Teaching

ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

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SUMMARY

Angiitis of the central nervous system is a rare disease which may result from numerous causes responsible for the presence of inflammatory lesions of the vascular wall. These inflammatory lesions may sometimes be associated with necrosis. Cerebral vessels of all sizes may be involved. The clinical presentation is highly variable, with focal to diffuse manifestations and acute to chronic evolution. Angiography is the cornerstone diagnostic procedure, showing multiple segmental stenoses of the cerebral arteries sometimes separated by fusiform dilatations. Although suggestive, this angiographical pattern is not unequivocal and other causes must be carefully ruled out. Only cerebral and/or leptomeningeal biopsy can provide a definite diagnosis of cerebral angiitis but this invasive diagnostic procedure is not performed in the majority of cases. Among the numerous causes of cerebral angiitis, one can individualize infectious diseases, primary systemic angiitis with cerebral involvement, angiitis secondary to various systemic diseases and other miscellaneous causes such as drug abuse or neoplasm.

Key words: Vasculitis, cerebrovascular, disorders (diagnosis), cerebral nervous system, MR imaging, angiography.

RÉSUMÉ

Angéites du système nerveux central

Les angéites du système nerveux central sont des affections rares d’origine multiple, dont le dénominateur commun est une lésion inflammatoire de la paroi vasculaire, parfois associée à une nécrose. Les vaisseaux cérébraux de tailles différentes peuvent être touchés. Les manifestations cliniques sont polymorphes, qu’il s’agisse du tableau initial ou de l’évolution. L’angiographie cérébrale est l’examen essentiel pour porter le diagnostic, même si l’aspect évocateur, rétrécissements segmentaires multiples, n’est pas pathognomonique. La certitude diagnostique repose sur la biopsie cérébrale et/ou leptoméningée mais un diagnostic de forte probabilité est souvent posé sans preuve histologique. Parmi les nombreuses causes d’angéites cérébrales, les principales catégories sont les angéites infectieuses, les angéites systémiques dites primitives, les angéites associées à une maladie de système, et diverses causes plus rares telles que les angéites associées à une pathologie néoplasique et celles secondaires à une toxicomanie.

Mots-clés : vasculite, maladies cérébrovasculaires (diagnostic), système nerveux central, IRM, angiographie.

INTRODUCTION

Angiitis of the central nervous system (CNS) is a heterogeneous group of disorders which have in common the presence of inflammatory lesions involving the vascular wall. These inflammatory lesions may sometimes be associated with necrosis and can involve blood vessels of various sizes. This review focuses on both infectious and non infectious inflammatory disorders responsible for angiitis of the CNS. The clinical setting and imaging pattern of these disorders vary and have many possible causes.

In this review, we have chosen to distinguish between infectious and non infectious causes of angiitis of the CNS. A number of infectious agents can cause angiitis such as tuberculosis, syphilis or varicella zoster, in which case the vascular involvement is usually thought to be a late onset complication. For the subgroup of non infectious angiitis, we decided to distinguish between those cases in which vascular involvement appears to be the primary lesion from those in which it falls into the setting of secondary involvement. A nether useful classification for the neuroradiologist is to distinguish angiitis according to the size of affected vessels (table I). It is beyond the scope of this paper to provide an exhaustive list of references concerning all of the causes of inflammatory angiitis of the CNS. These causes are listed in table II.
DIAGNOSIS OF ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

The results of clinical, laboratory and imaging work-up in favor of angiitis of the CNS are to a large extent common to both infectious and non infectious angiitis. The diagnostic situation is different depending on whether or not the patient presents with a disease known to potentially cause angiitis.

When a disorder of the CNS occurs in the course of a systemic disease the primary difficulty is in determining the mechanism of the disorder since, apart from angiitis, other mechanisms (often more common than angiitis itself), may be involved:
- parenchymal involvement (i.e.: granulomatosis);
- arterial hypertension (i.e.: renal failure);
- neurological complications due to involvement of other organ systems (cardiopathy);
- coagulopathy;
- immunological disorders;
- complications related to treatment.

In any case, final diagnosis depends on histopathological examination which is seldom performed in clinical practice. In the absence of histopathological examination, the mechanism of the CNS disorder is usually presumed on the basis of a combination of clinical, laboratory and imaging arguments. Obviously the choice of treatment regimen will depend on the mechanism of the CNS disorder which is identified. Thus, steroid treatment may be reinforced or reduced depending on the mechanism involved.

**Table I.** — Classification of angiitis according to affected vessels (from Hankey G. J., [39]).

<table>
<thead>
<tr>
<th>Vessels</th>
<th>Angiitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large arteries</td>
<td>Takayasu’s arteritis</td>
</tr>
<tr>
<td>Large and medium arteries</td>
<td>Temporal angiitis</td>
</tr>
<tr>
<td>Medium and small arteries</td>
<td>Polyarteritis nodosa and related disorders</td>
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<td></td>
<td>Angiitis secondary to systemic diseases</td>
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<tr>
<td></td>
<td>Varicella zoster angiitis</td>
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<td></td>
<td>Tuberculosis angiitis</td>
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<td></td>
<td>Angiitis associated with drug abuse</td>
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<tr>
<td></td>
<td>Isolated angiitis of the CNS</td>
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<tr>
<td>Small vessels</td>
<td>Isolated angiitis of the CNS</td>
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</table>

**Table II.** — Causes of cerebral angiitis.

<table>
<thead>
<tr>
<th>Type of Angiitis</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious angiitis</td>
<td>Purulent bacterial meningitis, Tuberculosis, Infective endocarditis, Brucellosis, Syphilis, Lyme disease, A mimic infection, E chinococcosis, Cysticercosis, Schistosomiasis, Varicella zoster / Herpes zoster, Cytomegalovirus infection, H uman immunodeficiency virus infection, A spergillosis, Cryptococcosis, M ucormycosis, Polyarteritis nodosa, Churg and Strauss angiitis, Cogan’s syndrome, Temporal angiitis, Takayasu’s arteritis, Wegener’s granulomatosis, Lymphomatoid granulomatosis, Hypersensitivity angiitis, K awasaki’s arteritis, B urger’s disease, S usac’s syndrome, K ohlmeier- D egos disease, acute posterior multifocal placoid pigment ep- thieliopathy,...</td>
</tr>
<tr>
<td>Primary systemic angiitis</td>
<td>Systemic lupus erythematosus, Sjogren’s syndrome, Behçet’s disease, Sarcoidosis, Rheumatoid polyarthritis, Scleroderma, M ised connectitivitis, D ermatomyositis, U lerative colitis, C oeliac disease</td>
</tr>
<tr>
<td>Angiitis secondary to systemic disease</td>
<td></td>
</tr>
<tr>
<td>Angiitis associated with neoplasia</td>
<td>H odgkin’s disease and non-H odg- kin type lymphoma, Malignant histiocytosis, H airy cell leukemia</td>
</tr>
<tr>
<td>Angiitis associated with drug abuse</td>
<td>Illicit drugs (cocaïne, « crack »), Sympathomimetic agents, A mphetamine and related drugs</td>
</tr>
<tr>
<td>Isolated angiitis of the CNS</td>
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When a CNS disorder is inaugural and/or isolated, the difficulty lies in suspecting angiitis when faced with non-specific neurological symptoms and then to confirm the diagnosis.

**Clinical signs**

In all types of CNS angiitis, a wide spectrum of clinical symptoms may be observed [96]. Signs may include focal cerebral involvement (hemiplegia, focal seizures, involvement of one or several cranial nerves, cerebellar ataxia, visual field amputation…) or symptoms indicating diffuse encephalopathy (altered mental status, confusion, altered cognitive functions, dementia). Headaches are often present, and are part of the clinical symptoms of subarachnoid hemorrhage found in few patients [72]. A rare pattern of isolated spinal cord involvement may also be seen. Any possible combinations of the above patterns are in fact possible and some patients may even present with concomitant signs of encephalitis involving the telencephalon as well as rhombencephalitis and myelitis. Patients should be explored for non-neurological symptoms which may have appeared simultaneously or prior to the onset of neurological signs, since such signs may definitely suggest a general systemic disease. It should be stressed that infectious angiitis cannot be ruled out by the simple absence of fever: zoster angiitis, for example, may develop in patients considered to be healthy. The time course pattern of CNS angiitis is also highly variable and the onset of symptoms may be either acute, subacute or chronic, regardless of the specific syndrome.

This highly variable clinical and temporal presentation accounts for the diagnostic difficulties. A number of neurological diseases may be discussed depending on each individual presentation. In the case of acute or subacute onset, differential diagnosis may include meningoencephalitis, multiple sclerosis, abscess or even stroke, through another mechanism. More progressive onset may suggest neoplastic disease or even dementia. Specific neurological signs are indicative of particular causes: headaches in an elderly person may suggest a temporal angiitis; chorea or acute onset of delirium in a young female suggest systemic lupus erythematosus; rhombencephalitis suggests Behçet’s disease.

Depending on the clinical presentation, work-up will be more or less extensive. The contribution of the workup is in fact variable. It may even be entirely normal, as for example in isolated CNS angiitis (ICNSA).

**Laboratory work-up**

Two levels of work-up should be considered: a general work-up, commonly performed in all neurological disorders and a more specific work-up. The general work-up allows to rule out the various disorders with a clinical presentation closely resembling that of CNS angiitis. This work-up includes complete blood cell count, erythrocyte sedimentation rate, protein electrophoresis, prothrombin time and APTT.

When the diagnosis of cerebral angiitis is suspected according to the results of vascular imaging, more sophisticated biological investigations are required including antiphospholipid antibodies, antinuclear antibodies, other circulating antibodies such as antineutrophil cytoplasmic antibodies, various serodiagnoses for infectious agents, depending on the context and CSF examination. Results of these latter investigations definitely guide the etiological diagnosis. It should be stressed that because the cerebral artery have unique characteristics that serve to protect the internal environment of the CNS, important arguments in favor of an inflammatory process may be missing in blood analyses. For example, elevation of the erythrocyte sedimentation rate, suggestive of a systemic disorder, may be missing in case of angiitis strictly localized to CNS.

**Computed tomography**

Head CT scan has a low sensitivity in the positive diagnosis of intracerebral angiitis since it can be normal (26% of the cases: 76) and the observed abnormalities are heterogeneous and non specific. The
The most common findings are related to cerebral ischemia: focal or multifocal low density areas of varying sizes, multiple parenchymal contrast enhancement and focal cerebral atrophy. Intracranial bleeding is less frequent (figure 1). Intracerebral hemorrhage may be caused by focal necrosis of the affected vessel wall. It appears to be more frequent in inflammatory than in infectious angiitis [76]. Subarachnoid hemorrhage may result from damage to the leptomeningeal arteries [67]. Meningeal contrast enhancement is possible and is sometimes included into a pachymeningitis presentation. It may be observed either in inflammatory [90] or in infectious angiitis (figure 2).

**MR imaging**

MR imaging is more sensitive than CT scan in detecting small brain lesions. Lesions of vasculitis are most often multiple, bilateral and supratentorial and frequently affect both gray and white matter [22, 34, 87, 93]. The main abnormalities are areas of non-specific high intensity signal of white matter on T2-weighted sequences (figure 3). Differential diagnosis of these signal abnormalities is often a difficult challenge. In favor of angiitis is the concommitance of isolated or multiple brain infarctions and of focal cortical atrophy [62, 76]. Furthermore, disseminated high intensity signals of white matter with no periventricular localization are suggestive of angiitis, in contrast with T2 hyperintensity signals described in multiple sclerosis [62]. In some cases of vasculitis periventricular hyperintensity signals may be seen but are often less pronounced than in case of multiple sclerosis. Despite the nonspecific appearance of

**Fig. 2.** — Tuberculous angiitis. Contrast enhanced CT scan. Leptomeningeal enhancement (black arrows). Hypodensity of the right centrum semi ovale (white arrows) caused by involvement of small penetrating arteries.

**Fig. 2.** — Angéite tuberculeuse. Scannographie injecté. Prise de contraste leptoméningée (flèches noires). Hypodensité du semi ovale central droit (flèches blanches) liée à l’angéite des artères pénétrantes.

**Fig. 3.** — Isolated angiitis of the central nervous system. MR imaging T1 (3a) and T2 (3b) weighted sequences. Infarction in both superficial (arrow) and deep (arrowheads) vascular territories associated with leucoencephalopathy.

**Fig. 3.** — Angéite isolée du système nerveux central. IRM, séquences pondérées en T1 (3a) et T2 (3b). Infarctus des territoires superficiel (flèche) et profond (tête de flèche) associés à une leucoencephalopathie.

MR abnormalities in cerebral angiitis, MR imaging remains of interest in the work up of this condition. Indeed, a normal MR examination is a very strong argument against the diagnosis of cerebral vasculitis [40]. As in CT, MR imaging often shows intraparen-
chymal hemorrhage either as initial manifestation or as a secondary transformation of an infarct [34, 40].

In the literature, there is no reported series comparing the diagnostic value of cerebral angiography and MR angiography in cerebral vasculitis. A recent study compared the two techniques in 15 patients with intracranial vascular stenosis related to arteriosclerosis [70]. Both 3D time-of-flight and 3D phase contrast were less contributive than cerebral angiography.

**Cerebral angiography**

At the present time, because of the flow artifacts and localization on small arteries, angioMR does not provide the same quality of information as that of cerebral angiography for the visualization of small intracerebral blood vessels. Therefore, cerebral angiography remains the diagnostic procedure of choice in most institutions whenever angiitis is suspected. The various practical situations in which cerebral angiitis may be suspected and which require angiography are listed in table III.

For optimal sensitivity, angiography should explore the four vascular axes or at least those feeding the regions which correspond to the symptoms or to CT and MR imaging abnormalities. While cerebral angiography is a relatively invasive procedure, postangiographic complications are exceptional in patients with suspected cerebral angiitis. In a recent series of 125 consecutive patients, one case (0.8%) of permanent deficit was observed following examination [97].

The most typical angiographic appearance of cerebral angiitis is the presence of multifocal, segmental vascular stenoses of the cerebral arteries (figure 4) which may sometimes be separated by segments of fusiform dilatations, presenting a « string of beads » appearance [27, 40]. Segmental stenoses are non specific since they have been reported in cases of arterial spasm (due to subarachnoid hemorrhage or severe arterial hypertension) and in various pathological conditions (table IV) such as intracranial arteriosclerosis, recanalization of embolisms, dissecting aneurysm [51] or radiation vasculopathy [95]. Other abnormalities may be observed in cerebral angiitis: irregularities of vascular walls, small artery occlusions, unperfused zones or aneurysms of variable size. Aneurysms can be induced by vascular wall fragility and subsequent self-repair resulting from angiitis [67]. A angiography may be normal particularly when vessels with diameters of less than 500 µm are involved. In some patients, abnormalities are observed only upon a second angiogram. Cerebral angiography is not so much of interest for determining the causes of angiitis as it is for establishing the diagnosis. Nevertheless, topography of the lesions may provide some etiologic information: unilateral involvement of proximal segments of the middle and anterior cerebral arteries are indicative of varicella zoster angiitis, focal stenosis of the first few centimeters of the middle cerebral and supraclinoid carotid arteries of tuberculous angiitis (table I).
Cerebral and leptomeningeal biopsy

While only biopsy can provide a definitive diagnosis of angiitis, its indications and modalities remain poorly defined: biopsy of a focal lesion, both parenchymal and leptomeningeal biopsy or leptomeningeal biopsy alone have all been proposed [13]. In clinical practice, treatment is often instituted without pathological proof when the clinical setting and/or imaging appearance are highly suggestive. This is particularly true in case of a known associated systemic disease.

Are repeated angiograms useful?

As previously detailed, the diagnosis of cerebral angiitis is more often made on statistical grounds than on definitive proof since cerebromeningeal biopsy is far from always performed, depending on the context. The diagnosis of cerebral angiitis, appears therefore « probable » or even « possible », and is founded on clinical, biological and mostly on angiographical arguments. In such cases, repeated angiogram or M R angiography is useful for the differential diagnosis with other causes of multiple segmental narrowings such as atherosclerosis, recanalizing embolisms or vasospasms [72]. The delay before repeating the procedure depends on the degree of clinical emergency.

In patients with proven cerebral angiitis, repeated vascular imagings may also be useful for therapeutic decisions. Although treatment regimens are poorly defined in cerebral angiitis, most clinicians tend to adjust medication according to clinical, biological as well as imaging follow-up.

Infectious angiitis of the CNS

Vasculitis may result from a number of infectious causes [20, 29] including bacterial spirochetal, parasitic, fungal and viral infections (table II).

Angiitis in purulent bacterial meningitis

Purulent bacterial meningitis, usually due to Haemophilus influenzae, is a common cause of cerebral vasulopathy in children. Cerebral infarction complicates such meningitis in children in up to one fourth of the cases [46] and may be due to either vasculitis, coagulopathy or vasospasm. A ngiography usually reveals narrowing of vessels at the base of the brain [34]. M R imaging usually shows multiple infarctions, predominating in the lenticulostriate territory.

Tuberculosis of the CNS

Tuberculosis of the CNS may present as tuberculous meningitis alone, as meningitis with generalized angiitis or as tuberculosis with adjacent focal angiitis. In the former case, generalized angiitis usually involves arteries at the base of the brain, such as the supraclinoid internal carotid arteries and the M 1 segment of the middle cerebral arteries [27, 57], and sometimes more distal branches (figure 5). Imaging studies are otherwise nonspecific, showing vascular narrowings and/or occlusions.

Syphilitic vasculitis

Brain infarcts may occur in patients with meningo-vascular syphilis [42]. The territory of middle cerebral artery seems to be the most frequently affected [88].

Parasitic diseases

Cerebrovascular complications, including brain infarction and intracranial hemorrhage, have been reported in cases of amebic infection [30, 55], hydatid disease [5] and schistosomiasis [84]. Neurocysticercosis can lead to brain infarction related to occlusion of arteries secondary to arachnoiditis and, seldomly, to mycotic aneurysms [11, 19, 64, 74].

Mycotic vasculitis

Mycotic vasculitis may be caused by various agents such as aspergillosis [3, 41, 61, 75, 92], cryptococcosis [78], mucormycosis [32].
ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

Viral vasculitis

Varicella zoster angiitis

Primary varicella infection may be complicated by large-vessel cerebral vasculopathy [23]. Furthermore, a particular syndrome may occur as a delayed complication after herpes zoster infection involving the trigeminal nerve (ophtalmic branches). It develops usually after several weeks or months and may be responsible for contralateral hemiplegia [31]. Characteristic angiographic patterns are, as previously described, restricted lesions to M1 and A1 segments of cerebral arteries ipsilateral to the involved trigeminal nerve [8, 31, 54].

Angitis in Herpes simplex encephalitis

Herpes simplex encephalitis may be caused by HSV 2 (genital herpes virus) in neonates and by HSV 1 (oral herpes virus) in children and adults [31]. HSV 1 is the most common nonepidemic cause of viral meningoencephalitis in the United States and Europe [71]. HSV 2 encephalitis is a diffuse infection, while HSV 1 encephalitis involves preferentially the limbic system [21, 43, 86]. HSV meningoencephalitis may cause a focal necrotizing vasculitis with perivascular and meningeal lymphocytic infiltration, petechial hemorrhages and focal tissue necrosis.

Isolated angiitis of the CNS (IA CNS)

By definition IA CNS exclusively involves the blood vessels of the CNS. Although autopsy sometimes reveals the presence of systemic angiitis (in peripheral nerves, lungs, kidneys or prostate), the presence of such silent vascular lesions does not alter the diagnosis of IA CNS as long as there are no associated parenchymal lesions of these different organ systems. While the cause of IA CNS remains obscure, it is thought to result from immunological response to various insults and particularly to neurotropic viruses which, if they indeed exist, remain completely undetermined at the present time [10].

Pathology

IA CNS has been referred to by several names including « granulomatous angiitis of the CNS (G A CNS) », « primary angiitis of the CNS (PA CNS) », « giant cell granulomatous angiitis of the CNS », « cerebral granulomatous angiitis » [17]. The variable terminology reflects the difficulty in individualizing IA CNS, even as a pathological entity, from systemic disorders such as giant cell temporal angiitis or sarcoidosis, which are sometimes responsible for angiitis of the CNS. While the pathology of IA CNS is nonspecific, it is characterized by the infiltration of vascular walls by mononuclear cells which may be associated at the acute phase to fibrinoid necrosis. In about 85 % of the cases, focal inflammatory lesions are found which include lymphocytes, macrophages, epithelioid cells and giant Langhans cells. These lesions may spread to all of the layers forming the vascular walls but preservation of the media is commonly observed. Vascular abnormalities involve small blood vessels less than 500 µm in diameter. In almost all cases, leptomeningeal involvement is the dominating feature, with less consistent parenchymal involvement.

Diagnosis

IA CNS is twice as frequent in males than in females and onset most often occurs after 40 years of age. It can however affect all age categories and several cases have been reported in children [10]. Clinical symptoms include all signs that are common to non infectious and infectious angiitis (18). Chronic diffuse white matter disease [28] and subarachnoid hemorrhage [72] have been reported to reveal patients with IA CNS. Patients usually present with no systemic signs, although fever may be present occasionally (about 15 % of the cases) and can add to diagnostic difficulty. Inaugural signs of myelopathic pain are rarely observed. Even more exceptional is the presence of spinal root pain which has been reported in association with angiitis limited to the dural sac. Perivascular inflammatory lesions may also

NON INFECTIOUS ANGIITIS OF THE CNS

Table II lists the different causes which may be associated with the onset of angiitis.
be seen in fundoscopy which may constitute a valuable diagnostic tool. The sedimentation rate is normal or moderately increased in 1/3 of the cases. Nonspecific signs of CSF inflammation are usually observed.

Cerebral computed tomography scan is normal in about 1/3 of the cases. A part from the previously described anomalies usually seen on CT scan and MRI [22], unusual presentations are sometimes described: pseudotumoral lesion, repeated parenchymal or ventricular bleeding, leptomeningeal contrast enhancement without significant parenchymal anomalies, and exceptional multiple punctuate parenchymal contrast enhancement (milliary appearance). Initial angiography is informative in only 30% of the cases (figure 6), which may be explained by the prominent involvement of small blood vessels of less than 500 µm in diameter. The angiographic features characteristic of IACNS include a distribution of segmental vascular stenosis to the small blood vessels of the convexity. Reports of intracerebral aneurysm are rare (39). Positive diagnosis can only be obtained through pathological study [66].

In 1989 criteria were proposed for the diagnosis of IACNS [66]:

— association of headaches and multiple neurological deficits which persisted for at least 6 months;
— segmental arterial stenoses on cerebral angiogram;
— exclusion of any infectious or inflammatory cause;
— inflammatory lesions of the vascular wall on cerebral and/or leptomeningeal biopsy or exclusion of all other causes of cerebral angiitis.

Treatment and prognosis

The spontaneous course of IA CNS in the majority of cases is progressive or successive phases of aggravation over a period of a few weeks to a few months. Prognosis seems to be spectacularly improved through the association of high doses of steroids and cyclophosphamide but it should be stressed that, to date, published data are based on retrospective series. In the largest series [10] involving 46 cases, 19 of the 20 non treated patients rapidly progressed either to death or to the persistence of severe sequelae, while 4 of the 13 patients treated by steroids alone and 10 of the 13 treated by a combination of steroids and cyclophosphamide showed favorable progression. Complete regression of symptoms have even been reported under such treatment. Regression of angiographic anomalies usually parallels clinical improvement [38]. In isolated cases, improvement of the MRI appearance after specific treatment has been reported as well as a close relationship between clinical improvement under treatment and normalization of the CSF.

Primary systemic angiitis with CNS involvement

Polyarteritis nodosa and other related systemic necrotizing vasculitides

Polyarteritis nodosa (PAN) is a multisystem necrotizing vasculitis with characteristic involvement of muscle and kidneys [79]. It is twice as frequent in males as in females and the average age of onset of the disease is 45 years. PAN is pathologically defined as a panangiitis, with fibrinoid necrosis predominating in the internal portion of the media with granulation tissue. Typically, lesions are seen at different stages of the inflammatory process which involves small to medium sized arteries [7].

CNS involvement can either be due to angiitis or to another mechanism (arterial hypertension, heart disease, kidney failure). It does not seem to alter the survival rate which now reaches 80% at 5 years since the wide spread use of the association of corticosteroids and cyclophosphamide [65]. CNS involvement is rarely a presenting feature [47]. Its prevalence is estimated between 10% and 20% and it reaches nearly 50% when such symptoms as headache, ocular involvement, and cranial neuropathy are taken into account [56]. The clinical presentation is polymorph, with diffuse symptomatic forms, such as encephalopathy, and forms with focal and multifocal brain involvement. Both forms are equally frequent. In addition to arterial stenosis, cerebral angiography sometimes shows aneurysmal development at arterial bifurcations, which is highly suggestive of diagnosis [24]. Renal or mesenteric angiography is the most useful imaging approach to diagnosis and shows multiple small aneurysms or angiitis in about 60% of cases [91]. PAN diagnosis is confirmed by nerve, muscle or kidney biopsy findings, showing characteristic arterial modifications.

Other pathologically similar syndromes such as Churg-Strauss angiitis (asthma, eosinophilia) and Cogan’s syndrome (vestibular involvement, bilateral deafness, interstitial keratitis) may exceptionally present with angiitis involving the CNS, but in such cases, in patients who present the diagnostic criteria of PAN [9].

Multiple cholesterol embolisms can simulate PAN and may cause ischemic stroke [16]. This differential diagnosis in the context of cutaneous lesions (livedo) or visceral lesions (kidney, intestinal), in a patient with arteriosclerosis, is confirmed by biopsy of an ischemic organ (particularly the muscle) showing crystals of cholesterol. Treatment is based on antiplatelets, colchicine and sometimes moderate doses of corticosteroids [7].

Giant cell angiitis

Temporal angiitis

Temporal angiitis is a panangiitis with segmental and multifocal involvement of medium and large cranial branches of arteries originating from the aortic arch, typically affecting elderly patients over 50 years of age. It is characterized by mononuclear cell infiltrates of giant cell granulomas involving the inner portion of the media and the intima with fragmentation of the internal elastic lamina [25, 44].

The diagnosis of temporal angiitis is based on the association in an elderly person, of permanent temporal or occipital headache, systemic symptoms such as malaise, anorexia and weight loss and an elevation of the sedimentation rate, which is not consistently found (absent in 10% of the cases). Biopsy of the superficial temporal branch of the external carotid artery, which may be performed bilaterally, is often diagnostic.

The prevalence of CNS involvement varies between 25% to 50% of the cases depending upon whether the neuropsychiatric symptoms are considered alone or if the neuro-ophthalmologic signs are taken into account as well [56]. One third or more of the patients develop partial or complete blindness, owing to acute ischemia of the optic nerve head, caused by the involvement of the ophthalmic artery and its central retinal and ciliary branches [96]. Visual impairment is the major complication of temporal angiitis and may be the presenting feature, making early diagnosis and treatment necessary. The onset
of ocular paresis (generally due to the involvement of the common ocular motor nerve) is uncommon but may foreshadow impending blindness.

Since biopsy of the superficial temporal artery is a simple diagnostic procedure, angiographic evaluation of patients in the absence of ischemic stroke is uncommon [37]. If angiography of the cervicocephalic arteries is deemed necessary, it may show segments of smooth tapering stenosis or complete vessel occlusion. Although the common carotid, extracranial internal carotid, vertebral and subclavian arteries, are rarely involved angiographically, histologic involvement of these vessels has been demonstrated [56, 73, 89]. Ophthalmic artery branches, although commonly affected clinically, are often too small to be angiographically visible. Cerebral and meningeal vessels are much less commonly involved than the superficial temporal artery.

Psychiatric symptoms, including depression, confusion or dementia, are common signs in the course of the disease and differential diagnosis may be difficult with secondary effects of corticosteroid therapy. According to various publications, the prevalence of ischemic stroke in the course of temporal angiitis ranges from 2.5 to 25%. In a recent series of 166 cases of pathologically proven temporal angiitis, the onset of transient ischemic attack or stroke was found in 12 patients (7% of the cases): involvement of the carotid territories was twice as frequent as that of the vertebrobasilar territories [12]. It may be difficult to attribute cerebrovascular symptoms to temporal angiitis given the frequency of other causes such as atherosclerosis in patients of the same age group.

While prognosis of temporal angiitis is usually favorable once corticosteroid therapy has been instituted, it is poorly evaluated in cases either with stroke or proven intracranial angiitis.

TAKAYASU’S ANGITIS

By contrast with to temporal angiitis, Takayasu’s angiitis affects young patients (usually between ages 20 to 40) most frequently women from Asia, West India or North Africa. In children there have been reports of severe and rapidly progressing forms. Prognosis of the disease (85% to 90% survival rate at 10 years) does not seem to be modified by CNS involvement [9].

The vasculitis tends to involve large vessels such as the aorta, the pulmonary arteries and the arteries arising from the aortic arch [14, 25, 59]. Involvement of the extracranial segments of the cervicocephalic arteries, contrasts with the absence of involvement of the intracranial arteries (figure 7). Segmental septa of the common carotid artery has been reported and seem to correspond to multisegmented dilations of the vessel with regions of normal-appearing arterial wall [58]. Because of this extracranial topography of arterial involvement, new vascular imaging procedures such as helical CT scan and MR angiography are useful for diagnosis and staging [59]. Histologic changes include adventitial mononuclear infiltrates, giant cell granulomas of the media with intimal proliferation and fibrosis, all changes that may lead to complete occlusion of the arterial lumen [36]. The internal portion of the media and the internal elastic lamina are usually spared, by contrast with temporal angiitis.

The diagnosis of Takayasu’s angiitis is difficult at the early (prepulseless) stage since the clinical features are highly non specific (fever, weakness, arthralgia, ...). However diagnosis at the early stage is important because the time at which steroid therapy is initiated can affect the prognosis [59]. Symptoms depend on the location of arterial lesions which may appear after months or years of disease progression. The prevalence of CNS involvement varies between 15% to 20% depending on whether visual impairment is taken into account [56]. Such visual impairment is caused by chronic retinal ischemia and may constitute the presenting symptom. It may be either uni or bilateral and may lead to blindness. The most
common neurological signs, per se, are sensations of malaise or syncopal episodes occurring during a physical effort or positional change. Focal neurological deficits due to ischemic strokes are less frequent. These strokes are of thrombotic origin (arterial lesions leading to occlusion), embolic origin (arterial embolisms of arterial origin) or hemodynamic origin. Intraparenchymal hemorrhages due to arterial hypertension are also observed.

The characteristic locations involving large vessels make biopsy impossible in most cases and angiography is therefore of crucial importance for diagnosis. Smooth tapering stenosis or occlusion of the proximal subclavian, innominate and common carotid arteries is the usual angiographic pattern. Aortic involvement with irregularities and luminal narrowings is sometimes observed [89].

Long term corticosteroid therapy is recommended by most authors, associated with antiplatelets for some. Patients resistant to corticosteroid therapy may respond to cyclophosphamide [7, 9].

Wegener’s granulomatosis and lymphomatoid granulomatosis

Both diseases are multisystemic necrotizing granulomatous vasculitis. Wegener’s granulomatosis primarily involves the respiratory tract and kidney (glomerulonephritis). Involvement of the CNS is exceptional as opposed to cranial nerve involvement (direct granulomatous invasion from contiguous nasal and paranasal lesions or through vasculitis). In a recent series of 324 patients with Wegener’s granulomatosis, signs of cerebrovascular involvement were noted in 4% of the cases [68]. In the context of inaugural neurological symptoms, Wegener’s granulomatosis may be suspected if highly elevated titers for antineutrophil cytoplasmic antibodies are found [69]. The spectrum of CT and MR findings includes dural thickening, meningeal enhancement, cerebral infarction. MR signals abnormalities are observed in the brainstem and hemispheric white matter [80]. When cerebral angiography is performed, it is usually normal (involvement of small vessels). Nevertheless, a few cases of intracranial vascular stenosis or even occlusion have been reported [83, 94].

Lymphomatoid granulomatosis, which preferentially involves the lungs, is characterized by the association of angiocentric necrosis with an inflammatory cell infiltrate composed of atypical lymphocytes and CNS involvement is observed in 19% of the cases and seems to worsen the already gloomy prognosis of the disease.

Exceptional forms of apparently primary angiitis

A few other exceptional forms of primary angiitis of unknown origin are noteworthy. Buerger’s disease, also known as thromboangiitis obliterans, has a predilection for men and is more readily observed in smokers. The disease initially involves distal extremities. Pathological study shows lesions which include granuloma in walls of small and middle sized vessels with no associated necrosis. CNS involvement is never a primary feature.

Susac’s syndrome (or retinal-cochlear encephalopathy) most commonly involves young women and associates bilateral deafness, visual impairment through multiple retinal arterial occlusions and signs of diffuse encephalopathy. The latter sign is related to cerebral microvasculitis. Since only small intracranial vessels are involved, angiography is normal in most cases (figure 8). In a significant number of cases, the syndrome progresses towards spontaneous remission. In other cases, the association of corticosteroids and cyclophosphamide may be beneficial.

A cute posterior multifocal placoid pigment epitheliopathy [15], usually limited to the retina, is responsible for severe visual impairment but outcome is favorable in most cases. It is exceptionally complicated by cerebral angiitis involving middle sized blood vessels, sometimes years after the visual abnormalities.

Kohlmeier-Degos disease, or malignant atrophic papulosis is easily diagnosed by the characteristic skin lesions. On the pathological level, there is proliferation of small sized arteries with intimal vacuolization and edema without a great deal of inflammatory reaction, which, according to some authors, excludes the disease from the group of cerebral angiitis. Despite sophisticated therapies (immunosuppressors, plasmapheresis), arterial involvement is responsible for en- teric as well as neurological complications, with multiple infarts leading rapidly towards death.

Angiitis secondary to systemic disease

CNS angiitis is exceptionally observed as a complication of various systemic diseases including scleroderma [6], mixed connectivitis, coeliac disease, ulcerative colitis or dermatomyositis.

In a number of individual cases, cerebral angiitis has been reported in the course of rheumatoid polyarthritis, but a recent series of 33 patients showed no increase in the prevalence of both high intensity white matter lesions and silent cerebral infarcts in the course of the disease, thereby suggesting that cerebral vascular involvement is uncommon in this condition [4].

In Behçet’s disease, signs of CNS involvement occur in 20% of the cases and may reveal the disease. Cerebral thrombophlebitis is much more common than angiitis. In the latter case, clinical presentation is usually a rhomboencephalitis with subacute onset. Pathological study shows parenchymal necrosis and hemorrhage with perivascular lymphocytic inflammatory infiltrates involving the arterial and venous
walls as well. Prognosis has been greatly improved in recent years by association of corticosteroids and immunosuppressors [82].

A granulomatous angiitis of the CNS has also been reported in cases of sarcoidosis, involving small and large sized cerebral vessels. One should consider the diagnosis of neurosarcoidosis when other suggestive neuroradiological signs are present such as pachymeningitis (figure 9).

CNS angiitis is best documented in cases of systemic lupus erythematosus (SLE) and Sjögren's syndrome (55).

Systemic erythematous lupus

CNS involvement is found in 25 % to 75 % of SLE patients depending on the series and is part of the initial presentation in about 15 % of the cases. Symptoms of CNS involvement are extremely varied and include mental disorders, seizures and focal signs [56]. Progression of the disease with recurrent manifestations may mimic multiple sclerosis and the diagnosis may therefore constitute as a difficult challenge. In 3 to 20 % of the patients [53], clinical symptoms suggesting stroke are observed [48]. Stroke itself exceptionally reveals the disease. It usually appears in the first 5 years following diagnosis and is more frequent in the presence of hypertension or elevated titers of antiphospholipid or anti DNA antibodies. CSF abnormalities (moderately elevated protein level, pleocytosis, modification of gammaglobulins) are inconsistent. CT scan in SLE patients with cerebral involvement, which is usually normal, may show cortical atrophy with or without ventricular dilatation and less commonly ischemic or hemorrhagic stroke. MRI is more sensitive than CT and frequently reveals nonspecific white matter high intensity signals [62]. In the great majority of cases, cerebral angiography is normal, but may show arterial occlusion or aneurysmal dilatation at arterial branch points [27, 53]. Diagnosis of SLE may be difficult when CNS involvement is inaugural since serum titers of anti DNA antibodies and complement or even sedimentation rate may all be normal.

CNS involvement can be due to various mechanisms: hypertension (with or without kidney involvement), endocarditis, cerebral thrombophlebitis, thrombocytopenia, anti phospholipid antibodies, anti neuronal antibodies, complication to treatment [56]. Compared to these mechanisms, angiitis is responsible for neurological symptoms in a minority of SLE patients only, contrasting with the high rate of vascular lesions (infarcts, intraparenchymal hematomas, diffuse patchy hemorrhages, subarachnoid hemorrhages) found at autopsy [48]. A true angiitis (presence of inflammatory cells within vessels wall) is rare (0 to 7 %) in postmortem studies [53]. This may be partly due to the delay between the clinical presentation and the histological study. Indeed, angiitis is more frequently found when an acute neuro-
Logical CNS complication is responsible for abrupt death. It should be stressed that angiitis is not the unique mechanism found to occlude cervico-cerebral arteries in SLE: arterio-arterial and cardio-arterial embolism, arterial dissection and atherosclerosis have all been reported [63].

CNS involvement, the second cause of mortality in the course of SLE after kidney disease, is a factor of poor prognosis with a drop in the 10-year survival rate from 83% to 50%. Cases resembling PAN with cerebellar and brainstem involvement or necrotizing vasculitic lesions leading quickly to death have been reported.
Angiitis associated with neoplastic disease

Sjögren’s syndrome

In more than half of cases, the clinical signs of CNS involvement observed in SS are associated with signs of peripheral nervous system involvement. These latter are most often secondary to vasculitis. Neuropsychiatric manifestations are the most prevalent symptoms of CNS involvement in the course of SS (present in more than 60% of SS patients). As with SLE, differential diagnosis with multiple sclerosis may be difficult. CSF analysis shows an increase in gammaglobulins (with oligoclonal pattern) in 50% of the cases. A series of 38 patients explored by cerebral MRI showed white matter abnormalities in 12 of 16 patients with neuropsychiatric symptoms and in 21 of 22 patients with no neurological symptoms [2]. In a series of 15 patients with Sjögren’s syndrome but no clinical evidence of CNS involvement, punctate areas of high signal were observed on T2-weighted images in 9 cases. A cortical atrophy was observed in 6 cases [77].

CNS involvement is sometimes attributed to histologically proven angiitis. In some cases, however, absence of cerebral angiitis in patients with central neurological signs has been demonstrated at autopsy. Other mechanisms, such as direct involvement of brain parenchyma by anti neuronal antibodies, are suspected. The efficacy of corticosteroids on the neurological manifestations of Sjögren’s syndrome has not been established. Some authors have suggested using plasmapheresis.

Angiitis associated with neoplastic disease

A number of mechanisms can account for the presence of stroke in a patient with a known neoplastic disease: coagulation disorder (particularly disseminated intravascular coagulation), non bacterial thrombotic endocarditis, cerebral thrombophlebitis, tumoral embolism, rupture of oncotic aneurysm in case of hemorrhagic stroke, infectious disease related to immunodepression or to side effects of the treatment [35]. Stroke is exceptionally caused by angiitis which seems to be more frequent in patients associated with immunosuppressors [9].

Sjögren’s syndrome may be associated with immunodepression or to side effects of the treatment [35]. Stroke is exceptionally caused by angiitis which seems to be more frequent in patients associated with immunosuppressors [9].

Vascular involvement in such cases is usually diffuse but cases of angiitis limited to the CNS have been reported. It usually appears in the absence of any malignant lymphomatous involvement of the brain. To a lesser extent, it may be observed as limited to the blood vessels adjacent to intraparenchymal lymphoma. In a few observations, symptoms related to angiitis preceded the discovery of hematologic disease by several years [35]. Hairy cell leukemia may be associated with a necrotizing angiitis identical to that observed in PAN.

Drug related cerebral angiopathy

A number of ischemic or hemorrhagic strokes have been reported in users of cocaine or its alkaloid derivative « crack » (widely used since 1983) or of heroin [45, 52, 60]. A radiographic evidence of segmental narrowing of the cerebral arteries may be observed in patients consuming the above mentioned substances and seems to be related to vasospasm due to acute hypertension. In a few rare cases however, authentic angiitis has been histologically proven, probably due to an allergic reaction either to the substance itself or to its adjuvants [96]. Inflammatory infiltrates of the distal internal carotid artery has been reported in cocaine users and lymphocytic infiltrates involving the small cerebral blood vessels in cocaine as well as crack users. Non necrotizing leukocytoclastic angiitis of the small vessels with normal cerebral angiography has also been reported [49]. Conversely, bleeding can occur in the absence of readily detectable vascular abnormalities in case of cocaine-associated intracranial hemorrhagis [1]. A few cases of documented cerebral angiitis related to drug abuse have shown improvement under cortico-steroids.

Several observations have been made of angiitis in amphetamine users (including the currently popular « ecstasy ») and sympathomimetic drugs such as ephedrine or phenylpropanolamine (which is present in a number of drug preparations including nasal decongestants).

Miscellaneous associations

Several observations have been reported of amyloid angiopathy associated with giant cell granulomatous angiitis. The clinical context is usually that of parenchymal hemorrhage suggestive of amyloid angiopathy with the discovery of associated angiitis on cerebral biopsy analysis. It has been suggested that such angiitis could develop in reaction to the presence of A 4 peptide deposits [33].

Reversible cerebral angiopathy

Reversible cerebral angiopathy is not a form of angiitis per se, since the changes in the caliber of
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Cerebral arteries are due to vasospasm. It is characterized by severe headache, vomiting and sometimes seizures and may be suggestive of subarachnoid hemorrhage or in case of transient neurological deficit, of cerebral thrombophlebitis. CSF analysis may be normal or show few red blood cells. Complete clinical recovery is the rule.

First described in the postpartum shortly after a normal delivery (and sometimes attributed to the prescription of ergot derivatives such as ergonovine or bromocriptine), reversible cerebral angiopathy has also been reported in toxemia gravidis or after the use of vasoconstricting drugs (amphetamines, phenylpropanolamine) or narcotics [50]. A predisposed context is important for the diagnosis. The disease mostly affects young adults (age range: 25-49 years). A angiographic features include multiple segmental stenoses of middle and small sized cerebral arteries, sparing the large arteries of the base. Superficial temporal artery may also be involved [85]. Follow-up angiography with confirmation of arterial normalization, is of diagnostic importance. Normalization occurs within a few days to a few weeks, which justifies an early initial angiogram (figure 10). Close neurological monitoring is required until the diagnosis is established because a rapid progression of the disease may suggest cerebral angiitis and should lead to considering a cerebral biopsy. In a few cases, the lifting of arterial stenosis has been shown using transcranial Doppler. The cause of arterial stenosis in reversible cerebral angiopathy is not completely elucidated but it seems to be a prolonged vasoconstrictive response to a sudden increase in arterial pressure, which could either be intermittent or prolonged. In the case reported by Serdaru et al., microscopical study of superficial temporal artery was normal suggesting a vasospasm rather than an angiitis [85].

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