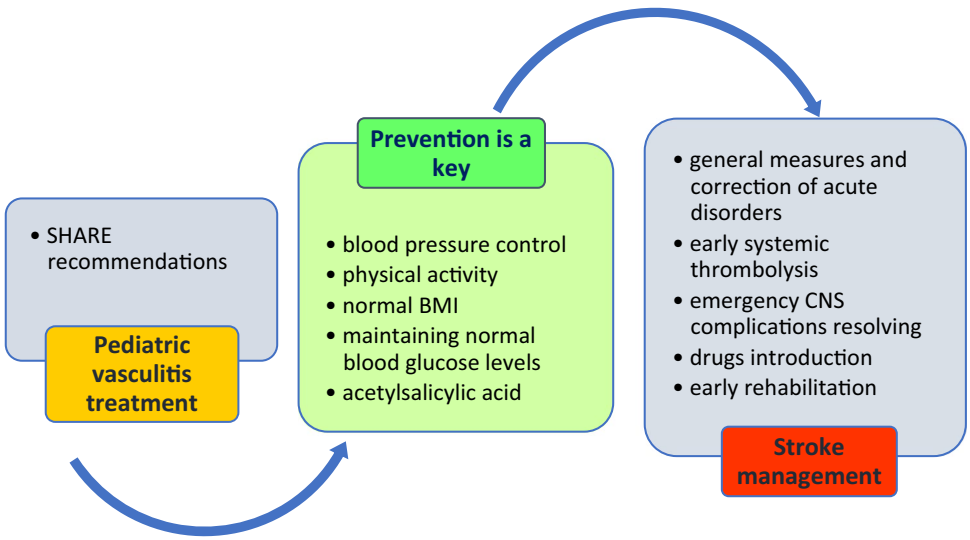

Fig. 3 A therapeutic and preventive management plan for cerebrovascular involvement in systemic pediatric vasculitides

priority for pediatric rheumatologists, as well as all other health care professionals dealing with pediatric vasculitides.

Author contribution MH reviewed the literature, analyzed the data, and wrote much of the manuscript. MS and NK reviewed the literature and wrote parts of the manuscript. MJ contributed to the conception and design of the work; she reviewed and revised the manuscript and supervised the work. All authors read and approved the final manuscript to be published. All co-authors are full responsible for all aspects of the study and the final manuscript. All authors accept responsibility for the accuracy and integrity of the final manuscript as submitted.

Data availability All data shown.

Declarations

Ethical approval The manuscript does not contain clinical studies or patient data.

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