Pediatric esophageal motility disorders: studies on (patho)physiology, diagnosis and management
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CHAPTER 9

Pediatric achalasia in the Netherlands: prevalence, diagnosis, management, clinical course and quality of life

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Submitted
ABSTRACT

Importance
Pediatric achalasia is a rare esophageal motility disorder. Data on prevalence, incidence, treatment, clinical course and quality of life (QoL) are scarce.

Methods
Registered pediatric achalasia data were assessed symptoms, diagnostic methods, treatment success, complication and recurrence rates. Incidence and prevalence was calculated. Current symptom severity was assessed using the Eckardt score and the Reflux Disease Questionnaire (RDQ). General QoL was measured using the KIDSCREEN-52 (<18yr) or SF-36 (>18yr) and compared to healthy population norms.

Results
Between 1990-2013 87 children (mean age 11.44 ± 3.43 years, 60% male) diagnosed with achalasia in The Netherlands were included in the study. Mean incidence was 0.10/100,000/year (range 0.03-0.21). Prevalence in 2012 was 0.90/100,000.
Initial treatment was pneumatic balloon dilation (PD) in 68 (79%) patients and Heller’s Myotomy (HM) in 18 (21%) patients. Re-treatment was required more often after initial PD compared to initial HM (88% vs. 22%; p<0.0001). However, more complications of initial treatment occurred after HM compared to PD (55.6% vs. 1.5%; p<0.0001). Three esophageal perforations were seen after HM (16.7%) and 1 after PD.
Seventy-two of 87 (83%) patients could prospectively be contacted for follow-up. Median Eckardt score was 3 (IQR 2-5), with 32 patients (44.5%) having positive scores suggesting active disease. RDQ scores were higher after initial HM vs. PD (1.71 (0.96 - 2.90) vs. 0.58 (0 - 1.56); p=0.005). SF-36 (n=52) was lower compared to healthy population norms for 7/8 domains. KIDSCREEN-52 (n=20) was similar to population norms.

Conclusions and Relevance
Pediatric achalasia is a rare motility disorder with an incidence of 0.10/100,000/year in The Netherlands. Our study shows high relapse rates after initial treatment, especially after pneumodilations and more complications after Heller’s myotomy. Symptoms persisted when assessed prospectively and QoL in adulthood was declined. There is a clear need for future studies evaluating standardized management to improve clinical outcome and transfer into adult care.
INTRODUCTION

Achalasia is a severe motor disorder of the esophagus, characterized by the absence of peristalsis and a defective relaxation of the lower esophageal sphincter, resulting in progressive impairment of esophageal bolus flow to the stomach. In childhood, symptoms vary with age and include progressive dysphagia, regurgitation and weight loss. Young children also express atypical symptoms, such as vomiting, chest pain, cough and respiratory problems. Achalasia can occur as part of several genetic syndromes such as Trisomy 21 and the Triple-A syndrome (achalasia, alacrima, and adrenocorticotropic hormone insensitivity). Other disorders described to be potentially associated are congenital hypoventilation syndrome, glucocorticoid insufficiency, eosinophilic esophagitis and familial dysautonomia. In previous studies, children with achalasia were shown to have lower general quality of life (QoL) compared to healthy children and children with inflammatory bowel disease.

The incidence of achalasia in adults is estimated to be 0.5-1.2 per 100,000 per year with a possible rise in incidence over the past decade. For children, two studies are available, both performed in the United Kingdom. The reported estimated incidence rates in these studies range from 0.1-0.18/100,000 children per year.

Esophageal High Resolution Manometry is currently the gold standard to diagnose achalasia. Other diagnostic tools, including esophagogastroscopy and barium contrast swallow study, can be used to substantiate the diagnosis or to rule out other causes of dysphagia, such as eosinophilic esophagitis and anatomical obstructions, but might be completely normal.

Currently, treatment is limited to ensuring bolus passage with mechanical disruption of the LES, either with pneumatic balloon dilation (PD) or by, open or laparoscopic, Heller’s myotomy (HM). Scarce data are available on evaluating efficacy, complication rate and long term outcome of PD and HM in children.

This study retrospectively reviews all registered cases of pediatric achalasia in The Netherlands (1990-2013) in academic centers and prospectively describes their current achalasia-associated symptom burden and QoL.
METHODS

Subjects
We retrospectively reviewed medical files of Dutch children (aged <18 years at time of diagnosis) who were registered as diagnosed with achalasia, in all 8 Dutch academic centers between January 1990 and December 2013. The departments of pediatric gastroenterology and pediatric surgery provided medical records of achalasia patients. In addition, per academic center, patients were also traced via their registered diagnosis used to build insurance claim databases, as used in the Netherlands. When a patient was transferred to a non-academic hospital, medical files were searched for data on clinical course in these hospitals as well.

The Medical Ethical Committee of the AMC Amsterdam and participating centers approved the study protocol. After review of the medical files, patients received a written notice on the prospective part of this study.

Data extraction
Charts were reviewed for gender, age at diagnosis, duration of symptoms, symptoms at first presentation, erroneous diagnoses prior to the diagnosis of achalasia, comorbidities and family history relevant to achalasia, weight loss prior to diagnosis, body weight and height at time of diagnosis, follow-up frequency, total follow-up time after first treatment until 18 years old, type of initial treatment, type of relapse treatment, symptom relieve and complications after each treatment.

Initial treatment and relapse treatment options were categorized into i) One or two pneumatic dilations within 14 days (PD) ii) Open or laparoscopic Heller’s Myotomy (HM) or iii) Open or laparoscopic Heller’s Myotomy with fundoplication (HMF).

Treatment success was defined as a documented statement of the treating physician that the patient was symptom free at first registered clinical visit after a treatment. Relapse was defined as recurrence of symptoms, requiring re-treatment >14 days after initial diagnosis, as documented by the treating physician.

Questionnaires
To assess symptoms of achalasia and QoL, all identified patients were prospectively approached by telephone. Patients were asked to fill out four questionnaires regarding their symptoms and current health state, either via a structured telephone interview or by self-administration in an online format, which was designed for this study. Administered questionnaires regarded achalasia symptoms (Eckardt score\textsuperscript{15}), symptoms of gastroesophageal reflux (Reflux disease questionnaire [RDQ]\textsuperscript{16,17}), general QoL (KIDSCREEN if patients were <18 year,\textsuperscript{18} SF-36 if patients were ≥ 18 year\textsuperscript{19}) and disease specific QoL (DSQoL if patients were <18 year,\textsuperscript{20} HRQoL\textsuperscript{21} if patients were ≥18 year). The details and scoring of the questionnaires are outlined in the supplemental information.

Additionally, patients were asked when their last achalasia treatment was performed and when their most recent clinical visit regarding achalasia took place. All included patients signed informed consent.
conent prior to filling out the questionnaires. If patients were aged <18 years at time of diagnosis, both parents/guardians signed the informed consent as well.

**Data analysis**

Incidence and prevalence were calculated based on the model of Rümke\(^2\) using the death- and birth-rates of the Dutch Governmental Database (Centraal Beheer voor de Statistiek - StatLine [CBS-StatLine]).\(^2\) At time of publication, CBS-StatLine provided the birth and death rates until 2012. Subsequently, incidence per year was calculated by dividing the number of achalasia patients by the total number of children <18 years in the relevant year. Linear regression analysis was used to calculate trends in incidence rates over the years. Prevalence was calculated over the most recent year for which death- and birthrates were available.

Age adjusted BMI z-scores (SDS) were calculated using Dutch reference data.\(^2\) BMIs z-scores were classified into severe underweight (<2 SDS), underweight (2<SDS<1), normal (1<SDS<0), overweight (0<SDS<1) and severe overweight (SDS>2).

All normally distributed data are presented with mean and SD. All other data are displayed as median and interquartile range (IQR). Specific tests for deviations from distribution were selected based on the distribution of the data (parametric/nonparametric). Association between balloon size (for pneumatic dilation) and treatment success was assessed using the Chi-square test for trends. A p-value of <0.05 was considered statistically significant.

**RESULTS**

**Incidence and prevalence**

Between 1990-2013, 87 children (52 [60%] boys) were diagnosed and treated for achalasia in one of the 8 Dutch academic centers. The mean age at time of diagnosis was 11.4 (±3.4) year. Twelve patients (14%) were <8 years old.

Mean achalasia incidence from 1990 to 2012 was 0.10/100,000 children per year. The incidence per year ranged from 0.03 to 0.21/100,000 children per year. Figure 1 shows no statistically significant increase in incidence of pediatric achalasia over the study period (p=0.296, R\(^2\)=0.052). In 2012, 31 children or adolescents with achalasia lived in the Netherlands and the prevalence of pediatric achalasia in 2012 was 0.90/100,000 children.

**Retrospective chart review**

Data on symptoms, treatment and clinical course were available for 86 out of 87 patients. For one patient, no data, apart from a letter confirming the diagnosis, could be found in the medical files. This patient was only included for prevalence and incidence calculations.
Symptoms

Patient characteristics are shown in Table 1. Six of 12 children <8 years (50%) presented with atypical symptoms, e.g. nocturnal cough and feeding difficulties. Based on BMI figures adjusted for age (overall mean BMI was 16.1±3.7, BMI z-score -1.0±1.5), 25% of patients were underweight and 18% were severely underweight at time of diagnosis according to Dutch government database. In 13 patients (15%), an erroneous diagnosis was documented prior to the diagnosis of achalasia: asthma (n=2), eosinophilic esophagitis (EoE, n=4), GERD (n=3), anorexia nervosa (n=1), functional stricture of the esophagus (n=1), unspecified mental problems (n=1) and cystic fibrosis (n=1). One patient was simultaneously diagnosed with achalasia as well as EoE and 4 patients were diagnosed with achalasia as part of the Triple A syndrome. Other comorbidities were allergies (n=6) and Berardinelli-Seip Syndrome (n=1). In three cases, first-degree relatives were known to suffer from achalasia, and motility disorders (not specified) within the first and second degree family members were mentioned in 2 cases.

Diagnostic testing

Data on diagnostic tests and results were obtained from 83 patients (95%) (Figure 2). Manometry was incorporated in the diagnostic evaluation in 72 patients (87%). In the patients in whom manometry was not performed, lasting success of initial treatment (27% required no re-treatment during childhood) was comparable to those with documented manometry (27.8% required no re-treatment).

Treatment: choices, success and complications

After diagnosis, 68 patients (79%) were initially treated with PD. Eighteen patients received a HM with or without fundoplication (HMF). Figure 3 depicts the longitudinal treatment trajectory per initial treatment. After the initial treatment, relapse of symptoms occurred in 65 patients (75%). The first relapse treatment was re-PD in 88% and HM(F) in 12% of the patients who initially received PD (Figure 2). After initial HM, first relapse treatment was PD in 50% and re-HM in 50% of the patients. Relapse >1 time occurred in 47 cases (54% of all patients). Recurrence of symptoms which required re-treatment occurred significantly more often in patients initially treated with PD compared to HM(F) (61/68=90% versus 4/18=22%, p<0.0001).

Median number of re-treatments was equal for boys and girls, (2[0-2] vs. 2[1-3] respectively, p=0.134), as was the success percentage at first clinical visit after treatment (24.6% vs. 28.6%, p=0.941).

Balloon sizes were documented in 136/209 PDs and subsequent treatment success was documented in 123/136 of those cases. Twelve patients underwent PD with balloons 18-30mm. In 10 of these cases no treatment success was established, in the 2 other cases treatment success was not documented. In the majority of children (n=124), balloons >30mm were used. Rate of success increased significantly (p=0.009) with increasing balloon size from 3.6% (30mm balloon, n=83) to 6.1% (35mm, n=33) and 37.5% (40mm, n=8).

Table 2 shows that complications occurred in 2% after a single PD and in 62% after HM(F). Complications of the initial treatment occurred significantly more after HM(F) compared to PD (10/18 vs.
1/68 p<0.0001). Similarly, the complication rate was higher for HM(F) during relapse treatments (3/135 vs. 20/22, p<0.0001). Eleven esophageal perforations occurred, 9/11 after HM(F) and 2 after PD (both balloon size 35mm). All complications after PD occurred when ≥35mm balloons were used.

Clinical care during childhood
Retrospective data on clinical care were obtained for visits carried out during childhood (<18 years old). Median (IQR) follow-up time after initial treatment was 3.9 (1.4-10.2) years (Figure 4). The percentage of children without data on clinical course increased from 7% two years after diagnosis to 76% ten years after diagnosis. In children with documented clinical care, the percentage that initially remained symptomatic decreased from 74% after two years to 42% after 6 years. In children with continued documented clinical care after 6 years, the percentage of symptomatic children increased again to over 80% 10-12 years after diagnosis. The frequency of clinical visits per year varied per physician, ranging from monthly visits to a single visit after initial treatment.

Prospective questionnaires
Seventy-two patients (83%) were included in the cross-sectional study evaluating the current achalasia-associated symptom burden and QoL. Fifteen patients of the original cohort (n=87) were excluded because they i) could not be located due to outdated contact addresses (n=7); ii) did not return questionnaires (n=3); iii) refused to participate in the study (n=2); iv) moved to another country (n=2); v) were unable to complete the questionnaires due to severe developmental delay (n=1).

Twenty of the included patients (28%) were <18 years of age at time of inclusion. The median (IQR) time from latest clinical contact to date of administration of the QoL questionnaires was 1.7 years (IQR 0.5-6.9 years, range 0-29.8 years). Twenty-two patients (31%) reported their latest follow-up visit was ≥5 years ago (median time 12.9 yrs [8.8 - 15.5]).

Eckardt
The median Eckardt score was 3 (IQR 2-5). Thirty-two patients (44.5%) had a positive score (>3), suggesting active disease. Elapsed time from diagnosis until administration of questionnaires did not correlate with Eckardt sum scores (p= 0.545, R= -0.073). The median Eckardt scores were not significantly different between male and female patients in terms of sum score (3 [2-5] vs. 3 [2-5.25] respectively, p=0.211) and rate of positive Eckardt scores (43% vs. 45% respectively, p=0.873). Patients initially treated with PD or HM(F) did not have different absolute Eckardt scores (3 [2-5] vs. 3 [2-7], p=0.391) or a different rate of positive Eckardt scores (41% vs. 75%, p=0.290).

RDQ
The median RDQ score (mean of scores on the 3 domains) was 0.92 (0.10-1.65), indicating no severe GER symptoms are present. There was no difference in scores between male and female patients (0.92 [0.17 -1.58] vs 0.92 [0.0-1.88], p=0.671).
Only 7 of 72 patients (10%) reported a mean score ≥ 3, a score known to correlate with objective gastroesophageal reflux (GER) disease. Overall, 28 patients (39%) met the Montreal definition for self-reported troublesome symptoms of GER. When comparing patients initially treated with PD (33% symptomatic) with HM(F) (67% symptomatic), troublesome symptoms of GER are significantly more reported patients initially treated with (F) vs. PD (p=0.04). Consequently, median RDQ scores were higher after initial HM(F) (1.58 [0.96-2.71]) compared to PD (0.58 [0.0-1.58]); p=0.005. Retrospectively, most reflux disease complications were noted in medical charts after HM(F) (14/16, 88%) and children with the documented complication “reflux disease” had significant higher prospective RDQ scores compared to those who had no or other complications (2.21 [1.65-2.92] vs. 0.63 [0.0-1.31] respectively, p<0.0001).

**KIDSCREEN and DSQoL**

Self-reported general QoL (KIDSCREEN-52, n=20) was similar to population norms in children <18 years at time of questionnaire administration. On two domains (‘school environment’, ‘financial resources’) achalasia patients scored significantly better (p=0.038 and p=0.049) when compared to population norms. Overall median (IQR) pediatric achalasia-specific DSQoL score was 17.5 (8-29). Main determinant of this score was the physical ‘swallowing problem’ subdomain, with a median (IQR) score of 9.5 (6.25-11.75). The scores of the other two domains ‘friends and family’ and ‘feelings’ were 3.5 (0-8.75) and 3.5 (0.25-7.0) respectively. Two children were initially treated with HMF and had a higher DSQoL score in the ‘swallowing problem’ domain (17 vs. 9 [5.5-11.25]) leading to a higher overall DSQoL score (24.5 vs. 17.5 [6.5-27]) as compared to children initially treated with PD. None of the children had a total DSQoL score of >50 (>50% of the maximum score). For children, the presence of persisting symptoms (Eckardt >3, n=9) did not relate to lower DSQoL compared with those achalasia patients without symptoms (14 [4.5-21] vs. 18 [11-32], p=0.331).

**SF-36 and HRQoL**

General QoL (SF-36) in adults (n=52) was lower compared to the healthy population norms for seven out of eight domains, with scores on ‘bodily pain’ and ‘general health perceptions’ domains (18-25 years) being significantly lower compared to age adjusted norm (p=0.018 and p<0.0001, Table 3). Patients who underwent initial HM(F) scored better on the subdomain ‘role limitations due to emotional problems’ compared to patients who were treated initially with PD (p=0.026). On all other domains scores were comparable. The overall median adult achalasia-specific HRQoL score was 61.3 (48.3-71.0). Higher scores were observed in patients initially treated with PD, however median scores were not significantly different compared to initially HM(F) treated patients (61.3 [48.4-71.7] vs. 48.4 [41.9-66.1]) respectively, p=0.169). In the adult HRQoL, n=33 (64%) of patients had a score of >50 out of 100. Disease-specific HRQoL was significantly lower in adults with persisting symptoms (Eckardt >3, n=23) compared with those achalasia patients without (20 [19-23] vs. 15 [13-19], p<0.0001).
DISCUSSION

In this study, we assessed presenting symptoms, diagnostic work-up and treatment (outcome) as well as current symptoms and quality of life of all registered patients in the Netherlands that were diagnosed with achalasia in childhood (0-18 years). We estimated a mean incidence of achalasia of 0.1 per 100,000 children/year and prevalence in 2012 of 0.9/100,000 children. In most of these children, pneumatic balloon dilation (PD) was the initial treatment of choice with low complication rate, but a high percentage of these patients (90%) needed re-treatment. In a minority of patients, Heller’s myotomy (HM) was performed as initial treatment and re-treatments. However, a high rate of complications was seen for this procedure. Here, we have shown that symptoms of achalasia tend to persist years after discharge with a declined achalasia-specific quality of life when growing into adulthood compared to controls.

The observed incidence and prevalence of pediatric achalasia in the Netherlands correspond with the only two other pediatric achalasia incidence studies, which were both performed in the United Kingdom in children ≤16 years. In accordance with other small studies, more male than female children were diagnosed with achalasia. In adult studies, equal distribution over the sexes is described, although some studies mention a higher rate of females. Only one adult study reported a higher percentage of male patients. Possibly, pathophysiological and etiological differences between adult and pediatric achalasia could result in different distribution across the sexes. While adult studies report a higher relapse risk for young men, we did not observe such between-gender differences in treatment success and relapse rates.

The most frequently reported presenting symptoms at diagnosis (dysphagia, regurgitation, weight loss and chest pain) in our cohort correspond with those reported in pediatric and adult literature. However, we found that almost half of the children <8 years presented with atypical symptoms, which was described earlier in young children.

Misinterpretation of symptoms is known to cause delayed diagnosis, which can explain the lengthy time until diagnosis and the 13 initial erroneous diagnoses in our cohort. Rarity of the disease, gradual worsening of symptoms, atypical symptoms at young age and the fact that achalasia symptoms can mimic more common diseases (such as EoE) could explain delayed and misdiagnosis of achalasia. Timely use of manometry in case of progressive symptoms, weight loss and no suspicion of EoE, could aid early detection of achalasia.

In 11 patients (14%) no high resolution or conventional manometry was performed. Identical symptoms and clinical course compared to the rest of the cohort strongly suggest these patients had true achalasia, however, without documented manometry this remains uncertain. The introduction of High Resolution Manometry (HRM) has led to a division of achalasia into three clinical relevant subtypes in adults, based on manometric patterns. Moreover, in adults, it was shown that type 2 achalasia (with esophageal compression) responds better to PD compared to type 1 (classic achalasia, no esophageal compression) or type 3 (≥ 2 spastic contractions) in adult patients. HRM was only recently introduced in pediatrics and it remains unclear whether these subtypes exist and corre-
Diagnosis and management

PART II | Diagnosis and management

spond with treatment outcome similar to adults. In our study, only 8 patients were diagnosed using HRM; 3 patients with type 1 and 5 patients with type 2 achalasia. These small numbers do not allow reliable analysis of treatment outcome according to manometric subtype. Future studies are necessary to define whether pediatric achalasia treatment should be adjusted accordingly.

Treatment success of initial single or double PD (10%) was low compared to previous pediatric studies, which reported a 67% success rate after one PD, and success up to 90% after more than one PD. These differences might be explained by the fact the former studies were all single-center studies, with relatively short follow-up, different definitions of treatment success and small cohort sizes. In accordance with adult data, only the use of adequately sized balloons (>30mm) induced symptom relief. This supports the use of balloons >30mm, even in young achalasia patients. However, it is known that the risk of complication increases with increasing balloon size. In our cohort, all 4 complications of PD occurred with balloons >30mm. In 13 PD procedures, the balloon size was known, however no clinical visit after PD was documented in those patients and treatment success could thus not be assessed. As it was impossible to impute data on treatment success, these cases were discarded for assessment of the relationship between balloon size and treatment success.

Our study showed that the success rate of HM (68%) was higher compared to initial single or double PD and corresponded with previous reported HM success rates varying from 60 to 95% in children and up to 90% in adults. In our study, complications occurred more often after HM(F) compared to PD, however both adult and pediatric data on this matter are unequivocal. Adult data show that PD is more likely to fail in relatively young patients, below 40 years of age. Consistent with these results, PD in our study required far more (re-)treatment procedures (total n=229) compared to Dutch patients initially treated with HM(F) (n=24). Frequent procedures, and accompanying anesthesia, pose a self-contained risk. On the other hand, adult studies have shown consistently that PD is the most cost-effective modality when compared to HM(F). Cost-effective studies in children are lacking.

Conducting a (partial) fundoplication simultaneously with HM is commonly used to prevent symptoms of gastroesophageal reflux. However, evidence to support this observation is lacking and our studies lacked sufficient numbers to draw firm conclusions on the use of fundoplication when performing HM. Peroral Oesophageal Endoscopic Myotomy (POEM) is a novel, less invasive therapy for patients with achalasia. Studies have shown that in adults, POEM induces fewer complications and, as compared to HM, POEM requires less operative time and induces better improvement of the Eckardt scores. POEM was found safe and effective in adults up to six months. In children, three studies describing 13 patients in total reported successful POEM procedures and symptom free follow-up up to twelve months. Still, POEM is not widely available and long-term prospective studies with a large number of patients are needed to ascertain efficacy and safety.

In almost half of patients, no documented clinical contact could be found 4 years after diagnosis and initial treatment of achalasia. It could be argued that only symptomatic children revisited their
Physician. Our telephone interview revealed, however, that many patients still have complaints resulting in positive Eckardt scores, suggesting active disease. These scores are not related to disease duration, implying that in many patients, permanent remission of symptoms was never achieved or achalasia symptoms recur shortly after treatment. There is an increased risk for missing out on early diagnosis of severe long term complications, e.g. megaesophagus, in achalasia patients who are lost from clinical care, especially when they are symptomatic. The most severe complication of achalasia is the development of squamous cell carcinoma and adult data indicate the need for regular screening after diagnosis.68–70 Achalasia patients are likely to adapt their lifestyle to gradually worsening symptoms, and might be unaware of the consequences of advanced achalasia. This resulted clearly from this study, as Eckardt scores indicate a high percent of symptomatic patients despite relatively good disease-specific and general QoL. Life-long regular evaluation is thus indispensable and novel follow-up regimes should be implemented in centers caring for pediatric achalasia patients.

Cross-sectional evaluation of now adult patients who were diagnosed with achalasia at a pediatric age showed they had lower general QoL compared to the norm population, although not as low as in other studies.6,7 Children had equal general QoL scores compared to healthy children. Reference literature on both adult and pediatric disease-specific QoL questionnaires is scarce,6,20,21 therefore we chose the arbitrarily cut-off point of 50% of maximum scores for the adults’ and childrens’ DSQoL. We showed that adults are more likely to score above this cut-off compared to children. In addition, and in accordance with earlier data,6 declined adult disease specific QoL was significantly related to persisting symptoms, whereas no such correlation existed in pediatric patients. Decreasing disease-specific and general QoL in older achalasia patients suggests either the impact or the severity of achalasia increases with duration of disease. It should be stressed that these disease-specific QoL questionnaires are not interchangeable with clinical symptom scores and thus results do not directly reflect disease severity.

The strength of this study is that we were able to include patients from all Dutch (academic tertiary) centers diagnosing and treating achalasia patients, allowing detailed calculation of prevalence and incidence rates. In addition, the response rate of our prospective administered questionnaires was high, enabling accurate mapping of current symptoms and QoL of achalasia patients diagnosed at pediatric age. Limitation of this study is the retrospective design, involving the risk of missing cases of pediatric achalasia, especially when for example adolescent children were treated in adult gastroenterology clinics.

In conclusion, pediatric achalasia is a rare disease in the Netherlands. PD is the predominant initial treatment of choice but this is characterized by high relapse rates. The high numbers of reported complications after HM, on the other hand, indicate the need for international, prospective, randomized studies comparing initial PD to HM and novel treatment strategies such as the POEM proce-
dure. International collaboration is the only solution to ensure sufficient group sizes. Despite the risk of serious late complications, many children had no documented clinical course after treatment. Moreover, nearly half of them were still symptomatic years after last follow up visit. This, and the reduced quality of life in patients >18 years illustrates the need for studies evaluating standardized treatment and follow-up regimes.

Figure 1. Incidence rates of pediatric achalasia (1990-2012). Linear regression showed no statistically significant increase in incidence rates (p=0.296, R²=0.052).

Figure 2. Diagnostic work-up in 83 patients suspected of achalasia
### Patient Characteristics and Symptoms

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</table>

### Symptoms at presentation

<table>
<thead>
<tr>
<th></th>
<th>reported</th>
<th>not reported</th>
</tr>
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<tbody>
<tr>
<td><strong>n</strong></td>
<td><strong>%</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Maneuvers *</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Retrosternal pain</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory tract infections</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 1.** Patient characteristics, BMI and symptoms at presentation. *‘Maneuvers’ refers to body movements during a meal that facilitate passage of the bolus through the esophagus, for example eating in standing position and walking or even jumping while eating.
### Table 2. Complications of achalasia treatment divided per type of treatment and moment of treatment (initial or relapse).

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Total procedures</th>
<th>Total complications</th>
<th>Type of complication</th>
<th>Initial treatment</th>
<th>Relapse treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumodilation</strong></td>
<td>209</td>
<td>4</td>
<td>2%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Perforation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reflux disease</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Heller’s Myotomy</strong></td>
<td>15</td>
<td>12</td>
<td>80%</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Perforation</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reflux disease</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Esophagectomy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Heller’s Myotomy with fundoplication</strong></td>
<td>33</td>
<td>18</td>
<td>55%</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Perforation</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reflux disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Retrosternal pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Esophagectomy</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 3. Flow diagram of relapse treatment procedure(s) per initial treatment. Note that PD requires more re-treatment and no initial HM required >2 times re-treatment. PD=pneumodilation; HM=Open or laparoscopic Heller's myotomy; HMF=Open or laparoscopic Heller's myotomy + fundoplication.
<table>
<thead>
<tr>
<th>SF-36 Domain</th>
<th>Mean (SD) scores all (n=52)</th>
<th>Mean Δ from norm score all (age adjusted)</th>
<th>P-value scores vs. normal scores all (age adjusted)</th>
<th>Mean(SD) scores IT PD (n=40)</th>
<th>Mean Δ from norm score (age adjusted) - PD</th>
<th>Mean (SD) scores IT HM(F) (n=11)</th>
<th>Mean Δ from norm score (age adjusted) - HM(F)</th>
<th>P-value Δ scores PD vs. HM(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td></td>
<td></td>
<td>18-25yr (n=27) 26-35yr (n=22) 36-45yr (n=3)</td>
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<tr>
<td>Role limitations physical</td>
<td></td>
<td></td>
<td>18-25yr (n=27) 26-35yr (n=22) 36-45yr (n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td></td>
<td></td>
<td>18-25yr (n=27) 26-35yr (n=22) 36-45yr (n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>General health perceptions</td>
<td></td>
<td></td>
<td>18-25yr (n=27) 26-35yr (n=22) 36-45yr (n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td></td>
<td></td>
<td>18-25yr (n=27) 26-35yr (n=22) 36-45yr (n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Social functioning</td>
<td></td>
<td></td>
<td>18-25yr (n=27) 26-35yr (n=22) 36-45yr (n=3)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Role limitations emotional</td>
<td></td>
<td></td>
<td>18-25yr (n=27) 26-35yr (n=22) 36-45yr (n=3)</td>
<td></td>
<td></td>
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<tr>
<td>Mental heath</td>
<td></td>
<td></td>
<td>18-25yr (n=27) 26-35yr (n=22) 36-45yr (n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. SF-36 scores. For one patient, initial treatment was unknown and therefore this patient was left out of the analysis comparing SF36 scores for PD vs. HM(F) treated patients. IT=initial treatment; PD=Pneumodilation; HM(F)=Heller’s Myotomy +/- Fundoplication. * P <0.05
Figure 4. Course of clinical care as obtained from medical charts. Bars show the percentage of patients from which clinical data were available per 2-year intervals, including patients with relapses. Hatched blocks show the percentage of patients with and without symptoms. On top, the percentage of patients for whom clinical notes are available within the two year intervals. Note the decrease in this number likely represents a decrease in children visiting their physician with time elapsing after diagnosis. Note that patients' clinical course was no longer obtained after they turned 18.
REFERENCES

1. Franklin AL, Petrosyan M, Kane TD. Childhood achalasia: A comprehensive review of disease, diagnosis and therapeutic management. World J Gastrointest Endosc. 2014;6(4):105-111


Chapter 9

Contributors’ statement

Marije Smits: Took part in design of the study, organizing and executing the study, collected and analyzed study data (medical files and administration of questionnaires), drafted the initial manuscript, and approved the final manuscript as submitted.

Marinde van Lennep: collected study data (medical file extraction), analyzed study data, reviewed and revised the manuscript and approved the final manuscript as submitted.

Remy Vrijlandt: collected study data (administration of questionnaires), analyzed study data, reviewed and revised the manuscript and approved the final manuscript as submitted.

Jac Oors, Roderick Houwen, Freddy Kokke, David van der Zee, Johanna Escher, Anita van den Neucker, Tim de Meij, Frank Bodewes, Joachim Schweizer, Gerard Damen, Olivier Busch: granted access to medical files, reviewed and revised the manuscript and approved the final manuscript as submitted.

Michiel van Wijk and Marc Benninga: Took part in design of the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.