Review Article

Role of Epileptic Activities in Acute Brain Failure Syndromes

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Brain function relies on efficient coordinated neuronal network activity. Neuronal cross talk and cerebral connectivity is fragile and occurs within tight metabolic and biochemical ranges. Breakdown in brain network dynamics by stressors that hamper cerebral metabolism or neuron neurophysiology led to "Acute Brain Failure" syndromes (ABF) [1]. ABF, under stressful event, is more likely to happen in individuals with baseline low brain resilience due to previous insults such as pre-existing neurodegenerative disorders, stroke or systemic comorbid conditions, similarly to acute exacerbation of chronic renal failure [2]. According to the context, ABF may manifest clinically as Altered Mental State (AMS), delirium or worsening of, already impaired, neurological function.

Although such model sets a good framework for the understanding of ABF, it does not provide pathophysiological mechanisms and therefore often confines the therapeutic interventions to symptomatic treatment. Precipitating factors of ABF such as electrolytic imbalances, hypo-glycemia, drug withdrawal, infection… are also known precipitating factors of epileptic activity and could represent one of the missing links between acute brain stressful events and ABF [3]. The aim of our studies was to assess the role of Interictal Epileptic Discharges (IED), Periodic Discharges (PDs) and Non-Convulsive Seizures (NCSz) in relationship to ABF in several different acute brain insults. Indeed, IED are generally thought to be asymptomatic but dedicated studies showed alterations of cognitive functions related to IED in both children [4-6] and adults [7,8] as well as brain network functional connectivity impairments [9-12]. Similarly, manifestations of PDs and NCSz range from subtle cognitive disturbances, with abnormal behaviour, mood changes, and higher function impairment to clouding of consciousness and unresponsiveness [13-15]. Epileptic activities, even IED [16-18], also increase brain metabolic rate, a phenomenon that can lead to a "metabolic crisis" and ABF in situations where the brain metabolism is already fragilized by acute stressors [19-20]. Our hypothesis was, thus, that IED, PDs and/or NCSz triggered by acute medical conditions could participate in ABF onset and perpetuation. We first focused on (i) broad-spectrum antibiotherapy in the Intensive Care Unit (ICU), then on (ii) delirium on older individuals and finally on (iii) Early Neurological Degradation (END) after ischemic stroke.

Broad spectrum antibiotherapy in ICU

The aim of this work was to assess the link between the broad-spectrum antibiotics selected for empirical monotherapy of febrile neutropenia or other hospital acquired infections in the Intensive Care Unit (ICU) and PDs, NCSz and Non-Convulsive Status Epilepticus (NCSE). The main broad-spectrum antibiotics that are prescribed in that setting are hydro chlorate cefepime and meropenem. Both these antibiotics have a β-lactam ring in their biochemical structure that is responsible for potential neurotoxicity: the β-lactam structure binds and inhibits the Ɣ-Aminobutyric Acid (GABA) receptors. The GABA receptors are responsible for interneurons inhibitory activity and, thus, GABA receptors inhibition leads to cortical increased excitability and higher likelihood of epileptic activities [21]. A meta-analysis suggested that the mortality rate was greater in patients treated with cefepime than in those treated with other β-lactam, giving no obvious explanation for these findings [22]. However, several reports of NCSE occurring in patients with renal dysfunction who were treated with cefepime suggested that neurologic complications could be involved [23]. So, we compared the proportion of patients who had experienced continuous epileptiform discharges while being treated with cefepime with that of patients who experienced those discharges while being treated with meropenem to determine whether continuous epileptiform discharges were more frequent with cefepime and could provide a partial explanation for the higher mortality rates reported in the literature. A total of 1120 charts of patients treated with cefepime and 1572 patients with meropenem were reviewed. Electroencephalographic testing was performed during antibiotic treatment in 59 patients treated with cefepime and 80 treated with meropenem (5.26% vs 5.08%, p = 0.85). Continuous epileptiform discharges were present in 14 patients in the cefepime group and 3 in the meropenem group (1.25% vs 0.19%, p<0.001). Periodic electroencephalographic patterns were thus 5-fold more frequent in the cefepime group than in the meropenem group, suggesting that cefepime was associated to a greater risk of brain toxicity that could partly account for the increased mortality observed with its use [24].

Delirium in older individuals

We, then, moved on to seek the potential relationship between older people delirium and epileptic activities. Delirium affects an estimated 14–56% of all hospitalized older people, and has important implications from both a functional and an economic standpoint as patients with delirium are twice as likely to die or to be institutionalized and ten times more likely to develop incident dementia [1,25,26]. The pathophysiology of delirium remains unclear, and is associated with neurotransmitter defi-

ciency, pro-inflammatory cytokines, acute stress responses and neuronal injury [27]. Interestingly, epilepsy and delirium share many common features: similarly to epilepsy, the development of delirium depends on a combination of intrinsic predisposing factors and precipitating extrinsic factors. Most classical causes of delirium are also risk factors for seizures, such as electrolytic imbalances, hypoglycemia, systemic inflammation, drugs and dementia [3]. Furthermore, the prevalence of epilepsy and delirium follows a similar path along ageing, the prevalence of epilepsy being the highest in older people, and doubling between the sixth and the eighth decade [15]. Finally, functionally, both epileptic activity and delirium are associated to acute brain network dysfunction [28]. Nevertheless, in clinical practice, a link between epileptic activities and delirium is seldom sought in older individuals. In a consecutive series of four studies, we first retrospectively assessed the prevalence of epileptic activity on 20 minutes EEG recording in older individuals presenting with delirium in the emergency room [29] and in older individuals presenting with delirium who benefited from 24 hours EEG monitoring (c-EEG) [30]. Then we led a prospective study comparing the yield of EEG and c-EEG in detecting epileptic activities in older individual with delirium [31] and confirmed the results in a different prospective cohort [32]. Retrospectively, in a cohort of ninety-eight older individuals that presented with delirium in the emergency room, whatever the delirium etiology, IEDs and NCSE were found in respectively 12% and 3% of the cases on 20 minute EEG whatever the delirium etiology [29], while in a cohort where c-EEG were realized for unexplained delirium in older individuals NCSE was unveiled in 33% of cases, NCSz in 20% of cases, PDs in 6% and IED in 6% of cases [30]. Those retrospective studies showed the high prevalence of epileptic activities in delirium but were limited by their retrospective nature. We, then prospectively, compared the yield of EEG and c-EEG in detecting epileptic activities in older adults' delirium. There, we found that c-EEG detected patterns compatible with NCSE in 28% and IEDs in 16% of the patients compared to EEG that disclosed patterns compatible with NCSE in "only" 6% and IEDs in 16% of the patients [33]. The other main findings from this study were that (i) no clinical or paraclinical parameter could reliably distinguish older patients with delirium with or without patterns compatible with NCSE in the absence of c-EEG monitoring and that (ii) patterns compatible with NCSE in older adults delirium were associated to significantly higher mortality rates and longer hospital stays.33 Due to the extremely high prevalence of epileptic activities in those cohort, we realized a confirmatory study on a separate cohort which replicated the findings by showing that prospective cEEG monitoring of older adults with delirium of unselected etiology, disclosed epileptic discharges in 42% of cases and electroencephalographic seizures in 14 % of cases, assessing the tight co-occurrence of epileptic activities in older adults delirium and a probable role in delirium pathophysiology [34].

Early neurological degradation after ischemic stroke

Finally, convinced that epileptic activities triggered by acute brain stressors participate to ABF onset and perpetuation, we focused on brain ischemic pathology. Indeed, after an Ischemic Stroke (IS), the brain metabolic balance is severely impaired. Beyond the core of the IS, a zone of ''penumbra'' can still fully recover thanks to compensatory mechanisms. The threshold between neuronal death and recovery in the penumbra is narrow and depends on a tight balance between metabolite supply and consumption by the affected neurons. Despite improvement in prevention and monitoring of complications, early neurological deterioration (END) after IS occurs in up to 38% of cases [35,36]. In half cases of END, the aetiology is unknown [37]. We postulated that IS triggered epileptic activities through hypoxemia and excitotoxicity and, that, in turn those epileptic activities increased the metabolic need of compromised neurons and led to clinical END [19,38,39]. We, thus, retrospectively reviewed a cohort of 81 patients who displayed END after IS who had c-EEG monitoring and found that in those patients NCSz-NCSE occurred in 10/81 (12%), PDs in 17/81 (21%) and IEDs in 14/81 (17%) [40]. Furthermore treating NCSz-NCSE and PDS led to improvement in respectively 7/8 and 10/16 of the treated patients [40]. Confirming the potential role of epileptic activities in END.

In summary, those studies showed that epileptic activities are associated to various acute brain failure syndromes ranging from altered mental state in sepsis antibiotic therapy, to older adults' delirium irrespective of its cause and early neurological deterioration after ischemic stroke. In those situations, epileptic activities are consistently found in over 40% and NCSz-NCSE in over 12% of the patients across the different studies and clinical situations. This prevalence of epileptic activities and NCSz-NCSE far exceeds what is expected both in older individuals, where IED are found in around 2% of subjects [41], or in IS where IEDs and NCSz are respectively described in 12% and 4% of cases [42]. Thus, the association of epileptic activities and ABF in our studies is unlikely to be fortuitous. Importantly, as in other studies, apart from c-EEG monitoring, no clinical nor ancillary examination could distinguish between the patients with and without epileptic activities, showing the paramount importance of electroencephalographic studies to highlight them [43,44]. The identification, in ABF, of patients with epileptic activities is essential as epileptic activities, in our studies, were associated to a worse prognosis and the treatment of NCSz-NCSE by Anti-Epileptic Drugs (AEDs) effective. The results of these works confirmed the hypothesis that IED, PDs and/or NCSz are associated to ABF. The role of epileptic activities in ABF onset and perpetuation remains to be clarify. Yet, the contribution of epileptic activities to acute cerebral dysfunction through inappropriate metabolic increases [19] and brain network disruption [9-12] is likely and could correspond to the common denominator explaining why various acute medical conditions, both neurologic and systemic, lead to similar patterns of ABF. These results also pave the way for further studies that will assess the value of AEDs as neuroprotective agent in ABF.

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