Aspiration Pneumonia and Dysphagia in the Elderly

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Pneumonia in the elderly has been increasing on an annual basis. To a greater or lesser extent, aspiration is a major contributor to the development of pneumonia in the elderly. Antimicrobials alone are not sufficient for the treatment of pneumonia, and the condition may become intractable or even recur repeatedly. In addition, some patients with pneumonia may have no problems with eating, while others are unable to receive the necessary nutrition due to severe dysphagia. It has been found that pneumonia decreases both the muscle mass and strength of the swallowing and respiratory muscles, a condition named pneumonia-associated sarcopenia. This contributes to a pathophysiological time-axis of aspiration pneumonia and dysphagia in the elderly, in which silent aspiration leads to the development of pneumonia, and further to dysphagia, malnutrition, and low immunity.

aspiration pneumonia pneumonia-related sarcopenia TRP agonist

1. Introduction

As Sir Osler stated, “Pneumonia is an old man’s friend”. Pneumonia among the elderly has been increasing in advanced countries, where populations are ageing at an accelerating rate. As most deaths from pneumonia in the elderly are attributed to aspiration pneumonia (AsP), its diagnosis, treatment, and prevention are important clinical topics. Clinically, AsP can be divided into ‘overt aspiration’, in which the aspiration is evident, and ‘silent aspiration’, in which the aspiration is not apparent. Videofluoroscopy is capable of detecting both overt and silent aspiration, but is unable to detect “micro-aspiration”; that is, the aspiration of small amounts of oropharyngeal secretions due to a depressed swallowing reflex during sleep. Micro-aspiration may or may not present with symptoms suggestive of aspiration, such as coughing. In particular, micro-aspiration without symptoms (i.e., silent aspiration) is important in the development of pneumonia. On the other hand, choking during a meal due to aspirated food debris or its detection in the sputum (macro-aspiration) is considered overt aspiration. As elderly patients with pneumonia often present with non-specific symptoms, such as general malaise, impaired consciousness, and loss of appetite, the onset of pneumonia may only be detected after a chest X-ray; moreover, the disease is often severe [1]. Therefore, it is important to determine the presence or absence of silent aspiration and the means for its prevention for the treatment of pneumonia in the elderly.

2. Prevalence

Pneumonia is a disease with high mortality and morbidity worldwide. In Japan, pneumonia is the leading cause of death in people aged 65 years and over, and is particularly prominent in men aged 80 years and over [2].

Despite AsP generally being more likely to occur in the elderly, the prevalence of AsP may be under-estimated. The prevalence of AsP in the USA has been estimated to be 5–15% among hospitalized patients with community- and hospital-acquired pneumonia [3][4]. Meanwhile, in a cross-sectional national survey of Japan, the prevalence rates of AsP in hospitalized community- and hospital-acquired pneumonia were 60.1% and 86.7%, respectively; this further increased with age, accounting for about 85% in those aged 80–89 years and more than 90% in those aged 90 years and older [5]. This Japanese survey involved a swallowing function test, in order to detect not only overt aspiration but also silent aspiration, and it was found that aspiration is greatly associated with the cause of pneumonia in the elderly.

3. Mechanism

The main responsible factor in the development of AsP is the deterioration of the swallowing reflex and cough reflex sensitivity due to reduced release of the neurotransmitter substance P from the nerve endings of the glossopharyngeal and the vagal nerves [6].

3.1. Cough Reflex Sensitivity

Coughs are provoked by the ligand substance P of the neurokinin 1 receptor, located in the respiratory tract and in the nucleus tractus solitarii of the brainstem [7][8][9]. In support, selective neurokinin 1 antagonists have been found to completely suppress coughing in a study in guinea pigs [10][11]. Another animal study has shown that aerosols of a substance P antagonist inhibited acetylcholine- and histamine-induced coughs, which are bronchoconstricting agents [12]. Additionally, coughing was induced through the inhalation of substance P by patients with pulmonary fibrosis [13].

However, contrary to general expectations, geriatric wards—where pneumonia patients are mainly hospitalized—are often quiet, with few coughing patients. The cough reflex sensitivity induced by chemical stimulants is typically blunted in elderly patients with repeated pneumonia [14]. Specifically, the threshold for coughing to citric acid mist in elderly people with repeated pneumonia was a concentration greater than 1.35 log mg mL^{-1}, compared to less than 0.5 log mg mL^{-1} in non-pneumonia patients [15].

3.2. Swallowing Reflex

Similar to the blunted cough reflex sensitivity, the triggering of the swallowing reflex is also blunted in elderly patients with repeated pneumonia; in particular, the latency of the swallowing reflex in patients with repeated pneumonia has been found to be >5 s [15]. The provocation of the swallowing reflex was mediated by substance P in a capsaicin concentration-dependent manner [16].

3.3. Lacunar Infarction and the Upper Respiratory Protective Reflexes

The blunted swallowing reflex and cough reflex sensitivity have been associated with lacunar infarction in the basal ganglia [17]. In patients with bilateral lacunar infarction, the swallowing reflex latency is significantly higher than in other patients with unilateral or no lacunar infarction, and the swallowing reflex latency gradually increases, not only during the day but also at night, with a greater rate of change from daytime than in other patients. Additionally, the incidence of aspiration—assessed using indium chloride—was reported to be higher in elderly patients with bilateral lacunar infarction [18]. The cough reflex sensitivity in the elderly with lacunar infractions has also been shown to be depressed. Furthermore, both the swallowing and coughing reflexes, among others, were greatly impaired in those who developed AsP [17].

The production of substance P is associated with dopamine metabolism. In animal models pre-treated with dopamine 1 receptor antagonists, the provocation of the swallowing reflex was delayed, and the swallowing frequency was increased with exogenously administered substance P, while substance P antagonists decreased the swallowing frequency. In other words, the swallowing reflex and swallowing frequency are substance P-dependent, while substance P is dopamine-dependent [19]. Taken together, the presence of lacunar infarcts may suggest that the blunted swallowing reflex latency and cough reflex sensitivity are due to the reduced release of substance P.

3.4. Brain and Swallowing

Reduced activity in the insular cortex has been reported in elderly patients with repeated AsP [20]. Functional cerebral imaging during swallowing in healthy adults has shown that the primary motor and sensory areas are most activated, with additional bilateral activation of the anterior cingulate cortex, insula and basal ganglia capsules, and globus pallidus and substantia nigra [21][22][23]. Therefore, the bilateral inactivation of the insula and basal ganglia may contribute to the development of AsP.

3.5. Breathing and Swallowing

Sensory inputs to the sensory nerves reach the medulla oblongata afferentially and integrate the activity of swallowing-related muscles through central pattern generators (CPGs), such that breathing and swallowing can be appropriately coordinated. Natural swallowing begins with laryngeal closure after inspiration (post-inspiratory activity). In more detail, glutamatergic–cholinergic neurons and excitatory networks that generate neural correlates of post-inspiratory activity and inhibitory neural networks, through gamma-aminobutyric acid, contribute to the regulation of timing involved in inspiration [24]. Furthermore, inputs to the CPG from the cortical swallowing area (including the insular cortex) have also been reported to modulate these coordinated respiratory–swallowing movements. In other words, failure to provoke the upper respiratory protective reflex may interfere with the inspiratory and post-inspiratory coordination, which may contribute to the onset of AsP [25].

3.6. Comorbidities Modifying the Development of Pneumonia

Several comorbidities contribute to the development of AsP. Gastrointestinal diseases with organic problems and dysfunction are representative comorbidities of AsP. In addition to age-related gastro-oesophageal motility

disorders, post-operative status following gastrectomy leads to a predisposition to aspiration of gastrointestinal contents due to reflux [26]. Furthermore, gastric reflux is more likely to occur in elderly people with hiatal hernia of the oesophagus, which has been estimated to affect one in two women over 80 years of age; furthermore, acidity (especially below pH 4) increases the swallowing reflex latency in a negatively pH-dependent manner [27]. The relationship between gastric acid and the swallowing reflex is considered as a factor affecting the occurrence of AsP. Elderly people often present with chronic constipation, some of whom may vomit due to impaired bowel peristalsis, leading to chemical pneumonitis [28]. Other factors contributing to the development of AsP have been previously reported, including dementia, physical activity impairment, gender, smoking history, decreased oral intake, and drugs such as neuroleptics, which exacerbate the swallowing reflex by lowering serum substance P, resulting in the development of AsP [29][30].

Anticholinergics are also a risk factor for AsP, as the incidence of AsP has been reported to increase in proportion to the intensity of anticholinergic side-effects such as falls, xerostomia, dry eyes, dizziness, confusion, and constipation [31]. It has also been reported that acid suppressants, such as histamine 2 inhibitors and proton pump inhibitors, tend to increase the pH of gastric juice, thereby altering the gastric flora and even the mesopharyngeal microbiota, facilitating the development of AsP [32][33]. Taken together, drugs with antidopaminergic, bowel peristalsis-reducing, or anticholinergic effects, as well as other drugs that alter the gastric microbiota, should be withdrawn and replaced by drugs with other mechanisms of action.

3.7. Pneumonia-Associated Sarcopenia

Initially, sarcopenia is defined as an age-related decrease in skeletal muscle mass and strength [34]. As a muscle atrophy other than ageing, it is already well-known in mouse models that hypoxia (8 h/day, 30 cycles/hour, FiO_2 nadir = 6%) reduces the contractile properties of the diaphragm, especially as a result of muscle atrophy due to increased autophagy, prompting a compensatory metabolic adaptation that increases fatigue tolerance [35].

Since sarcopenia (assessed by grip strength and lower leg circumference) was reported as a risk factor for the development of community-acquired pneumonia in the elderly [36], a number of reports have revealed the association between pneumonia and sarcopenia.

Acute inflammation and chronic inflammation of the lungs are known to cause muscle atrophy [37]. In a retrospective database study of 739 ventilated patients, a reduction in muscle mass was observed, of which about half also had reduced muscle fiber density [38]. Furthermore, it has recently been shown that chronic aspiration and pneumonia cause a reduction in the cross-sectional area of the muscle fibers, including swallowing and respiratory muscles. In an animal model of lipopolysaccharide-induced aspiration, it has been shown that muscle atrophy of the tongue is induced by autophagy, thinning of the diaphragm by inflammatory cytokine production and the ubiquitin–proteasome pathway, and atrophy of the anterior tibialis muscle—which represents skeletal muscle—by both pathways [39].

In elderly patients hospitalized with AsP, the cross-sectional area of the erector spinae muscle, a respiratory accessory muscle, has been reported to decrease by approximately 80% during the time between admission and pneumonia healing. Further, the previous cross-sectional prospective cohort study has shown that both the inspiratory and expiratory respiratory muscle strength and trunk muscle mass were lower in the elderly with pneumonia compared to those with other respiratory diseases, which can, thus, be considered as risk factors for the development and recurrence of pneumonia [40]. With regard to swallowing, it has also been reported that the swallowing and chewing ability is related to the whole-body muscle mass; that poor swallowing ability, as assessed by the water-swallowing test, is mildly related to the upper arm circumference; and that the tongue muscle mass and tongue pressure are significantly lower in people with dysphagia than those without [41][42][43][44][45].

Finally, chronic aspiration and pneumonia lead to decreases in muscle mass and strength, resulting in reduced swallowing capacity, dysphagia due to a reduced expiratory cough peak flow, respiratory muscle fatigue, and reduced respiratory ventilation efficiency. Pneumonia-related sarcopenia leads to a negative pattern of refractory and recurrent pneumonia, as well as further progression of sarcopenia.

3.8. End-of-Life in Aspiration Pneumonia and Dysphagia

To date, no studies have examined impaired upper respiratory protective reflexes (e.g., the swallowing reflex and cough reflex sensitivity) as a risk factor for mortality in the elderly. Researchers have recently reported that under-nutrition and an impaired swallowing reflex and cough reflex sensitivity—but not an impaired oral intake capacity—were predictors of death within 90 days in elderly AsP patients [46]. Furthermore, cholecystitis and cholangitis frequently occur in the terminal stages of the disease, which are thought to be due to the loss of gallbladder contractility caused by reduced lipid intake due to fasting, which increases the viscosity of the bile, causing it to become sludgy and unable to be expelled [47].

3.9. Pathophysiological Time-Axis of Aspiration Pneumonia and Dysphagia

A noteworthy emerging finding is the time-course of AsP and dysphagia in the elderly: starting with a delayed swallowing reflex, the sensitivity of the cough reflex gradually blunts and AsP develops. The onset of AsP leads to muscle atrophy and weakness of the swallowing and respiratory muscles; that is, a state of pneumonia-associated sarcopenia. Decreases in upper airway protective reflexes and sarcopenia are likely to lead to recurrent pneumonia and further sarcopenia progression, resulting in feeding difficulties and under-nutrition. The inability to meet nutritional requirements, whether by oral intake or other nutritional routes, can be considered terminal.

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