Esophagus-Related Symptoms in First-Degree Relatives of Patients with Achalasia: Is Screening Necessary?

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Keywords

Esophagus-related symptoms · First-degree relatives · Achalasia patients · Screening

Summary

Background: Despite an increasing understanding of the pathophysiology of achalasia, the etiology of this esophageal motility disorder remains largely unknown. However, the occurrence of familial achalasia, its association with well-defined genetic syndromes, the candidate gene approach, and recent presentation of the first systematic genome-wide association study on achalasia suggest the involvement of genetic factors. **Methods:** In this study we analyzed the frequency with which symptoms associated with esophageal function (swallowing difficulties, regurgitations, retrosternal cramps/pain, heartburn) occur in first-degree relatives of patients with achalasia to determine if screening is useful and justified against the background of early diagnosis in a genetically predisposed population. The survey of data was carried out in 759 relatives of the 359 achalasia patients included in this study by means of structured interviews. **Results:** Swallowing difficulties as the principal symptom of achalasia were found to occur at least occasionally in 11.2% of first-degree relatives. In comparison with the prevalence of dysphagia in the general population of 7–10% up to 22%, as described in the literature, the frequency of swallowing difficulties does not seem to be increased in our population of relatives. **Conclusion:** Screening measures do not appear to be justified in spite of the potential genetic background of achalasia.

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Introduction

Achalasia is a rare, generally progressive esophageal motility disorder with an annual incidence of approximately 1–3:100,000 and a prevalence rate of 1:10,000 in the general population. The disease affects men and women with equal frequency and usually manifests itself in the third to seventh decade of life [1]. Achalasia is characterized by the absence of propulsive peristalsis of the tubular esophagus, increased resting pressure of the lower esophageal sphincter (LES), and partial or incomplete swallow-induced LES relaxation due to the loss of inhibitory innervation in the esophageal myenteric plexus (Auerbach) [2]. The clinical picture is associated with dysphagia, regurgitation, retrosternal cramps or pain, as well as weight loss which develops in more advanced stages of achalasia. Possible complications include, among others, recurrent aspiration pneumonia and malignant degeneration which occur in the long-term course of achalasia. Important diagnostic tests for the exclusion of malignancy comprise a radiological examination of the esophagus using a contrast agent (esophagus barium swallow), manometry, and esophageal tissue biopsy [1]. The established treatment options encompass pneumatic dilatation of the LES and Heller's extramucosal cardiomyotomy, the latter being a surgical procedure which employs the laparoscopic technique, which has been shown to be particularly useful in younger patients with achalasia [3, 4]. The endoscopic injection of botulinum toxin into the LES plays only a minor role among the available therapeutic options. Promising results have been reported in recent studies conducted on the performance of peroral endoscopic myotomy (POEM) for achalasia [5, 6]. However, long-term results as well as prospective randomized studies comparing POEM with established therapeutic approaches are still anticipated.

The etiology of primary achalasia remains largely unknown despite an increased understanding of the pathophysiology of the disease. No convincing evidence to support the hypothesis of an ini-

tial infection of the esophagus with neurotropic viruses has thus far been found [1, 2]. Furthermore, primary neuronal degeneration has been discussed as a possible cause of idiopathic achalasia. However, the presence of a demonstrable inflammatory response of the ganglion cells precipitated by an unknown trigger in the large majority of patients contradicts the general significance of this process [2]. The current lack of evidence in support of exogenous causes of primary achalasia has led to an increased search for genetic factors in recent years. In fact, the occurrence of familial achalasia, the association of the disease with specific genetic syndromes, e.g. Down's syndrome or Allgrove syndrome, as well as the demonstration of an achalasia-like phenotype in mutant mouse models strongly suggest the involvement of genetic factors in the etiopathogenesis of primary achalasia [7]. Although a number of different candidate genes associated with an increased risk of disease development has also been identified in humans [8–12], their overall significance for primary achalasia is still unclear. Future studies need to be conducted in larger patient collectives to provide further clarification of a possible genetic background of achalasia.

The aim of the present study was to determine the frequency of the occurrence of associated symptoms of achalasia (swallowing difficulties, regurgitation, retrosternal cramps/pain, heartburn) in first-degree relatives of patients with primary achalasia. In order to answer the question whether screening is useful or justified in this genetically predisposed cohort, a comparison with the prevalence of dysphagia, as described in the literature, was carried out to identify a possible difference between the relatives of achalasia patients and the general population regarding the frequency of occurrence of swallowing difficulties.

Patients and Methods

The achalasia patients of this study were recruited from two medical centers (University Medical Center Mainz, Germany, and German Clinic for Diagnostics (DKD) Wiesbaden, Germany) as well as from a German self-help group (Achalasie-Selbsthilfe e.V.). The diagnosis of primary achalasia was reached with X-ray barium swallow, manometry, and endoscopy. Our study included 359 index patients, whereas a total number of 1,704 first-degree relatives were identified, 759 of whom were available for the telephone interview. 434 of the relatives had already died, 302 relatives refused to participate, and 209 relatives could not be contacted. The majority of the achalasia patients was from Germany (88.2% = 320 patients). In addition, 19 patients originated from other Western European countries, 19 from Eastern European countries, and 4 from Asia, and 1 patient was from an African country. Data collection was performed by telephone interview using a standardized questionnaire. The questionnaire used for the index patients comprised: i) questions on the medical history of achalasia and current complaints associated with esophageal function (lag time between onset of symptoms to diagnosis, therapeutic measures) and on the symptoms swallowing difficulties, retrosternal cramps/pain, regurgitation, weight loss, and heartburn; ii) questions about other previous and current illnesses; iii) questions regarding the desire to have children/the number of living children, and iv) questions on genetically predisposed illnesses of relatives. The questions asked of the first-degree relatives were similar to those for achalasia patients: i) questions on previous and current complaints suspected of being associated with esophageal function (swallowing difficulties, regurgitation, retrosternal cramps/pain, and heartburn), as well as the same questions as those asked of achalasia patients concerning ii), iii), and iv). A literature search was

conducted (7 studies available via PubMed/Medline) to compare the reported data on the prevalence of dysphagia with those collected by our study. All collected data were entered into SPSS for statistical analysis.

Results

Achalasia Patients

The group of achalasia patients was characterized by a fairly balanced ratio between women (50.7%) and men (49.3%). This corresponds to the data reported in the literature. Similarly, the age of disease onset found in our study to occur predominantly at the medium stage of life (median 34.7 years, standard deviation 16.7 years) coincides with results cited in the literature. The lag time between the onset of symptoms and the confirming diagnosis of achalasia varies significantly. In the majority of patients the diagnosis was established during the first 2 years after onset of the complaints.

Therapies

66.6% of the patients (n = 239) underwent surgical therapy (Heller's extramucosal cardiomyotomy with partial fundoplication); the procedure was performed once in 86.6% of patients (n = 207) and repeated at least one more time in 13.4% (n = 32) of the cases. In 25.3% of the patients (n = 91) this operation represented the sole therapeutic measure, while 37.9% of patients (n = 136) had at least one and, in some instances, several pneumatic dilatations prior to surgical intervention.

While 61% of the achalasia patients (n = 219) were treated at least once with pneumatic dilatation, at least one additional dilatation was required in 40.6% (n = 146) of cases. Botulinum toxin injections were applied in only 13.4% of the patients (n = 48), whereas 5.4% of patients (n = 19) required at least one repeated injection.

Symptoms

Difficulty in swallowing is the major symptom of achalasia in the group of index patients (developing at least occasionally in 68.6% of patients, and in 25.9% even at every meal). The difficulties are reported to occur particularly during the intake of solid food. Swallowing difficulties may be followed by retrosternal cramps/pain (at least occasionally in 62.4% of patients) and regurgitation (at least occasionally in 40.7% of patients) (table 1). Only 16.2% of patients complained of weight loss. In our survey, questions on heartburn as the major symptom of gastroesophageal reflux disease were also included. Heartburn was reported to develop at least occasionally by 40.4% of achalasia patients (n = 145) while it was stated as being absent in 59.6% of patients (n = 214) (table 1).

Familial Achalasia

In our patient collective one father and his daughter were affected by achalasia. The father was diagnosed with the disease at 56 years of age after symptom duration of approximately 20 years. The daughter was 28 years old when the diagnosis of achalasia was

Table 1. Symptoms of achalasia patients

	None	Occasionally	Every day	At each meal
Difficulty in swallowing	113 (31.5%)	138 (38.4%)	15 (4.2%)	93 (25.9%)
Regurgitation	213 (59.3%)	108 (30.1%)	25 (7.0%)	13 (3.6%)
Retrosternal pain/cramps	135 (37.6%)	192 (53.5%)	22 (6.1%)	10 (2.8%)
Heartburn	214 (59.6%)	118 (32.9%)	24 (6.7%)	3 (0.8%)

Table 2. Symptoms of first-degree relatives

	None	Occasionally	Every day	At each meal
Difficulty in swallowing	676 (88.8%)	73 (9.6%)	6 (0.8%)	6 (0.8%)
Regurgitation	719 (94.7%)	39 (5.1%)	–	1 (0.1%)
Retrosternal pain/cramps	652 (86.0%)	105 (13.9%)	1 (0.1%)	–
Heartburn	463 (61.2%)	260 (34.3%)	19 (2.5%)	15 (2.0%)

Table 3. Symptoms of relatives according to age and gender

	≤55 years, %	>55 years, %	Female, %	Male, %	Total, %
Difficulty in swallowing	11.0	11.6	13.8	8.8	11.2
Heartburn	34.2	47.3	33.9	43.9	38.8

made after 17 years of symptom duration; her two sisters (2 and 4 years younger) are unaffected by achalasia. Neither father nor daughter suffers from a syndromal disease.

Relatives

Swallowing Difficulties

88.8% of the first-degree relatives (n = 676) indicated the absence of swallowing difficulties. In contrast, 11.2% (n = 85) reported at least occasional swallowing difficulties, while 1.6% (n = 12) experienced these difficulties daily, and half of the first-degree relatives (0.6%) have swallowing problems at every meal (table 2). 8.5% of the relatives (n = 65) experience swallowing difficulties only with solid food, and 4.4% (n = 34) report problems swallowing pulpy food or liquids (table 2).

The gender-segregated evaluation of difficulties in swallowing indicates a higher prevalence of the symptom in women than in men (13.8 vs. 8.6%), although an evaluation with the chi-square test did not reveal a statistically significant difference. There was virtually no difference in the age-specific analysis of the symptom swallowing difficulties following the division of relatives into a group of up to 55-year-olds and a group for those aged >55 years (11.0 vs. 11.6%) (table 3). A closer examination of the individual age groups showed a particularly high incidence of swallowing difficulties in the group of 20- to 29-year-olds as well as in the group of 60- to 69-year-old relatives, ranging at 16.5 and 16.3%, respectively. The incidence of swallowing difficulties found in the group of relatives aged >70 years was only <10%. Overall, there was no clear correlation between this symptom and age in our collective.

Regurgitation and Retrosternal Pain

An even greater difference was found between symptom-free and only occasionally symptomatic relatives regarding the question

on regurgitation: 94.7% (n = 719) never suffered from the symptom and merely 5.1% (n = 39) reported an only occasional manifestation. Retrosternal cramps/pain reportedly never occurred in 86.0% of the relatives (n = 652), and 13.9% (n = 105) of this group indicated an at least occasional occurrence (table 2).

Heartburn

38.8% of the relatives (n = 293) suffered at least occasionally from heartburn (34.3% out of these only occasionally, 2.5% every day, and 2.0% at each meal) while, in contrast, 61.2% never experienced heartburn (table 2). The age-specific division indicates a significant increase in symptom frequency with increasing age, i.e. 34.2% of relatives up to 55 years of age versus 47.3% of those older than 55 years. A similar difference was noted for the gender-specific difference, i.e. 43.9% of the male relatives compared to only 33.9% in the group of female relatives reported to suffer from heartburn at least occasionally (table 3).

Swallowing Difficulties and Heartburn

Both swallowing difficulties and heartburn were reported by 16.7% of the relatives, although only 7.6% of these have difficulty in swallowing without the occurrence of heartburn. This marks a significant difference for the combination of these symptoms compared to the occurrence of dysphagia alone (table 4). The statistical evaluation (binary logistic regression) thus shows heartburn to serve as a significant predictor of swallowing difficulties (odds ratio: 2.626; 95% confidence interval: 1.638–4.209).

Differentiation of the Relatives According to the Potential Degree of Severity of Disease in the Index Patients

A further aim of the study was to determine as to whether the relatives of achalasia patients with a presumably particularly severe course of disease were characterized by an especially high prevalence of swallowing difficulties and heartburn. Patients with a

shorter length of symptom duration (≤ 12 months) before diagnosis were defined as clinically particularly severe cases of achalasia. However, no accumulation of symptoms related to the esophagus was identified in the relatives of patients with a shorter time to diagnosis (38.9% with an at least occasional occurrence of heartburn compared to 38.8% in the total number of relatives; 7.6% with an at least occasional occurrence of difficulties in swallowing compared to 11.2% of all relatives) (table 5).

Prevalence of Difficulties in Swallowing in the General Population

The findings of studies investigating the prevalence of dysphagia in the general population are shown in table 6. The reported prevalence rates range from 7 to 10% and up to 22%; the average value calculated based on the results reported by 7 studies ranges at 13.4%.

Discussion

Idiopathic achalasia occurring in the absence of associated syndromes is now generally accepted as a multifactorial disease. Since the 1960s an increasing number of studies describing cases of familial achalasia have suggested the possibility of a monogenic autosomal recessive inherited subtype of the disease which is associated with an early manifestation of clinical symptoms [7]. This does not apply to idiopathic achalasia which usually occurs sporadically. Nevertheless, there is increasing evidence that, as with other multifactorial diseases, genetic factors in the sense of a cumulative effect of genetic variants occurring in combination with specific environmental factors play a role in the etiopathogenesis of achalasia. The search for candidate genes has already been initiated and yielded initial important results [8–11]. Achalasia candidate genes mediating autoimmune response/inflammatory processes as well as mediating esophageal motor function are of special interest. Variation in genes resulting in an increased expression of certain human leukocyte antigen (HLA) class II antigens as well as variation in the protein tyrosine phosphatase N22 (*PTPN22*) gene encoding a lymphoid-specific phosphatase may contribute to an autoimmune initiation of chronic inflammation in achalasia. Most of the studies performed to test whether certain HLA polymorphisms increase the risk for achalasia have focused on *HLA-DQ*, and some have found an association between achalasia and various alleles (e.g. *HLA-DQw1*, *HLA-DQA1*0101*, *DQB1*0502*, *DQB1*0601*, and *DQB1*0602*) [7]. Our working group has recently published the first systematic association study of achalasia in a random sample of 1,068 cases and 4,242 controls. A genome-wide association was reached by 33 markers, all of which are located in the MHC region on chromosome 6. The strongest association with achalasia was shown for an eight-amino acid insertion at position 227–234 of *HLA-DQ β 1*. The results of the described study imply that genetically based immune-mediated processes are involved in the etiopathogenesis of achalasia [12]. Vasoactive intestinal peptide (VIP) is an important inhibitory neurotransmitter within the esophageal

Table 4. Cross-table of difficulty in swallowing and heartburn in relatives

			Heartburn		Total
			no	yes	
Difficulty in swallowing	no	number	428	244	672
		% heartburn	92.4	83.3	88.9
	yes	number	35	49	84
		% heartburn	7.6	16.7	11.1
Total		number	463	293	756
		% heartburn	100	100	100

Table 5. Differentiation of relatives according to severity of disease in index patients

	Symptom duration <12 months, %	Total, %
Achalasia patients	34	66
Pneumatic dilatation	69	61
Surgery	67.5	66
Botox injection	14.4	17
Difficulty in swallowing	7.6	11.2
Heartburn	38.9	38.8

Table 6. Prevalence of dysphagia: literature review

Source	Prevalence, %	Age group, years
Lindgren and Janzon, 1991 [16]	20–22	>50
Spieker, 2000 [17]	7–10	>50
Spieker, 2000 [17]	14	>60
Eslick and Talley, 2008 [18]	16	>18
Kawashima et al., 2004 [19]	13.8	>65
Bollschweiler et al., 2007 [20]	11.3	20–90
Groher and Bukatman, 1986 [21]	12–13	
Average	13.4	

myenteric plexus and is involved in both smooth muscle relaxation and the down-regulation of inflammatory processes [2]. The VIP/VIP receptor 1 (*VIPR1*) signaling is considered as a negative regulator of inflammatory reactions. Polymorphisms in the *VIPR1* gene may cause down-modulation of the *VIPR1* protein and, in turn, lead to immune activation and increased inflammation. Interestingly, one study has reported an association between a *VIPR1* polymorphism that promotes the proinflammatory response and late-onset, but not early-onset, forms of achalasia (>50 years) [13].

The primary goal of this study was to determine the frequency at which the symptoms associated with achalasia (difficulties in swallowing, regurgitation, and retrosternal cramps/pain) occur in first-degree relatives of patients with primary achalasia. Our study population was further asked a question on the prevalence of the symptom heartburn. Although heartburn is not a classical symptom of achalasia, it plays a pivotal role as one of the principal symptoms of a possible ‘overtreatment’ of achalasia, leading to the development of gastroesophageal reflux. Moreover, achalasia is associated with food stasis in the esophagus which leads to the fer-

mentation of food by lactic acid bacteria; the resulting lactic acid accumulation often renders it impossible for the patient to make a clinical differentiation from esophageal acid exposure in gastroesophageal reflux disease.

Although, not unexpectedly, the number of relatives consenting to participate in this study was lower than that of the achalasia patients, 44.5% of the first-degree relatives ($n = 759$) could nevertheless be included in the study. In particular against the background of previously conducted studies, the size of our study population, while being notable, is too small to identify an increased risk, not only for specific symptoms but also for achalasia itself. The only currently available systematic family study on achalasia was published in 1985 and investigated both the incidence of achalasia as well as the occurrence of the symptom dysphagia in 1,012 first-degree relatives of 159 adult patients with achalasia. Achalasia was, in fact, diagnosed in only 2 out of the 1,012 relatives, and only 14 relatives (1.4%) suffered from dysphagia without a confirmed diagnosis of achalasia. The described results led the authors to conclude that heredity is not an important factor in the etiology of achalasia [14]. However, a serious flaw in the study design was that only the achalasia patients were questioned while no relatives were contacted. The study was further flawed by the fact that the number of index patients was far too small against the background of a lifetime risk for the development of achalasia of approximately 1:10,000 in the general population. With a total number of approximately 759 first-degree relatives included in our study population, we therefore focused exclusively on predefined esophagus-related symptoms and not on the incidence of achalasia alone.

The data collected for the 359 achalasia patients included in the present study did not yield any surprising results regarding gender distribution, age at symptom onset, lag time between symptom onset and diagnosis, and (persistent) complaints at the date of questionnaire completion. The indicated changes in body weight (steady weight progression: 62%; weight gain: 20.7%; slight weight loss: only 16.2%) may be a reflection of improved swallowing function after treatment. However, 68.5% of the achalasia patients reported swallowing difficulties with different degrees of severity to manifest themselves at least occasionally (for comparison: reports in the literature cite up to 97% for patients without therapy) [15].

In the group of first-degree relatives, heartburn was the most frequently reported symptom and was indicated by 38.8% of the relatives to occur at least occasionally. Retrosternal pain/cramps were the second most common symptom reported by 14.0% of first-degree relatives. However, even though the symptoms swallowing difficulties and regurgitation are not the primary symptoms of achalasia, they are of greater value than heartburn and retrosternal pain/cramps with a view to our additional study objective, namely to identify a possible link between the prevalence of these symptoms in the group of relatives and the presence of achalasia in the index patients. A comparison with a meaningful norm collective is a prerequisite for the availability of significant information as to whether swallowing difficulties occur more frequently in first-degree relatives of achalasia patients than in the general population. A similar comparison is, however, encumbered by the fact

that a great number of published data on the prevalence of swallowing difficulties has been collected in preselected patient collectives. Furthermore, the exclusive consideration of studies that are not, or only to a lesser degree, affected by these flaws reveals a high degree of variation in the indicated age-dependent prevalence of dysphagia, ranging from 7–10% and up to 22% in patients older than 50 years (table 6) [15–21].

A total number of 11.2% out of all relatives included in our study who suffered at least occasionally from difficulty in swallowing is therefore slightly lower compared to the number reported for the patient collectives of the studies cited above (calculated mean value of 7 studies: 13.4%). A significant increase in swallowing difficulty was further noted in the group of >55-year-old relatives included in our study (11.6% compared with 11.0% of relatives up to 55 years of age), although an inconsistent picture emerges for another subgroup of this cohort (i.e. 16.3% of relatives with swallowing difficulties in the group of 60- to 69-year-olds compared with <10% in the group of >70-year-old relatives). While an increase in swallowing difficulty with age has been reported by a majority of published studies, this relationship was not observed by several other authors [18]. A separate analysis of swallowing difficulties according to gender reveals a higher prevalence in female relatives compared with male relatives (13.8 vs. 8.6%). However, this difference did not reach statistical significance in our study population of relatives. A comparison of the results reported by several other studies does not demonstrate a consistent correlation between gender and swallowing difficulties [16, 18, 22].

In the present study, an accumulation of the symptoms swallowing difficulty and heartburn cannot be confirmed in the relatives of patients with a presumably severe course of achalasia – insofar as shorter symptom duration of ≤ 12 months to diagnosis permits this conclusion. In fact, swallowing difficulties were reported to occur by only 7.6% of this group compared with 11.2% of all relatives, while the proportion is nearly identical for heartburn, ranging at 38.9% compared with 38.8%. A number of other criteria may, of course, also be used in defining a particularly severe course of achalasia (e.g. the number of pneumatic dilatations and/or heartburn). The fact that swallowing disorders occur more frequently in combination with heartburn than without reflux symptoms (in relatives up to 16.7 vs. 7.6%) is pathogenetically well justifiable and has also been described in other studies [23].

The assumption that the incidence of swallowing difficulties is higher in first-degree relatives than in the general population cannot be confirmed based on our data. While a confirmation of this premise would, in principle, support the hypothesis of the involvement of a genetic (co-)factor in idiopathic achalasia, although this needs to be confirmed with the use of other methods, the fact that the prevalence of dysphagia was not increased in our population of relatives precludes the presence of a genetic predisposition. Conversely, in the case of an increased incidence of swallowing difficulties in the group of relatives it would have to be taken into account that families with a relative suffering from achalasia would be informed of the clinical picture, which, e.g., might lead to more intensive self-observation and thus to a subsequent rise in reported

symptoms. The perception of swallowing difficulties is generally very subjective and the attempt at an exact quantitative depiction contingent on a questionnaire-based medical history is therefore possible only to a limited extent.

A further reason for the relatively low incidence of swallowing difficulty reported by the relatives in this study may be that this is only a minor sign which is therefore not possible to document in spite of our comparatively large study population.

It may further be hypothesized that the preselection of study participants described by the authors of the studies used for comparison purposes determined a false high prevalence of swallowing difficulties in the general population. If a possible involvement of genetic factors should nevertheless be assumed, this might range below the predetermined threshold value for a manifest disturbance of swallowing function.

Even when taking into account that a comparison with the general population is only possible to a limited extent, our findings suggest that there is no apparent increase in swallowing difficulties

in either first-degree relatives of the achalasia patients in our study population or in those relatives of the affected patients whose presumably more pronounced symptoms enabled a faster diagnosis. It may therefore be concluded that screening measures for the early diagnosis of swallowing difficulties in first-degree relatives do not appear to be justified in spite of the potential genetic background of achalasia. The current data support previous results in the literature that screening for achalasia cannot be advocated.

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References

- Francis CL, Katzka DA: Achalasia: update on the disease and treatment. *Gastroenterology* 2010;139:369–374.
- Park W, Vaezi MF: Etiology and pathogenesis of achalasia: the current understanding. *Am J Gastroenterol* 2005;100:1404–1414.
- Anselmius M, Pedikis G, Hinder RA, Polishuk PV, Wilson P, Terry JD, Lanspa SJ: Heller myotomy is superior to dilatation for the treatment of early achalasia. *Arch Surg* 1997;132:233–240.
- Gockel I, Junginger T, Eckardt VF: Long-term results of conventional myotomy in patients with achalasia: a prospective 20-year analysis. *J Gastrointest Surg* 2006;10:1400–1408.
- Inoue H, Sato H, Ikeda H, Onimaru M, Sato C, Minami H, Yokomichi H, Kobayashi H, Grimes KL, Kudo SE: Peroral endoscopic myotomy: a series of 500 patients. *J Am Coll Surg* 2015;221:256–264.
- Patel K, Abbassi-Ghadi N, Markar S, Kumar S, Jethwa P, Zaninotto G: Peroral endoscopic myotomy for the treatment of esophageal achalasia: systematic review and pooled analysis. *Dis Esophagus* 2015;DOI: 10.1111/dote.12387.
- Gockel HR, Schumacher J, Gockel I, Lang H, Haaf T, Nöthen MM: Achalasia: will genetic studies provide insights? *Hum Genet* 2010;128:353–364.
- Wong RK, Maydonovitch CL, Metz SJ, Baker JR Jr: Significant DQw1 association in achalasia. *Dig Dis Sci* 1989;34:349–352.
- Weber A, Wienker TF, Jung M, Easton D, Dean HJ, Heinrichs C, Reis A, Clark AJ: Linkage of the gene for the triple A syndrome to chromosome 12q13 near the type II keratin gene cluster. *Hum Mol Genet* 1996;5:2061–2066.
- Santiago JL, Martinez A, Benito MS, Ruiz de León A, Mendoza JL, Fernández-Arquero M, Figueredo MA, de la Concha EG, Urcelay E: Gender-specific association of the PTPN22 C1858T polymorphism with achalasia. *Hum Immunol* 2007;68:867–870.
- Sarnelli G: Impact of genetic polymorphisms on the pathogenesis of achalasia: an age-dependent paradigm? *Neurogastroenterol Motil* 2009;21:575–578.
- Gockel I, Becker J, Wouters MM, et al: Common variants in the HLA-DQ region confer susceptibility to idiopathic achalasia. *Nat Genet* 2014;46:901–904.
- Paladini F, Cocco E, Cascino I, Belfiore F, Badiali D, Piretta L, Alghisi F, Anzini F, Fiorillo MT, Corazzari E, Sorrentino R: Age-dependent association of idiopathic achalasia with vasoactive intestinal peptide receptor 1 gene. *Neurogastroenterol Motil* 2009;21:597–602.
- Mayberry JF, Atkinson M: A study of swallowing difficulties in first degree relatives of patients with achalasia. *Thorax* 1985;40:391–393.
- Howard PJ, Maher L, Pryde A, Cameron EW, Heading RC: Five year prospective study of the incidence, clinical features, and diagnosis of achalasia in Edinburgh. *Gut* 1992;33:1011–1015.
- Lindgren S, Janzon L: Prevalence of swallowing complaints and clinical findings among 50–79-year-old men and women in an urban population. *Dysphagia* 1991;192:187–192.
- Spieker MR: Evaluating dysphagia. *Am Fam Physician* 2000;61:3639–3648.
- Eslick GD, Talley NJ: Dysphagia: epidemiology, risk factors and impact on quality of life – a population-based study. *Aliment Pharmacol Ther* 2008;27:971–979.
- Kawashima K, Motohashi Y, Fujishima I: Prevalence of dysphagia among community-dwelling elderly individuals as estimated using a questionnaire for dysphagia screening. *Dysphagia* 2004;19:266–271.
- Bollschweiler E, Knoppe K, Wolfgarten E, Hölscher AH: Prevalence of reflux symptoms in the general population of Cologne. *Z Gastroenterol* 2007;45:177–181.
- Groher ME, Bukatman R: Dysphagia: the prevalence of swallowing disorders in two teaching hospitals. *Dysphagia* 1986;1:3–6.
- Bollschweiler E, Knoppe K, Wolfgarten E, Hölscher AH: Prevalence of dysphagia in patients with gastroesophageal reflux in Germany. *Dysphagia* 2008;23:172–176.
- Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ: Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology* 1997;112:1448–1456.