CLINICAL, NEUROLOGICAL AND NEUROPHYSIOLOGICAL FEATURES OF AFFECTIVE RESPIRATORY ATTACKS IN CHILDREN WITH IRON DEFICIENCY ANEMIA

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Abstract. The aim of this article is to present a clinical case of a child diagnosed with anemia and phenylketonuria (PKU), experiencing affective-respiratory attacks (ARA) accompanied by prolonged episodes of asystole. Given the similarity in the kinetics of paroxysms to epileptic seizures and the identified regional epileptiform activity, a differential diagnosis was conducted to distinguish the condition from epilepsy. Affective-respiratory attacks (ARA) with prolonged asystole can exhibit clinical similarities to epileptic seizures. In the context of an inherited metabolic disorder, there may be a generalized bioelectrical instability affecting both brain neurons and the cardiac conduction system. A reduction in phenylalanine (PA) levels in patients with phenylketonuria (PKU) may serve as a contributing factor in the pathogenesis of neurocardiogenic disorders.

Keywords: affective-respiratory attacks, anemia, phenylketonuria, epilepsy, Holter monitoring

INTRODUCTION

Affective-respiratory attacks (ARA) in children are classified as paroxysmal events of a non-epileptic nature, typically exhibiting a benign course and resolving with age. The prevalence of ARA in the pediatric population ranges from 0.1% to 4.7% [1].

Despite their relatively high occurrence, the etiology of ARA remains a topic of ongoing debate. Various etiological factors have been proposed, including delayed myelination processes in the brainstem, iron-deficiency anemia, hysterical reactions in infants, and disturbances in the mother-child relationship due to increased maternal anxiety and chronic stress [1, 3, 4]. The primary pathogenetic mechanism of ARA is an imbalance in the autonomic nervous system, with an overactive parasympathetic tone contributing to pallid-type episodes and an overactive sympathetic tone associated with cyanotic-type episodes.

MATERIALS AND METHODS

Various stimuli, such as fright, pain, fear, anger, dissatisfaction, and frustration, are known to trigger the clinical manifestations of affective-respiratory attacks (ARA) [1, 5].

For pediatric neurologists, differentiating ARA from epileptic seizures in young children remains a crucial aspect of clinical practice. According to S.O. Aivazyan, 6.2% of children with ARA were misdiagnosed with epilepsy [6].

Observational studies indicate that in 9.42% of cases, ARA are accompanied by generalized seizures, predominantly with clonic components. Additionally, more than 15% of children with ARA exhibit epileptiform activity on EEG. Atypical presentations of ARA have been reported, characterized by an absence of a triggering stimulus, apnea without preceding crying, tonic seizures, hypersalivation, and involuntary urination [2, 4].

From a cardiological perspective, this syndrome is of particular interest due to reports of paroxysmal bradycardia and asystole lasting up to 40 seconds, necessitating cardiopulmonary resuscitation [5, 7]. There have been isolated cases of sudden death occurring during cyanotic ARA, typically in children with underlying organic brain damage or respiratory tract pathology [5]. The diagnosis of ARA in children with residual-organic brain lesions and metabolic disorders is of particular significance. In this context, we present a clinical case of ARA in a child diagnosed with phenylketonuria (PKU).

RESULTS AND DISCUSSION

Clinical case

A 3-year-old girl, N., was first admitted to the clinic at the age of 1 year and 9 months due to recurrent episodes of loss of consciousness, which had been observed since she was 10 months old. In most cases, these episodes were triggered by negative affect and could occur either during crying or independently

of it. Some episodes were provoked by pain, while others occurred without an apparent cause.

The paroxysmal episodes manifested as respiratory arrest, upward rolling of the eyes, tonic limb tension, and subsequent collapse. Certain episodes were accompanied by involuntary urination and concluded with postictal sleep. Two instances of tonic limb tension occurred at night during crying episodes. One event took place in the bathtub during bathing, where the girl started crying, became limp, and submerged underwater. The frequency of paroxysmal episodes ranged from 1–2 times per week to 1–3 times per day.

The girl was diagnosed with **phenylketonuria (PKU)**, confirmed by an **R408W mutation in a homozygous state**, and was maintained on a specialized diet.

Medical History

She was born from the first pregnancy, which was uneventful. Delivery was at full term, with a birth weight of 3,630 grams and Apgar scores of 8/9. Neonatal screening revealed a phenylalanine (PA) concentration of 28.9 mg%, leading to the initiation of a specialized diet. Within the first month of life, PA levels fluctuated between 11.9–12.0 mg% and 15.2–28.8 mg%, but after dietary intervention, they remained within 0.4–6.6 mg%.

During the neonatal period, hyperexcitability, restless sleep, and frequent regurgitation were observed. Motor development was age-appropriate, but there was a delay in expressive speech development—by 1 year and 9 months, she could only pronounce 5–6 words.

There was no family history of epilepsy. At 1 year and 9 months, the child was evaluated by an epileptologist. At the time of examination, the girl was irritable, had difficulty engaging with the physician, and exhibited hyperactivity.

Neurological Examination

- Cranial nerves: No visible pathology.
- Muscle tone: Mild hypotonia.

- Reflexes: Increased deep tendon reflexes.

Electroencephalography (EEG) and Brain Imaging

- EEG video monitoring (3 hours):
  - During wakefulness: Moderate diffuse brain dysfunction with periodic slowing of background activity in the right frontocentral region.
  - During Stage 1 and Stage 2 sleep, isolated epileptiform activity (sharp-slow wave complexes) was recorded in the frontocentral-temporal regions, with varying lateralization.
- Magnetic Resonance Imaging (MRI) of the Brain:
  - No focal or diffuse brain abnormalities detected.

Preliminary Diagnosis

- Symptomatic focal epilepsy associated with phenylketonuria
- Differential diagnosis required to distinguish from affective-respiratory attacks (ARA) of mixed type

This case highlights the complex interplay between metabolic disorders and neurological manifestations, emphasizing the need for careful differential diagnosis between epileptic seizures and non-epileptic paroxysmal events, particularly in the context of inherited metabolic diseases like PKU.

Considering the kinetics of the seizures and EEG findings, valproic acid was prescribed, with gradual dose titration up to 20 mg/kg/day. However, no positive clinical response was observed. The seizures persisted daily, occurring 1–2 times per day.

Biochemical analysis revealed a mild increase in serum liver enzymes:

- ALT: 1.13 µkat/L
- AST: 1.24 µkat/L

Abdominal ultrasound (US) findings indicated moderate hepatomegaly and cholestasis.

EEG Video Monitoring and Clinical Observations

Nighttime EEG video monitoring was conducted, during which no typical epileptiform activity was recorded. However, in the morning, the child experienced a crying-induced episode followed by loss of consciousness and muscle flaccidity. Notably, during this episode, no epileptiform discharges were detected, suggesting a non-epileptic origin of the seizures.

Cardiological Assessment

- Electrocardiogram (ECG):
  - Sinus rhythm, regular
  - Heart rate (HR): 113 bpm
  - Normal cardiac axis
- Echocardiography (EchoCG) findings:
  - Patent foramen ovale with hemodynamically insignificant shunting
  - Diagonal trabecula in the left ventricular cavity
  - Mild mitral valve insufficiency (Grade 1)

Holter ECG Monitoring Results

- Sinus rhythm maintained
- Average HR:
  - Daytime: 127 bpm
  - Nighttime: 88 bpm
  - Maximum HR (during active play): 166 bpm
  - Minimum HR (during sleep): 72 bpm
- Ectopic supraventricular activity: 18 multifocal extrasystoles
- Ectopic ventricular activity: 1 isolated ventricular extrasystole
- Seven rhythm pauses recorded during physical activity
- Six sinoatrial (SA) node pauses, including:
  - Longest pause: 11.8 seconds, occurring during a loss-of-consciousness episode with tonic limb tension
  - Pause of 4.5 seconds, associated with mild malaise
  - Other pauses (2.3–3.4 seconds) were asymptomatic

Findings After Valproic Acid Withdrawal

Following the discontinuation of valproic acid, repeat Holter ECG monitoring revealed:

- Sinus rhythm maintained
- HR range: 57–189 bpm, with average HR within normal limits
- One episode of second-degree, Type 1 atrioventricular (AV) block detected during sleep
- SA node arrest was recorded during crying:
  - HR initially spiked to 143 bpm, followed by a sudden decrease to 64 bpm
  - A 3-second pause occurred, followed by one heartbeat, then a prolonged 12.4-second pause
  - Total cessation duration: 15.4 seconds

Discussion and Interpretation

The persistence of seizures despite antiepileptic therapy, the absence of epileptiform activity on EEG, and the presence of significant cardiac pauses suggest that the paroxysmal episodes are not epileptic but rather of neurocardiogenic origin. The crying-induced asystole, SA node dysfunction, and profound bradycardia point to a dysautonomic mechanism rather than an epileptic seizure disorder.

Given the presence of phenylketonuria (PKU) and its impact on neurotransmitter metabolism, a potential link between altered catecholamine levels and autonomic instability could be hypothesized. Additionally, the observed hepatic enzyme elevation and cholestasis may reflect valproic acid-induced hepatotoxicity, further supporting the decision to discontinue the medication.

The findings emphasize the importance of differentiating affective-respiratory attacks (ARA) with prolonged asystole from epileptic seizures, particularly in children with metabolic disorders. Further management should focus on cardiac monitoring, autonomic regulation, and supportive therapy rather than conventional antiepileptic treatment.

The cardiologist diagnosed the patient with pallid-type affective-respiratory attacks (ARA) characterized by sinus node arrest lasting up to 15 seconds during episodes, along with a confirmed diagnosis of phenylketonuria (PKU).

After careful evaluation, a decision was made to refrain from implanting a pacemaker, opting instead for a watchful waiting approach. Encouragingly, a positive clinical trend has been observed. The frequency of episodes has decreased to once or twice per month, or even once every two months, with each episode being brief (lasting 4–5 seconds) and triggered primarily by negative emotions or unmet needs. The child is currently on a treatment regimen consisting of piracetam (solution) in courses, levocarnitine (30%), and propranolol at a daily dose of 8 mg.

PKU and Its Role in the Clinical Manifestations

To assess the potential role of PKU in the child's symptoms, a two-year longitudinal analysis of phenylalanine (PA) fluctuations in blood was conducted. An interesting finding emerged: the child's PA levels frequently did not reach the lower threshold of the normal range (2–6 mg%).

At the initial diagnostic stage, differentiating pallid-type ARA from epilepsy posed a significant challenge. Later, during cardiological evaluation, distinguishing between pallid-type ARA and arrhythmogenic syncope necessitated further investigation, particularly regarding the potential need for pacemaker implantation.

Atypical Features and Diagnostic Complexity

This case exhibited an atypical presentation of ARA, including:

- Tonic convulsive components within the attack structure
- Involuntary urination during some episodes
- Absence of an obvious triggering factor in certain cases

Additionally, the child displayed expressive speech delay, pronounced hyperexcitability, and emotional lability. The presence of epileptiform activity during sleep on EEG video monitoring further complicated the differentiation between epilepsy and non-epileptic paroxysmal events.

Despite these findings, antiepileptic therapy yielded no improvement, and subsequent EEG studies, including nocturnal EEG video monitoring, did not confirm persistent epileptic activity. This necessitated an in-depth cardiological assessment, which ultimately revealed the presence of sinus node arrest during episodes.

REFLEX SYNCOPE AND CARDIAC INVOLVEMENT IN CHILDREN

Syncope in children is common, and in the vast majority of cases, it has a reflex origin. In early childhood, two primary conditions are encountered:

1. Reflex syncopal episodes (anoxic seizures)
   - Triggered by short-acting neurotransmitter-mediated events
   - Result from parasympathetic inhibition of cardiac rhythm
2. ARA with loss of consciousness due to cerebral hypoperfusion
   - Linked to transient cerebral blood flow reduction

Both conditions are often associated with asystole, although typically brief in duration. The incidence of asystolic events (due to either AV block or sinus node arrest) in children experiencing syncope associated with arrhythmogenic events varies significantly, ranging from 14% to 100% in small study samples [7].

Regarding electrical disturbances of the heart during ARA episodes, research indicates:

- Sinus node arrest lasting 3–40 seconds occurs in 82% of cases
- Complete AV block is documented in 11% of cases [7]

This case underscores the challenges of diagnosing and managing paroxysmal episodes in children with metabolic disorders, particularly distinguishing between epilepsy and neurocardiogenic syncope. The patient's clinical manifestations were initially suggestive of epilepsy, yet the absence of improvement on antiepileptic therapy, coupled with subsequent electrocardiographic findings, highlighted a cardiac rather than epileptic origin for the episodes.

The atypical nature of the child's ARA, combined with phenylketonuria, necessitated a comprehensive diagnostic approach involving neurology, cardiology, and metabolic medicine. Ultimately, the decision to withhold pacemaker implantation in favor of conservative management proved beneficial, as the child's condition showed marked improvement over time.

This case further emphasizes the importance of interdisciplinary collaboration in evaluating complex paroxysmal disorders in children and highlights the need for longitudinal monitoring to distinguish between neurological and cardiogenic causes of syncope and convulsive-like episodes.

In cases of prolonged asystole, the question arises regarding the necessity of permanent pacemaker implantation [4]. On one hand, the extreme duration of rhythm pauses, accompanied by syncope and cyanosis, suggests the need for permanent cardiac pacing. However, on the other hand, the clearly identified trigger—affective apnea—along with the positive age-related trend of affective-respiratory attacks (ARA), supports a more conservative approach involving watchful waiting and preventive therapy. Given that even in cases of vasovagal syncope with prolonged asystole, the overall prognosis is often benign, a watchful waiting strategy was chosen in this case.

The Role of Phenylketonuria (PKU) in the Development of ARA

This clinical case is particularly interesting due to the role of PKU as a contributing factor to the development of ARA. PKU is an inherited aminoacidopathy associated with impaired phenylalanine (PA) metabolism, leading to chronic neurotoxicity and central nervous system (CNS) damage, resulting in intellectual impairment and neurological deficits [8].

Recent research has highlighted the importance of monoamine neurotransmitter metabolism (including catecholamines and serotonin) in the pathogenesis of PKU. These neurotransmitters play a critical role in the maturation and function of the CNS. Elevated PA levels in the bloodstream exert neurotoxic effects on brain development, whereas insufficient PA intake can lead to negative

nitrogen balance and disruptions in neurotransmitter metabolism. This, in turn, may cause increased neuro-reflex excitability, potentially contributing to neurocardiogenic dysfunction.

Neurocardiogenic Dysfunction in PKU

Based on an analysis of this clinical case, it can be hypothesized that the patient exhibited a generalized bioelectrical instability affecting both cortical neurons and the cardiac conduction system, likely due to an inherited metabolic disorder. The reduction of PA levels below the normal reference range appears to play a role in the pathogenesis of neurocardiogenic disorders.

This case underscores the complex interplay between metabolic disorders and autonomic regulation, suggesting that in patients with PKU and unexplained paroxysmal events, a multidisciplinary approach involving neurology, cardiology, and metabolic medicine is essential. Understanding the neurotransmitter imbalances in PKU could provide new insights into the mechanisms underlying affective-respiratory attacks and their cardiovascular implications.

Further studies are needed to explore whether adjusting PA levels within the optimal range could mitigate autonomic dysfunction and reduce the frequency of ARA in PKU patients.

CONCLUSION

The presented clinical case holds practical relevance for neurologists, pediatricians, cardiologists, and medical geneticists. It highlights that pallid-type affective-respiratory attacks (ARA) with prolonged asystole can exhibit an atypical course and kinematic similarities to epileptic paroxysms.

In cases where atypical ARA develop in the setting of a hereditary metabolic disorder such as phenylketonuria (PKU), performing Holter ECG monitoring is recommended to identify potential cardiac conduction abnormalities and differentiate them from epileptic or vasovagal events.

For children with PKU, particularly in early childhood and those adhering to a specialized diet, it is crucial to monitor not only elevated but also reduced

phenylalanine (PA) levels. Maintaining an optimal PA balance is essential for timely nutritional support optimization, thereby preventing the development of neurological and cardiovascular complications.

This case underscores the importance of a comprehensive, multidisciplinary approach to diagnosing paroxysmal events in children with metabolic disorders, ensuring that both neurological and cardiological aspects are thoroughly assessed and managed.

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