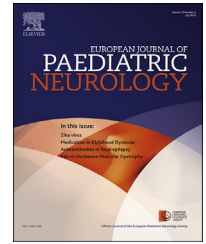




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## Review article

# What is new: Talk about status epilepticus in the neonatal period

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## ABSTRACT

Nowadays, no general consensus was achieved regarding neonatal status epilepticus and its definition. Indeed, different criteria (mainly based on seizure duration) were used. Whereas a recent proposal has been developed to define status epilepticus in older ages, it seems that the peculiar characteristics of neonatal seizures and of the immature brain make difficult to find a tailored definition for this period of life. Achieving a consensus on this entity would mean to make the first step toward a targeted therapeutic strategy of intervention.

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## 1. Introduction

Although a quite few number of papers has been published focused on neonatal status epilepticus (NSE),<sup>1–10</sup> this is still a debated entity, and no consensus has been achieved on its definition.

Recently, a special report by the ILAE Task force on Classification of status epilepticus (SE) proposed a new definition of status, considered as “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1) (...) which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures”.<sup>11</sup>

Whereas for some types of SE both or at least one of the two time-points are well-defined on the basis of the existing researches (see Trinka et al, 2015 for review),<sup>11</sup> for other types of SE convincing evidence is still insufficient. This is the case of NSE.

## 2. Time-point 1 and NSE definitions

Concerning the first time-point (t1), data show that the mean duration of seizures in neonates varies from a minimum of 2 min to a maximum of 19 min and some authors reported a maximum seizure duration of 6.3 min on average, being  $\leq 9$  min in 97% of cases and  $\geq 30$  min only in 0.4%.<sup>12–16</sup> However, differently from what recognized for older children,<sup>17</sup> a temporal duration after which a spontaneous resolution of the epileptic discharge is less probable has not yet been established in neonates.

As neonatal seizures are often brief and recurrent, the usual definition of SE as a continuous seizure activity lasting for at least 30 min or intermittent seizures lasting  $\geq 30$  min from which the patient does not regain consciousness<sup>18</sup> seems to be not applicable for newborns, and some authors concluded that its validity started since 2 months of age.<sup>19</sup> In order to widen the boundaries of this definition and better encounter the peculiarities of recurrent seizures in neonates, the most quoted definition of NSE is the one adopted by Scher et al (1993), in which NSE was reported as a continuous seizure activity for at least 30 min or recurrent seizures for greater than or equal to 50% of the recording time (1–3 h).<sup>12</sup> Other authors reported a different definition, considering NSE as a continuous seizure activity for at least 30 min or recurrent seizures lasting a total of  $\geq 30$  min without definite return to the baseline neurologic condition of the neonate between seizures, in any 1-h period.<sup>1,5</sup> The same group recently reported a hourly seizure burden range  $\geq 50\%$ –100%. However, in this last paper, they considered the 50% also in case of recurrent seizures lasting a total of  $\geq 30$  min without definite return to the baseline neurologic condition between seizures.<sup>1</sup> Other authors reported this period as “seizure period” and consider the “seizure burden” only when the electrographic activity is actually occurring, without considering the neurological condition of the neonate.<sup>20</sup>

However, although seizure(s) duration was the main criterion used to define NSE, adopted temporal criteria were

highly arbitrary and varied among authors from 15 min to few hours (see Pavlidis et al. for review<sup>1</sup>).<sup>8,9,13,21–24</sup>

Finally, as amplitude EEG (aEEG) is more and more used in order to monitor encephalopathic neonates, a definition of NSE on the base of aEEG was also given, considering status epilepticus when there is a repeated electrographic seizure activity, resulting in a regular pattern of increased cortical activity (sawtooth pattern) lasting for more than 50% of a period of the amplitude EEG, but no standardization of the recording duration has been proposed.<sup>25</sup>

A study on children older than 1 month of age already compared the characteristics of those subjects with status epilepticus lasting 5–29 min versus  $\geq 30$  min, finding that the two groups were similar regardless of the time threshold used and enabling an equal aggressive treatment of patients with seizure duration  $\geq 5$  min.<sup>26</sup> For children  $>5$  years old, an operational definition for convulsive SE has been proposed, referring to at least 5 min of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness.<sup>27</sup> Some authors consider that an operational definition should be applied also to neonates,<sup>28</sup> and, in clinical practise, the term NSE has taken a more operational meaning and is used when seizures are prolonged, recurrent and when they persist or recur during 5–15 min.<sup>29–31</sup>

## 3. Time point 2 and the controversies concerning neonatal status epilepticus/recurrent seizures and outcome

In the new definition it has been specified that SE causes injuries after a certain time-point (t2).<sup>11</sup>

In neonates, results regarding the harmful effects of seizures and NSE per se were controversial.

It is nowadays well known that immature brain is at higher risk of developing seizures and this seems to be related to both peculiar external factors of the neonatal period (such as, infections, hypoxic-ischaemic insults, birth trauma, ...) and some specific intrinsic factors related to brain immaturity (such as the lack of inhibitory role of the GABAergic system).<sup>32</sup> Even though, some studies have shown that immature brain is also more resistant to the effects of seizures due to a lower representation or an immaturity of possible damaging factors (such as, vulnerability to glutamate toxicity, density of active synapses, energy consumption, biochemical cascades that lead to cell death after insults) or a higher representation of protective factors (such as, high concentrations of brain-derived neurotrophic factor, reduced levels of cytokines associated with seizures, a better maintenance of GABA synthesis during prolonged seizures and reduced oxidative stress associated with seizures).<sup>32–38</sup> This is in accordance with authors that did not find a harmful effect of seizures in infants with hypoxic-ischaemic encephalopathy (HIE) when adjusted for study treatment and severity of encephalopathy<sup>39</sup> or of the SE on the outcome.<sup>40</sup>

Although brain damage occurs directly from the underlying aetiologies, there is also some evidence that seizures and SE themselves might cause further damage, producing neuronal death, disruption of programmed maturational processes and widespread neuronal injury,<sup>41–44</sup> or increase

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