UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM SAUDE DA CRIANÇA E DO ADOLESCENTE

ABORDAGENS DIAGNÓSTICAS NA AVALIAÇÃO DA GRAVIDADE DOS SINTOMAS CLÍNICOS RESPIRATÓRIOS EM PACIENTES COM SEQUÊNCIA DE ROBIN

TESE DE DOUTORADO

DENISE MANICA

Porto Alegre, Brasil
2016

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Orientador: Prof. Dr. Paulo José Cauduro Marostica

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Dedico este trabalho a todas as crianças

com Sequência de Robin e às suas famílias.

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Antoine de Saint-Exupéry, em "O Pequeno Príncipe

RESUMO

Introdução: Uma série de aspectos diagnósticos e terapêuticos relacionados à Sequência de Robin (SR) não possuem definição clara na literatura, conforme demonstrado em revisão sistemática presente nesta tese. Essas áreas de incerteza envolvem os métodos de classificação do grau de glossoptose por meio da endoscopia de via aérea (EVA), a associação com manifestações clínicas e a avaliação polissonográfica.

Objetivos: Avaliar, a partir de um estudo transversal aninhado em uma coorte, a associação entre duas classificações de glossoptose e a severidade dos sintomas em pacientes com SR, além de determinar a acurácia dessas classificações na determinação de pacientes com maior gravidade clínica. Avaliar a associação entre parâmetros de polissonografia e graus de gravidade de manifestações clínicas.

Métodos: Os pacientes com diagnóstico de SR tiveram suas manifestações clínicas classificadas conforme Cole *et al*. Foram submetidos à endoscopia do sono e as imagens foram classificadas de acordo com Yellon e De Sousa *et al* por pesquisador cegado. Os pacientes que não necessitavam de suporte ventilatório foram submetidos à polissonografia.

Resultados: Os resultados obtidos foram apresentados em quatro trabalhos: Artigo 1, aceito para publicação: revisão sistemática; Artigo 2, publicado: Associação entre classificação endoscópica da glossoptose e manifestação clínica grave: neste trabalho, um total de 58 pacientes foram incluídos. A probabilidade de apresentar sintomas graves conforme classificado por Cole *et al* foi maior nos pacientes Yellon grau 3 (68,4%, P=0,012) e de Sousa *et al* moderado e grave (61,5% e 62,5%, respectivamente, P=0,015) do que nos graus mais leves de obstrução; Artigo 3, submetido: Performance diagnóstica das classificações endoscópicas: neste trabalho foram incluídos 80 pacientes. A sensibilidade (Y: 56.2% x S: 28.1%, P<0.001) e a especificidade (Y: 85.4% x S: 93.8%, P=0.038) na identificação de

sintomas clínicos graves foram estatisticamente diferentes entre as classificações de Yellon e de Sousa *et al*. Calculou-se a Razão de Chances Diagnóstica para Yellon (RCD: 7,53 95%CI 4.15-10.90) e de Sousa (RCD: 5,87 95%CI 1.86-9.87). As diferenças encontradas não foram significativas (P=0,92); Artigo 4, submetido: Associação entre parâmetros polissonográficos e as manifestações clínicas conforme Cole *et al*. Determinou-se a Razão de Chances para cada variação nos seguintes parâmetros: índice de dessaturação (1.27; 1.07-1.51; R^2=19.8%; P=0.006), índice de apneia e hipopneia (1.13; 1.01-1.26; R^2=12.5%; P=0.02), média de saturação de oxigênio (0.16; 0.05-0.52; R^2=22.6%; P=0.002), nadir de saturação (0.73; 0.56-0.96; R^2=10.0%; P=0.02), porcentagem de tempo com saturação menor que 90% (9.49; 1.63-55.31, R^2=37.6%; P=0.012) e porcentagem de tempo com obstrução (2.5; 1.31-4.76; R^2=25.1%; P=0.006).

Conclusões: As alterações na EVA estão associadas com a gravidade das manifestações clínicas. Ao se aprofundar a abordagem de análise sob uma perspectiva diagnóstica, demonstrou-se que as classificações de Yellon e de Sousa *et al* possuem uma baixa sensibilidade, porém uma alta especificidade. A porcentagem do tempo com saturação menor que 90%, porcentagem do tempo apresentando obstrução e média de saturação de oxigênio durante o sono foram os parâmetros polissonográficos com a maior associação com as manifestações clínicas. Assim, recomenda-se que a avaliação endoscópica da via aérea em pacientes portadores de SR seja realizada com intuito de estratificar a gravidade, mas não para triagem diagnóstica. Da mesma forma, recomenda-se que os parâmetros acima destacados da polissonografia, sejam especialmente considerados no acompanhamento desses pacientes.

Palavras-chave: obstrução de via aérea, fenda palatina, laringoscopia, mandíbula, Síndrome de Pierre Robin, retrognatia

ABSTRACT

Introduction: Several diagnostic and therapeutic aspects concerning Robin Sequence (RS) are not clearly defined in medical literature, as demonstrated in a systematic review included in this thesis. These areas of uncertainty comprehend methods of glossoptosis degree classification, its association with clinical manifestations and polysomnographic evaluation.

Objectives: A cohort nested cross-sectional study was done to evaluate the association of two different glossoptosis classifications with symptom severity in RS patients, while determining its accuracy for the identification of severely symptomatic patients. The study also aimed to evaluate the association between polysomnographic parameters and clinical symptom severity.

Methods: RS patients had their clinical manifestations classified according to Cole et al. They were also examined with flexible fiberoptic laryngoscopy (FFL) and recordings were classified according to Yellon and De Sousa et al classifications by a blinded researcher. Those patients not needing ventilator support underwent polysomnographic testing.

Results: Overall results were divided into four distinct articles: Article 1, accepted for publication: systematic review; Article 2, published: Association between glossoptosis endoscopic classification and severe clinical manifestations: in this article, a total of 58 patients were enrolled. The probability of presenting severe clinical findings according to Cole et al classification was higher in patients classified as Yellon grade 3 (68.4%, P=0.012) and De Sousa et al moderate or severe levels (61.5% and 62.5%, respectively, P=0.015) than in milder degrees of obstruction. Article 3, submitted: Diagnostic performance of endoscopic classifications: in this article, additional 22 patients were enrolled, summing up 80 patients. The sensitivity (Y: 56.2% x S: 28.1%, P<0.001) and specificity (Y: 85.4% x S: 93.8%, P=0.038) in the identification of severe clinical symptoms were statistically different between classifications of Yellon and De Sousa et al. A Diagnostic Odds Ratio was computed for

Yellon (DOR: 7.53 95%CI 4.15-10.90) and De Sousa et al (DOR: 5.87 95%CI 1.86-9.87). No relevant differences were found between them (P=0.92). Article 4: submitted: Association between polysomnographic parameters and obstructive airway symptoms: odds ratios for severe clinical findings were computed for the variation of polysomnographic parameters: Dessaturation Index (1.27; 1.07-1.51; R^2=19.8%; P=0.006), Apnea/Hypopnea Index - AIH - (1.13; 1.01-1.26; R^2=12.5%; P=0.02), Sleep Mean Oxygen Saturation (0.16; 0.05-0.52; R^2=22.6%; P=0.002), Oxygen Saturation Nadir (0.73; 0.56-0.96; R^2=10.0%; P=0.02), Percentage of time under oxygen saturation of 90% (9.49; 1.63-55.31, R^2=37.6%; P=0.012) and Percentage of Time Presenting Obstruction (2.5; 1.31-4.76; R^2=25.1%; P=0.006).

Conclusions: FFL findings seem to have a fair association with the severity of clinical manifestations. However, this association was found to be probably a major influence of a high specificity, while observed sensitivity was less than would be desirable for diagnostic purposes. Percentage of time under 90% oxygen saturation, percentage of time with obstruction and mean oxygen saturation during sleep were the most associated parameters with clinical manifestations. Therefore, based on these findings, we would argue that airway endoscopic examination in RS patients should be approached aiming at clinical severity stratification, rather than for screening purposes. Also, we would recommend that those aforementioned parameters from polysomnography should be specifically addressed in the follow up of this peculiar group of patients.

Keywords: airway obstruction, cleft palate, laryngoscopy, mandible, Pierre Robin Syndrome, retrognathia

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LISTA DE ABREVIATURAS

AIH	Apnea and hypopnea index
AOS	Apneia Obstrutiva do Sono
DOR	Diagnostic Odds Ratio
EVA	Endoscopia de Via Aérea
FEES	Fiberoptic endoscopic evaluation of swallowing
FFL	Flexible fiberoptic laryngoscopy
HCPA	Hospital de Clínicas de Porto Alegre
MDO	Mandibular distraction osteogenesis
OSA	Obstrutive sleep apnea
PSG	Polissonografia
PSG	Polysomnography
RS	Robin Sequence
S	de Sousa
SR	Sequência de Robin
RCD	Razão de Chances Diagnóstica
VFSS	Videofluoroscopic swallowing study
Y	Yellon

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1. INTRODUÇÃO

A glossoptose é definida como a queda póstero-inferior da base da língua causando obstrução da via aérea. A parede da faringe posterior permanece em uma posição estática. É importante diferenciá-la da faringomalacia, na qual ocorre o colabamento concêntrico da faringe com movimentação de todas as paredes. Na glossoptose, apenas a base da língua move-se posteriormente (DONNELLY; STRIFE; MYER, 2000). O diagnóstico é sugerido pela presença de micrognatia na chamada Sequência de Robin (SR), podendo a hipotonia da musculatura da língua também resultar em glossoptose nas crianças com sequelas neurológicas.

Casos de associação entre alteração de mandíbula e fenda palatina têm sido descritos na literatura desde o século XIX (RANDALL; KROGMAN; JAHINS, 1965). Em 1923, Pierre Robin publicou, na literatura francesa, o primeiro de seus 17 artigos, chamando a atenção para essa associação que hoje leva seu nome e para os graves danos que a acompanham (ROBIN, 1923). A SR é, portanto, definida como a presença de micrognatia, glossoptose e disfunção respiratória. Fenda palatina pode estar associada (ROBIN, 1934).

O entendimento atual é que a associação de micrognatia, glossoptose e disfunção respiratória com ou sem fenda palatina é uma sequência, onde o evento primário é a micrognatia. Devido ao crescimento mandibular anormal, a língua cai sobre a faringe, obstruindo a via aérea. Durante o desenvolvimento palatal, a língua repousa sobre os processos palatinos. Em torno da sétima semana de desenvolvimento embrionário, a mandíbula começa a crescer ventral e inferiormente, tracionando a língua nessa direção. Isso permite que os processos palatais iniciem sua fusão do foramem incisivo em direção dorsal, ocorrendo o fechamento palatal por volta das 11 semanas. Há três principais hipóteses para explicar a sequência de eventos que ocorre na SR: 1. Hipoplasia da mandíbula, onde o defeito primário seria na cartilagem de Meckel, ocorrendo um desenvolvimento mandibular

insuficiente, que seria mais grave nos pacientes com fenda palatina (SCHUBERT, JAHN, BERGINSKI, 2005); 2. Deficiência muscular da orofaringe, onde se acredita que a atividade muscular oral fetal é necessária para o crescimento adequado da mandibula; 3. Compressão da mandíbula intra-uterina, especialmente naqueles que apresentam constrição fetal por algum motivo como oligodrâmnio e gestação gemelar (COTE *et al,* 2015).

A incidência de SR varia de 1/5000 (SCOTT & MADER, 2014) a 1/14000 (PRINTZLAU & ANDERSEN, 2004) nascidos vivos. Essa ampla variação pode ser resultado de diversidades regionais, mas é potencialmente consequência da falta de critérios diagnósticos claros, sendo possível encontrar na literatura até 15 diferentes definições (BREUGEM & COURTEMANCHE, 2010). Essa falta de clareza motivou a realização de um consenso que definiu SR como a presença concomitante de micrognatia, glossoptose e obstrução de via aérea. Fenda palatina é um achado comum e considerado característica adicional (BREUGEM *et al*, 2016).

Existem várias tentativas de classificar os pacientes com SR através de sintomatologia clínica (COLE; LYNCH; SLATOR, 2008; CAOUETTE; BAYET; LAROCQUE, 1994; COULY *et al,* 1988), de achados endoscópicos (YELLON, 2006; DE SOUSA *et al,* 2003; SHER, 1992) ou de associação com outras malformações (TAN; KILPATRICK; FARLIE, 2013), mas sem um consenso. É de suma importância a definição da melhor forma de classificar esses pacientes para que se tenha uma uniformidade principalmente para fins de pesquisa.

2. REVISÃO DA LITERATURA

Ao se realizar a busca na literatura sobre SR, encontram-se várias revisões sobre o assunto (COTE *et al,* 2015*;* BREUGEM *et al,* 2016*;* CIELO; MONTALVA; TAYLOR, 2016; MARQUES *et al, 2005*; OW & CHEUNG, 2008; ROTHCHILD; THOMPSON; CLONAN, 2008; SCHWEIGER, MANICA, KUHL, 2016; TAHIRI *et al,* 2014; KOCHEL *et al,* 2011), mas nenhuma enfocando a avaliação endoscópica desses pacientes, que cada vez mais têm sido parte integrante do diagnóstico das alterações obstrutivas em crianças. Tendo isso em vista, nos propusemos a fazer a revisão da literatura, através de revisão sistemática, que será apresentada a seguir sob a forma de artigo.

Após o artigo, apresentaremos uma revisão sobre o papel da polissonografia nos pacientes com SR.

2. 1 Artigo 1 em Inglês

The Role of Flexible Fiberoptic Laryngoscopy in Robin Sequence: a Systematic Review

Aceito no Journal of Cranio-Maxillo-Facial Surgery em 10/11/2016

Denise Manica, Cláudia Schweiger, Leo Sekine, Simone Chaves Fagondes, Gabriel Kuhl, Marcus Vinicius Martins Collares, Paulo José Cauduro Marostica.

Abstract

Objective: Systematically search literature for flexible fiberoptic laryngoscopy (FFL) application practice in Robin Sequence (RS) patients, on diverse clinical scenarios.

Data Sources: Pubmed, LILACS and SCIELO.

Review Methods: Systematic review using a sensitive search strategy focused on RS patients and FFL.

Results: There were 48 full text articles included in this systematic review. No summary meta-analytic measurement could be calculated due to heterogeneity of interventions and outcomes. FFL approaches were grouped in five topics, as follows: *Endoscopic classification:* no evidence on superiority of awake over light sedation and correlation of grading scales with symptoms severity. *Airway abnormalities:* high incidence of concomitant lesions besides glossoptosis. *Swallowing evaluation:* no validation against fluoroscopy (gold standard) yet. *Intubation aid for mechanical ventilation:* ultra-thin bronchoscopes improve success rates of intubation. *Treatment outcome monitoring:* no consensus on ideal parameters to be checked.

Conclusion: Some approaches have their roles already well established in the management of RS patients, like the evaluation of glossoptosis and associated lesions and as an intubation assistance tool, while others urge to be subject of further research, like the exact method of evaluation, its association with clinical manifestations, its role in swallowing investigation and as a postoperative success predictor.

Key words: endoscopy, intubation, laryngoscopy, mandible, Pierre Robin Syndrom

1. Introduction

Robin Sequence (RS) is a craniofacial abnormality involving mandibular hypoplasia and glossoptosis (with or without cleft palate), leading to life-threatening obstructive apnea and feeding difficulties during the neonatal period or even later in life. Respiratory disorders, generally associated with posterior displacement of the tongue and airway obstruction, require careful management and, in severe cases, may require extended treatment in neonatal intensive care units and surgical interventions to relieve airway obstruction. Those feeding and respiratory difficulties frequently continue well into childhood, affecting not only growth and development, but also impacting on long-term intellectual achievements. The diagnosis of RS depends on clinical features that are often easily recognizable, although eventual clinical manifestations can be very heterogeneous. Because symptoms severity is variable, treatment standardization is truly a challenge.

There have been reviews on RS (*Cielo., et al*, 2016, *Cote., et al*, 2015, *Kochel., et al*, 2011, *Marques., et al*, 2005, *Ow and Cheung*, 2008, *Rothchild., et al*, 2008, *Schweiger., et al*, 2016, *Tahiri., et al*, 2014), but none of them focused on endoscopic evaluation of these patients. The importance of discussing this matter is emphasized on a 2015 European survey (*van Lieshout., et al*, 2015) that revealed that, over 101 European clinics researched, only 63% used FFL and 16% used rigid laryngoscopy as a diagnostic tool in RS. In the present article, we highlight the role of flexible fiberoptic laryngoscopy (FFL) in RS in different management approaches described in the literature, concerning evaluation of glossoptosis itself and its classification, evaluation of airway abnormalities, swallowing evaluation, intubation aid and treatment outcome monitoring.

2. Material and methods

We have conceived a search strategy using the PICO (Population, Intervention, Control and Outcome) framework on different reference databases, using terms referring to RS, and FFL application. Databases included Pubmed (Medline), LILACS and SCIELO. Also, retrieved articles' references list, textbooks, abstracts from congresses and meetings were searched, and medical experts on the subject were consulted for ongoing relevant research. Search strategies for each database are available in Table 1.

Table 1. Search strategy (Accessed on 04/17/16).

Database	Search Strategy	References retrieved
Pubmed	(("Myopathy, congenital nonprogressive with Moebius and Robin sequences" [Supplementary Concept] OR "Pierre Robin Sequence with Facial and Digital Anomalies" [Supplementary Concept] OR "Robin Sequence with Distinctive Facial Appearance and Brachydactyly" [Supplementary Concept] OR "Corpus Callosum, Agenesis of, with Facial Anomalies and Robin Sequence" [Supplementary Concept] OR "Thrombocytopenia Robin sequence" [Supplementary Concept] OR "Ventricular extrasystoles perodactyly Robin sequence" [Supplementary Concept] OR "Radial defect Robin sequence" [Supplementary Concept] OR "Pierre Robin sequence with pectus excavatum and rib and scapular anomalies" [Supplementary Concept] OR "Robin sequence and oligodactyly" [Supplementary Concept] OR "Richieri Costa Pereira syndrome" [Supplementary Concept] OR "TARP syndrome" [Supplementary Concept] OR "Pierre Robin Syndrome"[Mesh] OR "Robin Sequence" OR "Pierre Robin Sequence" OR "Robin Syndrome") OR ("Micrognathism"[Mesh] OR "Clavicular Hypoplasia, Zygomatic Arch Hypoplasia, and Micrognathia" [Supplementary Concept] OR "Limb Deficiencies, Distal, with Micrognathia" [Supplementary Concept] OR "Trigonobrachycephaly, Bulbous Bifid Nose, Micrognathia, and Abnormalities of the Hands and Feet" [Supplementary Concept] OR "Corpus Callosum, Agenesis of, with Mental Retardation, Ocular Coloboma, and Micrognathia" [Supplementary Concept] OR "Ectrodactyly of Lower Limbs, Congenital Heart Defect, and Micrognathia" [Supplementary Concept] OR "Genito palato cardiac syndrome" [Supplementary Concept] OR "Micrognathia") OR ("Glossoptosis"[Mesh] OR "Cri-du-Chat Syndrome"[Mesh] OR "Glossoptosis") OR ("Mandibular Distraction Osteogenesis" OR "Mandibular Distraction")) AND ("Endoscopes"[Mesh] OR "flexible fiber optic nasopharyngoscopy" OR "flexible fiberoptic nasopharyngolaryngoscopy" OR "microlaryngoscopy" OR "bronchoscopy" OR "nasopharyngoscopy" OR "direct laryngoscopy" OR "airway endoscopy" OR "diagnostic laryngoscopy" OR "flexible fiber optic endoscopy" OR "flexible fiberoptic endoscopy" OR "endoscopic" OR "endoscopy")	118
LILACS	pierre robin AND endoscopy	2
SCIELO	pierre robin	21

Search results were peer reviewed by title and abstract by authors M.D. and S.C. separately. References considered to be included in full text appreciation were compared and agreed upon among reviewers. Where no agreement could be reached a third author (S.L.) took the final decision on inclusion. Included references where retrieved as full text articles to be further analyzed. After full text consideration, articles to be finally included on systematic review were again agreed upon by S.C. and M.D., with the aid of a third reviewer where necessary.

Included articles were then separated by FFL application and their contents were summarized altogether. As different methods, purposes and outcomes for the use of laryngoscopy were the aim of the various studies included it was not possible to compile data in a conventional meta-analysis. Therefore, a narrative discussion on separated topics was chosen as the format of this systematic review.

3. Results:

There were 48 full text articles included in this systematic review. The search process summary flowchart, as recommended by PRISMA (*Moher., et al*, 2009), is shown in Figure 1.

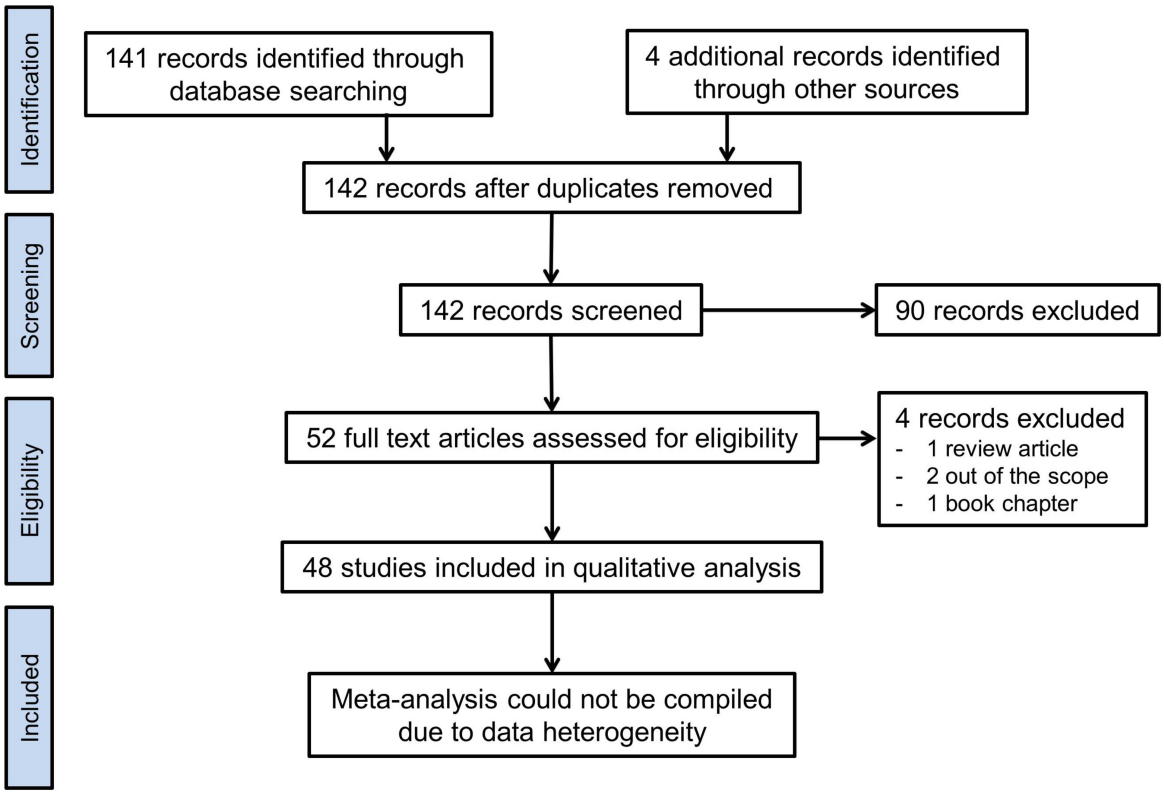

Figure 1. Flowchart as recommended by PRISMA (Moher, 2009).

Five main areas of application of FFL in RS patients were identified. Articles were grouped according to these criteria. They are discussed in separate sections ahead.

3. 1. Classification of endoscopic findings

Glossoptosis is defined by the backward and downward fall of the base of the tongue and this diagnosis is usually made during FFL with the patient breathing spontaneously either awake or lightly sedated. This is a subjective criteria and no objective way to measure it was reported yet. The classification of this defining aspect of RS is fundamental since it allows for an evaluation of surgical result among different patients and different surgeons. Besides that, a thorough classification would permit the discernment of clinical abnormalities, polysomnographic findings and swallowing characteristics.

Classifications systems found while searching the literature are described in detail in Table 2. Studies are scrutinized ahead.

Table 2. Different classifications systems of flexible fiberoptic laryngoscopy findings

Sher, 1986	
Type 1	True glossoptosis/ The tongue contacting the posterior pharyngeal wall below the soft palate
Type 2	The posterior contraction of the tongue towards the posterior pharyngeal wall, but the palate becomes sandwiched between the tongue and velum
Type 3	The medial contraction of the lateral pharyngeal walls
Type 4	Obstruction sphincteric
Schaefer, 2003	
Subdivision 1	No visible obstruction
Subdivision 2	Glottic/Infraglottic obstruction
Subdivision 3	Supraglottic/Tongue base obstruction
De Sousa, 2003	
Mild	The posterior region of the tongue does not touch the posterior wall of the pharynx
Moderate	The posterior region of the tongue touches the posterior wall of the pharynx but does not pressure it
Severe	The posterior region of the tongue pressures the posterior wall of the pharynx
Sorin, 2004	
Score 1	0 % of obstruction
Score 2	1-50% of obstruction
Score 3	51-75% of obstruction
Score 4	76-100% of obstruction
Bravo, 2005	
Grade 1	No obstruction
Grade 2	Adenoid tissue, lateral pharyngeal walls and tongue base obstruction between 25 and 50% of the aerial space
Grade 3	Adenoid tissue, lateral pharyngeal walls and tongue base obstruction between 50 and 75% of the aerial space
Grade 4	Adenoid tissue, lateral pharyngeal walls and tongue base obstruction more than 75%
Yellon, 2006	
Grade 0	Normal airway
Grade 1	Prolapse of the epiglottis against the posterior pharyngeal wall
Grade 2	Prolapse of the epiglottis and base of tongue with only the tip of the epiglottis visible and obliteration of the vallecula
Grade 3	Complete prolapse of the tongue against the posterior pharyngeal wall with no portion of the epiglottis visible

Sher *et al* (*Sher*, 1992, *Sher., et al*, 1986) described four mechanisms of obstruction in 33 patients with craniofacial anomalies, including RS, from birth to 24 years of age, examined while awake. Sher emphasized that other mechanisms of upper airway

obstruction were involved in RS, not only glossoptosis. The mechanism of airway obstruction could be useful to select the modality of therapy. This classification of airway findings (not glossoptosis) was used by other authors (*Argamaso*, 1992, *Kochel., et al*, 2011, *Marques., et al*, 2001, *Shprintzen and Singer*, 1992) and was considered crucial in the treatment choice.

De Sousa *et al* (2003) evaluated 56 children with RS, also examined while awake, without any type of sedation. They described a poor correlation between the severity of glossoptosis and the severity of clinical manifestations.

Schaefer et al (*Schaefer and Gosain*, 2003, *Schaefer., et al*, 2004) performed nasoendoscopy and bronchoscopy in RS patients under sedation in patients with desaturation during sleeping, feeding or wakefulness. They stratified these patients into three subdivisions, without a specific classification for glossoptosis.

Sorin *et al* (2004) evaluated 20 patients with RS with anesthesia by spontaneous breathing. The average compiled preoperative airway obstruction scores in decannulated patients were compared to those who remained tracheostomy dependent and were found not significantly different. They concluded that preoperative airway endoscopy alone is not a good predictor of the likelihood of successful decannulation after distraction osteogenesis.

Bravo *et al* (2005) evaluated 52 children with polysomnography and awake FFL classifying findings from categories 1 to 4. They successfully showed a significant correlation between FFL findings and apnea-hypopnea index, arousal index, snoring time and percentage of sleeping time spent at a measured oxygen saturation below 90%.

Yellon (2006) examined 14 children under light sedation and graduated the epiglottic and base-of-tongue prolapse from 0 to 3.

Some authors (*Genecov., et al*, 2009, *Miloro*, 2010, *Schaefer and Gosain*, 2003, *Schaefer., et al*, 2004) described the use of FFL in their evaluation, but did not mention any specific classification.

Concerning the awakened or sedated nature of the procedure, Berkowitz (1998) examined 110 neonates with symptoms suggestive of upper airway disease and proposed awake FFL. He reported that a definitive diagnosis was possible in 79 neonates, seven glossoptosis cases included.

He recommended direct laryngoscopy and bronchoscopy in situations where significant symptoms are present, but any of the following is true:

1. An inadequate view is obtained despite repeat FFL, no upper airway abnormality is found, the observed abnormality does not adequately explain the symptoms, or a functional upper airway abnormality is noted but an underlying structural cause is suspected;
2. A significant lower respiratory tract abnormality is clinically suspected;
3. General anesthesia is required form another procedure.

On the other hand, Ungkanont *et al* (1998) enrolled 62 neonates safely examined under conventional anesthesia and were an enthusiast of this endoscopic examination approach, as it allowed evaluation of the entire airway, bearing in mind that 77.4% of neonates in this cohort had more than one diagnosis. They reported RS as the most prevalent associated abnormality. Also Basart *et al* (2015) while studying awake FFL approach in RS patients concluded that this is not a reliable tool since the grading of findings such as “marked glossoptosis”, “mild glossoptosis”, “severity unknown” or “no glossoptosis” performed only fair to moderate inter-rater agreement and moderate intrarater agreement, but there was no comparison with a light sedated approach.

Mandell *et al* (2004) published their experience in airway endoscopy (flexible or rigid laryngoscopy) to confirm the tongue base collapse in 24 of a 26 patient cohort. They did not mention if the examination was performed while awake or under light sedation and also contraindicated mandibular distraction if a second airway lesion was identified.

Bell and Turvey *(2001)* shared experience on awake bronchoscopy preoperatively to locate the anatomic site of obstruction. They did not use any formal classification but stated that bronchoscopy was a valuable diagnostic tool and also could give rise to predictive information.

3. 2. Concomitant airway abnormalities

The diagnosis of concomitant airway anomalies at the time of diagnostic laryngoscopy defines if airway obstruction is only a consequence of glossoptosis or if there are other multiple sites of obstruction. Defining how much the presence of these abnormalities interferes in surgical success or establishing the diagnosis of alterations that could be approached simultaneously, as laryngomalacia, is fundamental in therapeutic planning of patients with RS.

Andrews *et al (2013)* described 23 of 83 RS patients (28%) with simultaneous upper or lower airway findings. These included laryngomalacia (53,3%), tracheal web (20%), vocal cord paralysis (13,3%), epiglottal collapse (6,7%) and infraglottal narrowing (6,7%). Planning of mandibular distraction osteogenesis was changed in all 23 cases, inasmuch as, according to the authors, in the existence of such concomitant airway malformations, distraction would be unlikely to be successful because it would not alleviate the abnormalities that might contribute to respiratory distress.

Cheng *et al (2011)* described six patients, all with associated airway problems which included congenitally hypoplastic epiglottis (2), laryngomalacia (2), unilateral choanal atresia (1) and long-segment tracheal stenosis (1).

Morovic (2004) described a prevalence of 19,4% of laryngomalacia in 31 RS patients.

Knapp *et al (2011)* showed a subglottic narrowing in 5 of 15 patients with RS (33%).

Waters *et al* (2005) reported a case of RS with double aortic arch and raised the attention to the importance of laryngobronchoscopy in any neonate with severe respiratory distress.

As shown, there is a high incidence of concomitant abnormalities in RS patients, emphasizing once more the need for endoscopic evaluation on these patients. Ching *et al* (2015) reported that anatomic abnormalities diagnosed by microlaryngoscopy and bronchoscopy were associated with a higher rate of tracheostomy, confirming the utility of preoperative airway evaluation.

3. 3. Swallowing evaluation

Feeding problems are frequent in children with RS and are thought to be secondary to both airway obstruction and associated cleft palate, if present. These definitely complicate daily management and sometimes behavior. Considering the morbidity and mortality related to dysphagia, early diagnosis of disorder extent is crucial in the management of these patients.

A fiberoptic endoscopic evaluation of swallowing (FEES), another reported use of FFL in RS, is an objective approach to evaluate swallowing with the advantage of not exposing the patient to radiation, as is the case for videofluoroscopic swallowing study (VFSS).

Marques *et al* (2010) evaluated 11 infants less than 2 months of age and showed a 72% risk of aspiration in the first evaluation that could be made less frequent when thickened milk was given, and also at subsequent evaluations. Pinheiro Neto *et al (2009)* evaluating eight patients reported moderate dysphagia in three patients.

Despite the importance of this evaluation, studies in this area are still very scarce.

3. 4. Intubation

Infants with RS are known to pose structural obstacles that render tracheal intubation a significant challenge. In the presence of micrognathia with temporomandibular joint ankylosis, intubation is even more challenging (*Zanaty., et al*, 2016). Appropriate preoperative evaluation and preparation of the patient with a difficult airway is paramount for successful endotracheal intubation. While evaluating such patients, examiner can predict a difficult intubation, anticipating the need for a fiberoptic bronchoscopic tracheal intubation (*Kleeman., et al*, 1987, *Lee., et al*, 2004, *Okawa., et al*, 2002).

In neonates, endoscopy assisted intubation was long limited by the size of conventional instruments. Currently, however, ultra-thin bronchoscopes make it feasible to use this technique even in newborns, with the adequately sized endotracheal tube placed over a gently lubricated 2.2 or 2.7 mm flexible bronchoscope (*Finer and Muzyka*, 1992). Another described alternative would be the use of a guide wire passed through the suction channel of a 3.6 fiberscope (*Howardy-Hansen and Berthelsen*, 1988, *Scheller and Schulman*, 1991, *Suriani and Kayne*, 1992). Also, orotracheal intubation using a fiberoptic endoscope through a laryngeal mask airway has been described (*Stricker., et al*, 2008).

Approaching RS patients with those techniques seems unequivocally indicated, inasmuch as it renders a relevant probability of success. Marston *et al* (2012) described a 63% demand of endoscopy assisted intubation using a 2.2 mm flexible fiberoptic bronchoscope in 35 newborns with RS. No significant difference in endoscopy requirement was observed between isolated and syndromic RS newborns. Blanco *et al* (2001) described 46 RS patients with challenging tracheal intubation, presenting an 80.4% of success on the first attempt, 15.2% on a second or third attempt and 4.3% of failures with the aid of 3.3 mm and 4.5 mm bronchoscopes.

3. 5. Treatment outcome evaluation

Mandibular distraction osteogenesis (MDO) is a common surgical correction procedure for RS patients. Surgical success is not readily predictive by symptomatology; therefore other approaches were proposed to quantify procedure results by endoscopic measures, while also attempting to predict long term success.

Sorin *et al* (2004) showed a significant change after distraction at the levels of the oropharynx and supraglottis. However, the average postdistraction airway scores in decannulated patients compared with those who remained tracheostomy dependent were not statistically different, suggesting that some children fail to advance to decannulation despite adequate mandibular distraction. Olson *et al (2011)* created standardized laryngoscopic measurements and compared pre and post MDO status and showed a significant increase in supraglottic space dimensions after MDO that was related to clinical improvement. Denny and Kalantarian *(2002)* described six patients in which FFL was performed under anesthesia before distraction. One patient did not undergo distraction because of other airway abnormalities. After distraction, patients remained under mechanical ventilation and the authors used bronchoscopy at the time of extubation. Heller *et al (2006)* studied five Treacher Collins patients and three Nager syndrome patients submitted to genioplasty distraction osteogenesis and hyoid advancement. They used the FFL to determine the position of the epiglottis at the time of hyoid advancement and after distraction to assess structural change in the airway. Follow-up endoscopy revealed that the epiglottis remained in a favorable elevated position. Izadi et al (2003) also used FFL to demonstrate improvement of glossoptosis before and after distraction. The criterion of improvement was the elevation of the tongue and epiglottis off the posterior pharyngeal wall. Monasterio *et al (2002)* compared pre and postoperative FFL and showed improvement in oropharynx airway collapse in 15 patients.

Preciado *et al* (2004) performed airway FFL before surgery, during the distraction process, and after decannulation under sedation and reported airway obstruction in percentages. They observed failure in only one of five patients with cerebral palsy.

4. Discussion

In this systematic review, different FFL applications were arranged in five groups. Some approaches have their usage already well established in the management of RS patients, while others still warrant further research. A summary of our findings is shown in table 3.

Table 3. Summary of findings.

Use of FFL in RS patients	Recommendation	Areas of Uncertainty
Glossoptosis evaluation	Highly recommended (Establish diagnosis)	Awake *versus* light sedation examination Proper classification to use
Airway abnormalities identification	Highly recommended	Indication for lower respiratory tract evaluation
Swallowing evaluation	Not established (Possible use in specific cases)	Performance compared to gold standard
Intubation aid	Highly recommended	None
Treatment outcome monitoring	Not established	Which parameters to consider in evaluation

FFL, flexible fiberoptic laryngoscopy. RS, Robin sequence.

There is uniform agreement on the need for a careful evaluation of the airway with FFL in all infants with RS, since a multitude of airway abnormalities may be present. Aside from the mechanical obstruction of glossoptosis, other factors can contribute to ventilation

compromise. There is a growing debate on whether awake (*Bravo., et al*, 2005, *de Sousa., et al*, 2003, *Sher*, 1992) or slight sedation (*Andrews., et al*, 2013, *Cheng., et al*, 2011, *Sorin., et al*, 2004, *Yellon*, 2006) endoscopic evaluation would be a better option for these patients. Côté et al (2015) recommend flexible laryngoscopy in the evaluation of all RS patients and rigid and/or flexible bronchoscopy prior to an already scheduled non-airway related surgical procedure, prior to surgical correction of tongue base obstruction in cases where non-invasive management fails and in cases of persistent obstruction despite surgical correction of tongue base obstruction. In our opinion, since the worst moment of obstruction in RS is during sleep, the drug-induced sleep endoscopy would be the best method to evaluate obstruction in RS patients, allowing a more physiologic and dynamic evaluation of the entire airway during sleep. Besides that, we understand that the information derived by the awake examination concerning the base of tongue is not accurate. Yet, the procedure obviously induce an amount of psychological stress and muscular tension that can lead to a tongue base positioning that is not representative of its real arrangement under rest and even more under sleep.

Attempts to classify glossoptosis severity were already reported (Table 2) although none specifically seems to be consensually accepted worldwide. Also, the predictive value on long term outcomes of those classifications was not yet evaluated. There is certainly a need for dedicated research on their informative value in a prospective context and their association with clinical and polysomnographic parameters. Polysomnography (PSG) provides objective information on the obstructive or central nature of the respiratory disorders and its severity. However, PSG does not provide information on the location of the obstruction. By defining their correlation with clinical and polysomnographic variables, we would also be able to weight their impact in the prediction of surgical success management.

RS patients can be divided according to their presentation in isolated RS, RS plus – associated with additional congenital malformations without a known specific diagnosis - and

syndromic RS (*Tan., et al*, 2013). RS can be associated with primary skeletal dysplasias and multiple congenital anomaly syndromes like arthrogryposis (*Laureano and Rybak*, 1990), CHARGE (*Roger., et al*, 1999) and Freeman-Sheldon Syndrome (*Okawa., et al*, 2002), neuromuscular conditions and chromosomal abnormalities like Cri-du-chat syndrome (*Chang., et al*, 2007). We know that these patients differ from each other, but we do not know exactly what are those differences, especially concerning therapeutic results and first choice treatments for each category. Probably, RS plus patients and syndromic patients have a higher incidence of concomitant lesions such as pharyngomalacia and laryngomalacia. It is imperative to better evaluate the impact of those concomitant lesions in surgical result and, in this context, differentiate those patients that would be best approached with alternative measures, like tracheostomy.

Endoscopy performance in the swallowing evaluation also needs to be further researched on, especially in pediatric population, as compared with the gold standard, videofluoroscopy.

5. Conclusion

The FFL has a fundamental role in RS patients, in the evaluation of glossoptosis and associated lesions and as an intubation assistance tool. However, extended research is still needed on the more precise method of evaluation, its association with clinical manifestations, and its role in swallowing investigation and as a postoperative success predictor.

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2.2 O papel da polissonografia na Sequência de Robin

Distúrbios respiratórios do sono, principalmente apneia obstrutiva do sono (AOS), são achados praticamente universais nos pacientes com SR. A morbidade associada à AOS é bem conhecida e envolve atraso no desenvolvimento, prejuízo nas funções intelectuais, *cor pulmonale* e até morte (BANGIYEV *et al,* 2016).

Métodos objetivos para avaliar a gravidade dessa obstrução da via aérea superior são essenciais na definição da melhor conduta. A polissonografia (PSG) é o padrão ouro para a detecção e quantificação da AOS. No entanto o seu papel na avaliação dos pacientes com SR não é bem definido.

Revisão recente sobre o assunto (REDDY, 2016) mostra que a literatura contempla estudos retrospectivos, a maioria utilizando a PSG para mostrar melhora de um ou mais parâmetros após intervenção cirúrgica. Detalhes sobre a forma de realização e estadiamento dos eventos respiratórios são incompletos ou simplesmente não relatados. Nos estudos que fornecem tais informações, vemos uma ampla variação de critérios.

A AOS em crianças é tipicamente caracterizada como leve quando IAH entre 1 e 5/h, saturação de oxigênio menor que 90% por 2 a 5% do tempo total de sono; moderada com IAH entre 5 e 10/h, saturação de oxigênio menor que 90% por 5 a 10% do tempo total de sono e grave com IAH maior que 10/h, saturação de oxigênio menor que 90% por mais de 10% do tempo total de sono (KATZ, MITCHELL, D`AMBROSIO, 2012). Tal definição não leva em conta as mudanças nos eventos respiratórios relacionadas à idade. A estimativa separada por idade (0- meses: índice de apneia obstrutiva 0,6 a 2/h; 5-6 meses: 0,4-1/h; 12 meses: menor que 0,5/h; 3 a 5 anos: menor que 0,1/h e 10 a 17 anos: menor que 0,1/h) (KATZ, MITCHELL, D`AMBROSIO, 2012) não inclui hipopneias e apneias centrais que fazem parte do IAH. Portanto, não temos claro qual a definição de AOS significativa em crianças. Ainda menos,

estudos que definam qual a melhor conduta conforme a gravidade da AOS nos pacientes com SR.

3. JUSTIFICATIVA

O diagnóstico de SR está associado a sofrimento das famílias que têm um filho com essa anormalidade. Da mesma forma, a comunidade médica vê esses pacientes como potencialmente graves mesmo após a correção do quadro obstrutivo, levando a abordagens desnecessárias e por vezes muito invasivas, o que reforça ainda mais o estigma dessas crianças. Isso sempre implicará uma preparação anestésica exagerada antes de qualquer procedimento, influenciará recomendações médicas sobre tratamento, possível crescimento da mandíbula, tempo de fechamento da fenda palatina se ela estiver associada. Dito isso, considera-se fundamental o esclarecimento sobre a melhor forma de avaliar esses pacientes para um diagnostico correto e permitir classificação e atenção adequadas. Isso permitirá uma uniformidade entre os estudos que possibilitará o melhor conhecimento do comportamento desses pacientes a longo prazo e da melhor forma de trata-los.

Ao realizarmos a revisão da literatura, concluímos que o papel da endoscopia de via aérea como método diagnóstico na SR e principalmente a correlação entre as alterações anatômicas encontradas no exame e a gravidade dos sintomas clínicos e achados polissonográficos não foram suficientemente estudados. Propusemo-nos a explorar melhor esse assunto, como apresentaremos ao longo desta tese no intuito de contribuir na formação do conhecimento a esse respeito.

4. OBJETIVOS

4.1 Objetivo Geral

Estudar pacientes pediátricos com SR atendidos no Hospital de Clínicas de Porto Alegre (HCPA), através da avaliação endoscópica de via aérea e polissonografia.

4.2 Objetivos Específicos

Realizar revisão sistemática sobre o papel da endoscopia de via aérea na SR.

Descrever a prevalência dos diferentes graus de glossoptose, diagnosticados por endoscopia, e a presença e gravidade da apneia obstrutiva do sono (AOS) em pacientes com SR.

Descrever a associação das classificações endoscópicas com a gravidade dos sintomas clínicos em pacientes com SR.

Descrever a acurácia das classificações endoscópicas na avaliação da gravidade dos sintomas clínicos em pacientes com SR.

Correlacionar os achados clínicos com a gravidade dos achados polissonográficos em pacientes com SR.

5. METODOLOGIA

5.1 Delineamento

Estudo de coorte prospectivo e revisão sistemática.

5.2 Amostragem

A amostragem foi consecutiva, incluindo todos os pacientes avaliados com diagnóstico de SR nos Serviços de Otorrinolaringologia, Cirurgia Craniomaxilofacial e Pediatria do HCPA no período de outubro de 2012 a junho de 2016. O diagnóstico da SR foi baseado em uma avaliação multidisciplinar. Os pacientes necessitavam preencher todos os critérios a seguir:

- Disfunção Respiratória: definida como qualquer sintoma de obstrução de via aérea seja na agitação, posição específica, alimentação ou repouso, reportada pelo cuidador ou observada no hospital e confirmada por polissonografia. Os pacientes com obstrução importante (em ventilação mecânica ou outro tipo de suporte ventilatório) não eram submetidos à polissonografia.
- Glossoptose: observada através da endoscopia do sono e definida, de acordo com Robin (1923; 1934), como a queda póstero-inferior da base da língua (Figura 1).

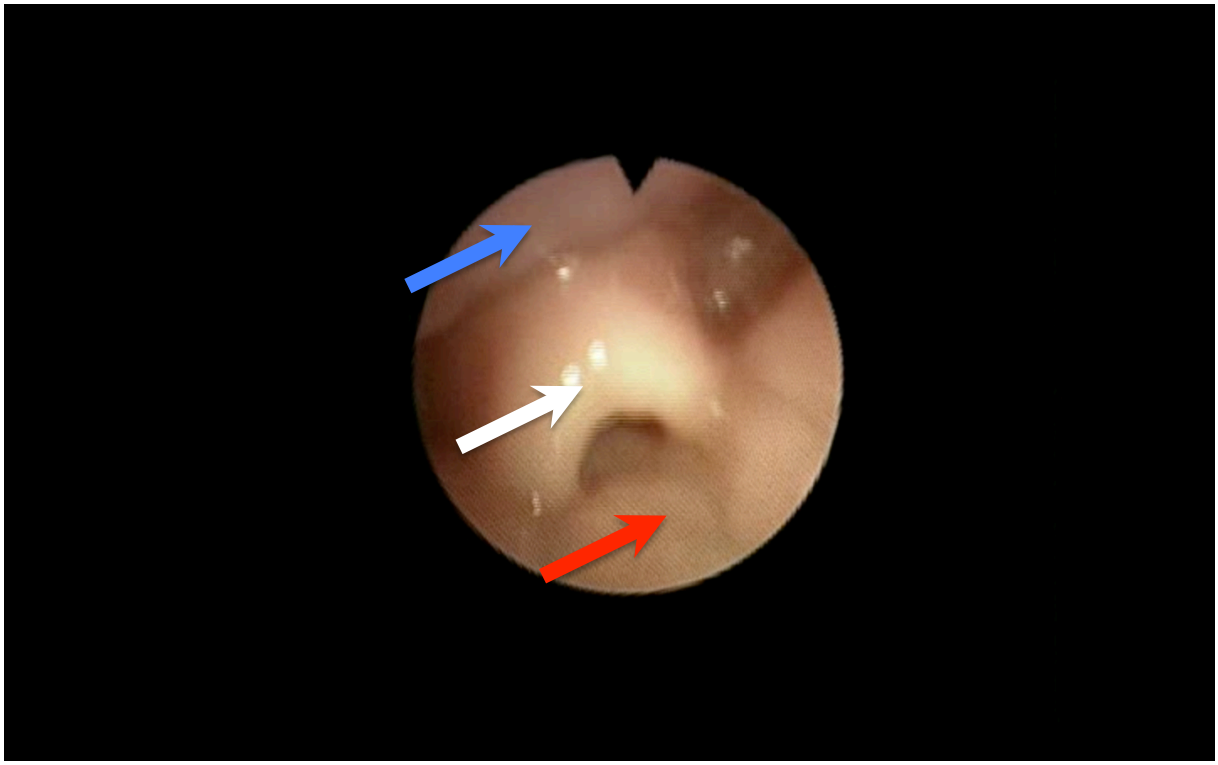

Figura 1. Glossoptose vista através da endoscopia flexível.

Seta azul: base de língua; Seta branca: epiglote; Seta vermelha: parede posterior da faringe.

- Micrognatia: definida no exame físico através de uma discrepância na relação maxilo-mandibular. Como não há critérios claros na literatura das medidas que definem micrognatia, os achados da tomografia computadorizada (Figura 2) são complementares para diagnóstico e fundamentais para planejamento cirúrgico.

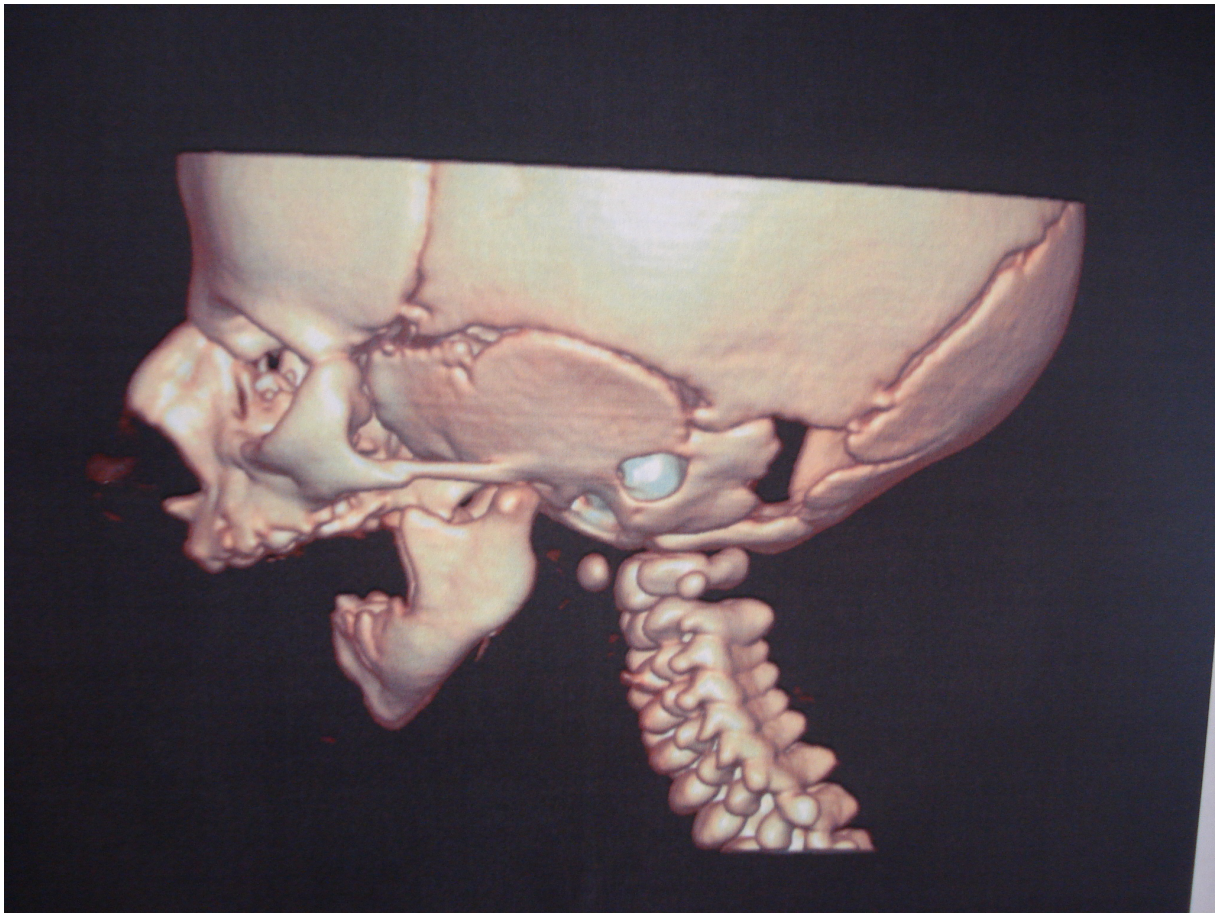

Figura 2. Micrognatia diagnosticada através de tomografia computadorizada

Após o diagnóstico, os pacientes eram divididos em três grupos de acordo com as malformações associadas:

- SR isolada;

- SR-plus (associada com outras malformações sem um diagnóstico sindrômico específico);

- SR sindrômica (TAN; KILPATRICK; FARLIE, 2013).

Além disso, o sistema de classificação descrito por COLE; LYNCH; SLATOR (2008) e baseado na gravidade dos sintomas foi aplicado em todos os pacientes:

- Grau 1: sem disfunção respiratória na posição supina;

- Grau 2: disfunção respiratória leve intermitente na posição supina e alimentação precipita algum desconforto respiratório;

- Grau 3: disfunção respiratória moderada a grave na posição supina, incapacidade de se alimentar por via oral.

Os dados referentes a sintomatologia, gestação, alimentação foram obtidos por meio do protocolo de inclusão (anexo 1).

5.3 Critérios de Inclusão

Foram incluídas todas as crianças com diagnóstico de SR no HCPA no período do estudo que tiveram autorização dos pais ou responsáveis para participar, através da assinatura do termo de consentimento livre e esclarecido (anexo 2).

5.4 Critérios de Exclusão

Não foram definidos critérios de exclusão.

5.5 Aspectos Éticos

O estudo foi aprovado pelo Comitê de Ética em Pesquisa do Grupo de Pesquisa e Pós Graduação do HCPA sob número 12-0513.

5.6 Técnica da Endoscopia de Via Aérea

A endoscopia de via aérea foi realizada no Centro Cirúrgico Ambulatorial ou no Bloco Cirúrgico do HCPA com o paciente em decúbito dorsal, sem hiperextensão cervical, sem cânula de Guedel, com anestesia geral sob ventilação espontânea, além de anestesia tópica na laringe com lidocaína a 1% para evitar laringoespasmo. A anestesia foi realizada por anestesiologista pediátrico, utilizando sevoflurano e/ou propofol. O exame foi realizado por médicos residentes do serviço de otorrinolaringologia com a supervisão de um dos pesquisadores (DM).

O exame inicia com a laringoscopia rígida para avaliação estática, palpação de estruturas e avaliação da dificuldade de exposição laríngea que foi classificada pelos autores em:

- Grau 0, sem dificuldade;
- Grau 1: dificuldade leve, comprometendo visualização do terço anterior das pregas vocais;
- Grau 2: dificuldade moderada, comprometendo visualização do terço posterior das pregas vocais;
- Grau 3: dificuldade grave, comprometendo visualização das aritenoides.

A exemplificação das diferentes laringoscopias pode ser visualizada na figura 3.

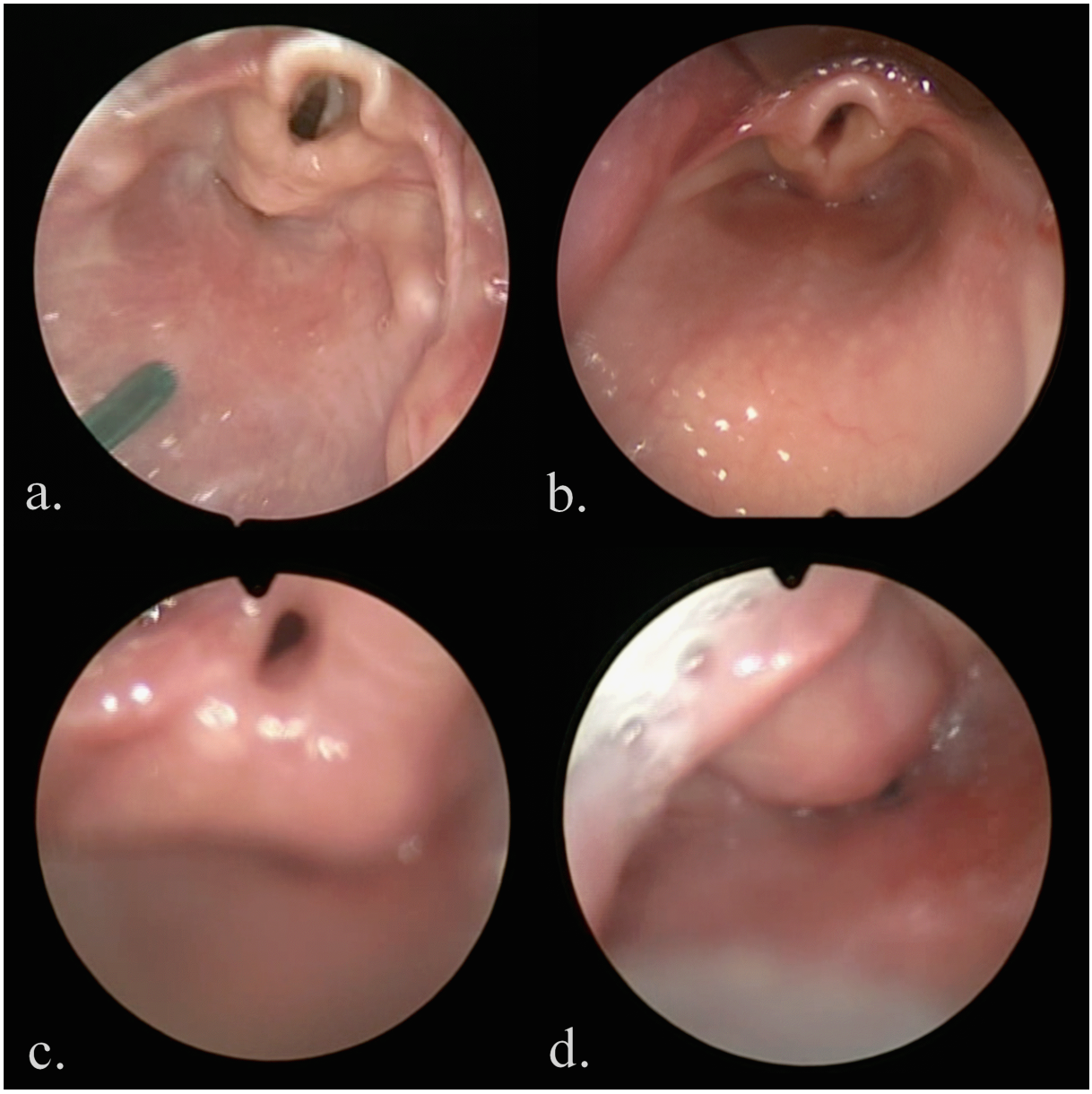

Figura 3. Diferentes graus de dificuldade de laringoscopia: a. Grau 0: sem dificuldade; b. Grau 1: dificuldade leve, comprometendo visualização do terço anterior das pregas vocais; c. Grau 2: dificuldade moderada, comprometendo visualização do terço posterior das pregas vocais; d. Grau 3: dificuldade grave, comprometendo visualização das aritenoides.

Segue-se exame com endoscópio flexível para avaliação dinâmica, com plano anestésico progressivamente mais superficial, sendo que o laringoscópio flexível (diâmetro de

2.8 ou 3.4mm) só foi removido no momento em que o paciente acordasse. Essa abordagem é chamada de endoscopia do sono que mimetiza o funcionamento da via aérea durante o sono. Manobra de tracionamento da mandíbula foi também realizada, para estimar o efeito do avanço mandibular na patência da via aérea.

As imagens endoscópicas foram gravadas e após graduadas conforme YELLON (2006) e DE SOUSA *et al* (2003) por um dos autores (CS), cegada aos demais dados do paciente. O protocolo de avaliação encontra-se no anexo 3.

A classificação de Yellon (ver figura 2 do artigo original 2 – página 63) separa os pacientes em:

- Grau 0: via aérea normal;
- Grau 1: prolapso da epiglote contra a parede posterior da faringe;
- Grau 2: prolapso da epiglote e da base de língua com visualização apenas do topo da epiglote;
- Grau 3: prolapso completo da base da língua contra a parede posterior da faringe sem visualização da epiglote.

Já a classificação de de Sousa *et al* (ver figura 1 do artigo original 2 – página 62) separa os pacientes em:

- Leve: a base da língua não toca a parede posterior da faringe na maior parte do tempo:
- Moderada: a base da língua toca a parede posterior da faringe mas não pressiona;
- Grave: a base da língua pressiona a parede posterior da faringe e algumas vezes a língua é encontrada na cavidade nasal.

5.7 Técnica da Polissonografia

Foi realizada avaliação polissonográfica em sono não induzido e com o paciente ventilando espontaneamente. Foram realizados exames noturnos e diurnos usando parâmetros

recomendados pela *American Academy of Sleep Medicine* (1996; BERRY *et al,* 2015). Os exames noturnos e diurnos tiveram a mesma montagem e os diurnos tinham duração de no mínimo quatro horas. A avaliação incluiu eletroencefalograma, eletro-oculograma e eletromiograma para classificação da fases do sono. Também foram utilizados eletromiografia de membros inferiores, eletrocardiograma, oximetria, detector de ronco e sensor de posição corporal. Uma cânula oronasal e termistor foram usados para detectar ausência de fluxo. Apneia foi definida como ausência de fluxo por mais de dois ciclos respiratórios. Apneia obstrutiva foi definida como ausência de fluxo associada a presença de aumento dos movimentos torácicos e/ou abdominais. Hipopneia foi considerada quando houvesse diminuição do fluxo aéreo de no mínimo 30% comparado com as duas ventilações prévias e com queda da oximetria de no mínimo 4% nos 30 segundos subsequentes.

A análise da polissonografia foi realizada de maneira cegada por um dos autores (SF), certificada em medicina do sono. O protocolo da avaliação polissonográfica encontra-se no anexo 4.

5.8 Análise Estatística

As variáveis descritivas foram reportadas como mediana e diferença interquartil (P25-P75) e as variáveis categóricas como porcentagem. O teste exato de Fisher foi usado para verificar diferenças nas proporções entre os diferentes grupos. A correlação de Spearman foi usada para avaliar a correlação entre os diferentes graus de gravidade nas classificações de Sousa e Yellon e os diferentes graus de dificuldade de laringoscopia. A idade é um importante fator no fenótipo dos pacientes com SR e por isso foi controlada como possível viés na nossa análise. Como o tamanho amostral foi limitado, não foi possível estratificar os dados entre os diferentes grupos etários (pelo aumento do erro do tipo II inerente). No entanto, uma análise

multivariável com distribuição binomial e função de ligação de logito foi desenvolvida para controlar o viés da idade. O modelo citado também foi usado para estimar comparação aos pares para as classificações endoscópicas. A linearidade do preditor idade foi avaliada através de abordagem por quartis utilizando o estimador de verossimilhança (-2 Log L) através da distribuição Chi quadrado. O ajuste do modelo foi avaliado através da análise de resíduos. A correção por "least significant difference" foi utilizada para ponderar o aumento do erro do tipo I devido às múltiplas comparações. Para o estudo da acurácia da EVA, uma tabela de contingência (2x2) foi construída com as classificações endoscópicas e o teste considerado como padrão-ouro (classificação clínica Cole *et al* 3). Sensibilidade, especificidade, valores preditivos positivo e negativo, razões de verossimilhança positiva e negativa foram calculadas conforme as fórmulas clássicas. Intervalos de confiança para esses valores foram calculados através de abordagem Clopper-Pearson ou "Log Method". Para comparações das sensibilidades e especificidades entre os testes foi usado Chi quadrado ou Exato de Fisher. Para *Odds Ratio* diagnóstica, as diferenças foram comparadas usando teste Z. Para o estudo da polissonografia, foi usado um modelo de regressão logística ordinal, com os odds proporcionais implementados em modelos univariados (para cada parâmetro estudado). Foi calculada uma estatística pseudo-R^2 que determina a proporção da variação do desfecho que pode ser explicada pela variação do preditor. O *Odds Ratio* ordinal representa a chance de progredir de uma categoria menos grave para uma mais grave, de maneira cumulativa. Um valor P inferior a 5% foi considerado significativo para as comparações. Todas as análises estatísticas foram realizadas utilizando o software SPSS versão 22.0 (IBM, Somers, NY), Microsoft Excel versão 14.4 (Microsoft Corp., Redmond, WA) and Diagnostic Test Calculator.

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7. ARTIGO ORIGINAL 2 EM INGLÊS

Severity of clinical manifestations and laryngeal exposure difficulty predicted by glossoptosis endoscopic grades in Robin sequence patients

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ABSTRACT

Objective: To evaluate the performance of two glossoptosis airway obstruction classifications in predicting symptom severity and laryngeal exposure difficulty in Robin Sequence (RS) patients.

Setting: Public tertiary hospital otolaryngology section (Hospital de Clínicas de Porto Alegre - HCPA)

Patients: All RS patients diagnosed at HCPA from October 2012 to February 2015 were enrolled, a total of 58 individuals. They were classified in isolated RS, RS-Plus and syndromic RS.

Intervention: Patients were submitted to sleep endoscopy and scored according to Yellon and de Sousa by a blinded researcher. Symptom severity evaluation was performed as defined by Cole classification.

Main outcome measure: Association between endoscopic findings and clinical symptoms severity and laryngeal exposure difficulty.

Results: Twenty-four patients were identified as isolated RS (41.4%), 19 patients presented as RS-Plus (32.7%) and 15 patients had well defined diagnosed syndromes (25.9%).

Concomitant airway anomalies were found in 18 patients (31%). Particularly 17.4% in isolated RS, 55.6% in RS- Plus and 28.6% in the syndromic group had such anomalies (P=0,03). Probability of presenting severe clinical symptoms as graded by Cole was higher in grade 3 Yellon classification (68.4%, P=0.012) and in moderate and severe de Sousa classification (61.5% and 62.5%, respectively, P= 0.015) than in milder grades of obstruction. Laryngeal exposure difficulty was correlated with de Sousa and Yellon (Rho=0,41 and Rho=0,43, respectively; P<0,05).

Conclusion: Patients with higher degrees of obstruction in sleep endoscopy had a higher probability of presenting a more severe clinical manifestation and more difficult laryngeal exposure. Since the number of patients included in the study was small for subgroup analyses, it is not clear if this association is restricted to a specific group of RS.

Key words: endoscopy, intubation, laryngoscopy, mandible, Pierre Robin Syndrome

1. INTRODUCTION

The Robin Sequence (RS) is defined as the concomitant presentation of micrognathia, glossoptosis and respiratory distress with or without a cleft palate [1, 2], while glossoptosis is defined by Pierre Robin as a backward and downward fall of the tongue base [2], leading to airway obstruction, which can be visualized through flexible fiberoptic laryngoscopy (FFL). Glossoptosis is a prevalent finding in micrognathic patients but it cannot be systematically presumed. Therefore, FFL has an important role on the identification of presence of glossoptosis in these patients. Moreover, FFL can aid in the evaluation of associated airway disturbances of interest. Often concomitant neurological diseases or even other miscellaneous disorders may cause hypotonia, leading to pharyngomalacia, laryngomalacia or tracheomalacia. Besides that, malformations like cysts, stenosis, vocal cord paralysis and many others can also coexist, aside from glossoptosis. Identification of parallel airway abnormalities is crucial to predict treatment outcomes [3]. In face of all these possible contributions, a diagnostic airway endoscopy is probably warranted in all RS patients. Another possible use of FFL is in outcome monitoring of osteogenesis advancement process [4].

Another valuable information FFL can provide is evaluation of the degree of airway obstruction. Notwithstanding, the method of respiratory obstruction evaluation is still subject to controversy. Different glossoptosis classification systems have already been reported. Sher [5, 6] classified airway obstruction in awake RS patients, depending on the cause of the obstruction, attributing a score from 1 (true glossoptosis) to 4 (pharyngomalacia). More than a decade later, de Sousa et al [7] classified glossoptosis in awake patients as mild, moderate and severe (Figure 1). Afterwards, Yellon [8], performing FFL under light sedation, classified epiglottic and base of tongue prolapse from 0 to 3, ranging from normal to complete obstruction of the pharynx (Figure 2). A uniform characteristic of these classifications is that

they define progressive degrees of airway compromise, and as a consequence one could expect that clinical manifestations in different subsets of patients would also show a continuing severity spectrum. Although tempting, the demonstration of this correlation was not consistently verified in research until today. Indeed, this limitation eventually compromises the usefulness of those classifications in clinical practice.

Albeit use of these classifications can be sporadically seen in research, it is far from being consensual. There is certainly a complex background that could disentangle the various reasons why this is true. Obviously, scarce applicability in a clinical context would be one of the most relevant. Furthermore for this unique type of patients, a more practical use of this research information would be valuable.

Accordingly, the primary goal of this study was to test the performance of de Sousa and Yellon classifications [7, 8] to predict severity of symptoms [9] and laryngeal exposure difficulty in a cohort of RS patients. Other characteristics such as concomitant airway lesions and associated malformations were also reported.

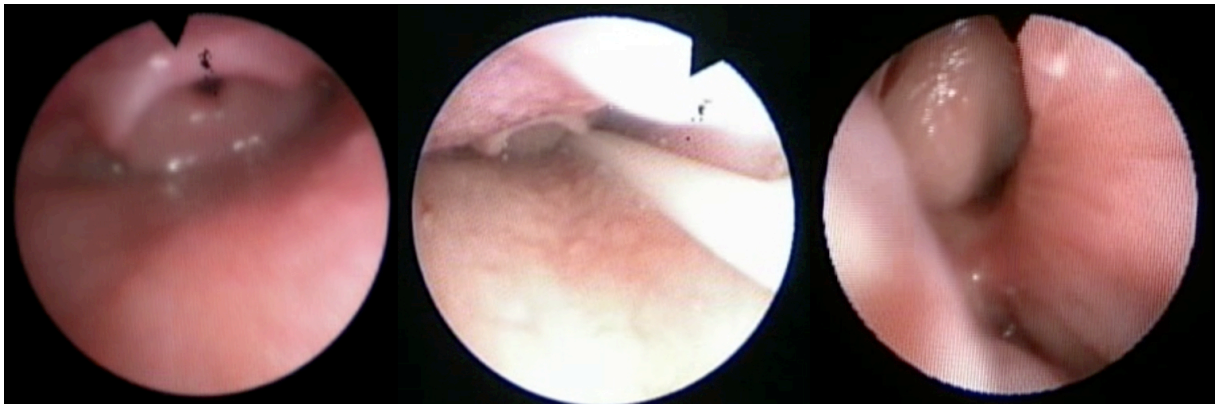

Figure 1: Endoscopic evaluation of glossoptosis. De Sousa classification illustrated: **a.** Mild: most of the time the posterior region of the tongue does not touch the posterior wall of the pharynx; **b.** Moderate: the posterior region of the tongue touches the posterior wall of the pharynx but does not pressure it; **c.** Severe: the posterior region of the tongue pressures the posterior wall of the pharynx and sometimes the tongue remains in the nasal cavity.

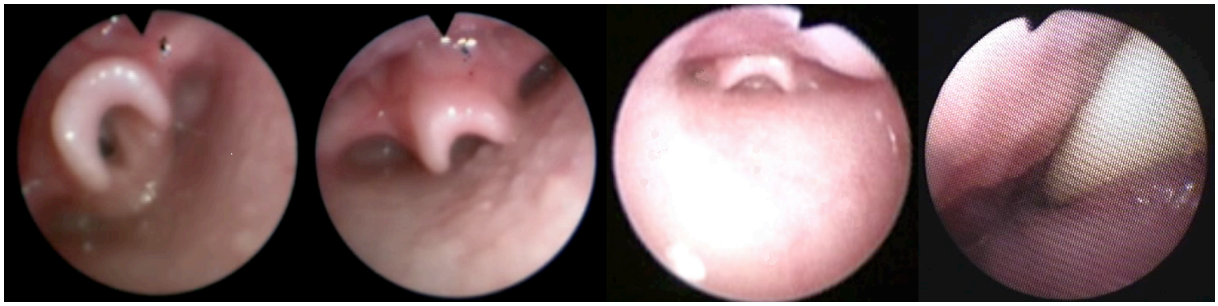

Figure 2: Endoscopic evaluation of glossoptosis. Yellon classification illustrated: **a.** Grade 0: normal airway; **b.** Grade 1: prolapse of the epiglottis against the posterior pharyngeal wall; **c.** Grade 2: prolapse of the epiglottis and base of tongue with only the tip of the epiglottis visible and obliteration of the vallecula; **d.** Grade 3: complete prolapse of the tongue against the posterior pharyngeal wall with no portion of the epiglottis visible.

2. MATERIAL AND METHODS

2.1 SITE OF STUDY

This prospective study took place at Hospital de Clínicas de Porto Alegre (Rio Grande do Sul, Brazil), from October 2012 to February 2015, and was submitted to Institution's Research Ethics Committee approval prior to initiation. All newly diagnosed RS patients at our institution during study period were enrolled. Written informed consent was obtained from parents or legal guardians of all enrolled patients. No exclusion criteria were defined.

2.2 DIAGNOSTIC WORKUP

Diagnosis of RS was established based on a multidisciplinary evaluation. Patients were required to meet all of the following criteria:

a) Respiratory dysfunction: defined as any respiratory symptom of airway obstruction, whether while on activity engagement, specific positioning, feeding or at rest (reported by caretaker or observed by hospital staff) confirmed by polysomnography. Only patients presenting obvious respiratory distress (on mechanical ventilation or other type of respiratory support) were not submitted to polysomnography.
b) Glossoptosis: observed through sleep endoscopy and according with the Pierre Robin definition [1, 2].
c) Micrognathia: assessed through three-dimensional CT and defined as a shortening of mandible body and/or ramus.

After initial diagnostic workup, patients were divided in groups according to concurrent findings as isolated RS, RS-plus (associated with additional congenital malformations but without a specific syndromic diagnosis) and syndromic RS [10].

2.3 SYMPTOMATOLOGY GRADING

A RS classification system, reported by Cole et al [9], based on symptom severity was applied to all patients as follows:

- Grade 1: no respiratory distress when nursed supine;
- Grade 2: intermittent evidence of mild respiratory obstruction when nursed supine and feeding precipitates some respiratory distress;
- Grade 3: moderate to severe respiratory distress when nursed supine, unable to feed orally.

Endoscopic studies and obstruction grading

The airway endoscopy was performed in all patients in the supine position under light sedation with sevofluorane and/or propofol administered by a pediatric anesthesiologist.

Examination sequence began in a drug-induced sleep state with a static evaluation, using a rigid laryngoscope, followed by a dynamic evaluation in a progressively more superficial sedation state, with a flexible laryngoscope (2.8 or 3.4 mm diameter) that was removed from the patient the moment the child woke up. This approach of nasolaryngoscopic examination is called “sleep endoscopy” which mimics more closely airway functioning during sleep. Jaw thrust maneuvers were performed while viewing the site of obstruction to assess the effect of mandibular advancement in overall tongue base airway patency.

Endoscopic examination was digitally recorded and later evaluated by one of the authors (CS), when she was not aware of patient’s identification. Yellon grading system and de Sousa grading system were both used in all examinations.

2.4 CORRELATION OF ENDOSCOPIC FINDINGS AND SYMPTOM SEVERITY

While attempting to establish reciprocity between endoscopic grading scales and clinical grading systems we aimed to analyze proportion of severely graded patients in clinical classification in each different Yellon [8] and de Sousa [7] levels. This was performed graphically on histogram and formally tested statistically.

Correlation of endoscopic findings and laryngeal exposure difficulty

We have also evaluated the difficulty posed by airway abnormalities during laryngoscopy examination. A classification was applied considering the following stratification: 0, No difficulty; 1, Minor difficulty (compromising visualization of the anterior aspect of the vocal folds); 2, Moderate difficulty (compromising visualization of the posterior aspect of the vocal folds); and 3, Major difficulty (compromising visualization of the arytenoids). Ordinal categories from this classification were correlated with both individual de Sousa e Yellon classifications grades.

2.5 STATISTICAL ANALYSIS

Descriptive data were reported as median and interquartile range (P25-P75). Proportions were reported as percentages. Fisher's exact test was used to verify differences in proportions across different groups. Spearman correlation was used to evaluated correlation between ordinal categories of de Sousa and Yellon classification and individual laryngoscopy difficulty grades. Patient age is an important determinant of clinical phenotype of RS patients and it was advisable to control for that potential bias in our analysis. As sample size was limited, it was not possible to stratify data among age groups. Instead, a multivariable generalized linear model with binomial distribution and logit link function was assembled to estimate significance levels for predictors of interest while controlling for patient age as a covariate. Also, the cited model was used to estimate pairwise comparisons for categories of endoscopic classifications. Linearity of age as a variable was evaluated by quartiles approach using the likelihood estimate (-2 Log L) on a Chi square distribution. Goodness-of-fit was evaluated by residual analysis. Least significant difference correction was used to account for multiple comparisons. A P-value of < 0.05 was considered statistically significant. All statistical analyses were performed using the software SPSS version 22.0 (IBM, Somers, NY).

3. RESULTS

A total of 58 patients were enrolled. Median age was 52.5 days, ranging from two days to 11 years of age. Baseline characteristics are shown in Table 1.

Table 1. Patient characteristics (n=58 patients).

Characteristic	Value
Age (days)	52.5 (24-173.7)
Male sex (%)	35 (60.3%)
Clinical Presentation	Grade 1: 22 (37.9%) Grade 2: 14 (24.1%) Grade 3: 22 (37.9%)
Nasogastric Tube/ Gastrostomy	29 (50%)
Tracheostomy*	11 (19%)
MDO	37 (63.8%)
Airway abnormalities	18 (31%)
Classification	Isolated RS: 24(41.4%) RS-Plus: 19 (32.7%) Syndromic RS: 15 (25.9%)
Cleft palate	18 (31%)

Quantitative parameters are described by median, 25th and 75th percentiles (in parentheses).

Categorical parameters are described by number of patients (n) and percentage (%).

*Patients submitted to tracheostomy as a first procedure. Additional 2 patients underwent tracheostomy after MDO.

MDO= Mandibular Distraction Osteogenesis

Twenty-four patients were identified as isolated RS (41.4%), 19 patients as RS-Plus (32.7%) and 15 patients had a defined syndromic diagnosis (25.9%). Identifiable syndromes were Treacher Collins Syndrome (3 patients), diastrophic dysplasia (2), microssomia (2), Moebius sequence (1), achondroplasia (1), primary dwarfism (1), oto-palato-digital syndrome type II

(1), 3q partial trisomy (1), CHARGE syndrome (1), 7q interstitial deletion (1) and 2q31 deletion (1).

On endoscopic examination, concomitant airway abnormalities were found in 18 patients (31%). Particularly 17.4% in isolated RS, 55.6% in RS- Plus and 28.6% in the syndromic group had such anomalies (P=0,03). Comorbid lesions were pharyngomalacia (8 patients), laryngomalacia (2), layngopharyngomalacia (2), tracheomalacia (1), nasal synechiae (1), maxillary atresia (1), maxillary atresia and submucosal palatine cleft (1), pharyngomalacia and nasal synechiae (1) and choanal atresia (1).

The frequency of patients considered highly symptomatic (grade 3) patients according to Cole classification was compared among different grades of Yellon et al and de Sousa et al classifications. Results are shown in Figure 3 and 4, respectively. Proportions of severely symptomatic patients in each Yellon and de Sousa et al classifications levels were considered statistically different (Global Fisher's Exact Test, P=0.012 and P=0.015, respectively).

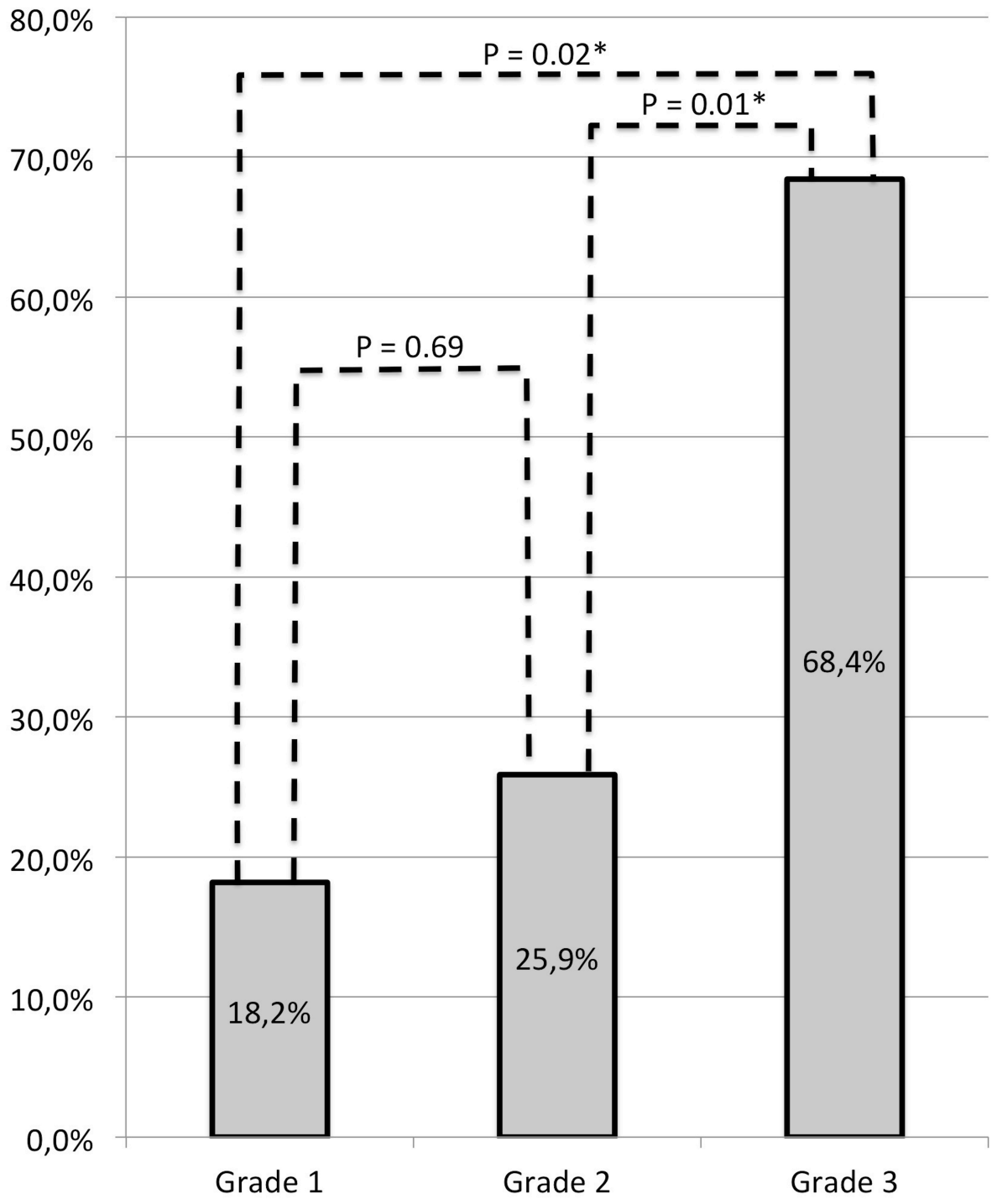

Figure 3. Frequency of severe clinical symptoms (grade 3 of Cole et al) in different grades of Yellon classification (Global P= 0.012). Pairwise comparisons significance levels are shown over dashed lines.

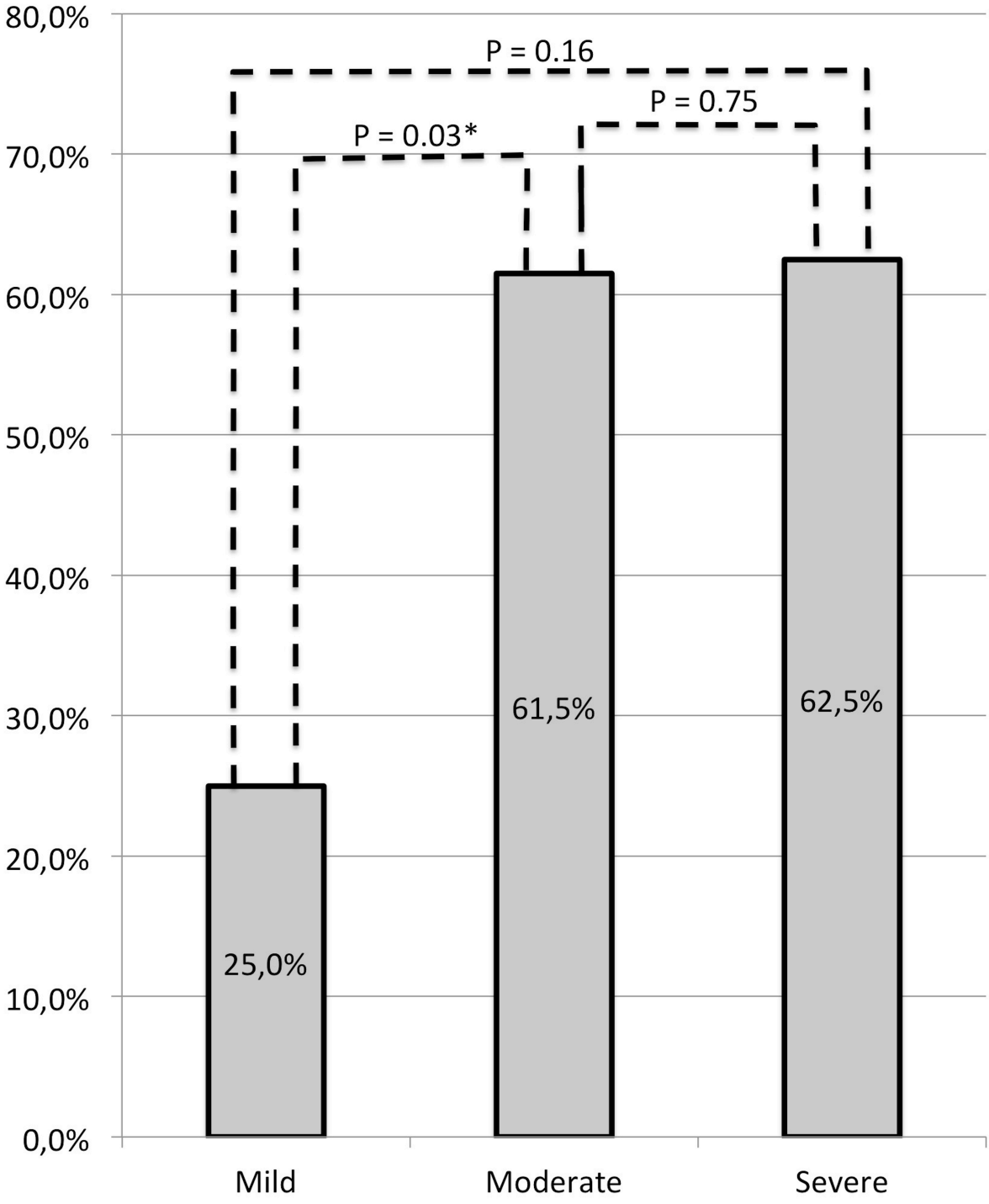

Figure 4. Frequency of severe clinical symptoms (grade 3 of Cole et al) in different grades of de Sousa classification (Global P= 0.015). Pairwise comparisons significance levels are shown over dashed lines.

Patient's age, incorporated in a multivariable model as described above, was not shown to be a significant factor (P=0,567 in Yellon model and P=0,584 in de Sousa model). Despite of this finding, we have maintained it in the multivariable model in order to control for potential biases. Pairwise comparisons between categories have shown statistically significant differences between "Grade 3" x "Grade 1" (Odds Ratio for Severe Symptoms = 6.6 95%CI 1.02-42.3) and "Grade 3" x "Grade 2" (Odds Ratio for Severe Symptoms = 4.6 95%CI 1.2-17.4), in Yellon classification, and "Moderate" x "Mild" (Odds Ratio for Severe Symptoms = 4.7 95%CI 1.1-20.0), in de Sousa classification.

No difficulty on laryngeal exposure was found in 29.3% of patients, minor difficulty in 20.7%, moderate difficulty in 17.2% and major difficulty in 15.5%. Correlation coefficient between Yellon grading and laryngeal exposure difficulty classification was Rho=0,43 (P=0,002). Similar findings (Rho=0,41, P=0,004) were encountered with de Sousa grading.

4. DISCUSSION

We believe that the main contribution of our findings is that in the majority of RS patients, the presence of clinical symptoms, precisely those considered more severe, actually find their anatomical substrate in endoscopic examination. This association could be verified in both Yellon and de Sousa endoscopic classifications. Besides that, technical difficulty in laryngoscopy was also correlated with endoscopic grading systems (in a similar fashion for both classifications), thus the worse the anatomical findings the more difficult the airway approach. Therefore, these glossoptosis scorings could be used as complementary tools for clinical severity and laryngeal exposure difficulty prediction in RS patients, discriminating those patients who would need a special and more focused assistance from those with a lesser chance of complications. When comparing performances between these two classification

systems, we would argue that the Yellon classification would have a more discriminative performance over de Sousa classification in predicting clinical phenotype, as we can see that severely compromised patients are prominently concentrated in the Yellon grade 3 category, while in de Sousa classification, those patients are scattered on the moderate and severe categories. No relevant difference could be seen concerning laryngoscopy difficulty.

Sleep endoscopy has limitations since its findings rely on the anesthetic level at which patient is maintained through examination. That is the reason why we managed to visualize the airway from deep to light sedation to adequately evaluate abnormalities at deep sleep state, like glossoptosis and pharyngomalacia, and abnormalities at superficial sleep state, like laryngomalacia and vocal cord paralysis.

Yellon [8] described a grading system for epiglottic and base-of-tongue prolapse in 14 children that was successful in discriminating the severity and location of airway obstruction. However, clinical aspects were not studied while conceiving this classification. To our knowledge, this is the first study designed to demonstrate such association.

De Sousa et al [7] reported their classification on awake patients. We have adapted it to perform examinations under sedation, specifically sleep endoscopy. Differently from our findings, de Sousa et al did not show a significant correlation between glossoptosis and respiratory distress (Spearman correlation, $\rho=0.26$, $P=0.09$). There is a chance that these discrepant results could be a consequence of the effect of awake *versus* "under sedation" endoscopy or sample size limitations.

Notwithstanding, we believe that the primary finding of this study may be especially valid for a specific subgroup of patients (isolated RS), while other subgroups (RS-Plus and syndromic patients) may not show such a strong association. We could not verify this subgroup effect as the study was underpowered to perform stratified analysis.

Bravo et al [11] published their own FFL classification of airway obstruction and showed a significant association with polysomnographic findings (apnea-hypopnea index, arousal index, snoring time, percentage of sleep time spent under 90% oxygen saturation) in 52 RS children. We decided not to use this classification because it considers adenoid tissue and tonsils, while the majority of our sample was less than one year (adenoid tissue and tonsils are not an important obstructive factor at this age). Furthermore we consider it troublesome to classify tongue base obstruction in a scale of 0 to 100%, the same approach used by Sorin et al [12]. Bravo et al themselves report this assessment as a limitation of their study due to its subjective nature and its implications on reproducibility.

Andrews et al [3] described a prevalence of 28% of concomitant lesions in a sample of 71% of isolated RS (remaining patients were syndromic RS, while they did not describe any RS-Plus). We have found a slightly higher rate of concomitant airway lesions (35.3%) that could be explained by a higher frequency of patients with additional malformations as we have demonstrated that syndromic RS and RS-Plus patients have a significant higher rate of associated airway lesions.

5. CONCLUSION

Endoscopic studies are valuable tools in the RS patient management. They have a prominent role in diagnosis, intubation approach, swallowing evaluation, treatment monitoring and, as we have shown, clinical severity and laryngeal exposure difficulty prediction. We emphasize not just the utility of such information to the assistant staff but also the effectiveness of sleep endoscopy as the preferred method of endoscopic dynamic airway evaluation, as we have systematically adopted at our institution.

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8. ARTIGO ORIGINAL 3 EM INGLÊS

Diagnostic Accuracy of Current Glossoptosis Classification System

Submetido no Laryngoscope em 10/11/2016

Denise Manica, Cláudia Schweiger, Leo Sekine, Simone Chaves Fagondes, Gabriel Kuhl, Marcus Vinicius Martins Collares, Paulo José Cauduro Marostica

Abstract

Objectives: To assess the performance of endoscopic grading systems of glossoptosis in predicting clinical manifestations in children.

Study Design: Cohort Nested Cross-Sectional Study.

Methods: All Robin Sequence patients diagnosed at Hospital de Clínicas de Porto Alegre from October 2012 to June 2016 were enrolled. Patients underwent sleep endoscopy and were classified according ~~t~~o Yellon (Y) and de Sousa (S) scales. Symptom severity evaluation was performed as defined by Cole et al (2008). Endoscopic classifications were tested against Cole's clinical classification.

Results: A total of 80 patients were enrolled. Sensitivity (Y: 56.2% x S: 28.1%, P<0.001) and specificity (Y: 85.4% x S: 93.8%, P=0.038) in predicting clinical symptoms were statistically different between Yellon and de Sousa classifications. There was a high level of agreement between both grading systems (Spearman Rho=0.793, P<0.001). In an attempt to summarize test performance in one unique measure, we have calculated the Diagnostic Odds Ratio (DOR) for Yellon (DOR: 7,53 95%CI 4.15-10.90) and de Sousa (DOR: 5,87 95%CI 1.86-9.87). DOR difference between classifications was not statistically significant (P=0,92). The strength by which a positive result would increase the probability of severe clinical manifestations in one given patient (Positive Likelihood Ratio) was 3.86 (95%CI 1.82-8.16) and 4.50 (95%CI 1.32-15.36) for Yellon and de Sousa, respectively.

Conclusions: Yellon and de Sousa grading systems showed a low sensitivity in detecting patients with severe clinical manifestations, being of little use from a screening standpoint. On the other hand, specificity seems to be an applicable attribute of these endoscopic tools.

Key words: glossoptosis, laryngoscopy, micrognathism, Pierre Robin Syndrome, respiratory sounds

Level of evidence: 2b

Introduction

Robin Sequence (RS) is defined by micrognathia, as a primary characteristic, aside from other mandatory diagnostic findings such as glossoptosis and airway obstruction [1]. Cleft palate may also be considered an additional feature. Pierre Robin [2] defined glossoptosis as a backward and downward fall of the tongue base. Donnelly et al [3] defined it as a posterior movement of the tongue during sleep reinforcing the dynamic nature of such hallmark and its main manifestations during sleep. That said, it seems to us that among the available tools for airway evaluation such as cephalometric films, three-dimensional airway computed tomography and airway magnetic resonance, flexible fiber-optic laryngoscopy (FFL), ideally under sedation on spontaneous ventilation, is the best approach to evaluate glossoptosis, avoiding radiation exposure and allowing better control of consciousness level. This approach permitts an accurate analysis of the anatomy from a deeper sedated state to a more superficial one. Besides that, FFL is a very important tool in the investigation of concomitant lesions associated with glossoptosis, which can influence patient therapeutic outcome. Andrews et al [4], for example, showed a change in the surgical plan of mandibular distraction osteogenesis in 28% of patients from his cohort, after diagnostic laryngoscopy and bronchoscopy.

Current RS consensus emphasizes the importance of uniform definitions and comparable assessments in these patients. Pursuing a better way of classifying glossoptosis, we have performed a systematic review on the subject. It seems that among different reported classifications, Yellon [5] and de Sousa et al [6] were the ones with a higher level of reproducibility. However, de Sousa et al evaluated awake patients, not being able to reproduce the sleep state. Based on these studies, our research group aimed at establishing a link between FFL findings and clinical manifestations[7]. Preliminary findings suggested an

existing association between worse classification grades and more severe clinical manifestations.

The main objective of the present research was to assess the role of endoscopic grading systems of glossoptosis as potential diagnostic tools, ascertaining their performance in predicting ominous clinical manifestations. In doing so, we aimed at verify the utility and accuracy of airway endoscopy in this disorder, and expand its application in clinical practice. Traditional diagnostic test performance assessments were then determined for each classification, and their potential application in decision-making process for glossoptosis patient care was discussed afterwards.

Materials and Methods:

The present study was based on the extension of a previously reported cohort of patients with glossoptosis [7].

Site of study

The prospective cohort patients, in which this cross-sectional study is nested, were enrolled at Hospital de Clínicas de Porto Alegre (Rio Grande do Sul, Brazil), from October 2012 to June 2016. The study was submitted to Institution's Research Ethics Committee and had approval prior to initiation. All newly diagnosed RS patients at our institution during study period were enrolled. Written informed consent was obtained from parents or legal guardians of all enrolled patients.

Diagnostic workup

Diagnosis of RS was established based on a multidisciplinary evaluation. Patients were required to meet all of the following criteria:

d) Respiratory dysfunction: defined as any airway obstruction symptom, whether while on activity, specific positioning, feeding or at rest (reported by caretaker or observed by hospital staff) and confirmed by polysomnography. Only patients presenting obvious respiratory distress (on mechanical ventilation or other type of respiratory support) were not submitted to polysomnography.

e) Glossoptosis: observed through sleep endoscopy and according with the Pierre Robin definition[2,8].

f) Micrognathia: assessed through three-dimensional CT and defined as a shortening of mandible body and/or ramus.

After initial diagnostic workup, patients were divided in groups according to concurrent findings as isolated RS, RS-plus (associated with additional congenital malformations but without a specific syndromic diagnosis) and syndromic RS[9].

Symptomatology grading

A RS classification system, reported by Cole et al [10], based on symptom severity was applied to all patients as follows:

- Grade 1: no respiratory distress when nursed supine;
- Grade 2: intermittent evidence of mild respiratory obstruction when nursed supine and feeding precipitates some respiratory distress;
- Grade 3: moderate to severe respiratory distress when nursed supine, unable to feed orally.

Airway endoscopy was performed in all patients in the supine position under light sedation with sevofluorane and/or propofol administered by a pediatric anesthesiologist. Examination sequence began in a drug-induced sleep state with a static evaluation, using a rigid laryngoscope, followed by a dynamic evaluation in a progressively more superficial sedation state, with a flexible laryngoscope (2.8 or 3.4 mm diameter) that was removed from the patient the moment the child woke up. This approach of nasolaryngoscopic examination is called "sleep endoscopy" which mimics more closely airway functioning during sleep. Jaw thrust maneuvers were performed while viewing the site of obstruction to assess the effect of mandibular advancement in overall tongue base airway patency.

Endoscopic examination was digitally recorded and later evaluated by one of the authors (CS), who was not aware of patient's identification. Yellon[5] grading system and de Sousa[6] grading system were both used in all examinations. De Sousa classification in this study was adapted, since an under sedation examination was performed, which was different from the technique used in its original report.

Statistical analysis

Statistical analysis was performed considering endoscopic classifications as a diagnostic test to be evaluated against a gold-standard test that was considered to be patient's clinical manifestations graded by Cole et al[10] classification. In order to allow for pertinent performance and accuracy analysis, we have transformed study variables into dichotomous parameters as follows:

- A positive endoscopic examination was considered to belong to Grade 3 Yellon[5] or Severe de Sousa et al[6] categories, while other classifications were considered negative results.

- A positive gold-standard test was considered to belong to Grade 3 Cole et al[10] category, while other classifications were considered negative results.

The choice to dichotomize categories in such a way was based on a previous study from our research group[7].

Continuous variables were described by median and interquartile range (25^{th} to 75^{th} percentiles). Categorical variables were described by absolute number (n) and percentage (%). A contingency table (2x2) was constructed for both endoscopic classifications and the gold-standard test. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios were calculated based on standard equations. Confidence intervals for such values were calculated through Clopper-Pearson or "Log Method" approach. For sensitivity and specificity comparisons between tests we used the Pearson Chi Square or Fisher-Freeman-Halton Exact test. Diagnostic Odds Ratio (DOR) is a summary measure accounting for sensitivity and specificity[11]. For DOR, we compared Log(Odds Ratio) differences and respective standard errors using a Z test. Correlation coefficients and significance levels were obtained through Spearman correlation test. A significance level of 5% was assumed for all comparisons.

Calculations were performed using softwares SPSS (BM Corp. Released 2011. IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp.), Microsoft Excel (Microsoft Corp. Released 2011. Microsoft Office for Mac, Version 14.4.0. Redmond, WA.) and Diagnostic Test Calculator [12].

Results

Descriptive Analysis of Study Sample

During the study period, a total of 80 eligible patients were enrolled. Baseline characteristics of the patients are shown in Table 1.

Table 1. Patients baseline characteristics.

Variable Name	n=80
Age (days)	50.5 (17 – 119.7)
Male sex (%)	49 (61.3%)
Cole et al Classification	Grade 1: 29 (36.3%) Grade 2: 19 (23.8%) Grade 3: 32 (40.0%)
Nasogastric Tube/ Gastrostomy	39 (48.8%)
Tracheostomy*	13 (16.9%)
Airway anomalies	24 (30.4%)
Classification	Isolated RS: 35 (43.75%) RS Plus: 25 (31.25%) Syndromic RS: 20 (25%)
Cleft palate	25 (31.3%)

There were 20 patients (25%) with syndromic type RS. Identifiable syndromes were Treacher Collins Syndrome (3 patients), microssomia (3), diastrophic dysplasia (2), Stickler Syndrome (1), Goldenhar Syndrome (1), Schizencephaly (1), Moebius sequence (1), achondroplasia (1), primordial dwarfism (1), oto-palato-digital syndrome type II (1), trisomy 21 (1), 3q partial trisomy (1), CHARGE syndrome (1), 7q interstitial deletion (1) and 2q31 deletion (1).

On endoscopic examination, concomitant airway abnormalities were found in 24 patients (30.6%). More specifically, 17.6% in isolated RS, 48.0% in RS-Plus and 30.0% in the syndromic group had such anomalies (P=0,039). Comorbid lesions were pharyngomalacia (10 patients), laryngomalacia (5), layngopharyngomalacia (2), tracheomalacia (1), nasal synechiae (1), maxillary atresia (1), maxillary atresia and submucous palatine cleft (1), pharyngomalacia and nasal synechiae (1), tracheal vascular compression (1) and choanal atresia (1).

Overall distribution of patients according with de Sousa et al and Yellon classifications is shown on Table 2.

Table 2. Overall distribution of patients according with de Sousa et al and Yellon classifications.

Classification System	n=80
de Sousa	Mild: 53 (66.2%) Moderate: 15 (18.8%) Severe: 12 (15.0%)
Yellon	Grade 1: 16 (20.0%) Grade 2: 39 (48.8%) Grade 3: 25 (31.2%)

Diagnostic Performance Evaluation of Glossoptosis Endoscopic Classifications

Results for conventional diagnostic test performance assessments are shown in Table 3.

Table 3. Results for conventional diagnostic test performance assessments.

Test Characteristic	Yellon	de Sousa et al
Prevalence of Disease	40%	
Sensitivity	56.2% (37.7-73.6)	28.1% (13.7-46.7)
Specificity	85.4% (72.2-93.9)	93.7% (82.8-98.7)
Positive Predictive Value	72.0% (50.6-87.9)	75.0% (42.8 94.5)
Negative Predictive Value	74.5% (61.0-85.3)	66.2% (53.7-77.2)
Positive Likelihood Ratio	3.86 (1.82-8.16)	4.50 (1.32-15.36)
Negative Likelihood Ratio	0.51 (0.34-0.77)	0.77 (0.61-0.96)

Overall, we found a higher sensitivity for severely symptomatic patients in Yellon classification (56.2% x 28.1%, P<0.001), while a higher specificity could be determined for de Sousa et al classification (93.8% x 85.4%, P=0.038).

Agreement among endoscopic classifications was assessed through correlation between the two of them and it was considered high (Spearman Rho=0.793, P<0.001). Notwithstanding, correlation between Yellon and Cole et al (Spearman's Rho=0.372, P<0.001) and de Sousa et al and Cole et al (Spearman's Rho=0.439, P<0.001) classifications were lower. Calculated DOR for Yellon was 7,53 (95%CI 4.15-10.90), while de Sousa et al showed a DOR of 5,87

(95%CI 1.86-9.87). Difference of DOR between classifications was not statistically significant (P=0,92).

The overall accuracy of each endoscopic classification was compared by means of the DOR. Nomograms for Yellon and de Sousa et al positive and negative likelihood ratios, based on a prior probability (prevalence of Cole et al Grade 3) of 40% are shown in Figures 1 and 2, respectively.

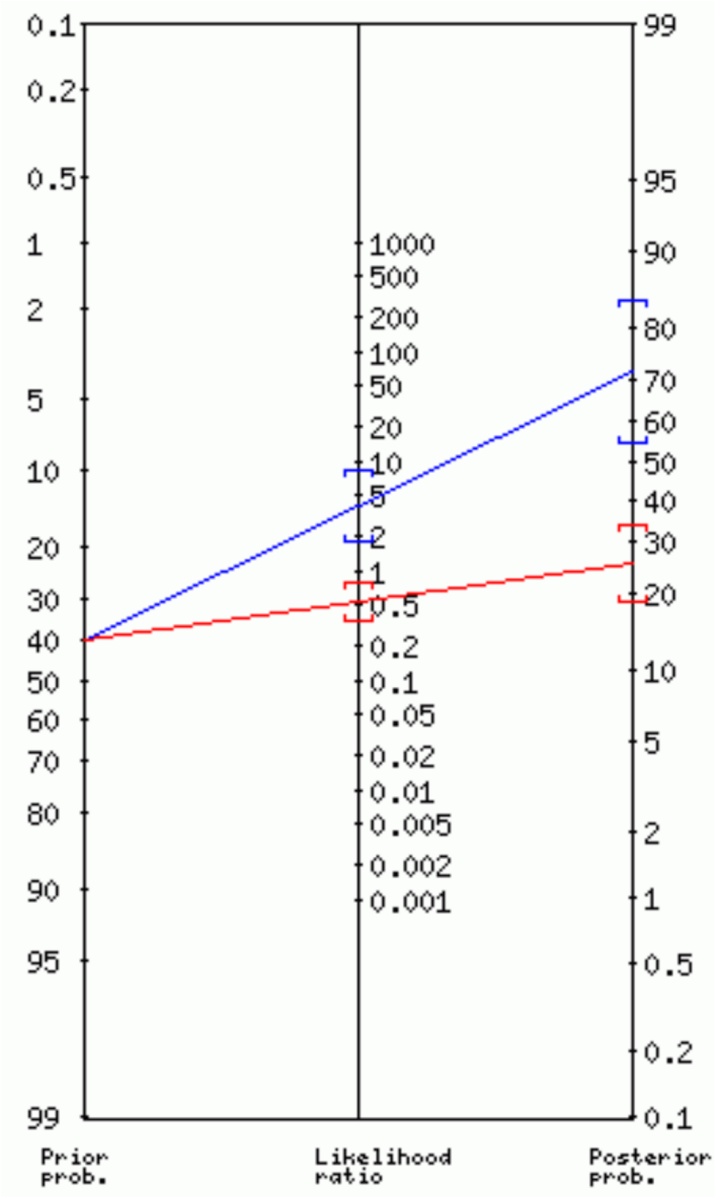

Figure 1. Nomogram for Positive (superior line) and Negative (inferior line) Likelihood Ratio for Yellon classification.

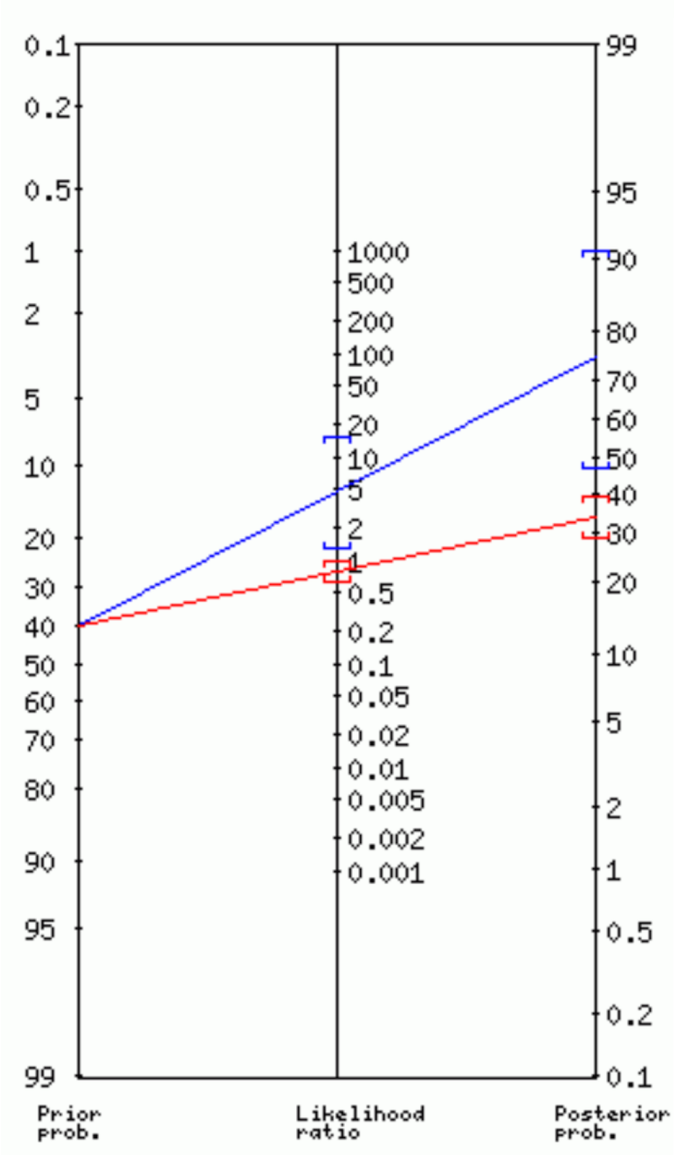

Figure 2. Nomogram for Positive (superior line) and Negative (inferior line) Likelihood Ratio for de Sousa et al classification.

Discussion

As the obstruction of the airway at the tongue base level is the hallmark of RS, its accurate measurement is essential. We have already reported preliminary findings that support the role

of endoscopic classifications in clinical manifestation prediction in glossoptosis patients. In the present study, we reinforce this finding, taking diagnostic accuracy assessment of these approaches to another level of analysis and also including additional patients.

Yellon classification showed a significantly higher sensitivity (though overall low) in detecting patients with worse clinical manifestations. In his original study, Yellon did not measure the correlation of the proposed classification with the symptomatology of the 14 patients included in the report. De Sousa classification, on the other hand, returned a very specific evaluation. De Sousa et al, in their report, did not find a very robust correlation between grading and symptoms (Spearman correlation Rho= 0,26, p=0,09), possibly because they performed an awake examination and had sample size limitations.

One could argue that comparing Yellon and de Sousa classifications, lack of DOR statistical significant difference would be a result of sensitivity and specificity trade off. So the exact situation in which to apply the information rendered by these scoring systems would be crucial to optimize their utility in clinical practice.

Due to low sensitivity issues, as aforementioned, the role of airway endoscopy on RS should not be on screening potential symptomatic patients. At the diagnosis of glossoptosis, it would be best applied solely to eliminate alternative causes of obstruction. Notwithstanding, based on specificity, once a positive result is elicited, one could anticipate that glossoptosis is effectively the cause of airway obstruction. Additionally, during mandibular distraction, the persistence of endoscopically observed severe glossoptosis should raise attention to the possibility of insufficient mandibular advancement, with permanence of obstructive symptoms.

Olson et al [13] using airway endoscopy as a tool for monitoring pre and post mandibular distraction osteogenesis process showed a significant increase in the anteroposterior and mediolateral dimensions of the supraglottic space from preoperative to early postoperative

images. However, such measurements were performed by direct laryngoscopy, an examination considered difficult to reproduce because it relies on individual technique and on the strength used to perform the maneuver. Sorin [14] evaluated 20 patients with RS with spontaneous breathing anesthesia. They created an airway endoscopy scale using the percentage of obstruction, which we consider difficult to evaluate the tongue base obstruction grade. The average compiled preoperative airway obstruction scores in decannulated patients were compared to those who remained tracheostomized and were found not significantly different. They concluded that preoperative airway endoscopy alone is not a good predictor of the likelihood of successful decannulation after distraction osteogenesis. Maybe this finding could be justified due to an inadequate classification instrument.

Several authors [15-18] reported the improvement in airway during the process of mandibular distraction, but all of them monitored surgery with radiological measures. As we consider radiation exposure potential harms and a worse control of the level of sedation during radiological examination, it would seem more interesting to use an endoscopic approach to monitor the postoperative period. Currently, more studies on this subject are needed.

The possibility of concomitant airway abnormalities detection is an important contribution from FFL. We have showed that RS- plus patients present more concomitant airway lesions, especially pharyngomalacia. This finding represents the type 4 (four) of obstruction described by Sher[19] in patients with craniofacial disorders. It has been described as a difficult problem because all aspects of the pharynx are moving medially so that one single component of obstruction cannot be identified.

Conclusion

Yellon and de Sousa grading systems showed a low sensitivity in detecting patients with severe clinical manifestations, being of little use from a screening standpoint. On the other hand, specificity (specially concerning de Sousa score) seems to be an applicable attribute from these endoscopic tools to some specific situations, as we have proposed. Based on these findings, they would not be formally considered an accurate diagnostic test, leaving a yet unfilled role in the appraisal of RS patients' endoscopy. Further research on the best use of endoscopic evaluation in these patients should be still pursued.

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9. ARTIGO ORIGINAL 4 EM INGLÊS

Polysomnographic parameters can estimate clinical severity in Robin Sequence patients: A cohort nested cross-sectional study

Submetido no Sleep em 21/11/2016

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Abstract

Objectives: To evaluate polysomnographic parameters association with clinical severity in Robin Sequence (RS) patients.

Study Design: Cohort Nested Cross-Sectional Study.

Methods: All RS patients diagnosed at Hospital de Clínicas de Porto Alegre from October 2012 to June 2016 were enrolled. They were classified as isolated RS, RS-Plus and syndromic RS. Patients complying eligibility criteria were submitted to polysomnography (PSG). Symptom severity evaluation was performed as defined by the Cole classification.

Results: Eighty patients were enrolled in the study. Fifty-five of these had polysomnography warranted. PSG parameters were associated with progressive severity clinical grades as evaluated by Odds Ratio: Dessaturation Index (1.27; 1.07-1.51; P=0.006), Apnea/Hypopnea Index - AIH - (1.13; 1.01-1.26; P=0.02), Sleep Mean Oxygen Saturation (0.16; 0.05-0.52; P=0.002), Oxygen Saturation Nadir (0.73; 0.56-0.96; P=0.02), Percentage of time under oxygen saturation of 90% (9.49; 1.63-55.31, P=0.012) and Percentage of Time Presenting Obstruction (2.5; 1.31-4.76; P=0.006).

Conclusions: This is the first study to establish association of polysomnographic parameters with clinical manifestations in RS patients. Percentage of time under 90% oxygen saturation, percentage of time presenting obstruction and mean sleep oxygen saturation were the three

parameters presenting the highest levels of association with clinical manifestations. Therefore, these parameters other than AIH, traditionally undervalued in other clinical settings, should be carefully monitored in pediatric polysomnographic evaluation.

Key words: glossoptosis, laryngoscopy, micrognathism, Pierre Robin Syndrome, polysomnography, respiratory sounds

Introduction

Robin Sequence (RS) is defined as the concomitant presence of micrognathia, glossoptosis and respiratory distress with or without cleft palate (1). In RS, there is an obstructive posterior obstructive displacement of the tongue and other possible associated lesions such as laryngomalacia, pharyngomalacia that determine largely variable respiratory symptoms. These children presentation varies from oligosymptomatic ones to severe cases that may require prolonged stay in neonatal intensive care unit and interventions to relieve airway obstruction. These respiratory issues frequently persist well into childhood, affecting not only growth and development but also impacting on long-term educational attainment. Because the severity of the symptoms is variable, an accurate and informative evaluation is very important (2). In infants, apnea often occurs without clinically obvious obstructive symptoms (3).

In the past, different mechanisms of airway obstruction were part of the main causes of death among RS patients. However, with the improvement seen in respiratory care and in the currently available interventions to alleviate obstruction, those fatal events turned into a rare complication nowadays(4).

Polysomnography (PSG) is the gold standard for the diagnosis of airway obstruction. Its objective nature makes it a good guide to the need of management of the airway in order to prevent obstructive sleep apnea (OSA) sequelae. In children, an obstructive apnea index below 1 is established as the cutoff for normality and an apnea index of 10 is considered to be severe, differently from adults (5, 6). Besides the strong association of OSA with RS, PSG is an important evaluation of central apneas that also appear to be more prevalent in RS(7).

The present study was designed aiming at the evaluation of polysomnographic parameters association with the severity of clinical manifestations. Moreover, we have quantified the

correlation of each of these parameters with the severity of the clinically obstructive disorder in RS patients through a determination coefficient.

Material and Methods:

The present study reports data from the extension of a cohort of patients presenting glossoptosis, already mentioned in a previous paper (8).

Site of study

The prospective cohort, in which this cross-sectional study is nested, took place in the Hospital de Clínicas de Porto Alegre (Rio Grande do Sul, Brazil), from October 2012 to June 2016, and was submitted to Institution's Research Ethics Committee approval prior to initiation. All newly diagnosed RS patients at our institution during study period were enrolled. Written informed consent was obtained from parents or legal guardians of all patients. No exclusion criteria were defined.

Diagnostic workup

Diagnosis of RS was established based on a multidisciplinary evaluation. Patients were required to meet all of the following criteria:

g) Respiratory dysfunction: defined as any airway obstruction symptom, whether while on activity engagement, specific positioning, feeding or at rest (reported by caretaker or observed by hospital staff) and confirmed by PSG. Only

patients presenting obvious respiratory distress (on mechanical ventilation or other type of respiratory support) were not submitted to PSG.

h) Glossoptosis: observed through sleep endoscopy and according to Pierre Robin definition(9, 10).

i) Micrognathia: assessed through three-dimensional CT and defined as a shortening of mandible body and/or ramus.

After initial diagnostic workup, patients were divided in three groups according to concurrent findings: 1. isolated RS; 2. RS-plus (associated with additional congenital malformations but without a specific syndromic diagnosis); 3. syndromic RS(11).

Symptomatology grading

The RS classification system based on symptom severity, reported by Cole et al (12), was applied to all patients as follows:

- Grade 1: no respiratory distress when nursed supine;
- Grade 2: intermittent evidence of mild respiratory obstruction when nursed supine; feeding precipitates some respiratory distress;
- Grade 3: moderate to severe respiratory distress when nursed supine, unable to feed orally.

Polysomnographic evaluation

Patients underwent a PSG, without any sleep deprivation or sedation. Overnight and daily sleep studies were performed using standard polysomnographic techniques according with the American Academy of Sleep Medicine (13, 14). Overnight and daytime examinations had the

same assembly, and daytime examinations had a minimum of four hours of duration. Data collection included number of obstructive, mixed and central apneas, number of hypopneas as well as apnea and hypopnea index (AHI), oxygen desaturation nadir, percentage of total sleep time with arterial oxygen saturation below 90%, oxygen desaturation index. Hypopnea was considered whenever nasal pressure amplitude decreased by 30% or more, compared to the previous two ventilations, and when blood oxygen level dropped by 4% or more in the subsequent 30 seconds. Besides typical polysomnographic parameters, the percentage of time presenting obstruction was included and calculated as (number of apneas + number of hypopneas) x mean duration of events / total sleep time in seconds. All sleep studies were interpreted by the same Pediatric Pulmonologist (S.F.) certified in sleep medicine.

Statistical Analysis

We have analyzed different polysomnographic parameters along progressing grades of Cole et al. Continuous variables were assessed for normality with Shapiro-Wilk test. Non-normally distributed variables were described as median and interquartile range (25^{th}-75^{th} percentiles). Discrete variables were described as total number of cases and percentage of total sample.

As the main outcome for this study was an ordinal dependent variable of 3 categories (Grades 1, 2 and 3 of Cole et al, with progressing clinical severity), we have constructed a mathematical model that could incorporate this information in the estimation of association measures. For this reason, we have chosen a cumulative odds ordinal logistic regression with proportional odds implemented in separated univariate models (one for each PSG parameter studied). We have adopted this approach due to the limited number of patients studied and possible multicolinearity among predictors, which could lead to uncontrollable instability of association measures on a multivariable model. Goodness of fit was assessed through Pearson

and deviance tests and proportionality of odds was tested with Paralell Lines Test. We have also computed Pseudo-R^2 statistics and reported it as Nagelkerke R^2 (a function similar to determination coefficient from Pearson Correlation). Briefly, Pseudo-R^2 statistics determinates the proportion of the variance of a dependent variable that could be explained solely by the variation of the predictor analyzed. Ordinal regression gives out an association measure (Odds Ratio) that represents the chance of progressing from a lower level category to a higher level category, in a cumulative manner, for each variation of the predictor variable. A significance level of 5% was assumed for all comparisons. Analyses were performed using SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Macintosh, Version 20.0. Armonk, NY: IBM Corp).

Results

During the enrollment period, a total of 80 patients were considered eligible to join the study cohort. Baseline characteristics for this population are shown in Table 1. From these patients, 55 (68,75%) underwent PSG studies and were included in the cross-sectional study.

Table 1. Patients baseline characteristics.

Variable	n=80
Age (days)◆	50.5 (17 – 119.7)
Male sex (%)*	49 (61.3%)
Cole et al Classification*	Grade 1: 29 (36.3%) Grade 2: 19 (23.8%) Grade 3: 32 (40.0%)
Nasogastric Tube/ Gastrostomy*	39 (48.8%)
Tracheostomy*	13 (16.9%)
Airway anomalies*	24 (30.4%)
Classification*	Isolated RS: 35 (43.75%) RS Plus: 25 (31.25%) Syndromic RS: 20 (25%)
Cleft palate*	25 (31.3%)

*N and Percentage. ◆Median and interquartile range (25^{th}-75^{th} percentiles).

Distribution of PSG parameters among Cole et al grades is shown on Table 2.

Table 2. Distribution of PSG parameters in total study sample and along increasing severities of Cole et al grading system.

PSG Parameter	Study Sample*	Cole Grade 1*	Cole Grade 2*	Cole Grade 3*
Desaturation Index	10.2 (4.7-25.4)	7.0 (3.7-12.5)	19.3 (6.6-30.5)	18.3 (3.8-42.5)
Apnea/Hypopnea Index	11.0 (4.7-27.0)	5.9 (3.2-18.5)	17.5 (10.0-27.8)	19.2 (6.1-33.6)
Sleep Mean Oxygen Saturation	96.9 (95.6-97.1)	97.0 (96.5-98.0)	96.1 (95.0-97.0)	95.0 (93.0-97.0)
Oxygen Saturation Nadir	83.0 (77.2-87.0)	85.0 (82.0-87.5)	81.0 (74.0-87.0)	77.0 (72.0-85.0)
Percentage of time under an oxygen saturation of 90%	1.39 (0.2-4.1)	0.5 (0.23-1.48)	2.3 (0.45-5.25)	8.1 (4.76-9.02)
Percentage of time presenting obstruction	2.17 (0.96-5.29)	1.0 (0.07-3.2)	2,9 (1.8-7.6)	4.5 (2.2-11.3)

*Median and interquartile range (25^{th}-75^{th} percentiles).

Odds ratios and Nagelkerke R^2 derived from univariate mathematical models are described for each PSG parameter in Table 3. Goodness of fit, based on Pearson and deviance statistics,

and proportionality of odds assumption, by Parallel Lines Test, were considered adequate for all models (P>0.05).

Table 3. Estimation of PSG parameters Odds Ratio and Pseudo-R^2 of belonging to a higher grade of Cole et al.

Predictor*	Ordinal OR	95%CI	Nagelkerke R^2	P-Value
Desaturation Index	1.269	1.070-1.506	19.8%	0.006
Apnea/Hypopnea Index	1.133	1.015-1.264	12.5%	0.027
Mean Sleep Oxygen Saturation	0.162	0.050-0.524	22.6%	0.002
Oxygen Saturation Nadir	0.733	0.560-0.961	10.0%	0.024
Percentage of time under an oxygen saturation of 90%	9.486	1.627-55.315	37.6%	0.012
Percentage of time presenting obstruction	2.496	1.308-4.764	25.1%	0.006

*A 5 units increase in predictor variable is considered for the purpose of OR calculation in these models.

Discussion

We performed a clinical and polysomnographic evaluation in a very specific group of patients. So far, this is the first study to ascertain association of polysomnography parameters with clinical manifestations, not only qualitatively, but also quantitatively. We were able to observe that PSG parameters behave indeed as they would be presumed to, showing increasing median measures for each progressing grade of clinical severity. Also, this pattern allowed us to quantify the magnitude of how much each PSG parameter relates to clinical severity, granting the possibility of predicting symptomology through PSG examination.

Nagelkerke R^2 statistics tell us about how much of outcome variation would possibly be explained by one particular predictor. In this study, percentage of time under 90% of oxygen saturation was strongly associated with clinical manifestations and also influenced more than

one third of severity grading variation. The fact that this parameter performs better than AHI reinforces the knowledge that children often have a greater decrease in oxygen saturation levels, as they have a lower functional residual capacity and a faster respiratory rate than adults(6). Also, percentage of time presenting obstruction and mean sleep oxygen saturation correlated well with Cole et al classification grades. We emphasize the importance of those parameters of respiratory obstruction severity evaluation. It seems that the AHI, extensively valued in the literature, is not adequately capable in discriminating subgroups of severity in patients, especially in the pediatric population. Many children, particularly those younger than three years of age, have a pattern of persistent, partial upper airway obstruction associated with hypercapnia and/or hypoxemia, rather than cyclic discrete obstructive apneas, rendering low AIHs (6).

We know that PSG, the primary approach for evaluating sleep-disordered breathing, is not a perfect tool, still lacking normative data on basic parameters. When we analyze polysomnographic measures assumed as normal references in studies with RS patients, we observe a relevant heterogeneity in the used criteria. Anderson et al(15) and Neto et al(16) classify OSA based on AHI: mild obstructive sleep apnea as 1 to < 5 events per hour, moderate as 5 to < 10 events/hour and severe as ≥ 10 events/hour. Bravo et al(17) used the obstructive respiratory distress index (ORDI), including hypopneas, obstructive and mixed apneas per hour of sleep, and defined as diagnostic of OSA an ORDI > 5, considering a mild disorder from 5 to 20, moderate, from 21 to 40 and severe, > 40. Monasterio et al(18) considered as diagnostic of OSA only apneas and recommend a cut-off of 5 events/hour.

Based on the findings of our study, we would recommend that traditionally undervalued parameters other than AIH should be carefully considered in polysomnographic evaluation of RS children.

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10. CONSIDERAÇÕES FINAIS

O presente estudo acrescenta à literatura o papel da endoscopia de via aérea na SR, mostrando que a classificação da glossoptose é pouco sensível, mas específica na identificação de manifestações clínicas graves. Além disso, mostramos que parâmetros polissonográficos (porcentagem do tempo com saturação menor que 90%, porcentagem do tempo apresentando obstrução e média de saturação de oxigênio durante o sono) pouco valorizados na análise da polissonografia são os que apresentam maior associação com os sintomas.

11. PERSPECTIVAS FUTURAS

Ainda temos muito pela frente. São necessários mais estudos para se verificar a melhor forma de indicar o tratamento e avaliar a resposta terapêutica na SR, o papel da videoendoscopia da deglutição, as diferenças entre SR isolada, sindrômica e *plus* nos aspectos estudados nessa tese e na resposta ao manejo indicado. Além disso, precisamos confirmar os achados dos dados polissonográficos com amostra maior de pacientes e, em confirmando tais achados, estudar o papel da polissonografia portátil nesses pacientes.

ANEXOS:

ANEXO 1:

PROTOCOLO DE INCLUSÃO NÚMERO: _____

IDENTIFICAÇÃO:
NOME: _____
PRONTUÁRIO: _____
SEXO: ( ) 1. FEMININO ( ) 2. MASCULINO
DATA DE NASCIMENTO: ____._____._____
FONE: _____
ENDEREÇO: _____

SINAIS E SINTOMAS:

	Pré- op	**Pós-op (**3 a 6 meses)
Ruído Respiratório?	1. ( ) sim 0. ( ) não	1. ( ) sim 0. ( ) não
Ruído é espontâneo?	1. ( ) sim 0. ( ) não 2. ( ) não se aplica	1. ( ) sim 0. ( ) não 2. ( ) não se aplica
Ruído x choro?	1.( )piora2.( )melhor3.( )não altera4. ( )não se aplica	1.( )piora2.( )melhor3.( )não altera4. ( )não se aplica
Ruído x sono?	1.( )piora2.( )melhor3.( )não altera4. ( )não se aplica	1.( )piora2.( )melhor3.( )não altera4. ( )não se aplica
Ruído x alimentação?	1.( )piora2.( )melhor3.( )não altera4. ( )não se aplica	1.( )piora2.( )melhor3.( )não altera4. ( )não se aplica
Episódios de cianose?	1. ( ) sim _____episódios 0. ( ) não	1. ( ) sim _____episódios 0. ( ) não
Apnéias	1. ( ) sim _____episódios 0. ( ) não	1. ( ) sim _____episódios 0. ( ) não
Dessaturações	1. ( ) sim 0. ( ) não	1. ( ) sim 0. ( ) não
Baixo ganho pondero-estatural?	1. ( ) sim_____ 0. ( ) não	1. ( ) sim_____ 0. ( ) não
Dificuldade de alimentação?	1. ( ) sim_____ 0. ( ) não	1. ( ) sim_____ 0. ( ) não
Pneumonia prévia?	1. ( ) sim _____episódios 0. ( ) não	1. ( ) sim _____episódios 0. ( ) não
Retração fúrcula/intercostal	1. ( ) sim 0. ( ) não	1. ( ) sim 0. ( ) não

COLE et al: 1. ( ) GRAU 1 2. ( ) GRAU 2 3. ( ) GRAU 3

Via Alimentação atual: 1.( ) VO 2.( ) SNG 3.( ) Gastrostomia
4.( ) VO + SNG 5.( ) VO + gastrostomia

	Pré- Op	**3-6m pós op**
Peso:	_____Kg (p____)	_____Kg (p____)
Altura:	_____cm (p____)	_____Kg (p____)

HISTÓRIA MÉDICA PREGRESSA:
Pré-natal sem intercorrências: 1. ( ) sim 0. ( ) não: _____
Parto: 1. ( ) normal 2. ( ) cesária _____

IG: _____ Apgar: 1'____; 5'_____; 10'_____
PESO AO NASCIMENTO: _____

CLASSIFICAÇÃO GENÉTICA: 0. ( ) ISOLADO
1. ( ) SINDROMICO _____

2. ( ) PLUS _____

DIAGNÓSTICO PRÉVIO SAOS? 1. ( ) sim 0. ( ) não

ECOCARDIOGRAMA: 1. ( ) sim _____ 0. ( ) não

Internação hospitalar: 1. ( ) desde o nascimento 2. ( ) após _____ dias de vida
Causa da internação: _____

HISTÓRIA DE INTUBAÇÃO TRAQUEAL: 1. ( ) sim : ( ) para procedimento ( )_____ dias (se for em UTI)
0. ( ) não

ANEXO 2:

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto: **DESCRIÇÃO DOS ACHADOS DE DEGLUTIÇÃO, POLISSONOGRAFIA E ENDOSCOPIA DE VIA AÉREA PRÉ E PÓS DISTRAÇÃO MANDIBULAR EM SÉRIE DE PACIENTES COM GLOSSOPTOSE**

Estamos convidando _____ a participar do estudo acima descrito, que será realizado no Hospital de Clínicas de Porto Alegre – HCPA. Portanto, na condição de pai/mãe ou representante legal do paciente, solicitamos a sua autorização. O estudo tem por objetivo realizar uma descrição das alterações encontradas nos pacientes que nascem com glossoptose para melhor entender a doença.

O paciente nasceu com esta alteração, que está sendo tratada e acompanhada pelos profissionais do HCPA. Solicitamos a sua autorização para utilizarmos neste estudo os resultados dos exames que serão realizados na avaliação assistencial da criança (endoscopia de via aérea e polissonografia).

Além disso, a avaliação da deglutição, apesar de importante, não é realizada de rotina nos pacientes que nascem com glossoptose no HCPA. Esta será a única avaliação exclusiva para este estudo. Solicitamos sua autorização para realizarmos essa avaliação adicional.

Para estudar a forma como o paciente está engolindo e verificar se ele tem uma dificuldade, faremos duas avaliações antes da cirurgia para corrigir a alteração na língua. A primeira é uma avaliação clínica feita pela fonoaudióloga. Ela vai examinar a boca, a língua, os dentes e outras estruturas da face e, em seguida, vai observar você oferecer o leite, sendo uma mamadeira com leite ralo (líquido normal) e outra com leite engrossado com mucilon. A avaliação será feita no HCPA, e você poderá acompanhar o paciente. Depois dessa avaliação, ele fará um exame chamado videofluoroscopia. Esse exame vai ser feito por outra fonoaudióloga. Você vai oferecer o leite da mesma forma como ofertou na avaliação anterior, sendo que será acrescentado o sulfato de bário para contraste. A videofluoroscopia é o registro dinâmico do momento em que se está engolindo o alimento, através da exposição à radiação. O exame é rápido – não vai ultrapassar 150 segundos (2 minutos e 30 segundos), não dói e não gera riscos à saúde da criança por ser extremamente controlada a quantidade de radiação emitida e a duração do exame.

Não são conhecidos riscos pela realização destas avaliações, mas poderá haver algum desconforto ao realizá-las. O benefício pela participação será a realização das avaliações adicionais, e, possível seguimento com fonoaudióloga, se necessário.

Solicitamos sua autorização para repetir essas avaliações 3 a 6 meses após a cirurgia.

Se for visto que a criança apresenta disfagia, ela será encaminhada à Clínica de Fonoaudiologia da Universidade Federal do Rio Grande do Sul (UFRGS), onde será acompanhada e a família será orientada sobre a dificuldade para engolir.

A participação é importante para estudarmos as verdadeiras repercussões da glossoptose nas crianças e a melhora com a cirurgia. Porém, se você não autorizar a participação na pesquisa, isso não impedirá nem irá interferir no atendimento que o paciente está recebendo no HCPA. Em qualquer momento do estudo você pode retirar a autorização, sem qualquer prejuízo ao atendimento do paciente.

Os resultados do estudo serão divulgados em conjunto, e os nomes dos participantes não serão divulgados.

Eu_____ (pai/mãe ou representante legal) do paciente, recebi as informações sobre os objetivos e a importância desta pesquisa de forma clara e autorizo a participação da mesma(o) na pesquisa. Em caso de dúvida, você poderá entrar em contato com os pesquisadores através dos telefones (51) 9843 1887 – Dra Denise Manica ou (51) 9804 7175 – Fga. Marisa Gasparin. Ou ainda, o pesquisador responsável: Prof. Dr. Paulo José Cauduro Marostica (51) 3359 8213. Em caso de dúvida, também poderá contatar o Comitê de Ética em Pesquisa do HCPA (51) 3359 7640.

Este Termo será assinado em duas vias, sendo uma via do participante e outra dos pesquisadores.

Nome do Responsável _____

Assinatura do Responsável _____

Nome do Pesquisador que aplicou o Termo _____

Assinatura do Pesquisador _____

Data: __/__/____

ANEXO 3:

NOME: _____

PROTOCOLO DA NASOFIBROLARINGOSCOPIA

DATA: _____ ( ) Pré DOM ( ) Pós DOM

Classificação de Yellon – 2006:

1. ( ) Grau 0
2. ( ) Grau 1
3. ( ) Grau 2
4. ( ) Grau 3

Com fenda: Classificação de de Sousa et al 2003:

1. ( ) leve
2. ( ) moderada
3. ( ) grave

0. ( ) não se aplica

Laringo com ótica: Dificuldade laringoscópica

1. ( ) nenhuma
2. ( ) leve: não vê parte anterior de PsVs
3. ( ) moderada: não vê parte posterior de PsVs
4. ( ) grave: não vê nem aritenóides

Laringo flexível

Laringomalacia: 0. ( ) não 1. ( ) sim:

0. ( ) não se aplica; 1. ( ) obstrutiva; 2. ( ) não obstrutiva

Faringomalacia: 0. ( ) não 1. ( ) sim:

0. ( ) não se aplica; 1. ( ) obstrutiva; 2. ( ) não obstrutiva

Epiglote: 1. ( ) normoposicionada
2. ( ) toca em parede posterior
3. ( ) não visualizada

Língua: 1. ( ) normoposicionada
2. ( ) oclui valecula
- Outras alterações: ( ) sim _____
( ) não

Tração do queixo desobstrui VA: 1. ( ) sim:
0. ( ) não se aplica; 1. ( ) totalmente; 2. ( ) parcialmente
0. ( ) não

Tempo do exame:

Complicações anestésicas:

1. ( )queda de saturação até 85% com recuperação rápida
2. ( )sangramento nasal leve
3. ( )laringoespasmo sem necessidade de ventilação.
4. ( ) dessaturação abaixo de 85%
5. ( ) bradicardia
6. ( )laringoespasmo com necessidade de ventilação ou intubação traqueaL

ANEXO 4:

NOME: _____

PROTOCOLO DA POLISSONOGRAFIA

POLISSONOGRAFIA 1: _____

- ( ) Diurno ou ( ) Noturno
- ( ) Estridor, ( ) Respiração paradoxal ou ( ) n.d.a.
- Posição durante o sono: ( ) DD, ( ) outras _____
- Uso de O2 durante o sono: ( ) sim ou ( ) não
- Sono induzido: ( ) sim (_____) ou ( ) não
- FC: _____ bpm
- SpO2: Média: _____ %
  Nadir: _____ %
  SpO2 < 90%: _____ do TTS
- Índice de dessaturação: _____/ hora
- EtCO2: _____ mmHg
- Apnéias obstrutivas: _____ Média de duração: _____ s
- Apnéias centrais: _____ Média de duração: _____ s
- Apnéias mistas: _____ Média de duração: _____ s
- Hipopnéias obstrutivas: _____ Média de duração: _____ s
- IAH: _____
- % obstrução/ TTS: _____
- Tempo total de registro (TTR): _____ min
- Tempo total de sono (TTS): _____ min
- Microdespertares: _____
- Acordares: _____
- Eficiência do sono: _____
- Todos estágios do sono previstos para a idade foram atingidos? ( ) sim ( ) não

- Conclusão: ( ) 1. Exame normal
  ( ) 2. Distúrbio respiratório obstrutivo leve durante o sono
  ( ) 3. Distúrbio respiratório obstrutivo moderado durante o sono
  ( ) 4. Distúrbio respiratório obstrutivo grave durante o sono

POLISSONOGRAFIA 2 (pós-tto): _____

- ( ) Diurno ou ( ) Noturno
- ( ) Estridor, ( ) Respiração paradoxal ou ( ) n.d.a.
- Posição durante o sono: ( ) DD, ( ) outras _____
- Uso de O2 durante o sono: ( ) sim ou ( ) não
- Sono induzido: ( ) sim (_____) ou ( ) não
- FC: _____ bpm
- SpO2: Média: _____ %
  Nadir: _____ %
  SpO2 < 90%: _____ do TTS
- Índice de dessaturação: _____/ hora
- EtCO2: _____ mmHg
- Apnéias obstrutivas: _____ Média de duração: _____ s
- Apnéias centrais: _____ Média de duração: _____ s
- Apnéias mistas: _____ Média de duração: _____ s
- Hipopnéias obstrutivas: _____ Média de duração: _____ s
- IAH: _____
- % obstrução/ TTS: _____

- Tempo total de registro (TTR): _____ min
- Tempo total de sono (TTS): _____ min
- Microdespertares: _____
- Acordares: _____
- Eficiência do sono: _____
- Todos estágios do sono previstos para a idade foram atingidos? ( ) sim ( ) não

- Conclusão: ( ) 1. Exame normal
( ) 2. Distúrbio respiratório obstrutivo leve durante o sono
( ) 3. Distúrbio respiratório obstrutivo moderado durante o sono
( ) 4. Distúrbio respiratório obstrutivo grave durante o sono