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Review

Generalized periodic discharges: Pathophysiology and clinical considerations

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ABSTRACT

Generalized periodic discharges (GPDs) are commonly encountered in metabolic encephalopathy and cerebral hypoxia/ischemia. The clinical significance of this EEG pattern is indistinct, and it is unclear whether treatment with antiepileptic drugs is beneficial. In this study, we discuss potential pathophysiological mechanisms. Based on the literature, supplemented with simulations in a minimal computational model, we conclude that selective synaptic failure or neuronal damage of inhibitory interneurons, leading to disinhibition of excitatory pyramidal cells, presumably plays a critical role. Reversibility probably depends on the potential for functional recovery of these interneurons. Whether antiepileptic drugs are helpful for regaining function is unclear.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

Normal brain function critically depends on sufficient energy supply [1] and maintenance of the right balance between excitation and inhibition [2,3]. Numerous homeostatic control mechanisms keep these processes in a physiological working range. These include regulation of blood pressure, heart rate, oxygen, pH, temperature, ion concentrations, and synaptic strengths [4,5]. As the demands imposed on brain function constantly fluctuate, the brain continuously modulates the excitatory–inhibitory balance for efficient information processing, mainly in the neocortex [3]. This may be accompanied by changes in energy consumption [6] and variations in cerebral blood flow [7].

A particular class of derangement of homeostatic control mechanisms is associated with excessive synchronization of neuronal activity: seizures [8]. In patients with epilepsy, the likelihood of seizures is persistently increased. Typically, both genetic and environmental factors are involved [9], together leading to recurrent changes in the physiological balance between excitation and inhibition [10]. During status epilepticus, seizures last relatively long, or sequential seizures occur without full recovery of consciousness [11]. Recently, the neurocritical care society defined this period as lasting 5 min or longer, because of the following reasons: (i) most clinical and electrographic seizures last less than 5 min, and if longer, they often do not stop spontaneously; and (ii) in animal models, permanent neuronal injury and pharmacoresistance have been observed early within the traditionally adopted period of 30 min [12].

Characteristics of electroencephalography (EEG) patterns in seizures and status epilepticus are highly variable [13], and often, the EEG evolves over a timescale of hours. Treiman reported on the characteristics of the EEG that can be observed in the transitional period towards generalized convulsive status epilepticus [14]. These observations were based on human EEGs recorded during episodes of generalized convulsive status epilepticus, and a similar sequence of EEG changes was observed in rats, where status epilepticus was induced. Initially, intermittent, discrete seizures occur, which are reflected in the EEG as recurring epileptiform discharges, with durations from one to several minutes (Treiman I). These may evolve to merging seizures with waxing and waning amplitude (Treiman II). In Treiman III, continuous ictal activity is present, which may change into continuous ictal activity punctuated by low-voltage periods (Treiman IV) and, finally, progress towards periodic epileptiform discharges on a 'flat' background (Treiman V). Most likely, in patients with nonconvulsive seizures, similar transitions occur [15]. These observations stress that, in prolonged status epilepticus, the waxing and waning characteristics may disappear and a periodic pattern may remain.

Here, we focus on generalized periodic discharges (GPDs). We discuss their incidence, potential mechanisms involved in their generation,

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and clinical dilemmas in whether or not to treat these EEG patterns. We present a computational model that allows simulation of GPDs and assists in the generation of hypotheses regarding the underlying pathophysiology.

2. Generalized periodic discharges

The American Clinical Neurophysiology Society recently published a guideline to standardize EEG terminology [16]. Periodic

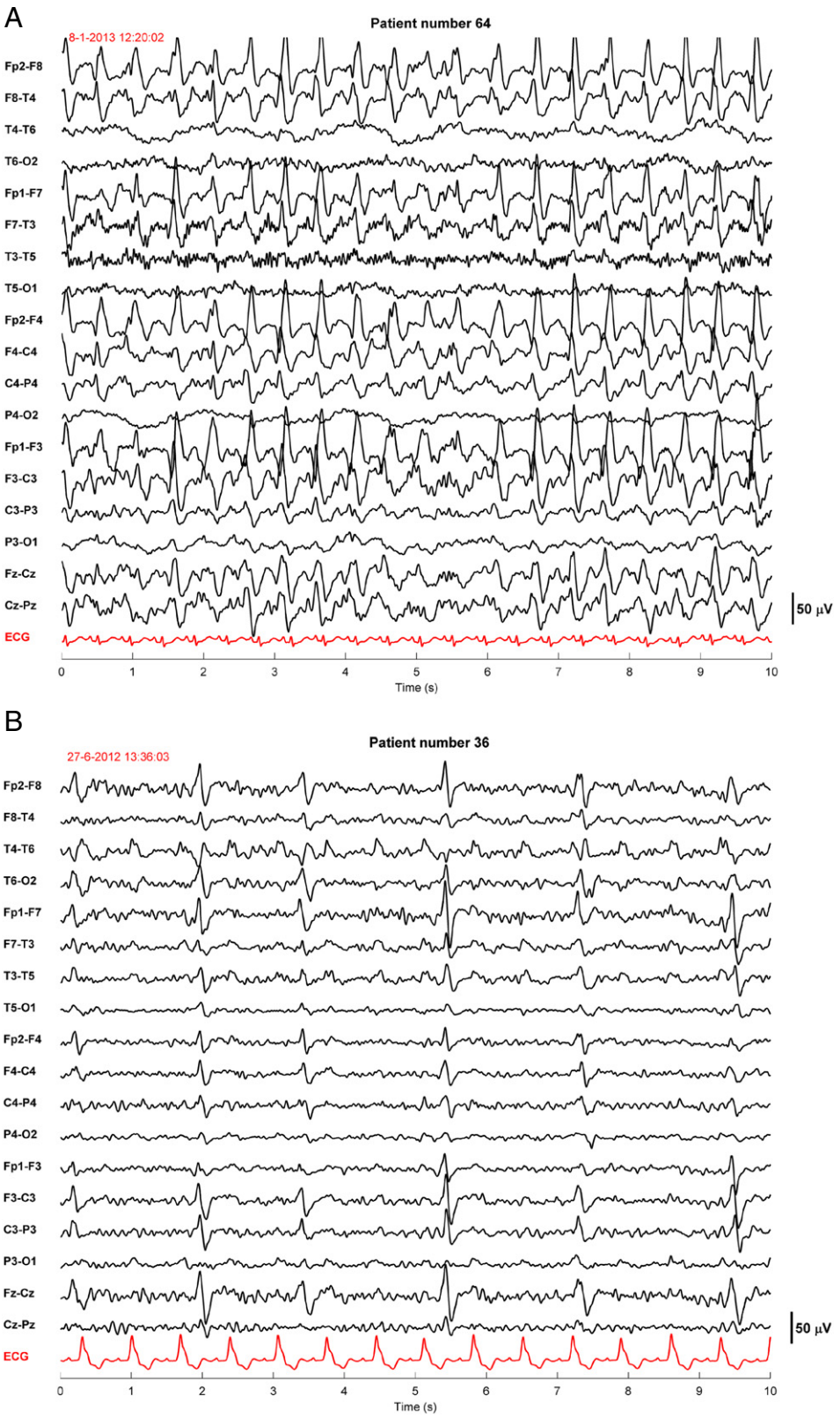

Fig. 1. Generalized periodic discharges with a frequency of approximately 2.5 Hz (upper panel) and approximately 0.5 Hz (lower panel). Both recordings are obtained from patients in coma with postanoxic encephalopathy after cardiac arrest. These two EEG examples were also used as illustrations in [57].