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Invited Review

Clinical characteristics and manometric findings of esophageal achalasia—a systematic review regarding differences among three subtypes

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Abstract

Esophageal achalasia is classified into three subtypes according to manometric findings. Since several factors, including clinical characteristics and treatment response, have been reported to differ among the subtypes, the underlying pathogenesis may also differ. However, a comprehensive understanding regarding the differences is still lacking. We therefore performed a systematic review of the differences among the three subtypes of achalasia to clarify the current level of comprehension. In terms of clinical features, type III, which is the least frequently diagnosed of the three subtypes, showed the oldest age and most severe symptoms, such as chest pain. In contrast, type I showed a higher prevalence of lung complications, and type II showed weight loss more frequently than the other types. Histopathologically, type I showed a high loss of ganglion cells in esophagus, and on a molecular basis, type III had elevated serum pro-inflammatory cytokine levels. In addition to peristalsis and the lower esophageal sphincter (LES) function, the upper esophageal sphincter (UES) function of achalasia has attracted attention, as an impaired UES function is associated with severe aspiration pneumonia, a fatal complication of achalasia. Previous studies have indicated that type II shows a higher UES pressure than the other subtypes, while an earlier decline in the UES function has been confirmed in type I. Differences in the treatment response are also crucial for managing achalasia patients. A number of studies have reported better responses in type II cases and less favorable responses in

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type III cases to pneumatic dilatation. These differences help shed light on the pathogenesis of achalasia and support its clinical management according to the subtype.

Key words: achalasia, high-resolution manometry, upper esophageal sphincter, peroral endoscopic myotomy

Introduction

Esophageal achalasia is one of the most well-studied esophageal motility disorders, characterized by impaired lower esophageal sphincter (LES) relaxation and esophageal aperistalsis (1). The pathophysiology of this disease and the underlying mechanisms have been intensely investigated for over 300 years, but the core question, namely why achalasia develops, is still unclear (2). In the end, ganglion cells are lost at the myenteric plexus of the distal esophagus and LES. Possible causes of this condition include infection with parasites and viruses, allergies, and autoimmune disorders (3).

Common symptoms of achalasia are dysphagia due to solids and liquids, regurgitation of undigested food and saliva, heartburn, and chest pain (1). These symptoms can result in other complications, including weight loss and aspiration pneumonia, for which the upper esophageal sphincter (UES) plays a crucial role.

Diagnosis and classification into three subtypes can be completed using high-resolution manometry (HRM) according to the Chicago classification (4, 5). Other examinations, including barium esophagography, computed tomography, and upper gastroendoscopy, supported the diagnosis of achalasia. In addition to these tests, emerging techniques such as functional luminal imaging probes (FLIP) can also be used to evaluate esophageal motility disorders (EMD).

Differences in several factors among the three subtypes, such as symptoms (6, 7), manometric findings (8), and treatment response (9, 10) have been reported so far; however, because of the limited number of studies, the differences are still controversial, and some argue that the three subtypes are the same consecutive disorders. Based on manometric and histopathological findings, a hypothetical clinical course in which achalasia progresses from type III to type II and then to type I has been suggested (11). However, some reports suggest that the clinical course of the disease differs from one another, and no consensus has been reached (12, 13).

To date, a comprehensive review of the differences among the three achalasia subtypes has been limited. We reviewed articles presenting differences among subtypes of achalasia, including our recently published report, which showed different demographic status and UES pressure among the three subtypes (14). Based on a systematic review and past studies, we investigated the comprehensive differences to lead to further understanding of its pathogenesis and better clinical management.

Methods

To investigate differences in the clinical characteristics of the three subtypes of achalasia, we preliminarily searched published papers using the following keywords: (‘achalasia’ or ‘esophageal achalasia’) AND (‘subtype’ or ‘Chicago classification’) in PubMed and MEDLINE from January 2008 to September 2022. The inclusion criteria for this review were as follows: 1) original articles; 2) three subtypes classified using the Chicago classification; 3) raw data on age and sex; and 4) publications written in English.

Result

We initially identified 241 studies through a database search. After screening procedures, such as ensuring the absence of unusual data, we evaluated the eligibility of the papers. Finally, 33 eligible studies were included in this review. The list of studies and their main findings are presented in Table 1.

Discussion

Clinical characteristics

Age

This disease usually occurs between 25 and 60 years of age but can occur at any age. The incidence and prevalence increase with age, and the mean age at diagnosis is approximately 50 years or more (15). We confirmed by a systematic review that several studies reported a higher age of type III than others (Table 2). Although a long-term prospective study is still required, the above-mentioned hypothesis that achalasia subtypes are the same disease and represent different statuses and that this disease progresses from type III to type II and then to type I does not seem acceptable based on this review. However, whether type II and type I are consecutive disorders is still unclear based on the age distribution reviewed here. Further prospective research to elucidate the clinical course and interdisciplinary research from a wide variety of aspects is crucial to this thesis.

Sex

As for sex differences, although a study showed a higher incidence in women age 45–64 years than in men in the United States (8), achalasia generally represents almost equal frequencies between men and women. Male patients complained of heartburn and regurgitation more frequently, whereas female patients complained of more severe dysphagia (16). In our systematic review, although one study showed a higher prevalence of males in type III (17), the sex distribution was almost similar among the three subtypes, and no study indicated sex differences in symptoms or treatment response in each subtype.

Symptoms

Among the common symptoms of achalasia, several studies have indicated differences among the subtypes. Although the results are still controversial, chest pain can be greater and more frequent in type III patients (14, 18, 19). Esophageal spasms and higher LES pressures may be associated with these results. Dysphasia and regurgitation are common in all subtypes; however, limited studies have reported that regurgitation is more frequent in type I (19) but more severe in type II (6). Previous studies indicated that type II patients reported weight loss more frequently than other subtypes (7, 20, 21). A possible association between weight loss and subtype of achalasia can include a higher catabolic state and different dietary adaptations in type II; however, further research, including investigation of the relationship between inflammatory status and weight loss, is required due to the small sample size.

Diagnosis

The diagnosis of achalasia can be achieved by assessing abnormal esophageal morphology and motility. Several examinations have been performed for the diagnosis of achalasia. In usual clinical settings, radiologic and endoscopic tests are initially performed in patients with suspected achalasia to exclude pseudoachalasia

Table 1. List of studies containing demographic data for each achalasia subtype

Year of publication	Author	Reference number	Country	Age	Sex	Main results
2008	Pandolfino et al.	(13)	United Stats	ns	ns	Type II: best response to BT injection, PD and myotomy
2011	Kahrilas et al.	(4)	India	ns	ns	Type II: best response to PD
2012	Min et al.	(19)	China	Type III: oldest	ns	Type II: most common and shows best treatment response
2012	Roman et al.	(32)	France	Type III: oldest	ns	Type II: most commonly diagnosed
2013	Rohof et al.	(9)	The Netherlands	ns	ns	Type II: better response to PD and LHM
2013	Lee et al.	(45)	Korea	Type III: oldest	ns	Type II: better response to PD and myotomy
2014	Khan et al.	(18)	Saudi Arabia	ns	ns	Type III: more frequent chest pain, higher distal esophageal amplitude
2014	Greene et al.	(53)	United Stats	ns	ns	Similar symptoms and response to Heller myotomy in all groups
2015	Tang et al.	(6)	China	ns	ns	Type III: more severe regurgitation
2015	Carlson et al.	(63)	United Stats	ns	ns	Type III: contractility was detected in all patients Type II: contractility was detected in two-thirds of patients Type I: contractility was detected in one-quarter of patients
2015	Lin et al.	(64)	United Stats	Type III: oldest	ns	Type I and II: lower bolus flow time
2016	Hamer et al.	(51)	Australia	ns	ns	Type III: worst response to cardiomyotomy
2016	Patel et al.	(52)	United Stats	ns	ns	Similar response to Heller myotomy in all groups
2017	Blais et al.	(8)	United Stats	ns	ns	Type II: highest nadir UES residual pressure
2017	Müller et al.	(21)	Germany	ns	ns	Similar long-term response to PD in all groups Type II: highest prevalence of weight loss
2017	Crespin et al.	(30)	United Stats	ns	ns	Similar response to LHM in all groups
2017	Hernández Mondragón et al.	(65)	Mexico	ns	ns	Type III: lowest QOL scores after POEM
2018	Kane et al.	(10)	United Stats	ns	ns	Type III: best response to POEM
2019	Chen et al.	(39)	China	ns	ns	Type III: more elevated serum inflammatory cytokines and chemokines
2019	Lee et al.	(47)	Korea	ns	ns	Type II: better response to PD and BT injection
2019	Kim et al.	(66)	Korea	ns	ns	Type III: less effectiveness of PD Better long-term response to POEM in all groups compared to PD
2020	Jain et al.	(7)	India	Type III: oldest	ns	Type III: more frequent chest pain Type II: highest prevalence of weight loss
2020	Holmstrom et al.	(33)	United Stats	Type III: oldest	ns	Type I: higher distensibility index before and after POEM
2020	Acharya et al.	(67)	United States	ns	ns	Type III: better mechanical work capacity assessed by FLIP
2020	López-Verdugo et al.	(68)	Mexico	ns	ns	Type III: lower neutrophil-to-lymphocyte ratio
2021	Carlson et al.	(17)	United States	Type III: oldest	TypeIII: male dominant	Type III: greatest contractility compared to other subtypes
2021	Sanagapalli et al.	(22)	United Kingdom	ns	ns	Type III: least stasis by barium esophagography
2021	Chen et al.	(37)	China	ns	ns	Type I: lowest number of interstitial cells of Cajal
2022	Katsumata et al.	(14)	Japan	Type III: oldest	ns	Type I: earlier decline of UES
2022	Tsuboi et al.	(23)	Japan	ns	ns	Type III: better clearance rate
2022	Sato et al.	(28)	Japan	Type III: oldest	ns	Type I: most commonly diagnosed
2022	Hsing et al.	(34)	Korea	Type III: oldest	ns	Type III: more frequent presence of contractility after POEM

PD: pneumatic dilatation; LHM: laparoscopic Heller myotomy; POEM: peroral endoscopic myotomy; UES: upper esophageal sphincter; QOL: quality of life; BT: botulinum toxin; FLIP: functional luminal imaging probe; ns: not significant.

Table 2. Characteristics of the subtypes of achalasia

	Type I	Type II	Type III
Epidemiology	Most common in Japan	Most common in western countries	Rare (approximately 5%)
Age			Oldest
Symptoms			More severe and frequent chest pain
Complications	Higher prevalence of lung complications	Higher prevalence of weight loss	
Histopathology	Greater loss of ganglion cells and interstitial cells of Cajal		Greater inflammation
Morphological findings	Greater dilatation		Better clearance
HRM findings	earlier decline of UES	Higher UES pressure	
Treatment response		Best response to PD, LHM, and POEM	Valid response to POEM More unfavorable response to treatment

HRM: high-resolution manometry; UES: upper esophageal sphincter; PD: pneumatic dilatation; LHM: laparoscopic Heller myotomy; POEM: peroral endoscopic myotomy.

due to esophageal cancer and/or esophagogastric junctional cancer. The gold standard method is HRM, which can also classify achalasia into 3 subtypes (4, 5).

Barium esophagography

Barium esophagography is a noninvasive radiological test used to assess abnormal morphology and motility. Timed barium swallow (TBS) is a modified esophagography study for the evaluation of EMD, such as achalasia and esophagogastric junction outflow obstruction (EGJOO). A typical morphological finding of achalasia is a dilated or tortuous esophagus with a narrowed LES, which is described as “bird’s beak appearance”. Functionally, the residual barium content in the esophagus after a 5-min interval is an important finding in achalasia. The differences among subtypes of TBS have been confirmed in Europe (22). Barium column height and width after 1 min and 5 min were greater in types I and II than in type III. Furthermore, other studies evaluating esophageal clearance using TBE showed greater clearance in type III, followed by types II and I (23). Typical esophagographic images of each subtype are shown in Fig. 1. The existence of spasms and preservation of peristalsis contributed to these results, and TBS can sufficiently reflect not only morphological but also functional alterations in achalasia.

Computed tomography (CT)

CT can also be used to diagnose achalasia, differentiate its subtypes, and detect lung and extra-esophageal complications. Sanja et al. reported that esophageal dilatation and esophageal wall thickness found on CT differed among subtypes. The diameter of the esophagus was the largest in type I, and the wall thickness at the distal esophageal segment was greatest in type III. In terms of pulmonary and extra-esophageal manifestations, ground-glass opacities were most frequently detected in type I (24).

Endoscopy

Classic endoscopic findings of achalasia include a dilated esophageal body with residue and puckered LES, also described “esophageal rosette” (25). Resistance when passing through the EGJ is reported to be a useful characteristic for identifying achalasia, and notably, an excessively tight LES and difficulty passing through the EGJ were associated with a significantly higher odds ratio of malignant disease (26). To our knowledge,

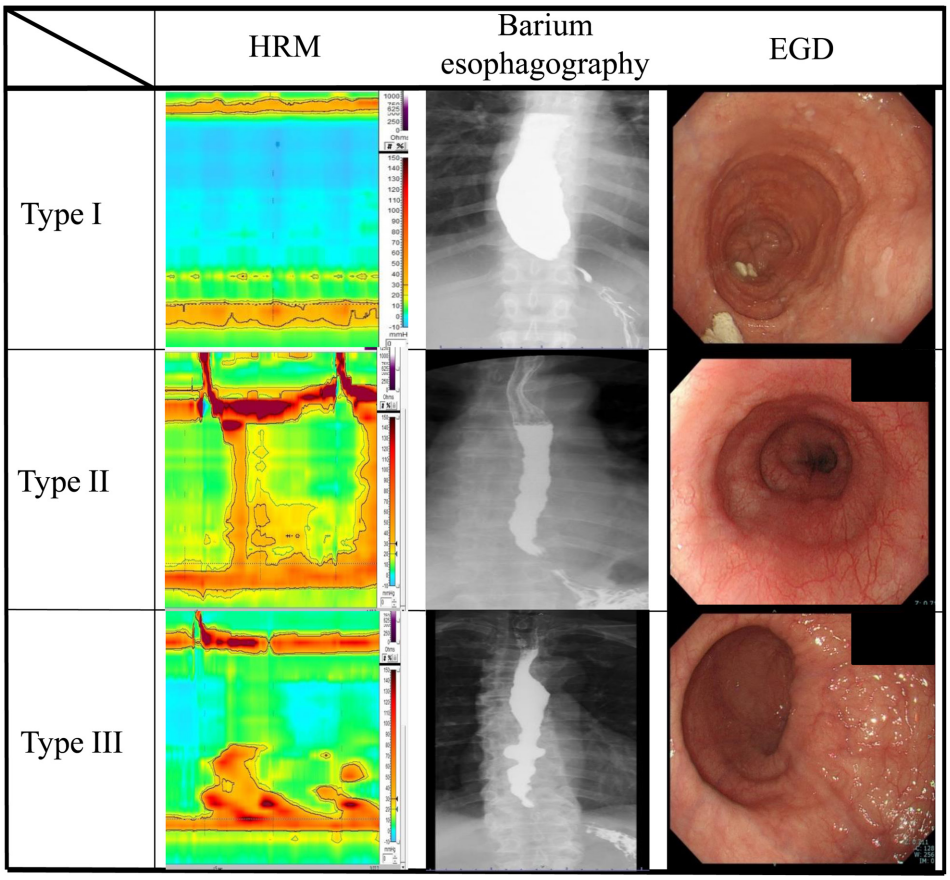

Fig. 1. Typical high-resolution manometry images, esophagographic images, and endoscopic images of each subtype.
HRM: high-resolution manometry; EGD: esophagogastroduodenoscopy.

there are no published data representing differences in endoscopic findings among the three subtypes. Similar to the different morphological and manometric findings detected in other examinations, different endoscopic findings among the three subtypes have been reported. Type I shows dilatation, type II shows nonocclusive contraction, and type III shows spastic contraction (27) (Fig. 1).

Manometric findings

According to the Chicago classification, in addition to an elevated integrated relaxation pressure (IRP), characteristic findings used to classify achalasia subtypes were as follows: aperistalsis for type I, pan-esophageal pressurization for type II, and spastic contraction at the distal esophagus for type III (Fig. 1). In Japan, type I is the most frequently diagnosed subtype (14, 28). A previous study using a large Japanese database reported that the frequency of type I was 58%, followed by type II at 48% and type III at 5%. In contrast, type II is the most common, with a prevalence of 50%–70%, compared to type I at 20%–40% and type III at 5% (29). The distal esophageal amplitude (6, 30), expressed as the distal contractile integral (DCI) and LES (14) pressure, has been reported to differ among subtypes in several studies. These results may reflect spastic contraction at the distal esophagus and be associated with clinical parameters, such as the severity of symptoms and treatment response, although a limited number of studies have addressed this association between HRM findings and achalasia symptoms (31). The UES pressure has also been reported to differ among the three subtypes. Several studies, including our own, have indicated that type II shows a more markedly elevated UES pressure

than the other subtypes (8, 14), while another study reported no notable difference in the UES pressure among subtypes (32). A higher pressure at the esophageal body can cause an elevated UES pressure; however, further research will be required to clarify the reason for this difference. We detected a negative correlation between the age and UES pressure in all subtypes and an earlier decline of UES in type I than in the other subtypes (14).

FLIP

A FLIP is a useful option for evaluating the biomechanical properties of luminal organs. This examination can assess the distensibility of the lumen, leading to a diagnosis of EGJ obstruction. In Japan, it is not yet covered by medical insurance and is thus rarely employed except for research purposes. Previous studies have reported different FLIP findings among subtypes in terms of distensibility and contractility. The distensibility index was higher in type I than in other subtypes before and after peroral endoscopic myotomy (POEM) (21), and type III had the greatest esophageal contractility among subtypes (17, 34). These results indicate that FLIP can detect contractility and distensibility, which cannot be detected by HRM. Thus, this method may be an alternative HRM option for diagnosing achalasia subtypes.

Histology and molecular parameters

Histopathology

Due to its rarity, only a few clinical studies reported the histological findings of achalasia. As confirmed previously, the loss of ganglion cells is a crucial feature of achalasia. Furthermore, a T-cell-mediated inflammatory response in the myenteric plexus has also been detected, prompting the notion that autoimmune-mediated inflammation causes neurodegeneration (35). In addition to histological findings, Furuzawa et al. showed a higher protein expression of proinflammatory cytokines, profibrogenic cytokines, and apoptosis-related factors in achalasia than in controls (36).

Regarding differences among subtypes, the inflammatory response, characterized by an increased density of regulatory T cells infiltration and elevated expression of proinflammatory cytokines, was greatest in type III among subtypes (36). In contrast, type I cells exhibited an elevated expression of profibrogenic cytokines. In addition, type I showed greater ganglion loss than types II and III (35). Similarly, the number of interstitial cells of Cajal, which regulate the motility of the gastrointestinal tract, was significantly lower in type I than in other subtypes (37). These results suggest that type I may be a progressive state of type II and III and result from an inflammatory process; however, prospective research is needed to confirm this hypothesis.

Serum cytokines and chemokines

An imbalance in serum parameters, including elevated serum levels of inflammatory cytokines, in patients with achalasia compared to healthy controls has been detected in several clinical studies (36, 38). To date, only a limited number of studies have reported the differences in serum cytokine and chemokine levels among the three subtypes of achalasia (16, 27). Twelve cytokines and chemokines have been reported to be significantly upregulated in patients with type III achalasia. Similar to the expression pattern in the esophageal mucosa, serum levels of proinflammatory cytokines, such as IFN-γ, were shown to be higher in patients with type III achalasia than in others (39). These findings also support the abovementioned hypothesis that type III achalasia may be a specific subtype and that its pathogenesis might therefore differ from those of types I and II (12). However, although a small number of achalasia cases have been reported, another study revealed no significant difference in the levels of serum cytokines, including IL-6, IL-17, IL-22, IL-23, TNF-α, and IFN-γ (38).

Treatment

The existence of differences in clinically significant treatment responses has been the most frequently investigated topic among the subtypes. For a wide variety of treatments, including medication, botulinum toxin (BT) injection, pneumatic dilatation (PD), surgical myotomy, and POEM, different treatment responses among the subtypes of PD, laparoscopic Heller myotomy (LHM), and POEM have been well reported. Among these options, PD, LHM, and POEM have been reported as safe and effective therapies for achalasia as well. In addition, previous studies and analyses have indicated differences in treatment response among the three subtypes.

Pharmacologic medication

Among a variety of smooth muscle relaxants, including nitrates, calcium channel blockers, anticholinergics, and phosphodiesterase inhibitors, nifedipine and isosorbide have been shown to reduce the resting LES pressures compared to placebo; however, they did not improve the symptoms of achalasia (40, 41). Furthermore, differences in treatment responses among the three subtypes have not yet been documented.

BT injection

A randomized control trial (RCT) proved that BT injection inhibiting the release of acetylcholine is an effective short-term therapy for achalasia (42). In a randomized trial, however, long-term efficacy assessed two years after treatment revealed that the percentage of symptom-free patients was extremely low (43). In addition, BT injection is less effective than surgical myotomy (43). Thus, BT injection should be adopted when patients have a high surgical risk, and clinicians must keep in mind that their symptoms typically recur within one year.

PD

PD is the most effective and least invasive nonsurgical treatment for achalasia. PD shows more favorable outcomes within a year than BT injection (44). However, this method shows a higher rate of symptom relapse and requires more frequent treatment than other options. Among the three subtypes, type II shows a more favorable response (9, 13, 45–48) to PD than types I and III. However, as a meta-analysis revealed similar acceptable success rates of PD compared with LHM and POEM in type II (49), PD can still be a viable treatment option, especially for type II.

Myotomy

LHM is a well-established, safe, and effective treatment for achalasia. LHM was found to show a higher treatment success rate at three months and a similar rate at two and five years of follow-up than PD (50). Similar to PD, several studies have reported better treatment responses to myotomy in type II PD than type I and III (9, 13, 45). In addition, type III showed the worst response among all subtypes (51). However, several studies have indicated no marked differences among subtypes after myotomy treatment (30, 52, 53). The difference in the treatment response seems to be more obvious than that between PD and POEM.

POEM

POEM has been proven to be an effective and safe treatment with acceptable adverse events, such as gastroesophageal reflux disease (GERD). Compared with PD (54) and LHM (55, 56), POEM showed better or similar clinical outcomes. Thus, POEM is recommended as one of the first treatment options for achalasia.

Regarding the differences among subtypes, several studies have shown the best response in type III pa-

tients (10, 34). In a meta-analysis to detect factors associated with treatment outcomes, type III, in addition to an older age, was shown to be associated with a better response to POEM (57). It was also reported that POEM was a favorable option for types I and II. In type I, POEM had a higher success rate than LHM in a meta-analysis. In addition, type II showed a similar but acceptable success rate to that of POEM compared to LHM. Thus, if technically feasible, POEM is an excellent treatment option for any type of achalasia.

Strategy

Based on these results, if tolerable, for types I and II, PD, LHM, or POEM are recommended as the first treatment option, whereas POEM is recommended for type III (38) (Fig. 2). When patients cannot tolerate these therapies and as additional options, medication and BT injection may be selected. Furthermore, careful monitoring and prevention are essential for achalasia, and we propose different management strategies be adopted according to the subtype. For example, type I patients, who are more susceptible to aspiration pneumonia than others, should receive more careful checks for pulmonary manifestations and preventive interventions, such as deglutition training.

Clinical course and the prognosis

After successful treatment of achalasia, symptom relapse can be troublesome for both patients and clinicians. A follow-up study monitoring patients for 40 years after PD and LHM indicated that the recurrence rate was approximately 60%, and the mean time to the need for repeated treatment was 7 years (58). Regarding symptoms, 30% of treated patients completely lost chest pain, and 90% of them at least showed decreased symptoms (59). However, 10% of patients showed progression, developing end-stage achalasia (58). In terms of differences among subtypes, the difference in the treatment response can reflect the clinical course of achalasia. Suitable treatment according to the subtype leads to a better clinical course and long-term symptom relief.

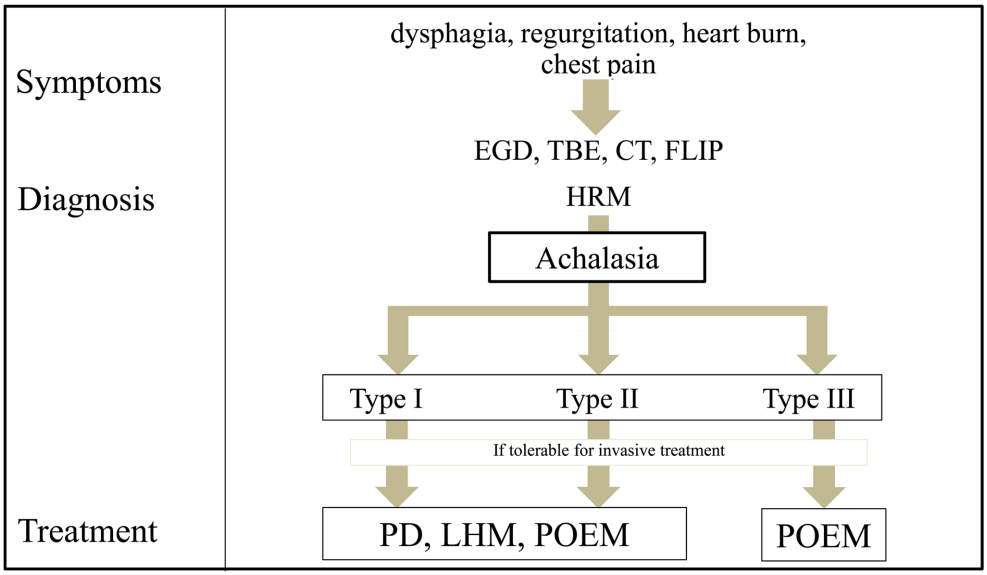

Fig. 2. Recommended management protocol for achalasia, including diagnostic methods and treatment, according to the subtypes.
EGD: esophagogastroduodenoscopy; TBE: timed-barium esophagram; CT: computed tomography; FLIP: functional luminal imaging probe; HRM: high-resolution manometry; PD: pneumatic dilatation; LHM: laparoscopic Heller myotomy; POEM: peroral endoscopic myotomy.

With regard to malignant lesions, it was proven that patients with achalasia cases showed a higher prevalence of esophageal cancer than controls (60). In a prospective study, Meijssen et al. revealed that patients with achalasia had a higher incidence (3.4/1,000 patients per year) than the expected rate (61). In a previous study conducted in Italy, the standardized incidence ratios of squamous cell carcinoma and adenocarcinoma were reported to be similarly higher than those in the general population (62). The difference in cancer incidence among subtypes has not yet been published and needs to be investigated in future studies.

Limitations

This review had several limitations, including selection bias and insufficient data resources. Although we selected articles systemically with predetermined criteria, this review was described narratively, and other articles that were not selected by systematic review were also referenced in other sections. Thus, this narrative review may carry some selection bias. Another limitation is the small number of studies included in this thesis. Because of the rarity of the entity and the newly developed classification (2008), differences among the subtypes of esophageal achalasia have not been adequately investigated. In particular, histopathological and molecular-based assessments, such as serum cytokine levels and endoscopic findings, are still insufficiently elucidated. Future research in this field can shed light on the underlying mechanisms of the differences in achalasia subtypes.

Conclusion

We reviewed the differences among the three subtypes of achalasia and identified several distinct characteristics for each type. Type I, which is most frequently diagnosed in Japan, is characterized by aperistalsis, leading to marked dilatation of the esophagus and a higher risk of lung complications. Type II showed a higher UES pressure and a more favorable treatment response than the other types. Type III showed more severe symptoms, such as chest pain, and its treatment response was more unfavorable than the other types. These findings support the hypothesis that these subtypes have different pathophysiologies and require subtype-based management.

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