International Journal of Pediatric Otorhinolaryngology 74 (2010) 743–746

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

The lipid laden macrophage index as a marker of aspiration in patients with type I and II laryngeal clefts☆

Stephen M. Kieran*, E. Katz, R. Rosen, U. Khatwa, T. Martin, R. Rahbar

Center for Aero-Digestive Disorders, Department of Otolaryngology, Children's Hospital Boston 300 Longwood Avenue, LO-367, Boston, MA 02115 USA

ARTICLE INFO

Article history:
Received 7 January 2010
Received in revised form 15 March 2010
Accepted 16 March 2010
Available online 14 April 2010

Keywords:
Laryngeal cleft
Lipid laden macrophage index
Pediatric aspiration
Laryngeal anomalies

ABSTRACT

Objectives: Laryngeal clefts are uncommon congenital anomalies that may cause pulmonary aspiration, leading to considerable morbidity including recurrent pneumonias. The lipid laden macrophage index (LLMI) is a potential marker of pulmonary aspiration. The objective of this study was to assess the utility of the lipid laden macrophage index as a marker of severity of pulmonary aspiration in children with laryngeal clefts and its role in the management of these patients.

Methods: An institutional review board approved retrospective review of all patients with laryngeal cleft who had also underwent direct laryngoscopy with rigid bronchoscopy and flexible bronchoscopy with bronchoalveolar lavage. The LLMI was measured from the lavage and compared to clinical and radiological data.

Results: Forty-four patients with laryngeal clefts (31 type I clefts and 13 type II clefts) underwent assessment with flexible bronchoscopy and bronchoalveolar lavage. The median age at first outpatient visit in our Center for Aero-digestive Disorder was 0.92 years in patients with type I clefts and 1.66 years in patients with type 2 clefts. All patients in this study had at least one modified barium swallow (MBS) performed to assess for aspiration. The mean LLMI was significantly higher in patients with type II (mean ± SEM) 81.8 ± 11.9 clefts compared to type I clefts 44.9 ± 5.6.

Conclusions: We recommend obtaining LLMI in patients with laryngeal cleft. The lipid laden macrophage index is increased in patients with more severe laryngeal clefts, thus potentially predicting those patients whom would most benefit from early surgical intervention.

1. Introduction

Laryngeal cleft is a rare congenital condition caused by incomplete development of the posterior larynx. It has a wide spectrum of severity from a mild, shallow notch, which some consider a normal anatomical variant, to a complete communication between the trachea and esophagus. In order to accurately describe patients at different points in the disease spectrum a number of classification systems have been proposed [1–4]. Those clefts that extend completely through the cricoid cartilage and into the trachea tend to be associated with obvious clinical manifestations of aspiration. However, patients with less severe clefts (type I and II in the Benjamin classification system), can have inconsistent and intermittent clinical and investigative findings. As such, deciding which patients, with laryngeal clefts, require surgical repair or which can be managed medically is a difficult clinical decision. Currently, in our institution management is decided on a case by case basis and influenced by a number of clinical and radiological parameters.

The lipid laden macrophage index (LLMI) is a measure of the accumulation of lipids in the cytoplasm of alveolar macrophages. This accumulation of lipids in alveolar macrophages is considered to be evidence of inflammation, potentially caused by number of different factors (infection, inflammatory process, aspiration, etc.) [5–7]. The LLMI has thus become a widely utilized marker of pediatric gastroesophageal reflux related respiratory disease, however evidence supporting its clinical usefulness has been inconsistent [8–13]. The hypothesis of this study was that the LLMI would be elevated in patients with a laryngeal cleft. The secondary hypothesis was that the magnitude of the raised LLMI would correlate with the clinical severity of disease, thus potentially predicting those patients whom would most benefit from surgical intervention.

2. Materials and methods

All patients undergoing "triple assessment" for chronic respiratory symptoms and who were ultimately diagnosed to have a laryngeal cleft were entered in a prospectively maintained

☆ This paper was presented at the Triological society eastern section meeting, held in Boston, MA, USA on the 24th January 2009.

* Corresponding author. Tel.: +1 617 355 5064; fax: +1 617 730 0611.
E-mail address: skieran@rcsi.ie (S.M. Kieran).

0165-5876/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijporl.2010.03.028

database of laryngeal cleft patients. This database contained patient demographics, medical history, history of respiratory symptoms and diagnoses, age at first diagnosis of laryngeal cleft, feeding history (including gastrostomy tube dependence), plain chest X-ray findings, and surgical procedure performed. A retrospective review of this prospectively maintained database was performed with appropriate prior local institutional review board approval. All patients in this series also underwent at least one modified barium swallow to evaluate swallowing function.

Triple assessment consisted of direct laryngoscopy and bronchoscopy (DLB), flexible bronchoscopy and flexible esophagogastroduodenoscopy performed by members of a multidisciplinary team with a united special interest in pediatric aspiration. The procedures were all performed under general anesthesia, DLB was performed prior to endotracheal intubation and the interarytenoid region was examined using a laryngeal probe to confirm the diagnosis of laryngeal cleft. Clefts were classified using the Benjamin classification system [4].

Following endotracheal intubation flexible bronchoscopy was performed. The bronchoscope was wedged in a sub-segmental bronchus (the location of which was chosen based on radiographic findings or gross findings during the examination) and 1 or 2 aliquots of 1 mL/kg of sterile normal saline instilled and suctioned for pathologic analysis. The technique used for evaluation of LLMI was that described by Columbo and Hallberg [11]. One hundred consecutive macrophages are scored, depending on their lipid content on a scale of 0–4. These scores are then totaled giving a score between 0 and 400.

Spearman correlations were performed to measure the strength of association between continuous variables. The independent *t* test was used to compare means of normally distributed data. Statistical analysis was performed using Analyse-it software (v2.04. Leeds, United Kingdom).

3. Results

Forty-four patients with a diagnosis of laryngeal cleft based on clinical and endoscopic findings underwent triple assessment with flexible bronchoscopy and bronchoalveolar lavage with assay of LLMI between 2003 and 2008. Table 1 depicts the patient demographics of our study group. Nineteen patients (43%) were male. Thirty-one patients were diagnosed with a type I cleft, 15 of these were treated surgically whilst 16 were treated with non-operative measures (thickened feeds and dietary management). Thirteen patients were diagnosed with type II clefts, all of whom underwent endoscopic repair. Seven patients had been diagnosed with a particular syndrome, 5 with type I clefts and 2 in the type II cleft group. Theses syndromes were Tetralogy of Fallot, Opitz G, Angelman, Vater, Fetal Alcohol, Trisomy 21 and CHARGE. The median age at first outpatient visit in our Aerodigestive Center was 0.92 years in patients with type I clefts and 1.66 years in patients with type II clefts. Seven patients (16%) had an associated tracheoesophageal fistula (TEF). All patients in this study had at least one modified barium swallow (MBS) performed to assess for aspiration. Table 2 depicts the patient's clinical data, including medical history.

The mean LLMI was significantly higher in patients with type II (mean ± SEM) 81.8 ± 11.9 clefts compared to type I clefts 44.9 ± 5.6. No significant difference was noted between the mean LLMI for patients with evidence of aspiration on at least one MBS (49.4 ± 7.8) compared to no evidence of aspiration (64.2 ± 8.6). This could be explained by the fact that majority of these patients aspirate intermittently and a negative MBS does not rule out intermittent aspiration. We also did not see any significant difference between those patients with a history of pneumonia (59.3 ± 9.9) and no history of pneumonia (53.0 ± 7.5) (Fig. 1). The mean LLMI was higher for patients with reactive airway disease; however there was no difference in the LLMI mean for patients with other medical co-morbidities and symptoms (GERD, TEF, chronic cough). In five patients the LLMI was >100, 4 of these patients had type II laryngeal clefts. Using Spearman correlations we looked for a correlation between the LLMI and linear factors possibly related to the severity of disease. We found little if any relationship between the LLMI and the number of pneumonias a patient had experience, but did find a possible weak correlation between the LLMI and age at first visit to our Aerodigestive Center (Table 3).

Table 1
Demographics of patients with type I and II laryngeal clefts.

	All patients	Type I	Type II
Patients (*n*)	44	31	13
Male:female	19:25	13:18	6:7
Age at 1st visit (median year)	1.16	0.92	1.66
Associated syndrome	7 (16%)	5 (16%)	2 (15%)
TEF	7 (16%)	2 (6.5%)	5 (39%)
Surgical repair	28 (64%)	15 (48%)	13 (100%)

TEF: tracheoesophageal fistula.

Table 2
Clinical symptoms and investigate findings for patients with type I and II laryngeal clefts.

	All patients	Type I	Type II
History of recurrent pneumonia	15 (34%)	7 (23%)	8 (62%)
Chronic cough	14 (32%)	9 (29%)	5 (39%)
Reactive airway disease	8 (18%)	4(13%)	4 (31%)
Other respiratory conditions	17 (30%)	9 (23%)	8 (46%)
GERD	17 (39%)	12 (39%)	2 (15%)
Aspiration on MBS	22 (50%)	17 (55%)	5 (39%)
PEG – tube	5 (11%)	2 (7%)	3 (23%)

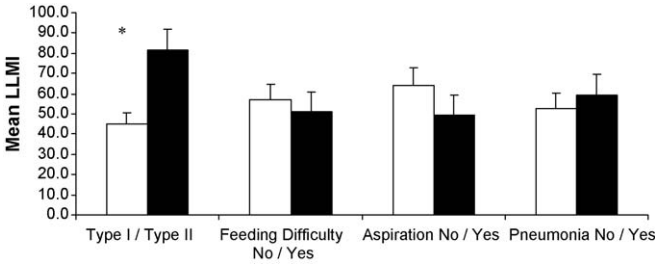

Fig. 1. Mean LLLMI for patients in different subgroups; type I and II clefts, feeding difficulty, no aspiration on MBS and aspiration, no history of pneumonia and definite history of pneumonia. Each bar represents mean ± SEM. $^{*}p < 0.05$.

4. Discussion

Laryngeal cleft is a rare condition with an overall incidence traditionally held to be in the region of 1 in 10,000 to 20,000 live births [14]. However, there may be a higher incidence of type I and type II clefts than previously thought [15]. In order to confirm the diagnosis, direct laryngoscopy under general anesthesia with probing of the interarytenoid region is required. Pre-operative videofluoroscopy, chest X-ray, barium swallow and fiberoptic endoscopic evaluation of swallowing (FEES) have been reported, but none remains a definitive diagnostic tool [16,17].

The management of laryngeal clefts type I and type II is also controversial, with some authors recommending early surgical intervention in all patients [18], whilst others recommend initial conservative management with positioning, antireflux medication and thickened feeds [19]. However, it is important to identify those