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Review Article

Mechanisms of Pediatric Cerebral Arteriopathy: An Inflammatory Debate

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ABSTRACT

Arteriopathy is the leading cause of childhood arterial ischemic stroke, but its mechanisms are poorly understood. This review explores the possible role of inflammatory mechanisms and evidence for inflammatory pathophysiology in specific pediatric cerebral arteriopathies. Pathologically proven small-vessel central nervous system vasculitis provides a definitive inflammatory model where available treatments are likely improving outcomes. In contrast, a common large-vessel arteriopathy presents many features suggestive of inflammation, but definitive proof remains elusive. Recent advances and future research directions, including biomarker, neuroimaging, and pathologic approaches and how they might address these important clinical questions, are discussed.

Introduction

Arteriopathy is the leading cause of childhood arterial ischemic stroke, but its mechanisms are poorly understood. This review explores the possible role of inflammatory mechanisms and the evidence for an inflammatory pathophysiology in specific pediatric cerebral arteriopathies. Pathologically proven small-vessel central nervous system vasculitis provides a definitive inflammatory model where available treatments are likely improving outcomes. In contrast, a common large-vessel arteriopathy presents many features suggestive of inflammation, but definitive proof remains elusive. Recent advances and future research directions, including biomarker, neuroimaging, and pathologic approaches and how they might address these important clinical questions, are discussed.

Impact

Childhood arterial ischemic stroke causes significant lifelong morbidity, mortality, and economic burden [1-3]. Arteriopathies are the leading mechanism of both cause and recurrence [4-6], but an incomplete understanding of pathophysiology has prevented the development of targeted therapies or prevention strategies. A recent large, international study of childhood arterial ischemic stroke listed "potential" inflammatory arteriopathies as the leading etiologies of childhood stroke [4]. An inflammatory pathophysiology presents direct and immediate therapeutic implications for readily available anti-inflammatory medications. However, the evidence for such treatments is minimal, and moreover, the issue is not thoroughly addressed in published pediatric stroke guidelines [7,8]. Such a lack of expert consensus opinion on this issue translates into confusion among those caring for children with stroke, and this problem will only be overcome by an improved understanding of disease mechanisms.

Classification and definitions

The adult classification of stroke etiologies according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) divides stroke subtypes into large-artery atherosclerotic, cardioembolic, small-vessel lacunar, other determined etiologies, and undetermined etiologies [9]. Such classification has been essential in advancing adult stroke care, but several studies have demonstrated limited applicability of these criteria in young stroke patients [10]. Moreover, the mechanisms of stroke overall are vastly different in children, in whom nonatherosclerotic arteriopathy causes most arterial ischemic strokes [4-6]. An

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improved system to classify pediatric stroke etiologies is currently in development. The Childhood Arterial Ischemic Stroke Standardized Classification and Diagnostic Evaluation is attempting to address the unique causes of stroke in children, including their predilection for arteriopathy [11]. This step forward is important but incomplete, because analyses were based on magnetic resonance or computed tomography angiography, and not on conventional angiography. It also highlights the confusion surrounding the consideration of inflammation as a primary mechanism (or not), which will have to be overcome to increase the accuracy of classification and clinical applicability. Both classification systems can define well established patterns of cerebral arteriopathy in both adults and children, such as dissection or moyamoya disease. However, these only account for a minority of pediatric arterial ischemic strokes.

Ironically, the most common pattern of childhood cerebral arteriopathy is also the least understood. Although it may represent one or multiple different diseases, a distinct pattern of large-vessel arteriopathy is frequently observed in otherwise healthy school-aged children. The clinical and radiographic features of this syndrome have much in common, consistently featuring four characteristics [5,11-13]:

(1) Unilateral arteriopathy of the large vessels of the anterior circulation, typically affecting the distal internal carotid artery and proximal segments of the middle cerebral artery and anterior cerebral artery;
(2) A unique angiographic appearance, with unilateral focal or segmental stenosis or occlusion of these vessels. Contiguous alternating areas of stenosis and dilatation with a "banding" or "striated" appearance are often described, whereas definitive features of other arteriopathies, such as dissection or moyamoya, are absent (differential diagnoses will be discussed later);
(3) A dynamic nature during the first days and weeks, with repeated imaging often demonstrating a fluctuating course of arterial changes; and
(4) A monophasic course over the long-term, with follow-up imaging after 6 months confirming no progression, and the potential for partial or complete resolution of the arteriopathy.

A representative case example of this syndrome is presented in Fig 1. Many different terms have emerged to describe this syndrome, some of which directly imply a parainfectious or inflammatory mechanism. Unfortunately, our understanding of pathophysiology is too limited to allow such definitive distinctions. Four different diagnostic terms that share many of these features have emerged, each with differing degrees of implication regarding inflammatory mechanisms.

Transient cerebral arteriopathy is a recognized term that features all of the characteristics we have listed. The diagnosis requires that angiography (computed tomographic angiography, magnetic resonance angiography, or conventional angiography) performed within 3 months of the acute stroke demonstrates unilateral focal or segmental stenosis or occlusion involving the distal carotid artery, the A1 segment of the anterior cerebral artery, or the M1 segment of the middle cerebral artery. Although the arteriopathy may progress during the acute period, follow-up imaging after 6 months must confirm a lack of progression of the arteriopathy [12-14].

Recognition that a syndrome of transient nature is impossible to determine acutely, and that the primary mechanism is unknown, has led some leading investigators to favor less specific terminology. The term "focal cerebral arteriopathy" has been increasingly adopted to serve this purpose [5,11]. Consistent with its vague definition, focal cerebral arteriopathy is the most inclusive label for children with the syndrome we have described. Consequently, less specificity increases the probability of categorizing different childhood cerebral arteriopathies as focal cerebral arteriopathy, particularly those that are progressive [11].

In contrast to the terminologies of transient cerebral arteriopathy and focal cerebral arteriopathy, two related classifications have attempted to imply the underlying mechanism more specifically. As will be described, the implication of either an inflammatory (e.g., childhood primary angiitis of the central nervous system) or infectious (e.g., postvaricella angiopathy) label risks the potential misassignment of true disease causation, but allows for the exploration of more specific mechanistic possibilities, with important treatment implications.

An expanding literature is based on the possibility that an arteriopathy syndrome involves a primary inflammatory mechanism unique to the cerebral arteries. Such cerebral vasculitis is considered primary when it occurs exclusively in the central nervous system, and the term "primary angiitis of the central nervous system" carries established diagnostic criteria in adults [15]. Accordingly, the term "childhood primary angiitis of the central nervous system" has emerged to represent similar conditions in children [16,17].

The most consistent classification of childhood primary angiitis of the central nervous system distinguishes subtypes based on vessel size, angiographic and pathologic findings, and the presence or absence of disease progression [18]. Large/medium-vessel vasculitis is divided into progressive and nonprogressive types [17,18], and the nonprogressive types are more common and bear marked similarity to the transient cerebral arteriopathy and focal cerebral arteriopathy syndromes already described. This classification system, which will be described further, has yet to be validated.

Large/medium-vessel childhood primary angiitis of the central nervous system

The nonprogressive type of this large/medium-vessel vasculitis shares many of the features already described for transient cerebral arteriopathy and focal cerebral arteriopathy, and they may represent the same disease or closely related diseases within a spectrum [16,17]. Progressive large-vessel childhood primary angiitis of the central nervous system is uncommon, but associated features may include neurocognitive dysfunction, headaches, and seizures at presentation, multifocal and bilateral parenchymal lesions on magnetic resonance imaging, and multiple, bilateral, and distal vessel stenoses on angiography [18]. Because of the selective involvement of larger intracranial arteries, antemortem tissue diagnosis is generally not possible. The

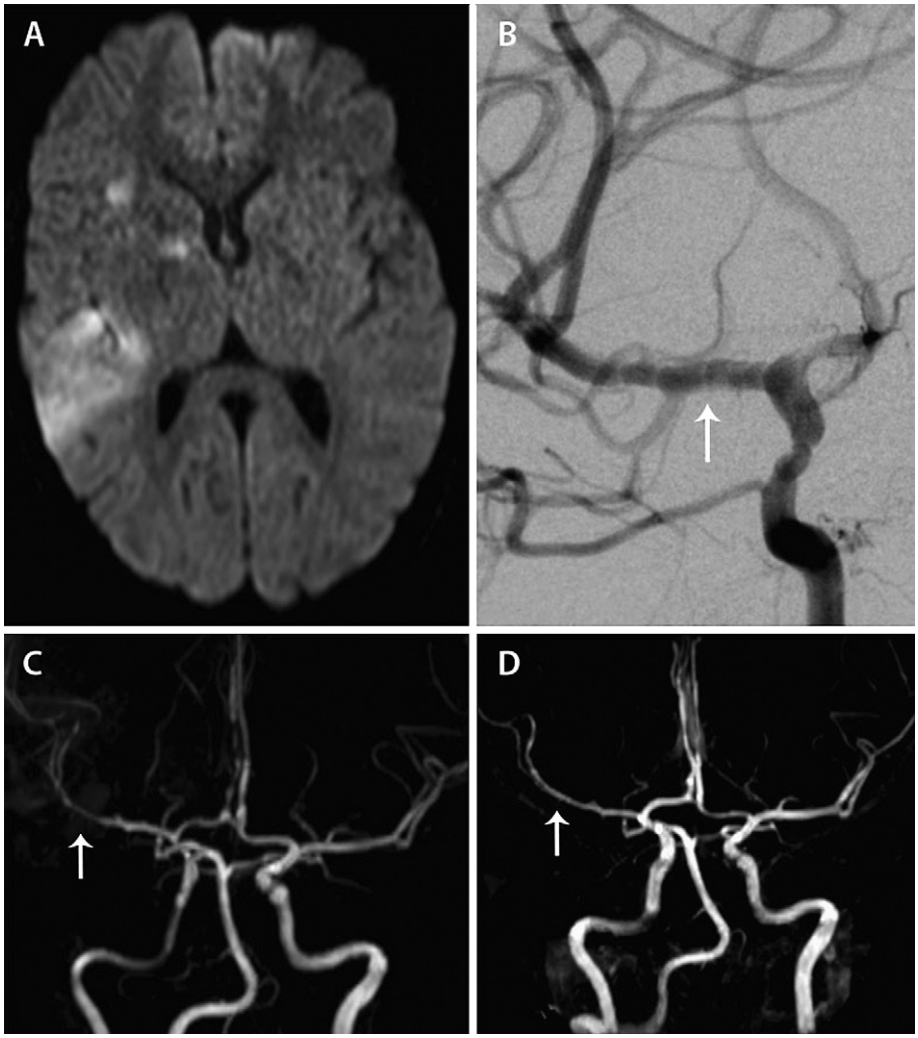

Figure 1. Focal cerebral arteriopathy. A 14-year-old previously healthy girl with no history of trauma presented with acute left hemiparesis. She had demonstrated viral upper respiratory tract signs 2 weeks earlier. (A) Initial axial diffusion weighted imaging magnetic resonance imaging reveals restricted diffusion involving the right middle cerebral artery territory, consistent with an acute arterial ischemic stroke. (B) Conventional cerebral angiogram of the right internal carotid artery indicates abnormal striae in the distal internal carotid artery and middle cerebral artery (arrow). (C) Initial magnetic resonance angiography demonstrates irregularity of the right M1 and M2 segments (arrow). The patient was treated with antithrombotics and steroids. (D) Follow-up magnetic resonance angiography at 6 months demonstrates the improved caliber of these vessels (arrow).

result involves a reliance on neuroimaging, specifically angiography, which continues to improve but cannot definitively implicate inflammation (as will be described). Long-term surveillance and outcome studies are required to better understand the natural history and predictors of recurrent forms of large/medium-vessel childhood primary angiitis of the central nervous system.

Small-vessel childhood primary angiitis of the central nervous system

The distinctly different disease of primary vasculitis of the small cerebral blood vessels is also well defined. In contrast to large/medium-vessel vasculitis, definitive evidence of vessel wall inflammation is often obtainable by brain biopsy, allowing for pathologic confirmation of the mechanism [19,20] and definitive inclusion criteria within research studies [21,22]. Patients may present with focal signs, but are more likely to develop subacute, nonlocalizing neurologic complaints such as headache, behavioral changes, seizures, or cognitive decline [20,22,23]. Strokes, when they occur, are not limited to large-vessel territories [19,20]. Results of neuroimaging are far less specific compared with the large-vessel varieties already described. The results of parenchymal magnetic resonance imaging can range from normal to diffusely abnormal, with a wide array of lesion characteristics described [20]. Even conventional angiography often reveals negative findings, and this disease is sometimes also referred to as angiography-negative small-vessel vasculitis [16,20-22]. Recent evidence from a single-center cohort study suggests that patients with angiography-negative childhood primary angiitis of the central nervous system manifest persistently higher disease activity than patients with angiography positive childhood primary angiitis of the central nervous system [24]. Small-vessel cerebral vasculitis can be subdivided into primary (affecting only the central nervous system, e.g., small-vessel childhood primary angiitis of the central nervous system) or

secondary (e.g., associated with other systemic disorders) [16]. The diagnostic criteria of Calabrese et al. [15] for adults with primary angiitis of the central nervous system have also been applied to the pediatric population [17,25]. These include: (1) an acquired neurologic deficit that remains unexplained after thorough evaluation, (2) either classic angiographic or histopathologic features of angiitis within the central nervous system, and (3) no evidence of systemic vasculitis or any other condition to which the angiographic or pathologic features could be attributed [15].

Association with infection

Infection represents both a differential diagnosis (e.g., the direct infection of cerebral arteries) and a potential "trigger" for inflammatory cerebral arteriopathy (e.g., parainfectious or postinfectious). The association of pediatric stroke with infection has long been suspected [26]. The simplest, most direct evidence is observed in patients with proven bacterial meningitis and stroke. Here, the pathophysiology is presumed to represent an inflammation of the vessels coursing through the subarachnoid space and traversing infected meninges, consistent with the common involvement of perforating and pial arteries [27,28]. However, both perforating and large-artery involvement has been reported in bacterial meningitis [27,28]. An additional, poorly understood condition involves a late large-vessel arteriopathy beginning during the recovery phases of bacterial meningitis that often leads to a severe outcome [29,30]. The incidence of this arteriopathy may be underestimated, because it was common (37%) in a consecutive series of adults undergoing conventional angiography after meningitis [31]. The role of infection in vascular injury can include direct invasion by the pathogen, the promotion of vascular cell-wall infiltration by inflammatory cells, the stimulation of vascular smooth muscle cell proliferation, or the activation of prothrombotic states [32,33]. This diagnosis is relatively easy to establish, given readily available clinical findings and biomarkers for the presence of bacterial meningitis, but other infectious mechanisms may be more occult.

Further evidence for an inflammatory association with large-vessel cerebral arteriopathy in children arises from its similarities to postvaricella angiopathy. Large case-control [34] and cohort studies [35] have indicated a link between childhood arterial ischemic stroke and *Varicella zoster* infection within the year preceding the stroke. A relationship between stroke and *Varicella zoster* has been recognized for many years [36]. Many case reports have implied an association between recent *Varicella zoster* infection and focal arteriopathy [37-44]. Pleocytosis [42,43,45] or *Varicella zoster* antigens [37,40,41,43] in the cerebrospinal fluid of patients with stroke and recent infection with *Varicella zoster* have been described. *Herpes zoster* ophthalmicus, associated with adult middle cerebral artery arteriopathy and stroke [46-48], has also been reported in children [49-51]. Biopsy specimens of a patient with postvaricella angiopathy revealed vasculitis with lymphocytic infiltration surrounded by macrophages [52]. An autopsy in another patient revealed an immunohistochemistry positive for *Varicella zoster* in the affected vessel, with antigen deposition in the smooth muscle cell layer of the vessel wall [53].

Postvaricella angiopathy therefore represents a fourth possibility when considering unilateral large-vessel childhood arteriopathy syndrome. In terms of clinical presentation and imaging, postvaricella angiopathy is virtually indistinguishable from transient cerebral arteriopathy, except for the history of *Varicella zoster* infection within the (arguably arbitrary) preceding 12 months [12]. This natural history also parallels that of transient cerebral arteriopathy, with a monophasic course and the subsequent stabilization or improvement of arteriopathy over months [54]. Consistent with selective proximal middle cerebral artery involvement, infarct patterns typically involve lenticulostriate territories [13,14] and the proximal segments of the internal carotid artery and anterior cerebral artery, again sounding very much like transient cerebral arteriopathy, focal cerebral arteriopathy, and childhood primary angiitis of the central nervous system.

Other infectious agents are less commonly associated with arteriopathic stroke in children. Fusiform aneurysms, focal arteriopathy, and stroke occur in children with human immunodeficiency virus [55-57], and vasculitis has been demonstrated pathologically in children with acquired immunodeficiency syndrome [58]. Isolated reports have associated neuroborreliosis [59-61], parvovirus B19 [62,63], influenza A [64], enterovirus [65], and *Mycoplasma pneumoniae* [66-68] with focal cerebral arteriopathy and stroke in the pediatric population. Although such case reports and small series may suggest associations, we emphasize that these associations do not prove causation. These data only strengthen the need for further research into the influence of infections on the pathophysiology of arteriopathy and childhood stroke.

Parainfectious or postinfectious mechanisms have also been implicated in childhood cerebral arteriopathy pathogenesis, whereby the activation of the immune system induced by common or specific infections increases stroke risk. Recent population-based studies demonstrated significant associations between recent infections and arterial strokes in children [5]. Previous case-control studies demonstrated an increased risk of stroke with preceding infection [69-73]. The Vascular Effects of Infection in Pediatric Stroke Study, currently underway, was designed to test the hypothesis that infection predisposes children to arteriopathy, arterial ischemic stroke, and recurrence [74].

Differential diagnosis

Several other pediatric cerebral arteriopathies may present with similar clinical and radiographic appearance as the large vessel diseases described above. We present some examples of important disorders that need to be considered in the differential diagnosis of pediatric cerebral inflammatory arteriopathies. To distinguish between these syndromes is challenging, particularly when imaging characteristics may be similar, serologic markers are nonspecific, and presenting features are identical. Future advancements in the understanding of the pathophysiology and diagnostic strategies of inflammatory arteriopathies will aid in separating these disease entities.

Dissection is an important cause of stroke in children, and may be more common intracranially compared with adults [4,75]. Recently, the importance of differentiating focal

cerebral arteriopathy from intracranial dissection was made evident by the description of four patients with classic clinical focal cerebral arteriopathy presentations, but with definitive evidence (three pathologic, and one with detailed wall imaging) confirming intracranial dissection [76]. Additional well defined or very distinct examples of childhood arteriopathies include moyamoya disease [77], post-radiation vasculopathy [78], and a variety of congenital arteriopathies [12]. Reversible cerebral vasoconstriction syndrome (also known as Call-Flemming syndrome) can occur in children [79]. Fibromuscular dysplasias are probably different in children compared with adults, but are associated with arteriopathic stroke and historically may have been confused with focal cerebral arteriopathy [16,18,25].

Different disorders may mimic small-vessel vasculitis in children. Given the protean nature of both the clinical and imaging findings, broad categories must be considered, including demyelinating, toxic, metabolic, hypertensive, and other mechanisms. A difficult diagnostic distinction is rendered between small-vessel childhood primary angiitis of the central nervous system and the ever increasing number of autoimmune encephalitides. Patients may present with similar neurologic signs of headaches, personality changes, and other neurologic findings with a variety of lesions on imaging indistinguishable from small-vessel childhood primary angiitis of the central nervous system. Patients with autoimmune encephalitis will exhibit normal cerebral angiograms and different serum biomarkers or brain biopsy pathology [80]. A variety of systemic vasculitides and collagen vascular disease can present with a small-vessel central nervous system vasculitis [16,25]. As will be discussed, with the possibility of skipped lesions, a false-negative biopsy may occur in primary central nervous system vasculitis [81]. This possibility is minimized via lesional, full-thickness biopsies [16,82].

Diagnosis and investigations

Imaging

Neuroimaging (specifically, much improved cerebral vascular imaging modalities) has increased the sensitivity of detecting and defining the unique features of these arteriopathies. Readily available angiography, including computed tomography, magnetic resonance, and conventional modalities, confirm arteriopathy in most children with arterial ischemic stroke. Common features of stenosis, narrowing, or occlusion with luminal irregularities or other suggestions of arterial wall disease, without definitive evidence of dissection, often raise the consideration of inflammation. However, we emphasize that *there are no validated imaging biomarkers of inflammation in childhood stroke*.

Without the availability of brain biopsy, the diagnosis of large/medium-vessel primary angiitis of the central nervous system according to the criteria of Calabrese et al. requires conventional cerebral angiography demonstrating findings of arteritis [15]. Conventional angiography is the preferred modality for demonstrating specific vascular abnormalities such as banding or striae in large/medium-vessel vasculitis or alternating areas of stenosis and dilatation in distal arterial beds in small-vessel childhood primary angiitis of the central nervous system (Fig 1B) [18,25]. Sensitivity is only moderate for predominantly distal, small-vessel disease [83]. Conventional angiography is very safe in pediatric populations [84], and should be considered among children with arterial ischemic stroke in whom a specific mechanism has not yet been determined.

Less invasive vascular imaging modalities are preferable, particularly for the ongoing surveillance of fluctuating diseases with a high risk of recurrence. Magnetic resonance imaging and magnetic resonance angiography were evaluated in a single-center cohort study [85]. All patients with abnormal conventional angiography demonstrated abnormalities on magnetic resonance imaging at time of diagnosis if T_2-weighted, fluid attenuated inversion recovery, and diffusion weighted imaging/apparent diffusion coefficient sequences were included. However, only 71% manifested magnetic resonance angiography abnormalities [85]. When comparing magnetic resonance angiography with conventional angiography, sensitivity and specificity amounted to 70% and 98%, respectively, in one study [83]. However, angiography-negative cases are well-documented, and are estimated at 16% in the pediatric population [83].

The characteristics of parenchymal magnetic resonance imaging lesions in small-vessel cerebral vasculitis, although not specific for inflammation, may be helpful when combined with other clinical markers. Magnetic resonance imaging abnormalities are often present even in angiogram-negative cases [17,21,85]. Variability is great, but hallmark abnormalities may include supratentorial, asymmetric, and anterior circulation lesions of the white matter or deep gray structures, observed most commonly as T_2/fluid attenuated inversion recovery hyperintensities [17,85]. Imaging predictors of progressive vasculitis include multifocal, bilateral, and gray matter lesions, combined with multiple, bilateral, or distal vessel stenoses [17]. Areas of restricted diffusion, observed on diffusion weighted imaging/apparent diffusion coefficient sequences, are reported in up to 60% in some series [17,85]. Gadolinium enhancement is occasionally observed; hemorrhagic lesions are rare [21,85]. These parenchymal abnormalities do not definitively exclude other possible diagnoses, and the lack of specificity further emphasizes the need for research into improved diagnostic strategies.

Recently, various vessel-wall imaging techniques were used to describe arterial pathology in adult central nervous system vasculitis [86-90]. These include high-resolution anatomic and blood-sensitive sequences that attempt to delineate pathologic processes within the vessel wall. Such approaches have yet to be validated and are not yet well described in children, but demonstrate excellent potential to address the pathophysiologic questions discussed here. Case reports of focal cerebral arteriopathy have suggested reversible wall enhancement [91]. We recently described normal cerebral arterial wall enhancement that may assist in defining abnormal patterns in children with stroke [92,93]. Further studies in this area could provide additional noninvasive imaging biomarkers of inflammation or other processes, and could help delineate the evolution of disease over time and response to treatment.

Serology

Consistent with the isolated and primary nature of their condition, many children with cerebral arteriopathy do not

manifest systemic inflammatory markers. However, mild nonspecific elevations may be observed [18]. Elevations in acute-phase reactants such as erythrocyte sedimentation rate, C-reactive protein, and von Willebrand factor are reported [20,23,94], although many studies suggest that such serum inflammatory markers are often normal [19,20,23,95]. A single-center retrospective study of 62 children with childhood primary angiitis of the central nervous system reported that elevations in erythrocyte sedimentation rate (51%) and C-reactive protein (74%) were common. The same study described proportions of elevated immunoglobulin G (35%) and anticardiolipin antibodies (44%), although antineutrophil cytoplasmic antibodies were normal. Inflammatory markers were not predictive of outcome, progression of disease, or type of vasculopathy [17]. Elevations in antinuclear antibodies have been reported but are very nonspecific, whereas more distinctive antibody testing typically produces normal results [23,94]. Therefore, studies to date have failed to identify serologic biomarkers of vascular inflammation or other insights into childhood arterial ischemic stroke pathophysiology. Whether such unimpressive findings denote the weak biomarker of an inflammatory process, a secondary response to acute brain injury, or some other epiphenomenon remains to be determined.

Cerebrospinal fluid

Could direct sampling of spinal fluid provide more sensitive detection of pathophysiologic processes in pediatric cerebral arteriopathy? The postvaricella angiopathy story may provide the best, albeit limited, evidence. Isolated case reports of children with postvaricella angiopathy have indicated mild cerebrospinal fluid pleocytosis [50]. The detection of cerebrospinal fluid anti-*Varicella zoster* immunoglobulin G antibodies is more sensitive than testing for *Varicella zoster* DNA using the polymerase chain reaction, and some have suggested that the diagnosis can be excluded when cerebrospinal fluid is negative for both [96]. The use of an antibody index to better determine significant elevations of *Varicella zoster* antibodies in cerebrospinal fluid has also been suggested, e.g., (cerebrospinal fluid/serum anti-*Varicella zoster*-specific immunoglobulin G)/(cerebrospinal fluid/serum total immunoglobulin G) [97]. With the exact role of *Varicella zoster* in childhood arteriopathy yet to be determined, these findings and other isolated cases of infection-associated arteriopathy [59-61,65] at least suggest the means by which cerebrospinal fluid infectious biomarkers may be investigated in the future [74].

Elevated opening pressures, pleocytosis, and increased levels of cerebrospinal fluid protein have also been described in both the large-vessel and small-vessel varieties of childhood primary angiitis of the central nervous system [20,22,94], although these parameters are often normal [19,20,23,95]. A single-center, retrospective study of 62 children with childhood primary angiitis of the central nervous system described abnormal cerebrospinal fluid in 39% (9/23 with biosamples). Findings included a nonspecific or lymphocyte-predominant pleocytosis in 32%, and elevated protein in 32%. Oligoclonal bands were never evident. Cerebrospinal fluid markers did not demonstrate significant associations with outcomes, the progression of disease, or subtypes of vasculopathy [17]. Similarly, as with the results reported for serologic markers, it is impossible to discern at this stage whether any changes in these cerebrospinal fluid parameters constitute indicators of an inflammatory process, a secondary response to acute brain injury, or other epiphenomena.

Tissue pathology

A definitive pathologic diagnosis of inflammation is often available in small-vessel childhood primary angiitis of the central nervous system, but postmortem samples from larger-vessel arteriopathies are rare. The typical pathologic description in adult small-vessel primary angiitis of the central nervous system involves granulomatous or nongranulomatous infiltration of the walls of arterioles and venules [15,81,82,98]. Both forms can occur in the same patient, limiting the utility of the distinction between granulomatous and nongranulomatous [81,98]. Lesions are also often focal, with a tendency for skipped lesions likely contributing to a significant false-negative biopsy rate [81]. The granulomatous form consists of a predominantly lymphocytic vasculitis, although various proportions of plasma cells, histiocytes, and giant cells have been described [81].

Nongranulomatous, predominantly T-cell lymphocytic vasculitis of the small vessels in both lesional and nonlesional biopsies of angiography-negative childhood primary angiitis of the central nervous system has been described in children. Occasional macrophages, polymorphonuclear cells, and eosinophils may also be present. The vessels involved may be widely distributed, including the leptomeninges, cortical gray matter, white matter, or all three layers. Inflammatory infiltrates are typically observed, both intramurally and perivascularly [20-22,94]. Surrounding reactive changes are also common [22]. Granulomatous inflammatory vasculitis is more rarely described in children [95]. A full-thickness leptomeningeal-cortical biopsy, ideally localized to imaging-based evidence of disease, should be considered for confirmatory diagnoses or the exclusion of small-vessel childhood primary angiitis of the central nervous system [16,82]. A definitive diagnosis is important in cases where long-term immunosuppressive treatment will be initiated, and future biopsy results may be compromised.

One autopsy involving *Varicella*-associated angiopathy revealed granulomatous arteritis with multinuclear giant cells and a lymphocytic infiltrate of the vascular cell wall, and destruction of the internal elastic lamina. Staining for *Varicella zoster* produced positive results, with the deposition of *Varicella zoster* antigen in the smooth muscle cell layer [53]. The biopsy of a patient with postvaricella angiopathy revealed a lymphocytic arteriopathy of the small vessels, but no viral inclusions and a polymerase chain reaction negative for *Varicella zoster*. However, for obvious reasons, the affected large vessel was not included in the biopsy [52].

No animal models of pediatric cerebral arteriopathies are yet available.

Disease-specific inflammatory markers

As already demonstrated, the diagnosis of primary central nervous system vasculitis is often difficult, because diverse clinical presentations are coupled with insensitive and

nonspecific serologic and cerebrospinal fluid biomarkers. Imaging, although steadily improving, may be normal or nonspecific, particularly in small-vessel vasculitis, whereas tissue-based diagnoses are invasive or impossible. Therefore, the search for more specific and sensitive diagnostic markers continues. The overlapping goals are twofold: (1) to provide novel insights into disease pathophysiology, especially the role of specific disease mechanisms such as inflammation; and (2) to help guide clinical care, including appropriate treatment options, prognoses, and surveillance over time.

Several avenues have been explored, but results to date are limited. Cerebrospinal fluid neurofilament and glial fibrillary acidic protein was elevated in the cerebrospinal fluid of 32 adult patients with central nervous system vasculitis, compared with control subjects [99]. Studies evaluating biomarkers in pediatric stroke are also scarce. One study suggested elevated D-dimers and C-reactive protein in childhood arterial ischemic stroke [100], whereas another suggested differences in more specific inflammatory proteins such as tumor necrosis factor-α, interleukin-2, interleukin-6, and interleukin-8 [101]. We recently demonstrated the potential of multiplex assay platforms (Eve Technologies, Calgary, AB, Canada) to compare dozens of inflammatory biomarkers among children with focal cerebral arteriopathy and cardioembolic stroke and control subjects [93]. Further studies will require careful differentiation between primary stroke mechanisms such as inflammation and secondary responses to brain injury and illness.

Further indirect evidence of inflammatory pathophysiology in pediatric stroke can be gleaned from genetic studies. One case-control study reported a higher incidence of single-nucleotide polymorphisms in the cytotoxic T lymphocyte antigen-4 (*CTLA-4*) gene among children with idiopathic stroke compared with control subjects [102].

Treatment: Implications and options

The possible but unproven role of inflammation in children with stroke and cerebral arteriopathy raises difficult treatment issues. Pediatric stroke consensus guidelines acknowledge the possibility of considering anti-inflammatory or immunosuppressive interventions, but offer little direction [7]. Perhaps the single largest factor involves the questionable classification of disease, as already described. Definitive or suggestive evidence of inflammation in childhood primary angiitis of central nervous system syndromes, coupled with generally favorable short-term side-effect profiles, appears to make anti-inflammatory interventions such as corticosteroids very appealing. In contrast, the lack of certainty surrounding transient cerebral arteriopathy or focal cerebral arteriopathy pathophysiology, or even then possibility of “active” infection in postvaricella angiopathy, may strongly influence some to avoid immunosuppressive or otherwise potentially toxic treatments.

The added certainty of biopsy-proven inflammation and an often chronic and recurring course has led some with extensive experience in small-vessel childhood primary angiitis of the central nervous system to suggest immunomodulatory intervention. Possible protocols include a combination of 6 months of treatment-dose steroids coupled with monthly pulses of intravenous cyclophosphamide (500-750 mg/m^2), followed by maintenance with azathioprine (2 mg/kg) plus low-dose steroids for an additional 18 months [16,20,21]. Case reports of other immunomodulatory therapies such as methotrexate or mycophenolate mofetil for longer-term maintenance have been reported [23,25,94]. Evidence for intravenous immunoglobulin in any variety of childhood strokes is lacking, perhaps partly because of the increased risk of thrombosis [103].

The immunosuppressive treatment of focal cerebral arteriopathy or transient cerebral arteriopathy is much less certain, with minimal data available regarding safety or efficacy, and a limited ability to distinguish progressive from transient cases. However, focal cerebral arteriopathy demonstrates measurable mortality, often extensive morbidity, and a high risk of early stroke recurrence, all of which emphasize an imperative need to define effective therapies. A treatment course of high-dose steroids for a duration of 3 months has been suggested [16]. For progressive forms of large-vessel childhood primary angiitis of the central nervous system, protocols comparable to those for small-vessel childhood primary angiitis of the central nervous system methods, including high-dose steroids for 6 months followed by maintenance with oral mycophenolate mofetil or azathioprine for 18 months [16,104], have been suggested. We emphasize that the dose-dependent toxicities of these agents are generally well established through other uses in children, whereas steroids are unlikely to be harmful in adults with stroke [105].

The treatment of postvaricella angiopathy also remains controversial. Patients with postvaricella angiopathy have been treated with short-course pulses of intravenous methylprednisolone and a 2-week course of acyclovir [32,37,106]. Others reported that acute antiviral treatment may not be necessary [35,54]. Acyclovir suppresses active viral replication and may exert no effect on the autoimmune reaction to dormant virus [97]. A review of antiviral and immunosuppressive treatments in varicella-associated stroke indicated no benefit, because most patients recovered almost completely regardless of therapy [50].

Regardless of the presence of inflammation, the basic principles of childhood stroke care are established, including antithrombotic therapy in most patients and supportive neuroprotective care [16,21,25]. An improved understanding of more specific disease mechanisms should advance therapeutic options and their testing through clinical trials.

Conclusions

Arteriopathy causes most strokes in children, and most of these strokes involve focal arteriopathies of an unknown mechanism. Inflammation and vasculitis constitute popular considerations that, although unproven in most cases, carry important implications for current treatment approaches and future research directions.

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