Apnea events in neonatal age: A case report and literature review

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\textbf{A B S T R A C T}

Background: Among the most common autonomic signs visible in preterm neonates, apnea can represent the first sign of several neurologic and non-neurologic disorders, and seizure is a relatively infrequent cause. Herein authors present a case of neonatal autonomic apnea, discussing the polygraphic video-EEG features of this pathological entity and the differential diagnosis with central apnea and autonomic apnea.

Case report: A female preterm Caucasian infant (29 + 4 weeks' gestational age (GA)), first twin of a twin pregnancy, at birth was intubated and surfactant administration was performed. She was ventilated via invasive ventilation for three days, with subsequent weaning with non-invasive ventilation for other two days, when she stopped requiring any ventilator support. After one week the ventilation weaning, the child presented episodes of cyanosis associated with sudden oxygen desaturation, skin pallor, apnea, and bradycardia. Therefore, the child underwent a continuous video-eeg recording with polygraphic study. The exam showed the presence of apneic episodes with an abrupt and clear start, associated with oxygen desaturation at 70%, with minimal thoracic effort at onset, and then evolving into central apnea. Central apnea lasted about 16 s and presented clear start- and end-points. These episodes were also associated with suppression of the EEG trace in frequency and amplitude, and after about 10 s of central apnea an abrupt decrease of the child's heart rate (more than 50% variation, from 160 bpm to 65 bpm) was recorded. In the suspect of epileptic apneas of autonomic origin, a therapy with oral Levetiracetam, at a starting dose of 10 mg/Kg/day, then increased up to 40 mg/Kg/day, was initiated, and after about 48 h the first administration of the anticonvulsant therapy, no new episodes of cyanosis or electrical apneas were recorded.

Hypothesis: Herein the authors suggest to consider the diagnosis of autonomic seizures in those neonates with apneic events associated with EEG suppression.

Considering that apnea events are not only present in preterm infants but also in term neonates, it is mandatory to diagnose in this context neonatal seizures for a correct diagnosis and a proper therapeutic choice.

\section*{Introduction}

Among the most common autonomic signs visible in preterm neonates, apnea can represent the first sign of several neurologic and non-neurologic disorders [1–3], and seizure is a relatively infrequent cause.

Central apnea, defined by the Task Force of the American Academy of Sleep Medicine (AASM) as a drop of the airflow for at least 2 respiratory cycles or longer than 20 s, without thoracic effort, associated with a drop in the peak signal excursion by ≥90% of the pre-event baseline [4], is often considered the first sign of neurologic disorders. Nevertheless, the differential diagnosis of a verosimilar central apnea (CA), includes different neurologic and non-neurologic aetiologies, representing a challenge for both neonatologists and pediatric neurologists.

Among all neurologic diseases causing apnoea, ictal apnea (IA) has been noted in both focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures [5–7], and it has also been found in 30–60% of focal seizures without generalized convulsions [6], and in 44–48% of non-generalizing focal seizures [6,8–10]. IA has also been described as the main manifestation of focal seizures in a few case reports [11–18], and severe alterations in breathing patterns after such seizures have been suggested as possible mechanisms of sudden unexplained death in epilepsy (SUDEP) [11].

The hypothesis

Even if literature data have often described the association between central apnoea and seizures, with such important echo that new terms such as Ictal Apnea (IA) and Autonomic Apnea (AA) have been introduced, to date there are no clear definition and diagnostic criteria for this pathological entity. As a matter of fact three pathological entities can be attributed to the pathogenesis of apnoea in neonatal age, so that we can distinguish three forms of apnoea: 1) central apnoea as above defined by the AASM; 2) Ictal Apnea (IA), characterized by the association of apnoic episodes with cortical EEG activation; 3) Autonomic Apnoea, characterized by activation of the autonomic nervous system, without EEG correlates contrarily to the definition of neonatal seizures.

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according to the ILAE committee [1].

In the literature it has already been described in a neonate a case of apneic episodes associated with EEG suppression. The authors also evidenced how apneic episodes in neonates can be either associated or not associated with EEG suppression [19].

Herein authors present a case of neonatal AA, discussing the polygraphic video-EEG features of this pathological entity and the differential diagnosis between CA and AA.

Case report

A female preterm Caucasian infant (29 + 4 weeks' gestational age (GA)), first twin of a twin pregnancy, with a family history relevant for a previous preterm birth (27 weeks' gestation), and exitus of the neonate after one week of life, was admitted to our NICU, Santo Bambino Hospital, University of Catania, Italy, for respiratory distress. Her mother had an uneventful pregnancy and normal Doppler ultrasound findings before giving birth via vaginal delivery.

At birth, the child's APGAR score was 5/7 at 1 and 5 min, respectively and her birth weight was 1145 gr. At birth, the child was intubated and surfactant administration was performed. She was ventilated via invasive ventilation for three days, with subsequent weaning with non-invasive ventilation for other two days, when she stopped requiring any ventilator support.

At birth the child was fed by total parenteral nutrition via the umbilical catheter first and then via a central venous catheter.

Blood tests at admission (pH, Pco2, bicarbonate, complete blood cell count and biochemistry) and electrocardiography results were normal. Thorax X-ray findings were compatible with images of prematurity ventilator alterations that normalized after surfactant therapy, ventilator support, and i.v. antibiotic therapy. Signs and symptoms of septicaemia were excluded by clinical evaluation and laboratory test results.

After one week the ventilation weaning, the child presented episodes of cyanosis associated with sudden oxygen desaturation, skin pallor, apnea, and bradycardia, which required resuscitation with tactile stimulation, oxygen therapy, and intermittent positive pressure ventilation, resulting in transient full recovery. Complementary examination findings, including echocardiography, neurosonography, basic biochemistry and metabolic studies were normal. These episodes were recorded although the child was on therapy with caffeine according to standard protocols for apneas of the preterm infant.

For the persistence of these cyanotic episodes associated with apnea, the child underwent a continuous video-EEG recording with polygraphic study. The exam showed the presence of apneic episodes associated with oxygen desaturation down to 70%, with minimal thoracic effort at onset, and then evolving into central apnea. Central apnea lasted about 16 s (Figs. 1–3).

Apnea was defined as cessation of airflow lasting more than 20 sec, or cessation of airflow associated with bradycardia (20% below the baseline heart rate), or cessation of airflow for less than 20 sec with oxygen desaturation less than 80% [4].

These episodes were also associated with suppression of the EEG trace frequency and amplitude (Fig. 2 blue arrow), and after about 10 s of central apnea an abrupt decrease of the child's heart rate (more than 50% variation, from 160 bpm to 65 bpm) was recorded (Fig. 2, red arrow). The drop in the heart rate was followed by a new onset of thoracic efforts, associated with mixed central apnea at the final stage, which lasted about 10 s, and then the episode resolved with a clear endpoint (Fig. 3).

Suppression of EEG activity to below 5 micronVolts in all EEG channels for 10 sec was defined as complete EEG suppression [19].

EEG background activity was characterized by a normal discontinuous EEG pattern often present in preterm infants. The electrical activity within the bursts included age-appropriate graphoelements such as rhythmic occipital delta activity. Maximum Interburst Interval (IBI) was 10 s (Fig. 4).

These apneic episodes associated with EEG suppression presented with a frequency of 8 in number per day, and they transiently recovered after tactile stimulation and mechanical positive ventilation. For the persistence of these apneic episodes, in the suspect of epileptic apneas of autonomic origin, a therapy with oral Levetiracetam, at a starting dose of 10 mg/Kg/day, then increased up to 40 mg/Kg/day, was initiated, and after about 48 h the first administration of the anticonvulsant therapy, no new episodes of cyanosis or electrical apneas were recorded.

Table 1 shows the physiological and EEG characteristics of these apneic events.

The hypothesis and discussion of the consequences of the hypothesis

Herein the authors present a case of neonatal apnea of autonomic origin in a preterm infant without other neurologic symptoms and/or signs associated with EEG suppression. The baseline EEG activity was appropriate for corrected gestational age.

To date, published cases of apneic seizures have involved the use of standard EEG recordings, and many of these failed to include the ictal episode [13]. In regards, there are published cases of apnea as the only manifestation of neonatal seizure, both associated with bradyrdycardia and without heart rate changes [13], some of which with no ictal EEG findings as in our case. This could be explained by the fact that both the cortical organization and degree of myelination required for propagation and generalization of seizures are not present in neonates [13], above all when preterm.

Studies on the developmental aspects of the functional wiring in the human brain confirmed that pruning of synapse terminals and myelination occurs during postnatal life [14]. However, it seems that subcortical-cortical, cortico-subcortical, and most large cortico-cortical connections are drawn before 36 weeks of gestation [15].

Data obtained from different imaging techniques [16] showed that retrosplenial and adjacent posterior cingulate regions project to the hippocampus in the medial temporal cortex through the cingulum bundle, and thereafter to the midbrain respiratory centers through descending projections. This pathway probably involves the medial forebrain bundle, including the amygdalar and hippocampal formations, thus explaining the epileptic apnea associated with mesial temporal lesions [17].

As reported above, several autonomic changes in seizures can be detected by EEG studies, the most of them showing normal interictal recordings and abnormal ictal findings, others having both interictal and ictal EEG abnormalities, some of the ictal findings captured after long video-EEG monitoring. Yet, the problem arises when apneic seizures are not associated with ictal EEG abnormalities. In regards, apneic seizures have been considered as non-motor seizures of the neonatal age and the frequency with which these clinical seizure types are associated with concomitant EEG activity is controversial [18]. As a matter of fact, these seizures show sometimes no electrical correlation [18].

The challenge in the differential diagnosis between apneas caused by autonomic seizures and those caused by other neurologic and non-neurologic diseases, represents a crucial problem for neonatologists and pediatric neurologists that have to establish whether an anticonvulsant therapy has to be administered. In regards, according to the Task Force of the American Academy of Sleep Medicine the criteria to diagnose a central apnea in pediatric age include the following parameters: 1) a drop of the airflow for at least 2 respiratory cycles during baseline breathing with absent respiratory effort throughout the entire apneic period; 2) the event lasts 20 s or longer; 3) the event lasts at least the duration of 2 respiratory cycles and is associated with an arousal and ≥3% oxygen desaturation; 4) for infants younger than one year of age, the event lasts at least the duration of 2 respiratory cycles during baseline breathing and is associated with a decrease in heart rate less
than 50 beats per minute for at least 5 s or less than 60 beats per minute for at least 15 s [19]. The apnoeic episodes described in our case have different features from the standardized criteria necessary to diagnose a central apnoea. Our apnoea started as a mixed apnoea, with minimal thoracic effort present for about 11 s, then evolving into central apnoea. This last had duration of 16 s, and bradycardia was present only at the final stage of the apnoeic episode. In fact, heart rate decreases are often associated with central apnoea, but they usually precede or appear at the onset of a central apnoea episode. In our case, we had an abrupt heart rate decrease, with a heart rate variation > 50%, and this was observed at the end of the apnoeic episode, after 16 s the onset of central apnoea. Moreover these episodes presented with a frequency of

![Fig. 1. Onset of the apneic episodes, with an abrupt and clear start point (red arrow), and a minimal thoracic effort at the onset (blue arrow), presenting as mixed apnea at onset, then evolving into central apnea. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image)

![Fig. 2. Apnea presented as mixed apnea at onset (with minimal thoracic effort (green arrow)), for about 11 s, and then evolved into central apnea for about 16 s (pink arrow). It was also noted an abrupt variation in the EEG trace frequency and amplitude (blue arrow), following the onset of the apneic episode, and abrupt decrease of heart rate (more than 50% variation (red arrow)), after about 10 s from the onset of apnea. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image)
about 8 episodes per day. As above-mentioned, these episodes had different features from standard central apneas, therefore, in the suspect of seizures of autonomic origin, the infant was submitted to a therapeutic protocol with Levetiracetam, with improvement of her clinical condition, gradual decrease in frequency and duration of her apneic episodes that resolved after the first two weeks of therapy.

Another important finding in our case was the presence of EEG suppression, probably related to hypoxia and hypercapnia during the apneic episodes. In regards EEG suppression associated with apneic episodes have been described by Low et al, in 2011. The authors described the EEG results from an ex-preterm neonate who presented with intermittent but prolonged apneic episodes, which were presumed to be convulsive events. A total of 8 apneic events were captured during EEG monitoring. The baseline EEG activity was appropriate for corrected gestational age. No EEG seizure activity was recorded. Nevertheless, the authors recorded periods of complete EEG suppression (lasting from 68 to 179 s) during 2 of these 8 apneic episodes. Both events were associated with bradycardia (< 70 bpm) and oxygen saturation levels of

Fig. 3. Resolution of the apneic episode, with reappearance of the thoracic effort and abrupt increase of heart rate up to normal ranges (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 4. EEG background activity was characterized by a normal discontinuous EEG pattern often present in preterm infants. The electrical activity within the bursts included age-appropriate graphoelements such as rhythmic occipital delta activity. Maximum Interburst Interval (IBI) was 10 s (Fig. 4).
less than 20%. In both episodes with EEG suppression, bradycardia preceded the complete EEG suppression and EEG amplitude did not become profoundly suppressed until oxygen saturation fell below 20%. They concluded that EEG suppression during these episodes might be related to the secondary state of hypoxia and hypercapnia [19]. Differently from this case, in our report EEG suppression was reported associated with the onset of central apnea, when oxygen saturation was still within the normal range, and bradycardia followed both oxygen desaturation and complete EEG suppression.

To our knowledge, there are neither similar studies performed on neonates nor other neonatal case reports of apneic episodes associated with complete EEG suppression. There is only one study performed in piglets showing the effects of hypoxia to induce complete EEG suppression [20]. In this animal studies the authors showed that in piglets EEG amplitude decreased markedly after approximately 30 sec of apnea induced induced by stimulation of the superior laryngeal nerves [20]. Only those piglets that were preoxygenated preserved the EEG amplitude during stimulation until desaturation decreased down to 50% the normal oxygenation [20].

This case highlights the importance of performing a correct differential diagnosis in order to establish a correct therapeutic choice. Apneas are frequent in neonates and premature babies, but the challenge for neonatologists is the differential diagnosis among all neurologic and non-neurologic diseases causing apnea. In regards, autonomic seizures presenting with central apnea alone are difficult to detect and present with different features than the standard criteria describing central apneas. Therefore, in this context, the polygraphic Video-EEG has been proposed as an efficient diagnostic method as it allows monitoring different vital parameters involved in the pathogenesis of neonatal seizures. In fact, polygraphic Video-EEG allows measuring cortical electrical activity associated with clinical signs and symptoms (by Video-EEG study), heart rate variability, oxygen saturation changes, respiratory activity (by analysis of abdominal and muscular thorax movements), and study of muscular movements when associated with electromyography. All these data allow correlating electrical cerebral activity with sub cortex and limbic functions, in order to assess whether the origin of the disease has cortical or autonomic features.

Therefore, herein the authors suggest to consider the diagnosis of autonomic seizures in those neonates with apneic events with no response to caffeine. In those cases not responding to caffeine, a positive result of the polygraphic Video-EEG study with long-term recordings as routine diagnostic tool in NICU is not mandatory as proposed by the ILAE commitment. This would allow a correct diagnosis and a proper therapeutic choice.

Declaration of Competing Interest

All authors declare not to have any conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109296.

References


Table 1

<table>
<thead>
<tr>
<th>In relation to apneic episodes</th>
<th>Apneic episodes with complete EEG suppression (Mean range)</th>
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<tr>
<td>Number of episodes</td>
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<td>Duration of episodes (secs)</td>
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<td>Lowest oxygen desaturation</td>
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<td>Lowest bradycardia (beats per min)</td>
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<td>Duration of bradycardia (secs)</td>
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<td>Duration of complete EEG suppression</td>
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<td>Recovery time from O₂ desaturation after EEG complete suppression ended (sec)</td>
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