Childhood Central Nervous System Vasculitis

Mahendranath Moharir, MD, MSc, FRACP[a],
Manohar Shroff, MD, DABR, FRCPC[b],
Susanne M. Benseler, MD, PhD[c,*]

KEYWORDS

• Vasculitis • Neuroinflammation • Angiitis • Stroke • MRI • Angiography • Treatment • Immunosuppression

KEY POINTS

- Inflammation has to be considered as the underlying pathomechanism in children presenting with newly acquired neurological and/or psychiatric deficit. Inflammation of the cerebral blood vessel walls can solely target the brain and spinal cord and is then termed primary CNS vasculitis. Several underlying conditions have been found to be associated with a secondary CNS vasculitis; a careful diagnostic evaluation for these conditions is mandatory.
- Neuroimaging is crucial in guiding the diagnostic evaluation in childhood CNS vasculitis. It identifies characteristic features of distinct CNS vasculitis subtypes. Children with angiography positive CNS vasculitis commonly present with stroke features, have vascular stenoses or other abnormalities and may have evidence of contrast in the thickened, inflamed cerebral vessel wall. In contrast, neuroimaging may demonstrate multiple T2/Flair positive lesions in non-large vessel territories in children with angiography-negative small vessel vasculitis, which is confirmed on brain biopsy. Neuroimaging has a high sensitivity, but lacks specificity for distinct subtypes of childhood inflammatory brain diseases.
- Early recognition, rapid diagnostic evaluation including novel imaging strategies such as contrast wall enhancement and timely initiation of targeted immunosuppressive therapy have dramatically improved the outcome of children with primary and secondary CNS vasculitis.

INTRODUCTION

Inflammation is an increasingly recognized underlying pathologic condition in children presenting with acquired neurologic deficits. All the individual components of the central nervous system (CNS) and peripheral nervous system can be targets of a dysregulated innate or adaptive immune system.[1,2] The interaction between the target structure and the specific antibodies or cellular response will determine the clinical phenotype of the disease, including the mode of onset, severity, and long-term evolution. A typical clinical presentation of inflammatory brain disease in children is subacute, often multifocal, with a fluctuating but rapid progressive course, either idiopathic or less frequently in the context of a systemic illness or paraneoplastic process.[3–6]

Primary inflammatory brain diseases solely affect the brain and/or spinal cord and encompass vasculitis and nonvasculitic diseases, such as demyelination, neuronal antibody mediated inflammation, T-cell mediated diseases, and granulomatous inflammatory brain diseases.[3,6,7] Secondary

[a] Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; [b] Department of Diagnostic Imaging, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; [c] Division of Rheumatology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada
* Corresponding author.
E-mail address: Susanne.benseler@sickkids.ca

Neuroimag Clin N Am 23 (2013) 293–308
http://dx.doi.org/10.1016/j.nic.2012.12.008
1052-5149/13/$ – see front matter

inflammatory brain diseases result when brain inflammation occurs in the context of a systemic disease, such as infections, rheumatic diseases, systemic inflammatory diseases, and other systemic illness or exposures.[4,8–29] The diagnosis of inflammatory brain disease is based on a thorough clinical evaluation, including features of systemic inflammatory illnesses; blood and cerebrospinal fluid (CSF) analysis; neuroimaging studies; supportive testing, such as electromyography/nerve conduction studies and electroencephalography; and targeted tests, such as specific antibodies or brain biopsies.[30]

Every child with a newly acquired neurologic deficit (focal or systemic) should be investigated for an underlying inflammatory cause. The differential diagnosis for neuro-inflammatory conditions is very wide and rapidly expanding. This article focuses on childhood CNS vasculitis, whereby the target of inflammation is the blood vessels, and its resultant effects on neurologic functioning.

PRIMARY CNS VASCULITIS

Primary angiitis of the central nervous system (PACNS) is the most common cause of severe, acquired neurologic deficits in previously healthy children.[15,31,32] PACNS was first described in adults in 1959.[33] Initial cases were almost exclusively diagnosed at autopsy, demonstrating granulomatous inflammation of the cerebral arteries.[34] In 1988, Calabrese and Mallek[31] described 8 new cases and summarized the available literature of PACNS in adults. He coined the term *PACNS* and proposed diagnostic criteria for adults. These criteria mandate (1) a newly acquired neurologic deficit, (2) angiographic and/or histologic evidence of CNS vasculitis, and (3) the absence of a systemic condition that could explain these findings.[31] The Calabrese criteria were adopted and modified for childhood PACNS (cPACNS), requiring a newly acquired neurologic deficit and/or psychiatric symptom in patients aged 18 years or younger.[15] In the authors' tertiary care center, cPACNS was the most frequently diagnosed inflammatory brain disease over the past 5 years. The current classification of cPACNS is based on affected cerebral vessel size and disease presentation and natural history.[15,35] Three subtypes are currently recognized: (1) nonprogressive (NP) large-medium vessel cPACNS (angiography positive), (2) progressive (P), large-medium vessel cPACNS (angiography positive), and (3) small vessel (SV) cPACNS (angiography negative, biopsy positive).[15,35] The 3 subtypes display distinct presenting symptoms, laboratory findings, disease course, and treatment outcome.[15,35]

Angiography-Positive NP-cPACNS

Clinical features

Children with NP-cPACNS typically present with sudden-onset focal neurologic deficits and are frequently diagnosed with arterial ischemic stroke.[15] This subtype affects boys more commonly than girls, corresponding to the gender predilection in stroke overall.[36] Focal deficits can include abrupt onset of aphasia, visual disturbance, ataxia, hemiparesis, hemifacial weakness, hemisensory loss, and fine motor skill loss.[15] The presentation can either be hyperacute and acute or sometimes of a stutteringtype.[37] The latter refers to recurrent focal deficits lasting few minutes/hours, eventually progressing to a complete irreversible deficit either within one or multiple vascular territories depending on the extent of the vasculitis. Approximately 10% of children present with additional diffuse focal deficits, such as decreased cognition or behavior change. Overall, headaches are present in 40% of the children with NP-cPACNS.[15] Seizures are not a frequent feature but can be present, particularly in younger children.

Laboratory tests

Systemic inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate (ESR), are frequently normal. The endothelial cell marker von Willebrand Factor antigen has been documented to be elevated in some patients but remains to be studied systematically in this population. In NP-cPACNS, less than 50% of the patients have an elevated protein level or evidence of leukocytosis on CSF analysis.[15,38] The role of the opening pressure remains uncertain. Thus, the value of seeking inflammatory markers either in blood and CSF seems limited from the diagnostic point of view. The presence of inflammatory abnormalities can certainly help in diagnosis, but their absence does not rule out CNS vessel wall inflammation. Thus, there is a clear need for other diagnostic markers, which could be potentially used to reliably detect CNS inflammation in the absence of systemic signs of inflammation. One such marker, CSF neopterin, which is released by CNS macrophages, appears[39] and merits further research because it has been demonstrated to be elevated in a variety of inflammatory disorders affecting the CNS, although it is not clear whether the elevated levels represent a primary inflammation in the CNS or a secondary inflammatory response to non–immune-mediated brain damage.

The evaluation of potential prothrombotic abnormalities is mandatory in most patients. But the role of thrombophilia testing has not been carefully studied in this specific population, although testing