Maturational Dysautonomia and Facial Anomalies Associated With Esophageal Atresia: Support for Neural Crest Involvement

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● **Patients with esophageal atresia (EA) or choanal atresia/stenosis (CA) present with many clinical features of maturational dysautonomia (DY). Since CA and DY are considered manifestations of cephalic neurocristopathy, we tested the hypothesis that EA may also be related to faulty development of cephalic neural crest. Forty-eight patients with EA and 53 with CA were followed up to study the frequency of the facial anomalies which are regarded as the phenotypic expression of an abnormal cephalic neural crest contribution to facial embryogenesis. Forty-eight patients with EA and 51 with CA had clinical manifestations of DY. Forty-four patients with EA (91%) and 49 with CA (92%) had one or more facial anomalies. Comparing the groups, patients with EA had an increased frequency of unilateral facial anomalies of branchial arch derivatives ($P < .01$); those with CA had an increased frequency of anomalies of frontonasal process derivatives ($P < .01$). These findings support the hypothesis that EA may be related to an abnormal contribution from the cephalic neural crest. The presence of facial anomalies may facilitate the diagnosis of subclinical DY.**

INDEX WORDS: Esophageal atresia; facial anomalies; choanal atresia; maturational dysautonomia; neurocristopathy.

INFANTS with choanal atresia (CA) as well as those with esophageal atresia (EA) have an abnormal autonomic control of upper airway dilating muscles.[1,2] The upper airway instability results in recurrent episodes of "glossoptosis" with partial or complete obstruction of pharyngeal airway (obstructive hypopnea or apnea).[1,2] The consequent dyspnea is characterized by signs of inspiratory obstruction caused by glossoptosis frequently associated with signs of expiratory obstruction. The obstruction during the expiratory phase is probably the result of an active braking of the expiratory flow (grunting) rather than a passive obstruction caused by glossoptosis.[2]

Inspiratory and expiratory dyspnea are very often associated with an abnormal autonomic control of sucking and swallowing and with other disautonomic disorders, including reflex apnea and/or bradycardia, gastroesophageal reflux, hyperhydrosis, sialorrhea, and sudden death.[1,2] Since the autonomic nervous system develops from neural crest cells, it has been postulated that these disautonomic disturbances may be manifestations of a neurocristopathy.[3-6] This term was coined by Bolande to describe lesions resulting from the maldevelopment of neural crest derivatives.[7]

Neural crest cells migration is currently a major focus of research. Evidence from animal experiments indicates that the cephalic neural crest also has a significant profound effect on the embryogenesis of the face.[8] Consequently, facial anomalies are considered markers of an abnormal developmental activity of the cefalic neural crest.[9,10] The increased frequency of facial anomalies in patients with CA and multiple anomalies (CHARGE association) suggests that CA should also be considered a manifestation of a neurocristopathy.[11,12]

How to explain the association between dysautonomia (DY) and EA? It is tempting to speculate that DY, CA, and EA may be linked by the neural crest. To test this hypothesis, we studied the frequency of facial anomalies in a series of patients with either CA or EA.

MATERIALS AND METHODS

During the period January 1970 to December 1990, 86 patients with EA and 63 patients with choanal atresia or stenosis or "symptomatic rhinitis" were admitted to the Division of Pediatric Surgery of the University of Rome "La Sapienza." Of the surviving patients, 48 with repaired EA and 53 with CA were evaluated at a special follow-up clinic to study the frequency of DY clinical features and of associated facial anomalies. The records of the patients followed-up were reviewed.

Infants referred for symptoms suggestive of choanal stenosis, who presented at rhinoscopy with severely congested nasal mucosa and no anatomical obstruction, were classified as patients with "symptomatic rhinitis." In this study, hyperhidrosis during sleep or feeding was regarded as significant if the subject's clothes were wet from dripping sweat. We classified as reflex apnea and/or bradycardia all apneic and/or bradycardic episodes necessitating resuscitation.[1,2] Sialorrhea was regarded as significant if it required numerous daily replacements of wet bibs. Recurrent febrile episodes without clinical and laboratory evidence of infection were classified as hyperthermia.[2]

The physical examination was always made by the same examiners, who all agreed on the diagnosis of even more subtle dysmorphic facial features. Since accurate anthropometric measurements are very difficult in infants and young children, we used the apparent rather than measured description of facial anomalies. We recorded the presence of those facial anomalies previously found in patients with CHARGE association.[12,14-16] These facial anomalies were classified as follows: (1) anomalies of frontonasal process

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derivatives; (2) ear anomalies; and (3) asymmetric anomalies of branchial arch derivatives.

Anomalies of frontonasal process derivatives included defects with a deficiency of ethmoid bone (flat nasal bridge, epicanthal folds, broad nasal bridge, antiverted nares) or of other structures embryologically related to the frontonasal process (hypoplastic philtrum and/or upper lip, anomalies of maxillary incisors). Anomalies of the ears included discrepancy in size (one ear smaller than the other), lop ears, deafness, structural anomalies of the pinna, low set ears, and preauricolar tags or pits. Asymmetric anomalies of branchial arch derivatives included facial asymmetry, unilateral facial paresis, and other unilateral facial dysmorphism.

The differences in distribution of facial anomalies were tested by means of χ^2 test.

RESULTS

Dysautonomic Clinical Features

Two patients with CA were asymptomatic. All the other 99 patients (51 with CA and 48 with EA) had one or more clinical manifestations of DY, either before or after surgical repair of the anomaly (Table 1).

Ninety-two subjects had episodes of dyspnea characterized by signs of inspiratory obstruction (polypnea, noisy inspiration, opisthotonus, chest retraction with poor or absent air entry) often associated with signs of expiratory obstruction (barrel-shaped chest, prolonged expiration, wheezing and/or grunting respiration). Frequently there was a discrepancy between the severity of respiratory distress and lung lesions detected on chest films. The dyspnea was precipitated or exarcebated by inflammatory airway obstruction, feeding, crying, exercise, the supine position, flexion of neck, sleeping, or anesthesia. The dyspnea was lessened by the prone position, pulling the mandible forward, extending the neck, pharyngeal or tracheal intubation with or without application of a positive end-expiratory pressure.

Fifty-two patients had life-threatening episodes of reflex apnea and/or bradycardia. Identified triggering factors included pharingeal or tracheal suctioning, accumulation of secretions, feeding, vomiting, and crying.

Table 1. Main Dysautonomic Clinical Features in 48 Patients With EA and 53 Patients With CA

	EA		CA	
	No.	%	No.	%
Inspiratory dyspnea	41	85.4	51	96.2
Oropharyngeal dysphagia	28	58.3	32	60.3
Vomiting	27	56.2	28	52.8
Expiratory dyspnea	22	45.8	27	50.9
Hyperydrosis	16	33.3	11	20.7
Reflex apnea	14	29.1	19	35.8
Reflex bradycardia	13	27.0	6	11.3
Sialorrhea	8	16.6	9	16.9
Hypertermia	7	14.5	11	20.7

Table 2. Facial Anomalies in 48 Patients With EA and 53 Patients With CA

	EA		CA	
	No.	%	No.	%
Ear defects	41	85.4	42	79.2
Asymmetric facial defects	38	79.1	22	41.5*
Frontonasal process defects	19	39.5	37	69.8*

*$P < .01$.

Sixty patients had sucking and/or swallowing difficulties. Fifty-five had vomiting or gastroesophageal reflux. Additional autonomic disturbances were hyperhydrosis during feeding and/or sleeping (27 subjects), sialorrhea (17 subjects), and hyperthermia (18 subjects).

Facial Anomalies

Forty-four patients with EA (91%) and 49 patients with CA (92%) had one or more facial anomalies (Table 2). Ear abnormalities were found in 41 with EA and 42 with CA. Most patients had abnormal pinnae and/or low set ears. Six patients with EA and eight with CA had the typical external features of bat ears. Two patients with EA and two with CA had unilateral deafness.

Unilateral facial anomalies were present in 38 patients with EA and 22 with CA ($P < .01$). Most patients had one side of the face smaller and flatter with the head often tilded to the affected side of the face. Four patients with EA and six with CA had an associated unilateral facial palsy. The facial asymmetry was always associated with an abnormality of the auricolar region on the affected side. The hypoplasia of one side of the face was so evident in one patients with EA, that an erroneous diagnosis of sternomastoid torticollis had previously been made.

Abnormalities of frontonasal process derivatives were identified in 19 patients with EA and 37 with CA ($P < .01$). Most subjects had a hypoplastic nose with a flat and/or broad nasal bridge. Anteverted nares and epicanthal folds were often associated features. Four patients with EA and eight with CA had various types of anomalies of maxillary incisors. A hypoplastic nasal filtrum and upper lip was found in three patients with EA and four with CA.

DISCUSSION

Dysautonomia

We have previously reported that patients with congenital micrognathia, CA, or EA have many clinical manifestations of a maturational DY, enabling a common syndrome to be recognized.[1,2,13] Similar clinical findings of an autonomic dysfunction

have been found in some patients with neuroblastoma and/or Hirschsprung's disease.[3,4-6,17-20] The neuroblasts, the intestinal intramural neurons, and the autonomic nervous system derive from the neural crest. Therefore, dysautonomia, neuroblastoma, and/or Hirschsprung's disease are considered as manifestations of a neurocristopathy.[3,4-6,19]

Choanal Atresia

In this study we found that nearly all patients with isolated CA had the same facial anomalies previously described in patients with CHARGE association.[12,14-16] The significantly increased frequency of midface anomalies in patients with CA (69.8%) when compared with patients with EA (39.5%) supports the hypothesis that CA is one of the frontonasal process neurocristopathies.[9,12] However, patients with isolated CA also had ear anomalies (79%) and/or unilateral facial anomalies (41%). These percentages are remarkably similar to those found in patients with CHARGE association[14-16] and suggest a more generalized alteration in the development of the face.

Esophageal Atresia

An increased frequency of facial anomalies was also identified in patients with EA. Failure to consider these minor facial defects as being of any significance may account for the lack of previous reports regarding this association. Another factor is that many of the facial anomalies are subtle and may frequently pass unnoticed.

The facial anomalies we looked for are considered minor malformations that occur in 39.9% of normal infants with no major malformations and in 62.3% of those with major malformations.[21] Normal infants with three or more minor anomalies are at increased risk for having an associated major malformation.[21] In the present series, therefore, it is not surprising that about 90% of the patients with EA, like those with CA, had one or more facial anomalies. Patients with EA had an increased frequency (79.1%) of asymmetric facial defects when compared with patients with CA (41.5%). This difference is significant ($P < .01$) and suggests that patients with EA may have a greater disturbance of neural crest migration in the branchial arch mesenchyma. Therefore, we conclude that EA should be considered a branchial arch neurocrystopathy.

The Mesenchimal Dysplasia

The concept that the association between EA and facial anomalies may be due to a neurocristopathy is similar to that formulated for the VATER association, which is the most widely known variety of multiple defects found in patients with EA. The VATER association was first described by Quan and Smith,[22] who speculated that the simultaneous occurrence of many defects in various organs could be explained by an erly defect of mesodermal organogenesis. In their view the esophageal malformations are due to an abnormal development of the mesenchymal septum which divides the foregut into esophagus and trachea. The increased frequency of facial anomalies and the overlapping of other defects in patients with VATER and CHARGE association have subsequently suggested that the primary cause of the "axial mesodermal dysplasia" may be a disturbance of the neural crest cells mesodermal migration.[23,24]

Relationship to Sudden Infant Death Syndrome

Blake et al[14] have recently reemphasized the predictive value of the "typical" facial appearence of patients with CHARGE association. The facial anomalies should be used as a "high index of suspicion" of other malformations found in patients with CHARGE association.[14,15]

In this study we found that nearly all patients with facial anomalies had clinical features of DY. Our clinical experience indicates that facial anomalies should alert the observer to the possibility of subclinical dysautonomia. The predictive value can be of great clinical relevance since infants with maturational dysautonomia may present life-threatening episodes of apnea and/or bradycardia in relation to anesthesia, sleeping, gastroesophageal reflux, etc. Therefore, we suggest that the presence of various facial anomalies should imply a full clinical and laboratory evaluation of autonomic nervous system function, including cardiorespiratory and blood pressure monitoring, pupillary response to congiunctival pilocarpin instilation, histamine test, etc.

Since the "glossoptotic syndrome" due to DY may be related to sudden infant death syndrome (SIDS),[1,13,25,26] it is tempting to speculate that infants with facial anom- alies are at increased risk of SIDS. We believe that this hypothesis should be prospectively investigated.

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