A comment on impaired peri-nidal cerebrovascular reserve in seizure patients with brain arteriovenous malformations

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Sir, We read with great interest the article by Fierstra et al. (2011), recently published in your journal. This article reopens the debate regarding the unsolved problem of the origin of seizures in patients with brain arteriovenous malformations, the pathophysiology of which remains poorly understood. Although angiographic studies have shown some associations between different brain arteriovenous malformation angioarchitectural features and epilepsy, they have not elucidated the underlying pathophysiology (Turjman et al., 1995a, b; Hoh et al., 2002). Similarly, MRI studies have often shown gliosis and chronic ischaemic changes in peri-nidal tissue as well as in remote regions, but any significant correlation has been demonstrated between extent of gliosis and clinical symptoms (Essig et al., 2000).

The main pathophysiological hypotheses to date include: (i) focal cerebral ischaemia attributable to a steal phenomenon as described by Spetzler et al. (1992) and Taylor et al. (2002); (ii) gliosis, demyelination and haemosiderin deposits in peri-nidal tissue; and (iii) secondary epileptogenesis in ipsilateral temporomesial cortex (Yeh et al., 1990), or at a distant site, attributable to a ‘kindling’ phenomenon, in which epileptic discharges are enhanced by excitatory synaptic connections from brain arteriovenous malformations (Hoh et al., 2002). Bleeding was deemed responsible for triggering seizure activity by Turjman et al. (1995a) and Stein and Wolpert (1980); in contrast, in the study by Hoh et al. (2002), intracranial haemorrhage was not a statistically significant factor associated with epilepsy.

Fierstra et al. (2011) studied in vivo the possible haemodynamic effect of an arteriovenous shunt in the remaining brain, and in particular, in peri-nidal tissue. They evaluated the reactivity of cerebrovascular bed (a measure of the existing autoregulatory reserve) through the changes in blood oxygen level-dependent (BOLD) MRI signal in response to alterations in end-tidal partial pressure of CO2. Although this technique does not measure an arterial flow and cannot quantify an eventual steal phenomenon, when present, the BOLD signal would exhibit a paradoxical decrease in response to hypercarbia. Comparing the reactivity maps of patients with brain arteriovenous malformations with healthy controls, they found that cerebrovascular reserve did not show any global difference between the two groups or between patients with brain arteriovenous malformations with and without epilepsy, when calculating for the entire brain or segmenting by single hemisphere and grey or white matter only. Only the analysis of the regions of interest immediately adjacent to the nidus revealed that seizure-prone patients showed a statistically significant impaired cerebrovascular reactivity as compared with those without seizures. Expanding the regions of interest concentrically, the difference in cerebrovascular reactivity appeared greatest in the 2 mm (P < 0.01) around the nidus and became smaller at each more distal region of interest, showing a loss of statistical significance beyond 8 mm (P = 0.05). Finally, comparing the peri-nidal tissue with the contralateral corresponding brain area, a cerebrovascular reactivity difference was shown in the first 4 mm in the seizure group. Logistic regression likewise revealed that the first 6 mm of brain tissue around the nidus demonstrated a significant effect on seizures (P = 0.03). However, peri-nidal cerebrovascular reactivity in the cohort of patients with brain arteriovenous malformations was not so impaired as to reach negative values, which would have implied arterial steal from the affected tissue. Accordingly, the venous congestion exhibited on angiography study by the seizure group, was considered as the cause adversely affecting neuronal function by impairing microvascular
autoregulation in the tissue surrounding brain arteriovenous malformations. They therefore concluded that probably venous congestion, and not vascular steal, impairs peri-nidal cerebrovascular reactivity, and could be associated with epileptogenesis (Fierstra et al., 2011).

In our opinion, Fierstra et al. (2011) should have correlated the modifications of the cerebrovascular reactivity around the nidus with the anatomo-electro-clinical data, in order to obtain a stronger significance of their pathophysiological hypothesis. In fact, they did not specify if the seizure-prone patients with brain arteriovenous malformations had also been studied clinically, electrophysiologically and neuropsychologically. The electroclinical correlation of seizures semiology with EEG pattern and neuropsychological evaluation is essential to clarify, as much as possible, the localization of the active epileptogenic foci as well as the possible involvement of omolateral or contralateral temporomesial structures (Yeh et al., 1990), or otherwise, a multifocal origin.

Although, brain arteriovenous malformation-related epilepsy is thought to be mainly focally originated, it still remains to be demonstrated why several surgical series in the literature have shown such discrepant results in seizures control.

Forster et al. (1972) and Parkinson et al. (1980) reported poor epilepsy outcome after surgery, with seizure-free patients close to 14% and 4%, and new epilepsy appearance in 22% and in 8%, respectively. Other studies have reported seizure-free patients after surgery at ~50% (Murphy, 1985; Heros et al., 1990). Piepgras et al. (1993) reported, in their large surgical series, a good seizure outcome in ~83% of cases, with 6% of new seizures appearance. Similarly, Thorpe et al. (2000) reported a good outcome in almost 80% of cases, however, these authors approached their patients by removing the brain arteriovenous malformations nidus, without preoperative anatomo-electro-clinical correlation for delineating the topography of the epileptogenic foci.

Yeh et al. (1990) routinely performed preoperative EEG recording, along with neuropsychological evaluation and intraoperative electrocorticography. They identified and eliminated epileptic foci, ‘away’ from the nidus, in 67% of cases, while in the remaining they removed only the nidus and the peri-nidal gliotic tissue, allowing successful results in 78% of cases.

These results may depend on the extent of peri-nidal gliotic tissue resection. However, on the other hand, endovascular-treated patients, with partial or complete nidus obliteration, but without any cortical excision, showed a seizure control in 18–56% of cases (Weinand, 1995).

We believe that the problem of epileptogenesis in patients with brain arteriovenous malformations may be a more complex phenomenon, combining a local vascular steal event or venous congestion, that leads to progressive gliosis and neuronal-glial cells interaction rearrangement in sensitive nuclei like in temporomesial structures and in distant cortical areas, besides in peri-nidal tissue.

The disappointing seizures outcomes reported in several surgical series, the evidence of epilepsy associated with deep located brain arteriovenous malformations, and the high rate of more extended or distant foci identified by electrocorticography recording (Yeh et al., 1990) seem to support a greater role of far epileptogenic areas. In agreement, Drake (1979) and Rasmussen (1975) have stressed the importance of first identifying and then removing the epileptogenic foci, in addition to the nidus resection. Finally, a congenital low epileptogenic threshold, in the context of a probable disembrionic disease, may explain the observation that similar appearing brain arteriovenous malformations can present either with or without seizures. Moreover, in a way, the brain ‘learns’ to have seizures as it learns any other activity, a process known as ‘kindling’, so that long-term repetitive seizures, also with focal origin, may trigger several distant epileptic foci altering their threshold, and making more difficult their characterization and treatment (Hoh et al., 2002; Bertram, 2007).

Because all individual assessment methods failed to provide an exhaustive explanation regarding the pathophysiology of brain arteriovenous malformation-related epilepsy, further in vivo studies are necessary. Intraoperative electrocorticography alone, however, cannot be considered an extensive method, since it explores only the area surgically exposed. Therefore, all new investigations, as accepted by most epileptologists, should also take into account the localization value of the seizures semiology, functional neuroimaging and preoperative and intraoperative EEG pattern. The integration of the anatomo-electro-clinical data will provide the best chance to clarify the epileptic areas.

In conclusion, although the emphasis of brain arteriovenous malformations treatment has been, to date, mainly placed on eliminating the risk of intracranial haemorrhage rather than control of the seizures; in the future, the elucidation of the underlying pathophysiology and a routinely preoperative epileptologic approach, should make the epilepsy treatment a primary goal.

References


