Cerebral vasoconstriction, headache and sometimes stroke: one syndrome or many?

In this issue, Dr Ducros, Professor Bousser and others from the Lariboisière hospital in Paris report the largest case series to date on the so-called ‘reversible cerebral vasoconstriction syndrome’, or RCVS (Ducros et al., 2007, p. 3091). The two key features of the syndrome are ‘thunderclap headaches’ and multifocal but transient narrowing of cerebral arteries. In addition, ischaemic or haemorrhagic stroke may supervene. The authors specify this further in that the headache should come on within a minute (less often within 5 min) and should be unusually severe; generally there are several similar episodes over a period of days or weeks. The angiographic signs of arterial narrowing disappear within a few weeks or months. Specific other conditions are ruled out by standard investigations of the brain, serum and cerebrospinal fluid. The authors not only carefully list the range of each symptom and angiographic feature within their group of 67 patients but also, thanks to the prospective study design, they tabulate possible precipitating factors and include a follow-up period in order to demonstrate the episodic nature of the disorder. Before addressing the robustness of these definitions, I shall make a short detour to reflect briefly on the rise and fall of ‘vasospasm’ as an explanation for vascular disorders of the brain, and also address the question of what actually constitutes any nosological entity.

Arterial spasm as a cause of gangrene of the extremities was described by Raynaud (1834–1881) in his doctoral thesis (Raynaud, 1862). Others extrapolated his theory of vasospasm to the cerebral circulation in order to explain transient episodes of cerebral ischaemia. Even the great Osler mounted the bandwagon to explain transient attacks of aphasia and paralysis: ‘We have plenty of evidence that arteries may pass into a state of spasm with obliteration of the lumen and loss of function in the parts supplied’ (Osler, 1911). Vasospasm remained the most popular theory to explain transient brain ischaemia in the first half of the 20th century and provided the rationale for so-called cerebral vasodilating drugs. The vasospastic theory went into decline soon after World War II, when the notion of haemodynamic insufficiency (‘cerebral intermittent claudication’) gained popularity. In turn, this was replaced by the concept of artery-to-artery embolism, for a large part because C. M. Fisher confirmed some older reports about the relationship between stroke and atheromatous lesions of the carotid bifurcation, while also providing direct observations of the ocular fundus in patients during an attack of transient monocular blindness (Warlow et al., 2007). The return of vasospasm as an explanation for fluctuating motor and sensory deficits, but now in patients who also had headaches, was heralded by a 1988 publication from Boston, with Gregory K. Call and Marie C. Fleming as the leads and the omnipresent C. M. Fisher as senior author (Call et al., 1988). In subsequent years, many others have reported similar patients, including patients with permanent neurological deficits instead of with headaches and vasoconstriction alone. Several names have been used (Ducros et al., 2007; Calabrese et al., 2007), but the terms RCVS or Call-Fleming syndrome are the most familiar.

But is such a syndrome a ‘real’ disease? Definition of a disease is merely a matter of convention (Wulff and Gøtzsche, 2000). The nosological system of medicine can be compared to a venerable old palace, to which repairs and additions have been made by each new generation, in different styles and with different materials. A fairly recent but robust segment is represented by diseases of which a necessary cause is known, such as Wilson’s disease or pneumococcal meningitis. Almost equally solid is the part of the nosological construct in which the defining principle is a specific structural change in a body organ, for example subarachnoid haemorrhage from a ruptured cerebral aneurysm or congestive myelopathy of the spinal cord secondary to a spinal dural arteriovenous fistula. A third and completely different disease category consists of pathophysiological changes, observed through examination (hypertension, schizophrenia) or investigation (vasospasm). The fourth and least ‘respectable’ section consists of diseases defined only by a particular symptom from the history, such as restless legs syndrome or idiopathic thunderclap headache. ‘ Syndromes’ are made up by any combination of features from the last two disease categories: they represent a cluster of symptoms, generally recognized (migraine) or controversial (‘whiplash syndrome’), or they may consist of a mixture of symptoms and pathophysiological changes. RCVS is an example of a more or less arbitrary syndrome, being characterized by
symptoms (episodes of sudden-onset headache) and pathophysiological changes (reversible vasospasm, with or without cerebral ischaemia). In the recent past some diseases have moved upwards, from lower to higher categories: pneumococcal meningitis used to be just one of the ‘fevers’, ‘brachialgia paraesthetica nocturna’ (symptom) has become ‘carpal tunnel syndrome’ (anatomically defined), and the discovery of gene mutations has elevated some syndromes to the category of causally defined disorders.

Will the ‘reversible cerebral vasoconstriction syndrome’ stand the test of time as a nosological entity? This can be doubted on several counts: the difficulty in defining ‘vasoconstriction’, the overlap with other syndromes and the multitude of precipitating factors identified so far. The Lariboisière group assessed vasoconstriction by means of MRA or conventional angiography and defined this characteristic as ‘at least two narrowings per artery on two different cerebral arteries’. But what constitutes arterial narrowing? The more subtle the changes in calibre in the course of an artery, the more often observers will disagree about the presence or absence of arterial narrowing, especially in distal branches of the cerebral vascular tree. Substantial interobserver variation occurs in the angiographic assessment of the degree of stenosis in carotid, middle cerebral or coronary arteries (Wong et al., 1995; Dippel et al., 1997; Dewey et al., 2007), while such a study has not even been attempted in the contentious issue of ‘vasospasm’ following aneurysmal subarachnoid haemorrhage. Ducros and colleagues have not classified the severity and distribution of the arterial changes according to clinical characteristics; one cannot help wondering whether narrowing was perhaps relatively mild in the group of 51 patients (of the total 67) who had no associated strokes or seizures. It would be worthwhile to compare arteriograms of patients with these recurrent episodes of sudden headache as the only feature with those of controls, in a blinded fashion. Since all patients were seen in a single institution within a 3-year period, the authors argue that RCVS is more common than generally assumed. One might also conjecture that other clinicians might not have classified the arterial changes as pathological.

So there may well be overlap between RCVS on the one hand and common types of headache such as migraine and daily chronic headaches on the other. Of course the onset of the pain in those ubiquitous types of headache is typically gradual, but by virtue of their commonness the exceptions to this rule may still outnumber rarer disorders; the same reasoning explains the paradox that most children with Down syndrome are born from women under 35 years of age, despite the relatively low risk in the younger group. In general practice, ‘idiopathic thunderclap headache’—regardless of arterial narrowing—is almost 10 times as common as subarachnoid haemorrhage, at least in patients with headache as the only symptom (Linn et al., 1994); years later at least 10–20% of them recall similar attacks of headache in the intermediate period (Wijdicks et al., 1988; Linn et al., 1999), which implies that the true recurrence rate must be higher. It depends on local referral patterns whether or not neurologists see this milder end of the spectrum of sudden headaches. Also at the severe end of the spectrum some disorders overlap with RCVS, such as arterial dissection and reversible posterior leukoencephalopathy syndrome, as the French authors themselves point out. The latter condition is associated not only with hypertension and eclampsia, but also with renal failure and cytotoxic drugs (Hinchey et al., 1996).

Not surprisingly, the pathophysiology of RCVS is ill understood and probably multifactorial, given the heterogeneity of precipitating events. In the Lariboisière series, more than half the patients reported previous use of vasoactive substances (cocaine, cannabis, nasal decongestants, serotonin reuptake inhibitors, interferon, nicotine patches, in some cases combined with binge drinking). Recent parturition preceded the disorder in about 10%, while no possible clue was found in the remaining one third of patients. A recent review also mentioned hypercalcaemia, porphyria, pheochromocytoma, bronchial carcinoma, unruptured saccular cerebral aneurysm, head trauma, spinal subdural hematoma and neurosurgical procedures (Calabrese et al., 2007). It remains to be established to what extent such preceding events are causally related to RCVS, or to certain subtypes. For example, it is conceivable that many or even most patients with several bouts of sudden headache but without concomitant ischaemia or haemorrhage will have an unremarkable history and at the same time only mild or equivocal narrowing of cerebral arteries. Other clusters of etiological, clinical and morphological characteristics may well emerge in times to come. Future studies should include all patients with sudden onset headache and also objective measures of irregularities in arterial diameter.

Treatment may eventually depend more on the causal factors than on the final common pathway of vasospasm. For now, the less said about that the better, in view of the unpredictable and often favourable course of RCVS. Osler should be given the last word, this time spot on: ‘A desire to take medicine is one feature which distinguishes man from his fellow creatures’ (Osler, 1906). Our understanding of the complex pathophysiology of what now is called RCVS should improve before systematic therapeutic experiments are undertaken. The authors from the Lariboisière deserve congratulations for having provided the neurological community with a firm stimulus to recognize and understand cerebral vasoconstriction syndromes.

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References