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Oroesophageal Motor Disorders in Pierre Robin Syndrome

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ABSTRACT

Background: Feeding disorders are one of the main clinical features in PRS, which combines a posterior U-shaped cleft palate, retrognathia, and glossoptosis. The aim of this study was to evaluate the oral and esophageal motor function of children with PRS without additional neurologic symptoms.

Methods: All children hospitalized with Pierre Robin syndrome either isolated (n = 27) or associated with Stickler syndrome (n = 8) were included. Clinical evaluation of their oroesophageal disorders and systematic esophageal manometry were performed.

Results: Feeding disorders were always present, but type of disorder varied from one child to another. Esophageal disorders were frequent and seemed to be resistant to classic gastroesophageal reflux treatment. Eighty-six percent of the children required nasogastric tube feeding for a mean duration of 8.6 months. Esophageal manometric abnormalities were noted in 50% of the children: lower esophageal sphincter hypertonia, failure of lower esophageal sphincter relaxation at deglutition, and esophageal dyskinesia. These clinical and manometric disorders showed a trend to spontaneous regression after 12 months.

Conclusion: In the current Pierre Robin syndrome series, clinical and manometric anomalies of oroesophageal motility were always present. The authors identified an unusual manometric pattern that has also been described in situations of neurovegetative instability. It could reflect dysregulation of the control of the central pattern generators of swallowing in the brain stem. ***JPGN 32:297–302, 2001.*** **Key Words:** Pierre Robin syndrome—Feeding disorders—Esophageal manometry—Sucking and swallowing—Brain stem. © 2001 Lippincott Williams & Wilkins, Inc.

Pierre Robin syndrome (PRS) is a facial malformation characterized by a posterior U-shaped cleft palate, retrognathia, and glossoptosis (1). Although it was first described more than 50 years ago (2), the pathogenesis and etiologic factors of this sequence are still open to discussion (3,4). Several arguments favor an embryonic origin consisting of an anomaly in the caudal hind brain development (5). Clinical arguments are based on the early postnatal observation of dysfunction of the structures innervated by the last cranial nerves (5,6). Embryologic arguments include (1) the potential role of the persistence of the vertical embryologic position of the tongue in the genesis of cleft palate and (2) the possible association of similar cleft palate and functional disorders in malformation syndromes related to embryologic anomalies of the migration of cephalic neural crest cells (7). (3) In mice, alterations of developmental genes active during hind brain segmentation, which is a highly conserved process in vertebrate embryogenesis, are responsible for anomalies of breathing and sucking rhythm after birth (8).

Feeding disorders are the most important functional symptom of children with PRS. They involve feeding skill disorders and esophageal disorders. The esophagus is innervated by the glossopharyngeal and vagal nerves and, consequently, is the ideal organ in which to search for anomalies of caudal brain stem control (9). For these reasons, since 1992, we have performed prospective investigations of the motor function of the esophagus in all children with PRS. These include clinical analysis of feeding and esophageal disorders and esophageal manometry. We found that anomalies of the oral and esophageal motor function in children with PRS, either isolated or associated with Stickler syndrome, are always present, both according to clinical features and manometric data. The prognosis, specificity, and significance of these oroesophageal disorders are discussed herein.

PATIENTS AND METHODS

Patients

Between 1992 and 1998, 87 children born with PRS were seen in the Pediatrics Department of the Hôpital Necker-

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Enfants Malades. To analyze only the esophageal disorders caused by PRS itself and not by associated neurologic profiles, apart from Stickler syndrome, children with PRS associated with other malformation were excluded in the study (n = 33). Children with Stickler syndrome were included because the neurologic course is similar to that in isolated PRS. Stickler syndrome is characterized by the variable combination of PRS, ocular anomalies (early myopia type), skeletal anomalies, hearing impairment, and specific facial features. Cognitive development is normal (10). We also excluded children whose functional symptoms were minor and did not necessitate hospital treatment other than surgical closing of the cleft palate (n = 16). Finally, we excluded children for whom the manometric plot was impossible to interpret (n = 2). Thirty-five children were included: 27 children had isolated PRS and 8 had Stickler syndrome. Seventeen were girls and 18 were boys, 1 was premature; birth weight ranged from 1210 to 4470 g (mean, 3020 g). None showed significant perinatal distress. They were referred to our pediatrics department at a mean age of 17 days (range, 0–63 days; median, 7 days).

The 35 children were classified into three groups of severity according to the Couly classification (5): grade I included minor feeding symptoms, permitting autonomous nutrition, and minor respiratory disorders (arterial oxygen saturation [Sa_{O_2}] > 90%, P_{CO_2} < 50 mm Hg); grade II included insufficient or dangerous bottle feeding necessitating nasogastric tube feeding, and moderate respiratory disorders (Sa_{O_2} > 90%, P_{CO_2} < 50 mm Hg); grade III included major upper airway obstruction resistant to oxygen (Sa_{O_2} < 90%, P_{CO_2} > 50 mm Hg), whatever the feeding disorders are.

Results were expressed as a percentage of the 35 children who were classified among the three groups as follows: grade I, n = 5; grade II, n = 10; grade III, n = 20.

Clinical Evaluation of Oroesophageal Disorders

The quality of sucking was clinically defined as normal, slow (bottle feeding lasting more than 45 minutes), slow and weak (insufficient for normal intake), or dangerous (associated with tracheal aspiration or cyanotic attack). Incidents during bottle feeding, including apparent life-threatening events (ALTE), pallor attacks, or tracheal aspirations, were noted. Feeding behavior during the first 3 months and at 8, 12, and 24 months was noted. Esophageal disorders were analyzed on the basis of the presence and complication of vomiting and regurgitation (i.e., resistance to gastroesophageal reflux medical treatment, esophagitis, or aspiration pneumonia).

Esophageal Investigations

Each child underwent manometry at least once at the age of 1 to 14 weeks (mean, 4.8 weeks). Thirteen infants (grades II and III only) underwent subsequent manometry between 2 and 7 months of age (mean, 4 months; median, 3 months) because, in the first years of the study, results of the second manometry contributed to the decision to return to normal feeding.

Manometric recordings were performed according to the continuous perfusion catheter technique (11). The infant, who underwent fasting for 4 hours, was placed in the lateral decubitus position. Medical treatment during this period was recorded. The infant received no sedation and was calmed only with a pacifier. Because of the risk of aspiration, only dry swallows were recorded. The catheter, placed through the nose or the mouth, was inserted as far as the stomach, and its position was checked by positive transmission of inspiratory pressures. The outside measurement catheters, diameter 2 to 3.3 mm, were of flexible silicone. Distal orifices were positioned so that each rotated 90° from its neighbor. Each canal was perfused at a constant flow rate of 0.5 ml/min using an Arndorfer-type pump. A multitrack polygraphic recorder was used to convert and amplify the signal and record it on a paper roll. The operator who performed the investigation performed an initial analysis of the plots. A second blind analysis was performed off-line by two different specialists, then all results were pooled.

The following esophageal motility variables were studied. Lower esophageal sphincter (LES) pressure was measured at the midrespiratory pressure, with intragastric pressure as the zero reference. Normal values for LES pressure were defined according to the literature (11–13) and to our own experience (24 ± 10 mm Hg). Lower esophageal sphincter relaxation in response to swallows was expressed as the mean percentage reduction in LES pressure (normal > 90%). Lower esophageal sphincter failure to relax was defined as an LES relaxation less than 80% of the basal LES pressure in more than 50% of the swallows. Evaluation of the upper esophageal sphincter (UES) included the relaxation of the UES (normal > 80%) and assessment of the coordination between UES relaxation and pharyngeal contractions. Esophageal contraction amplitude, duration, and velocity were measured in the esophagus body. Contractions were considered to be abnormal when their amplitude was too low (< 40 mm Hg) or too high (>160 mm Hg), or when they were not transmitted, triple peaked, or retrograde in more than 20% of contractions. Giant waves were defined as contractions with too high an amplitude (>160 mm Hg) and too long a duration (> 7 seconds).

Other esophageal investigations were performed in accordance with recommended guidelines, e.g., when regurgitation resisted classic gastroesophageal reflux (GER) treatment or when a surgical procedure was being considered (14). Eleven children underwent 24-hour esophageal pH recording with no antacid and with fragmented feeding. Thirteen children underwent esophagogastroradiography series. Eleven children underwent upper gastrointestinal fiberendoscopy. Association between manometric anomalies and clinical severity was tested using the Fisher exact test. Clinical and manometric results of children with isolated PRS and those with Stickler syndrome were not compared using statistical tests because the sample of children with Stickler syndrome was too small (n = 8).

RESULTS

Oroesophageal Clinical Data

The quality of sucking was abnormal in all cases. It was slow in six patients (17%), slow and weak in 14 patients (40%), and dangerous in 15 patients (43% of the whole group, 60% of grade II and 45% of grade III infants). Breast-feeding was tried in three patients and was ineffective in all of them. Thirty infants (86%) required nasogastric tube feeding, either initially exclusively (n = 23) or directly partially (n = 7). Mean

duration (± SD) of exclusive tube feeding was 5 ± 1.1 months, then partial tube feeding replaced exclusive tube feeding and was continued for an average of 4.6 months. The mean duration of direct partial tube feeding was 5.3 ± 1.2 months. The total duration of tube feeding was 8.6 ± 1.7 months (grade II: 5.9 ± 2.1 months, grade III: 10.4 ± 2.1 months). At the age of 8 months, 20 children were being fed normally (60%) and only grade III children still required tube feeding (72% of grade III). At the age of 12 months, 7 children (21%) still required tube feeding. At 24 months, all the children were being fed normally. Transient dysphagia with solid morsels after the age of 2 years was noted in three patients.

All 35 children experienced at least minor regurgitation, but 14 children (41%) had intractable regurgitation despite GER medical treatment, including prescription of a prokinetic agent (cisapride, domperidone, and metoclopramide were tested) and an antacid (ranitidine). Of these 14 children, 11 were grade III (55% of grade III). Because of this intractable regurgitation (n = 2) or after aspiration pneumonia related to GER (n = 3), five grade III children underwent successful Nissen fundoplication associated with gastrostomy.

Results of Esophageal Manometry

First Manometry

For all children except two (94%), results of manometry were abnormal. For the two patients in whom the results of this first manometry were normal, the procedure had been performed in the first week of life, and results of subsequent manometry at 3 months proved to be abnormal. Esophageal motor anomalies are summarized in Table 1. Lower esophageal sphincter hypertonia was noted in nearly 50% of the children (n = 15), from 40% to 45% in groups I and III, respectively. Only two cases of LES hypotonia were shown, both in group I. Lower esophageal sphincter failure to relax was observed in nearly 50% of the patients (n = 16) but not in grade I patients. Seven children had LES hypertonia and failure to relax. Esophageal dyskinesia was observed in 54% of the children, and the proportion was similar in the three groups. Giant waves were found in three patients, two in the grade II group and one in the grade III group. Relaxation of the UES was insufficient in five patients (14%), and the proportion was similar in the three groups. There were eight cases (23%) of abnormal pharyngoesophageal synchronism in groups grade III (25%), grade II (10%), and grade I (40%).

Second Manometry

A decrease in LES pressure was always observed between the first and second manometry. All LES hypertonia decreased and no new hypertonia appeared. Only once, an absence of LES relaxation appeared.

Results of Other Investigations

Nine esophageal pH recordings of 11 were normal (acid reflux time < 4%). Twelve radiography series of 13 showed gastroesophageal reflux without anatomic malformation. Seven endoscopies of 11 showed mild esophagitis (erythema = grade I).

Relations Between Clinical Data and Investigation

Three manometric abnormalities (LES hypertonia, LES failure to relax, and esophageal dyskinesia) occurred more frequently in high grades of gravity, with no statistical significance of the comparison of percentages, except for LES failure to relax. For this last criterion, no significant difference between grade II and III groups was observed. The other manometric criteria had no relation to clinical gravity (Table 1). The presence of LES hypertonia was not related to other clinical or manometric parameters. Children with abnormal pH recordings, radiography results, or endoscopy results had manometric patterns similar to those of the others. Manometric anomalies in children who received prokinetic treatment (cisapride [n = 15], domperidone [n = 4], or metoclopramide [n = 2]) were similar to those in children who did not.

Comparison of clinical and manometric results be-

TABLE 1. *Results of the first esophageal manometry*

	TOTAL (n = 35)	Grade I (n = 5)	Grade II (n = 10)	Grade III (n = 20)	*P*
LES hypertonia	15 (43%)	2 (40%)	4 (40%)	9 (45%)	NS
LES hypotonia	2	2	0	0	NS
LES failure to relax	16 (46%)	0	7 (70%)	9 (45%)	0.05
Esophageal dyskinesia	19 (54%)	2 (40%)	5 (50%)	12 (60%)	NS
Giant waves	3 (9%)	0	2 (20%)	1 (5%)	NS
Abs of UES relax	5 (14%)	1 (20%)	1 (10%)	3 (15%)	NS
P/E asynchrony	8 (23%)	2 (40%)	1 (10%)	5 (20%)	NS

LES, low esophageal sphincter; UES, upper esophageal sphincter; Abs of UES relax, absence of upper esophageal sphincter relaxation; P/E, pharyngoesophageal; *P:* Fisher exact test.

tween children with isolated PRS and those with Stickler syndrome showed that infants with Stickler syndrome had a higher clinical gravity and no difference in manometric results. No statistical test was possible because of the small number of children with Stickler syndrome (Table 2).

DISCUSSION

Our study shows that oroesophageal motor disorders are always present in a series of 35 infants with PRS, either isolated or associated with Stickler syndrome. This result may be a result of the fact that only children admitted to the hospital were included, corresponding to the most severe functional phenotypes. Nevertheless, whatever the grade of severity, none of the infants of this series had normal sucking skills. This high frequency of feeding disorders contrasts with the low frequency of such disorders in infants with cleft lip and palate (July, 2000, unpublished personal data). This suggests that the mechanical effect of the cleft palate is not a factor sufficient to explain PRS feeding disorders. These feeding disorders were sufficiently worrying to justify nasogastric tube feeding during the first months of life in a large proportion of the patients. Nevertheless, these disorders were transient, allowing an early optimistic prognosis. Esophageal disorders were less specific because regurgitation is common during the first months of life, but in this series, regurgitation was often resistant to usual GER medical treatment. Regurgitation in PRS is not optimally evaluated by classic GER investigations. Indeed, 80% of pH recordings in our series were normal, radiography series did not show significant anatomic anomalies, and none of the esophagitis cases was severe. These data suggest that a different mechanism may be involved in the esophageal symptoms of PRS than in those of usual GER. Esophageal disorders in PRS seem to be related to esophageal motor disorders, as shown by the high frequency of manometric anomalies. Three anomalies predominated: LES hypertonia, LES failure to relax, and dyskinesia of the esophagus body. Lower esophageal sphincter hypertonia and failure to relax seem to be unusual and specific signs. They have been described only in a few clinical pediatric settings: infant "nutcracker esophagus," (15) ALTE (13,16), vagal overactivity, and isolated swallowing disorders (17,18). All these situations have a common origin in neurovegetative instability (19). In one study, analysis of 380 pediatric manometries showed only 15 cases of LES hypertonia (3.9%), with a mean age of onset of 2 months and clinical signs of painful regurgitation intractable to medical treatment, ALTE, vagal overactivity, and swallowing disorders. The authors noted spontaneous regression of clinical disorders and a trend toward normal manometric results (18). These data are similar to those of our series. In addition, after surgical vagotomy in adults, manometry can show a significant decrease in LES pressure (20). Theoretically, esophagogastric prokinetic agents may have an impact on LES pressure (21). Methylcholine carbamate, metoclopramide, and domperidone may increase basic LES pressure (22). The action of cisapride on LES pressure is controversial (23). In our series, LES hypertonia occurred as frequently in children prescribed prokinetic agents as in the others. Therefore, it is likely that they do not change the manometry result. However, because there is some doubt, we are performing all esophageal manometry without treatment.

TABLE 2. *Gravity grades and manometric results in isolated PR sequence and Stickler syndrome*

	Isolated Pierre Robin sequence (n = 27)	Stickler syndrome (n = 8)
Grade I	5 (18.5%)	0
Grade II	8 (30%)	2 (25%)
Grade III	14 (52%)	6 (75%)
LES hypertonia	12 (44%)	3 (37.5%)
LES failure to relax	12 (44%)	4 (50%)
Esophageal dyskinesia	15 (56%)	4 (50%)

LES, low esophageal sphincter.

Although occurring frequently in this series, dyskinesia of the esophagus body is difficult to interpret because it is a nonspecific feature, which can be observed in GER (24–26), a nonspecific neurologic impairment (27), or esophagitis (28,29). Nevertheless, in our series, a small number of children had an abnormal pH recording, esophagitis, or LES hypotonia, and none had inappropriate LES relaxation. Consequences of nonspecific psychomotor retardation on esophagus motility were excluded because all children included had a normal neurologic course. Therefore, esophagus body dyskinesia in this context might be considered to be a sign of disorders of central control of esophageal motility. Interpretation of manometric UES signs is also difficult because this sphincter moves during the examination (30) and requires more sensitive probes than the probes we used. Nevertheless, pharyngoesophageal asynchrony and achalasia of the UES were observed in 23% and 14% of the patients, respectively, and have not been observed in control groups of the same age using a similar procedure (31).

The manometric anomalies we described do not resemble those of classic GER, in which LES hypotonia and transient inappropriate relaxation of the LES were implicated (24–26,32–34). Neither do our manometric data resemble those observed in premature infants in whom initial LES hypotonia and progressive increase in LES pressure with age are described (35). Therefore, the manometric pattern in our children is not a problem of maturation delay. The manometric pattern we described has features common to esophageal achalasia. However, esophageal achalasia is rare in neonates and involves hypoperistalsis of the entire esophagus.

Thus, the manometric pattern in infants with PRS described here is unusual and suggests a defect in the central control of esophageal motility. This hypothesis is consistent with the frequency of clinical orodigestive disorders of the children in this study. Sucking, swallowing, and esophageal motility are integrated functions in central pattern generators of the brain stem. These central pattern generators are located in the reticular network of the caudal brain stem, receiving afferent fibers mainly from the buccopharyngeal, esophageal, and laryngeal region, and the corticosubcortical regions, and sending efferent fibers to nuclei of cranial nerves (V, VII, IX, X, and XII) (9). We suggest that an early defect of this network function could be responsible for a decrease in fetal sucking and swallowing movements, thereby explaining the anatomic and functional features of children with PRS, especially those born without other malformations or neuromuscular disorders. In Stickler syndrome, intrinsic mandibular hypoplasia may be suggested as the primary feature (3). This hypothesis may explain the tendency of children with Stickler syndrome to have more severe disease than the whole group. It is likely that the two mechanisms, osseous and functional, may be present to produce PRS in Stickler syndrome.

At approximately 6 months of age, the voluntary oral phase of mastication begins, involving maturation of cortical afferences (36). Thus, children of this study have transient feeding disorders that improve at the end of the first year of life with development of the voluntary phase of feeding skills. Similarly, our results show that manometric anomalies improve between the first and the second manometry procedure, i.e., after 4 months of age. This finding is important because manometry in PRS must be interpreted as a function of age. These results have practical implications in the management of feeding disorders in children with PRS who need effective artificial feeding to prevent nutritional and respiratory complications so that they remain in good physical condition until the disorders improve.

Statistical correlation between the manometric anomalies we consider to be specific and clinical gravity was only observed for LES failure to relax, which was mainly observed in children who required nasogastric tube feeding (groups grade II and grade III). Lower esophageal sphincter hypertonia frequency of occurrence was similar in all groups. However, comparison of percentages in such small samples has poor significance. In addition, these manometric anomalies were noted in only 50% of the group. This may be because of a lack of sensitivity of the manometric technique or because other parameters influence the sucking abilities of these children. Finding those anomalies leads to additional carefulness in the feeding observation of PRS children. Despite its lack of sensitivity, esophageal manometry in PRS might provide relevant answers regarding PRS mechanisms, revealing an original pattern of LES anomalies resembling ortho- or parasympathetic dyscontrol of the esophagus. These results encourage further research of the embryonic cause of this hind brain dysfunction in experimental models. Further studies are also necessary in children with PRS, to improve the materials and conditions of manometry and to improve correlation between clinical data and investigation. Lastly, pharmacologic studies to identify substances that can modify esophageal motility must be performed to improve clinical treatment of these children.

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