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Epilepsy associated with Leukoaraiosis mainly affects temporal lobe: a casual or causal relationship?

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Summary
Objective: To compare anatomo-electro-clinical findings between patients with epilepsy associated with leukoaraiosis only (EAL) and patients with a well-defined vascular lesion, i.e. post-stroke epilepsy (PSE).
Methods: Two hundred eighty-three subjects with epilepsy and cerebrovascular disease, consecutively seen in our epilepsy centres from January 2000 to March 2014, were retrospectively considered. Inclusion criteria were: history of one or more unprovoked seizures and MRI evidence of one or more vascular lesions. Exclusion criteria were: inadequate neuroimaging data, coexistence of nonvascular lesions, and psychogenic seizures. Subjects were divided in two groups: PSE and EAL, based onclinical and MRI findings. Epileptogenic focus was identified according to ictal semiology and EEG findings. In PSE group, coherence between the vascular lesion(s) and epileptogenic focus was scored as likely or unlikely.

Abbreviations: CI, confidence interval; EAL, epilepsy associated with leukoaraiosis; FLAIR, fluid-attenuated inversion-recovery; OR, odds ratio; PSE, post-stroke epilepsy; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

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Results: One hundred seventeen subjects were included: 58 had PSE, 59 EAL. Coherence was identified as likely in 38 (95%) and unlikely in 2 (5%). At univariate analysis, abnormal EEG and frontal localization were associated with a lower EAL probability [odds ratio (OR) 0.36, 95% confidence interval (CI) 0.15—0.87, $p = 0.02$ and OR 0.12, 95% CI 0.04—0.37, $p < 0.001$, respectively], while temporal localization was associated with a higher EAL probability (OR 4.0, 95% CI 1.8—9.0, $p < 0.001$). Multivariate confirmed these associations.
Conclusions: While in PSE epileptogenic focus is coherent with the vascular lesions, in EAL temporal lobe epilepsy predominates. In EAL, causal relationship between vascular lesions and epilepsy is not straightforward, and the role of adjunctive factors needs to be elucidated.

Introduction

Epilepsy and stroke are common neurologic disorders and their association has been extensively documented (Hauser et al., 1991; Tellez-Zenteno et al., 2005). Seizures occurring after a cerebrovascular event should be considered ''early'' if they occur at the onset or within 7 days (Beghi et al., 2010); otherwise, they should be considered late. ''Early'' or ''provoked'' seizures are not necessarily followed by epilepsy; conversely, ''late'' or ''remote symptomatic'' seizures are the expression of an enduring brain predisposition to develop seizures (Kessler et al., 2002). This is in keeping with the results of a population-based study (Hesdorffer et al., 2009) that documented a significantly higher risk of recurrence for individuals with a first unprovoked post-stroke seizure, compared to those with a first acute symptomatic seizure. According to the new operational definition of epilepsy (Fisher et al., 2014), the occurrence of the first unprovoked seizure is sufficient to diagnose post-stroke epilepsy.

Several studies have elucidated epidemiologic and prognostic characteristics of post-stroke seizures and vascular epilepsy (Awada et al., 1999; Bladin et al., 2000; Lamy et al., 2013; Graham et al., 2013; Huang et al., 2014), but little attention has been dedicated to epilepsy associated with leukoaraiosis (Schreiner et al., 1995; Maxwell et al., 2013) in the absence of a manifest stroke. Data about the involvement of blood vessels in epileptogenesis come from experimental studies on animal models and surgically removed human brain tissue (Mott et al., 2009; Biagini et al., 2008; Gualtieri et al., 2012, 2013). In particular, focal hippocampal and extra-hippocampal lesions, likely of ischaemic origin, were visible after pilocarpine-induced status epilepticus in adult rats, and these lesions contributed to the development of epileptogenesis (Biagini et al., 2008; Gualtieri et al., 2012). Clinical and electroencephalographic features of epilepsy occurring in the context of cerebrovascular disease of any kind have been poorly investigated. This is probably due to the lack of collaboration between stroke physicians and epileptologists: this led to focus on studies on the clinical characteristics of strokes rather than on electro-clinical features of seizures in post-stroke epilepsies. In the present study we identified features of both cerebrovascular disease (e.g. aetiology of strokes, involved brain territories, severity of leukoaraiosis) and epileptogenic focus (electro-clinical data) in order to compare anatomo-electro-clinical findings between patients with epilepsy associated with leukoaraiosis only (EAL) and patients with epilepsy associated with a well defined vascular lesion, i.e. post-stroke epilepsy (PSE).

Methods

Two hundred and eighty-three subjects consecutively observed from January 1, 2000 to March 31, 2014 in three Epilepsy Centres (located in Reggio Calabria, Catanzaro, and Catania, Italy) were retrospectively evaluated. Patients were recruited from both Emergency Department and an epilepsy centre in Reggio Calabria, and from epilepsy centres only in Catanzaro and Catania. According to the Italian regulations, this observational, retrospective study did not require approval by ethics committee. Inclusion criteria were: history of one or more unprovoked epileptic seizures and MRI evidence of one or more vascular lesions. Exclusion criteria were: normal brain MRI even with a clinical history of stroke, MRI performed exclusively before seizures onset or more than 6 months later, unavailability of MRI images, coexistence of psychogenic seizures or of a non-vascular brain lesion, cognitive decline not compatible with a diagnosis of vascular dementia (American Psychiatric Association, 2000; Sorbia et al., 2010).

All subjects underwent a full neurological examination at first visit and periodically during follow-up. A Mini Mental State Examination was administered as a screening test: if score was pathological (adjusted score <24/30), further neuropsychological evaluation was done to establish a diagnosis of dementia, as advised by the European Federation of Neurological Societies'guidelines (Sorbia et al., 2010). Subjects with vascular dementia were not excluded from the study.

For all included subjects, the following data were registered: age at inclusion in study, sex, features of each stroke (when existing: age at onset; ischaemic or haemorrhagic nature; involved vascular territory: anterior cerebral artery, middle cerebral artery, posterior cerebral artery, vertebral or basilar artery, small vessels; aetiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (Adams et al., 1993), age at onset of epilepsy, time interval between clinically manifested stroke (when existing) and epilepsy, family history of epilepsy in first or second-degree relatives, interictal or ictal EEG, lobar localization of epilepsy on the basis of seizure semiology (according to Commission on Classification, 1981) and Commission on Classification, 1989) and EEG data, response to treatment or drug resistance according to ILAE (Kwan et al., 2010), presence of main