RESEARCH ARTICLE

Achalasia is associated with a higher incidence of depression in outpatients in Germany

Sven H. Loosen¹‡, Jennis Kandler¹‡, Tom Luedde¹, Karel Kostev²‡, Christoph Roderburg⁶¹‡*

¹ Clinic for Gastroenterology, Hepatology and Infectious Diseases, University Hospital Düsseldorf, Medical Faculty of Heinrich Heine University Düsseldorf, Düsseldorf, Germany, ² Epidemiology, IQVIA, Frankfurt, Germany

‡ SHL and JK share first authorship on this work. KK and CR share senior authorship on this work.

* christoph.roderburg@med.uni-duesseldorf.de

Abstract

Background and aim

Achalasia represents a chronic motility disorder of the esophagus featuring an impaired lower esophageal sphincter relaxation and loss of esophageal peristalsis. By causing dysphagia, regurgitation, aspiration and chest pain, achalasia might tremendously affect life quality of patients. However, the impact of achalasia on the development of mood disorders including depression has largely remained unclear. The aim of this study was to evaluate the incidence of depression in achalasia patients.

Methods

We analyzed a large primary care cohort database in Germany capturing data from 7.49 million patients.

Results

A total of n = 1,057 patients with achalasia diagnosed between January 2005 and December 2018 were matched to a cohort of n = 3,171 patients without achalasia controlling for age, sex, physician, index year, and the Charlson comorbidity index. Interestingly, while the frequency of depression prior to the diagnosis of achalasia was comparable in both groups, new diagnoses of depression were significantly higher within one year after the diagnosis of achalasia compared to the control group, suggesting a direct and previously unrecognized association between achalasia and depression.

Conclusion

Our data suggest that the clinical management of patients with achalasia should include a careful and structured work-up for mood disorders in order to improve long-term quality of life in these patients.
Introduction

The first description of achalasia goes back to Sir Thomas Willis in 1674. Today, achalasia is defined as a chronic disorder of esophageal motility characterized by an impaired lower esophageal sphincter (LES) relaxation and the loss of esophageal peristalsis [1]. Achalasia is an exceptionally rare disease. Different studies estimate the incidence at 1.6 per 100,000 population and the prevalence at 10.8 per 100,000 population. Males and females are equally affected, most patients are diagnosed between 30 to 60 years of age [2, 3]. Only about 3% of cases occur in children [2].

Achalasia is characterized by a lack of relaxation of the lower esophageal sphincter. There is often also a disturbance in the peristaltic contractions of the esophageal muscles. In approximately 50% of cases, there is a fixed hypertensive contraction of the lower esophageal sphincter. All of these pathologies lead to the pathognomonic functional obstruction at the gastroesophageal junction. The specific pathophysiology of achalasia is only poorly understood. Different studies suggested that achalasia might occur due to a degeneration of the myenteric plexus and vagus nerve fibers of the lower esophageal sphincter [4, 5]. This might occur as a result of autoimmune diseases, viral infections, neurodegenerative disorders, eosinophilic gastroenteritis, or esophageal infiltration by gastric carcinoma [6].

The goal of achalasia treatment is to relieve the symptoms caused by the disorder. Both, surgical (e.g. myotomy and peroral endoscopic myotomy (POEM)) as well as non-surgical procedures are available [7–9]. However, in some patients, optimal symptom control cannot be achieved, leaving these with long-term distress symptoms. We therefore hypothesized that this distress could be associated with an increased incidence of depression and anxiety disorders in achalasia patients as recently demonstrated for other esophagus related diseases [10–12]. Due to the rarity of the disease, such a question can only be answered by analyzing large patient registries. We therefore used a primary care provider database covering 7.5 million health data from Germany [13, 14], to analyze an association of depression in patients with achalasia compared to matched controls as recently described (e.g. [15]).

Methods

Database

This study used data from the Disease Analyzer database (IQVIA). Full details of the database have been published before [14]. Briefly, the Disease Analyzer database is composed of sociodemographic, diagnosis, and prescription data obtained in general and specialized practices in Germany. Diagnosis data are based on the German adaptation of the International Classification of Diseases, 10th revision (ICD-10), while prescription data are coded using the European Pharmaceutical Marketing Research Association (EphMRA) Anatomical Therapeutic Chemical (ATC) classification system. The quality of the data is assessed regularly by IQVIA based on a number of criteria (e.g., completeness of documentation and linkage between diagnoses and prescriptions). The database includes only anonymized data in compliance with the regulations of the applicable data protection laws. It has previously been found that the panel of practices included in the Disease Analyzer database is representative of general and specialized practices in Germany [14]. The "Disease Analyzer" database contains anonymized electronic patient records. Patient data was analyzed in aggregated form without individual health data being available. An individual consent form was not obtained.

Study population and variables

This mixed retrospective case-control and cohort study included adult outpatients (≥18 years) with an initial diagnosis of achalasia (ICD-10: K22.0) in 1,262 general practices in Germany.
between January 2005 and December 2018 (index date). Patients with achalasia were matched to patients without achalasia 1:3 by age, sex, physician, index year, obesity diagnosis, and Charlson comorbidity index (CCI). The CCI is a weighted index that accounts for the number and severity of comorbidities in administrative database studies and includes a wide range of comorbidities (e.g. macrovascular diseases, pulmonary diseases, gastrointestinal diseases, liver and renal diseases, diabetes, tumors, and acquired immune deficiency syndrome [16]).

Study outcomes and covariates
The main outcome of the study was the cumulative incidence of depression (ICD-10: F32, F33) as a function of achalasia. Depression incidence was estimated in three time periods: within one year prior to the index date, within more than one year prior to the index date, and within one year after the index date. Additionally, the proportion of depression patients with an antidepressant prescription was estimated.

Statistical analyses
Differences in the sample characteristics between those with and those without achalasia were tested using chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. The cumulative incidence of depression was estimated in three time periods and compared between patients with and without achalasia using chi-squared tests. Univariate logistic regression analyses were further conducted to investigate the association between achalasia and depression in three time periods. Results from the logistic regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). Both descriptive analyses and logistic regression analyses were performed for total cohorts and separately for men and women, as well as five age groups. In regression analyses, p-values were corrected using the Bonferroni adjustment method and were considered statistically significant at < = 0.006 calculated as 0.05/8 (8 comparisons). Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, USA).

Results
Cohort characteristics
We included a total of n = 1057 patients as well as n = 3171 matched patients without achalasia (Fig 1). Detailed patient characteristics are given in Table 1. 46.9% of patients were male, 53.1% of patients were female. The mean age was 61.9 years (SD 16.1), the mean CCI was 2.6 (SD 2.3). The patients were distributed in a balanced way over the different age groups, with a maximum in the age group of patients between 51–60 years and 71–80 years (23.9% of patients each, Table 1).

Incidence of depression and antidepressant therapy before diagnosis of achalasia
We first compared the incidence of depression between achalasia patients and matched controls more than one year prior to the index data as well as within the last year prior to the index date. There were small differences between the two groups (18.8% vs. 17.0%, p = 0.181; and 4.8% vs. 3.5%, p = 0.049) (Fig 2). In the time period more than one year prior to the index date, 13.0% vs. 8.0% (p<0.001) received antidepressant prescription; within one year prior to the index date, 1.4% vs. 1.2% (p = 0.626) received antidepressants. In regression analyses, no significant association was observed between achalasia and depression diagnosis in both time periods prior to the index date (OR: 1.13, 95% CI: 0.95–1.35 for more than one year prior to the index date, and OR: 1.40, 95% CI: 1.00–1.97 for within one year prior to the index date). No significant associations were seen in sex- and age-subgroups (Table 2). However, achalasia
was significantly associated with antidepressant prescription in the time period more than one year prior to index date (OR: 1.70, 95% CI: 1.37–2.12).

**Incidence of depression and antidepressant therapy after diagnosis of achalasia**

Within 1 years of the index date, 4.5% of patients with achalasia and 2.7% of individuals without achalasia were diagnosed with depression (p = 0.006, Fig 2). In addition, 1.1% vs. 0.9% received an antidepressant prescription (p = 0.456). In regression analyses, achalasia was significantly associated with the incidence of depression (OR: 1.66, 95% CI: 1.15–2.38). In age- and sex-stratified analyses, however, the association was only significant in the age group 51–
60 years (OR: 2.69, 95% CI: 1.38–5.18). There was no significant association between achalasia and antidepressant prescription.

Discussion

In this study, we demonstrate that patients with achalasia, after the diagnosis of achalasia, develop depression at significantly higher rates than patients without achalasia. Of note, this effect was observed both in males and females. In line to our results, in a recent analysis, patients with gastroesophageal reflux disease, which might display similar symptoms than achalasia were demonstrated to exhibit psychological symptoms at higher rates than controls. In this analysis, long symptom duration turned out as a risk factor for development of depression, highlighting that esophagus related diseases might be associated to depressive disease states as recently demonstrated (e.g. [10–12]).

Achalasia represent a very rare disease with a prevalence of about 10 cases per 100,000 inhabitants [2]. To examine an association between achalasia and depression, we used a primary care provider database covering over 7.5 million health data records with a coded prevalence of 0.046%, which is somewhat higher than the previously reported values. Out of the 3925 patients with achalasia in the database, n = 1057 fulfilled the criteria for further analysis (see Fig 1) and were matched according to their age, sex and CCI with a 1:3 ratio to n = 3171 controls.

Achalasia most probably results from a loss of the myenteric plexus and vagus nerve fibers of the lower esophageal sphincter [5]. It has been hypothesized that achalasia is not a moncausal disease involving only one pathway but rather results from a combination of infectious, autoimmune, and genetic components [17]. Of note, all of these have been linked to psychiatric disorders such as anxiety and depression. As an example, histopathological studies have revealed the degeneration of neurons that are part of the cholinergic system [6], which is also involved in the regulation of emotion and motivation [18]. In line, Duarte-Silva et al. have recently described shared neuroimmune and oxidative pathways underpinning Chagas disease and major depressive disorder, providing a direct link between the pathophysiology of achalasia and depressive disorders [19]. Additionally, the loss of life quality due to achalasia might be tremendous, with dysphagia to solids and liquids, regurgitation, weight loss and chest pain representing the most important symptoms [20]. Despite recent data, linking achalasia and depression on a pathophysiological level, it is important to note that our data do not allow to differentiate between reactive depression and idiopathic depression caused by pathways
common to achalasia and depressive disorders. Thus, further studies are warranted to further elucidate the association between achalasia and mood disorder, described in our study.

Our study has several limitations: Despite the German Disease Analyzer database used here has been validated in several medical studies [14], the conducted analysis relies on ICD-10 codes for establishing diagnoses, which may cause misclassification bias. Moreover, the database did not include (longitudinal) data on patients’ symptoms and potential alleviation of

Fig 2. Cumulative incidence of documented depression among individuals with and without achalasia diagnoses followed in general practices.

https://doi.org/10.1371/journal.pone.0250503.g002
these symptoms due to treatment. Thus, we cannot exclude that the development of depression is restricted to patients failing to respond to treatment, and that, in turn, a successful treatment of achalasia might be prevent depression in these patients. In this context it is important to note that success rates of the different treatments for achalasia vary between 20 and 80%, leaving many patients symptomatic despite optimal treatment. Furthermore, we had no data on factors known to have a significant impact on mental health (e.g., loneliness, social support, alcohol use), and this may have biased our findings. Moreover, this was a retrospective study, and it was thus not possible to determine causality in the association between achalasia and depression. Finally, it is important to note that we cannot exclude a selection bias in our study for those with achalasia diagnosis. It seems possible that patients who have an established diagnosis of achalasia may have higher levels of care-seeking behavior and are therefore more likely to be screened for depression.

In summary, our study is the first using a primary care provider database to demonstrate that achalasia is associated with an increased incidence of depression irrespective of other comorbidities or patients’ characteristics. Our data suggest that the clinical management of patients with achalasia should include a careful and structured work-up for mood disorders in order to improve long-term quality of life for these patients.

Author Contributions

Conceptualization: Sven H. Loosen, Jennis Kandler, Christoph Roderburg.

Data curation: Karel Kostev.

Formal analysis: Karel Kostev.

Investigation: Karel Kostev.

Supervision: Tom Luedde, Christoph Roderburg.

Validation: Sven H. Loosen, Christoph Roderburg.

Visualization: Karel Kostev, Christoph Roderburg.

Writing – original draft: Sven H. Loosen, Jennis Kandler, Tom Luedde, Karel Kostev, Christoph Roderburg.

Writing – review & editing: Sven H. Loosen, Jennis Kandler, Tom Luedde, Karel Kostev, Christoph Roderburg.

Table 2. Association between achalasia and depression in patients followed in general practices in the Germany.

| Population       | More than one year prior to the index date | Within one year prior to the index date | Within one year after the index date |
|------------------|-------------------------------------------|----------------------------------------|-------------------------------------|
|                  | OR (95% CI)†                              | OR (95% CI)†                           | OR (95% CI)†                        |
| Overall          | 1.13 (0.95–1.35)                          | 1.40 (1.00–1.97)                       | 1.66 (1.15–2.38)                    |
| Women            | 1.07 (0.85–1.35)                          | 1.42 (0.93–2.17)                       | 1.59 (0.98–2.58)                    |
| Men              | 1.25 (0.92–1.68)                          | 1.37 (0.78–2.42)                       | 1.75 (1.01–3.01)                    |
| Age 18–50 years  | 1.16 (0.73–1.83)                          | 1.18 (0.59–2.33)                       | 1.01 (0.36–2.80)                    |
| Age 51–60 years  | 1.41 (0.99–1.99)                          | 1.02 (0.55–1.92)                       | 2.69 (1.38–5.18)                    |
| Age 61–70 years  | 0.88 (0.57–1.35)                          | 1.64 (0.64–4.17)                       | 1.09 (0.34–3.47)                    |
| Age 71–80 years  | 1.18 (0.83–1.68)                          | 2.12 (0.97–4.64)                       | 1.75 (0.87–3.50)                    |
| Age >80 years    | 0.95 (0.58–1.55)                          | 2.17 (0.81–5.83)                       | 1.36 (0.58–3.21)                    |

†OR = Odds Ratio, 95% CI = 95% confidence intervals.

*p < 0.006 is considered statistically significant (adjusted for Bonferroni).
References

1. Krill JT, Naik RD, Vaezi MF (2016) Clinical management of achalasia: Current state of the art. Clinical and Experimental Gastroenterology 9:71–82 https://doi.org/10.2147/CEG.S84019 PMID: 27110134

2. Wadhwa V, Thota PN, Parikh MP, Lopez R, Sanaka MR (2017) Changing Trends in Age, Gender, Racial Distribution and Inpatient Burden of Achalasia. Gastroenterology Research 10:70–77 https://doi.org/10.14740/gr723w PMID: 28496526

3. Arora Z, Thota PN, Sanaka MR (2017) Achalasia: current therapeutic options. Therapeutic Advances in Chronic Disease 8:101–108 https://doi.org/10.1177/20406223177110010 PMID: 28717439

4. Adler DG, Romero Y (2001) Primary Esophageal Motility Disorders. Mayo Clinic Proceedings 76:195–200 https://doi.org/10.1016/S0025-6196(11)63127-3 PMID: 11213308

5. Kraichely RE, Farrugia G (2006) Achalasia: Physiology and etiopathogenesis. Diseases of the Esophagus 19:213–223 https://doi.org/10.1111/j.1442-2050.2006.00569.x PMID: 16866850

6. Francis DL, Katzka DA (2010) Achalasia: Update on the disease and its treatment. Gastroenterology. https://doi.org/10.1053/j.gastro.2010.06.024 PMID: 20600038

7. Torreesan F, Ioannou A, Azzaroli F, Bazzoli F (2015) Treatment of achalasia in the era of high-resolution manometry. Annals of Gastroenterology 28:299–306 PMID: 26126550

8. Boeckxstaens GE, Annese V, Varannes SB des, et al (2011) Pneumatic Dilation versus Laparoscopic Heller’s Myotomy for Idiopathic Achalasia. New England Journal of Medicine 364:1807–1816 https://doi.org/10.1056/NEJMoai1010502 PMID: 21561346

9. Zaninotto G, Annese V, Costantini M, et al (2004) Randomized Controlled Trial of Botulinum Toxin Versus Laparoscopic Heller Myotomy for Esophageal Achalasia. Annals of Surgery 239:364–370 https://doi.org/10.1097/01.sla.0000114217.52941.c5 PMID: 15075653

10. Mohammad S, Chando B, Soomro AA, Lakho S, Ali Z, Ali Soomro Z, et al. (2019) Depression and Anxiety in Patients with Gastroesophageal Reflux Disorder With and Without Chest Pain. Cureus 11:e6103 https://doi.org/10.7759/cureus.6103 PMID: 31763106

11. Suganami Y, Oka K, Hanayama Y, Honda H, Hamahara J, Obika M, et al. (2019) Correlations between depressive condition and gastroesophageal reflux symptoms in patients visiting a department of general medicine. Acta Medica Okayama 73:479–486 https://doi.org/10.18926/AMO/57711 PMID: 31871329

12. Chen X, Li P, Wang F, Ji G, Miao L, You S (2017) Psychological Results of 438 Patients with persisting Gastroesophageal Reflux Disease Symptoms by Symptom Checklist 90-Revised Questionnaire. Euro-asian Journal of Hepato-Gastroenterology 7:117–121 https://doi.org/10.5005/jp-journals-10018-1230 PMID: 29201791

13. Becher H, Kostev K, Schröder-Bernhardi D (2009) Validity and representativeness of the “Disease Analyzer” patient database for use in pharmaco-epidemiological and pharmacoeconomic studies. Int Journal of Clinical Pharmacology and Therapeutics 47:617–626 https://doi.org/10.5414/cpp47617 PMID: 19825325

14. Rathmann W, Bongaerts B, Carius HJ, Kruppert S, Kostev K (2018) Basic characteristics and representativeness of the German Disease Analyzer database. International Journal of Clinical Pharmacology and Therapeutics 56:459–466 https://doi.org/10.5414/CP203320 PMID: 30168417

15. Labenz C, Huber Y, Michel M, Nagel M, Galle PR, Kostev K, et al. (2020) Nonalcoholic Fatty Liver Disease Increases the Risk of Anxiety and Depression. Hepatology Communications 4:1293–1301 https://doi.org/10.1002/hep4.1541 PMID: 3293833

16. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. (2005) Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical Care 43:1130–1139 https://doi.org/10.1097/01.mlr.0000182534.19832.83 PMID: 16224307

17. Rieder E, Fernandez-Becker NQ, Sarosiek J, Guillaume A, Azagury DE, Clarke JO (2020) Achalasia: physiology and diagnosis. Annals of the New York Academy of Sciences. https://doi.org/10.1111/nyas.14516 PMID: 33140485

18. Mu P, Huang YH (2019) Cholinergic system in sleep regulation of emotion and motivation. Pharmacological Research 143:113–118 https://doi.org/10.1016/j.phrs.2019.03.013 PMID: 30894329

19. Duarte-Silva E, Maes M, Macedo D, Savino W, Peixoto CA (2020) Shared neuroimmune and oxidative pathways underpinning Chagas disease and major depressive disorder. Translational Psychiatry 10:419 https://doi.org/10.1038/s41398-020-01105-9 PMID: 33268766

20. Patel DA, Lappas BM, Vaezi MF (2017) An overview of Achalasia and its subtypes. Gastroenterology and Hepatology 13:411–421 PMID: 28867969