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Research Article

Elevated Induced-Sputum Neutrophil Elastase and Osteopontin Levels and Dysphagia in Elderly Persons

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Abstract

Background: Dysphagia has been shown to trigger recurrent aspiration pneumonia in elderly persons. It is well known that abnormal cytokine production by innate immune disorders is involved in the pathogenesis of aspiration pneumonia. Elderly persons with repeated episodes of silent aspiration can develop chronic lung inflammation by producing inflammatory cytokines. Swallowing disorder scores and serum and/or induced-sputum cytokine levels were compared in elderly patients.

Methods: The subjects were 108 patients aged 70 years or older (51 males, 57 females; age 76.09 ± 8.15 years) who underwent videofluoroscopic swallowing examinations from April 1, 2015 to March 31, 2018. A total of 37 cases (18 males, 19 females; 78.5 ± 4.1 years) were included in this analysis. Serum and induced-sputum concentrations of neutrophil elastase (NE), osteopontin, interleukin (IL)-17A, hypoxia- induced factor-1alpha, and IL-36 gamma were measured by enzyme-linked immunosorbent assays. Overall, 29 patients had dysphagia, and the control group without dysphagia had 8 cases. These patients' health status was followed for 2 years after the measurements.

Results: Induced-sputum NE, IL-36 gamma, IL-17A, and osteopontin levels were higher in the dysphagia group than in the control group. There was a weak positive correlation between dysphagia scores and induced-sputum osteopontin and NE levels. Of the 37 patients, 7 developed aspiration pneumonia during the 2-year follow-up period. The sputum osteopontin level was higher in recurrent aspiration pneumonia cases.

Conclusion: These findings suggest that higher induced-sputum NE and osteopontin levels might correlate with micro-aspiration and pneumonia in elderly persons.

Keywords: osteopontin, elderly, aspiration pneumonia, swallowing disorder, neutrophil elastase

Abbreviations

IL: Interleukin; OPN: Osteopontin; NE: Neutrophil Elastase; HIF: Hypoxia-Induced Factor; SD: Standard Deviation; PAS: Penetration-Aspiration Scale; ELISA: Enzyme-Linked Immunosorbent Assay; COPD: Chronic Obstructive Lung Disease

Introduction

Aspiration pneumonia is one of the leading causes of death in elderly persons worldwide, and recurrence is common [1]. Swallowing disorders with micro-aspiration are known to trigger recurrent aspiration pneumonia [2]. It is well known that abnormal cytokine production and innate immunity disorders are involved in the pathogenesis of aspiration pneumonia and consequent acute lung injury in elderly persons [3]. We previously reported that serum interleukin (IL)-17A was elevated in elderly aspiration pneumonia cases [4], and there was an increased rate of cerebrovascular diseases as concomitant diseases in those with progressive disease [5]. Aspiration including gastric acid aspiration, bile acid aspiration, and saliva-containing oral bacteria flora can result in the development of a cytokine-induced inflammatory cascade in the lower respiratory tract [1-3,6]. Osteopontin (OPN) is also known as a pluripotent mediator, and elevated plasma OPN levels were previously reported in bacterial pneumonia cases [7]. In addition, neutralization of OPN attenuated neutrophil migration in sepsis-induced acute lung injury in mice [8]. However, the involvement of OPN in aspiration pneumonia in elderly patients still remains uncertain. On the other hand, IL-36 gamma was also associated with respiratory diseases including pneumonia [9], and increased pulmonary IL-17 was reported in an acid-aspiration pneumonia animal model [10]. Recently, serum hypoxia-induced factor (HIF)-1 alpha was reported in an animal aspiration pneumonia model [11]. As one of the inflammatory mediators, neutrophil elastase (NE) cooperates with inflammatory cytokines, and NE- stimulating cytokines were previously shown to be involved in drug-induced lung injury in mice [12]. However, detailed concerns about silent aspiration in elderly persons remain unclear. We hypothesized that elderly patients with repeated micro-aspiration develop latent lung inflammation and produce these inflammatory cytokines. In this study, swallowing disorder scores and serum and/or induced cytokine levels were compared in elderly patients.

Materials and Methods

Study design and entry of cases: Elderly patients more than 70 years old who provided their informed consent were entered into the study. The study was conducted in Akiota Hospital (Hiroshima, Japan). From April 1, 2015 to March 31, 2017, a total of 108 cases (51 males, 57 females; age 76.1 ± 8.2 years) underwent video-guided swallowing evaluations for dysphagia, and 37 of them (18 males, 19 females; age 78.5 ± 4.1 years) who provided their informed consent entered the study (Figure 1). From April 1, 2017 to March 31, 2019, the clinical course and health status of these 37 patients were followed after sample collection. Of these patients, 7 developed aspiration pneumonia during the 2-year follow-up period, and 2 of them died of aspiration pneumonia. The research team followed all cases by recording clinical and laboratory data and then compared them retrospectively. This study was approved by the local ethics committee of Akiota Hospital (approval number: 04-01-2015), and all subjects gave their written, informed consent for participation in the study.

Endpoint of observation: The health status of the patient was followed for two years after the swallowing test. The development of pneumonia and their outcomes were confirmed.

Measurement of serum or induced-sputum cytokine levels: Induced-sputum was collected as previously reported [13]. Briefly, the subjects inhaled 3.0% hypertonic saline solution for 15 minutes using an ultrasonic nebulizer. The subjects were encouraged to cough deeply at 3-minute intervals for up to 15 minutes, and then the samples were collected. There were no major complications from sputum collection. Induced-sputum was mixed with an equal volume of 0.1% dithiothreitol (Sigma-Aldrich, St. Louis, MO, USA) in phosphate-buffered saline solution (Sigma-Aldrich). The samples were mixed and filtered through nylon mesh into sterile tubes. The samples were then centrifuged at 2,000g for 10 minutes, and the supernatants were aspirated and stored in a freezer until cytokine assay. At the same time as the induced-sputum collection, serum was stored in the freezer for later cytokine assay. Serum and induced- sputum concentrations of NE, OPN (R&D Systems, Inc, Minneapolis, MN, USA), IL-17A (Invitrogen Life Technologies, Carlsbad, CA, USA), HIF-1alpha (Invitrogen Life Technologies), and IL-36 gamma (R&D Systems, Inc) were measured by commercial enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions [4].

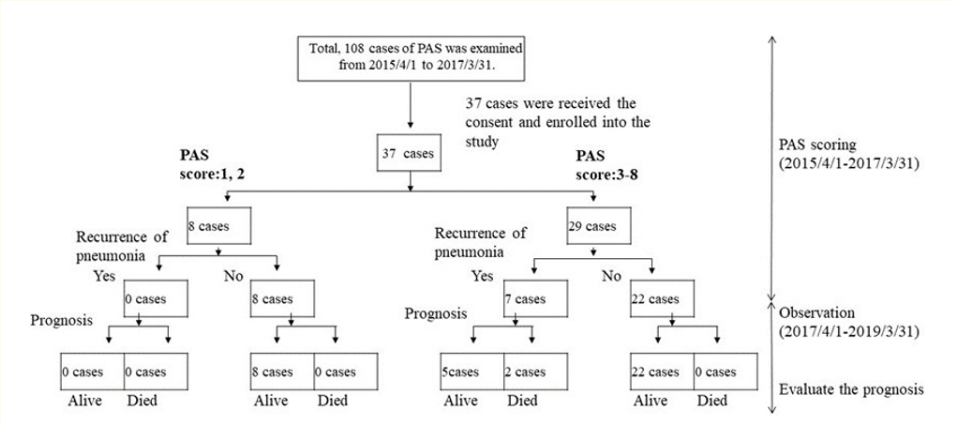

Figure 1: *Design of the study: Of 108 elderly persons aged 70 years or older who underwent videofluoroscopic swallowing examinations from April 2015 to March 2017, 37 cases who underwent sputum induction examinations were included in the study; 29 cases were in the dysphagia group, and 8 cases without dysphagia were in the control group. After measurement, the cases were followed for 2 years.*

Swallowing disorder scoring: The 8-point penetration-aspiration scale (PAS) reported by Rosenbek., *et al*. [14] was used for swallowing disorder scoring. They classified aspiration disorders in 8 categories, as follows: 1. material did not enter the airway; 2. material entered the airway, remained above the vocal folds, and was ejected from the airway; 3. material entered the airway, remained above the vocal folds, and was not ejected from the airway; 4. material entered the airway, contacted the vocal folds, and was ejected from the airway; 5. material entered the airway, contacted the vocal folds, and was not ejected from the airway; 6. material entered the airway, passed below the vocal folds, and was ejected into the larynx or out of the airway; 7. material entered the airway, passed below the vocal folds, and was not ejected from the trachea despite effort; and 8. material entered the airway, passed below the vocal folds, and no effort was made to eject it. A PAS score of 1 or 2 was considered no swallowing disorder, and a PAS score ≥ 3 was considered to indicate the presence of a swallowing disorder according to a previous report [14].

Statistical analysis: Statistical analysis was performed using Excel Statistics (SSRI Co., Ltd., Tokyo, Japan) and KaleidaGraph 4.1 (Synergy Software Corp., Reading, PA, USA). All data are expressed as means ± standard deviation (SD). Fisher's exact test or the Mann-Whitney U test was used to detect differences between the groups. Spearman's rank correlation coefficient was used to evaluate the relationships between the groups. A probability value of less than 0.05 was considered significant.

Results and Discussion

A total of 37 cases were analyzed for the study (Table 1), and both the non-dysphagia group (8 cases) (PAS 1 or 2) and the dysphagia group (29 cases) (PAS ≥ 3) did not have pneumonia at the time samples were collected. In the dysphagia group, there was a past history of pneumonia within 2 years in 11 of 29 cases (37.9%). Age and sex were not significantly different between the groups. As concomitant diseases, cerebrovascular diseases were more frequent in the dysphagia group (41.4%) than in the non-dysphagia group (0%). Dementia was more common in the dysphagia group (20.7%) than in the non-dysphagia group (12.5%), but there was no significant difference between them.

	Total	PAS		p value
		1 or 2 (non-dyspasia gruop)	More than 3 (dyaphasia group)	
Number of cases	37	8	29	
Age	78.5 ± 4.1	77.6 ± 4.5	78.7 ± 3.9	0.8276
Gender (male; female)	18;19	4;4	16;13	0.553
Concomitant diseases				
Cerebral vascular disease	12 (32.4 %)	0 (0 %)	12 (41.4 %)	0.0282
Chronic heart failure	6 (6.2%)	1 (12.5 %)	5 (17.2 %)	0.613
Diabetes mellites	4 (10.8%)	1 (12.5 %)	3 (10.3 %)	0.6404
Dementia	7 (18.9%)	1 (12.5 %)	6 (20.7%)	0.5207
COPD	3 (8.1%)	1 (12.5 %)	2 (6.8 %)	0.5297
Past history of pneumonia				
Within 2 years	11 (27.7%)	0 (0 %)	11 (37.9 %)	0.0465
				(Mean ± SD)

Table 1: *Characteristics of the dysphagia and control groups.*

COPD: Chronic Obstructive Lung Disease; PAS: Penetration-Aspiration Scale; SD: Standard Deviation.

Serum and induced-sputum concentrations of cytokines and NE are shown in table 2. Serum NE, OPN, IL-17A, HIF-1 alpha, and IL-36 gamma levels were not significantly different between the groups. On the other hand, induced-sputum NE, IL- 36 gamma, IL-1beta, IL-17A, and OPN levels were significantly higher in the dysphagia group. There was no significant difference between the groups in induced-sputum HIF-1 alpha concentrations.

	Total	PAS 1 or 2 (non-dysphagia group)	More than 3 (dyaphasia group)	p value
Number of cases	37	8	29	
Serum NE (ng/ml)	71.5 ± 13.7	69.3 ± 14.5	71.6 ± 13.8	0.6708
Serum OPN (pg/ml)	449.1 +126.1	441.8 +128.6	436.9 +125.6	0.0944
Serum IL-17A (pg/ml)	4.3 ± 1.3	4.4 ± 0.9	4.2 ± 1.4	0.5776
Serum IL-36gamma (pg/ml)	39.6 ± 14.9	35.6 ± 13.8	41.1 ± 14.4	0.4453
Serum HIF-1alpha (pg/ml)	53.3 ± 18.5	49.8 ± 14.0	53.9 ± 19.9	0.9835
Sputum NE (ng/ml)	105.3 ± 23.0	73.0 ± 19.9	112.5 ± 16.1	0.0003
Sputum OPN (pg/ml)	52.4 ± 17.2	34.1 ± 9.0	57.0 ± 16.1	0.0001
Sputum IL-17A (pg/ml)	3.2 ± 1.1	2.5 ± 0.9	3.4 ± 1.1	0.0477
Sputum IL-36gamma (pg/ml)	94.5 ± 27.0	72.9 ± 13.0	98.5 ± 26.6	0.015
Sputum HIF-1alpha (pg/ml)	3.7 ± 1.4	3.3 ± 1.7	3.7 ± 1.3	0.5092
				(Mean ± SD)

Table 2: *Serum and induced-sputum cytokine levels of the dysphagia and control groups.*

IL: Interleukin, OPN: Osteopontin, NE: Neutrophil Elastase, HIF: Hypoxia-Induced Factor, PAS: penetration-Aspiration Scale, SD: Standard Deviation.

Next, Spearman's rank correlation coefficients between PAS scores and cytokine or NE concentrations were examined. The rank coefficients between the serum cytokine levels and the PAS score were as follows: serum NE (r = -0.0319, p = 0.8535), serum OPN (r = -0.1319, p = 0.4432), serum IL-17A (r = 0.0463, p = 0.7884), serum IL-36gamma (r = -0.1240, p = 0.4711), and serum HIF-1alpha (r = -0.2380, p = 0.1621). The coefficients between sputum-induced cytokines and the PAS score were as follows: sputum NE (r = 0.3476, p = 0.0491), sputum OPN (r = 0.4264, p = 0.0095), sputum IL-17A (r = 0.3223, p = 0.0552), sputum IL-36gamma (r = 0.2080, p = 0.2234), and sputum HIF-1alpha (r = 0.0686, p = 0.6909). There were no significant correlations between the PAS score and serum cytokine or serum NE levels. The correlations between the PAS score (dysphagia score) and concentrations of induced-sputum cytokines and NE are shown in figure 2. Induced-sputum levels of NE and OPN were weakly but significantly correlated with the PAS score.

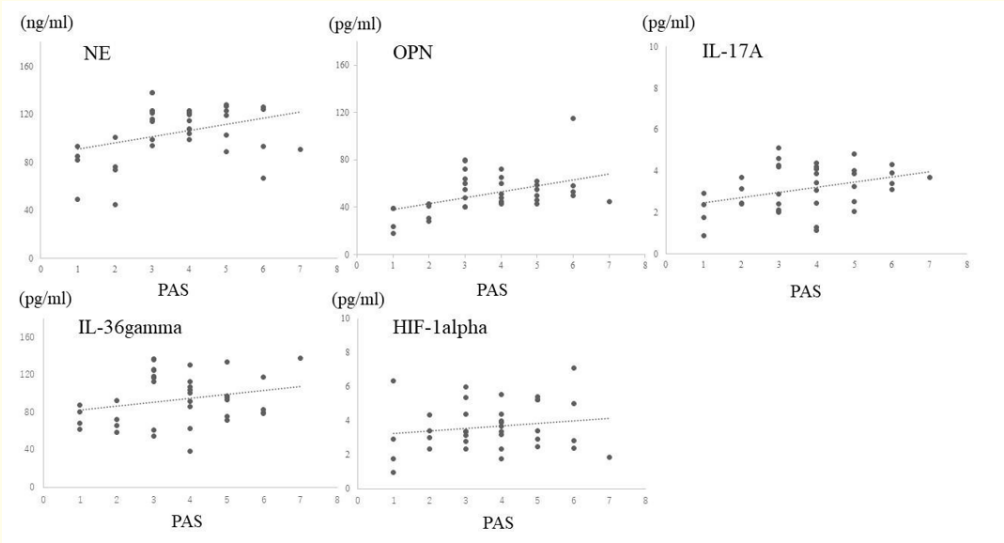

Figure 2: *Comparing rank correlation coefficients between sputum-induced cytokine levels and dysphagia scores (penetration-aspiration scale). IL: Interleukin; OPN: Osteopontin; NE: Neutrophil Elastase; HIF: Hypoxia-Induced Factor; PAS: Penetration-Aspiration Scale.*

During the 2-year follow-up after collecting serum and induced-sputum samples, 7 of the 29 cases (24.1%) in the dysphagia group had episodes of pneumonia (Figure 1). All cases were aspiration pneumonia, and 2 of the 7 pneumonia cases died of pneumonia within 30 days after onset of aspiration pneumonia, and 5 cases remained alive. On the other hand, the non-dysphagia group had no episodes of pneumonia during the 2-year follow-up period. When the 37 cases were divided into two sub- groups, 7 cases with and 30 without an episode of aspiration pneumonia (Table 3), age and sex were not different between the groups. The PAS score and the induced-sputum OPN level were significantly higher in the pneumonia group that in the without pneumonia group. However, other serum or induced-sputum cytokine and NE levels were not significantly different between the groups.

In the present study, it was shown that the induced-sputum levels of NE, IL-36 gamma, OPN, and IL-17A were higher in the dysphagia group than in the non-dysphagia group. In addition, the swallowing score (PAS score) was weakly correlated with the induced-sputum NE and OPN levels. During the 2-year follow-up period after PAS scoring, 24.1% (7 of 37 cases) of the dysphagia group developed aspiration

	Complication with pneumonia	Complication without pneumonia	p value
Number of cases	7	30	
Age	80.3 ± 4.7	78.0 ± 3.8	0.1917
Gender (male; female)	4;3	14;16	0.4677
PAS	5.3 ± 1.4	3.3 ± 1.4	0.0045
Serum NE (ng/ml)	75.9 ± 10.2	69.9 ± 14.4	0.1931
Serum OPN (pg/ml)	468.0 ± 113.1	442.6 ± 128.7	0.449
Serum IL-17A (pg/ml)	4.7 ± 1.1	4.2 ± 1.3	0.1685
Serum IL-36gamma (pg/ml)	41.5 ± 22.7	39.1 ± 12.0	0.5871
Serum HIF-1alpha (pg/ml)	57.7 ± 24.1	51.9 ± 17.1	0.4031
Sputum NE (ng/ml)	115.3 ± 16.0	102.5 ± 23.7	0.0911
Sputum OPN (pg/ml)	68.9 ± 23.6	47.6 ± 13.4	0.0116
Sputum IL-17A (pg/ml)	3.2 ± 0.9	3.1 ± 1.1	0.8615
Sputum IL-36 gamma (pg/ml)	105.0 ± 25.6	91.6 ± 26.7	0.2146
Sputum HIF-1alpha (pg/ml)	3.9 ± 1.8	3.6 ± 1.4	0.892
			(Mean ± SD)

Table 3: *Comparison of cytokine levels between cases with and without pneumonia during the 2-year follow-up period. IL: Interleukin, OPN: Osteopontin, NE: Neutrophil Elastase, HIF: Hypoxia-Induced Factor, PAS: Penetration-Aspiration Scale, SD: Standard Deviation.*

pneumonia. Furthermore, higher induced-sputum OPN and higher PAS scores were correlated with pneumonia recurrence. Though the sample size was rather small, these findings suggest that induced-sputum NE, IL-17A, OPN, and IL-36 gamma levels might be correlated with micro-aspiration in elderly persons. As far as we know, this is the first report describing swallowing disorder scoring and induced-sputum cytokine levels. Micro-aspirated saliva contains inflammatory cells, inflammatory cytokines, and bacterial plaque, and induced sputum reflects the condition of the lower respiratory tract [1-3]. Therefore, the increased NE, IL-36 gamma, OPN, and IL-17A levels in this study might suggest increased cytokine levels in the lower respiratory tract in elderly persons with dysphagia.

In general, gastric acid aspiration, bile juice aspiration, and oral bacterial flora aspiration are involved in silent aspiration in a complex manner [1-3]. Therefore, increased sputum cytokines might be associated with these three factors, which could complicate the interpretation of the results of this study. For instance, according to previous reports [10], acid aspiration affected IL-17A production in a mice pneumonia model. Previous reports showed that bacterial infection affected NE [15], OPN [7,8], HIF-1alpha [6,11], and IL-36 gamma production [9]. That was also the reason that these items were measured in the present study. Though we predicted that HIF-1alpha could also be elevated prior to the study, an increase in sputum HIF-1alpha levels was not confirmed. There are no data explaining the reason for the unexpected results regarding HIF-1alpha. It might be derived from the lack of involvement of bile acid aspiration in the present study or the inhibitory effects of other cytokines. The detailed mechanism of the interrelationships of these increased cytokines and NE was not clear from the present experimental data. It has also been reported that these cytokines do not unilaterally exacerbate inflammation, but, on the other hand, play a role in reducing inflammation. For example, there is a report about the anti-inflammatory effect of OPN [16]. In another report, neutrophil elastase was found to suppress the activity of IL-36gamma [17].

Although the PAS was used to score swallowing disorders, several other kinds of methods of evaluating swallowing disorders have been reported [18]. The PAS scoring system was selected for the present study, because there are several merits to its use: it is easy to score; and many scientific papers about PAS scores have been published [19,20].

The limitations of the present study included: the small sample number; the short observation period; and the end-point was not survival after pneumonia. Another limitation was that factors other than dysphagia could affect sputum-induced cytokine production levels. For example, COPD patients showed increased induced-sputum and serum OPN levels [21] and IL-36 gamma levels [22]. However, in the present study, there were very few COPD cases, so that the possibility that COPD could have increased the sputum OPN level could be effectively discounted. To overcome these limitations, further studies might be needed. On the other hand, recently, the salivary OPN concentration was reported to be a bio-marker of oral mucositis by Gebri., *et al* [23]. Salivary OPN levels were not measured in the present study, but silent saliva aspiration is common in elderly patients with dysphagia, which might support the present results. Even if these things are taken into consideration, OPN might be related to micro-aspiration-induced lower respiratory inflammation, and higher OPN levels may be a prognostic factor for recurrent aspiration pneumonia.

Conclusion

In summary, swallowing disorder scores were correlated with induced-sputum NE and OPN levels. In dysphagia cases with higher sputum OPN levels, there was a correlation with the development of aspiration pneumonia during follow-up. It might be possible that the induced-sputum OPN level might be a candidate predictor for the development of aspiration pneumonia in elderly persons.

Conflicts of Interest

The authors declare that they have no competing interests.

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Ethical Statement

This study was approved by the local ethics committee of Akiota Hospital (approval number: 04-01-2015), and all subjects gave their written, informed consent for participation in the study.

Consent for Publication

Manuscript does not contain any individual person's data.

Data Availability Statements

All data generated or analysed during this study are included in this published article (and its supplementary information files).

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