Gastroesophageal Reflux in Severe Cases of Robin Sequence Treated With Nasopharyngeal Intubation

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Objective: **To study the prevalence of abnormal gastroesophageal reflux in infants with Robin sequence who had severe respiratory obstruction treated with nasopharyngeal intubation and to evaluate the efficacy of nonsurgical treatment.**

Design: **Longitudinal prospective study.**

Setting: **Hospital de Reabilitação de Anomalias Craniofaciais, University of São Paulo, Brazil.**

Patients: **Twenty infants with severe isolated Robin sequence treated with nasopharyngeal intubation.**

Interventions: **We performed 24-hour esophageal pH monitoring on each child at 2, 4, and 6 months of age. Respiratory and feeding status were evaluated. We considered abnormal gastroesophageal reflux as reflux index values above the 95th percentile of the Vandenplas reference for normal children.**

Results: **The prevalence of reflux index above the 95th percentile at the first exam was 6/20, a value significantly higher than the reference (5/103, $p < .01$). At the second and third exams, reflux index values were decreased. Ninety percent of the infants showed improvement of respiratory difficulty and developed oral feeding capacity.**

Conclusions: **The prevalence of abnormal gastroesophageal reflux is higher in infants with severe cases of Robin sequence than in normal infants. Nonsurgical procedures improved respiratory and feeding difficulties of most of these infants.**

KEY WORDS: *airway obstruction, cleft palate, gastroesophageal reflux, Pierre Robin sequence, swallowing disorders*

Robin sequence (RS), defined as retromicrognathia and glossoptosis, with or without cleft palate, is characterized clinically by obstruction of the upper airways and respiratory and feeding difficulties, which are more frequent and more severe during the first months of life. This anomaly may arise as an isolated entity (isolated Robin sequence [IRS]), as a component of a known syndrome, or in association with other malformations that do not characterize a known syndrome (Shprintzen, 1992). The clinical expression of RS is quite heterogeneous, ranging from a discrete respiratory and/or feeding difficulty to severe crises of asphyxia and severe dysphagia, requiring rapid medical intervention for the survival of the child (Marques et al., 2001a; Marques et al., 2001b).

Prolonged nasopharyngeal intubation (NPI) has been used as a treatment modality in infants with RS who present with crises of cyanosis and/or apnea and/or excessive respiratory effort. This procedure is used even in cases with severe respiratory obstruction (Freeman and Manners, 1980; Marques et al., 2001a; Marques et al., 2001b; Marques et al., 2004; Marques et al., 2005; Marques et al., 2008). The efficacy of NPI in improving the respiratory difficulties of these infants has been demonstrated by different investigators (Freeman and Manners, 1980; Heaf et al., 1982; Marques et al., 2001b; Wagener et al., 2003, Anderson et al., 2007). Improvement of the respiratory difficulties may lead to improvement of feeding difficulties (Marques et al., 2001b; Marques et al., 2004; Marques et al., 2005; Marques et al., 2008).

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Manometric studies have demonstrated motor dysfunction of the upper digestive tract of infants with RS (Baudon et al., 2002). Some studies have reported a predisposition of infants with RS to abnormal gastroesophageal reflux (AGER) (Dudkiewicz et al., 2000; Marques et al., 2001a; Marques et al., 2001b). According to these authors, the respiratory obstruction and the consequent inspiratory effort may lead to an increase in intrathoracic negative pressure and thereby trigger gastroesophageal reflux. Other investigators have demonstrated the presence of AGER in small infants with RS and the occurrence of its improvement after the treatment of respiratory obstruction with osteogenic distraction of the mandible (Monasterio et al., 2004). However, few studies have evaluated AGER in RS and its relation to the treatment of respiratory and feeding difficulties.

The objective of the present study was to assess the following aspects in severe cases of RS treated with NPI: (1) the prevalence of AGER during the first 6 months of life; (2) the length of time of NPI use, the age at the beginning of exclusively oral feeding, and their correlation with the prevalence of AGER; (3) the efficacy of nonsurgical procedures for the improvement of respiratory and feeding difficulties.

Methods

The study was conducted on 22 infants with severe IRS aged 60 days or less who were admitted to Hospital de Reabilitação de Anomalias Craniofaciais da Universidade de São Paulo (HRAC-USP) and treated with NPI. Preterm infants, infants with genetic syndromes, neurological problems, or other associated malformations that might aggravate their general condition were excluded from the study. Two infants missed scheduled visits because they came from distant localities, and their families had socioeconomic difficulties that prevented them from returning to HRAC-USP at the frequency required by the study. Thus, they were excluded from the investigation. The remaining 20 infants completed the study and represented the total sample.

The study was approved by the Research Ethics Committee of HRAC-USP, and all caretakers gave written informed consent for infants' participation in the study.

The studied infants were classified as being severe cases, according to Sousa et al. (2003), when they presented with recurrent crises of pallor and/or cyanosis and/or apnea, O_2 saturation $<90\%$ measured by continuous pulse oximetry with an oxygen requirement to improve this condition, and severe feeding difficulties for which feeding tubes were necessary.

The NPI was performed during the first days of hospitalization and consisted of a silicone tube, usually employed for tracheal intubation and adapted for NPI as follows: cut at the level of 9 cm, introduced 7 to 8 cm through the nostril, fixed with surgical tape, cut 1 cm outside the nostril and kept positioned slightly above the epiglottis (Marques et al., 2001b; Marques et al., 2005). The position of the NPI tube was confirmed by nasopharyngoscopy.

For the study of AGER frequency, each infant was prospectively evaluated by 24-hour monitoring of esophageal pH at 2 months $\pm$ 7 days, 4 months $\pm$ 7 days, and 6 months $\pm$ 7 days of age using a portable Digitrapper pHmeter (Medtronic Synetics, Stockholm, Sweden). For the calculation of normality and for the diagnosis of AGER, this instrument uses the statistical variations (in percentiles), determined for each age (in months) by Vandenplas et al. (1991). Episodes of reflux with values above the 95th percentile for normal children were considered to correspond to AGER. These values correspond to reflux index (RI) values >10 for the age range studied (2 to 6 months) (Vandenplas et al., 1991).

Severe RS cases (i.e., patients presenting with a drop in O_2 saturation) were considered to be emergencies, and NPI was performed immediately in order to relieve respiratory discomfort. Thus, all infants had been under NPI for more than 3 days (29.25 $\pm$ 19.51) at the first pH monitoring. During the exam the infants were hospitalized for 24 hours. All infants used nasopharyngeal intubation at the first pH monitoring. The tube for NPI was left in one of the nostrils to guarantee the patency of the airways while the pH probe was introduced into the other nostril. When the infant needed to be fed by tube, a nasogastric tube was introduced in the nostril with the pH probe at the time of feeding only and was removed afterward. At the second and third pH monitoring (at 4 and 6 months of age) the respiratory discomfort of most infants had improved with development and NPI was no longer required. During the exams the infants were fed every 4 hours. All infants received formula milk (NAN 1 [Nestlé Infant Nutrition, Brazil]) before and during the first, second, and third 24-hour pH-monitoring procedures in order to guarantee gastric acidity and make the results of pHmetry more reliable.

For ethical reasons, the infants who presented with RI values of more than 10 ($>$95th percentile of the normal reference) received drug treatment (ranitidine and domperidone) and postural treatment (elevated decubitus). If they were still using a nasogastric tube, this was replaced with a duodenal tube. The medications were discontinued 10 days before the subsequent 24-hour pH monitoring and were reintroduced only if this exam showed RI > 10.

Improvement of respiratory discomfort with NPI was considered to have occurred when O_2 saturation, measured by continuous pulse oximetry, was maintained above 90% in ambient air (with no oxygen requirement) during 24 hours; when the respiratory effort was reduced (reduction of pallor and cyanosis crises, of intercostal and furcula retraction and of inspiratory noise characteristic of glossoptosis observed by pulmonary auscultation); when it was possible to stimulate oral feeding and the child became comfortable with NPI, without accumulation of

secretions and saliva in the oral and/or nasal cavity and/or in the tube for NPI.

After improvement of the infant's respiratory discomfort and training of the parents about the management of NPI and of feeding, the infant was discharged from the hospital. Return visits were scheduled according to a preestablished protocol: every 2 weeks until the definitive discontinuation of NPI, monthly until the definitive removal of the feeding tube, and according to the schedule described above for pH monitoring.

The definitive discontinuation of NPI was carried out according to the protocol of the HRAC-USP (Marques et al., 2001b; Marques et al., 2005): After discharge from the hospital, return visits to the hospital were scheduled every 15 days during its continuous use. At each return the infant was hospitalized for 24 hours for observation, and the definitive removal of NPI was performed only when, in the absence of the NPI, O_2 saturation remained above 90% in ambient air for 24 hours with no onset or worsening of respiratory discomfort. Otherwise, NPI was maintained until reevaluation on subsequent return visits.

For the definitive removal of the feeding tube, the HRAC-USP protocol also was followed (Marques et al., 2005; Marques et al., 2008): The tube was removed only when the child demonstrated the ability to ingest 70% of the volume of milk recommended for his or her age within 30 minutes, without the occurrence of choking or a fall in O_2 saturation during oral feeding.

Age at hospitalization, length of time of NPI use, age at the beginning of exclusively oral feeding, and length of time of hospitalization were determined for the evaluation of the clinical condition.

Statistical Analysis

The Fisher exact test (Fleiss et al., 2003) was used to compare the incidence of RI > 10 (AGER) in infants with RS with that observed by Vandenplas et al. (1991) in normal children at each studied age. The relationship between RI and disease severity, expressed as the number of days of NPI use or as when (age in days) the exclusively oral feeding started, was evaluated by the Spearman correlation coefficient (Daniel, 1991) at each studied age.

The Mann-Whitney test (Daniel, 1991) was used to verify whether infants with AGER were different from those without AGER in relation to the length of time of NPI use. The median RI values for infants with RS were compared at each age with those obtained for normal children by Vandenplas et al. (1991). The Friedman test was used to compare RI values over time (Daniel, 1991).

Results

The final sample consisted of 20 infants with IRS, all of them with cleft palate, admitted to HRAC-USP at 2 months of age or younger, identified as serious cases according to the classification of clinical severity (Sousa et al., 2003). All infants were using nasogastric tubes for feeding at admission to the hospital.

TABLE 1 Reflux Index (RI) Percentiles According to the Age of Infants With Robin Sequence (RS) and of Normal Children (Vandenplas et al., 1991)

Percentile—RI	*RS—Age (mo)*			*Normal Children*
	2 (n = 20)	*4 (n = 20)*	*6 (n = 20)*	*3 d to 1 y (n = 509)*
5	0.25	0.15	0.10	0
10	0.30	0.20	0.45	1
25	0.55	0.60	1.10	2
50	2.40	1.90	1.65	4
75	11.10	7.00	2.45	7
90	18.40	9.15	6.30	10
95	24.75	10.10	9.20	10

The prevalence of AGER (RI > 10) was 6/20 at the first 24-hour pH monitoring, a value higher than that detected by Vandenplas et al. (1991) in normal children (5/103) at 2 months of age ($p < .01$). In contrast, at the second 24-hour pH monitoring, performed on the IRS infants at 4 months of age, the RI > 10 proportion detected was 2/20, as compared with 2/41 detected by Vandenplas et al. (1991) in normal children, with no significant difference between studies ($p = .59$). At the third 24-hour pH monitoring, none of the 20 infants with IRS demonstrated AGER, as compared with 1/20 also reported by Vandenplas et al. (1991), with the difference, again, being nonsignificant ($p = 1.00$).

Table 1 compares the RI percentiles obtained at the three pH monitoring determinations with the corresponding percentiles obtained by Vandenplas et al. (1991) for infants aged 3 weeks to 1 year. There was no significant difference ($p = .71$) in the distribution of RI in infants with RS over time, but the values tended to fall with age. However, considering only patients with AGER (n = 6), the Friedman test detected significance ($p < .01$), and the corresponding multiple comparison procedure indicated a difference between the first and third 24-hour pH monitoring procedures. Table 2 presents the values of RI, number of acid episodes, number of prolonged episodes, the duration of the longest reflux in minutes, and respective medians at the first, second, and third 24-hour pH monitoring for patients with AGER, showing a marked fall of all these parameters from the first to the second and third pHmetry. Starting with the second pHmetry, these patients showed RI values comparable to those of normal individuals.

The means and standard deviations of age at hospitalization, length of time of hospitalization, length of time of NPI use, and age at the beginning of exclusively oral feeding were 31.0 ± 20.0 days, 17.0 ± 19.2 days, 39.5 ± 27.2 days, and 69.0 ± 53.2 days, respectively.

No correlation was observed between the length of time of NPI use and prevalence of AGER ($p = .33$) and between the length of time of NPI use and RI values at 2 months ($r = -.39$, $p = .11$), 4 months ($r = .01$, $p = .95$), or 6 months ($r = .12$, $p = .64$). Considering only children without AGER (i.e.,

TABLE 2 Reflux Index (RI), Number of Acid Episodes (Nep), Number of Prolonged Episodes (Nep > 5), the Duration of the Longest Episode in Minutes (Longest), and Respective Medians at the 1st, 2nd, and 3rd 24-Hour pH Monitoring for Robin Sequence With Abnormal Gastroesophageal Reflux at the First pHmetry

	1st pHmetry				*2nd pHmetry*				*3rd pHmetry*			
Infants	*RI*	*Nep*	*Nep >5*	*Longest*	*RI*	*Nep*	*Nep >5*	*Longest*	*RI*	*Nep*	*Nep >5*	*Longest*
1	11.6	64.0	58.0	32.0	4.6	237.0	1.0	9.0	0.2	1.0	0.0	2.0
2	29.2	114.0	18.0	33.0	1.3	27.0	0.0	3.0	1.1	21.0	0.0	1.0
3	20.3	99.0	18.0	22.0	10.1	53.0	6.0	32.0	0.0	0.2	0.0	0.0
4	10.6	56.0	2.0	24.0	2.0	27.0	1.0	8.0	8.9	92.0	7.0	20.0
5	16.5	23.0	4.0	26.0	0.2	8.0	0.0	0.0	1.3	2.0	1.0	13.0
6	15.4	59.0	7.0	22.0	3.1	20.0	2.0	7.0	1.9	17.0	1.0	6.0
Median	16.2	61.5	12.5	25.0	2.6	27.0	1.0	7.5	1.2	9.5	0.5	4.0

infants who did not receive antireflux medical treatment), a negative correlation was observed between the length of time of NPI use and RI values at 2 months ($r = -.55$, $p = .04$), and no correlation was observed at 4 months ($r = -.09$, $p = .76$) or at 6 months ($r = .08$, $p = .79$).

No correlation was observed between the age at the beginning of exclusively oral feeding and RI values at 2 months ($r = -.10$, $p = .70$), 4 months ($r = -.18$, $p = .46$), or 6 months ($r = .29$, $p = .24$).

In the present study, according to the preestablished and previously mentioned criteria, there was relief of respiratory discomfort and improvement in the ability to feed orally in 18 infants (90%) with the use of NPI. The two infants who did not improve with this procedure were submitted to tracheotomy and one of them to gastrostomy as well. No episodes of bronchoaspiration, pneumonia, or death occurred throughout the study.

Considering only the infants treated medically (without surgical procedures), 4/18 demonstrated AGER at the first 24-hours pH monitoring, as opposed to 5/103 in the reference series of Vandenplas et al. (1991), with the difference being statistically significant ($p < .01$).

Ninety-five percent of the sample progressed to exclusively oral feeding by the age of 69.9 ± 53.2 days, with 90% of the sample obtaining improvement of the respiratory and feeding difficulties just through medical procedures, with no need for surgical procedures. For the 18 infants treated only medically (90% of the sample), the mean time of hospitalization was 15.8 ± 8.2 days.

Discussion

Some studies (Spaulding et al., 1982; Boix-Uxoa, 1986; Badriul and Vandenplas, 1999; Peter et al., 2002) have suggested that the prolonged use of feeding tubes may increase the risk of the onset of gastroesophageal reflux disease (GERD). GERD has been defined as AGER with symptoms such as frequent vomiting, weight loss, pain, discomfort, irritability, aversion to feeding, or complications such as respiratory problems (Rudolph et al., 2001).

A clinical diagnosis of GERD is very difficult for infants with RS because these children can exhibit a higher frequency of vomiting, regurgitation, and poor weight gain resulting from the work of breathing, with consequent oropharyngeal dysphagia. This dysphagia may be aggravated by the tongue retroposition and the presence of the cleft palate, which predisposes to the inability to perform effective oral suction and to excessive air swallowing during feeding.

Due to the difficulty in characterizing GERD in infants with RS, abnormal values (AGER) were defined as values higher than the 95th percentile of the reference of Vandenplas et al. (1991) for the different pH-monitoring parameters, especially RI.

In the present study, the treatment with NPI before the first pHmetry may have interfered with the result regarding the prevalence of AGER in IRS. If we consider respiratory obstruction to be a factor triggering GER, we may state that, if we had not started treatment of airway obstruction before the first pH monitoring, the prevalence of AGER might have been even higher that that observed.

The first pH monitoring was performed at 2 months because gastric acidity is well established and the cardia is more developed at this age, making the results of pHmetry more reliable (Rudolph et al., 2001; Lopez-Alonso et al., 2006). The regular intervals between the exams facilitated the statistical analysis.

Considering the high prevalence of AGER at the first examination of the sample, the reduced prevalence on the occasion of the subsequent exams and the distribution of RI values similar to those of normal infants, we cannot exclude the possibility that the antireflux medication alone reduced RI values, but the marked fall of these values and other pHmetry parameters from the first 24-hour pH monitoring procedure to the subsequent ones in cases with AGER (Table 2) may suggest that the opening of the airways reduces AGER in combination with the antireflux treatment.

There are no studies in the literature defining the length of time of feeding tube use that will predispose a small infant to AGER. In the present study, there was no correlation between the time of use of the feeding tube (i.e., age at the beginning of exclusively oral feeding) and the RI values detected at the first, second, and third pH monitorings; although, high RI levels were detected at the first pH monitoring compared with the values obtained for 2-month-old normal infants. These values decreased with

age; although, part of the sample continued to have a nasogastric tube after 2 months of age (69.9 ± 53.2 days). The fact that the correlation between the age at the beginning of exclusively oral feeding and RI was not statistically significant suggests that respiratory obstruction is a more important predisposing factor than feeding tubes in infants with RS younger than 6 months.

The series reported here does not represent IRS cases in general but rather cases considered to be serious according to the classification of clinical severity proposed by Sousa et al. (2003), which are at the center of major debates in the literature regarding appropriate treatment. Although some investigators supported the use of surgical procedures, such as osteogenic distraction of the mandible during the neonatal period in order to resolve the respiratory problems of these small infants (Denny and Kalantarian, 2002; Monasterio et al., 2004; Wittenborn et al., 2004; Burstein and Williams, 2005), others questioned the necessity of surgical procedures in this age range and described the efficacy of some medical procedures such as NPI (Freeman and Manners, 1980; Heaf et al., 1982; Marques et al., 2001; Wagener et al., 2003; Marques et al., 2004; Marques et al., 2005; Anderson et al., 2007).

With the experience acquired over time and the extensive practice with the management of NPI at HRAC-USP, this technique has been used on a large-scale basis for the treatment of severe cases of RS (Marques et al., 2001a; Marques et al., 2001b; Marques et al., 2004; Marques et al., 2005; Marques et al., 2008). This procedure, besides promoting anteriorization of the tongue, permits the child to breathe through the NPI tube. As a consequence of improved breathing, this procedure also can improve the ability to feed orally. The management of NPI is extremely simple and the procedure can be performed at home by the parents of the infant themselves after being duly trained by the nursing staff during hospitalization (Marques et al., 2001b; Marques et al., 2005). The ideal procedure would be to start the treatment during the very first days of life; however, because HRAC-USP is one of the major referral centers for craniofacial malformations in Brazil and receives patients from distant locations, very early treatment is not always possible.

For this study, we did not perform polysomnographies. Oximetry in combination with clinical evaluation (which corresponds to the pediatric practice in our institution) was sufficient to detect clinical improvement. Polysomnography is a more sophisticated method to assess respiratory patterns and may highlight differences among babies not identified by oxygen saturation monitoring. It would be interesting to perform polysomnography in future studies, comparing RS newborns with normal newborns in order to obtain more in-depth knowledge of the respiratory pattern of infants with RS, which was not the main objective of the present paper.

HRAC-USP does not perform osteogenic distraction of the mandible for the treatment of respiratory obstruction in RS. In this procedure, the mandible can be advanced by placing an appropriate distractor, with consequent anteriorization of the tongue in an attempt to clear the airways. Several studies have been conducted in order to refine this surgical technique for neonates (Denny and Kalantarian, 2002; Monasterio et al., 2004; Wittenborn et al., 2004; Burstein and Williams, 2005), but no consensus has been reached regarding the risks and benefits of this procedure for these individuals. Over the last few years, glossopexy surgery has been used less and less because the postsurgical results have been unsatisfactory for improvement of the respiratory obstruction, especially in severe cases. The prone position is used only in mild cases (Marques et al., 2001a; Marques et al., 2001b; Wagener et al., 2003; Nassar et al., 2006).

Prolonged use of NPI represents a support measure in neonatology that is used on a long-term basis in infants with RS (Marques et al., 2001; Marques et al., 2001a; Wagener et al., 2003; Nassar et al., 2006; Marques et al., 2008). This technique was developed in order to improve the respiratory and feeding difficulties of these neonates during a critical period of life while waiting for neuromotor development for the acquisition of the ability to anteriorize the tongue. This protocol can obviate the need for surgical procedures for airway clearance and their attendant risks (Marques et al., 2001a; Marques et al., 2001b; Wagener et al., 2003; Nassar et al., 2006; Anderson et al., 2007; Marques et al., 2008).

Considering respiratory obstruction to be a factor predisposing to AGER (Chiaretti et al., 1998; Dudkiewicz et al., 2000; Baudon et al., 2002; Monasterio et al., 2004), much of our data suggests the efficacy of the prolonged use of NPI for airway clearance: the lack of positive correlations between the length of time of NPI use and AGER, RI values of the entire sample at the first, second, and third 24-hour pH monitoring, and RI values of infants without AGER (who did not receive antireflux medical treatment and could develop AGER over time) at the three evaluations.

In the present study, the duration of hospitalization being less than 30 days was also a result in favor of treatment with NPI, as opposed to surgical treatments that may require more prolonged periods of hospitalization (Denny and Kalantarian, 2002).

The two infants who did not improve with NPI exhibited AGER at the first pHmetry with a high RI value. This value decreased after tracheostomy. Some questions can be raised regarding these infants who did not improve with the use of NPI. One is whether the severity of respiratory obstruction may lead to the onset of GERD, impairing the use of NPI, or if the presence of GERD may aggravate the respiratory obstruction, reducing the efficacy of NPI.

In conclusion, the prevalence of AGER was higher in severe RS cases than in normal infants. It could be reduced by airway clearance in combination with clinical treatment of reflux. Nonsurgical procedures improved both the respiratory and the feeding problems of 90% of the patients

with IRS and severe respiratory obstruction. Gastroesophageal reflux should be investigated in all severe cases.

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