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Clinical Study

Ten year clinical experience with stroke and cerebral vasculitis

Peter A. Kempster [a], Catriona A. McLean [b], Thanh G. Phan [a,c,*]

[a] Stroke Unit and Department of Neurology, Monash Medical Centre, Melbourne, Australia
[b] Anatomical Pathology Department, The Alfred Hospital, Melbourne, Australia
[c] Stroke and Ageing Research Group, Southern Clinical School, Department of Medicine, Monash University, Melbourne, Australia

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ABSTRACT

Angiitis of the central nervous system (CNS) is difficult to diagnose but potentially fatal. When stroke occurs in a younger individual or is associated with multiple infarcts on imaging, clinicians must decide how far to pursue a possible diagnosis of vasculitis. The aim of this study is to establish the prevalence of primary and secondary cerebral angiitis among patients presenting with stroke. Hospital attendances over a 10 year period were surveyed by searching for diagnostic codes and key words specific for cerebral vasculitis/angiitis. Case notes were reviewed by the authors using two sets of criteria for angiitis of the CNS. Thirty-two patients were initially considered likely to have cerebral angiitis by treating physicians. Thirteen had been admitted to hospital with stroke. During this period, there were 7475 admissions for ischaemic and haemorrhagic stroke. Six patients had a final diagnosis of vasculitic stroke but only one had definite CNS angiitis with a first presentation as ischaemic stroke (0.02%). Most patients who did have cerebral vasculitis developed multifocal or subacute neurological deficits, or already had an immunological disorder known to be associated with secondary CNS angiitis. Of 19 patients given an alternative final diagnosis, the most common were atherosclerotic/embolic cerebrovascular disease (n = 9) and reversible cerebral vasoconstriction syndrome (n = 7). Stroke is rarely the first manifestation of cerebral vasculitis. Our findings suggest that routine screening for angiitis in stroke patients may not be warranted.

1. Introduction

Cerebral angiitis is an uncommon but dangerous disorder. The annual incidence of primary central nervous system angiitis (PACNS) been estimated to be 2.4 cases per million [1]. PACNS is by definition an organ specific disorder that can only be detected by neurological investigations. When neurological disturbance develops in a patient with a known connective tissue disorder, the clinician faces a different challenge to distinguish angiitis from other types of nervous system involvement. Central nervous system (CNS) vasculitis can present with ischaemic stroke, but also with haemorrhage, encephalopathy and tumour-like brain lesions.

The incidence of stroke in Australia adjusted to "world" population is estimated to be 100 (95% confidence interval 80 to 119) per 100,000 per year [2]. As many as 18.5% of cases of stroke occur in patients who are aged 55 or younger [3]. These statistics and the available diagnostic criteria [4,5] provide little guidance on how common it is for stroke to be the sole and initial manifestation of cerebral angiitis. The possibility of angiitis is often considered in stroke patients who are young or who have multiple cerebral infarcts on imaging studies, although the scientific basis for this reasoning is not clear. In practice, common atherosclerotic and embolic stroke mechanisms predominate in this group, so clinicians must judge how far to pursue with investigations differential diagnoses that are rare causes of stroke [6]. There are therapeutic implications to over-enthusiastic diagnosis of CNS angiitis. Corticosteroids may be harmful to patients with non-vasculitic ischaemic stroke [7], and they may not receive more appropriate secondary prevention therapy [8].

The widespread availability of good quality non-invasive MR and CT angiography for imaging the intracranial arteries may have contributed to uncertainty about when cerebral angiitis should be diagnosed. Criteria that give equal weighting to angiography and histology in supporting a diagnosis of definite PACNS were first promulgated by Calabrese and colleagues in 1988 [4]. Theoretically, they allow a definite diagnosis of CNS angiitis to be based solely on young age, multiple infarcts and angiographic abnormalities. Modifications proposed by Birnbaum and Hellmann [5] in 2009 give gold standard status to histology, but these criteria have not replaced the previous ones [4].

* Corresponding author. Tel.: +61 3 9594 2240; fax: +61 3 9594 6241.
E-mail address: Thanh.Phan@monash.edu (T.G. Phan).

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Authoritative reviews on the subject use either set of criteria, with different emphasis on the importance of histological evidence [5,9,10]. As recently as 2011, a case series of PACNS was reported in which no patient had a cerebral biopsy to support the diagnosis [11].

The aim of this study was to establish the prevalence of CNS angiitis, both primary and secondary, in patients who presented to a tertiary referral hospital with stroke. By surveying all hospital attendances because of stroke, as well as all hospital attendances because of suspected or proven cerebral angiitis, we tried to understand which clinical features distinguish cerebral angiitis/vasculitis from non-arteritic stroke.

2. Methods

Discharge coding databases on patients admitted to Monash Medical Centre, Australia, under the care of the Neurosciences Department between 2003 and 2013 were searched. In addition, outpatient correspondence files covering the same time period were searched to identify the use of the words "angiitis", "vasculitis", "arteritis", "arteriopathy", "vasculopathy" and "biopsy". Medical records were then reviewed to determine patients in whom a diagnosis of cerebral vasculitis had been considered likely by treating clinicians. The characteristics of clinical presentations were registered, and all investigations were reviewed. Statistics on the incidence and classification of stroke were derived from a survey of all hospital admissions to the Stroke Unit and all attendances at outpatient stroke clinics over the same time interval. Stroke was defined as a rapidly developing clinical syndrome of focal loss of brain function, lasting more than 24 hours, and of presumed vascular origin [12].

Two sets of criteria for the diagnosis of PACNS were applied.

1. Definite PACNS: the presence of an acquired otherwise unexplained neurological or psychiatric deficit; the presence of either classic angiographic or histopathological features of angiitis within the CNS; and no evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disease [9].
2. Definite PACNS: confirmation of vasculitis on analysis of a tissue biopsy specimen and the other requirements of Criteria 1 are satisfied.
   Probable PACNS: in the absence of tissue confirmation, high probability findings on an angiogram with abnormal findings on MRI, a cerebrospinal fluid (CSF) profile consistent with PACNS, and the other requirements of Criteria 1 are satisfied [5].

A diagnosis of secondary CNS angiitis was confirmed if all other conditions except the absence of evidence of a connective tissue, neoplastic or infectious disorder known to cause CNS angiitis [9] were satisfied in either set of PACNS criteria. Brain biopsy specimens from patients who received a final diagnosis of CNS angiitis were reviewed by a neuropathologist (C.M.). The histopathological diagnosis of cerebral angiitis was based on previously published criteria that require inflammatory cells infiltrating vessel walls, structural alterations in vessel walls, and evidence of parenchymal cerebral ischaemic damage [1]).

A definite diagnosis of reversible cerebral vasoconstriction syndrome (RCVS) required three criteria to be met: (i) unusual, recent, severe headaches of progressive or sudden onset, with or without focal neurological deficit; (ii) cerebral vasoconstriction assessed by MR, CT or conventional angiography, with at least two narrowings per artery on two different cerebral arteries; and (iii) disappearance of arterial abnormalities in less than 3 months [14].

3. Results

Forty-five patients were identified by the computerised medical record search. Thirteen were excluded after review of clinical information established that a diagnosis of autoimmune cerebral vasculitis had not been considered likely by treating clinicians during the survey period. The remaining 32 patients (10 men and 22 women) had a mean age of 50.1 ± standard deviation of 18 years. Figure 1 shows the presenting neurological features and final classification of all patients.

3.1. Prevalence of vasculitis in patients presenting with stroke

During the 10 year survey period, there had been 4783 admissions for ischaemic stroke, 1674 for intracerebral haemorrhage and 928 for subarachnoid haemorrhage. There were 13 patients in whom vasculitis was initially suspected to be the cause of their stroke. The most frequent reason for this suspicion was the finding of multiple infarcts on MR scanning together with evidence of arterial narrowing on vascular imaging. Stroke in one patient was preceded by anterior ischaemic optic neuropathy. After investigations, two were diagnosed with RCVS, four with non-vasculitic stroke (two infarcts, two haemorrhages), and one with acute disseminated encephalomyelitis. Brain biopsies in five of these patients (two of whom were finally diagnosed with RCVS) helped to negate possible diagnoses of vasculitic stroke (Fig. 2).

Six of the 4783 ischaemic stroke patients had a final clinical diagnosis of vasculitic ischaemic stroke. One fulfilled both diagnostic criteria for definite PACNS. Another four had clinically conspicuous systemic or ophthalmological evidence for an immunological disorder associated with secondary angiitis of the CNS at the time of their stroke presentation, although none of these patients had a brain biopsy. The prevalence of vasculitic stroke was thus 0.13%, and the prevalence of definite angiitis of the CNS causing an isolated presentation with ischaemic stroke was 0.02%.

3.2. RCVS

Seven patients received a final diagnosis of RCVS. Two had convexity subarachnoid haemorrhage. Five conformed to all criteria for RCVS. RCVS was strongly suspected in the other two patients, one of whom had been using amphetamines and did not attend for follow up cerebral vascular imaging. All had changes on an angiographic study that were initially interpreted as suggesting vasculitis, although reporting radiologists may not have had access to full clinical details in some cases. After review of all clinical and neuroimaging information, these diagnoses were revised to RCVS. All recovered without immunosuppressive treatment.

3.3. Final diagnosis of cerebral vasculitis

Irrespective of presenting clinical features, 13 patients had, after full investigation, received a diagnosis of cerebral vasculitis (Fig. 3, Table 1). Of these, five biopsy-proven cases fulfilled both sets of criteria for definite PACNS and a sixth biopsy-proven case had secondary cerebral vasculitis related to sarcoidosis. Two of the definite PACNS patients had amyloid-beta related angiitis.

Another five patients had a diagnosis of secondary CNS vasculitis that was strongly based on systemic or ophthalmological grounds — one case each of CNS vasculitic involvement from Sjögren's syndrome, giant cell arteritis, microscopic polyarteritis nodosa, acute posterior multifocal placoid pigment epitheliopathy, and an undifferentiated uveo-meningeal syndrome. Three of these had angiographic abnormalities.