Review article

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Postictal generalized EEG suppression and postictal immobility: what do we know?

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ABSTRACT – Despite representing the leading cause of epilepsy-related mortality, the pathophysiology of sudden unexpected death in epilepsy (SUDEP) remains elusive. In this context, the identification of clinical markers of SUDEP assumes a great importance and has been the target of many studies aimed at stratifying patients' individual risk. Among the potentially most hazardous post-ictal phenomena observed following convulsive seizures in monitored SUDEP cases, postictal generalized EEG suppression and postictal immobility have attracted attention as potential SUDEP risk factors. In this manuscript, we review the current knowledge on postictal generalized EEG suppression and postictal immobility, aiming to identify their pathophysiological mechanisms, reported frequencies and associated clinical factors, and critically evaluate the evidence on their potential relevance as SUDEP risk markers.

Key words: epilepsy, sudden unexpected death in epilepsy (SUDEP), postictal generalized EEG suppression, postictal immobility

Sudden unexpected death in epilepsy (SUDEP) is a major leading cause of epilepsy-related death and is particularly prevalent in treatment-resistant patients (Tomson *et al*., 2008). The pathophysiological mechanisms underlying SUDEP remain elusive and the identification of clinical markers has been the target of many epidemiological studies, aimed at identifying patients at high risk. Among these factors, the observation of a diffuse EEG "flattening or attenuation" following a seizure, defined as postictal generalized EEG suppression (PGES), has received considerable attention as it was observed in cases of SUDEP who were undergoing clinical monitoring at the time of death (Purves *et al*., 1992; Bird *et al*., 1997; Lee, 1998; McLean and Wimalaratna, 2007; Bateman *et al*., 2010; Lhatoo *et al*., 2010; Tao *et al*., 2010; Ryvlin *et al*., 2013). Although the role played by PGES in the cascade of events leading to SUDEP is still unclear, PGES continues to attract attention and to be considered as a SUDEP risk marker. Moreover, it is often used in clinical studies to assess the role of other variables as potential SUDEP markers. Another interesting

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factor observed in the context of SUDEP cases is the absence of motion following a seizure, called postictal immobility (PI) (Semmelroch *et al*., 2012; Seyal *et al*., 2013). Unlike PGES and despite its potential clinical relevance, PI and its mechanisms have received less attention in recent years, and the literature exploring this topic and its connection to PGES is smaller.

We aimed to review the literature to assess the current knowledge on these two phenomena, their relationship and their significance in the context of SUDEP.

Postictal generalized EEG suppression (PGES)

Definition and aetiology

Before the term "postictal generalized EEG suppression" (PGES) was adopted (Lhatoo *et al*., 2010), the observation of postictal attenuation of EEG activity was described as a sudden EEG "flattening" (Bird *et al*., 1997), an "abruptly attenuated termination pattern" (Kim *et al*., 2006) or an "electrocerebral shutdown" (McLean and Wimalaratna, 2007). Currently, the most commonly adopted definition is the one proposed by Lhatoo *et al*. (2010), as "the immediate postictal (within 30 seconds) generalized absence of electroencephalographic activity <10 μV in amplitude, allowing for muscle, movement, breathing, and electrode artefacts". This definition has a significant practical value and has been enriched by other authors, introducing additional minimum duration criteria of one second (Surges *et al*., 2011; Tao *et al*., 2013) or two seconds (Seyal *et al*., 2012).

Despite the mechanism leading to the occurrence of PGES not being clearly elucidated and explored in humans, some hypotheses, based on mechanisms studied in animal models, have been outlined and supported by clinical findings in some studies. Bird *et al*. (1997), suggested that the activation of a neuromodulatory reticular-thalamo-cortical inhibitory network, probably involved in the seizure termination mechanism, may be responsible for "switching off" cortical activity or hampering a reactivation of cortical activity after suppression, including consciousness. This mechanism may be particularly active during sleep and may explain the relationship between PGES and the higher incidence of SUDEP during sleep or when patients are unsupervised and not stimulated.

Lhatoo *et al*. (2010) have expanded this hypothesis and postulated the presence of a wider subcortical inhibitory mechanism disrupting brainstem functions. Similarly, a recent study including patients undergoing intracerebral EEG recordings suggested a possible involvement of the brainstem at the level of the bulbar-reticular formation, based on the finding of, and association between, oral tonicity and PGES (Marchi *et al*., 2019). However, other authors have questioned the degree of brainstem involvement, highlighting how preserved respiratory brainstem responses during periods of PGES (Seyal *et al*., 2010) and normal postictal cardiac functions (Lamberts *et al*., 2013a) would rather suggest an absent or partial brainstem shutdown in PGES. According to other theories, PGES might be seen as a "passive" process, either caused by a seizure-related prolonged and hypersynchronous neuronal excitation with consequent neurotransmitter depletion and neural exhaustion (Kim *et al*., 2006; McLean and Wimalaratna, 2007; Lhatoo *et al*., 2010) or by cortical spreading depression triggered by neuronal stimulation or depletion of energy substrates (Tao *et al*., 2013; Aiba and Noebels, 2015; Alexandre *et al*., 2015; Marchi *et al*., 2019). While the abrupt onset of PGES and the lack of correlation between PGES and seizure duration go against this hypothesis, the relationship between PGES and the duration of the tonic phase (Freitas *et al*., 2013; Tao *et al*., 2013; Alexandre *et al*., 2015; Asadollahi *et al*., 2018), characterized by significant hypersynchronous neuronal excitation (Lado and Moshe, 2008; Yang *et al*., 2012), and between PGES and oral tonicity, which may represent a clinical marker of bilateral tonic discharge involving the brainstem at the level of bulbar nuclei (Marchi *et al*., 2019), add some support to it.

Another recently published paper (Jansen *et al*., 2019) demonstrated that, in SUDEP-prone transgenic mice, seizures with brainstem spreading depolarization are followed by suppression of the electrocorticogram. Interestingly, brainstem spreading depolarization reaching the brainstem medullary respiratory centres initiates apnoea and hypoxia, which are relevant to mechanisms leading to SUDEP. However, a genetic predisposition to a lower threshold for brainstem spreading depolarization has been highlighted in other animal models (Aiba and Noebels, 2015), supporting the role of additional predisposing factors to PGES.

Finally, findings including the prevention of PGES with early oxygen administration (Alexandre *et al*., 2015), the reduction in duration of PGES with early perictal nursing interventions and oxygen administration (Seyal *et al*., 2013) and the termination of PGES correlating with blood pressure normalization (Bozorgi *et al*., 2013) suggest that seizure-induced respiratory and cardiac dysfunctions may also play a role in the genesis and termination of PGES and, once again, point to brainstem involvement.

Overall, the evidence for a mechanism leading to PGES is speculative and indirect and has emerged from animal models. Although brainstem structures are likely playing a role, findings have not consistently been replicated and the mechanism leading to PGES remains elusive.

Frequency and duration

There is a great variability in the reported frequency of PGES with estimates from 1% (Surges *et al*., 2011) to 81% (Poh *et al*., 2012). As well as reflecting the sample size, the heterogenicity of the studied populations and their different clinical characteristics (described under *Other associated clinical factors*), the wide range of estimates likely indicate a difficulty in identifying the presence of a true EEG suppression on scalp EEG, highlighted in a study using simultaneous scalp and intracranial EEG (Altenmüller *et al*., 2016) and the presence of substantial disagreements among clinicians when identifying the presence of PGES and its duration (Theeranaew *et al*., 2018).

In addition to this, a large intraindividual variability has also been demonstrated. In fact, the same individual can present with seizures with PGES and seizures without PGES and the inconsistency increases with the number of seizures recorded from each individual (Lamberts *et al*., 2013b).

In general, a lower prevalence of PGES has been reported among children as compared to adults (Kim *et al*., 2006; Semmelroch *et al*., 2012; Freitas *et al*., 2013; Pavlova *et al*., 2013) and no PGES was observed in infants younger than six months in one study (Kim *et al*., 2006).

Nevertheless, the major and more frequently explored PGES determinant seems to be seizure type, given that PGES has been more commonly observed following convulsive seizures (27-81%) (Tao *et al*., 2010; Poh *et al*., 2012; Seyal *et al*., 2012; Lamberts *et al*., 2013a; Tao *et al*., 2013) as compared with focal seizures (1-2%) (Lhatoo *et al*., 2010; Surges *et al*., 2011).

Although the mean PGES duration ranges from 38 to 128 seconds in several case series (Lhatoo *et al*., 2010; Surges *et al*., 2011; Poh *et al*., 2012; Semmelroch *et al*., 2012; Seyal *et al*., 2012), patients can present with seizures with short PGES and others with more prolonged PGES (Sarkis *et al*., 2015). Moreover, shorter PGES durations were reported in children (Freitas *et al*., 2013; Sarkis *et al*., 2015) while longer durations were found in focal seizures evolving into a bilateral convulsive seizure versus primary generalized seizures (Freitas *et al*., 2013). In a case-control study, Lhatoo *et al*. (2010) concluded that the duration of PGES was significantly prolonged in SUDEP cases as compared to non-SUDEP cases and demonstrated that the risk of SUDEP increased proportionally with the duration of PGES (each one-second increase producing an increased SUDEP odds of 1.7%). However, these findings were not replicated in a subsequent case-control study (Surges *et al*., 2011); disagreement between these studies reflects that the number of SUDEP cases in each were relatively few.

Despite the clinical importance of findings by Lathoo *et al*. (2010), they represent the only evidence that PGES is directly associated with SUDEP, highlighting that there is no well-established link between SUDEP and PGES of any duration.

Other associated clinical factors

The association between PGES with SUDEP has prompted a lot of research aimed at finding clinical factors correlated with this potential SUDEP marker. Many studies have failed to demonstrate any correlation with gender, total seizure duration (Lhatoo *et al*., 2010; Surges *et al*., 2011; Poh *et al*., 2012; Semmelroch *et al*., 2012; Seyal *et al*., 2012; Freitas *et al*., 2013; Lee *et al*., 2013; Moseley *et al*., 2013; Pavlova *et al*., 2013; Tao *et al*., 2013), tonic phase duration, clonic phase duration, epilepsy duration, brain imaging abnormalities and seizure type (generalized tonic-clonic versus focal to bilateral tonic-clonic) (Lhatoo *et al*., 2010; Surges *et al*., 2011; Poh *et al*., 2012; Semmelroch *et al*., 2012; Seyal *et al*., 2012; Tao *et al*., 2013; Kuo *et al*., 2016). Contradictory results have been obtained by other studies where the occurrence of PGES was associated with the presence and a nearly doubled duration of the tonic phase (Semmelroch *et al*., 2012; Freitas *et al*., 2013; Tao *et al*., 2013) as well as with a bilateral symmetrical tonic extension of the limbs (Alexandre *et al*., 2015; Marchi *et al*., 2019) and oral tonicity (wide mouth opening and vocalization) (Marchi *et al*., 2019). Tonic muscle contraction, PGES and their association with brain hypoxia have also been highlighted in a recent paper, where postictal tonic electromyography activity following some generalized convulsive seizures was associated with PGES and with a greater severity of respiratory dysfunction (Park and Seyal, 2019). PGES has also been considered a possible marker of postictal autonomic dysregulation. In particular, it has been associated with a sympathetic over-activation, demonstrated as a surge of electrodermal activity, the magnitude of which correlated with the duration of PGES (Poh *et al*., 2012; Sarkis *et al*., 2015). On the other hand, a possible correlation with a parasympathetic suppression (vagal suppression, reduction of HF power) demonstrated in one small study (Poh *et al*., 2012) was not confirmed in a larger population (Sarkis *et al*., 2015). Additionally, PGES did not appear to be associated with peri-ictal cardiac autonomic instability as a comparable peri-ictal heart rate and heart rate variability characterized convulsive seizures presenting with and without PGES (Lamberts *et al*., 2013a). In contradiction to this, another study highlighted the presence of relative bradycardia in a patient with PGES (Tao *et al*., 2013).

Respiratory disturbances and their severity have also been associated with the occurrence of PGES (Semmelroch *et al*., 2012; Seyal *et al*., 2012) and PGES of any duration has a significant association with ictal and post-ictal respiratory dysfunction (Kuo *et al*., 2016), including ictal hypoxemia and hypercapnia (Seyal *et al*., 2012), post-ictal tachypnea (Seyal *et al*., 2010) and post-ictal hypoxemia (Seyal *et al*., 2012; Tao *et al*., 2013). However, in contradiction to the finding of Lhatoo *et al*. (2010) suggesting that a prolonged PGES following convulsive seizures may lead to central apnoea (and eventually SUDEP), another study showed no association between post-ictal central apnoea and PGES using respiratory parameter monitoring (Seyal *et al*., 2012). Similarly, a more recent study (Vilella *et al*., 2019a) demonstrated that ictal central apnoea and postconvulsive central apnoea (PCCA) were not related to PGES incidence and duration. However, the same authors highlighted how seizures with PGES were more frequently followed by postconvulsive central apnoea, a possible predictor of SUDEP (Vilella *et al*., 2019b).

The association between PGES and state of arousal is unclear, with studies demonstrating no difference in PGES occurrence between nocturnal or diurnal seizures (Lee *et al*., 2013) and others suggesting a higher PGES incidence in seizures presenting during sleep, also in conjunction with more severe desaturations (Latreille *et al*., 2017).

The use of antiepileptic drugs (AEDs) was not related to the presence of PGES in some studies (Lhatoo *et al*., 2010; Hesdorffer *et al*., 2011), while others suggested that treatment reduction may facilitate the occurrence of PGES of long duration (Lamberts *et al*., 2013a), akin to inadequate or ineffective treatment, or non-adherence (Freitas *et al*., 2013), and treatment restoration decreases its severity (Tilz *et al*., 2006).

Overall, PGES has been demonstrated as a common, although inconsistent, phenomena following convulsive seizures. However, the relationship between specific seizure characteristics, cardiorespiratory dysfunctions, autonomic dysregulation, use of AEDs and PGES remains unclear and results are sparse and mainly contradictory. The variability of the presence of PGES after a seizure, the lack of systematic recording of physiological data during and between seizures, and the inclusion of poorly characterized patient populations are the major limitations of the evidence collected so far. Conflicting findings and important open questions could perhaps be clarified by those new technologies allowing systematic and continuous recording of physiological data. Moreover, novel automated tools could assist clinicians and experts allowing a more objective and uniform assessment of PGES periods across studies and populations (Theeranaew *et al*., 2018).

Post-ictal immobility

Definition and aetiology

The absence of motion following a seizure is a frequently observed clinical manifestation, typically occurring after convulsive seizures, and has been recognized by clinicians for more than a century.

The first clear description of post-ictal immobility was made in 1855 by Todd (Todd, 1855), who reported the presence of motor paralysis, of different degree, pattern and duration, following a seizure. This observation was confirmed by Robertson in 1869 (Robertson, 1869) and later by Jackson who coined the term "post-epileptic paralysis" (Jackson, 1875). Although probably self-defined by the terminology alone, a definition of "absence of active non-respiratory movements after the end of the seizures" has been only recently provided and may assume a practical value in clinical studies, although with some limitations (Kuo *et al*., 2016).

Despite the early recognition of PI in the past, its mechanism has remained largely unclear. The first observations of this phenomenon attributed it to cerebral exhaustion, changes in neuronal threshold and cortical hypoxemia following a seizure (Meyer and Portnoy, 1959). A transient neuronal anoxia was subsequently demonstrated in experimental observation in primates (Meyer and Portnoy, 1959) and some support for this observation was provided by studies reporting a link between PI, PGES and respiratory dysfunction (Seyal *et al*., 2013; Kuo *et al*., 2016). However, the relationship between PGES and respiratory dysfunction can also point towards the presence of some common pathophysiological mechanisms, involving seizure-activated cortical and subcortical inhibitory networks. A theoretical role of other circuits has been proposed but not proven: in particular seizure-related dysfunction of the 5-HT and glutamatergic systems, with inhibition of the subcortical arousal system and consequent impaired consciousness and motionlessness (Kinney and Thach, 2009; Kothare and Singh, 2014), and decreased cholinergic transmission from subcortical arousal structures to the thalamus and frontal cortex with possible involvement of motor circuits (Farzampour and Huguenard, 2015; Motelow *et al*., 2015).

Association with PGES and clinical factors

Postictal immobility has been reported following convulsive seizures with and without PGES (Semmelroch *et al*., 2012, Seyal *et al*., 2013; Tao *et al*., 2013; Kuo *et al*., 2016; Asadollahi *et al*., 2018).

Higher frequencies (92.3% [Semmelroch *et al*., 2012] and 95.3% [Tao *et al*., 2013]) and longer durations, with mean time to first movement between 156.24 (Asadollahi *et al*., 2018) and 251.96 seconds (Kuo *et al*.,

2016), were found to be associated with PGES seizures as compared to seizures not followed by PGES (frequency between 26.7% and 33.3% [Semmelroch *et al*., 2012; Tao *et al*., 2013]) with mean durations of 66.06-139.1 seconds (Seyal *et al*., 2013; Kuo *et al*., 2016).

One study found no association between the duration of PGES and the duration of PI, which conversely correlated with the duration of ictal oxygen desaturation (Seyal *et al*., 2013). In 1881, Gowers reported the lack of association between PI and seizure duration (Gowers, 1881). This finding was confirmed in later studies (Seyal *et al*., 2013; Kuo *et al*., 2016) and additional observations demonstrated no correlation with either the duration of the convulsive phase or tonic phase of the seizure (Kuo *et al*., 2016), with some exceptions (Asadollahi *et al*., 2018).

The observation of recorded SUDEP cases found prone in their beds (Purves *et al*., 1992; Bird *et al*., 1997; McLean and Wimalaratna, 2007; Bateman *et al*., 2010; Lhatoo *et al*., 2010; Tao *et al*., 2010; Ryvlin *et al*., 2013; Liebenthal *et al*., 2015) have suggested a potential life-threatening role of prolonged PI. In this situation, PI could prevent adequate body and head repositioning, which are necessary for an optimal airflow and which could lead to post-ictal cardiorespiratory dysfunctions and death. However, the association of PI with respiratory and cardiac disturbances, including apnoea and bradycardia, has not been adequately investigated and may represent a future area of interest to improve our understanding on mechanisms leading to SUDEP.

Conclusion: PGES, PI and SUDEP

PGES is certainly a common post-ictal EEG pattern, especially after convulsive seizures, and does not exclusively occur in SUDEP cases. The evidence from the current literature demonstrates a great variability in the presentation of this phenomenon, whether occurrence and duration are influenced by different clinical variables, as well as the presence of intraindividual variability and of possible discrepancies in PGES identification. These results highlight the lack of predictive value of PGES alone as a marker of SUDEP risk. On the other hand, there is an interesting correlation between PGES and other SUDEP risk factors, including the occurrence of convulsive seizures, PI, peri-ictal respiratory and cardiac disturbances, and possibly state of arousal and AED withdrawal. Nevertheless, although the significance of PGES in the pathogenesis or as an initiating event in SUDEP cases remains elusive, its presentation in the context of SUDEP is undoubted: PGES was found in all SUDEP cases occurring during medical monitoring (Purves *et al*., 1992; Bird *et al*., 1997; Lee, 1998; McLean and Wimalaratna, 2007; Bateman *et al*., 2010; Lhatoo *et al*., 2010; Tao *et al*., 2010; Ryvlin *et al*., 2013) and a long-duration PGES was found with every terminal seizure in the MORTEMUS study (Ryvlin *et al*., 2013). Case studies have also demonstrated that seven of the eight SUDEP cases published over the last 20 years died when unsupervised in the prone position (Purves *et al*., 1992; Bird *et al*., 1997; McLean and Wimalaratna, 2007; Bateman *et al*., 2010; Lhatoo *et al*., 2010; Tao *et al*., 2010; Ryvlin *et al*., 2013; Liebenthal *et al*., 2015) suggesting a potential role of PI in the terminal cascade of events leading to death. In fact, in the postictal period, a persistent immobility and inability to change body position may exacerbate postictal hypoxemia (Kinney and Thach, 2009) and seizure-related homeostatic alterations, such as pulmonary oedema (Kennedy *et al*., 2015), leading to asphyxia and asystole. However, the evidence that these two phenomena contribute directly to SUDEP is contradictory, not exhaustive, and primarily obtained from studies performed in the artificial setting of epilepsy monitoring units. The presence of a common pathophysiological mechanism seems likely and deserves further exploration, as well as their relationship and the role played in the sequence of events predisposing to the "perfect storm" (Sarkis *et al*., 2015) leading to SUDEP. Large studies using accurate cardiovascular monitoring and reporting of critical physiological parameters are needed to enrich our understanding of this important topic. At the current time, there are no accurate predictors of SUDEP in individual patients, and SUDEP risk assessment for each individual seizure should take into account a combination of multiple variables, including PGES, PI and other clinical factors. Current evidence is certainly insufficient and suboptimal for planning and setting up adequate preventive strategies at the patient level, especially in unsupervised out-of-hospital environments. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) Which is the most commonly adopted definition of PGES?

(2) Which is the more frequently reported PGES determinant?

(3) How might PI influence SUDEP?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".