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Congenital Laryngomalacia: Is It an Inflammatory Disease? The Role of Vitamin D

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Objectives/Hypothesis: Laryngomalacia is the most common cause of stridor in infants. The exact pathophysiology is still not well understood. Our objective was to investigate whether laryngomalacia is an inflammatory disease, focusing on the possible role of vitamin D.

Study Design: Case-control study.

Methods: Sixty Egyptian infants and 60 mothers were included in this study. They were divided into four equal groups (n = 30 for each): infants with laryngomalacia (LM-infants), control infants (C-infants), mothers of the infants with laryngomalacia (LM-mothers), and mothers of the control infants (C-mothers). Laryngoscopy was performed and serum 25-hydroxyvitamin D (25[OH]-vitamin-D) and interleukin 6 (IL-6) were estimated.

Results: Significant increase of serum IL-6 associated with a significant decrease in serum 25(OH)-vitamin D was observed in the LM-infants compared to the C-infants ($P < .001$ for both). LM-mothers had significantly lower 25(OH)-vitamin D status compared to C-mothers ($P < .001$).

Conclusions: Deficiency of 25(OH)-vitamin D in LM-infants may result in dysregulation of the immune responses with elevation of a proinflammatory cytokine (IL-6). Laryngomalacia could be an inflammatory disease due to 25(OH)-vitamin D deficiency as evidenced by the high level of IL-6. This finding may open the door to the appropriate prevention, diagnosis, and treatment, especially for moderate to severe laryngomalacia.

Key Words: Laryngomalacia, 25-hydroxyvitamin D, interleukin 6, inflammatory disease, laryngoscopy.

Level of Evidence: 3b

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INTRODUCTION

Maternal vitamin D (VD) deficiency is a common public health problem.[1] The role of maternal nutrient status in normal fetal development has engendered substantial interest in research. High prevalence of VD deficiency has been demonstrated worldwide in many reports.[2–5] In pregnant women, VD diffuses through the placenta from mother to fetus; therefore, the mother is the only source of VD substrate for the developing fetus. Maternal VD deficiency, which is defined as serum 25-hydroxyvitamin D (25-[OH]-vitamin-D) level below 50 nmol/L, has been shown to also be associated with a VD-deficient fetus.[6]

It is well established that many tissues and cells in the body express VD receptors (VDRs),[7] including both placenta and embryonic kidneys, that exhibit an enzymatic machinery that converts the inactive VD metabolite into an active one.[8]

Low VD status during pregnancy has been associated with skeletal problems such as rickets and growth retardation,[9] as well as various adverse extraskeletal outcomes including type 2 diabetes mellitus and inflammatory disorders in offspring.[10] VD is well known for its role in regulating calcium and phosphorus for healthy mineralization of bone. Increasing evidence has broadened interest to the role of VD in many extraskeletal functions, including inflammation and immunoregulation.[11]

VD deficiency is widespread all over the world and is increasing as a result of sedentary lifestyles and deprivation of sunlight exposure.[12] VD deficiency has been recognized in the pathophysiology of many inflammatory and autoimmune diseases such as rheumatoid arthritis, Crohn's disease, and in conditions related to chronic low-grade inflammation, such as obesity, insulin resistance, type 2 diabetes mellitus, and cardiovascular disease.[13]

Expression of the VD receptor has been detected on a variety of immune cells including monocytes, T lymphocytes, dendritic cells, and macrophages.[14] VD acts as an influential immune moderator of both the adaptive and innate immune systems through its ability to alter cytokine secretion.[8]

Laryngomalacia is defined as collapse of supraglottic structures during inspiration.[15] Laryngomalacia is the most common cause of congenital stridor and is responsible for 45% to 75% of neonatal stridor. Most infants with laryngomalacia have mild symptoms with a benign disease course that resolves by the age of 2 years; however, some infants may have severe stridor that needs surgical intervention.[16] The exact etiology and pathophysiology of laryngomalacia is still

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unknown. However, some theories suggested that it may have neurological causes due to submucosal nerve hypertrophy[17] or altered sensorimotor integrative function of the larynx.[18]

Pathophysiology of laryngomalacia is still an important issue for medical research. Our hypothesis claims that laryngomalacia is an inflammatory disease due to a low neonatal serum 25-[OH]-vitamin-D level.

MATERIALS AND METHODS

Subjects

This case-control study was carried out in Sohag University Hospital, Sohag, Egypt, with collaboration of the Phoniatrics Unit, Otolaryngology Department, and Pediatric and Physiology Departments in the period from January 2016 to February 2018. The study protocol was approved by theSohag Faculty of Medicine Research Ethics Committee. Written informed consent was obtained from all parents. Infants aged from 1 ro 10 months who presented with laryngomalacia were included in the study (n = 30). The inclusion criteria were infants with laryngomalacia who were exclusively breast-fed and less than 1 year old. This group was referred to as LM-infants. These infants were presented to any of three clinics (phoniatric, ear, nose, and throat, or pediatric). Mothers of the infants with laryngomalacia were also included and referred as LM-mothers. Exclusion criteria were other congenital anomalies (e.g., subglottic hemangioma and stenosis), acquired causes of stridor (e.g., croup infection and endotracheal intubation), and infants with neurological disorders and syndromic identification. Another 30 breast-fed apparently healthy infants presented to the outpatient clinics with mild nonspecific complaints that needed endoscopy (e.g., mild snoring). These infants and their mothers represented the control groups and were referred as C-infants and C-mothers, respectively. All groups were recruited from the same population, and both matched groups had similar ages, and environmental, socioeconomic, and nutritional factors.

Methods

Infants included in this study were subjected to the following: 1) thorough history taking with special attention to inspiratory stridor and its aggravating factors such as crying, feeding, or supine position; 2) complete physical examination with stress on suprasternal retraction and the presence of any congenital anomalies; 3) laryngeal examination; and 4) laboratory investigations. All infants with laryngomalacia and their controls underwent endoscopy and were tested for serum 25(OH)-vitamin D, calcium, and interleukin 6 (IL-6). LM-mothers and C-mothers were tested for 25(OH)-vitamin D and serum calcium.

Laryngeal Examination

Flexible laryngoscopy (model 20045020, Karl-Storz, Tuttlingen, Germany) was performed in the phoniatrics clinic. Every infant was held in the upright position, and a flexible fiberoptic laryngoscope was passed through the nose, pharynx, and positioned above the larynx. Both phoniatricians and otolaryngologists performed endoscopy for the dynamic movement of the laryngeal structures during spontaneous respiration. Diagnosis of laryngomalacia was confirmed by supraglottic tissue collapse including the following situations: 1) partial obstruction of the laryngeal inlet during inspiration by dynamic infolding of both aryepiglottic folds, 2) tubular and/or curled omega-shaped epiglottis, 3) redundancy and prolapse of mucosa over both arytenoid cartilages drawn into the airway during inspiration, 4) shortening of the aryepiglottic folds, and 5) retroflexed epiglottis. All video recordings of the LM-infants and C-infants were assessed blindly and individually by four doctors (two otolaryngologists and two phoniatricians). Silent videos of LM-infants and C-infants were mixed and presented blindly to the examiners. The findings reported by more than two doctors were considered. The aim of this blind and individual assessment was to reduce bias in the diagnosis.

Sample Collection

Five milliliters of venous blood samples were drawn from all patients and control groups under aseptic conditions. The collected samples were centrifuged at 3000 rpm for 10 minutes. Then, the serum was stored at −80°C for further assessment of 25(OH)-vitamin D and IL-6.

Estimations of 25(OH)-Vitamin D

25-OH-vitamin-D was performed on an ARCHITECT i2000SR system using ARCHITECT 25-(OH)-vitamin-D kits supplied by Abbott Laboratories (Abbott Park, IL). 25-(OH)-vitamin-D was estimated by chemiluminescent microparticle immunoassay technology.[19]

Estimations of Serum Calcium

Serum calcium was performed on a Roche/Hitachi cobas c311 system and was determined by the use of a kit supplied by Roche Diagnostics (Indianapolis, IN).

Estimation of IL-6

The IL-6 was measured in duplicate with high-sensitivity, enzyme-linked immune absorbent assays (ELISA) using commercial kits (Bio Source International Inc., Camarillo, CA) according to the manufacture's instructions.[20]

Statistics

Data were analyzed by using IBM-SPSS statistics software version 24 (IBM, Armonk, NY). Data were expressed as mean ± standard deviation (SD). For comparison of the means between cases and controls, the Student *t*- test was used, considering a *P* value of <.05 as statistically significant. Analysis of the receiver operating characteristic (ROC) curve) was applied to estimate the predictive value of IL-6 to differentiate cases from controls and also to calculate the most relevant cutoff value for IL-6 that had the highest accuracy (sensitivity and specificity) to differentiate cases from controls.

RESULTS

Laryngeal examination showed common findings in the LM-infants that were 1) prolapse of the mucosa covering the arytenoid cartilages into the airway during inspiration (90%), 2) collapse of the laryngeal inlet by dynamic infolding of both aryepiglottic folds during inspiration (100%), 3) shortening of aryepiglottic folds and omega-shaped and tubular epiglottis (96.66%), and 4) mucosal congestion of the supraglottic area (90%). Endoscopy of the C-infants revealed a free larynx with no evidence of laryngomalacia apart from mild congestion of the nasopharynx and/or the larynx in 11 infants (36.66%).

VD status was defined as average (30 ng/mL or more), insufficiency (20–29 ng/mL), deficiency (10–19 ng/mL), and severe deficiency (<10 ng/mL). The VD statuses of both LM-infants and C-infants groups are shown in Table I.

TABLE I.
Comparison of Mean and Standard Deviations of 25(OH)-Vitamin D Between Infants With Laryngomalacia and Control Infants.

	LM-Infants (N = 30)		C-Infants (N = 30)	
	No. of Cases	Mean ± SD, 25(OH)- Vitamin D	No. of Cases	Mean ± SD, 25(OH)- Vitamin D
Normal	8	56.5 ± 27.6	15	56 ± 17.4
Insufficiency	1	25.8	8	25.3 ± 3.5
Deficiency	8	14.2 ± 3.2	5	14.6 ± 2
Severe deficiency	13	5.3 ± 2.3	2	8.9 ± 0.9

Vitamin D deficiency was found in 70% of LM-infants, whereas it was about 23% in C-infants, indicating the possible role of vitamin D deficiency in congenital laryngomalacia.

25(OH)-vitamin D = 25-hydroxyvitamin D; C-Infants = control infants; LM-Infants = infants with laryngomalacia; SD = standard deviation.

An independent *t* test was conducted to compare 25-(OH)-vitamin-D levels between infants with congenital laryngomalacia and controls (LM-infants and C-infants). The *P* values were two-tailed with a confidence interval of 95%. Results revealed that LM-infants had lower serum 25-(OH)-vitamin-D than C-infants, with highly significant difference as shown in Figure 1. The mean ± SD of 25(OH)-vitamin D in LM-infants and C-infants were 18.6 ± 22.15 and 37.85 ± 22.58, respectively. On the other hand, the serum calcium level did not show any significant difference between the two groups. The mean ± SD of calcium in LM-infants and C-infants were 9.32 ± 1.3 and 9.7 ± 0.63, respectively (Fig. 2).

The mean values of IL-6 were compared between both LM-infants and C-infants groups. The LM-infants revealed a higher level of IL-6 than the C-infants, with highly significant difference as shown in Table II. The ROC curve revealed that IL-6 can be used to differentiate between LM-infants and C-infants with highly a significant difference between the two groups ($P < .001$, 95%confidence interval with lower and upper bounds of 0.846 and 0.982) (Fig. 3). Moreover, analysis of the ROC curve showed that the maternal VD level can be used to predict hypovitaminosis D in the infants, with a highly significant difference ($P < .001$, 95% confidence interval with lower and upper bounds of 0.054 and 0.246) (Fig. 4).

The LM-mothers had lower serum 25(OH)-vitamin D than the C-mothers with a highly significant difference ($P < .001$) as shown in Table III. However, the LM-mothers and C-mothers had serum calcium levels of 8.8 ± 0.2 mg/dL and 9.7 ± 0.7 mg/dL, respectively, which revealed an insignificant difference.

Both LM-infants and C-infants had nearly similar ages and socioeconomic and nutritional statuses. The descriptive statistics for the age in both groups are shown in Table IV. Similarly, both mothers' groups (LM-mothers and C-mothers) had nearly similar ages and environmental, socioeconomic, and nutritional factors. The descriptive statistics for mothers' age are shown in Table III. The mean gestational age of LM-mothers was 23.8 ± 5.3 years and that of C-mothers was 24.6 ± 4.9 years with an insignificant difference.

DISCUSSION

Laryngomalacia is the most common cause of stridor in the newborns affecting up to 75%.[16] To the best of our knowledge, this is the first study concerning the relationship between congenital laryngomalacia and serum 25(OH)-vitamin D status in both infants and their mothers. All of our infants in the current research were exclusively breast fed. Our results demonstrated a statistically significant

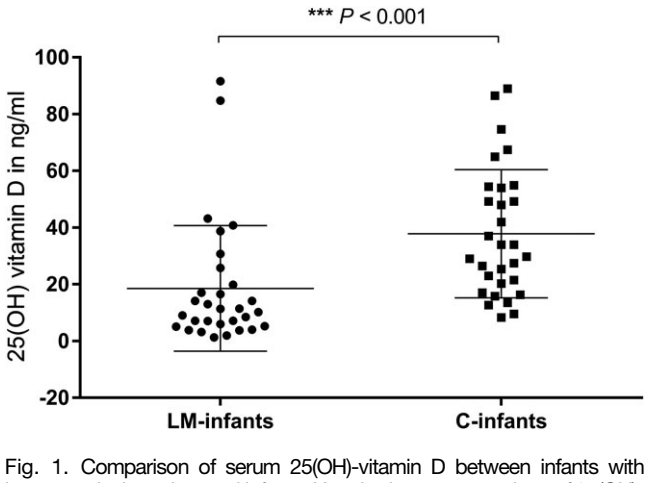

Fig. 1. Comparison of serum 25(OH)-vitamin D between infants with laryngomalacia and control infants. Unpaired *t* test comparison of 25(OH)-vitamin D showed lower vitamin level in infants with laryngomalacia (LM-infants) than control infants (C-infants) with a highly significant difference. The *P* value was two-tailed, with a confidence interval of 95%; $t = 3.716$ and $df = 29$. 25(OH)-vitamin D = 25-hydroxyvitamin D.

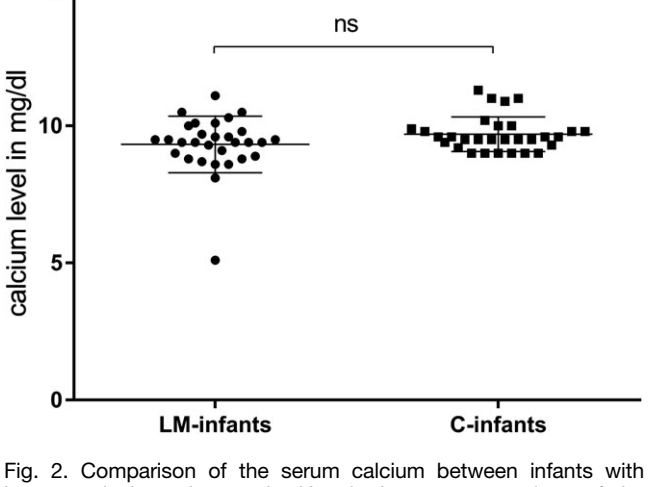

Fig. 2. Comparison of the serum calcium between infants with laryngomalacia and controls. Unpaired *t* test comparison of the serum calcium revealed no significant difference between infants with laryngomalacia (LM-infants) and control infants (C-infants). The *P* value was two-tailed, with a confidence interval of 95%; $t = 1.98$, and $df = 29$. ns = not significant.

TABLE II.
Comparison of IL-6 Between Infants With Laryngomalacia and Controls.

Group	N	Mean IL-6	SD	Standard Error of the Mean	*P* Value
LM-infants	30	9.57	3.720	0.679	<.001
C-infants	30	3.97	2.282	0.417	

Infants with laryngomalacia showed elevation of IL-6 compared to control infants with a significant difference. Unpaired *t* test: $t = 7.028$, $P < .001$ (highly significant). Mann-Whitney test = 77.000, $P < .001$ (highly significant).

C-infants = control infants; IL-6 = interleukin 6; LM-infants = infants with laryngomalacia; SD = standard deviation.

decrease in serum 25(OH)-vitamin D in LM-infants in comparison with C-infants. Similarly, LM-mothers revealed lower serum 25(OH)-vitamin D compared with C-mothers with a statistically significant difference. Moreover, a significant increase of serum IL-6 level in LM-infants was noticed in comparison with C-infants. These results are in accordance with Laird et al.[21] and Francesca et al.,[20] as they found significant associations between hypovitaminosis D (25[OH]-vitamin-D <25 nmol/L) and inflammatory marker levels including IL-6. In this article, IL-6 can be used to differentiate between LM-infants and C-infants (Fig. 3). Therefore, the key problem in LM-infants may be deficiency of the 25(OH)-vitamin D, with the resultant disturbance of its immune-modulatory function. On the other hand, serum calcium did not reveal any significant decrease in LM-infants. Hence, traditionally used oral calcium had no role in the treatment. Similarly, LM-mothers and C-mothers had no significant decrease or differences in calcium. In newborn and exclusively breast-fed infants, mothers are considered the only source for VD substrate. The VD diffuses through the placenta from mother to the developing fetus. Therefore, maternal deficiency of VD is associated with fetal VD deficiency,[6] as our results show in Figure 4.

Although dynamic obstruction was noticed in all LM-infants in the current study, it was more severe in infants with severe deficiency of VD. The anatomical abnormalities were varied among LM-infants, with no specific relation to VD status. Endoscopy of the C-infants revealed a normal larynx with no evidence of laryngomalacia apart from mild mucosal congestion in 11 subjects (36.66%). Among these, seven infants had deficiency and severe deficiency of VD. Two infants had VD insufficiency, and two had normal VD status. The VD-deficient infants may be at higher risk for repeated infection and airway obstruction than the rest of the C-infants.

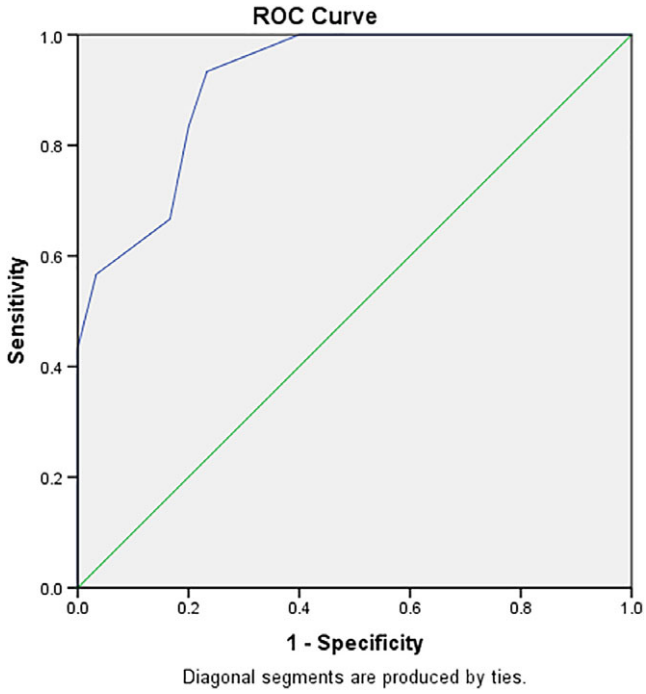

Fig. 3. ROC curve analysis for interleukin 6 level. Analysis of this ROC curve and table shows that interleukin 6 can be used to differentiate cases from controls, with a highly significant difference. Taking the coordinate points of the above curve, we found that the most relevant cutoff point is 5 ng/mL, with a sensitivity of 93.3% and specificity of 76.7%. ROC = receiver operating characteristic; Std. error = standard error. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

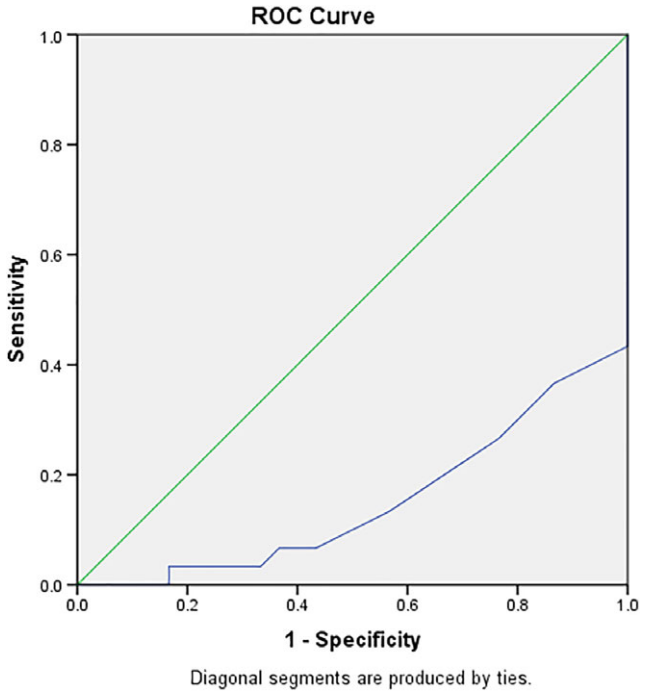

Fig. 4. ROC curve analysis for 25(OH)-vitamin D. The ROC curve and table show that the maternal vitamin D level can be used to predict hypovitaminosis D in the infants, with a highly significant difference. Using the coordinate points of the ROC curve, we found that the most relevant cutoff point of the 25(OH)-vitamin D was 37.5 mg, below which we can predict hypovitaminosis D in infants, with a sensitivity of 33% and a specificity of 83.3%. ROC = receiver operating characteristic; Std. error = standard error. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE III.
Comparison of Age and 25(OH)-Vitamin D Between Mothers of Infants With Laryngomalacia and Control Mothers.

				Unpaired *t* Test	
	Group	Mean	SD	*t*	*P* Value
Age	LM-mothers	25.23	4.761	0.689	.493
	C-mothers	26.07	4.601		
25(OH)-vitamin D	LM-mothers	18.617	6.2473	4.397	<.001
	C-mothers	29.733	12.3594		

This table shows no significant difference between the two groups regarding age, whereas LM-mothers revealed lower 25(OH)-D levels compared to C-mothers, with a highly significant difference.

25(OH)-vitamin D = 25-hydroxyvitamin D; C-mothers = control mothers; LM-mothers = mothers of infants with laryngomalacia; SD = standard deviation.

Neurological dysfunction with submucosal nerve hypertrophy has been demonstrated in severe laryngomalacia.[17] Another study found that laryngeal tone and sensorimotor integrative function of the larynx was altered, and the degree of alteration correlated with disease severity. This indicates that factors altering the peripheral and central pathways of the laryngeal adductor reflex have a role in the etiology of signs and symptoms of laryngomalacia.[18] These factor could be maternal and fetal deficiency of 25(OH)-vitamin D. Some researchers suggested that low maternal VD status may adversely affect neuronal development in the fetus.[9,10] Neurological theories for laryngomalacia[17,18] may primarily involve VD deficiency. The mechanism could be delayed neuronal development or inflammation of laryngeal structures. In the current research, the mucosal congestion seen in 90% of LM-infants and the elevated IL-6 proved the inflammatory hypothesis for laryngomalacia. Therefore, an inflammatory process of the laryngeal structures secondary to VD deficiency and consequent immune dysregulation may be responsible for laryngomalacia. This is the alternative hypothesis we suggest to explain the etiology and pathophysiology of the congenital laryngomalacia. Our theory, as well as previous theories,[17,18] may have a common link of the predisposing factor of 25(OH)-vitamin D deficiency. Functioning as a steroid hormone, 1,25-dihydroxyvitamin D and binds to a nuclear VDR. These receptors has been found in most inflammatory cells, with particularly high VDR levels in dendritic cells, macrophages, and T and B lymphocytes. This supports the concept that VD may have a role in inflammatory and immune diseases and related health issues.[22] Inflammation of the larynx best explains the dynamic form of laryngomalacia with poor neuromuscular tone. Our hypothesis might explain the anatomical abnormalities by similar inflammatory mechanism. However, a prior article did not show any histologic differences in the cartilages of children with laryngomalacia.[23] Nevertheless, duplicating a histological study in infants with high IL-6 may be required to refute or confirm any possible cartilage inflammation.

The possible mechanism by which VD deficiency can increases inflammatory cytokines (e.g., IL-6) is that VD promotes monocyte differentiation into macrophages, preventing them from releasing inflammatory cytokines.[24] VD downregulates proinflammatory cytokines such as IL-6, while upregulating the anti-inflammatory cytokines such as IL-10.[12] The reverse will happen in cases of VD deficiency (elevated IL-6) as was found in the current study. Another possible mechanism is the cholinergic anti-inflammatory pathway, which is a strong regulator of cytokine-mediated damage in local and systemic experimental disease. Depressed vagal nerve activity might facilitate the inflammatory response underlying and worsening the disease.[25]

Mucosal edema of the laryngeal structures has been reported in laryngomalacia.[15] Chandra et al. demonstrated that laryngeal edema histologically predisposes to tissue collapse in laryngomalacia.[26] In this research, laryngeal edema has been detected clinically by laryngoscopy in the majority of cases (90%). Whatever the mechanism by which 25(OH)-vitamin D deficiency can increase inflammatory cytokines (IL-6), inflammatory cytokines may lead to local laryngeal edema, erythema, or even laryngeal tissue redundancy. Surgical treatment for laryngomalacia is needed in about one-fifth of cases.[27] However, finding proper preventive measures and medical treatments are increasingly in demand to avoid attacks of stridor, possible cyanosis, and invasive surgical intervention. Our findings may open the door to achieve these goals after their duplication by further research. Longitudinal study for VD status is recommended in pregnant mothers and their fetuses. It may also be helpful to follow-up with testing of VD and IL-6 following vitamin D3 supplementation.

TABLE IV.
Age Distribution in Infants With Laryngomalacia and Controls Showing Age Range and Mean ± SD.

Age Statistics	LM-Infants	C-Infants	Unpaired *t* Test
Range, mo	1–10	1–10	*t* = 1.21
Mean ± SD, mo	5.1 ± 3	6 ± 2.7	*P* = .23 (NS)

Comparison of age between the two groups revealed no significant difference. The two-tailed option was used in the unpaired *t* test.

C-Infants = control infants; LM-Infants = infants with laryngomalacia; NS = not significant; SD = standard deviation.

CONCLUSION

Infants with laryngomalacia showed 25(OH)-vitamin D deficiency and elevated proinflammatory cytokine IL-6, which may result from dysregulation of the immune responses. Laryngomalacia could be an inflammatory disease secondary to maternal deficiency of 25(OH)-vitamin D with subsequent VD deficiency in exclusively breast-fed infants during neonatal and infantile periods. Laryngomalacia with laboratory abnormalities—low 25(OH)-vitamin D and high IL-6—may receive a benefit from early vitamin D supplementation. Further research is highly recommended to clarify the role of early

supplementation of CD with adequate sunlight exposure for the treatment of moderate to severe laryngomalacia.

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