Transient Cerebral Arteriopathy, Postvaricella Arteriopathy, and Focal Cerebral Arteriopathy or the Unique Susceptibility of the M1 Segment in Children With Stroke

Stéphane Chabrier, MD; Guillaume Sébire, MD, PhD; Joel Fluss, MD

See related article, p 2443.

Like many disorders, the incidence of arterial ischemic stroke (AIS) throughout life is represented by a U-shaped curve. The peripartum period carries the highest risk, whereas people from 29 days to 18 years have the lowest risk. The incidence then gradually increases from adolescence to old age. Furthermore, the mechanisms of AIS are also age dependent. Placental–cerebral embolism is the most widely accepted hypothesis in perinatal AIS, whereas long-standing and diffuse arterial disease (namely, atherosclerosis) is the leading cause in adults. In childhood as well, stenosing arteriopathies are the most frequent causes of AIS. Some of them, such as cervical dissection, moyamoya, sickle-cell arteriopathy or other specific diagnoses (postirradiation arteriopathy, neurofibromatosis, fibromuscular dysplasia, reversible vasoconstriction syndrome) are well recognized. Nevertheless, after exclusion of these disorders, a large proportion of children (notably those previously healthy) are diagnosed with another type of arterial disease, which is characteristically focal, intracranial, and monophasic. Because the nature of the arterial insult is largely unknown, patients with these features have been reported under diverse nosography (Table), which refers to the angiographic appearance and the time course rather than to a pathophysiological mechanism. Each definition has its proper advantages and limitations. Yet the great majority of cases of focal cerebral arteriopathy (FCA) regress or stabilize along time, thus being a posteriori defined as transient cerebral arteriopathy (TCA), and a large proportion of these are preceded by varicella, thus reaching the definition of postvaricella arteriopathy (PVA). Finally, TCA also shares the imaging features of the nonprogressive form of medium-large vessel childhood primary angiitis of the central nervous system, mostly reported in the rheumatologic literature.

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In this issue of Stroke, Bernard et al and the Colorado Group confirm the high prevalence of FCA in their assessment of the metrological properties of the CASCADE classification (Childhood Arterial Ischemic Stroke Standardized Classification and Diagnostic Evaluation), based on a random sample from a large international population of children with AIS. But, another striking finding is that—although a near-perfect inter-rater agreement is reached for the nonambiguous causes of stroke: cardioembolic process (κ=0.84) and bilateral arteriopathies (probably moyamoya or other progressive diffuse intracranial arteriopathies; κ=0.90)—the agreement is moderate when assessing FCA (κ=0.49). This is particularly noticeable, when considering that the study was performed with highly experienced practitioners, who moreover had participated in a previous training session. Eventually, it highlights the challenges in categorizing specific childhood cerebral arteriopathies.

The considerable overlap between TCA, PVA, and FCA suggests that they might represent the end point of similar vascular pathogenic processes triggered by various insults. Indeed, the prominent imaging feature is the unique distribution of the arterial lesions along the M1 segment, the distal internal carotid artery, and the proximal anterior cerebral artery. One can only speculate on the explanations for such a high susceptibility of the carotid trifurcation, while acknowledging that a similar distribution is also observed in other childhood arteriopathies, such as moyamoya, meningitis induced–cerebral vasculopathy, HIV arteriopathy, sickle-cell disease… The growing evidence that infection is a major contributor of childhood AIS could point to direct contiguous parietal effects from an inflammatory cerebrospinal fluid. Yet, true large vessel arteritis is rarely demonstrated in the setting of purulent meningitis. In addition, a purely contiguity mechanism does not explain the sparing of the posterior circulation. In the specific case of PVA, the latent varicella zoster virus that has reactivated in the Gasser ganglion can reach the carotid and the middle cerebral arteries via axonal flow and then spread through the vessel wall. The subsequent localized parietal inflammation induces stenosis and endoluminal thrombosis. But this seductive mechanism, supported by pathological specimens, cannot be applied to other infectious agents. So how can one explain that, clinically and radiologically, PVA does not really differ from TCA? It seems reasonable to presume that the tortuous carotid trifurcation is more vulnerable whatever the trigger is, due to specific rheological characteristics and eventually to other mechanical stressors, such as dissection, and immunologic properties. We can hypothesize that the initial vascular insult is more spread out
Table. Nosography of the TCA/PVA/FCA Complex

<table>
<thead>
<tr>
<th>Nosology (Year of Description)</th>
<th>Definition</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
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<tbody>
<tr>
<td>Transient cerebral arteriopathy (TCA, 1998)</td>
<td>Unilateral focal/segmental stenosis or occlusion involving distal part of internal carotid and initial segments of anterior or middle cerebral artery. Nonprogression of arterial lesions &gt;6 mo, compared with baseline angiogram</td>
<td>Arteriopathic course correlated with outcome. Recognized for a long time</td>
<td>Diagnosis only suspected initially; needs time to be confirmed</td>
</tr>
</tbody>
</table>

Postvaricella arteriopathy (PVA, 2005) Stroke occurring <1 y after varicella. Unilateral disease affecting the supraclinoid internal carotid artery or proximal anterior or middle cerebral arteries. No identified cause other than PVA. | A well-described childhood arteriopathy | No evidence that postvaricella TCA is different from other forms of TCA |

Focal cerebral arteriopathy (FCA, 2009) Unifocal or multifocal, unilateral or bilateral stenosis of the large- or medium-sized vessels. Not otherwise classified as dissection, moyamoya, sickle-cell arteriopathy, PVA, vasculitis, or other specific diagnoses. | Diagnosis established early in the course of the disease | A descriptive term that can refer to many entities |

Childhood primary angiitis of the central nervous system (nonprogressive form, 2006) Angiography findings demonstrating arterial stenosis not attributable to other causes. Nonprogression and no appearance of new areas of stenosis at >3 mo after baseline angiogram | Arteriopathic course correlated with outcome | Diagnosis only suspected initially; needs time to be confirmed. Follow-up at 3 mo probably too short. Some arteriopathies continue to progress until 6 mo, whereas they remain nonprogressive in the long term |

issue. Indeed, the outcome depends primarily on the evolution (progression versus stability/regression) of the arteriopathy, knowing that stroke rarely recurs when the stenosis has stopped its progression.6–7 It is, thus, a crucial challenge for the clinician and a key issue for the patient to determine early predictors of the arteriopathic course and to distinguish a space- and time-limiting pathological process from the early stages of a chronic and diffuse arterial disease. Earlier diagnosis, cognitive dysfunction at presentation, multifocal/bilateral parenchymal and arterial lesions, occlusion rather than stenosis and moyamoya vessels are predictors of progressive arteriopathy, whereas preceding varicella, basal ganglia infarction, and arterial heaping are protective.7,8,16,17 Classical determinants for stroke and biomarkers reflecting endothelial injury and repair can also predict outcome.17,19,20,22 There is also a trend for a better outcome26 and few recurrences27 in children treated with aspirin. In our former report of TCA, recurrence occurred in 3 of 4 children without treatment versus only one of 11 who received aspirin.22 A similar figure was found in Braun TCA study, where 91% of children received antithrombotics, mostly with aspirin alone.7 Recurrence was observed in 10 children, of whom 6 were not receiving any antithrombotics at the time of recurrence.23 In our experience, when an otherwise healthy child with AIS presents with an intracranial unilateral focal arterial stenosis and is promptly treated by aspirin until the arteriopathy stabilizes or regresses, the risk of recurrence is low.24,25

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References

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