Unique Severe HyperEkplexia-Like Apneic Events (SHELAE) Improved by High-Dose Piracetam

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Abstract
Breath-holding spells are common non-epileptic events with onset between 6 months and 18 months of age that are usually triggered by minor painful events or strong emotions. Symptomatic treatments for breath-holding spells include iron supplementation, glycopyrrolate and piracetam. Hyperekplexia is a rare non-epileptic disorder characterized by generalized hypertonia and exaggerated startle. Prolonged stiffening triggered by startle can lead to desaturation, cardiac asystole and sudden infant death. It is commonly treated with Clonazepam and other anti-epileptic drugs. Piracetam has been reported to be effective in some anecdotal cases. We describe a case of an infant with frequent hyperekplexia-like breath-holding events who failed to respond adequately to glycopyrrolate, pace-maker insertion and clonazepam, who had marked improvement in his symptoms with high dose Piracetam. High dose Piracetam should be considered in infants with similar severe hyperekplexia-like/breath-holding events as it may be beneficial in ameliorating the acute and chronic course in these children.

Keywords
hyperekplexia, piracetam, apnea, developmental delay

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Introduction
Hyperekplexia is a rare non-epileptic disorder typically manifesting in newborns as generalized hypertonia and exaggerated startle.1 Generalized hypertonia is triggered or exacerbated by handling and can result in apneic spells, which can be fatal and has been associated with sudden infant death syndrome (SIDS). Hyperekplexia can be classified into hereditary, sporadic or symptomatic forms. Hereditary hyperekplexia involves genes encoding various proteins in the glycine neurotransmitter pathway including GLRA1, SLC6A5, GLRB, GPHN, and ARHGEF9. Sporadic hyperekplexia does not have an established genetic or clear neurological aetiology. Symptomatic hyperekplexia is associated with acquired brain injury, genetic neurodevelopmental disorders and neurodegenerative/neurometabolic disease.1

Breath-holding spells are common non-epileptic events, affecting 0.1- 4.5% of children and are triggered by minor painful events or strong emotions (fear, frustration).2 They can be cyanotic or pallid and onset is usually between 6 and 18 months of age. It is mild in the majority who outgrow it. Rarely there are anecdotal reports of severe cases, with some benefit with iron supplementation and piracetam treatment. We report a neonate with extremely severe hyperekplexia-like apneic events who required prolonged intensive care unit (ICU) admission, ventilation and pacemaker insertion and who showed a marked reduction in events with high-dose piracetam.

Case report
This child presented in Bangladesh in the neonatal period with recurrent bradycardia and desaturation episodes. Born at 39 weeks via Caesarean section to consanguineous parents (birth weight 3000 g, Apgar score of 7 [1 min] and 8 [5 min of life], he developed respiratory distress with chest retractions soon

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after birth and was treated for congenital pneumonia with oxygen and multiple antibiotics. He was transferred to our centre at 27 days of age and was admitted to the high-dependency unit for bilateral pneumonia and received positive airway ventilation [CPAP]. Multiple spells of apnoea and desaturation with bradycardia and marked respiratory acidoses on blood gases were noted and he was transferred to intensive care for intubation and ventilation. Episodes of apnoea and desaturation occurred spontaneously or were triggered by handling. While many spontaneously resolved, some were prolonged and required manual resuscitation. Neurological examination was unremarkable except for bilateral adducted thumbs. Septic and metabolic workup were performed and negative. Micro-laryngoscopy showed no laryngomalacia and bronchoscopy revealed normal airway anatomy with no secretions or mucus plugging. MRI brain with spectroscopy showed absence of expected myelination signal in the posterior limbs of both internal capsules, likely hypoxic sequelae from recurrent desaturations and consistent with observed acquired microcephaly. MRI cervical spine was normal. Electroencephalography [EEG] showed no electrographic correlates during events.

Whole exome sequencing performed on skin biopsy samples revealed no significant pathogenic variants. 24-hour Holter monitoring demonstrated significant pauses of up to 13 s. A sleep study did not differentiate primary sinus pauses from secondary bradycardia due to apnoea and pacemaker implantation was performed at 7 weeks of age for possible sinus node dysfunction. Following this, there was no significant improvement in his symptoms and he continued having severe apnoeic spells with desaturation. Oral fludrocortisone was trialled for suspected abnormal vagal tone and secondary decreased vascular resistance/sinus pause but this was discontinued after 2 weeks due to lack of clinical improvement.

As most events were triggered by crying and/or agitation, glycopyrrolate 200μg TDS was started for possible severe breath-holding. This caused thickened secretions, did not improve events and was discontinued after one week.

Hyperekplexia was considered as these events were associated with generalised stiffening, desaturation and bradycardia. The Vigevano manoeuvre did not consistently abort events. Clonazepam was started at 0.125 mg twice daily and gradually increased to 0.5 mg twice daily. The patient was extubated to CPAP +8 cm H2O with 2L/min oxygen but continued to have about 7-8 episodes of apnoea daily with desaturation and bradycardia requiring manual bagging. At 10 weeks’ age, piracetam was started at a dose of 100 mg/day, with associated improvement in apnoeic events. Piracetam dose was gradually increased beyond the recommended pediatric dose of 15 mg/kg/dose (max 800 mg) 8 hly to 600 mg twice a day (180 mg/kg/day). Mean number of events per day fell significantly (Figure 1), from 7.4 (sd 2.99) to 2.5 (sd 1.66) (p < 0.0005, two-tailed independent t-test, 95% CI). Clinical events lessened in frequency and severity, with days without life-threatening events. CPAP was discontinued and respiratory support weaned to oxygen 0.5L/min via nasal cannula. Occasional suctioning/crying-related apneas and desaturations were observed in relation to secretions improved on stopping clonazepam. He was transferred from ICU to the high dependency unit 3 weeks after starting Piracetam. Bouts of hospital-acquired pneumonia and bronchiolitis required brief ventilator support/CPAP but were not associated with worsening of apnoeic spells. He improved enough to be transferred overseas with minimal respiratory support.

**Discussion**

We describe a unique case of Severe HyperEKplexia-Like Apneic Events (SHELAE), who underwent prolonged ICU care, mechanical ventilation and pace-maker implantation. This rare case appears distinct from known entities and presents a major medical management challenge.

Symptomatic hyperekplexia secondary to an undiagnosed neurogenic or neurodegenerative condition was considered given the child’s high tone and generalised stiffening during events. The spontaneous nature of some events went against this diagnosis. Severe breath-holding spells were considered as a differential but the family history of consanguinity, age at presentation, neurological findings, developmental delay and absence of triggers in some episodes precluded this from being the primary or sole diagnosis. The clinical presentation was not in keeping with congenital hypoventilation syndrome and PHOX2B mutation was absent. We trialled glycopyrrolate based on reported efficacy in severe pallid breath-holding spells and clonazepam as a first-line drug in hyperekplexia. Both were ineffective in this patient.

Piracetam is a cyclic derivative of γ-aminobutyric acid (GABA) with a mechanism of action not mediated by GABA. Its mechanism of action is poorly understood but it has been shown to weakly bind to L-glutamate and MRI studies of synthetic phospholipid bilayers show it re-organizes the lipid layer by interaction with the phosphate heads. It facilitates interhemispheric transfer, learning and cognition and enhances cerebral resistance to noxious stimuli such as hypoxia, and has putative protective effect on hippocampal cells and synapses in the alcohol-withdrawal rat model of neurodegeneration.

Piracetam has been trialled in many neurological disorders including stroke, progressive myoclonic epilepsy (PME), dementia, vertigo and tardive dyskinesia. It has a good safety profile and few adverse effects. Piracetam use has been reported in breath-holding spells and in treating hyperekplexia unresponsive to clonazepam.
High-dose piracetam markedly reduced the number and severity of clinical event in our patient. Dose titration was rapidly increased due to the severity and frequency of the previously-described events, and the clinical improvement seen with each increase. The final piracetam dose was significantly higher than that previously reported in the literature, but enabled transition out of the ICU. No adverse side effects were seen and it enabled clonazepam to be weaned off.

High-dose Piracetam should be considered for use in children with severe hyperekplexia-like apneic events and can ameliorate the acute course, enabling reduction of support needs.

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Author Contributions
Janardhan Krishnappa wrote the manuscript with input from all authors. Ngoh, Adeline and Yeo, Tong Hong contributed to sample preparation and provided critical feedback. Chen, Chun Liang: worked out the medication doses and charts. Chan, Derrick contributed towards planning and supervised the work, helped in processing the data performed the analysis and designed the figures.

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