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Is Autonomic Nervous System Involved in the Epileptogenesis in Preterm Neonates?

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Abstract

Autonomic nervous system dysfunction has been described with focal and generalized epileptic seizures; occurring during their ictal, interictal, or postictal states. International League Against Epilepsy Seizure Classification Manual defines autonomic seizures as a distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, and thermoregulatory functions. Autonomic seizures represent a great challenge for neonatologists and neurophysiologists; and distinguishing between ictal and non-ictal autonomic changes in neonates is rarely straightforward, especially in the premature ones. To avoid overdiagnosis and overtreatment, International League Against Epilepsy and American Clinical Neurophysiology Society currently require electrographic correlation for any seizure diagnosis, including preterm neonates. There is very little scientific evidence about the pathophysiology of autonomic seizures. The data reporting on their incidence, clinical features, and diagnostic pathway is also insufficient. In this paper we hypothesize that in the developing brain of preterm neonates, seizures involving deeper autonomic networks and subcortical structures might not propagate sufficiently to the cortex, and therefore the association of the seizures with specific ictal electrographic changes on surface electroencephalogram might be lacking. We propose considering autonomic seizures in the differential diagnosis of unexplained autonomic changes in neonates, especially preterm neonates, even in the absence of clear initial electrographic correlation. Unexplained autonomic changes could therefore be thought of as a "seizure alarm" in this population.

Keywords: Premature; Apnea; Autonomic seizures; Brain; Neonatal epilepsy; Neonates

Introduction

Seizures in the newborns signal a significant brain pathology; they are associated with increased mortality and adverse neurodevelopmental outcomes in the survivors. Neonatal seizures may present as autonomic changes, clinical, subclinical, electroclinical or electrographic seizures only; and the distinction between the epileptic and non-epileptic events can present a great challenge for those caring for newborns.[1,2] As a result, both, under recognition and over reporting of neonatal seizures are known to occur. To date there is little consensus on whether clinical events suggesting seizures but without electrographic correlate should be treated.[3] Autonomic symptoms in preterm neonates without electrographic correlation often present such challenge. Moreover, administration of anti-epileptic medications can increase risk of autonomic dysfunction, leading to further confusion about the event etiology.

Both American Clinical Neurophysiology Society and International League Against Epilepsy define neonatal seizures by their electroencephalogram (EEG) signature and clearly state that events without clear EEG correlate should not be treated as true neonatal seizures.

To date, there is no specific definition for autonomic seizures in newborns. They are thought to be a result of a "brainstem release" within subcortical structures.[4] In term neonates, variety of ictal EEG changes have been described during autonomic seizures; depending on the involvement of cortical structures, however; therefore, there is no "typical" ictal EEG pattern for autonomic seizures. This becomes even more challenging in preterm neonates in whom rapid changes can be seen on the EEG with increasing post-conceptual age (PCA).

Hypothesis and theory

We hypothesize that in preterm neonates, apnea or other autonomic signs and symptoms, such as changes in heart rate (HR), temperature, blood pressure, oxygenation, and

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respiration may represent the first and sometimes the only clinical signs of epileptic event in early stages when other clinical and electroclinical signs and symptoms are not recognizable.

We further hypothesize that autonomic changes in preterm neonates, and specifically unexplained and unusual autonomic symptoms, such as apnea without bradycardia, can help to raise suspicion for epileptic process and select those preterm infants who can benefit from further monitoring.

To support our hypothesis, we will discuss the current evidence on autonomic nervous system (ANS) dysfunction during seizures with focus on pathophysiological mechanisms specific to preterm neonates.

Premature brain and seizures

The cerebral cortex of the premature infants differs from the cortex of term infants. During the third trimester of pregnancy, the fetal cerebral cortex evolves from a smooth surface to a folded structure with high complexity and morphology resembling the adult cortex.[5] Changes in cortical surface area and cortical folding in preterm infants are thought to correlate with functional and cognitive development[6] (Table 1).

Furthermore, studies comparing grey matter volumes in preterm and term neonates, found significant differences in several cortical and subcortical regions,[7–9] likely contributing to the difference in clinical manifestation of seizures with autonomic symptoms in preterm compared to term neonates. Injuries involving white matter (including cystic periventricular leukomalacia, punctate unmyelinated white matter (UWM) lesions, diffuse UWM disease) may lead to secondary maturational and trophic consequences, further affecting the microstructural integrity and connectivity between thalamus and cortex,[10] and therefore, interfering with the early formation, development, and maturation of the cerebral cortex.[6] Even in the absence of major brain injury, brain maturation at full-term corrected gestational age is different in ex-preterm and ex-full-term neonates.[11] These cortical abnormalities may result from subtle impairments in neuronal migration and cortico-cortical connections.

In preterm neonates, prelimbic cortex is relatively more active than other cortical structures. Thus, the connection of prelimbic and limbic structures to brainstem and diencephalon likely contribute to more common presence of autonomic signs and symptoms, oral-buccal-lingual movements, and oculomotor phenomena during seizures in preterm neonates.[2] However, due to cortical immaturity in preterm neonates, the brainstem release subtending autonomic seizures would not be necessarily expected to reach the cortex. Therefore, what we can see is a poor correlation of synchronous discharges recorded from surface EEG with behavioral seizure manifestation.[2]

In summary, we hypothesize that the earlier development of limbic structures, preceding the development of subcortical-cortical networks in the premature brain, could explain why autonomic changes might represent the only seizure manifestations in preterm infants, and why these changes are often difficult to correlate with ictal EEG changes.

Development of the premature brain

The cerebral cortex of the premature infant is still immature. In this age period, primitive areas (such as the peri-limbic cortex) seem to predominate, and are responsible for the autonomic signs and symptoms of neonatal seizures, above all in preterm neonates. These pathological entities usually differ clinically from the motor manifestations of seizures commonly seen in infants born at term.[12]

Literature data demonstrate that during the third trimester of pregnancy, the neonatal cerebral cortex evolves from having a smooth surface to a folded structure with high morphology, and complexity resembling the adult cortex.[5] Changes in cortical surface folding and brain areas in preterm infants may correlate with cognitive and functional development.[6] In addition, preterm infants exhibit abnormal development of cortical thickness when compared to children later in life.[12–14] Some studies have found that when comparing preterm to term neonates, larger volumes of cortical grey matter are found in several cortical regions,[7,8] while others present smaller volumes.[9]

Injuries involving white matter (including punctate UWM lesions, cystic periventricular leukomalacia, diffuse UVM diseases) may cause secondary maturational and trophic consequences, involving the microstructural integrity and connectivity between thalamus, as expression of subcortical areas activation, and cortex.[10,15] This may interfere with the early formation, development, and maturation of the cerebral cortex.[15] Altered cortical development has been reported in preterm neonates when at term-equivalent age, childhood, and adolescence.[16]

Table 1

Differences in the brain structure, activity, and development between preterm and on term newborns.

Items	Preterm	On term
Cortex surface	Smooth	Folded
Cortex higher activity	Limbic/prelimbic*	Surface
Seizures extent	Not expected to reach the cortex†	Major cortical activity hiding the subcortical one
Cortical development	40 weeks post-conceptual	40 weeks post-conceptual
Occipital lobe maturation timing‡	Between 30 and 40 weeks	At 40 weeks

* The connection of prelimbic and limbic structures to brainstem and diencephalon likely contribute to more common presence of autonomic signs and symptoms, oral-buccal-lingual movements, and oculomotor phenomena during seizures in preterm neonates.

† Due to cortical immaturity in preterm neonates, the brainstem release subtending autonomic seizures would not be necessarily expected to reach the cortex.

‡ Maturation of the occipital lobes compared to frontal and temporal areas is defined by two parameters: gyrification index and global mean curvature.

Moeskops *et al.* performed a brain magnetic resonance imaging (MRI) study on infants between 30 and 40 weeks of gestation. They evaluated, by longitudinal imaging, the cortical grey matter volume, UWM volume, inner and outer cortical surface area, gyrification index, cortical thickness, and global mean curvature in preterm infants.[6] The authors showed an increase in all measures studied between 30 and 40 weeks post-menstrual age. Significantly more rapid development was described in the occipital lobes than in other brain areas. Interestingly, a significant decrease in cortical folding (in terms of global mean curvature and gyrification index) and increase in cortical thickness were found in neonates with higher brain abnormality scores according to Kidokoro *et al.*[17] These effects were more evident at 40 weeks of gestation than at 30.

Cross-sectional studies of similar cortical indices with preterm neonatal,[5–27] as well as fetal MRI,[18–20] showed an association with age. This result was also found in the study of Moeskops *et al.*[6] This could indicate that the extra-uterine environment, or other diseases of preterm birth, do not show an effect on cortical development at 30 weeks PCA, but have an effect between 30 and 40 weeks, and are more evident at 40 weeks, depending on postnatal complications.[6] In addition, cortical development occurs less rapidly around 40 weeks post-menstrual age than at 30 weeks,[25] resulting in less cortical abnormalities being noted by imaging at 40 weeks rather than at 30 weeks.

Wright *et al.*[18] studied different global curvature indices applied to fetal brain MRI between 21 and 39 weeks gestational age. With increasing age, similar increases in these indices were found. However, this study did not evaluate cortical thickness.[16–18]

Moeskops *et al.*[6] also evaluated cortical development in neonates between 30 and 40 weeks of gestation age. The authors found that at 40 weeks of gestation, the occipital lobes were more mature than the frontal and temporal areas in terms of global mean curvature and gyrification index. Between 30 and 40 weeks of gestation, the largest changes took place in the occipital lobes. These results were in concordance with literature data suggesting that brain development takes place in an occipital-frontal direction,[19] thus explaining the earlier functional use and activity of the visual system in preterm infants, in contrast to, for example, behavioral functions involving the frontal cerebral areas.[6] Moreover, it has been demonstrated that early neuronal activity of preterm infants relates to subsequent brain growth.[21] Consequently, rapid occipital development could make this cerebral area more vulnerable to diseases, explaining the high risk of visual dysfunction in preterm infants.[13]

The processes involved in the development of the neonatal cerebral cortex are not still clear. Suggested factors include: genetics,[22,23] neuronal differentiation[24] and mechanical or extra-uterine effects.[22–24] With respect to the mechanical effects, Toro and Burnod[25] suggested a morphogenetic model of cortical folding in which cortical growth can induce cortical folding by itself. On the contrary, other studies suggested that the specific shape and location of sulci are determined by viscoelastic tensions from white matter tracts connecting cortical regions.[26,27] The latter hypothesis might explain why specific abnormalities in cortical sulci pattern are observed in preterm infants in certain brain developmental disorders.[28] These cortical abnormalities may result from subtle impairments in cortico-cortical connections and neuronal migration.

The underdevelopment of cortical areas in preterm infants may explain why autonomic seizures, and in particular "pure autonomic seizures", occur predominantly in preterm neonates. In regards, animal studies have confirmed that delayed gyral formation during mid-gestation is caused by sub-acute hypoxemia,[29] often occurring also in preterm infants. Dean,[30] in studies on animal models, found that in the fetal sheep brain reversible cerebral ischemia, even without cerebral loss, showed a significant diffuse failure of maturation of cortical pyramidal neurons, thus explaining the less common occurrence of motor seizures and the higher frequency of autonomic seizures in the premature brain. This was associated with impaired synapse formation and dendritic growth, consistent with altered neuronal connectivity. In conclusion, it appears that in preterm infants the brainstem release subtending autonomic seizures cannot be propagated within the cortex because of the preterm cortical immaturity, explaining why autonomic seizures in preterm infants present as "clinical only" seizures, and are often only detected by EEG studies with difficulty.

ANS and seizures in preterm neonates

The ANS plays a crucial role in fetal adaptation to stress and a successful transition from fetal to postnatal life.[31,32] ANS maturation during the fetal and early postnatal period follows specific pathways, closely related to the maturation of the neuronal circuits within the cerebral cortex.[33] The developing cortex shows complex patterns of discontinuous network activities.[34,35] Their diversity (evidenced, eg, in the fast discharge interspersing slow rhythms) and large frequency spectrum (from delta band to high-frequency oscillations), bring up the question whether these early network oscillations control the functional maturation of the neocortex.[36] Available data also indicate a predominant activity of excitatory systems and relative underdevelopment of inhibitory activity in the developing brain,[2] making seizures a common complication of prematurity.

Recently, a specific group of cells named von Economo Neurons (VEN), has been identified in a developing brain. The VENs are large bipolar neurons located in the frontoinsular cortex and anterior limbic area in great apes and humans, but not in primates.[37] They appear to project into regions that participate in autonomic-visceral-nociceptive processing, such as the amygdala, hypothalamus, periaqueductal grey matter, parabrachial nucleus, nucleus of the solitary tract, nucleus ambiguous, and the dorsal motor nucleus of the vagus nerve.[38] VEN are not present in the developing brain up until 35 weeks PCA, and even at 36 weeks PCA, VENs seem to be fewer in numbers, compared to a significantly greater number in term-neonates (38–40 weeks post-conception). These neurons in particular could perhaps be contributing to the development and maturation of active networks between subcortical and cortical structures in term and late-preterm neonates. Meanwhile, in preterm infants these networks

are not established, and therefore the signals from brainstem, limbic, and prelimbic structures might not readily reach the cortex.

Due to the advanced development of limbic structures before the subcortical-cortical connections are established, seizures originating from the prelimbic cortex would then be more likely to occur in preterm neonates. Furthermore, these seizures would not be easily detected using surface EEG electrodes compared to the term infants.

Exploring our hypothesis further, if cortical structures present an inhibitory activity on subcortical areas, then better developed subcortical-cortical networks in term neonates would lead to electro-clinical seizures with milder autonomic component, more likely associated motor phenomena and the presence of electrographic correlate. In contrast, lack of continuous networks throughout cortical layers and predominance of excitatory systems[2] in preterm neonates may explain the lack of an inhibition on subcortical structures and higher likelihood of ictal autonomic changes with inconsistent electrographic correlation.

Clinical features of autonomic seizures in the neonate

The concepts of which motor and autonomic signs and symptoms constitute clinical seizures in neonates have changed over the years. Many behaviors in neonates are not consistently accompanied by electrical seizure activity, reflecting likely presence of different pathophysiological mechanisms. Despite the variability in relation of electrographic abnormalities to clinical changes, all clinical seizures in preterm neonates reliably reflect brain pathology,[39] and therefore warrant further monitoring.

Based on clinical semiology, neonatal seizures can be classified as: (1) clonic (repetitive clonic jerking of the limbs or head or trunk); (2) tonic (stiffening of limbs or trunk); (3) myoclonic (single jerk or slow serial jerking of the limbs or trunk); (4) ocular (features around eyes, blinking, nystagmus, eye deviation, wide opening); (5) orolingual (tongue thrusting/movements, mouthing/chewing type movements; crying/grimacing type movements, dry retching, noises/vocalizations); (6) autonomic (changing in breathing pattern; oxygen desaturation, apnea, skin color changes, blood pressure, and HR changes); (7) hypomotor (decrease or cessation of behavioral activity, staring); and (8) other.[40] It has been shown that as many as 85% of electrographic seizures in preterm neonates can be clinically silent or present with very subtle clinical symptoms or autonomic symptoms only.[41]

When there is a clear association between clinical symptoms and presence of ictal epileptic EEG discharges, the diagnosis of "electroclinical seizures" is fairly straightforward. However, one peculiar feature of neonatal seizures is the phenomenon of electro-clinical dissociation. Therefore, neonatal seizures can present as either electroclinical, electrographic (subclinical) or clinical only seizures.[3] Clinical only neonatal seizures may be difficult to recognize even among trained observers, and they must be differentiated from normal behaviors or abnormal movements of non-epileptic origin.[42] In preterm neonates, covered basinets further complicate clinical seizure detection and autonomic changes are often the first sign to alert neonatal intensive care unit (NICU) staff about CNS dysfunction (Table 2). Moreover, administration of some anti-epileptic medications can increase risk of autonomic dysfunction, leading to further confusion about the event etiology.

Scher *et al.*, performed a study of 92 preterm and term neonates with electrographically confirmed seizures.[43] The authors found that subtle seizures were the most common category of seizures in both groups, with autonomic signs being more frequent in preterm infants than in term neonates; 37% *vs.* 16%, respectively. Only in one-third of premature neonates the subtle seizures could be consistently correlated to electrographic changes.[43] Longer interictal intervals were seen in older compared to younger preterm infants,[40] bringing into question whether conventional 1-hour EEG study is in fact always sufficient to confirm seizures electrographically. However, prolonged EEGs are not always feasible in preterm neonates; they are very resource intensive; they can interfere with the care in NICU, and their interpretation requires highly skilled neonatal neurologists with expertise in EEG maturational changes, often also not readily available. Therefore, careful selection of neonates at high risk for seizures who should undergo continuing video EEG evaluation is the key to prevent over and underdiagnosis of seizure burden in this population.

The classification of 2017 ILAE considers "autonomic seizures" as subgroup of non-motor seizures; defined as a distinct alteration of ANS function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, and thermoregulatory functions.[1] As neonatal autonomic seizures have rarely been considered independent of subtle seizures, their incidence is likely underreported. The data are limited and the information available often come from term and near-term neonates. Analysis of the clinical semiology of neonatal seizures correlated with EEG in 24 near-term neonates confirmed autonomic phenomena in 56% of all electroclinical seizures.[40] Autonomic symptoms included change in blood pressure and/or HR, pallor, increased salivation or secretions, and central apnea. Early ictal autonomic phenomena were observed in 8 seizures and included oxygen desaturation (4 patients), color change (1 patient), change in breathing pattern (1 patient), apnea (1 patient), and increase in HR (1 patient). The concomitant ictal EEG discharges demonstrated right-sided onset in 5 and left-sided onset in 3 subjects. The ictal discharges originated in the temporal region in 5 and paracentral regions in 3 patients. Apnea at the seizure onset was more likely associated with left temporal discharges. The apneic seizures presented with oxygen desaturation and hypomotor features. Seizures with early ictal autonomic features were associated with abnormal eye movements in all patients but one. The authors did not identify any seizures with pure autonomic features.[40] The authors highlighted that in their cohort orolingual and autonomic signs at onset were more frequently associated with a temporal focus, whereas ocular symptoms at onset were mostly associated with a paracentral focus.[40] In term and near-term neonates, seizures with autonomic features are more likely to be associated with ictal motor symptoms, even though the manifestations can be subtle.

Unfortunately, what we know about seizures with autonomic features in preterm neonates is very limited.

Table 2

Literature data on autonomic seizures correlated to EEG findings in term and preterm newborns.

Author/ year of publication	Number of population studied	Semeiology of seizures in preterm babies	Semiology of seizures in term babies	Frequency of autonomic phenomena in preterm babies	Frequency of autonomic phenomena in term babies	EEG finding (ictal and background) and BAS
Scher *et al.*[43] (2002)	92	Subtle seizures associated with autonomic phenomena	Subtle seizures associated with autonomic phenomena	16%	37%	Longer interictal intervals
Nagarajan *et al.*[40] (2012)	24	NR	Change in blood pressure and/or heart rate, pallor, increased salivation or secretions, and central apnea. Orolingual and autonomic signs at onset were more frequently associated with a temporal focus, whereas ocular symptoms at onset were mostly associated with a paracentral focus	NR	56%	Ictal EEG: right-sided onset in 5 and left-sided onset in 3 subjects. The ictal discharges originated in the temporal region in 5 and paracentral regions in 3 patients. Apnea at the seizure onset was more likely associated with left temporal discharges; BAS: temporal area
Tramonte and Goodkin[51] (2004)	1	NR	Apneic seizures	NR	NR	Ictal EEG: prolonged Video-EEG monitoring captured electrographic seizures in the right-central temporal region, which correlated with clinical bouts of apnea. The longest event lasted more than 1 mins, without development of bradycardia. The clinical seizures resolved after administration of phenobarbital with normalization of the EEG several days later; BAS: right Temporal lobe with hemorrhage
Sirsi *et al.*[48] (2007)	3	NR	Apneic seizures	NR	NR	Ictal EEG: electrographic seizures in the right centro-temporal region, which correlated with the onset and duration of clinical bouts of apnea and oxygen desaturation; BAS: temporal lobe hemorrhage
Castro Conde *et al.*[50] (2012)	2	NR	Apneic seizures	NR	NR	Icatal EEG (patient 1): the discharge extended to the temporal lobe first, with subtle motor manifestations and tachycardia, then synchronously to both hemispheres (with bradypnea/hypopnea), Background EEG: suppressed, at which point the infant experienced apnea; BAS: temporal lobe first, secondarily involving both hemispheres. Icatl EEG (patient 2): focal discharges observed in the occipital areas; Interictal EEG (patient 2): background EEG activity became suppressed right at the end of the focal discharge, coinciding with the appearance of apnea; BAS: occipital areas (In neither case did the clinical description by observers coincide with video-EEG findings)

BAS: Brain area source; EEG: Electroencephalogram; NR: Not reported.

Autonomic seizures in preterm neonates are thought to be less stereotyped, more likely to be suppressible by restraints or triggered by stimulation.[40] They do share some clinical features with subtle seizures, such as duration of more than 20 seconds and clear start- and end-point. The origin of subtle seizures in preterm neonates is thought to be subcortical (limbic and prelimbic cortex), making these seizures different from the neonatal seizures of cortical origin in older neonates.

Apnea is among the most common autonomic sign seen in neonates, especially preterm neonates. Apnea can be associated with CNS or non-CNS dysfunction.[44–46] Central apnea is defined as a halt to airflow for at least 2 respiratory cycles, and it is associated with desaturation to $\leq$80%, or apnea longer than 20 seconds.[47] Ischemic and hemorrhagic injuries of the temporal lobe have been more likely associated with apnea than extratemporal brain injuries[48,49]; however, ictal apnea has also been described in occipital lobe lesions.[49]

What makes the seizure diagnosis difficult is that apneic events in preterm neonates are common, and many are not epileptic. Ictal apnea, although not common, has been reported.[50] It remains unclear which neonates with ictal apneas might have underlying epileptic process. However, in preterm neonates with increased risk for seizures, such as presence of hemorrhagic injury or infection, or in the presence of unusual autonomic symptoms, such as apneas without associated bradycardia bring into question the relationship between autonomic signs and epileptogenic process. Lack of electrographic correlation of these events using the standard EEG contributes to the diagnostic dilemma. Furthermore, undeveloped cortical organization and immature myelination in preterm likely contributes to more limited seizure propagation to the cortex as would be seen in older neonates and children.[48] Some authors reported normal interictal and abnormal ictal findings; others found both, interictal and ictal EEG abnormalities, including some of the ictal findings captured during prolonged video-EEG monitoring. In majority of neonates, apneic seizures are not consistently associated with ictal or interictal EEG findings, and the electroclinical correlation of apneic seizures with EEG changes remains controversial.[51]

Recent comprehensive review focused on neonatal seizure etiology and EEG findings reported that autonomic seizures are more likely to be associated with intracerebral hemorrhage.[52] Incidence of periventricular and intraventricular hemorrhage is higher in preterm neonates. If the brain injury affects the development and function of the autonomic networks and therefore the continuing development of the subcortical-cortical networks, then perhaps unexplained autonomic symptoms could be a result autonomic system being directly involved or at least contributing to epileptogenesis in preterm infants with cerebrovascular, or hypoxic-ischemic brain injuries.

This hypothesis requires further research into seizures and epileptogenesis in preterm infants as well as deeper understanding of the involvement of autonomic networks in seizure onset, propagation, and manifestation. Even though incidence of seizures is higher in neonates, the prevalence is still relatively low, making research studies in this population limited.

In preterm neonates with unexplained autonomic events, and particularly in those neonates with hemorrhagic injuries or infection, epileptic events should enter the differential diagnosis and further monitoring of these neonates should be considered.

Is automated seizure detection a solution?

Considering the limited availability of experienced electroencephalographers around-the-clock and the risk of long-term brain damage caused by untreated seizures in neonates, there is a need for an accurate automatic seizure detection system.[53] Faul and colleagues[54] evaluated three previously published automated algorithms for seizure detection on neonatal EEG. They concluded that there were no reliable automated seizure detection schemes for clinical use even if the multi-channel EEG were used. Deburchgraeve and colleagues[55] suggested an automated neonatal seizure detection system focused on mimicking the human analysis of EEG. Their approach was based on the analysis of two major characteristics of seizures: repetitiveness of the ictal events and changes relative to the EEG background, but the sensitivity and specificity of this approach was not sufficient. A few studies showed a promising evidence that HR and root mean square amplitude of the EEG could be correlated with seizures.[56] Encouraging results by Greene *et al.*,[57] and Malarvili *et al.*[58] pointed to HR as a potentially useful target for seizure detection having a higher signal-to-noise ratio than EEG. Other clinical studies focused on HR variability during adult epileptic seizures followed. Zijlmans *et al.*[59] found that 80% of epileptic seizures were associated with changes in HR of at least 10 beats per minute. Similarly, van Elmpt *et al.*[60] found HR changes to be stereotyped for each individual patient. Unfortunately, in a similar study in newborns, Cherian and colleagues found HR monitoring and its variability insensitive for neonatal seizures detection.[61]

To further explore HR changes in newborns, Greene *et al.*[62] proposed an improved automated seizure detection system based on a combination of ECG and EEG. The study's specificity and sensitivity were 77.32% and 55.6%, respectively. Malarvili *et al.*[63] investigated the potential of a time-frequency analysis of HR variability for seizure detection. The authors concluded that time-frequency features extracted from the analysis of HR variability could be potentially useful for newborn seizure detection. Altogether, studies combining information from simultaneously recorded EEG and ECG reported an improved seizure detection compared to seizure detection based on either modality alone, the sensitivity and specificity, particularly in neonatal populations remains poor. Recently, Doyle *et al.*[53] investigated the efficacy of HR based measures for patient-independent, automatic detection of neonatal seizures. The authors evaluated data from 14 neonates recorded over 208 hours. Although their method showed a good reliability in two individual patients, the reliability for the entire group was poor.

In summary, currently available devices for autonomic seizure detection including those analyzing ictal autonomic changes have been shown to be unreliable for seizure detection in neonates, children, and adults.

Polygraphy for the early detection of autonomic seizures in the newborn

As we showed above, clinical diagnosis of suspected neonatal seizures, without the use of EEG monitoring is insufficient. This becomes even more difficult after an administration of anticonvulsants, which in neonates can lead to electroclinical dissociation, presenting as reduction of clinical events in the presence of electrographic seizures only.[64]

Study by Murray *et al.*[65] compared the clinical detection of neonatal seizures by experienced medical and nursing staff, with the retrospective analysis of continuous multichannel video-EEG interpreted by a clinical neurophysiologist with experience in neonatal EEGs. The EEG analysis identified a total of 526 electrographic seizures, but only 179 (34%) with clinical manifestations evident on the video, and only 48 seizures in total (9%) were correctly clinically identified by the experienced staff. Conversely,

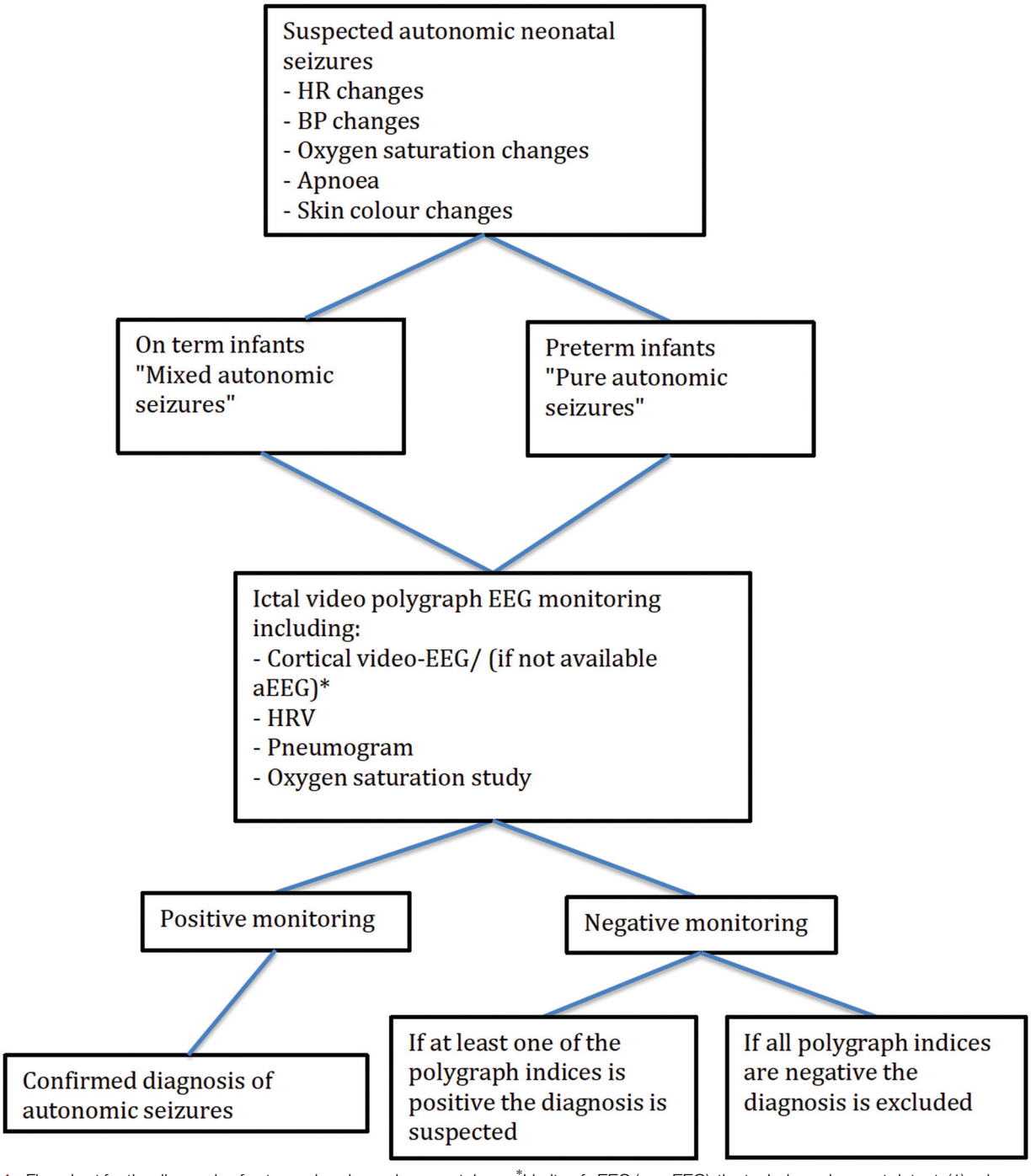

Figure 1. Flowchart for the diagnosis of autonomic seizures in neonatal age. *Limits of aEEG (*vs.* vEEG)-the technique does not detect: (1) seizures lasting less than 60 seconds; (2) seizures with low voltage variations; (3) seizures not involving the parieto-temporal areas. aEEG should be performed when vEEG is not available. aEEG: Amplitude-integrated electroencephalography; BP: Blood pressure; EEG: Electroencephalography; HR: Heart rate; HRV: Heart rate variability; vEEG: Video-electroencephalography..

staff identified 177 clinically suspected seizures, out of which only 48 events had electrographic correlate. The authors concluded that most seizures in NICU were not detected clinically and overdiagnosis was common.

Seizures with subcortical origin, including seizures with predominantly autonomic features, are even more difficult to diagnose and present significant dilemma about their etiology. Depth electrodes have been used to help identify subcortical seizures, however, these are risky, invasive and clearly impractical in newborns. Moreover, seizures are just one of the differential diagnosis for autonomic symptoms in newborn infants.

To detect subtle neonatal seizures, video-EEG polygraphy emerged as a tool allowing for monitoring of multiple vital parameters involved in the symptomatology of neonatal seizures. Recent study looking into the association of paroxysmal vital signs changes and seizures in pediatric population found that events characterized by apnea and non-autonomic symptoms, such as abnormal eye movements and abrupt change of tone were most likely to be ictal.[66,67] Furthermore, additional risk factors increased likelihood of paroxysmal vital signs changes to be ictal. Considering that abnormal eye movements would be very difficult to clinically reliably observe in preterm neonates, video-EEG polygraphy might be helpful in preterm infants with episodes of apnea in the presence of additional risk factors, such as brain injury or CNS infection.

Relevance of our hypothesis

The goal of our paper is to increase awareness among neonatologists and neonatal neurologists about potential link between autonomic changes and developing epileptic activity in preterm neonates. One particular group of neonates we would like to highlight are the preterm infants with additional seizure risk, such as infection and/or intraventricular and periventricular hemorrhage.

As described above, in preterm neonates the earlier development of prelimbic and limbic structures and their early projections to brainstem and diencephalon, relative to underdevelopment of subcortical-cortical connections, as well as the vulnerability of the developing brain to injuries in preterm neonates, they all contribute to a unique presentation of the epileptic events in the developing brain, distinguishing them from seizures occurring in older neonates and children. Seizures with autonomic symptoms appear to be more common in preterm infants; presumably due to specific anatomic differences in the developing brain compared to more mature neural networks.

Considering morbidity associated with ongoing seizures in preterm neonates, and at the same time recognizing the peculiar risk of overdiagnosis and overtreatment of seizures in this population, we suggest a combination of careful clinical observation and prolonged video-EEG polygraphy, including EEG, HR, blood pressure, and oxygen saturation recording as the next step for better characterization of the events in preterm neonates, especially those with additional risk factors (Fig. 1).

We believe that a careful selection of preterm neonates at risk for ongoing epileptic process could lead to better allocation of the resources for prolonged video EEG in the preterm neonates.

We further hypothesize that better understanding of the ANS involvement in seizures and epilepsy, and subsequent better understanding of autonomic seizures and their diagnosis and management, may be clinically highly relevant for understanding other poorly understood events such as sudden infant death syndrome or sudden unexplained death in epilepsy.

Undoubtedly, more research is needed to improve our understanding of the involvement of ANS in epileptogenesis and symptomatology of seizures, and to validate our hypothesis.

Conclusions

Unexplained autonomic signs and symptoms, especially apnea without bradycardia, in preterm neonates with increased seizure risk, such as presence of hemorrhage, hypoxic-ischemic injury or infection, might be used as a "seizure alarm" leading to consideration of further monitoring using prolonged video EEG polygraphy.

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Author Contributions

Raffaele Falsaperla, Giovanna Vitaliti, and Janette Mailo participated in research design, writing the paper, literature data research, and data analysis.

Martino Ruggieri and Giovanni Corsello participated in research design and writing the paper.

Conflicts of Interest

None.

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