Recurrence apnoea in a term infant: the role of gastroesophageal reflux

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Introduction

A relationship between apnoea and gastroesophageal reflux has frequently been suggested. A review of current evidence, however, does not support a clearly strong relationship between apnoea and gastroesophageal reflux in infants. We report a case of term infant who presented in his first day of life with recurrent apneic episodes associated with acidic gastroesophageal reflux.

Case Report

A baby boy who was born at 38+6week gestation by normal vaginal delivery was admitted to our unit from the postnatal ward for central cyanosis on day 1 of life. The antenatal and birth history were uneventful. There was no maternal narcotic or other drugs use. The Apgar score was 8 at 1 minute of life and 9 at 5 minute of life. He was found to have central cyanosis in the postnatal ward at ~7 hour of life when he was picked up for feeding. He had been fed for twice since birth. There was no vomiting or regurgitation noted. The apical rate was 140/min, the respiratory rate was 56/min and the SpO\textsubscript{2} was 100% in room air. He was then transferred to the Special Baby Care Unit of our department for further management. Physical examination after admission showed no facial dysmorphism. Both choanae were patent and no stridor was noted. The neurological, respiratory, cardiovascular and abdominal examination were normal. Soon after admission, he was noted to have an apneic episode with no chest movement and central cyanosis. SpO\textsubscript{2} dropped to 69% with AR of 82/min. The whole episode lasted for 20 seconds and he recovered after tactile stimulation and oxygen supplement. He was then transferred to the neonatal intensive care unit for close observation and further management. Full septic work up including lumbar puncture was done. Patient was kept nil by mouth and started on intravenous antibiotics of penicillin G and gentamycin. CXR showed normal heart shadow and clear lung field. Bedside ultrasound brain did not reveal intraventricular haemorrhage. Blood investigations showed normal white cell counts and differential counts, normal haemoglobin level, normal electrolyes. CSF microscopy and biochemistry did not reveal any abnormality. In the next 9 hours, he continued to exhibit 9 more episodes of central apnoea without breathing effort. Nasal CPAP was empirically given at 17 hour of life with 5 further episodes of apnoea in his first day of life. There was no more apnoea or desaturation or bradycardia in his second day of life while he was kept nil by mouth and given continuous nasul CPAP. In his day 3 of life feeding was resumed in small frequent amount and nasul CPAP was given intermittently and he suffered 2 episodes of desaturation down to 68% with shallow breathing efforts and one episode of apnoea with cessation of breathing effort during the time when CPAP was off. There was no bradycardia. CPAP was taken off on day 4 of life and patient was continued on oral feeding. Five similar episodes of desaturations with shallow breathing without bradycardia occurred. Clinically they did not coincide with the immediate post-feeding period and no regurgitation nor vomiting were noted. He remained otherwise well and serial serum CRP showed normal results while the cultures results all returned negative and antibiotics were stopped. A 24-hour distal esophageal pH study was done on day 4/day 5 of life. The reflux index was 6.7 and there were 4 prolonged reflux episodes, i.e. within normal limit for age, vide infra. However, there were 3 episodes of desaturation during the 24-hour esophageal study and all were associated with acidic reflux. Gastroesophageal reflux-related central apnoea was diagnosed and domperidone and ranitidine were initiated. He remained well afterward with no further apnoea or desaturation. He was discharged on day 10 of life.

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Discussion

Gastroesophageal reflux (GER) is common in infants. It is the involuntary passage of gastric contents into the esophagus. Daily regurgitation is reported to occur as a physiological and benign phenomenon in 40-60% of normal 3-to-4-month infants and it still occurs in around 55% of infants at the age of 10-month. It decreases to 5% or less of infants when they reached one year of age.\(^1\)\(^-\)\(^5\) It becomes pathological and defined as gastroesophageal disease (GERD) when there is mucosal damage causing esophagitis or there is the presence of related complications like anaemia, haematemesis, chronic respiratory disease.\(^6\) However, there is no clear cut off separating physiological and pathological reflux as a continuum exists between the two. Feeding or sleeping difficulties or impaired quality of life can be resulted from exposure of the esophageal mucosa to refluxed gastric contents.\(^6\)\(^-\)\(^8\) Although 24 hours esophageal pH study was mentioned as a sensitive method for the diagnosis of GERD\(^9\)\(^-\)\(^10\) and the Gastroesophageal Reflux Guidelines Committee of the North American Society for Paediatric Gastroenterology and Nutrition had defined the upper limit of normal for the Reflux Index in 24-hour pH probe study to be 12% in the first year of life and 6% thereafter\(^11\) after an evidence-based review, it is still not easy to define pathological reflux as it is not uncommon in our practice with patients who have reflux index within "the normal limit" on 24 hours esophageal pH study that suffer from complications like esophagitis, apnoea etc. The dual pH probe study which includes also a proximal esophageal or pharyngeal electrode is considered useful for the diagnosis of otolaryngologic manifestations of gastropharyngoesophageal reflux\(^12\) but there is a lack of normal control data on the proximal electrodes. The new intraluminal impedance technique (IMP) allows detection of pH independent reflux and when used with pH probe allows determination not only the presence of reflux in the esophagus but also the composition (acidic or otherwise, gas or liquid or mixed reflux) and height of the reflux.\(^13\) Unfortunately, there are no normal values for children and interpretation of the study is time consuming as computer scoring is not reliable. Hence, IMP requires careful evaluation before it could be widely applied to paediatric clinical practice.

For the influence of GER on the airways, it has long been a topic of debate and more than 1000 articles on the topic were published in the last decade.\(^13\) The association between GER and apnoea in infants is frequently mentioned especially in the preterm infants. It is based on the clinical observation that apnoea frequently occurred in period immediate after feeding\(^14\) and in the animal studies, apnoea could be induced by instillation of small amount of fluid into the larynx.\(^15\) Several mechanisms have been put forth for how GER could cause apnoea. The first is the laryngospasm resulted from GERD followed by aspiration of stomach contents into the glottis, subglottis or tracheobronchial tree. The second mechanism is a reflex related one. "The laryngeal chemoreflex" described by Thach\(^16\) consists of several aspiration preventive reflex responses mediated by stimulation of the specialised nerve endings located in the mucosa covering the inter-arytenoid space at the entrance to the larynx. These responses include swallowing, cessation of breathing, airway constriction or closure, and coughing. In certain infants, a hyperactive laryngeal chemoreflex response may result in episodic prolonged apnoea. Another mechanism involves the importance of mucosal adhesive forces in decreasing the upper airway patency. Once upper airway closure occurs, a high surface mucosal adhesive force could impede subsequent upper airway opening. It is possible that the reflux induced upper airway mucosal inflammation could promote upper airway collapse by increasing the mucosal adhesive forces but this concept remained to be proven.\(^17\)

Despite large pool of literature investigating the relationship between apnoea and GER, controversy remains for GER's role as a cause of apnoea for previous studies on the subject have shown conflicting results. Early studies suggested a relationship between GER and apnoea in term and preterm infants.\(^18\)\(^-\)\(^21\) Herbst et al\(^18\) described apnoea in 14 infants with clinical and radiographic evidence of pulmonary aspiration. Menon et al\(^21\) studied 10 infants with postprandial regurgitation and apnoea and found majority of the short apnoeas occurred more frequently during episodes of regurgitation. However, the majority of the prolonged apnoeas did not coincide with regurgitation. Spitzer et al\(^20\) found evidence of apnoea during GER episodes in a selected group of infants with wake apnoea. Wenzl et al\(^22\) studied 22 infants with the simultaneous use of IMP and pH monitoring and demonstrated that 29.7% of the apnoeas were associated with GER and the mean time spent apneic during GER was significantly greater than
those spent during reflux free period. However, more recent studies have consistently failed to support the relationship between GER and apnoea. Arad-Cohen et al.119 studied 21 infants and found most of the apnoeas (81%) did not show a temporal relationship with episodes of reflux and for those apnoeas associated with GER, a majority (93%) occurred before the episodes of reflux. Peter et al.24 used IMP and studied 19 preterm infants with a total of 2039 episodes of apnoea, the frequency of apnoea occurring within +/- 20 seconds of a reflux episode was not significantly different from that occurring during reflux free epochs and the same was true for desaturations and bradycardias. Only 4.8% of desaturations and 2.2% of bradycardias were associated with a reflux episode. Kohelet et al.26 performed 24 hours distal esophageal pH monitoring in 134 infants who presented with one or more of the followings: regurgitation, vomiting, apnoea, bradycardia, and cyanotic episodes. Logistic regression analysis failed to detect an association between GER and apnoea, bradycardia and cyanotic episodes. Mousa et al. examined 25 infants aged 1 to 19 months using IMP together with pH probe and failed to demonstrate a temporal relationship between GER and apnoea. Only 15.2% of the total 527 apneic episodes was temporally linked with GER with 7.0% were acid reflux and 8.2% non-acid reflux. No significant correlation between apnoea and frequency or duration of reflux episodes were demonstrated by using scatterplots. Chi square analysis within subjects found only limited association between reflux and apnoea. In a recent study by Di Fiore et al.119 preterm infants were studied with 6255 episodes of GER, only 1% of GER episodes were associated with apnoea ±15 seconds and there was no difference in the rate of apnoea before, during and after GER. The presence of GER during apnoea did not prolong apnoea duration and GER had no effect on the lowest SaO₂, heart rate during apnoea.

Meta analysis from these studies is not possible as there are major differences in these studies in terms of subject selection criteria, the method used to detect GER, the duration of monitoring for GER, the duration of apnoea and the criteria used to define a temporal relationship between GER and apnoea. Nevertheless, current evidence does not support a close relationship between apnoea and GER. Moreover, the beneficial effects of anti-GER therapy on the incidence or severity of apnoea were not demonstrated as the safety and efficacy of anti-GER agents in infants are yet to be addressed. It does not justify the widespread use of antireflux agents in treating infants with recurrent apnoea especially in the preterm infants as it was estimated from a clinical practice survey that 19% of preterm infants had received cisapride. Treatment for GER should only given to patients with unequivocal evidence of apnoea following a proven reflux as shown by the current case report, i.e. all desaturations were associated with reflux episodes.

In conclusion, the role of GER as a common cause of neonatal apnoea remained unclear. Empirical treatment for those infants with apnoea and regurgitation with anti-GER especially in the preterm infants is not supported. Treatment should be individualised to those whose symptoms showed a definite temporal relationship between GER and apnoea.

References