Received: 18 July 2018 | Accepted: 15 December 2018
DOI: 10.1002/ppul.24250

REVIEW

WILEY PEDIATRIC PULMONOLOGY

Magnetic resonance imaging of the larynx in the pediatric population: A systematic review

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Abstract

Background: Magnetic Resonance Imaging (MRI) techniques to image the larynx have evolved rapidly into a promising and safe imaging modality, without need for sedation or ionizing radiation. MRI is therefore of great interest to image pediatric laryngeal diseases. Our aim was to review MRI developments relevant for the pediatric larynx and to discuss future imaging options.

Methods: A systematic search was conducted to identify all morphological and diagnostic studies in which MRI was used to image the pediatric larynx, laryngeal disease, or vocal cords.

Results: Fourteen articles were included: three studies on anatomical imaging of the larynx, two studies on Diffusion Weighted Imaging, four studies on vocal cord imaging and five studies on the effect of anaesthesiology on the pediatric larynx. MRI has been used for pediatric laryngeal imaging since 1991. MRI provides excellent soft tissue contrast and good visualization of vascular diseases such as haemangiomas. However, visualization of cartilaginous structures, with varying ossification during childhood, and tissue differentiation remain challenging. The latter has been partly overcome with diffusion weighted imaging (DWI), differentiating between benign and malignant masses with excellent sensitivity (94-94.4%) and specificity (91.2-100%). Vocal cord imaging evolved from static images focused on vocal tract growth to dynamic images able to detect abnormal vocal cord movement.

Conclusion: MRI is promising to evaluate the pediatric larynx, but studies using MRI as diagnostic imaging modality are scarce. New static and dynamic MR imaging techniques could be implemented in the pediatric population. Further research on imaging of pediatric laryngeal diseases should be conducted.

KEYWORDS
imaging, larynx, magnetic resonance imaging, pediatric

1 | INTRODUCTION

Pathologies of the larynx in children are rare but severe conditions, and can have life-long consequences. The development of the larynx, normally completed around the 10th week of gestation, can fail at various time-points resulting in a variety of congenital laryngeal diseases.[1] After birth, the pediatric larynx is sensitive to acquired laryngeal insults, such as infectious diseases, inflammatory processes, and traumatic injuries (Table 1).[1] Severe cases might be in need for surgical intervention, such as micro- laryngeal surgery, laryngotracheal reconstruction, or tracheostomy.[1] In the adult population, the most common diseases in the laryngeal region are of neoplastic origin.[2]

To understand the nature of laryngeal pathologies, multiple imaging modalities can be used.[1,3,4] In the pediatric population, the choice of the right modality should be carefully considered according to the wide variety of pathologies and the patient's age. Direct laryngoscopy is the gold standard for early diagnostics of the pediatric larynx and vocal cords, but its disadvantages are the operator-dependant diagnostic accuracy, the absence of objective measurements, limited detailed imaging, and the need for anesthetics to get a clear view of the subglottis.[5–7] Computed Tomography (CT) is used for extensive imaging of the larynx after surgical intervention. A limitation of CT is the exposure to radiation, which is especially important in laryngeal imaging because it exposes the thyroid, one of the most sensitive organs, to radiation.[8] This explains the limited use of CT for dynamic imaging of the larynx.

Over the past decades, Magnetic Resonance Imaging (MRI) techniques have rapidly evolved into a promising and safe modality to image the larynx, with the availability of faster sequences and specialized surface coils.[3,9–11] However, most studies have been conducted in the adult population and are focused on laryngeal malignancies. There is a dearth of pediatric MR laryngeal imaging. Though, MRI is of great interest for imaging pediatric laryngeal diseases, as sedation is not needed in older children and the use of MRI is not accompanied by exposure to radiation. This makes MRI ideal for dynamic evaluation of the larynx and vocal cords.

The aim of this study is to review the existing literature for recent developments in MR imaging of the pediatric larynx and discuss future innovative MR imaging.

2 | METHODS

2.1 | Search strategy

A systematic search was developed to identify all morphological and diagnostic studies in which MRI was used to image the pediatric larynx. The search protocol was set up according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[12] A search was conducted on "pediatric" and "larynx" or "laryngeal disease" or "vocal cords" and "magnetic resonance imaging," the detailed search strategy is attached in online supplement S1. Data bases used were: EMBASE, Medline Ovid, Web of Science, Cochran and Google Scholar. In addition, the reference lists of the included

TABLE 1 Pediatric laryngeal pathologies for which MR imaging of the laryngeal region could be of use, freely adapted from Cummings Otolaryngology[46]

Congenital	Acquired	Infectious/inflammatory	Neoplasms	Vocal cord disorders
Laryngomalacia	Trauma	Laryngotracheobronchitis	Benign	Vocal cord nodule
Laryngeal atresia	Acquired glottic stenosis	Epiglottitis	Haemangioma	Vocal cord polyp
Laryngeal web	Mucosal trauma	Retropharyngeal abscess	Papillomatosis	Vocal cord granuloma
Laryngeal cleft	Blunt trauma	Diphtheria	Laryngeal/saccular cysts	Vocal cord paralysis
Congenital glottic stenosis		Tuberculosis	Laryngocele	Acquired
	Penetrating trauma	Granulomatosis Sarcoidosis	Subglottic cyst	Congenital Paradoxic vocal cord motion
	Gastro-pharyngeal reflux	Rheumatic disease	Neurofibroma	
			Malignant	
		Recurrent respiratory papillomatosis	Sarcoma	
		Relapsing polychondritis	Squamous cell carcinoma	
			Lymphoma	
			Mucoepidermoid carcinoma	
			Neuroectodermal tumour	
			Metastatic carcinoma	

articles were searched for additional articles of interest. Only original papers were included in this review. Reviews and case reports on less than ten patients were excluded due to risk of bias. The search was conducted in October 2017 and updated in December 2018.

2.2 | Article selection

The article selection was done by two independent reviewers (BE, SH). Each reviewer evaluated the abstracts on the type of article, the imaged anatomic region and cohort size ($n \geq 10$) and age (≤18 years). Selected full-text articles were again read on the type of article, imaged anatomic region, and the cohort size and age, and sufficient MR imaging data. "Sufficient" was defined as the following elements; MR scanner type and field strength, imaging parameters used, contrast, and/or sedation requirements. Disagreement on inclusion/exclusion based on abstract or full text of the articles was resolved by consensus.

3 | RESULTS

3.1 | Study selection

Eight hundred sixty-three articles were identified. Duplicate studies were eliminated and 860 articles were screened for title and abstract based on article type, anatomical area imaged, and number of patients included. The full text of 76 selected articles was reviewed for sufficient methodological information. Five articles were excluded based on incorrect article type, 18 on incorrect anatomic region, 12 on cohort size, 9 on cohort age, and 18 on insufficient MRI data, resulting in a final inclusion of 14 articles. The flowchart of the article selection is shown in Figure 1. Table 2 shows the final 14 articles selected for this review, online supplement S2 shows technical MRI information on the articles selected.

3.2 | Anatomical imaging

The first description of the pediatric larynx on MRI dates from 1991.[13] On 53 MRIs of patients aged between 1 day and 18 years, various laryngeal lesions, such as haemangioma, were evaluated and compared to CT in 25 cases. The images were evaluated by looking at four lesion characteristics: tissue contrast, detectability, extent, and origin. All MRIs were made on a 0.5 or 1.5T scanner, and at least one T1 weighted image and one T2 weighted image were obtained. Despite the use of these early scanning techniques, good anatomical visualization of mainly soft tissue was achieved. MRI was found to be excellent for all four lesion characteristics. T1 weighted images showed the best anatomical detail and T2 weighted images showed the best image contrast. Disadvantages

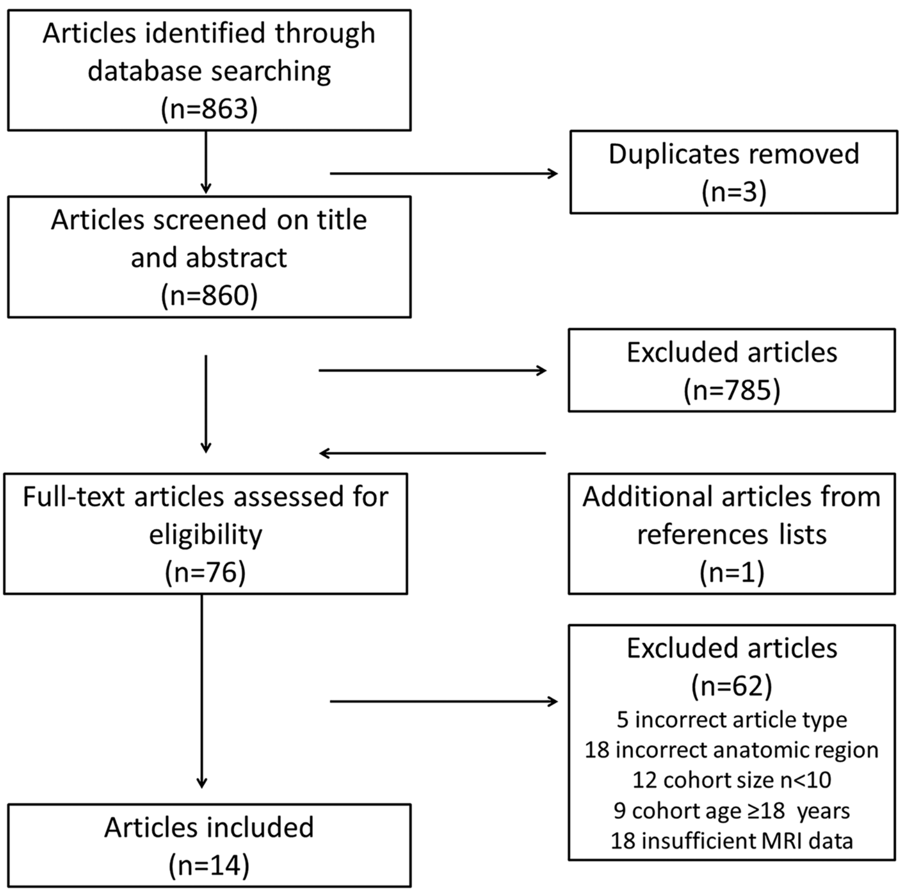

FIGURE 1 Flowchart of the article selection

TABLE 2 Key features for all selected articles that resulted from our systematic review

Study	Study population (*n*)	Age range (years)	Scanner	Sedation or anesthetics	Contrast (yes/no)	Sequences	Study aim	Main study result
Yuh[13]	53	0-18	Picker International, 0.5T GE, 1.5T	No	Both	T1, T2	Characterization of pediatric head/neck masses	MRI can accurately characterize pediatric head/neck masses
Hudgins[14]	15	0-16	Not defined, 1.5T	No	No	T1, FSE T2	Visualization of the normal pediatric larynx	The pediatric and adult larynx differ in size, position, consistency, and shape as seen on MRI
Fitch[20]	129	2.8-25	GE, 1.5T	No	No	T1	Quantification of vocal tract morphology during development	The post pubertal vocal tract is larger in males compared to females
Faust[21]	10	0-16	Siemens, 1.5T	No	No	SE T1, SE T2, cine-MRI	Dynamic visualization of the pediatric airway	Cine MRI can be used to visualize vocal cord movement in children (feasibility study)
Mahboubi[15]	45	0-2	Siemens, 1.5T	No	Both	SE T1	Visualization of pediatric upper airway obstruction	MRI can characterize pediatric airway abnormalities with high image quality
Litman[25]	99	0-14	GE, 1.5T	Sedation	No	SE T1	Determination of the effect of age on pediatric laryngeal diameter	In sedated children of all ages the narrowest part of the airway is the glottic opening
Litman[26]	17	2-11	Siemens, 1.5T	Anesthesia	No	T1	Evaluation of the effect of lateral positioning on the pediatric laryngeal diameter	Lateral positioning increases the airway dimensions in children
Vorperian[22]	63	0-6.6	GE, 1.5T Resonex, T not specified	Sedation	No	T1, T2	Evaluation of the growth pattern of the vocal tract	The vocal tract continues to grow from birth until 6.6 years of age without gender differences
Vialet[27]	30	0-8.8	Siemens, 1.5T	Anesthesia	No	SE T1	Evaluation of the effect of head extension on pediatric laryngeal diameter	Head extension increases the laryngeal visualization in pediatric patients
Abdel Razek[18]	78	0-15	Siemens, 1.5T	Sedation	Both	T1, FSE T2, DWI	Characterization of pediatric laryngeal masses with DWI	DWI can differentiate benign from malignant laryngeal masses with sensitivity 94.4% and specificity 91.2%
Vorperian[24]	307	0-19	GE, 1.5T Resonex, T not specified	Sedation	No	SE T1, FSE T2	Evaluation of developmental sex differences in vocal tract length	Sex differences in vocal tract length exist before puberty
Taha[19]	49	5-82	Philips, 1.5T	No	Yes	T1, T2, DWI	Characterization of laryngeal masses with DWI	DWI can differentiate benign from malignant laryngeal masses with sensitivity 94% and specificity 100%
Bécret[28]	155	0-18.5	Siemens, 1.5T	Anesthesia	No	SE T1	Quantification of the effect of age on airway modifications due to head extension	In children of all ages head extension increases the visualization of the larynx
Aqil[29]	60	0-12	Siemens, 3T	Anesthesia	No	RGE T1	Visualization of anatomical changes caused by different pediatric airway devices	Supraglottic airway devices alter pediatric airway dimensions

DWI, diffusion weighted imaging; FSE, fast spin- echo; RGE, rapid gradient echo; SE, spin-echo; T, Tesla; T1, T1 weighted image; T2, T2 weighted imaging.

of MRI were the difficulty to distinguish between inflammatory and malignant lesions, and difficulty to identify bony involvement due to changing ossification of cartilaginous structures in the developing pediatric larynx. Despite these disadvantages, MRI was proposed as an imaging tool to be superior to CT for the visualization of complex laryngeal structures, because of its excellent anatomical visualization.

In 1997 a 1.5T scanner was used to compare differences in anatomy and pathologies of the larynx between children and adults.[14] Despite the increased field strength of the MRI scanner, difficulties in the visualization of bony involvement, motion artefacts, poor spatial resolution compared to CT, and the inability to generate thin slices were seen as disadvantages for the clinical use of MRI.

However, in 2001 Mahboubi et al[15] using a 1.5T scanner, managed to produce remarkably good images of pediatric laryngeal lesions, such as haemangiomas and lymphangiomas, and their surrounding structures. Although visualization of bony involvement remained superior on CT, this study confirmed the great potential of MRI as a possible diagnostic modality for pediatric laryngeal lesions.

3.3 | Diffusion weighted imaging

For use of MRI for the diagnostics of pediatric laryngeal lesions, the most important disadvantages had to be overcome, especially the visualization of bony structures and tissue characterization. Inflammatory and malignant masses may have similar MRI signal intensity and the extent of mass can be hard to visualize, but is important to determine treatment options and prognosis. To overcome these difficulties Diffusion Weighted Imaging (DWI) of the laryngeal region was introduced in 2001 to characterize masses by their cellular density based on free motion of water protons.[16,17] Structures with cellular swelling or a high cellular density, such as malignancies, have less free water proton movement. In the first study that used DWI to image the pediatric larynx, multiple benign, and malignant masses; such as haemangioma, neurofibroma, and non-Hodgkin lymphoma, were visualized.[18] Benign masses could easily be discriminated from malignant masses with a sensitivity of 94.4% and a specificity of 91.2%.[18] Only two benign masses were falsely characterized as malignant due to the presence of high cellular compact bodies and fibrosis. In 2015 Taha et al[19] confirmed the feasibility of DWI to differentiate between benign and malignant laryngeal masses. They were able to detect the nature of laryngeal masses with a sensitivity of 94% and a specificity of 100% in an adult and pediatric cohort.

3.4 | Vocal cord imaging

The development of MRI sequences to visualize soft tissue allowed imaging of the vocal cords. The vocal cords were first imaged using MRI to define the differences in growth and maturation of the vocal tract between genders. In 129 children aged between 2 and 25 years the vocal tract was measured on MRI.[20] The laryngeal length increased over the years and its length correlated to body composition. Only small differences in vocal tract length were observed between boys and girls before puberty. However, in post pubertal boys a highly significant lengthening of the vocal tract was observed compared to girls. These differences were seen as a possible explanation for voice differences between the post pubertal genders.

In 2001 the first dynamic study of the vocal tract was conducted.[21] Faust et al[21] used cine- MRI to image the vocal tract in pediatric patients with impaired vocal function and healthy volunteers. The images, obtained during respiration and phonation, were viewed in a cine loop format. These cine-MRI images could easily identify impaired vocal cord movement and even showed patient-reported symptoms that could not be seen on endoscopy or static MRI. Figure 2 shows an axial MRI image of a healthy larynx during respiration (A) and phonation (B) from this study.[21]

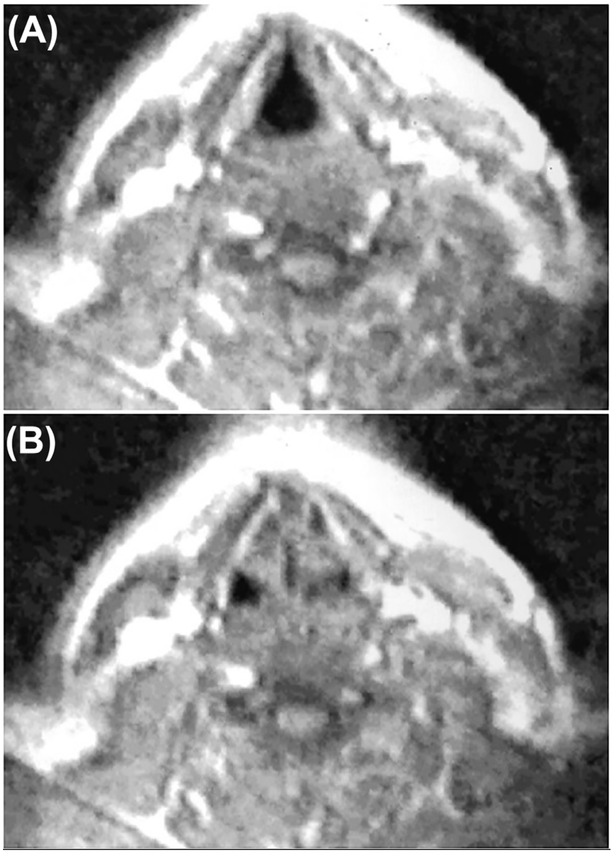

FIGURE 2 Axial TurboFLASH cine-MRI image (TR 2.5 ms, TE 1.2 ms, acquisition time 10 s per slice) with the use of a 1.5T MR imaging system (Siemens) of a healthy larynx during respiration (A) and phonation (B), showing bilateral symmetric vocal cord adduction during phonation.[21] (With permission)

Vorperian et al[22] imaged the vocal tract in 63 children aged between 2 weeks and 6.6 years old. The MRIs were used to assess the effect of the development of soft and hard laryngeal structures on the vocal tract. During childhood the larynx descends from the spinal level C3-C4 to C6-C7.[23] This laryngeal descent was found to account for 45-65% of the vocal tract lengthening, depending on specific age ranges. These findings emphasized the contribution of the larynx on voice development and showed that MRI was able to visualize the laryngeal region in different age groups. Vorperian et al[24] also evaluated vocal tract differences between genders, by measuring the vocal tract length on 307 MRIs of children aged between 0 and 19 years. The vocal tract length, measured on sagittal images as the length from the lips until the larynx, was significantly increased in boys compared to girls starting from an age of 12 years. This confirmed the gender differences shown in their earlier study.[22]

3.5 | Anesthetics in imaging

An important advantage of MRI for imaging of the pediatric larynx is the limited need for anesthetics. However, many of the earlier studies on MR imaging of the pediatric larynx had the primary aim to visualize the effects of anesthesia and deep sedation on the airway.[25–29] A reported side effect of anesthetics is respiratory distress, which in children is mainly caused by apnoea and upper airway collapse.[30] Despite multiple studies reporting the anatomy of the sedated pediatric larynx, none of the studies made a direct comparison between sedated and non-sedated patients.

The effect of sedation on the pediatric larynx was first described by Litman et al,[25] using MRI to study the effect of deep sedation on the airway in children between 0 and 14 years. The most narrow part of the airway was at the level of the glottic opening in all age groups. In contrast to previous cadaver studies describing the cricoid ring as the most narrow part of the airway. This discrepancy might have been caused by the lack of volume standardization during the MRIs, such as the use of a spirometer controlled MRI acquisition.[31] This might have resulted in images acquired during airway expiration, showing minor collapse of the laryngeal region. Another possible explanation is the use of propofol which can induce vocal cord tension, although this is not expected when sedation is maintained at a constant level.

Litman et al, Vialet et al, and Bécret et al further investigated the sedated laryngeal dimensions, concluding that the collapse of the pediatric airway during sedation can be partly overcome by positioning the child in either lateral or neutral position with a slight head extension.[26–28]

In the above mentioned studies, anesthetics was used as part of the research protocol, aiming to image the sedated airway. In other studies, anesthetics was used according to clinical protocols for scanning of non-cooperative young children.[14,15,18,22,24] In the study by Fitch et al,[20] where children as young as 2 years were instructed to lie still instead of using sedation, some images had to be excluded because of motion artefacts, which made it impossible to visualize the glottis.

4 | DISCUSSION

Current MRI protocols are well capable of visualizing soft tissue and vascular structures of the larynx (Figure 3 and online supplement S3). Fourteen publications on MR imaging of the larynx in the pediatric population were identified, mainly focusing on anatomy and anesthetics, however these findings show that MRI can be a valuable imaging tool for the visualization of several pediatric laryngeal diseases (Table 1).

4.1 | Anatomical imaging

The studies found show that MRI is the best imaging modality for detailed anatomy of the healthy pediatric larynx,[14] and laryngeal lesions such as haemangioma and cysts.[13,15]

MR imaging of the pediatric larynx remains challenging due to the developing anatomy and the variety of laryngeal pathologies. Limitations of MRI include limited spatial resolution and longer scanning times when compared to CT. Images can be degraded by

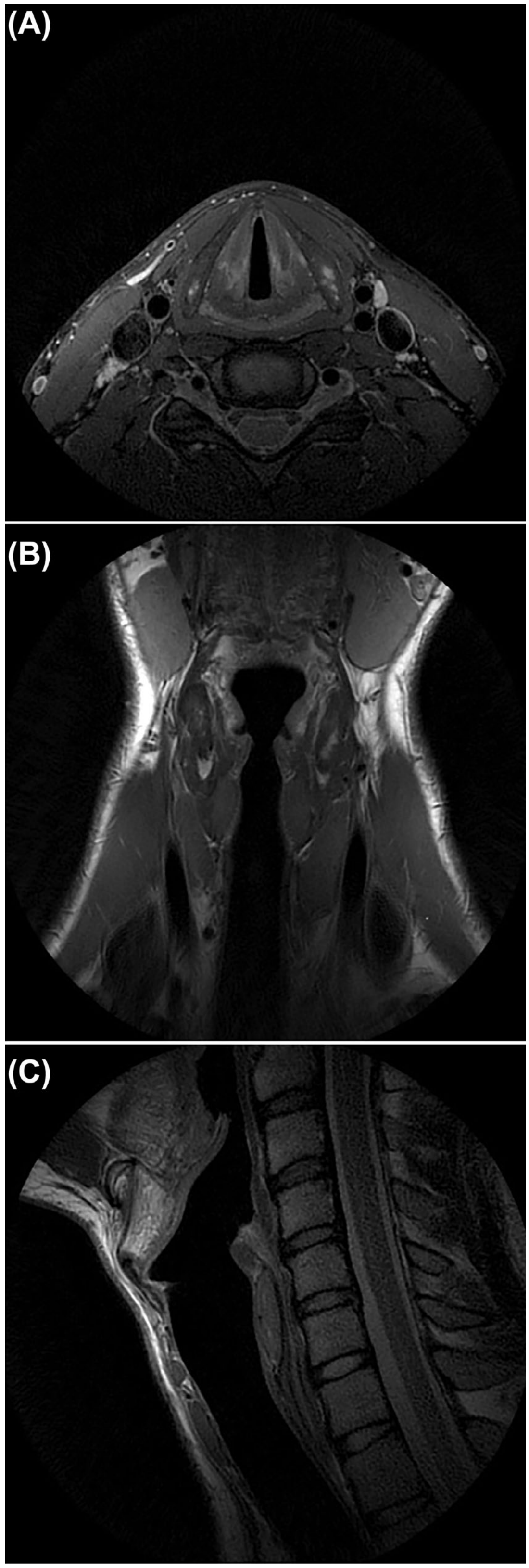

FIGURE 3 High-resolution T2 FSE weighted (PROPELLER) axial (A), coronal (B), and sagittal (C) images of the larynx of a healthy volunteer. Pediatric laryngeal MRI protocol developed at the Erasmus MC—Sophia Children's Hospital, with the use of a 3T MRI (GE Healthcare) using a 6 Chanel Carotid coil (spatial resolution 0.5x.0.5 (in plane) x 2 mm).

artefacts due to general patient movement or by swallowing or coughing.[32–34] Interestingly in this series of publications MR was described as an imaging technique that is relatively insensitive to motion and since the larynx stays in the same horizontal plane during respiration, the presence of respiratory artefacts is unlikely.[14,20] Technical developments in recent years have resulted in improved spatial resolution and dedicated hardware, such as the availability of 3T scanners and neck surface coils, are expected to further decrease scanning times and increase image quality.[35]

The findings described in pediatric studies are in line with studies conducted in the adult population, describing T1 and T2 sequences to provide excellent soft tissue characterization of the larynx.[11,32,36] This is particularly important for laryngeal diseases with complex anatomy, such as laryngotracheal stenosis, laryngoceles, and haemangioma which are easily identified on MRI.[3,32] Most selected studies compared the anatomy as shown on MRI to CT. No pediatric studies comparing MRI to laryngoscopy were found, but a comparative study in the adult population shows promising results in favor of MRI.[6]

4.2 | Tissue characterization

The visualization of cartilaginous structures of the pediatric larynx, with varying ossification stages during childhood, and the differentiation between inflammatory and malignant masses remain challenging on MRI,[11] but these are considered important factors in disease treatment and prognosis.[9,11,32] In the pediatric population, malignant masses are extremely rare, but benign lesions such as cysts and haemangioma are more common.[37–39] Two studies on the imaging of pediatric laryngeal lesions with T1 and T2 sequences were identified. These studies both described the differentiation between benign and malignant lesions and bony involvement to be inferior on MRI compared to CT. However, studies by Abdel Razek et al and Taha et al showed that the latter can be partly overcome with DWI,[18,19] which is in line with adult studies.[9,11,40] Tissue characterization over time has been shown in adult cohorts to be challenging, because inflammation and fibrosis after surgery or radiation is hard to distinguish from the primary lesion.[40] These challenges were not reviewed in this series, hence there is need for longitudinal studies in the pediatric population.

Another option to improve tissue characterization is the use of intravenous contrast. In three of the studies identified, contrast enhanced MRI was used.[15,18,19] In the studies by Taha et al and Abdel Razek et al gadolinium contrast was used in a diagnostic setting, but the advantage of contrast enhancement is not described.[18,19] Only the study by Mahboubi et al[15] described contrast administration to aid in the diagnosis of pediatric laryngeal lesions by enhancing vascular and malignant lesions. It should be taken into account that intravenous contrast has important disadvantages related to costs, renal impairment, possible allergic reactions, and the need for an intravenous cannula. Moreover, recent publications related to deposition of MRI contrast in human tissue have compelled the European Medicines Agency (EMA) to ban the use of specific gadolinium contrast media limiting their use to specific oncological purposes.[41–44]

TABLE 3 Advantages and disadvantages of pediatric laryngeal MRI

Advantages	Disadvantages
No sedation needed	Inferior spatial resolution to CT
Free of ionizing radiation	Long scanning time compared to CT
Excellent soft tissue contrast	Differentiation between malignant and inflammatory lesions can be challenging
Good visualization of vascular structures	Bony involvement can be challenging
Dynamic imaging possible	

4.3 | Vocal cord imaging

The imaging of the vocal cords has evolved from static images evaluating the growth of the vocal tract to dynamic cine-MRI for the visualization of (impaired) vocal cord movement.

The studies identified show promising results of using MRI for dynamic imaging of vocal cord function. Studies in the adult population show that quantification of vocal cord function is possible using dynamic MRI.[10,45]

4.4 | Anesthetics in imaging

The narrow and noisy environment of an MRI scanner, together with the need for a subject to lie still during the MRI examination often requires the use of anesthetics for laryngeal MRI investigations in children younger than 5 years.[18,24] Many of the studies identified in relation to anesthetics were conducted primarily for the development of safer methods for pediatric airway management during sedation or anesthesia.[25–29] These studies do not clearly answer the question if anesthetics is a prerequisite for laryngeal MRI in the pediatric population. However, these studies do show that the dimensions of the larynx on MRI change due to the administration of anesthetics and thus these images cannot be fully compared to the un-sedated airway. With the development of faster scanning protocols the need for anesthetics is likely to be reduced. The studies identified report scanning times up to 10 min per sequence.[21,25,29] However, a pediatric laryngeal MRI protocol developed at the Erasmus MC—Sophia Children's Hospital shows the possibility of an extensive anatomical and dynamic evaluation within 30 min. In addition, in the neonatal population where laryngeal MRI would be of interest to image congenital lesions, increasing experience with the use of the “feed and sleep”—method will make it possible to omit sedation. Likewise, dynamic laryngeal MRI techniques require full cooperation without the influence of anesthetics.

5 | CONCLUSION

MRI is a promising modality for the evaluation of pediatric laryngeal diseases (Table 3). Most of the MRI studies on the anatomy of the pediatric larynx were conducted before 2001, so with the recent technological advancements of MRI, image quality has definitely improved. The most recent studies focused on tissue characterization and on the effect of anesthesia in the larynx. Studies using MRI as a diagnostic imaging modality and longitudinal studies are scarce. In addition, although dynamic imaging of the vocal cords has been proven feasible in the adult population, implementation in the pediatric population is still lacking. Clinical studies on the technical use of MRI in the spectrum of pediatric laryngeal diseases, such as laryngeal stenosis and vocal cord dysfunction, are lacking. Further research should be conducted to explore these options.

ACKNOWLEDGEMENTS

We would like to acknowledge W.M. Bramer, from the Erasmus MC—medical library, for his assistance in the literature search. There is no funding to report for this study.

CONFLICTS OF INTEREST

Dr B. Elders, Dr S. Hermelijn, Dr B. Pullens, and P. Wielopolski report no disclosures. Prof Dr H. Tiddens reports to be involved in an industry symposium on cystic fibrosis with Roche, to be involved in lectures and the advisory board of Novartis. He has obtained grants from Vertex, Gilead, and Chiesi; outside this submitted work. He also has a patent licensed for Vectura and PRAGMA-CF and he is head of the Erasmus MC—Sophia Children's Hospital core laboratory Lung Analysis. Dr P. Ciet reports to have obtained personal fees from Vertex, outside this submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Elders BBLJ, Hermelijn SM, Tiddens HAWM, Pullens B, Wielopolski PA, Ciet P. Magnetic resonance imaging of the larynx in the pediatric population: A systematic review. *Pediatric Pulmonology*. 2019;54:478–486. https://doi.org/10.1002/ppul.24250