Esophageal Atresia, Choanal Atresia, and Dysautonomia

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● **Patients with esophageal atresia (EA) or choanal atresia (CA) manifest similar clinical and pathophysiological features. To determine the significance of this observation, the clinical records of 80 patients with EA and 57 with CA were reviewed. This survey showed that similarities between the two conditions included inspiratory and expiratory dyspnea, episodes of reflex apnea and/or bradycardia, oropharyngeal dysphagia, vomiting, convulsions, hyperhydrosis, hyperthermia, sialorrhea, and sudden death. After the second year of life most symptoms disappeared spontaneously. In both conditions, respiratory effort resulted in partial or complete obstruction affecting both the inspiratory and expiratory phases of the respiratory cycle. Support for this finding was obtained by studying the breathing pattern of 3 patients with EA and 3 with CA, before and during postural respiratory loading. The data suggest that patients with EA are similar to those with CA, having upper airway instability that may result in obstructive hypopnea or apnea associated with expiratory grunting. It is possible that this upper airway instability is a manifestation of more general maturational dysautonomia previously not recognised in patients with EA.**

INDEX WORDS: Esophageal atresia; choanal atresia; tracheomalacia; obstructive apnea; reflex apnea; Pierre-Robin syndrome; familial dysautonomia.

IT IS WIDELY assumed that infants with choanal atresia (CA) develop respiratory distress because they are obligate nasal breathers. We have previously reported that the inability of infants with CA to breathe through the mouth can be attributed to obstruction of the oropharyngeal airway resulting from backward displacement of the tongue.[1] This is comparable to the obstruction described by Pierre-Robin in patients with micrognathia, which is now referred to as glossoptosis-apnea.[1-3] The respiratory obstruction apparently results from the inability of the genioglossus muscle to counterbalance the upper airway constricting forces generated by the inspiratory efforts necessary to overcome an increased airway resistance.[1-3]

Babies with CA appear to have an abnormal response to a vagal reflex (triggered by stimulation of lung mechanoreceptors) that normally helps to ensure upper airway patency.[3] This hypothesis is supported by evidence that glossoptosis-apnea is associated with many clinical manifestations of dysautonomia, enabling a common syndrome to be recognised.[2-4] The clinical picture resembles that described in infants and children with the sleep-apnea syndrome that may be associated with various anatomical causes of airway obstruction.[2,5] However, because sleeping is not an essential prerequisite for the development of apnea in infants, it is preferable to use the term "glossoptotic syndrome," originally proposed by Pierre-Robin.[2]

Subsequent to the report on the pathogenesis of apneic spells in infants with CA, it was suggested that infants with esophageal atresia (EA) may have similar episodes of glossoptosis-apnea.[1] In this article, the results of 20-year clinical and respiratory observations are reported to support this thesis by providing evidence that patients with either EA or CA have similar clinical and pathophysiological manifestations.

MATERIALS AND METHODS

We reviewed the records of 80 patients with EA and/or tracheoesophageal fistula (TEF) (EA group), and 57 patients with CA, choanal stenosis, or symptomatic rhinitis (CA group) admitted to the Division of Pediatric Surgery of the University of Rome "La Sapienza" during the period from January 1970 to December 1989. Of the 56 surviving patients with EA, 43 were evaluated at a special follow-up clinic by the two senior authors (F.C. and N.A.M.). In addition, we updated the information on our series of patients with CA.[3]

The diagnostic criteria and definitions of the clinical features and laboratory findings in dysautonomia have previously been reported.[2,3] In this study, reflex apnea and/or bradycardia was regarded as significant if such episodes necessitated resuscitation.

In three infants with EA and three with CA, randomly selected, the breathing pattern was studied in order to determine the physiological abnormalities before and during postural respiratory loading and to correlate the findings with the clinical features. Flow signals were obtained from a pneumotachograph connected to a tight-fitting mask. The differential pressure signals from the pneumotachograph were measured with a Validyne transducer (model DP250; Validyne Engineering Corp, Northridge, CA). The esophageal pressure was measured with an 8F polythene feeding tube filled with water and kept free of bubbles by flushing with 2 mL of water between measurements. The catheter was inserted through the nose or mouth into the blind upper pouch or the lower esophagus and connected to a pressure transducer (Statham PM 15 ETC; Gould Inc, Oxnard, CA). All signals were recorded oscillographically at high sensitivity (SE Oscillograph 3006/DL; SE Laboratories, Feltham, England). Inspection of breathing move-

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ments and auscultation with a stethoscope of respiratory sounds were accomplished during recording.

The respiratory pattern in the infants with EA was studied in the lateral and supine positions and in the infants with CA in the supine position, with or without an oropharyngeal airway, and with the neck extended. In two patients with EA the response to the respiratory loading imposed by the supine position was investigated before esophageal repair and in one, the study was performed after esophageal repair.

RESULTS

Clinical Features

The clinical findings are summarised in Table 1. There were no differences in the distribution of the main clinical manifestations between patients with EA or CA.

CA. The clinical characteristics of the patients with CA were described previously and were similar in the 57 patients included in this study.

EA. In the majority of patients with EA, respiratory distress was present during their first admission before operation; however, a review of the chest radiographs found that 50% were normal. Patients manifesting respiratory distress had one or more of the following signs of inspiratory obstruction: stridor, snoring, chest retraction, glossoptosis, indrawing of the cheeks and lips, opisthotonus, and diminished or absent air entry. In many patients with inspiratory obstruction, there were also signs of expiratory obstruction, such as prolonged expiration, wheezing, grunting, and a "barrel chest."

The respiratory problems noted during the first or subsequent admissions were most often precipitated or exacerbated by inflammatory airway obstruction, motility disturbance of the esophagus and/or anastomotic stricture, feeding, the supine position, crying, exercise, flexion of the neck, sleeping, and anesthesia. In most patients the respiratory distress was lessened by the prone position, pulling the chin forward, or extending the neck. When respiratory distress was more severe, pharyngeal or tracheal intubation was required, complemented by positive end-expiratory pressure (PEEP), and this too had a beneficial effect.

Table 1. Distribution of Main Clinical Features of 80 Patients With EA and 57 Patients With CA

	EA		CA	
	No.	Percent	No.	Percent
Inspiratory dyspnea	71	88.7	56	98.2
Expiratory dyspnea	35	43.7	28	49.2
Reflex apnea	28	35.0	17	29.8
Reflex bradycardia	20	25.0	7	12.2
Oropharyngeal dysphagia	27	62.7*	33	57.8
Vomiting/GER	26	60.4*	30	52.6
Hyperhydrosis	15	34.8*	13	22.8
Convulsions	19	23.7	14	24.5
Sialorrhea	8	18.6*	10	17.5
Hyperthermia	13	16.2	12	21.0
Sudden death	3	3.7	2	3.5

Abbreviation: GER, gastroesophageal reflux.
*Percentage calculated on the 43 patients followed-up.

In 28 patients with EA, apneic episodes occurred, most frequently during or after feeding. In 8 of these, the episodes occurred soon after delivery. Apart from feeding, apneic episodes were triggered by pharyngeal or tracheal suctioning, accumulation of secretions in the blind upper esophageal pouch (prior to repair), ingestion of a large bolus of food in the older patients, gastrostomy feeding or crying. The following associated factors were also identified: prematurity, Down's syndrome, anesthesia, sleeping, and hypoxemia. Feeding the infant in the lateral position with hyperextension of the neck was the best way of avoiding cyanotic attacks, and in some babies it was also necessary to hold the mandible forward.

In 20 infants with EA there were episodes of bradycardia, unassociated with apneic spells. Three patients were noted to have had prenatal bradycardia detected during the later weeks of pregnancy or during delivery, and in these babies emergency cesarean section was necessary. A few infants developed bradycardia following pharyngeal or tracheal suctioning, but usually the mechanism triggering the bradycardia could not be identified. On one occasion, during the course of esophageal repair, bradycardia was followed by cardiac arrest, necessitating cardiac massage; it appeared that this episode was a direct result of vagus nerve manipulation. This patient subsequently had two further episodes of reversible cardiac arrest during esophageal dilatation under general anesthesia, and prior to esophageal dilatation several cyanotic attacks during or after feeding.

Following esophageal repair, difficulties with sucking and/or swallowing were frequent, and in 60% of patients vomiting, with or without documented gastroesophageal reflux, occurred. Approximately one third of the patients with EA had excessive sweating during sleeping or feeding; in one patient, minor stimuli resulted in profuse sweating of the right side of the face and body.

In 13 of the EA patients febrile episodes occured without clinical or laboratory evidence of infection, and in one infant, recurrent episodes of high fever (40°C to 41°C) necessitated parenteral rehydration. This patient died at the age of 16 months during an episode of uncontrolled hyperthermia. Another patient had an episode of "malignant hyperpyrexia" following a pull-through operation for anorectal atresia. Excessive salivation occurred in 8 patients;

this was not related to the excessive secretions noted prior to EA repair.

Sudden death occurred in 3 infants following successful repair of the EA. One was a "cot death," another died during a cyanotic episode following food bolus impaction in the esophagus, and the third death was during one of several recurrent episodes of inspiratory obstruction with stridor and chest retraction.

It is encouraging that symptoms were most frequently seen during the first 2 years of life, and then spontaneously disappeared with increasing age.

Physiological Data

All six infants studied showed similar breathing patterns.

Reflex hypopnea. In the lateral or supine position with an oropharynged airway in situ, all patients had one or more episodes of central hypopnea with decreased inspiratory flow and a parallel reduction in the amplitude of the inspiratory pressure changes (Fig 1). Frequently, such episodes were associated with swallowing. The episode of central hypopnea was followed by a prolongation of the expiratory time and an interruption of the expiratory flow associated sometimes with positive expiratory intrathoracic pressure.

Obstructive hypopnea. When tilted from the lateral to the supine position (or when the oropharyngeal airway was withdrawn), all patients had a sharp reduction in, or an absence of inspiratory flow, despite markedly increased inspiratory efforts (the equivalent of Muller's manoeuvre) (Fig 2). The expiratory time was prolonged and the expiratory flow pattern was interrupted dispite a positive expiratory intrathoracic pressure (the equivalent of Valsava's manoeuvre). Clinically, inspiration was often accompanied by inspiratory stridor and paradoxical retraction of the anterior chest wall. Expiration was often accompanied by audible grunting and contraction of the anterior abdominal wall muscles. Auscultation of the chest showed little or no air entry during inspiration and expiratory wheezing, loudest over the neck.

DISCUSSION

On the evidence available, patients with EA, as well as those with CA, are unable to compensate for increased respiratory load. The fine balance controlling the forces acting on the upper airway may be disturbed by factors that increase the negative intrathoracic pressure (dilated upper esophagus compressing the trachea, inflammatory airway obstruction, crying); factors that decrease the upper airway dilating muscle activity (anesthesia, sleeping); or factors that decrease the size of the upper airway (flexion of the neck or falling back of the tongue in the supine position). The consequent episodes of obstructive apnea or hypopnea have not been described previously as a cause of respiratory problems in patients with EA.

In this study we found that about one third of patients with EA, like those with CA, have apneic spells during or after feeding, or after various kinds of stimulation of the upper airway or esophagus. This reflex hypopnea or apnea closely resembled the apnea of preterm infants with swallowing, which is a characteristic component of "upper airway chemoreflex apnea."[6-8] Therefore, it is reasonable to assume

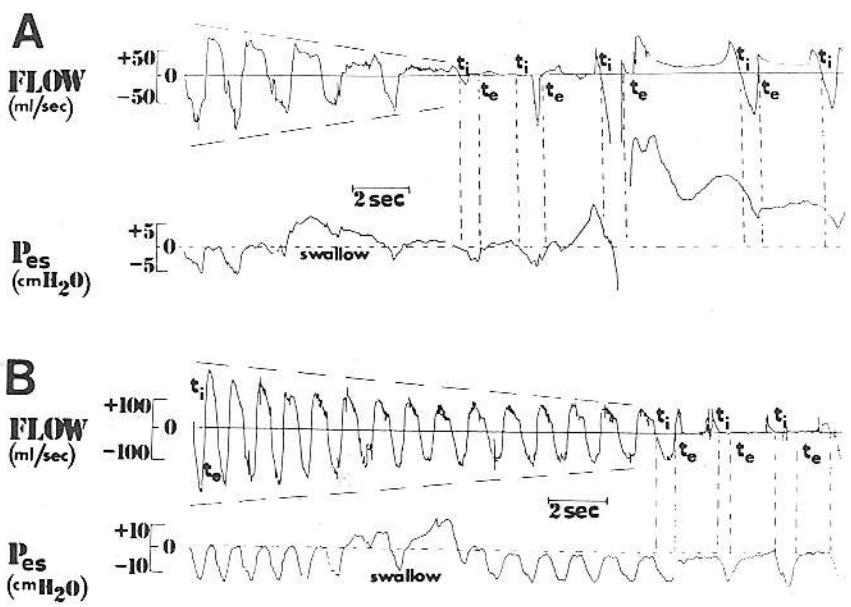

Fig 1. Central hypopnea associated with swallowing in (A) a baby with EA and distal TEF and (B) an infant with bilateral CA. The breathing pattern is characterized by parallel reduction of inspiratory flow and inspiratory esophageal pressure (P_{es}), prolongation of expiratory time (t_e), and interruption of expiratory flow.

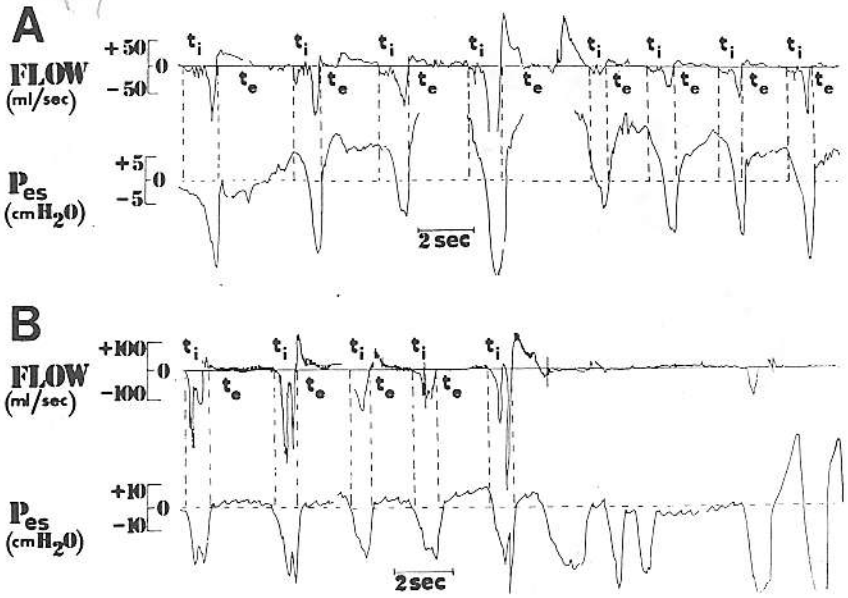

Fig 2. Obstructive hypopnea during postural respiratory loading in (A) a baby with EA and distal TEF and (B) an infant with bilateral CA. The breathing pattern is characterized by reduction or absence of inspiratory flow in spite of increased inspiratory esophageal pressure (P_{es}), prolongation of expiratory time (t_e) and interruption of expiration flow despite positive expiratory (P_{es}).

that this kind of apnea is due to an exaggerated inhibition of respiratory centres from an abnormal response to the upper airway protective reflex.

Infants with EA or CA may have audible grunting in association with an expiratory flow pattern comparable to that described in hyaline membrane disease,[9] suggesting that the expiratory obstruction is in fact a protective mechanism. In healthy preterm infants, and some full-term infants, there may be active interruption of the expiratory flow during the first days of life.[10,11] As a result of obstructive or reflex hypopnea or apnea, alveolar atelectasis may ensue and with this, a right-to-left shunt. A low lung volume and/or hypoxemia will elicit prolonged and forced expiration through the adducted glottis, the effect of which is improvement of alveolar ventilation by maintaining patency of the alveoli.[9,12] Therefore, the grunting respiration observed in patients with EA or CA may well be an exaggeration of the normal physiological pattern.

The beneficial effects of PEEP are in keeping with the successful use of this modality in treating sleep apnea at all ages. An important implication is that early closure of a TEF allows not only an effective ventilation of infants with respiratory distress syndrome,[13-15] but also an efficient grunting expiration to compensate or to prevent atelectasis.

Vagal reflexes from lung mechanoreceptors probably play an important role in the organization of active expiration and if there is an abnormal response to this protective lung reflex, this would provide an explanation for "prolonged expiratory apnea."[12,16] Recent reports have suggested that apnea of this type may be the cause of cyanotic attacks and sudden death in an infant with repaired EA.[16,17] It has been postulated that surgical repair may damage the autonomic innervation of the lungs and lead to abnormality in lung reflexes.[17]

Having demonstrated apnea prior to operation we can exclude surgical impairment of autonomic nervous function as a *modus operandi.* The evidence supports the unifying hypothesis that the common denominator for the mechanism of various kinds of apnea is an exaggerated inhibition of the respiratory centre from immaturity of various protective reflexes.[18]

Many of the present patients with EA or CA have manifested several symptoms and signs of an autonomic disorder, supporting the hypothesis of underling functional immaturity of different vagal protective reflexes. Features we have found to be present (including fetal bradycardia, respiratory distress, opisthotonus, grunting respiration, cyanotic attacks, cardiac arrhythmia, oropharyngeal dysphagia, vomiting, hyperthermia, and hyperhydrosis) have also been described in infants with familial dysautonomia.[19,20]

Most patients with familial dysautonomia are likely to die during late adolescence, common causes of death including pulmonary complications or sudden death following passage of a nasogastric tube, micturition, or change of posture.[21] In addition, in this group there have been unexplained deaths occuring during sleep. However, only a few patients with EA or CA die suddenly; most become asymptomatic with increasing age and enjoy a normal life. Therefore, it is concluded that many patients with EA, like those with CA, may have an associated maturational dysautonomia.

Some respiratory problems in patients with EA are conventionally attributed to tracheomalacia and/or gastroesophageal reflux. However, these problems are very similar to those found in infants with the glossoptotic syndrome associated with congenital micrognathia,[2] or in infants with reflex apnea syndrome associated with a vascular ring.[22] Therefore, it is conceivable that tracheomalacia or gastroesophageal reflux are triggering factors that, like many others, activate or precipitate maturational dysautonomia, which may be associated with various malformations involving the airway.

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