Cerebral vasculitides and non-arteriosclerotic vasculopathies: A Theoretical Review

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Abstract

Gross division of vasculitides is still today dependent upon the histological characteristics of the disease; nevertheless anatomic-pathological classifications mainly rely upon the diameter of the injured vessel and also upon the fact that the process is granulomatous, or not.

Authors describe main cerebral vasculitides of primary and secondary origin, as well as some of the main non-atherosclerotic vasculopathies (CADASIL, Moya-Moya syndrome and fibromuscular dysplasia).

A review of several updated bibliographic sources is thereby completed.

Review

Gross division of vasculitides is still today dependent upon the histological characteristics of the disease; nevertheless anatomic-pathological classifications mainly rely upon the diameter of the injured vessel and also upon the fact that the process is granulomatous, or not.

The table below summarizes the majority of the vasculitides that to some extent or not, will at a moment of the disease involve even cerebral territories (Table 1).

1. PRIMARY SYSTEMIC VASCULITIDES

Hereby we may count:

1.1. Arteritis temporalis and Takayasu arteritis

Both processes might cause important stenosis of inflammatory characteristic, as for example of the subclavia, coronary territories. Both nosologies cause panoply of symptoms in the central as well as in the peripheral nerve system. Severe headache, claudicatio masticatoria and general malaise have been described (1, 2).

1.2. Churg-Strauss syndrome

Considered as an allergic granulomatosis, the disease is mainly characterized from relapses of lung infiltrates, and a multiple mononeuropathy, due to an abundant eosinophilic presence; a necrotic vasculitis is rarely registered (3).

1.3. Wegener granulomatosis

ORL sphere and eyes are initially involved, but lungs and kidneys will not be spared. Ischemic brain infarcts are the main neurological symptom, but mononeuropathies and hemorrhagic stroke is seen as well (4).

1.4. Behcet disease

The process represents a mucosal – cutaneous syndrome, with systemic vasculitis, genital aphthous involvement and uveitis (5).

2. NON-ARTERIOSCLEROTIC VASCULOPATHIES

2.1. CADASIL

CADASIL (Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a clinical syndrome whose characteristics were not described systematically until the early ’90s of the last century, when it was considered a nosology per se and a gene locus was identified precisely on the chromosome 19q12 (6). It was almost the same team of French authors that grouped the symptomatology, just two years before their discovery of the responsible chromosome (7). In their description, authors considered as a typical scenario for the nosology the triad of stroke or stroke-like episodes, combined with headache (mainly depicted as migraine), and with psychic changes (7). Three years after uncovering the responsible chromosome, the defective gene was identified as well (8).

Stroke-like episodes and brain infarcts seem to interest mainly the subcortical territories, with lacunar symptomatology (9). Ischemic stroke is found in almost 85% of symptomatic patients suffering from CADASIL (10). Although the mean onset age of ischemic episodes and stroke is 45 years, specific mutations have been identified that might cause an early onset of stroke (11).

Patients quite often complain migraine with aura, and the percentage of patients suffering from headache might be as high as 64% (10). Mood disorders and cognitive deterioration, mainly accumulative in its progression, might be as well early signs of the condition, albeit the cognitive decline has a stepwise course, and depression seems by large the most
frequent psychiatric feature (12).

The implicated Notch proteins represent a family of transmembrane receptors, and Notch with its ligands modulate the cell-fate decisions of various cell types, forming a signaling pathway, through exerting a modulating role in the vasculogenesis, angiogenesis, as well as in the vascular remodeling, as well as by means of controlling the stability and functionality of vascular smooth muscle cells (10, 12). Notch receptors have been widely blamed even for other and different pathological conditions, such as osseous pathologies [Notch2 receptor and the so-called syndrome of Hajdu-Cheney]; aortic valve pathologies [Notch1] and obviously, CADASIL [Notch3] (13).

The identified gene mutations actually are more than eighty, all of them distributed in the repetitions of the epidermal growth factor, representing the extracellular domain of Notch3 (14). The mutations responsible for CADASIL lead to an odd number of cysteine residues (12). De novo mutations have been identified as well, thus explaining situations when the family history suggested no previous cases, since the condition is per definition an autosomal-dominant one (15).

**Figure 1:** Severe hypoxic changes leading to brain atrophy, in a case with clinical dementia.

Since the condition is heterogenous and complex in its clinical features, attempts to stage chronologically the clinical and radiological course of CADASIL have been proposed (16). The same authors define three stages; Stage I (patients aged 20-40 years) when migraine is the main complaint, with white matter lesions delineated in the magnetic resonance imaging [MRI]; Stage II (patients between 40 and 60 years) with stroke, transient ischemic attacks and psychotic disorders, as well as more impressive MRI changes; and finally stage III (patients older than 60 years) when subcortical dementia (CT scan image; Figure 1) represents the main clinical characteristic of the condition, with diffuse leukoencephalopathy and basal ganglia involvement seen of the imaging [CT, MRI] (16).

The clinical course, the positive family history, and MRI findings might raise strong doubts about the existence of CADASIL, but genetic analysis is indispensable for a definite diagnosis. Skin biopsy has as well been generally considered as of value (17); whereas the angiography in all of its modalities, such as digital-subtraction angiography (DSA) seems to yield negative outcomes, maybe because the vessels interested from the pathological process are of a small caliber (18, 19).

**2.2. Fibromuscular dysplasia (FMD)**

FMD is a non-arteriosclerotic vasculopathy, encountered mainly in women of young and middle age (20). Internal carotid artery and intracranial territories are frequently involved; but the disease might quite well stay in a subclinical course for several years.

There have been encountered also embolic or hemodynamic infarcts, but nevertheless the prognosis seems a good one.

**2.3. Moya-Moya Syndrome**

This is a syndrome characterized on one side from stenosis or obstructions of intracranial portions of the internal carotid artery, namely of the cerebri media, cerebri anterior or posterior; and on the other side the syndrome is characterized through the creation of a network of collateral vessels, creating the radiological image of a puff of smoke.

The syndrome was initially described in Asians, in its typical bilateral form (21).

**References**

Illustrations

Illustration 1

Table 1

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<td>Leukocytoclastic vasculitis</td>
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</tr>
</tbody>
</table>
Illustration 2

Figure 1: severe hypoxic changes leading to brain atrophy, in a case with clinical dementia.
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