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Esophageal Achalasia in children

THESIS

PRESENTED AND DEFENDED PUBLICLY THE 22 /02/2023

BY

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Born on the 3rd of December 1994 in Beni Mellal

TO OBTAIN THE DEGREE OF DOCTOR OF MEDICINE

KEYWORDS

Esophageal Achalasia, Children, Regurgitation, Dysphagia, Heller Myotomy, Fundoplication, Quality of Life, PedsQL.

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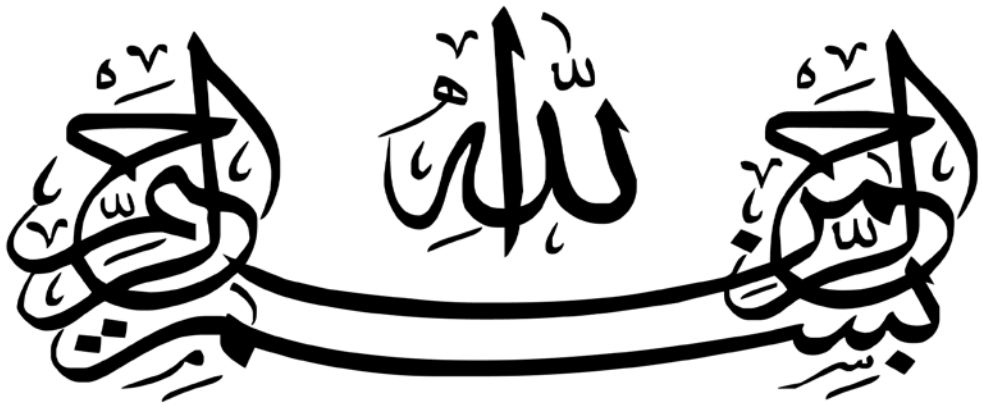

"رب أوزعني أن أشكر نعمتك التي

أنعمت عليَ وعلى والديَ وأن أعمل

صالحا ترضاه وأصلح لي في ذريتي إني

تبت إليك وإني من المسلمين"

HIPPOCRATIC OATH

At the time of being admitted as a member of the medical profession: I solemnly pledge to dedicate my life to the service of humanity;

the health and well-being of my patient will be my first consideration;

I will respect the autonomy and dignity of my patient;

I will maintain the utmost respect for human life;

I will not permit considerations of age, disease or disability, greed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient;

I will respect the secrets that are confided in me, even after the patient has died;

I will practice my profession with conscience and dignity and in accordance with good medical practices;

I will foster the honor and noble traditions of the medical profession;

I will give to my teachers, colleagues, and students the respect and gratitude that is their due

I will share my medical knowledge for the benefit of the patient and the advancement of healthcare;

I will attend to my health, well-being, and abilities in order to provide care of the highest standard;

I will not use my medical knowledge to violate human rights and civil liberties, even under threat;

I make these promises solemnly, freely and upon my honour.

Declaration of Geneva, 1948

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DEDICATIONS

To my dearest mother TAIBI Naima

In our sojourn through existence, we encounter colourful souls that paint our lives. Whenever the vibrant shades are overtaken by the embrace of darkness, you have always been a beacon of radiance, elevating my spirit to soaring heights. From the instant I opened my eyes to the world, I've had your smile to guide my path and your prayers to shield me through life's vicissitudes. You held my hand when I stumbled and fell and picked me up when life was just too much to bear and dwell. You've listened to my worries and dried my tears, and with your endless support, filled my heart with hope and joy. Your love is a gift, an ever-present reminder that I am not alone, no matter what life may bring. You are my rock, my guide, my friend, and my dearest mother, and I am so blessed to call you mine. My heart overflows with the boundless love I encompass for you and still my words, so inadequate, can't convey its true magnitude. Thank you for every sacrifice you've resolutely made for our family; Your unwavering selflessness, strength and resilience have always left me with revere awe. I love you, and be sure that this love will endure all eternity for you are the very beating of my heart.

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To my dear brother, my best friend Houssam

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My wish for you all is to experience abundant happiness, great success, and good health.
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Professor of Pediatric surgery and esteemed chief of the Pediatrics Surgery department Division "B" in the Mohamed VI University Hospital of Marrakech.

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Judge of my thesis
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Judge of my thesis
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the testimony of my high consideration and deep appreciation.

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ABBREVIATIONS

LIST OF ABBREVIATIONS

EA : Esophageal Achalasia
LES : lower esophageal sphincter
UGI : Upper Gastro-intestinal
LFTs : The liver function tests
HL : Hepatic lipase
GGT : Gamma Glutamyl Transferase
CRP : C-reactive protein
PPIs : Proton pump inhibitors
NSAIDs : nonsteroidal anti-inflammatory medications
PedsQL : Pediatric Quality of Life Inventory
GI-PedsQL : Pediatric Quality of Life Gastrointestinal Symptoms Scales and Module
ESS : Eckardt Symptom Score
IQR : interquartile range
VZV : Varicella Zoster virus
HIV : Human Immunodeficiency virus
HLA : Human leukocyte antigen
DMN : dorsal motor nucleus
CNS : central nervous system
ANS : autonomic nervous system
FTT : Failure to Thrive
TBE : Timed barium esophagram
EGJ : esophagogastric junction
EGD : esophagogastroduodenoscopy
EoE : Eosinophilic esophagitis
GERD : Gastro Esophageal Reflux Disease
HREM : High-Resolution Esophageal Manometry
IRP : Integrated Relaxation Pressure
LHM : Laparoscopic Heller Myotomy
GI : Gastro-intestinal
BUN : Blood Urea Nitrogen
NLR : Neutrophil-to-lymphocyte ratio
MLR : Mixed Lymphocyte Reaction
IL-6 : Interleukin 6
IL-10 : Interleukin 10
BTx : Botulinum toxin injection

PD : Pneumatic Dilation
HM : Heller Myotomy
GER : Gastroesophageal reflux
EPD : Endoscopic pneumatic dilation
POEM : Peroral endoscopic myotomy
OHM : Open Heller Myotomy
ES : Eckardt Score
PRO : Patient-reported outcome
HRQoL : health-related quality of life
FGIDs : functional gastrointestinal disorders
QoL : Quality of Life
JOG : jonction œsogastrique

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OUTLINE

INTRODUCTION

Esophageal Achalasia (EA) in children is a rare but quintessential neurodegenerative dysmotility disorder of the esophagus.

The primary motor disorder is characterized by insufficient relaxation of the lower esophageal sphincter (LES), absence of peristalsis in the esophageal body, and increased LES resting pressure during swallowing which produce difficulties in the emptying of food from the esophagus into the stomach, causing food stasis. [1]

The pathophysiology of the motor dysmotility seen in achalasia involves the selective degeneration of inhibitory neurons of the esophageal myenteric (Auerbach's) plexus that innervates the LES and esophageal body. The precise aetiology of this degeneration process, on the other hand, is still mainly unknown.[2]

The possible implication of certain viruses, such as herpes simplex virus 1, varicella-zoster, and human papillomavirus as inciting antigens of an inflammatory response in genetically susceptible individuals leading to damaged myenteric neurons has been suggested.[3,4] However, no identification of these specific aforementioned viruses was established in myotomy specimens from achalasia patients, yet an infectious hypothesis was not ruled out.[5,6]

An autoimmune mechanism has also been proposed with supporting presence of circulating anti-myenteric neuronal antibodies[7]. Furthermore, a genetic origin for the disease has been postulated suggesting an autosomal recessive mode of transmission with reports of familial occurrences such as the case report of Esophageal Achalasia in monozygotic twins.[8]

Esophageal Achalasia is a very rare disease in the paediatric population with an estimated annual incidence of 0.02 to 0.31 cases per 100,000 kids—nearly 10 times less than that in adults— without racial or gender predilection.[9]

In childhood, achalasia is most often misdiagnosed due to an overlap of symptoms profile in common childhood diseases including mainly progressive dysphagia, vomiting, and regurgitation. Symptoms vary with age and more atypical presentations are seen in toddlers and infants, counting recurrent pneumonia, nocturnal cough or choking all of which can become so debilitating that profound weight loss and failure to thrive occurs.[10] Achalasia is also often

described in association with Allgrove syndrome, Trisomy 21, familial dysautonomia and glucocorticoid insufficiency, as well as, congenital central hypoventilation syndrome. [11]

Although the diagnosis of EA can be suspected on clinical symptoms, the current definitive diagnosis workup consists of barium/gastrografin esophagram, upper endoscopy and esophageal manometry. The latter being the golden standard for diagnosis confirmation.[12]

Achalasia treatment aims to improve esophageal emptying by decreasing LES tone using pharmaceutical, endoscopic, or surgical means. However, Esophageal myotomy (Heller myotomy) remains the treatment of choice and seemingly the safest and most effective in paediatric patients. [13]

The purpose of our study is to yield an insight into Achalasia epidemiology, assess the diagnosis process, the surgical management as well as providing a long-term outcome of the Quality of Life of patients who underwent a surgical closure of their Esophageal Achalasia in the Pediatric Surgical department Division "B" of the Mohammed VI Marrakech teaching hospital during a 15-year period.

PATIENTS & METHODS

I. TYPE OF STUDY:

We conducted a retrospective, single-centre, descriptive study of the preoperative, intraoperative, and postoperative data of 15 patients who underwent Heller Myotomy surgery for Esophageal Achalasia in the Pediatric Surgery department Division "B" of the Mohamed VI Teaching Hospital in Marrakech over a period of 15 years, from February 2008 to October 2022.

II. AIM OF THE STUDY:

This study aims to review the experience of our department in the diagnosis process and the surgical management of Esophageal achalasia in children with an outline of its long-term outcomes. We will also assess the epidemiological, clinical, and paraclinical features' findings in comparison to existing literature and present an outlook on current Quality of Life of our study participants.

III. PATIENTS:

1. INCLUSION CRITERIA

The following criteria for inclusion were established:

- ♣ Patients under the age of 16 years old who underwent surgical treatment for a confirmed Esophageal Achalasia in the Pediatric surgery department "B" of the Mohamed VI University Hospital of Marrakech.
- ♣ Patients with at least 3 months follow-up data.

2. EXCLUSION CRITERIA

- ♣ Patients lost to follow-up.
- ♣ Patients with unusable or lost medical records.

IV. METHODS:

1. DATA COLLECTION

- ♣ The preoperative data (epidemiology, medical and surgical history, clinical exams, paraclinical data) as well as the follow-up data were provided by a thorough review of medical records in the Pediatric surgery department archives.
- ♣ The data from each patient was summarized in a patient medical sheet which contains our different studied criterions inclusive of: demographic characteristics, past medical history, clinical presentation, paraclinical investigations, surgical management and postoperative management with follow-up results. (Detailed in **Appendix I**)
- ♣ We next performed a prospective survey assessment of long-term Quality of Life. Parents' patients were contacted by telephone call and consent to participate was obtained prior to administering both the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and the PedsQL Gastrointestinal Symptoms Scales and Module (GI-PedsQL). These data were later compared to legacy-matched healthy controls. (Detailed in **Appendix II**)

2. STATISTICAL ANALYSIS

- ♣ We recorded the collected data and performed a data analysis using Microsoft Excel 2021 version.
- ♣ Continuous variables were reported as mean ± standard deviation and range, when appropriate. Categorical data were presented as the number of patients and their relative percentages.

RESULTS

I. Socio-demographic variables among children with Esophageal Achalasia:

1. Incidence:

During a 15 years period, between February 2008 and October 2022, we have identified 15 cases of Esophageal Achalasia patients admitted in our pediatric surgery department.

Table I: Distribution of the number of cases of EA by years

Year	Number of cases of EA
2011	1
2015	1
2018	1
2019	4
2020	4
2021	3
2022	1
Total	**15**

2. Age:

The mean age of our patients was 6 years-old with a standard deviation of 5.08 ranging from 2 months-old to 15 years-old.

Table II presents the age distribution of patients in our case series.

Table II: Age distribution of our patients

Age group	Number (N)
Neonates (Birth - 1 month)	0
Infants (> 1 month - 2 years)	6
Preschooler child (>2 - 6 years)	2
School age child (> 6 - 12 years)	5
Adolescent (> 12 years)	2
Total	15

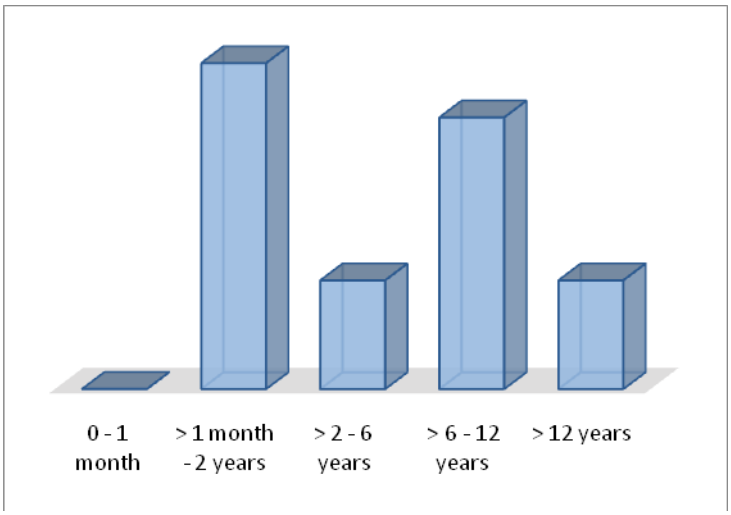

Figure 01: Age distribution of our patients

3. Gender:

In our study sample of 15 patients, 7 were males while 8 were females establishing, therefore, a sex ratio of 0.875.

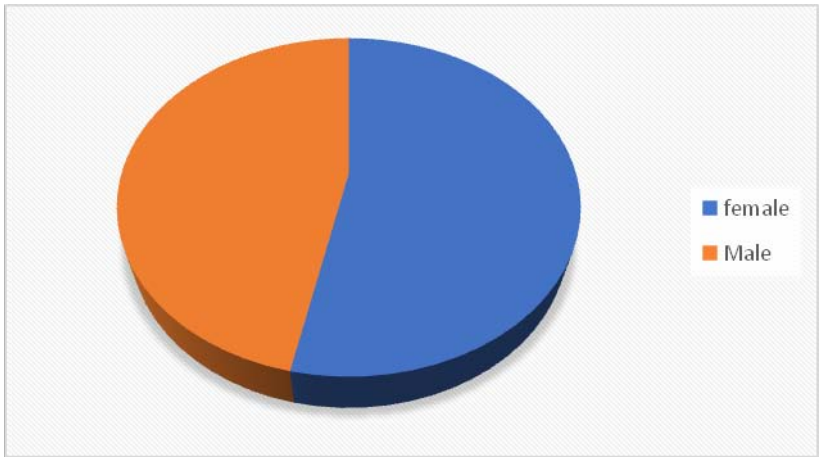

Figure 02: Gender distribution of our patients

4. Areas of residence:

11 patients lived in rural areas, while 4 patients lived in urban areas.

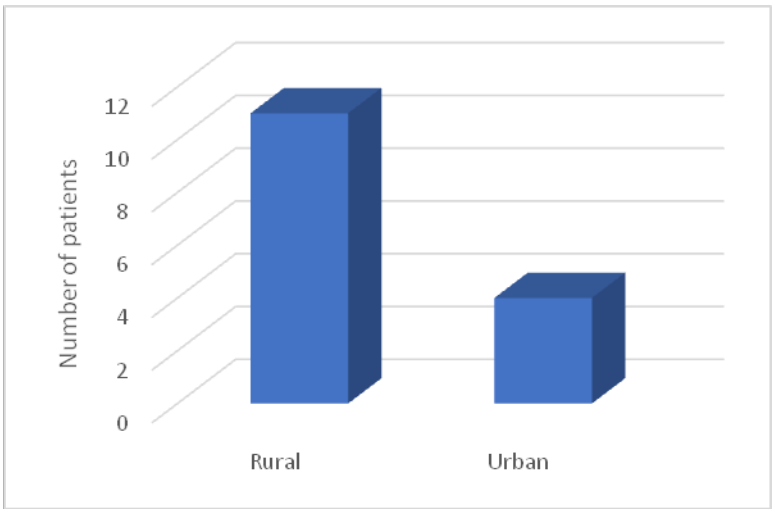

Figure 03: Area of residence distribution of our patients

5. Consanguinity:

The notion of consanguinity was found in 7 patients with 6 cases of 1st degree consanguinity and 1 case of 2nd degree consanguinity.

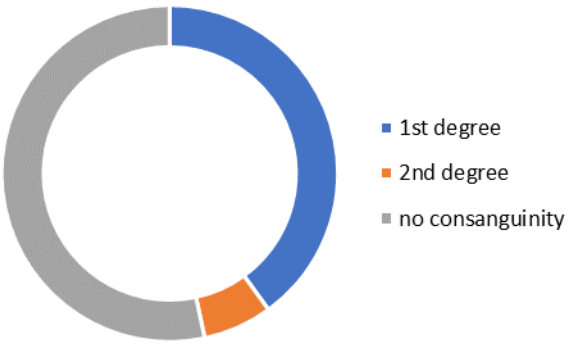

Figure 04: Distribution of the notion of consanguinity of our patients

II. Past medical history:

1. Medical history:

Among our patients:

- ♣ Seven had Allgrove Syndrome.
- ♣ Two had a history of recurrent respiratory infections for which hospitalization in a Pediatrics department was needed.
- ♣ One patient presented with Down's Syndrome.
- ♣ One mentioned a history of cerebral palsy with epilepsy, laryngomalacia and microcephaly.
- ♣ One had a history of an Ischemic stroke 17 days prior his Achalasia surgical treatment.

Table III: Distribution of previous medical conditions presented by our patients

Medical history	Number of patients
Allgrove Syndrome	7
Down's Syndrome	1
Recurrent respiratory infections	2
Cerebral palsy + Microcephaly+ Laryngomalacia	1
Other non-Achalasia-specific history	1

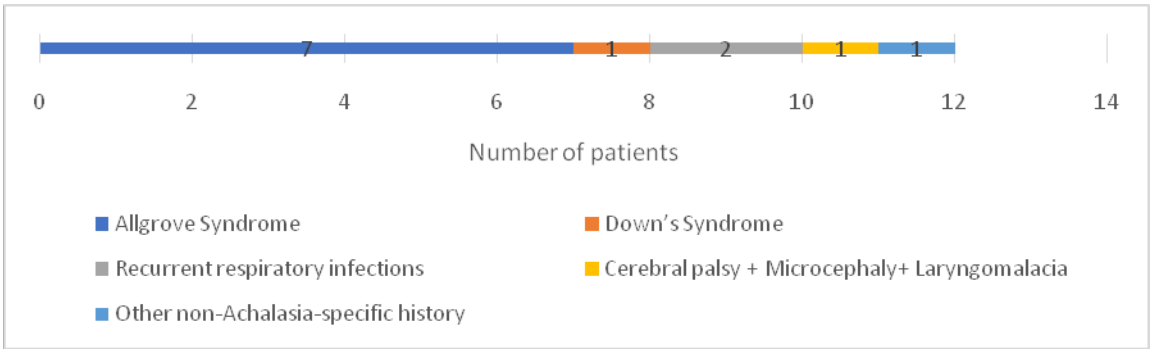

Figure 05: Distribution of previous medical conditions leading to EA in our patients

2. Surgical history:

Patients in our study group had never undergone any previous surgical intervention.

III. History of presenting illness:

1. Symptoms:

- ♣ The predominant presenting symptom in our study is regurgitation of undigested food following every meal, which is reported by all 15 of our patients and has an insidious onset in each of them.
- ♣ Ten patients had dysphagia, of which five had paradoxical dysphagia (difficulty swallowing liquids while comfortably ingesting solids), three had symptomatic dysphagia for solids alone, and one case had a 6-month-old child with dysphagia for liquids. Following the observation of an initial different symptom, dysphagia gradually emerged in each of our ten patients and frequently persisted after each meal.
- ♣ Nine patients were suffering from a failure to thrive with a mean average of -1.06 and a standard deviation of 1.09 in height percentile and a mean average of -1.2 in weight percentile with a standard deviation of 1.26.
- ♣ Seven patients experienced weight loss, with losses ranging from 2 to 15 kg and an average of 7.71 kg.
- ♣ Asthenia and retrosternal pain were also observed in seven patients; retrosternal pain manifested only intermittently in all cases and was connected to heartburn in one patient.
- ♣ Three patients reported experiencing respiratory symptoms, with two of them presenting an active pneumonia, 1 case of dyspnea and 2 incidences of coughing.
- ♣ We also noted hematemesis and melena presented by one of our studied patients.

Table IV: Distribution of EA symptoms in our patients

Symptom	Number of presenting patients
Regurgitation	15
Dysphagia	10
Failure to thrive	9
Weight loss	7
Asthenia	7
Retrosternal pain	7
Respiratory symptoms	3
Heartburn	1
Hematemesis and melena	1

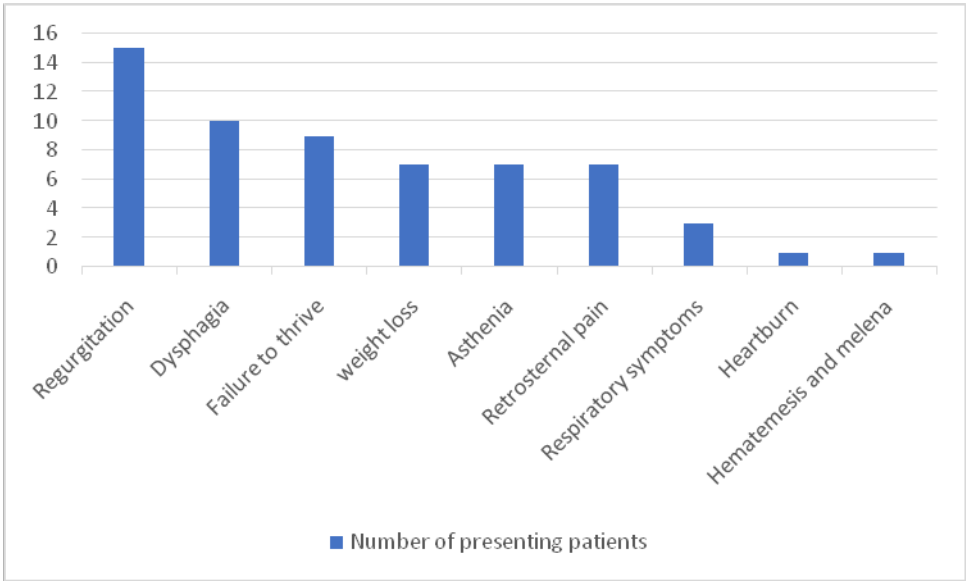

Figure 06: Distribution of EA symptoms in our patients

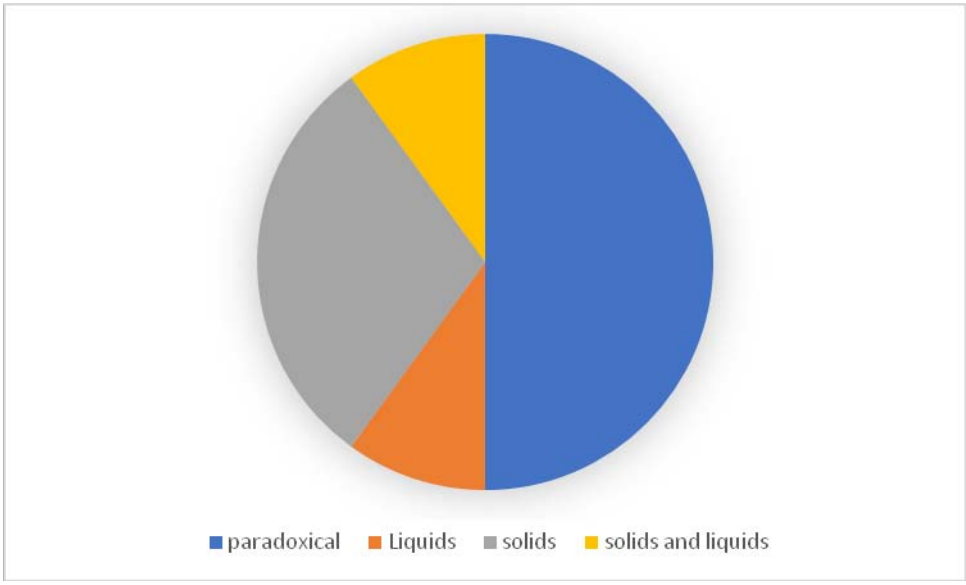

Figure 07: Distribution of Dysphagia types in our patients

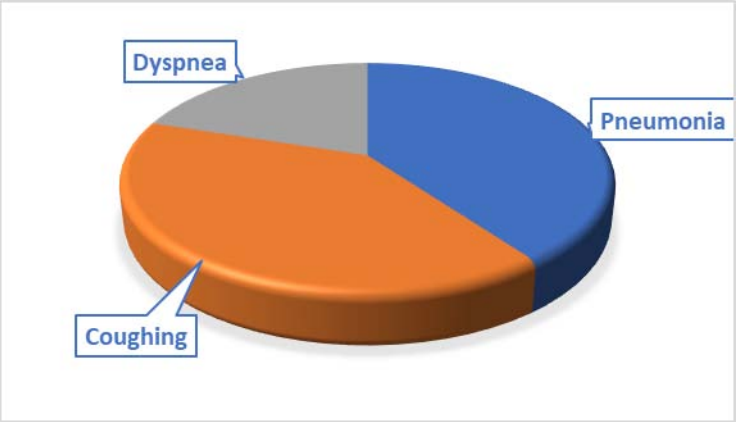

Figure 08: Distribution of respiratory symptoms in our patients

2. Clinical Eckardt score

- For each patient, we preoperatively determined the Eckardt Symptom Score (ESS) as a trustworthy method to assess achalasia symptoms, we also subsequently utilized it as a postoperative tool to assess the effectiveness or failure of the intervention.
- The median preoperative Eckardt score was 6.26 with a range from 3 to 10 and a standard deviation SD = 2.6.

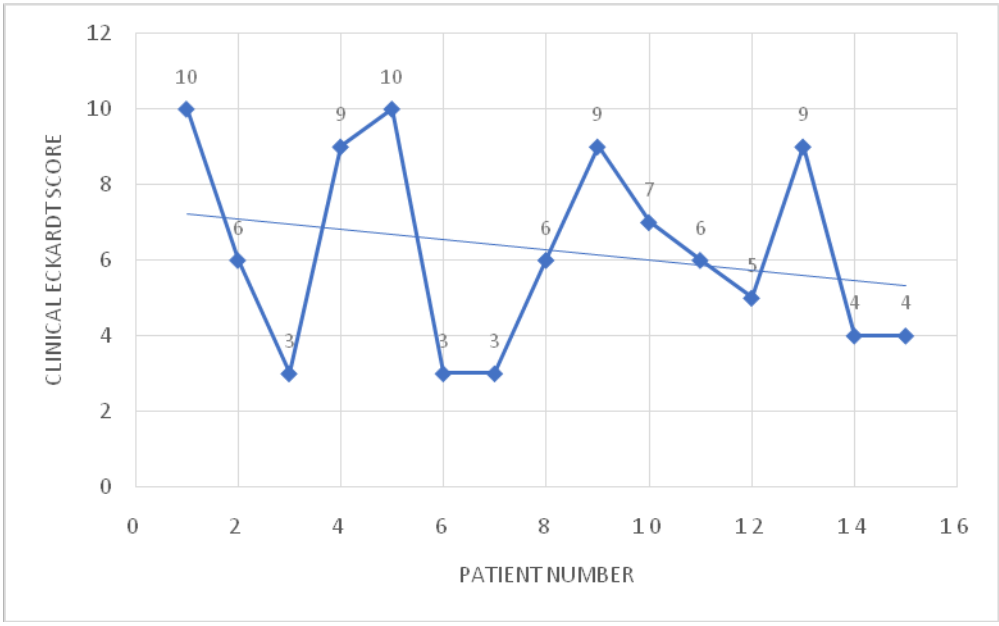

Figure 09: A review of each patient's preoperative clinical Eckardt score.

3. Patients delay:

The time interval between the onset of symptoms and the first visit to the doctor, when the diagnosis was confirmed by UGI gastrografin radiography, varied from 2 months to 10 years, with a mean average of 33.25 months (2.77 years).

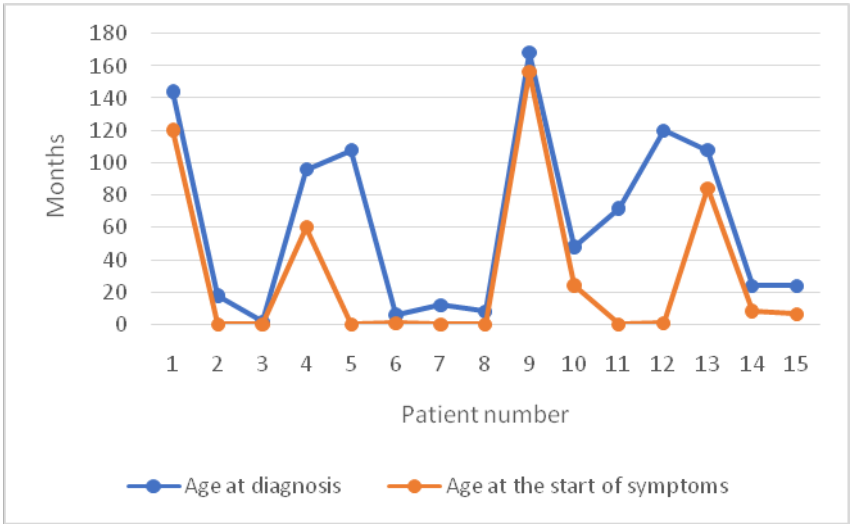

Figure 10: The time interval between the start of symptoms and EA Diagnosis.

IV. Physical examination:

During pulmonary examination, two patients presented right basal crackles which was related to their underlining aspiration pneumonia. One of these patients displayed nasal flaring and tachypnea.

The physical examination of the remaining 13 patients presented no abnormality.

V. Paraclinical Investigations:

1. Timed esophagram:

A timed UGI gastrografin exam was performed in all patients of our study group and it showed the following results:

Table V: Distribution of different findings in UGI radiography of our patients

Findings after gastrografin swallow	Number of patients
Tapering at the gastroesophageal junction	15
Bird beak appearance of LES	12
Dilated esophagus in all cervical abdominal and thoracic parts	9
Dilated esophagus in abdominal and thoracic parts	4
Dilated esophagus localized in the abdominal part	2
Persistence of gastrografin in esophagus over 10 minutes of the exam	4
Hypotonic esophagus	1
Tertiary contractions of the esophagus	1

Table VI: Distribution of EA grades in our patients according to Rezende's classification

Esophageal Achalasia grade	Number of patients
Grade I	1
Grade II	0
Grade III	14
Grade IV	0

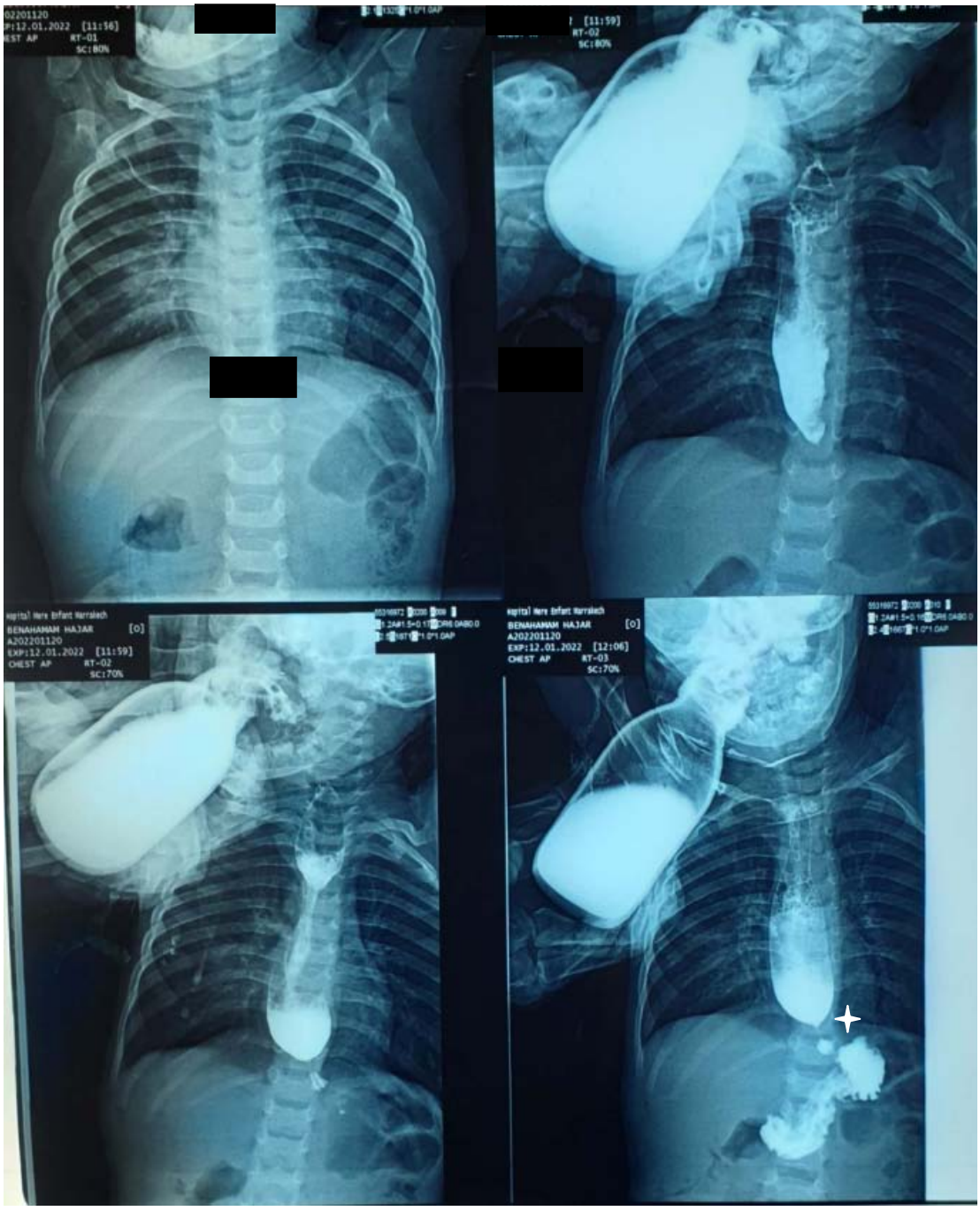

Figure 11: UGI gastrografin exam showing a dilated esophagus with a Bird beak appearance of LES (asterix) in our 8 months old female patient.

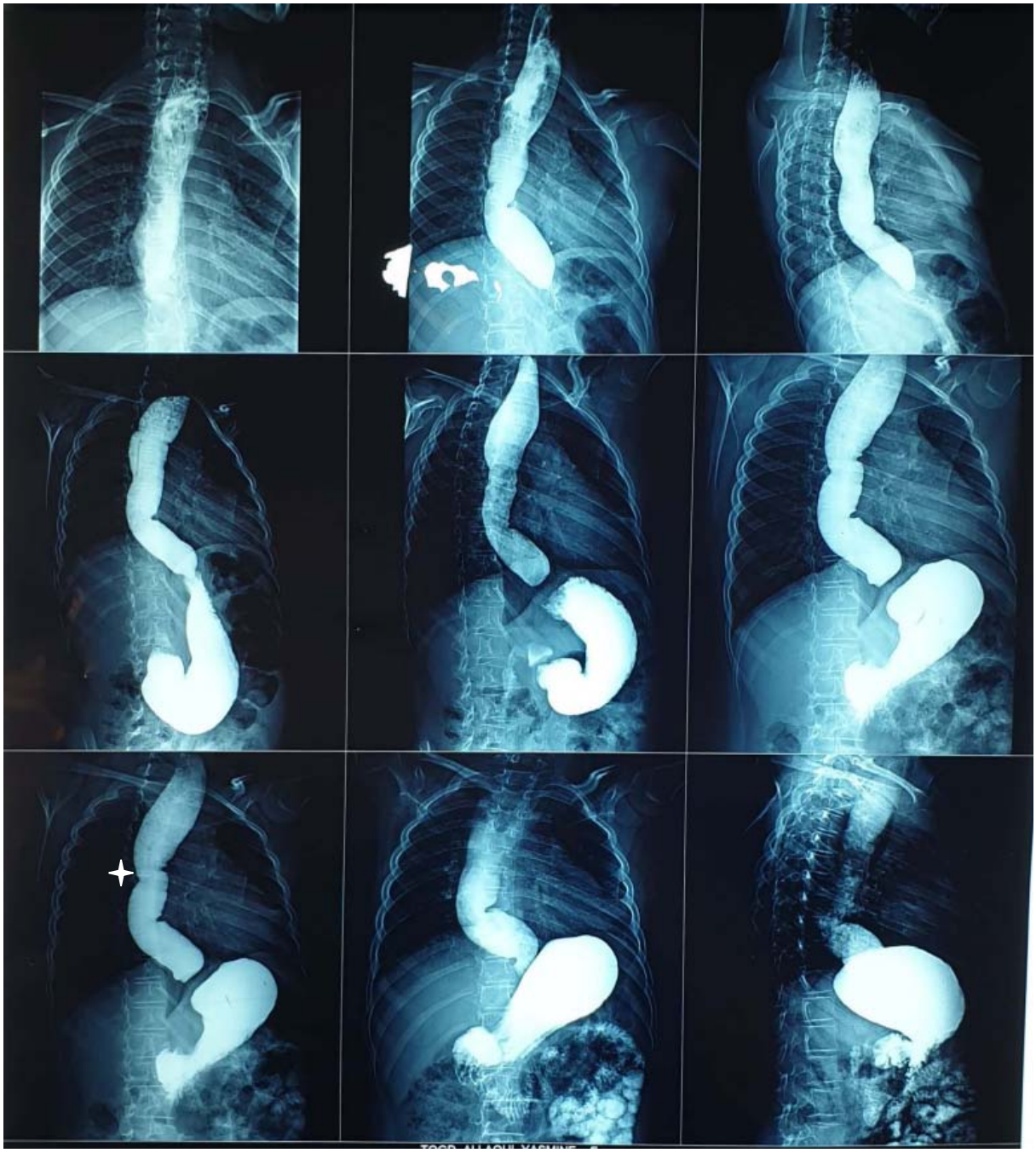

Figure 12: UGI gastrografin exam showing a tortuous dilated esophagus (asterix) and acute tapering at the gastroesophageal junction in our 15 years old female patient.

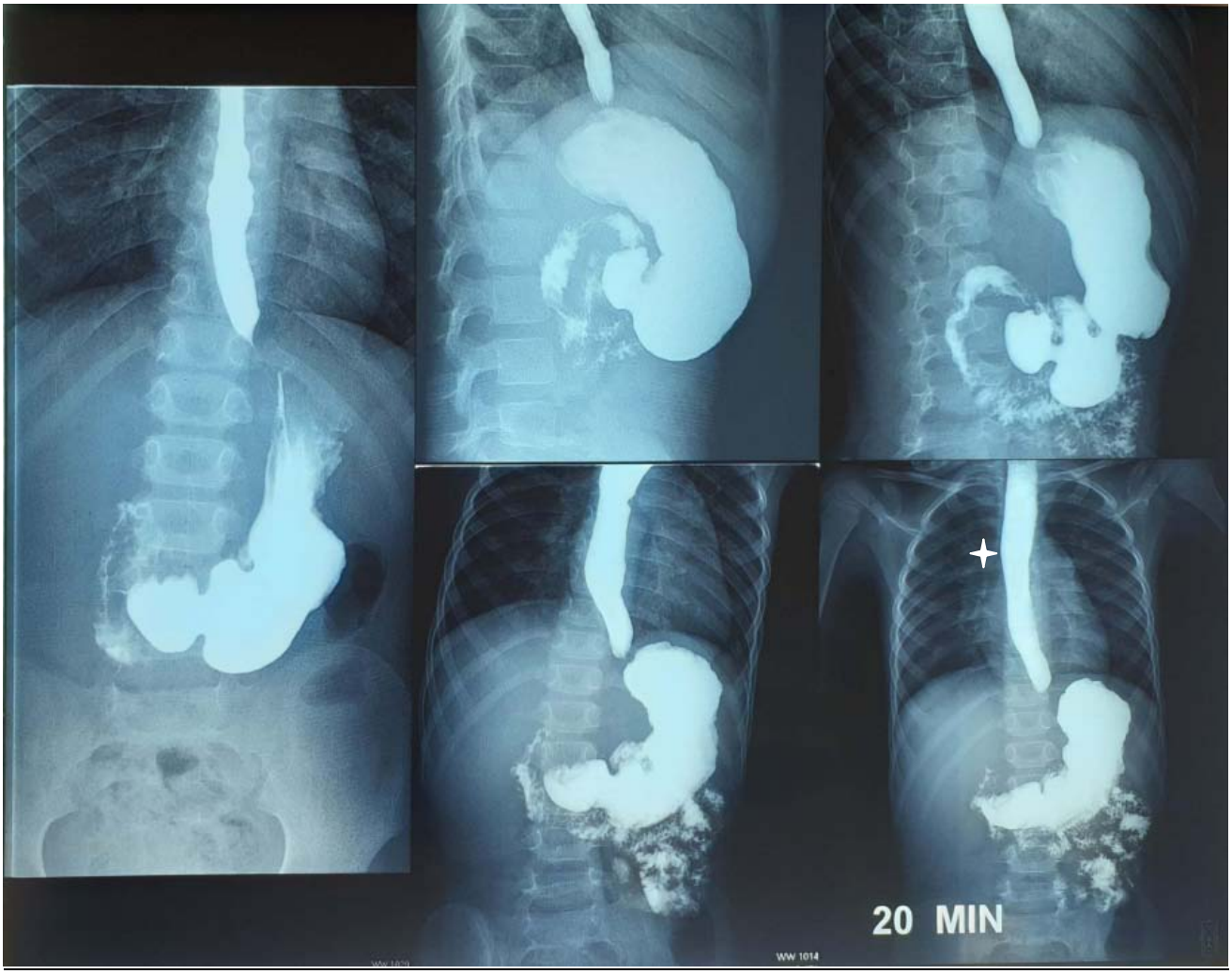

Figure 13: UGI gastrografin exam showing an acute tapering at the gastroesophageal junction with persistence of gastrografin after 20mins of the swallow (asterix) in our 8 years old male patient.

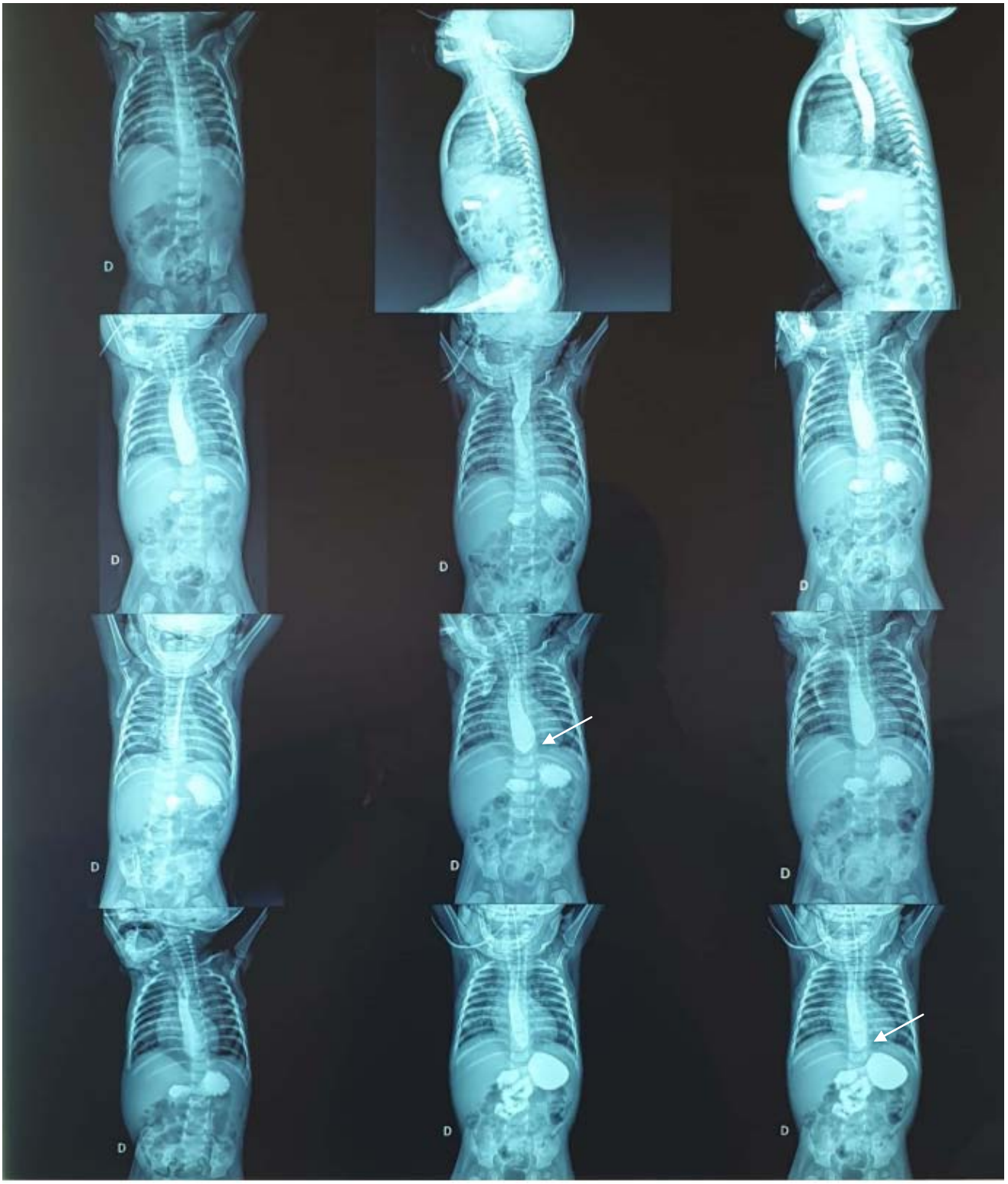

Figure 14: UGI gastrografin exam showing a dilated esophagus with a Bird's beak appearance at the gastroesophageal junction (arrows) in our 6 months-old male patient.

2. UGI Endoscopy:

A UGI endoscopic exam was performed in 11 of our 15 patients, yielding the following results:

Table VII: Distribution of different findings in UGI endoscopy of our patients

UGI endoscopy abnormality	Number
Resistance at the gastroesophageal puckered junction	9
Dilated esophagus with retained food	8
Impenetrable gastroesophageal junction after multiple attempts	1
Nodular gastritis	1

3. Esophageal Manometry:

Esophageal manometry was not conducted on any of our study participants.

4. Pulmonary X-rays:

A pulmonary X-ray was performed on 5 patients in our 15-study group, with only one instance displaying an anomaly comprised of: convex opacity overlapping the right mediastinum. and mediastinum widening.

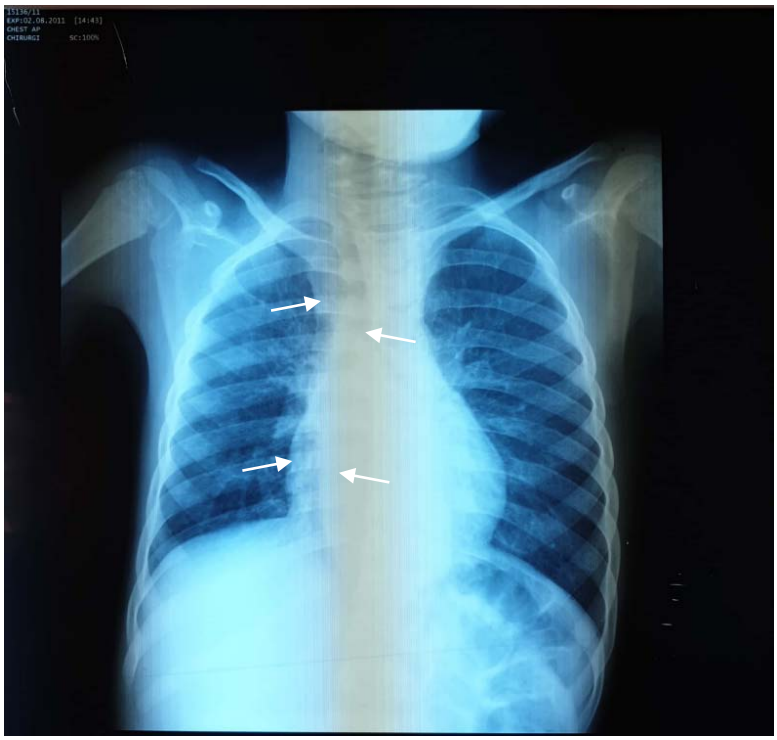

Figure 15: Chest X-ray of our 12-year-old male patient presenting a widening of mediastinum and double contour at the right mediastinum border presenting the right contour of the heart and the silhouette of the dialated esophagus (arrows).

5. Biological tests:

- Four patients had microcytic anemia, with two severe cases requiring blood transfusions. Additionally, three patients developed neutrophilic leukocytosis, and one participant had thrombocytopenia.
- In 10 cases, the creatinine screening revealed low creatinine levels.
- The liver function tests (LFTs) were performed on three patients, one of whom had high liver enzymes bilirubin, Hepatic lipase (HL), and Gamma-glutamyl Transferase (GGT).
- We also discovered an elevated level of C-reactive protein (CRP) in two patients.

VI. MANAGEMENT:

1. Nonsurgical treatment:

Out of our 15 study participants, one patient received pneumatic dilation treatment. The two-year-old child underwent two sessions, each of which resulted in a failed dilatation.

2. Surgical treatment:

2.1. Surgical procedure:

The surgical treatment of choice for all of our patients was an Open Heller Myotomy coupled with a fundoplication.

At the surgeon's discretion, 14 patients received a Dor surgery (180°-200° anterior partial wrap), while 1 patient underwent a Thal fundoplication (90° anterior partial wrap).

Within our study group, there were no documented perioperative complications.

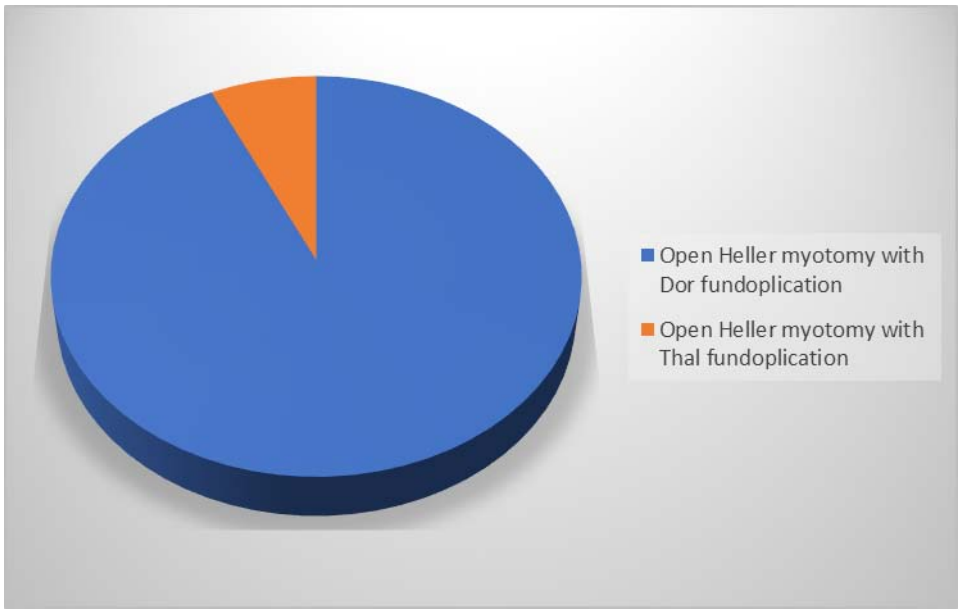

Figure 16: Distribution of different surgical techniques used in our study.

2.2. Post-operative management:

a. Feeding:

All of our patients had a gastric tube inserted prior to the start of the procedure to ensure the evacuation of saliva in the esophagus. When there is significant food stasis, the tubing was also beneficial to reduce the risk of aspiration and avoid regurgitation during anesthetic induction.

The gastric tube was maintained post intervention for a mean average of 2.93 days varying from 1 day to 5 days.

b. Medication:

- ♣ All of our patients received post-prophylactic short-term antimicrobial therapy consisting of cephalosporins administered intravenously for the first 24 hours and afterwards orally for 5 days on amoxicillin/clavulanate.
- ♣ Eleven of our patients had a recorded use of Proton pump inhibitors (PPIs) with a double dosing of 2mg/kg/day for a duration ranging from 15 days to 3 months, with a mean average of 2.04 months.
- ♣ Paracetamol and nonsteroidal anti-inflammatory medications were administered to all of our patients as analgesics (NSAIDs).

c. Postoperative immediate complications:

No complication was reported in any of our cases.

2.3. Length of post-operative hospitalization stay:

Post-operative stay varied from 3 to 8 days with a mean average of 5.53 days.

2.4. Duration of post-surgery liquids diet:

All of our patients were placed on a full liquid diet for periods ranging from 15 days to 3 months, with a mean average of 29 days.

VII. Evolution:

1. Follow-up length

The average length of follow-up was 11.26 months (0.94 years), ranging from 30.7 months to 3 months.

2. Mortality:

There were no deaths reported in our research group.

3. Complete symptom relief:

12 of our patients had a complete symptom relief with no persistent or recurrent symptoms.

4. Symptoms persistence:

3 patients registered a persistence of their symptoms:

- One patient continued to suffer from a discrete intermittent dysphagia for solids
- Two patients noted a severe post-feeding regurgitation up to 3 times per day.

5. Post operative sequela

- The patient with persistent discrete intermittent dysphagia for solids eventually reported disappearance of dysphagia but developed mild regurgitation 6 months post-intervention.

- ♣ The two patients with the severe persistent regurgitation showed no disappearance of this symptom 3 months post-intervention in one child and a development of severe dysphagia for solids 10 months post-intervention for the second child.

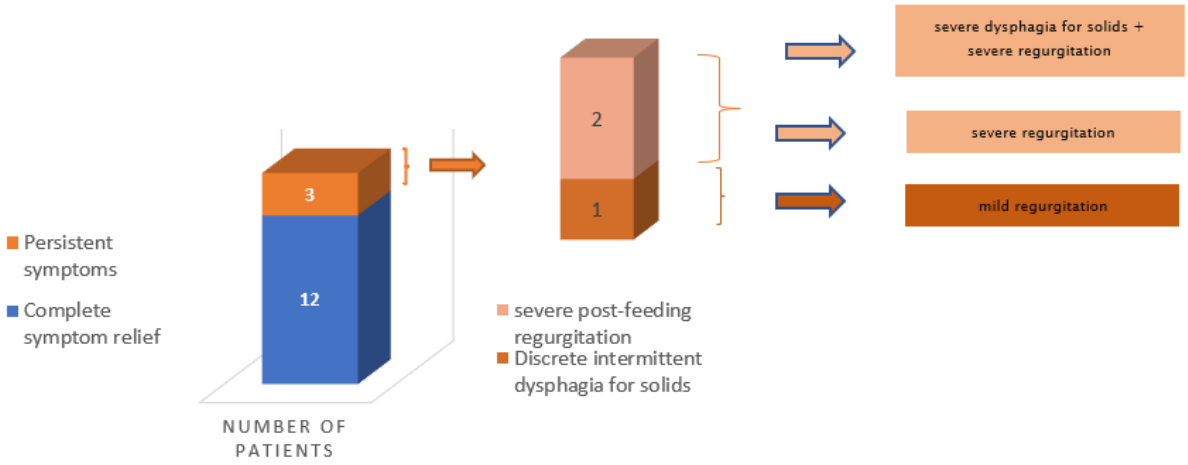

Figure 17: Distribution of postoperative evolution of symptoms in our study.

6. Follow-up paraclinical exams:

Only the three patients who showed a persistence or recurrence of their symptoms underwent a follow-up UGI endoscopy or gastrografin exam. The paraclinical exam was chosen based on the surgeon's preferences.

The following table summarizes these 3 cases:

Table VIII: Follow-up of patients with post-operative persistent symptoms and sequela

Cases / Features	Case 1	Case 2	Case 3
Gender	**Female**	**Male**	**Female**
Age	**15 years old**	**4 years old**	**15 months old**
Associated disease	Allgrove syndrome	cerebral palsy with epilepsy, Laryngomalacia, microcephaly	No
Initial pre-surgery symptoms	Weight-loss, failure to thrive, regurgitation, paradoxical dysphagia, retrosternal pain	Failure to thrive, regurgitation, retrosternal pain, pneumonia	Regurgitation, dysphagia for solids, Hiatal Hernia, melena and hematemesis.
Surgical management choice	Open heller myotomy with Dor fundoplication	Open heller myotomy with Dor fundoplication	Open heller myotomy with Dor fundoplication
Symptoms persistence	Discrete intermittent dysphagia	Severe post-feeding regurgitation	Severe post-feeding regurgitation
Post-operative sequela	Mild regurgitation	Severe regurgitation	Severe dysphagia for solids
Time of occurrence	6 months	3 months	10 months
Follow-up UGI gastrografin exam	Mildly dilated esophagus, acute tapering at the gastroesophageal junction	None	Type III Hiatal Hernia, moderate dilation of the esophagus, GE reflux reaching thoracic esophagus
Follow-up endoscopy	None	Dilated esophagus, incompetent cardia, minor irreducible Hiatal Hernia	Incompetent cardia, grade 1 esophagitis
Subsequent treatment	Prescription of Proton pump inhibitors	Redo-surgery	Redo-surgery

7. Post-operative Clinical Eckardt score:

The median post-operative Eckardt score was 0.8 with a range from 0 to 6 and a standard deviation SD = 1.8.

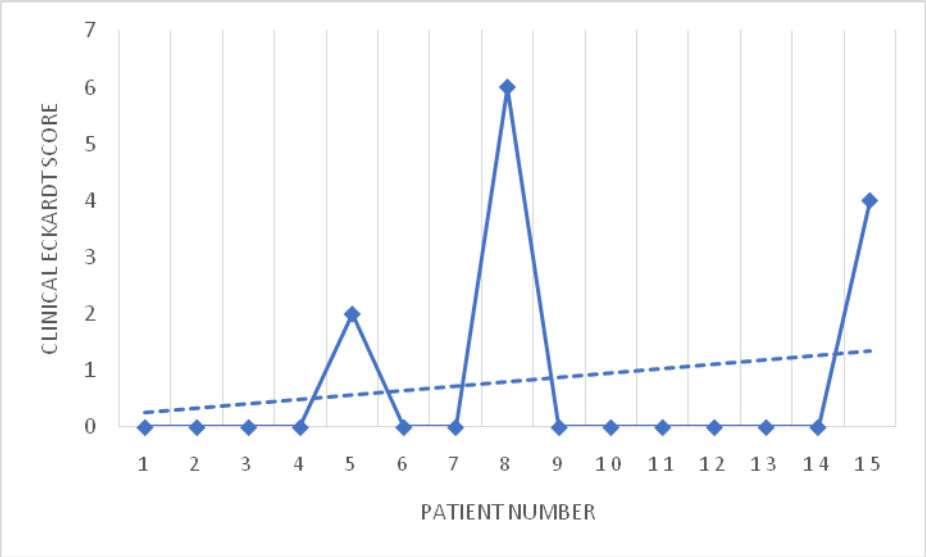

Figure 18: A review of each patient's post-operative clinical Eckardt score.

8. Redo surgery:

- ♣ Among our 15 patients who underwent primary Heller myotomy for Achalasia, two patients underwent a revisional procedure. These patients' demographics and clinical features as well as follow-up paraclinical exams were summarized in the previous Table VIII.
- ♣ The main concern of all patients was recurrent dysphagia and regurgitation.
- ♣ The median time between initial surgical procedure and symptom recurrences is 6.3 months. The median time between initial surgical procedure and redo-surgery is 2.375 years.
- ♣ The primary factor contributing to the first procedure's failure was an overly tight fundoplication leading to dysphagia in our case 3 patient meanwhile our case 2

patient presented with complete dehiscence of initial Dor fundoplication suture points resulting in symptom recurrence.

- ♣ No endoscopic dilatations nor medical therapy were attempted between the first operation and the redo-surgery in our study group.
- ♣ The redo-surgery was executed using laparotomy in all patients.
- ♣ An anti-reflux procedure based on a Nissen fundoplication technique was the procedure of choice for both children complemented with a hiatal hernia repair.
- ♣ At a median follow-up of 3.5 months, the outcome of the revisional surgery was favorable with complete symptom relief (Eckardt score < 3) in both patients (case3).
- ♣ The second patient's evolution (case2) was marked with an intestinal obstruction needing hospitalization and treated medically following conservative therapy: nasoenteric decompression, enemas, intravenous fluid resuscitation, and correction of electrolyte levels' abnormalities as well as antibiotic therapy. The patient was later discharged with complete symptom relief and without further complications in their 3 months post-hospitalization follow-up.
- ♣ The following **Table IX** describes the evolution of the two patients in our research who required redo surgery.

Table IX: Evolution of the 2 patients who underwent a redo-surgery.

Features	Case2	Case 3
Age at redo- surgery	7 years old	3 years old
Time between primary and redo procedure	3 years	1 year and 9months
Type of redo procedure	Hiatal Hernia repair + Nissen fundoplication	Hiatal Hernia repair + Nissen fundoplication
Redo-surgery hospitalization length	10 days	12 days
Evolution	Intestinal pseudo-obstruction with bilious vomiting associated with hyperkalemia +hyponatremia + decreased renal function+ neutrophilia and elevated CRP	Complete symptom relief
Time of complication occurrence	1-month post-redo surgery	_____
Management of post-operative complications	-Hospitalized for 22 days -Conservative therapy: Nasogastric tube, enemas, fluid resuscitation, correction of electrolyte abnormalities and antibiotic therapy	_____
Evolution of post-operative complications	Complete symptom relief	_____
Follow-up length of redo-surgery	4 months	3 months

9. Assessment of long-term Quality of Life:

The Quality of Life was assessed through both the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core and the PedsQL Gastrointestinal Symptoms (GI-PedsQL) questionnaires.

We used the validated Arabic version of the parent proxy-report for parents of children aged 2 to 4, 5 to 7, 8 to 12, and 13 to 18 for both questionnaires.

All patients' parents were approached by telephone call and were asked to fill out the 2 questionnaires by means of a structured and assisted telephone interview. Consent was acquired prior to the questionnaires' administration.

13 patients were included in our Quality of Life evaluation. Out of the 15 patients in our study, 2 were unreachable by telephone following multiple failed attempts.

The median (IQR) time from latest clinical contact to date of inclusion was 2.9 years (IQR 0.3-8.8 years).

The mean age of our study patients during the Quality of Life assessment was 8.9 years with a standard deviation of 4.9.

The most frequently reported symptom complaint was dysphagia for solids with the requirement to drink fluids while eating, which impacted daily life in a substantial manner for 7 out of the 13 patients. Vomiting and heartburn were the second most frequently reported symptom with a complaint from 4 out of 13 patients.

Table X: PedsQL Gastrointestinal Symptoms Scales and Module Parent proxy-report survey results:

GI-PedsQL Section	Mean ± SD
Stomach Pain	76.3 ± 22
Stomach discomfort when eating	78.8 ± 20.9
Food and Drink Limits	61.5 ± 11
Trouble Swallowing	41.66 ± 19.5
Heartburn/Reflux	66.8 ± 16.1
Nausea/Vomiting	66.6 ± 19.2
Gas/Bloating	77.0 ± 21
Constipating	98.07 ± 6.9
Blood in poop	98.07 ± 6.9
Diarrhea	95.63 ± 5
Symptom total score	**76.0 ± 14.9**

Table XI: Pediatric quality of life inventory (PedsQL)Parent proxy-report survey results:

PedsQL Section	Mean ± SD
Physical functioning	79 ± 18
Emotional functioning	67 ± 10
Social functioning	78 ± 18
School functioning	62 ± 20
Overall score	**72 ± 17**

DISCUSSION

I. EPIDEMIOLOGICAL DATA

1. Incidence:

According to SWENSON[14], PAYNE[15], and MOERSCH[16] childhood achalasia accounts for less than 5% of all cases of achalasia. The most recent epidemiological studies for childhood achalasia present a correlating report of annual incidence estimated at 0.18/100.000 without racial proclivity in the UK[17] and an incidence of 0.1/100.000/year in the Netherlands[18]. The rarity of this disease is further pronounced in patients under the age of 15 years old with only less than 5% of patients with presenting symptoms.[19]

In our study, 15 patients were treated in our department during a 15 years period resulting in an incidence of 1case/year. Our estimate was likely understated because it assumed that every incident achalasia case in the Marrakech-Safi region was diagnosed. Achalasia is not a terminal condition, and we are simply unsure how many cases go unrecognized. A large population-based investigation would be necessary to truly address this issue.

However, and regardless of this fact the value we report is consistent with the previously reported global single-centered incidences detailed in Table XII.

Table XII: Incidence of achalasia globally, in ascending order from oldest to newest.

Author	Year of publication	Country	Number of cases	Number of years	Incidence Cases/year
Chirdan &al[20]	2001	Zaria, Nigeria	7	19	0.36
Viola & al[21]	2004	Paris, France	20	24	0.83
Hussain & al[22]	2002	Detroit, USA	33	25	1.32
Pastor & al[23]	2009	Toronto, Canada	30	26	1.15
Zhang & al[24]	2009	Shanghai, China	13	12	1.08
Hallal& al[25]	2012	Porto Alegre, Brazil	13	12	1.08
Wakhlu& al[26]	2012	Lucknow, India	40	13	3.07
Erginel& al[27]	2015	Istanbul, Turkey	22	22	1
Meyer & al[28]	2016	Melbourne,Australia	42	31	1.35
Saliakellis& al[29]	2017	London,UK	48	18	2.66
Jarzębicka& al[30]	2021	Warsaw, Poland	60	21	2.85
Idrissa & al[31]	2021	Fez,Morocco	14	10	1.4
Our case series	**2023**	**Marrakech,Morocco**	**15**	**15**	**1**

2. Gender:

A systemic review published in 2020 of all pediatric esophageal achalasia papers reported a 55% masculine predominance[32]. However, this predominance is inconsistently divided globally with a sex-ratio varying from an equal 1 in the MEYER & al[28] series to 6 in the Nigerian CHIRDAN& al[20] experience.

In an Egyptian study by HAMZA& al on the management of childhood EA, the gender of the patients was described as a non-risk factor for surgical outcome[33].

In our case study we reported a subtle female predominance with a male: female ratio of 7:8.

Our findings were consistent with the only other Moroccan study of Idrissa & al[31] which identified an 8:6 sex ratio.

Table XIII: Sex ratio reported by authors.

Author	Country	Number of EA patients	Number of males	Number of females	Sex Ratio M/F
Chirdan &al[20]	Nigeria	7	6	1	6
Viola & al[21]	France	20	13	7	1.85
Meyer & al[28]	Australia	42	21	21	1
Marlais & al[17]	UK	228	128	100	1.28
Smits &al[18]	Netherlands	87	52	35	1.48
Hamza & al[33]	Egypt	11	8	3	2.6
Pham & al[34]	Norway	84	50	34	1.47
Rafeeqi & al[35]	USA	33	21	12	1.75
Peng & al[36]	China	24	14	10	1.4
Idrissa & al[31]	Fez, Morocco	14	6	8	0.75
Our case series	**Marrakech, Morocco**	**15**	**7**	**8**	**0.875**

3. Age:

The incidence and prevalence of Achalasia seem to increase with age[37].The average age at surgery in our series was 6 ± 5.08 years old ranging from 2 months to 15 years old.

It was closer to the series to the series of authors such VIOLA& al[21], IDRISSA& al[31] and ALTOKHAIS& al[39].

Despite the fact that more specialized diagnosis tools, such as Esophageal High-Resolution Manometry, are much more widely available in specialized paediatric surgery centers in Western developed countries, the age of our population study was sensibly lower than most of case studies conducted there. Namely, the mean age of 14 years-old of the CHONÉ & al series study population, an international, multicenter research carried out in 14 tertiary institutions (3 US, 8 European, 3 Asian)[38].

Table XIV: Age of patients (Literature review of single-center experiences).

Author	Country	Year of publication	Mean Age ± SD (years)
Chirdan &al[20]	Nigeria	2001	10 ± 4.8
Viola & al[21]	France	2004	6.4
Smits &al[18]	Netherlands	2016	11.4 ± 3.4
Altokhais & al[39]	Saudi Arabia	2016	7
Grabowski &al[40]	Poland	2017	13 ± 3.5
Idrissa & al[31]	Fez, Morocco	2021	5.2 ± 3.0
Nicolas& al[13]	France	2022	12
Petrosyan & al[41]	USA	2022	11.6 ± 4.5
Our case series	**Marrakech, Morocco**	**2023**	**6± 5.08**

4. Medical history:

The true etiology of achalasia remains largely unknown, although idiopathic in nature, many documented factors are incriminated: autoimmune, environmental, infectious and genetic.

Achalasia, as outlined by RAKE in 1927, is a neurologic disorder characterized by a loss of ganglion cells in Auerbach's plexus of the smooth esophageal muscle.[42] The recent emerging evidence shows that this neuronal degeneration is possibly the consequence of a neurotropic virus infection, the effects of a neurotoxin, or myopathy of the smooth muscle cells.[43]

The immunogenetic etiology of the disease is supported by reports in which patients express common variants within the HLA-DQ region[44].The existence of isolated familial cases of idiopathic achalasia further suggests a genetic predisposition via autosomal recessive transmission with case reports in parents and their offspring[45,46,47].

Several diverse pathological associations in childhood have been reported in the literature with various incidence: Allgrove syndrome (Alacrimia, Achalasia, Adrenal insufficiency)[48], Down Syndrome[49], Sjögren's syndrome[50], Congenital central hypoventilation syndrome[51] and other genetic diseases (familial dysautonomia, glucocorticoid insufficiency, Rozycki syndrome)[52].There was even a rare association with panhypopituitarismin in Turkey described by SIMSEK& al[53] and another association with Moyamoya Disease 6 described in India by Ramesh & al[54].

In our series, the notion of consanguinity was reported in 7 patients, 6 of these patients presented an association of Allgrove syndrome. Overall, the Allgrove syndrome was found in 7 of our patients.

DUMARS & al was the pioneer to describe the Achalasia-microcephaly syndrome association in 1980[55] with the latest case report presented by Wafik & al[56] in 2017 highlighting the consanguinity aspect of this association. In our study one patient born to consanguineous parents (1st degree) presented with microcephaly.

We noted a cerebral palsy diagnosis in one of our patients similar to the findings of Hussain & al[22] but no reported literature, as of now, reviews a possible association between these two entities.

II. ETHIOPATHOGENESIS

Multiple hypotheses have been advanced in an attempt to understand the etiopathogenesis of idiopathic Esophageal Achalasia. Each hypothesis endeavors to explain the absence of ganglia cells in the esophageal myenteric plexus. It is indeed possible that these various theories do not however operate independently but rather present a multifactorial etiology meaning that, like the majority of other human diseases, This disorder results from a combination of mutations in multiple risk genes and environmental factors.

1. Genetic Hypothesis:

Familial and paediatric achalasia cases are extremely rare and consequently cannot be solely used to confirm the existence of a genetic predisposition to esophageal achalasia[57].

Furthermore, several scenarios have been reported in the international literature, including cases of apparent vertical transmission of achalasia and some cases of siblings with esophageal achalasia[58], many of whom were born from consanguineous parents[59]. Meanwhile, only three pairs of monozygotic twins with esophageal achalasia have been mentioned in the literature (ECKRICH and WINANS in 1979[60], STEIN and KNAUER 1982 [8], ZIlBERSTEIN& al in 2005[61]).

In light of these reports, some authors have proposed that the condition has a hereditary component with an autosomal recessive transmission[62].

2. Viral Hypothesis:

Viruses have been implicated in multiple studies as the initiating agent in idiopathic achalasia.

The most known viral infections that are associated with achalasia are the herpes virus family (Herpes Simplex virus, Epstein–Barr virus, Varicella Zoster virus (VZV), and Cytomegalovirus)[63], Paramyxoviruses[64], and Human Immunodeficiency virus (HIV)[65] without consensus among investigators.

The herpes virus family was specifically targeted given their nature as neurotropic viruses[66]. The predilection of herpes viruses for the squamous epithelium makes this a plausible hypothesis given that such tissue selectivity could explain why achalasia involves only the esophagus and spares the rest of the gastrointestinal tract.

A preliminary report by JONES &al noticed a significant increase in the antibody titer against the measles virus in achalasia patients compared to 12 control subjects[64]. In addition, a recent 2021 study's findings by NAIK &al support that the causal reactivation effect of VZV from

latency in esophageal neurons gives rise to chronic VZV infection hence impairing the functional regulation of esophageal motility and control of the LES in achalasia[67].

Contrasting to these papers, other researches have failed to detect the presence of measles, herpes, cytomegalovirus or human papilloma viruses in myotomy specimens from patients with esophageal achalasia[5]. These negative studies do not exclude the possibility of another viral type or a resolved viral infection with disappearance of the pathogenic viral antigen host tissue as a probable etiology of achalasia.

All evidence points to viruses laying the groundwork for autoimmune responses that target inhibitory neurons. A recent 2022 study following the COVID pandemic by FURUZAWA-CARBALLEDA &al, reinforces this theory, and demonstrates the expression of SARS-CoV2 and its receptor in the lower esophageal sphincter muscle of 6/7 achalasia patients who posteriorly had COVID-19 (diagnosed by PCR). The SARS-CoV-2 was undetectable in the LES muscle of the other ten achalasia patients and ten controls without COVID-19[68].

3. Autoimmune:

Early historical descriptions pointed to an infiltration inflammation of the affected regions of the esophagus. This led researchers to evoke a possible role of autoimmunity in the pathogenesis of Esophageal Achalasia.

This inflammatory infiltration of the myenteric plexus was present in all specimens in the historical GOLDBLUM & al analysis of 42 esophagectomy specimens[69].

Immunohistochemical studies have identified these inflammatory cells as CD3-positive/CD8-positive myenteric lymphocytes with granzyme B expression, lending credence to the theory that achalasia is an immune-mediated disease[70].

Molecular studies have shown in particular the association between achalasia and class II human leucocyte antigen (HLA) alleles. Reports on HLA mainly show an association between HLA-DQ and achalasia with HLA-DQB1 being the most commonly reported[71]. DR alleles have

also been identified, however, in an ethnicity-specific manner with for example a DRB1*12 trend in black patients[72].

Moreover, HLA-DQB1 and HLA-DRB1 are important risk genes for several autoimmune diseases (multiple sclerosis[73], Pemphigoid[74]) and viral infections (HIV and hepatic C virus[75]) further supporting that immunogenetics mechanism underlie achalasia too.

4. Neurodegenerative:

Peristalsis in the distal esophagus is the result of complex interactions between vagal innervation, the myenteric plexus, and contraction of both layers of the muscularis propria.

With their cell bodies in the dorsal motor nucleus (DMN) of the vagus, vagal efferent nerve fibers are essential for starting and controlling LES relaxation and esophageal peristalsis[76].

This fact has led investigators to question whether proven vagal impairment is secondary to the loss of inhibitory neurons in the esophageal myenteric plexus, or to a primary defect in the vagal nerve.

In 1929, KIMURA[77] was the pioneer in finding degenerated vagus nerve cells in the DMN of 3 postmortem specimens of achalasia patients. On the other hand, significant esophageal dysfunction is a rare clinical manifestation in patients who have benefited from a vagotomy, raising the possibility that vagal nerve degeneration and DMN neuron degeneration is a secondary phenomenon caused by the loss of contact with the myenteric plexus[78].

Neural inflammation has not been described in other components of the central nervous system (CNS) or autonomic nervous system (ANS) in patients with Esophageal Achalasia[79]. Furthermore, the flaws in the vagal innervation would be expected to lead to other extra-esophageal clinical abnormalities which would include gastric emptying disorders; the latter are uncommon in achalasia, thus challenging the neurodegenerative hypothesis[80,81].

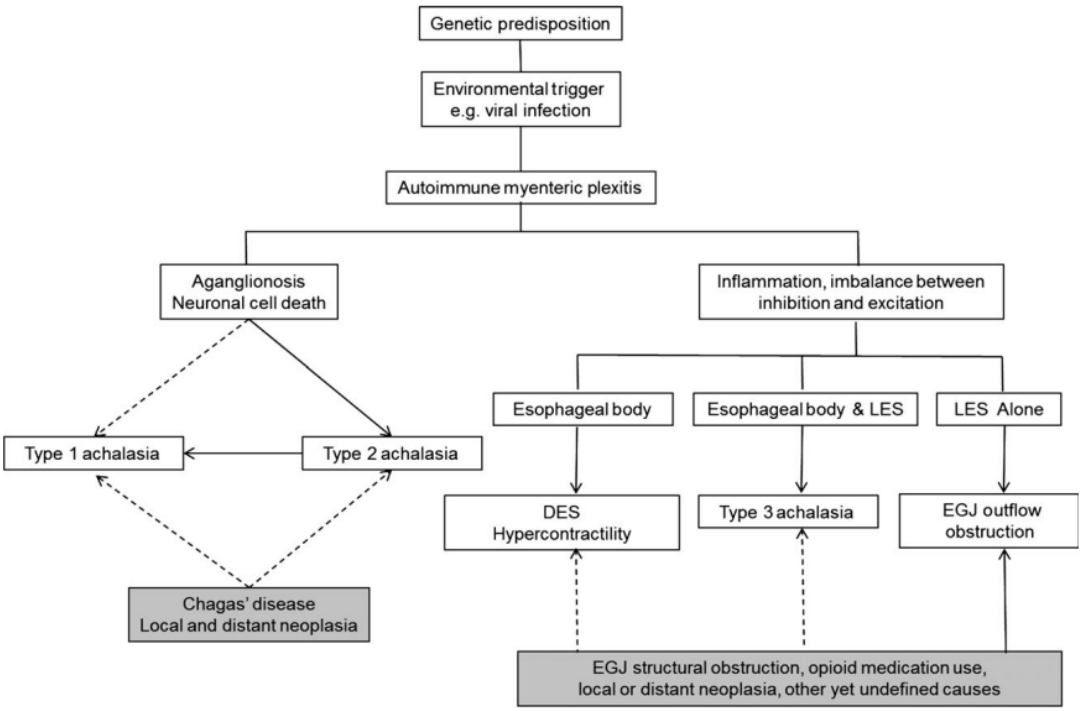

Figure 19: A suggested pathophysiologic template for achalasia and spastic disorders, with alternate processes highlighted in the bottom shade boxes that could result in identical motor findings[82].

III. CLINICAL FEATURES

1. Symptoms:

1.1. Regurgitation:

Regurgitation in pediatric patients with esophageal achalasia is a common and clinically significant symptom. It is defined as the involuntary return of partially digested or undigested food from the esophagus into the mouth.

Regurgitation is often described as a symptom that appears in the later stages of EA evolution, however in the pediatric population it may be the first appearing symptom of the disease[83].

The hemorrhagic nature of regurgitation should raise suspicion of a present complication (esophagitis or dysplasia)[84].

Regurgitation was a consistent symptom in all of our patients, similarly to the French VIOLA &al[21] study which, interestingly, shares a similar age group to our patients and had 19 out of 20 children present with regurgitation.

1.2. Dysphagia:

Dysphagia, or difficulty swallowing, is a hallmark symptom of esophageal achalasia in children. In esophageal achalasia, it has several distinctive features:

1. Progressive nature: The difficulty swallowing in esophageal achalasia is usually progressive and worsens over time as the disease advances.
2. Liquid and solid food involvement: Children with esophageal achalasia often experience difficulty swallowing both liquids and solids. Dysphagia is more suggestive of EA when it is paradoxical (affecting electively liquids), capricious (variable from one meal to another or even in the same meal), and resolving during inspiratory maneuvers or changes in position.

Dysphagia is unanimously present in childhood EA case studies and our study is no exception.

Ten of our patients had a dysphagia with a progressive onset joining the results of works such as VAOS & al[85] with 93.3% , TANNURI & al[86] with 66% and PAIDAS & al[87] with 69.2%.

1.3. Failure to thrive and weight loss:

Failure to thrive (FTT) is a descriptive term for insufficient growth, usually identified in infancy.

Numerous published studies have found that failure to thrive is a significant issue in children with esophageal achalasia[88,89,90]. A great proportion of children with achalasia have growth problems, undernutrition and the severity of their achalasia evolution was directly related

to the extent of their growth retardation. In older children and adolescents, the malnutrition manifests through weight loss such as in the Melbourne study where 76% of patients were suffering from weight loss[28].

Concordantly, nine of our patients were suffering from a failure to thrive and seven patients experienced on average a 7.71 kg weight loss.

These findings highlight the importance of early and aggressive intervention in children with esophageal achalasia to prevent failure to thrive and promote normal growth and development.

1.4. Retrosternal pain:

Retrosternal pain is usually described as a burning or pressure-like sensation behind the sternum and in achalasia it predominantly affects younger patients and can be associated with a heartburn sensation.

It is mostly described as an early sign of achalasia and it can sometimes obscure the much more typical symptoms of esophageal achalasia potentially delaying a correct diagnosis. However, its intensity gradually subsides as the dilation of the esophagus increases of volume[91].

ECKARDT & al presented a study in which two-thirds of achalasia patients complained of chest pain[92], and in our work, seven patients, or nearly two-thirds of our patients, experienced intermittent retrosternal pain.

1.5. Respiratory symptoms:

Esophageal Achalasia in children is very frequently complicated by respiratory disorders.

These can occur by inhalation during regurgitation, especially in infants.

In children, respiratory problems are most commonly presented in the form of a chronic cough.[93]

Earlier studies on the esophageal achalasia had shown that respiratory disorders only appeared in 10% of cases, whereas in more recent studies put the rate at 51%.[94]

ROSKIES & al report the cases of 2 boys with achalasia, revealed by dyspnea on exertion in the first and a cyclical fever with nocturnal cough in the second.[95]

In children, esophageal achalasia can take on the form of an acute or recurrent pneumopathies, which runs the risk of misdiagnosis if no further radiological exploration of the digestive tract is established[96].

In the series by SMITS & al[18], 22 of the 87 patients studied suffered a chronic cough. In our 15 observations, two patients were admitted in our department with active pneumonia, 1 case of dyspnea and 2 patients complained of coughing. We also noted a history of documented hospitalizations for recurrent respiratory infections in two patients.

Table XV: Incidence of different symptoms in literature review.

Author /Date	Number of patients	Regurgitation	Dysphagia	Failure to thrive	Weight loss	Retrosternal pain	Respiratory symptoms
KARNAK &al[97], 2001	20	90%	55%	-	25%	-	15%
HALLAL& al[25], 2012	13	84.6%	69.2%	-	46%	-	46.1%
MEYER&al[28], 2016	42	83%	76%		76%	34%	39%
Saliakellis & al[29], 2017	48	58%	100%	13%	20%	13%	2%
JARZĘBICKA &al[30],2021	46	91.3%	84.8%	41.6%	26%	47.8%	37%
IDRISSA & al[31],2021	14	100%	35.7%	-	71.4%	21.4%	42.9%
NICOLAS&al[13], 2022	97	79.8%	96.6%	-	62.9%	47.2%	66.7%
Our case study	**15**	**100%**	**67%**	**60%**	**47%**	**47%**	**20%**

2. Patient delay:

The time interval between the onset of symptoms and the diagnosis confirmation took in average 33.25 months. We remark that only 3 patients benefitted from a diagnosis confirmation of their Esophageal Achalasia in our department; the remaining 12 patients were referrals from different specialized medical doctors and primary or secondary health centers.

This delay is relatively longer than most studies described in literature[22,23,24], However our experience shows a much shorter patient delay in comparison with the only other Moroccan published study completed in FEZ[33].

ECKARDT& al investigated multiple potential risk factors for the diagnostic delay in EA from atypical symptoms, misleading diagnostic features and number of consultations and deducted that earlier diagnosis of this illness can be achieved through a review of esophagram by a second radiologist and/or a completion of manometry in case of equivocal or negative results in patients with symptomatic dysphagia. Additionally, their report further solidifies the importance of physician education in the diagnosis process of esophageal dysmotility disorders[98].

Table XVI: Distribution of patient delay average in literature review

Author	Number of patients	Patients Delay (months)
Hussain &al[22]	33	11.6
Pastor &al[23]	30	15.9
Wakhlu&al[26]	24	27.88
Zhang &al[24]	13	31
Idrissa &al[31]	14	36.3
Our case study	**15**	**33.25**

3. Associated diseases:

3.1. Allgrove Syndrome:

The Allgrove syndrome, also known as the triple A syndrome, is defined by the triple association of achalasia, alacrimia, and adrenal insufficiency. A more recently popularized possible naming is "4 A syndrome" as a result to the association of a fourth element: autonomic dysfunction, with motor neuropathy, sensory disorder, mental retardation, and related neurologic diseases[99].

This progressive disorder is typically observed in the first decades of life and has been linked to a mutation to the AAS gene[100]. Patients of North African decent express a common mutation: "c.1331 + 1G > A" with a recent unique Moroccan study in 2018[101] joining its Tunisian, Algerian and Libyan counterparts[102].

Achalasia is the primary presenting feature in approximately 75% of Allgrove syndrome patients. It is usually diagnosed in infancy in contrast to the remaining symptoms of triple A syndrome that most clinically manifest at puberty or adulthood[103].

Table XVII: Distribution of number of Allgrove syndrome associations in literature review

Author	Number of Achalasia patients	Number of Allgrove syndrome association
Choné & al[38]	117	3
Zhang& al[24]	13	3
Jarzębicka& al[30]	60	9
Idrissa & al[31]	14	4
Our case study	15	7

3.2. Down's Syndrome or Trisomy 21:

The most common chromosomal abnormality in humans is Down syndrome.

Gastrointestinal abnormalities, which may be anatomical or functional in character, account for up to 77% of Trisomy 21 children[104].

Until now, it is unknown which of the approximately 425 genes on chromosome 21 contribute to the development of achalasia[105].

The association of Esophageal Achalasia and Down's syndrome is rare with only very few reports in the pediatric population, counting to our knowledge, only one child case reports respectively in the OKAWADA &al[106], PIQUER & al[107], SANTHA & al[108], STOICESCU & al[109] and MASELLI &al[110] experiences and 2 children in the Zarate & al study[111].

Our study joins these single-case reports with an association of Achalasia and Down's syndrome in only one patient.

3.3. Achalasia microcephaly syndrome:

The achalasia microcephaly syndrome refers to the combination of achalasia, microcephaly, and mental retardation viewed in a small number of families.

A literature review precisely mentions 4 families from Mexican and Libyan background with a notion of consanguineous parents in half of them leading to the assumption to an autosomal recessive inheritance in the achalasia microcephaly syndrome[56,112,113,114].

We note that no specific gene has been identified to support this claim. However, our study gives an interesting insight joining these unique reports with one patient born to 1st degree consanguineous parents presenting with Achalasia-microcephaly syndrome.

IV. PARACLINICAL FEATURES

1. Timed esophagram

Timed esophagram (TBE) is valuable for diagnosing achalasia and provides a precise assessment of post-therapy success.

TBE has various advantages, including being simple, affordable, non-invasive and well-tolerated by patients. It also allows an enhanced look in determining whether food stasis is due to an EGJ obstruction or a possible abnormal anatomy[115].

The narrow esophagogastric junction (EGJ) with a "bird beak" appearance, aperistalsis, and poor barium/gastrofin emptying on the esophagram all support the diagnosis of achalasia.

Additionally, an end-stage achalasia diagnosis can be made with evident esophagus changes such as angulation and tortuosity.

Before treatment, most achalasia patients have barium/gastrografin remaining in their esophagus at different time intervals (1,2 and 5minutes) after swallowing a large bolus. Subsequently, an achalasia treatment is deemed successful if there is a 50% decrease in the barium/gastrografin column after five minutes[116].

In the ZHANG &al[24] study, esophagram examination was performed in all patients and showed diagnostic signs of achalasia: an esophageal dilation and a "bird beak" at the cardia in every single case. The dilated esophagus was also noted by IDRISSA &al[31] however, the specific “bird’s beak” appearance was only present in 50% cases.

Similarly in our study all 15 patients undergone a timed esophagram in which all patients presented a dilated esophagus and a tapering of the EGJ meanwhile 12/15 cases adorned a “bird’s beak”.

Esophagram X-ray findings can be further evaluated on a radiological scale of EA according to Rezende &al[117] classification.

Among our 15 evaluated patients, the Rezende’s classification was grade II in 1 and grade III in 14 patients.

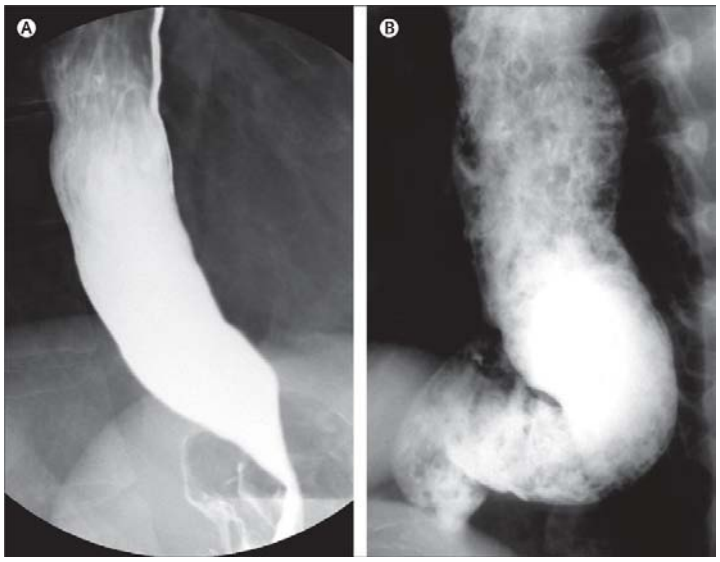

Figure 20: (A) Typical bird-beak appearance in early achalasia[118]. (B) Sigmoid-like appearance of decompensated esophagus[119].

Table XVIII: Rezende's classification for esophageal achalasia

Grade I	The esophagus shows difficult emptying and mild hypotonia, with episodes of tertiary waves and no dilation.
Grade II	Contraction of the muscles of the gastric cardia (achalasia). The esophagus shows a mild to moderate increase in caliber; tertiary waves are more frequent.
Grade III	The esophagus shows an evident increase in caliber. The distal portion has the classic "bird beak" sign. The majority of cases with total akinesis of the esophagus show violent contractions of the circular musculature.
Grade IV	In addition to the changes described for grade III involvement, we observed intense dilation of the esophagus, which seems to rest on the right phrenic hemidiaphragm. We refer to this as severe (sigmoid) megaesophagus.

2. UGI Endoscopy

The main purpose of an EGD (esophagogastroduodenoscopy) in the evaluation of achalasia is to exclude the possibility of a mechanical blockage or pseudo-achalasia as they can mimic achalasia both clinically and manometrically[120,121,122]. Mechanical obstruction in the esophagus can lead, identically to the manometric features in achalasia, in both impaired EGJ relaxation and abnormal esophageal body function (aperistalsis or spastic contractions)[123].

During an EGD, treatment procedures such as dilation of strictures and esophageal biopsies can be done. It is necessary to get a biopsy for diagnosis when a mass is identified in the esophagus. However, even if that is not the case, it's still recommended to take biopsies in search of eosinophilic esophagitis (EoE)[124] or even an achalasia-mimicking cancer[125].

The first step in diagnosing achalasia for patients who have been wrongly diagnosed with gastroesophageal reflux disease (GERD) can be aided by an endoscopic evaluation. Endoscopic findings such as a dilated esophagus with retained food or saliva and a contracted gastroesophageal junction can support a correct diagnosis.

The endoscopic appearance in achalasia patients can range from normal to a distorted and enlarged sigmoid esophagus. In cases where the esophagus is not dilated, an esophageal motility test may be necessary particularly in case of clinical suspicion for achalasia.

Following EA treatment, endoscopy can also be used to determine if the symptoms have returned, and whether it is due to the return of a contracted EGJ or stricturing caused by GERD.

In the Jarzębicka& al[30] study, UGI endoscopy demonstrated abnormalities in 86.8% of patients with food stasis in the esophagus being the most recurring finding (75.5%) and no other non-achalasia specific feature.

Table XIX: Comparison of endoscopy findings in our case study vs Jarzębicka& al study

	Our case study 2023	Jarzębicka& al[30] 2021
Number of patients	15	53
Any EA feature	9	46
Residual food in the esophagus	8	40
Esophageal enlargement	8	31
Closed stomach cardia	9	39
Esophageal mucosa lesions	0	15

3. High-resolution Esophageal Manometry

The most precise investigative method and the most reliable standard for diagnosing achalasia is high-resolution esophageal manometry (HREM)[126]. It's effective in the study of esophageal motility and the functioning of LES even when endoscopic and radiologic tests fail to clarify a cause[127].

HREM has numerous benefits when compared to traditional manometry, such as improved identification of the lower esophageal sphincter, faster examination duration, reduced variation in results among observers, and exceptional evaluation of the contractions in the esophageal body, including detection of minor disruptions[128].

The process of high-resolution manometry involves the insertion of a catheter equipped with 36 pressure sensors placed at close intervals through the esophagus and the EGJ to

measure pressure changes.; the pressure throughout the entire esophagus is measured all at once, so the catheter does not have to be moved to get pressure readings from different zones. The results of the manometry test are shown as a continuous graph with pressure displayed in different colors, where warmer colors indicate higher pressure and cooler colors indicate lower pressure[129]. This provides a clear visual topographic representation of the movement of the esophageal muscles and precise identification of the location of the LES **(Figure 21)**.

The key indication of achalasia in high-resolution esophageal manometry is the absence of peristalsis and high integrated relaxation pressure (IRP)[130].

An IRP value above 15 mmHg suggests the presence of achalasia, which is classified into three subtypes according to the Chicago Classification, currently, in its fourth version (CCv4.0). Type I is defined by complete absence of peristalsis and elevated IRP. In Type II, peristalsis is replaced by pan-esophageal pressurizations in at least 20% of swallows. Type III is marked by the occurrence of at least 20% of premature, spastic contractions and elevated IRP[131].

Additionally, the presence or absence and size of a hiatal hernia can be assessed with HREM, with a higher sensitivity than with endoscopy or radiography alone[132].

A large citywide study in Chicago performed by SAMO& al and concerning 379 adult achalasia patients provided an increase by 2 to 3-fold in incidence and prevalence of achalasia simultaneous to the incorporation of HREM in all clinical cases[133].

The utilization of conventional manometry during a Heller myotomy surgery has been studied in multiple reports, with the goal of investigating how the myotomy affects the baseline tone of the lower esophageal sphincter (LES) in the region closer to the gastric cardia and its association with symptom improvement. Recently, Triantafyllou & al described the use of high-resolution esophageal manometry in real-time during a LHM (laparoscopic Heller myotomy) and Dor fundoplication to allow for personalized surgical treatment of achalasia in adults[134]. To the best of our knowledge, there has been only one study reported in the literature by YU &al on the use of intraoperative HREM in children which concluded to an improvement of Quality of Life and a sustained long term symptom relief[135].

The Esophageal Achalasia diagnosis confirmation in our case study didn't include an esophageal manometry whether in its conventional or higher-resolution form for any of our patients.

This evokes a limitation to our study, However, in a paediatric setting, esophageal manometry is often difficult for children with having to perform standard wet swallows in manometry studies. Moreover, sedation is often required for such patients, making it a more invasive examination and arguably an accurate but not indispensable diagnostic tool[136]. Furthermore, the evidence regarding HREM as a tool for predicting treatment failure and the need for repeat intervention is limited in children with some studies comparing TBE to HRM and finding similar specificity value[137].

Beside these reasons, esophageal manometry is not available in most public primary and secondary health facilities in Morocco due to disparities in health resources. If patients are referred to higher centers where these advanced tools are available, they face long wait times and may not be able to afford such treatment[138].Therefore, in the absence of other causes for the bird's beak sign on an esophagram, it was used as the sole diagnostic method in our study confronted with supportive endoscopy findings.

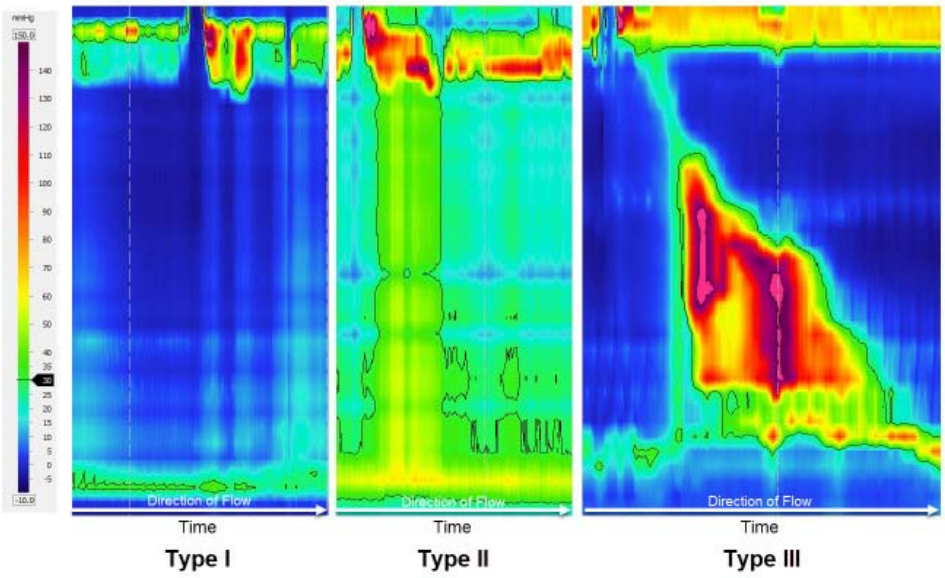

Figure 21: The three Esophageal Achalasia subtypes determined by the Chicago Classification[139].

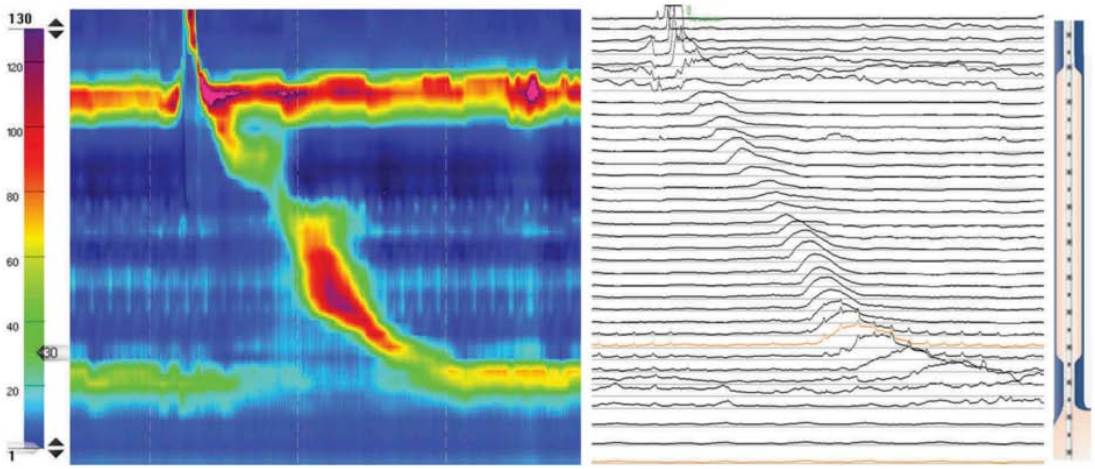

Figure 22: Visualization of a normal swallow recorded by esophageal HRM versus conventional manometry (reference anatomy in the right panel). In the color plot deep red colors indicate high pressure zones, while blue colors indicate low pressures[140].

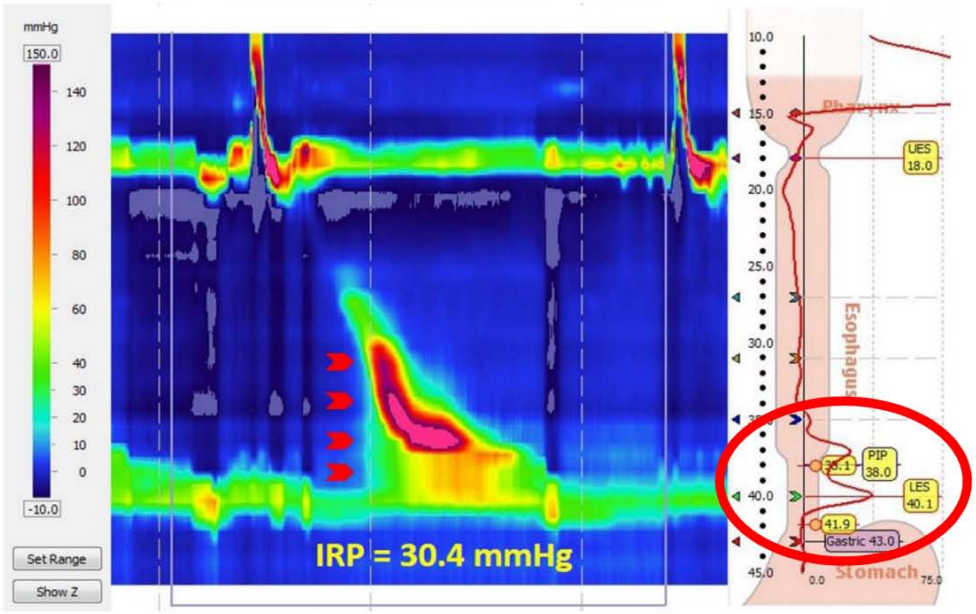

Figure 23 : Intraoperatively, LES manometry profile (red circle) is used to determine high pressure zone; myotomy is continued until the pressure reading contour flattens as close as possible so that LES pressure reaches similar pressures seen in the esophageal body and stomach[135].

4. Pulmonary X-rays

The diagnosis of Esophageal Achalasia is not greatly aided by chest X-rays since it is only positive if the esophagus is largely dilated.

Possible pulmonary X-ray findings in EA include:

- ♣ convex opacity overlapping the right mediastinum.
- ♣ air-fluid level due to food stasis in the esophagus
- ♣ small or absent gastric bubble
- ♣ anterior displacement and bowing of the trachea on the lateral view

In the HUSSAIN& al[22] study, chest X-ray was done in 27 out of 33patients and an air-fluid level was demonstrated in 16 cases (59.3%); The dilated esophagus with air-fluid level was more significantly common in children above the age of 5 years old.

IDRISSA &al[31] described 5 patients with air-fluid (35.7%), meanwhile in our study there was one case of evident widening of the mediastinum among our 5 out of 15 patients.

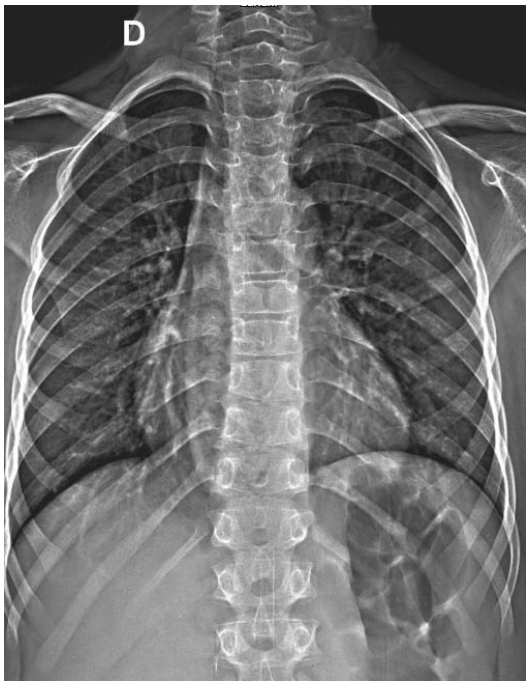

Figure 24: Chest x-ray demonstrates a convex opacity overlapping the right mediastinum which may be due to dilated esophagus filled with retained secretions and food. Small gastric bubble with aerated splenic flexure[141].

5. EndoFLIP:

The functional lumen imaging probe (FLIP) offers a well-tolerated technique for assessing esophageal motility, particularly for achalasia, during upper endoscopy[142].

FLIP is advantageous in identifying the expandability of the esophagogastric junction (EGJ) using the EGJ distensibility index. The previously discussed technic of manometry gives a measurement of the inner active contractility of GI tract. However, without active swallowing of bolus, manometry cannot generate a significant signal. FLIP on the other hand, measures the passive outer distensibility of the GI tract, thus complementing the standardly used HREM[143].

6. Biological tests:

Laboratory tests in a surgical department setting are primarily used as an assessment tool to overall complications of severe malnutrition, weight loss and dehydration.

The minimum of laboratory tests include: complete blood cell count, electrolytes, CRP, and blood urea nitrogen (BUN) to creatinine ratio (BUN/Creatinine). At the moment, available laboratory tests do not aid in the diagnosis of Idiopathic Esophageal Achalasia, however they can orient the clinical suspicion of anemia and acute kidney injury due to dehydration and hypovolemia[144]. In our study, four of our patients were anemic with two severe cases requiring blood transfusions and ten patients presented azotemia with an elevated BUN/Creatinine.

A recent 2022 study by Li-YUN &al[145] explored the inflammatory markers in a large 341 achalasia patient population in comparison to a healthy control group; the result was a much higher levels of Neutrophil-to-lymphocyte ratio (NLR), Mixed Lymphocyte Reaction (MLR), CRP, globulin, Interleukin 6 (IL-6) and Interleukin 10 (IL-10) attesting to a chronic Immune-mediated neuroinflammation. Coherently, we noted an elevated level of C-reactive protein in two patients.

V. Differential Diagnosis

Esophageal Achalasia is often subject of misdiagnosis especially in the earlier stages of the illness: Symptoms have the potential to be misinterpreted as other common ailments such as GERD, eating aversion, eating disorders like anorexia nervosa, asthma, failure to thrive, and eosinophilic esophagitis[146,25].

In the 35 children- based study conducted by LEE& al A significant 50% of patients had received treatment with prokinetics or acid-reducing drugs before being diagnosed with achalasia[147].

In our study, 13 patients reported initially being prescribed GERD therapy with frequent and repetitive PPI-based treatment vomiting and 2 patients were prescribed asthma therapy because of persistent cough.

Table XX: Differential Diagnosis of EA

Gastrointestinal	Respiratory	Functional disorders	Other
- Eosinophilic esophagitis - Esophageal stricture - Esophageal motility disorder - Gastroesophageal reflux disease	Asthma	- Functional dysphagia - Functional gastrointestinal disorders	- Eating disorders - Chagas disease - Failure to thrive

VI. MANAGEMENT

1. The Goal of treatment

For children with Esophageal Achalasia, the approach to management involves interventions designed to alleviate symptoms by decreasing pressure within the lower esophageal sphincter. All types of therapeutic approaches for achalasia are directed at relieving

the obstruction, rather than providing a definitive cure for the underlying causes of the disease either by:

- ♣ Pharmacological therapy
- ♣ Instrumental (endoscopic) intervention
- ♣ Surgical treatment

2. Therapeutic approaches:

2.1. Medical management

Only 2 medical treatments are described in literature: Nitrates and Nifedipine.

- ♣ Nitrates inhibit LES contraction by dephosphorylation of myosin chains. The review of WEN & al[148] found only 2 cross-over randomized trials that asserts the clinical efficacy of Nitrates; however, they all concluded that the long-term effect of symptom relief is insufficient[149].
- ♣ The therapeutic use of Nifedipine for achalasia is mostly for adults. Nifedipine is a calcium channel blocker that restricts the flow of calcium through the membranes of cardiac and smooth muscles[150].

However, research on the effectiveness and safety of nifedipine for children with achalasia is limited. Maksimak &al[151] reported administering nifedipine before meals to four children as a form of treatment, which relieved symptoms possibly as a result of the decrease in pressure within the lower esophageal sphincter. For both children and adults, nifedipine should only be regarded as a temporary measure for symptom relief, while more conclusive treatments such as pneumatic dilatation, Botox injections, or myotomy are being scheduled[152].

In the VIOLA & al[21] study, 9 patients received an initial treatment by Nifedipine. This approach was proven inefficient for 3 patients. Meanwhile the HALLAL& al[25] study presented one asymptomatic patient post Nifedipine therapy with no noted side effects during 3years of follow-up but who later needed complementary surgery due to dysphagia.

Furthermore, Nifedipine can present serious side effects including and not limited to tachycardia, syncope and hypotension; making it even a non-licensed drug in countries such as the United Kingdom[151].

In our study no medical treatment of achalasia was attempted.

2.2. Endoscopic management

a. Botulinum toxin injection (BTx):

The injection of botulinum toxin into the lower esophageal sphincter (LES) interferes with the release of acetylcholine from excitatory nerve endings at the myoneural junctions. This affects the tone of the basal muscle[153]. It has not been fully determined as to the ideal amount and frequency for using botulinum toxin for achalasia in children, both as a diagnostic and therapeutic measure.

The average symptom relief from a single botulinum injection lasts for 4 months and multiple treatments are often required in a year[154]. However, only 10-40% of adult patients experience permanent relief from the toxin[155].

A study by SING IP &al[156] ventured into examining the effectiveness of BTx in the pediatric population. Seven patients were included with symptom improvement in all patients and a maintained response beyond 6 months in 43% of these children.

Botulinum toxin injection remains an expensive treatment choice and can be reserved to patients when other more conventional treatments fail[157].

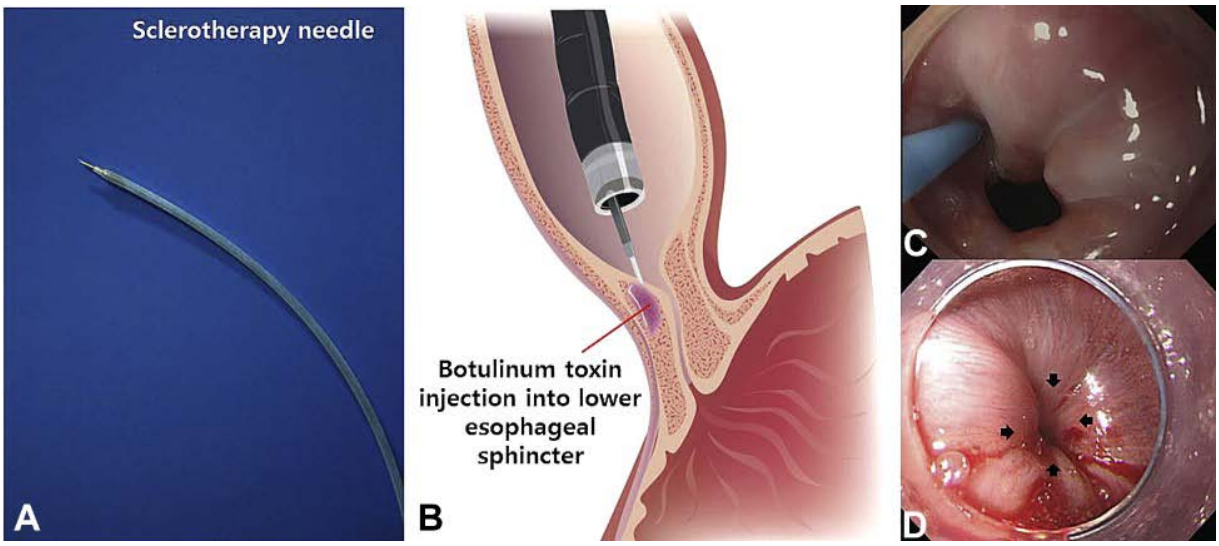

Figure 25: Botulinum toxin injection technic: The injection needle (A) is produced 1 cm proximally into the squamocolumnar junction (B) with injections carefully spaced in a circumferential manner[158].

b. Pneumatic Dilation (PD):

The pneumatic dilation of the lower esophageal sphincter is often the preferred primary treatment, particularly for patients who are not suitable for surgery.

This approach entails progressively widening the LES by exerting pressure using a rigid balloon under guided endoscopy or fluoroscopy therefore providing a relief of the EGJ obstruction.

Currently the most commonly used is the microinvasive Rigiflex balloon system with 3 gradually expanding diameters (25,30,35 and 40 mm).

This method has been a substitute for surgical intervention for many years, with reports of successful outcomes in children as far back as 1983[152].

The procedure is attractive due to its low rate of complications, decreased cost, shorter recovery time and widespread availability[159]. However, it has the main disadvantage of requiring multiple dilations in nearly 90% of patients to achieve successful relief, and its long-term results are not as good as those of surgical myotomy[160].

Endoscopic pneumatic dilation (EPD) may not always be effective and 30 to 75% of children may need additional surgery due to persistent symptoms[161].

In the Jarzębicka& al[30] study half of the patients initially underwent endoscopic PD, but most eventually needed a more invasive procedure namely Heller myotomy (HM). These authors also noticed that the results of HM were more favorable when PD was performed first.

Although some studies have shown that this approach could negatively affect the outcomes of surgery[162], it is consistent with other pediatric studies that have found PD to be an effective first-line treatment[163].

In pediatric population, PD is considered more efficient in children after the age of 5 years old[157,161].

In the comparative article of JUNG C &al[163] between Pneumatic dilation and Heller myotomy results further support this latter concept painting PD as a trusted method of treatment in children older than 6years old and with weight superior to 20kg.

In fact, out of 22 patients, 14 children above the age of 6 years old were treated by either pneumatic dilation or Heller myotomy meanwhile the remaining 8 were treated surgically. Complete remission in the 6 years-old or older group was achieved by Heller myotomy in 44.5% vs. 55.5% by pneumatic dilatation after six months, and in 40% vs. 65%, respectively, after 24 months.

Contrastingly, in the most recent 2022 Nicolas& al[13] study that follows the evolution of 97 achalasia children with a mean age of 12 years old. 37 children were treated by Heller's myotomy while 60 undergone endoscopy dilation. The outcome showed that the surgical line of treatment was more successful with a median survival period without failure of 49 and 7 months, respectively, and with no significant difference in the occurrence of complications (35.2% for Heller's myotomy, 29.7% for endoscopy dilatation).

The first notable pneumatic dilation complication is esophageal perforation. A large study of 260 pneumatic dilations performed in children for different esophageal stricture disorders resulting from several causes including Esophageal Achalasia the rate of esophageal perforations was 1.5%, a result similar to that reported in the literature in adults[164,165].

Several risk factors of esophageal perforation have been suggested: malnutrition, recent esophageal biopsy, Epiphrenic diverticula, low LES pressure, high inflation pressure and prolonged inflation time[166].

Other Pneumatic dilation complications include: postprocedural retrosternal pain, gastroesophageal reflux, digestive hemorrhage, mediastinal emphysema and pleural effusion.

In our study only one patient primarily underwent endoscopic PD, and in this case was followed by Heller myotomy after failure.

Table XXI: Comparison of studies in children with achalasia treated with pneumatic dilatation

Study author	Year	Number of PD patients	Percentage of patients with good outcome	Following treatment	Complications
Azizkhan&al[167]	1980	8	25	50% EPD	12.5% Aspiration – 25% GER
Boyle &al[168]	1981	10	40	20% EPD – 20% HM	10% Sever pain – no perforation
Upadhyaya &al[169]	2002	12	83.3	17% EPD	None
Hussain &al[22]	2002	9	0	100% HM	Non specified
Smits &al[18]	2016	68	10.3	22% EPD	1.5% Perforation
Saliakellis &al[29]	2017	20	30	25% EPD – 60% HM	5% Esophageal perforation
Meyer &al[28]	2017	3	33.3	66% BTx	Non specified
Nicolas & al[13]	2022	60	20	60% EPD – 20% HM	21.3% GER – 13% Esophageal perforation
Our case study	2023	1	0	100% HM	None

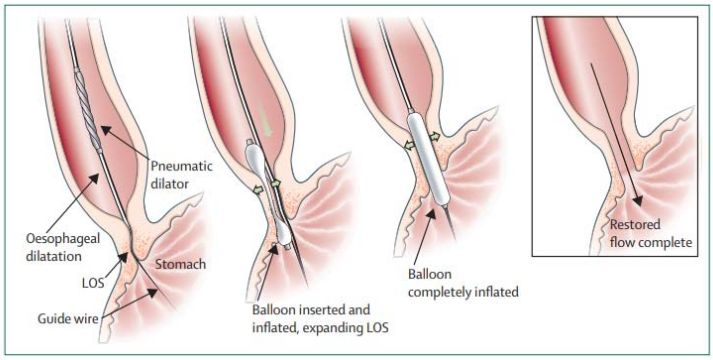

Figure 26: Pneumatic dilation with a Rigiflex system[170]

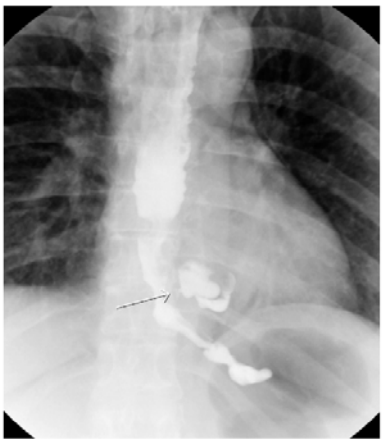

Figure 27: Post-pneumatic dilation esophagogram with water-soluble contrast medium showing contrast extravasation at EGJ (arrow), indicating a transmural esophageal perforation in an adult patient[171].

c. Peroral endoscopic myotomy (POEM):

Per oral endoscopic myotomy is a novel method of performing a myotomy using an endoscope that is inserted through a submucosal tunnel in the esophagus and into the EGJ. Endoscopic cutting tools are used to forcibly separate the circular muscle fibers of the LES and extend distally into the stomach and proximally into the esophageal body[172].

POEM offers several benefits, including being less invasive with shorter hospital stays and having the potential to extend the myotomy higher into the esophageal body for conditions such as type 3 achalasia and hypercontractile esophagus[173].

In a Nabi &al[174] study including a total of 69 children who underwent POEM with a long-term follow up, the durability of this revolutionary technic proved truthful to expectations with patients maintaining their POEM response for a period surpassing 4years.

Nevertheless, some studies have pointed out that it does carry a risk of GERD as detailed in **Table XXII**.

Table XXII: Results of POEM with follow-up, success rate and complications as treatment for esophageal achalasia according to studies' reports

Author	*Number of patients*	Success rate (%)	Subsequent treatment	Complications
Caldaro &al[175]	9	100	None	11%Mucosaltear-11%pneumoperitoneum
Chen &al[176]	27	96.2	N/S	18.5%Mucosaltear - 3.7%pneumothorax
Tan &al[177]	12	100	N/S	16.7%GOR-8.3%subcutaneousemphysema
Nabi &al[178]	15	100	None	20%GOR-6.7%perforation
Stavropoulos & al[179]	10	100	None	None
Miao &al[180]	21	100	None	29%GOR-9.5%perforation

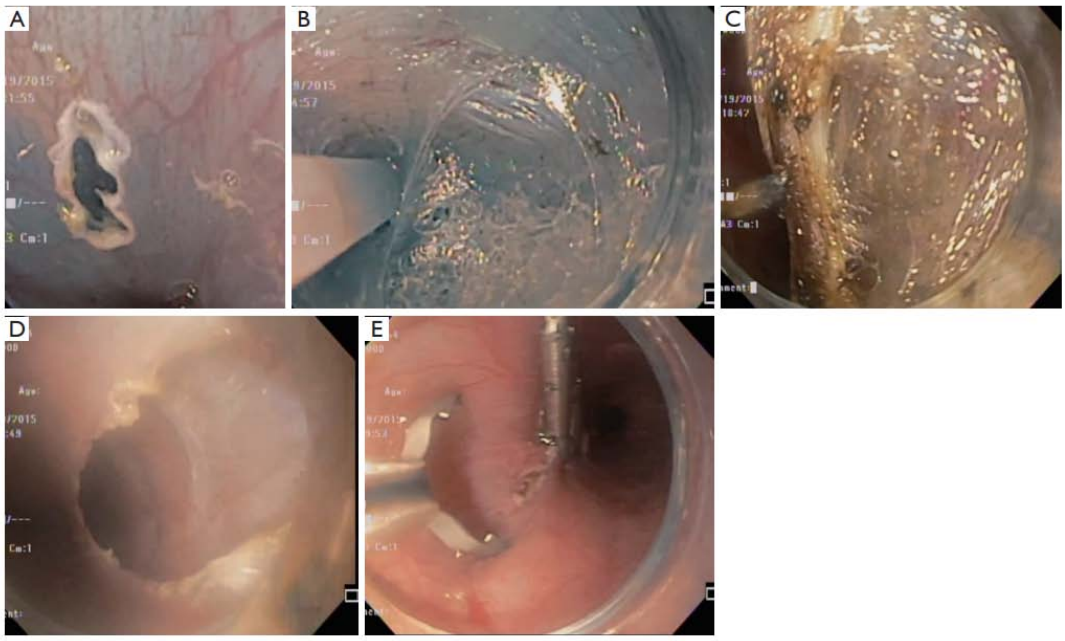

Figure 28: POEM surgical steps : (A) Making a mucosotomy and inserting the endoscope into the submucosal space. (B) Extending a tunnel distally through the submucosal space. (C) Carrying out the myotomy using an electrocautery blade. (D) Inspecting the tunnel after performing the myotomy. (E) Sealing the mucosotomy using endoscopic clips[172].

2.3. Surgical management

Esophageal Achalasia is a challenging condition to manage and can result in both physical and psychological complications.

In the surgical management of EA in children there is still no international science-based guidelines on a single validated standard intervention that provides long-term benefit while posing minimal risk.

a. Description of different Surgical techniques:

a.1. Conventional Open Heller Myotomy (OHM):

An incision is made either on the upper midline or the left paramedian.

The abdomen is then inspected with focus on the duodenal wall for any signs of scarring or abnormality.

The left lobe of the liver is mobilized by cutting the triangular ligament to access the lower esophagus. Small connections between the stomach and spleen are also severed to prevent damage to the splenic capsule. In some cases, the xiphoid may have to be removed for proper exposure.

The peritoneum above the esophagus is dissected and the stomach is retracted down. The gastrohepatic ligament is clamped and divided to facilitate the anterior mobilization of the esophagogastric junction.

The phrenoesophageal ligaments are then cut and the esophageal fat pad is removed. The surgeon's finger is used to finalize the mobilization of the esophagus and to identify the constricted area.

All tissues are cleared from the anterior surface of the esophagus using right-angle clamps

The myotomy is performed by dividing all circular and longitudinal muscles above the constricted area. The incision is extended 4-6 cm on the esophagus and 1.5-3 cm on the gastric

cardia to lower outflow resistance. The muscularis should be impaired to allow ample esophageal muscles' separation, However, care must be taken to not cut through the mucosa entirely.

The surgeon then checks for any accidental cuts made in the mucosa and any such injuries are repaired with silk. Pyloroplasty or posterior gastroenterostomy may be done if vagotomy was performed.

A Foley catheter can act as a temporary gastrostomy after being secured and anchoring the stomach to the abdominal wall. Finally, the fascia and skin are closed marking the end of the procedure.

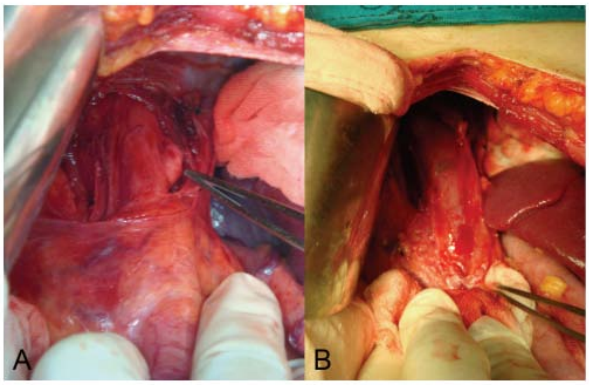

Figure29 : A) Opened phrenoesophageal membrane and retracted vagus nerve
B) Incision into the high pressure EGJ zone into the submucosal layer anteriorly[181]

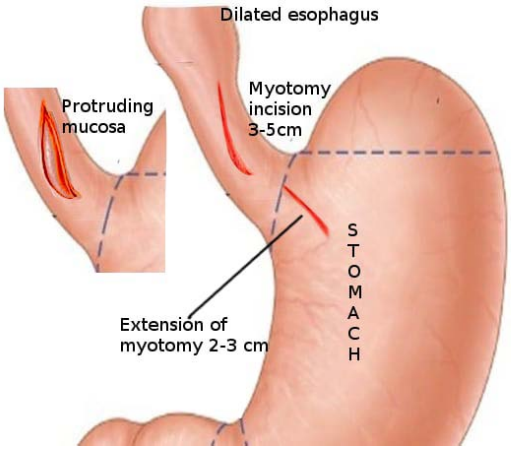

Figure 30: Incision for Heller myotomy[182]

a.2. Laparoscopic Heller Myotomy (LHM):

In preoperative, pressure points on the patient's body are padded and the surgeon either stands between the patient's legs or on their left side with the assistant on their right. Laparoscopic monitors are positioned at the head of the bed.

The first trocar can be inserted in the midline between 13–18 cm from the xyphoid process using an open cut-down technique, pre-insufflation with a Veress needle and trocar placement, or optical trocar placement. Three to four additional ports, with a diameter of 5–12 mm, can be placed on either side of the abdomen above the umbilicus to serve as the surgeon's working ports, an assistant port, and a liver retraction port (if needed). A liver retractor is then used to elevate the left lobe of the liver to provide visibility of the esophageal hiatus.

The gastrohepatic ligament is then entered, followed by dissection of the esophagophrenic ligaments. The anterior vagus nerve should be identified and preserved.

The gastroesophageal junction is identified and exposed by retracting the gastroesophageal fat pad caudally. A monopolar hook cautery or ultrasonic device is then used to divide the outer, longitudinal muscle fibers of the esophagus on its right anterolateral surface.

Some surgeons may use concurrent upper endoscopy to visualize the high-pressure zone while dividing the esophageal muscle layer, and the circular fibers can be dissected under direct visualization. This dissection is performed with care, extending 2–3 cm into the stomach. After the procedure, an air leak test can be performed.

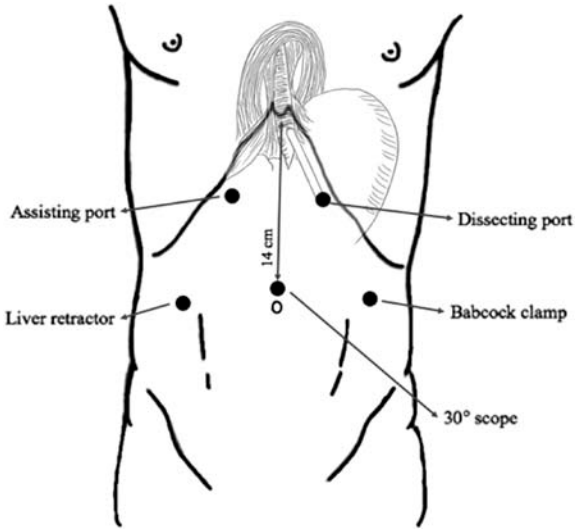

Figure 31: Port placement for Laparoscopic Heller Myotomy[183]

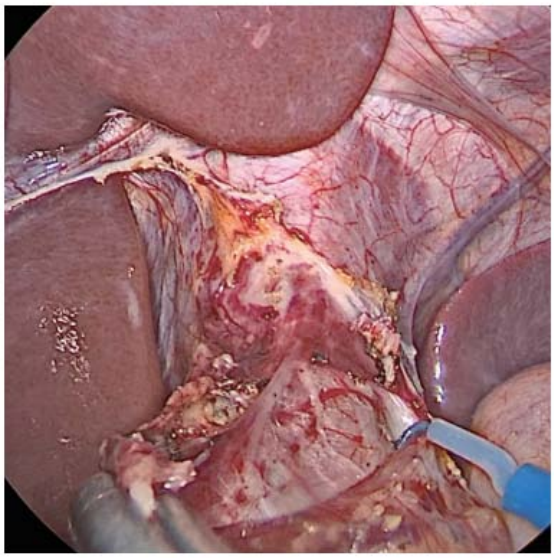

Figure 32: The Nathanson liver retractor is employed to reveal the phrenoesophageal ligament. Subsequently, the phrenogastric and gastrohepatic ligaments are incised[172] .

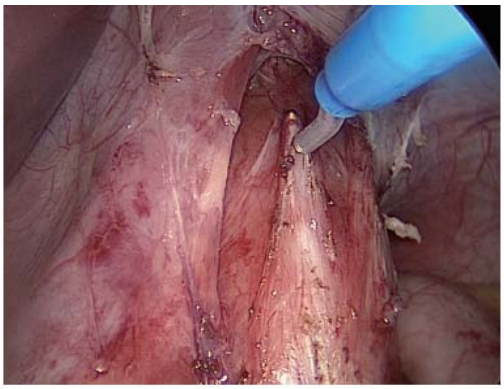

Figure 33: A carried out incision of the esophagus fibers.[172]

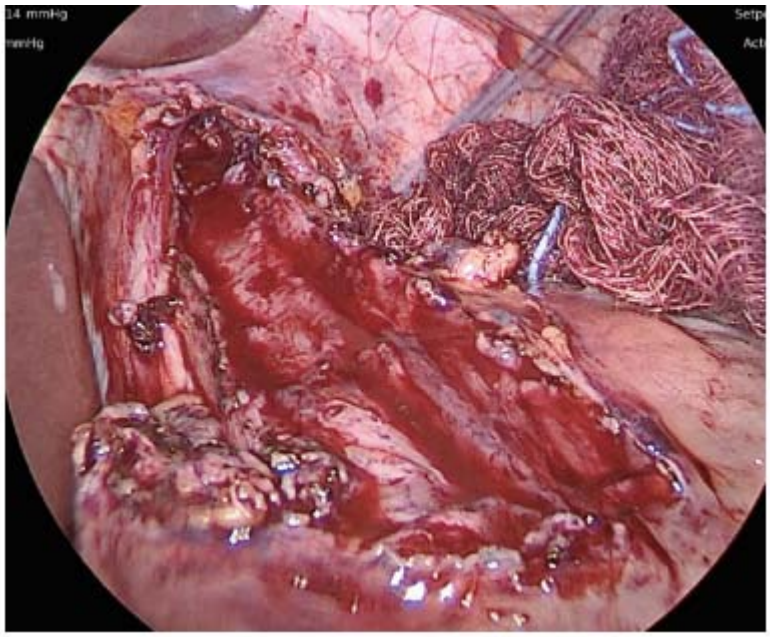

Figure 34: Complete LHM carried 3cm to the GEJ and 6cm to the esophagus[172].

a.3. Adjacent Anti-Reflux procedure:

Dr. Rudolph Nissen first performed a Nissen fundoplication procedure in 1955 and published the results of two cases in the Swiss Medical Weekly in 1956. He later published a more comprehensive overview of the procedure in 1961, initially referred to as gastroplication[184]. During the procedure, the upper part of the gastric fundus is wrapped around the lower portion of the esophagus, and then sutured to enhance the closing ability of the lower esophageal sphincter. The esophageal hiatus is also narrowed by sutures to treat or prevent concurrent hiatal hernia.

Nissen fundoplication involves wrapping the fundus around the esophagus 360 degrees, while surgery for achalasia often involves a less extensive Dor or Toupet partial fundoplication.

The procedure can be performed laparoscopically or through a laparotomy.

Possible complications of the surgery include infection, uncontrolled bleeding, difficulty swallowing, return of reflux symptoms, limited ability to burp or vomit, gas pains, organ damage, anesthesia-related issues, and, in rare cases, the need for a repeat procedure if the wrap is too tight or has slipped.

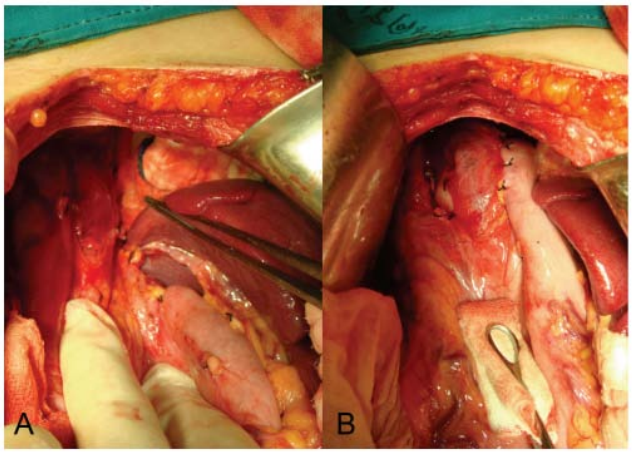

Figure 35: A) gastric fundus with ligated short gastric artery
B) Posterior half "Toupet's fundoplication"[185]

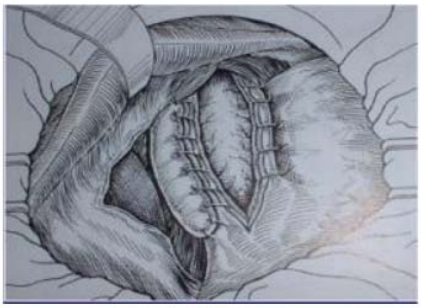

Figure 36: Toupet fundoplication[185]

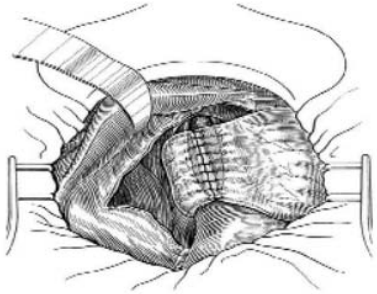

Figure 37: Nissen Fundoplication[185]

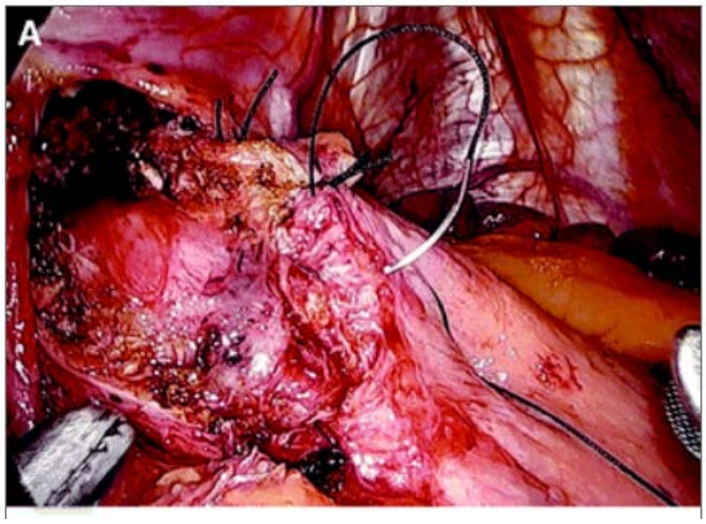

Figure 38: First row of suture for anterior 180° Dor Fundoplication[186]

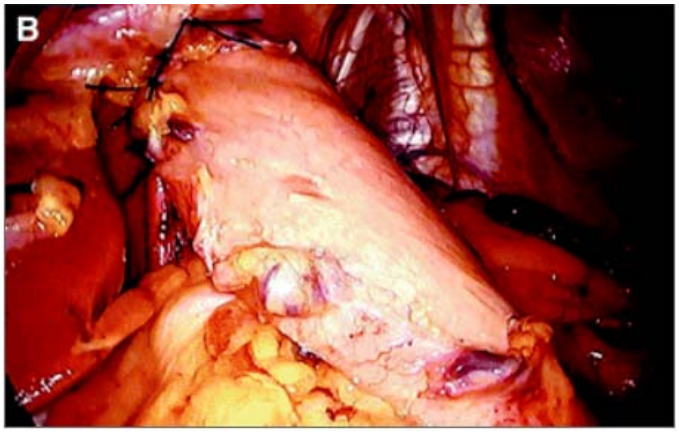

Figure 39: Anterior 180° Dor Fundoplication[186]

b. Choice of Surgical technique:

b.1. Heller myotomy

The Heller myotomy surgical technique with or without an anti-reflux fundoplication procedure is the standard treatment care for children with achalasia[187].

Ernest Heller first outlined the surgical technique in 1913[188] and was later modified by De BruneGroenveldt in 1918[189]. Nowadays, the procedure is commonly performed in various centers to relieve symptoms in both adults and children.

Historically, the procedure was performed using an open method, either through a thoracotomy or a laparotomy. However, in 1991, the first minimally invasive myotomy in the US was performed using Laparoscopic Heller's myotomy approach by SHIMI & al[190] in adults, and in 1996, Holcomb and his team reported the successful treatment of two children with achalasia through the same procedure[191].

Since then and over the past 32 years, there has been a move towards minimally invasive HM surgery as opposed to open surgery in the treatment of Esophageal Achalasia[155].

Although most studies do not diminish the efficiency of conventional open heller myotomy, Laparoscopic Heller Myotomy has become a preferred method of treatment due to benefits such as a magnified view and improved surgical field exposure[172].

Paraclinical classification of achalasia has also made it easier to customize treatment plans. For instance, recent findings indicate that subtype III of achalasia has a greater response to Heller Myotomy in comparison to other forms of treatment, meanwhile, both PD and HM can provide positive outcomes in the other subtypes with a noted higher success rate of HM in Grade I esophageal achalasia[192].

14 of our patients presented with Grade III achalasia and 1 patient presented with Grade I hence we opted for the surgical management by Heller myotomy in all our patients.

Additionally, in developing countries such as Morocco another important aspect besides patients' characteristic is the economical background of parents[193] and the majority of our patients come from rural areas raising therefore, the issue of accessibility to specialized facilities, affordability and illiteracy that hinder the compliance of parents with repeated pneumatic dilations or Botox injections.

In a study conducted by Esposito& al, out of eight patients who underwent LHM, two had gastroesophageal mucosal perforations and one had an overly tight anti-reflux procedure resulting in dysphagia[194].

Although our current study has no noted experience with laparoscopic repair, we noted no perioperative complications with the use of laparotomy.

b.2. Fundoplication

In accordance with the guidelines for adults, laparoscopic myotomy should be combined with partial fundoplication[195]. However, in the paediatric population, at present, it is uncertain based on current evidence whether a simultaneous anti-reflux procedure should be performed on all children during Heller Myotomy.

The primary incentive for a simultaneous anti-reflux procedure is to reduce the likelihood of dysphagia recurring after the surgery. Additionally, some situations logically require an added anti-reflux valve, such as an associated hiatal hernia, or the occurrence of a mucosal wound.

In literature a lot of centers report performing anti-reflux procedures with a low rate of complications[196], However, other series advocate for the inessentiality of fundoplication[197,198].

A meta-analysis report by CAMPOS &al evidently concludes in favor of fundoplication as a preventive measure, estimating the incidence of GER at 31.5% in the case of myotomy alone and a 8.8% estimate if association with a fundoplication system is made[165].

In our practice, we have seen only 2 out of our 15 patients still experience recurrent dysphagia and need further treatment after their fundoplication.

The type of fundoplication in itself is much debated. Supporters of a Nissen fundoplication are few and justify their choice by its better result on Gastric reflux[199]. However, this technique leads to more dysphagia, thus running the risk of losing the primary benefit of Heller myotomy, and should therefore be discouraged[200,201].

The Toupet posterior wrap is also reputed to be effective against reflux but it presents the disadvantage of requiring a posterior dissection of the cardia and, moreover, it does not cover the myotomy dissection site.

On the other hand, the anterior wrap technique whether in the form of Dor (180°-200° anterior partial wrap) or Thal (90° anterior partial wrap) does not have these disadvantages.

With this technique we can be satisfied with a minimal dissection of the cardia, and the valve covers the myotomy while also separating it from the liver, thus making easier a possible reoperation.

Many non-randomized studies compare the two Toupet and Dor procedures: if few conclude in favor of the posterior hemivalve of Toupet[202,203,204], the majority gives preference to the anterior hemivalve of Dor[205,206,207].

MATTIOLI et al[208] reported the case of 20 children with Esophageal Achalasia, all of whom underwent surgical treatment according to the HELLER-DOR combination. In this series the DOR anti-reflux system has been carried out on 180° which considerably reduces the risk of post-operative dysphagia. The children treated in their series all had favorable postoperative clinical and manometric results.

In our series, 11 patients benefited from an anti-reflux system, 14 through the technique of DOR and 1 of THAL.

Follow-up in our case study was evidently shorter than series described in literature with an average of 0.94 years. This can be attributed to the fact that 9 out of 15 patients were last to follow-up after their 3 months post-operative routine check-up.

TableXXIII: Results of Heller myotomy with follow-up, success rate and complications as treatment for esophageal achalasia according to studies' reports

Author	Publishing year	Number of patients	Follow-up (mean years)	Success rate (%)	Complications
Azizkhan &al[167]	1980	19	4	81.8%	9% Hemorrhage-9% mild GER
Vane &al[209]	1988	21	6.3	85.7%	9.5% Perforation
Morris-Stiff &al[210]	1997	10	8	80%	30% minorcomplications
Patti &al[211]	2001	13	9.5	100%	None
Hussain &al[22]	2002	33	4.7	88.2%	17% GER
Paidas &al[87]	2007	14	3	78.6%	7%Perforation
Zhang &al[24]	2009	13	1.26	86.7%	None
Jung &al[163]	2010	22	2	66.7%	6.6% Aspiration
Esposito &al[194]	2013	31	NS	96.8%	9.6% Perforation
Meyer &al[28]	2017	42	4.4	35%	18% Gastricperforation
Grabowski & al[40]	2017	11	2.5	54.5%	16% Perforation
Saliakellis &al[29]	2017	48	3	60.7%	5.5% Esophagealperforation
Duggan &al[212]	2019	31	1.5	71%	7% GER -6.5% perforation
Idrissa& al[31]	2021	14	3.6	78.6%	14.3% Perforation - 7% liver bleeding
Our case study	2023	15	0.94	80%	20% GER

VII. EVOLUTION

1. Mortality

Heller's procedure is very safe with a low rate of surgical mortality. Since 1960, there have been no reported deaths in published results of Heller myotomy in children[86].

In our study no death was encountered.

2. Clinical Eckardt score evaluation

The Eckardt Score (ES) was firstly achieved in 1922 as an evaluative tool to assess positive response factors to pneumatic dilation in adults suffering from achalasia[213].

The ES is a straightforward patient-reported outcome (PRO) measurement created to evaluate results following achalasia treatment and is currently the most widely used metric in nearly all therapy trials[214,215]. Its widespread use is based on expert consensus, and in recent years, the ES has been favored over the Vantrappen classification[216] and the Modified Achalasia Dysphagia Score[217].

The Eckardt Score concentrates on the three primary symptoms of achalasia: dysphagia, regurgitation, and chest pain, and also takes into account weight loss as an indicator of the patient's ability to uphold a good nutrition. Each of the four components is respectively scored from 0 to 3, yielding a total range of 0 to 12, with a score greater than 3 being considered a positive Esophageal Achalasia indicator[218].

Although Eckardt score has not been validated for pediatric patients, the majority of Esophageal Achalasia case researches in literature demonstrate that the ES score improves after intervention and higher scores after intervention are linked to more symptoms' recurrence and the chance of repeat treatment.

The reliability of this achalasia-centered tool has been recently further approved by two studies: TAFT & al in 2018[219] and CISTERNAS & al in 2020[20].

In our study, the median preoperative Eckardt score was 6.26 with a significant improvement in post-operative characterized by an average Eckardt score of 0.8.

Furthermore, we noticed that an Eckardt score higher than 3 was only recorded post-operatively in the two patients who further required a redo-surgery: an ES of 4 in our case (2) patient and an ES of 6 in our case (3) child.

TableXXIV :Esophageal Achalasia Severity: Eckardt Score

Symptom/sign	Score for each symptom/sign			
	0	1	2	3
Weight loss (kg)	None	<5	5-10	>10
Dysphagia	None	occasional	daily	Each meal
Chest pain	None	occasional	daily	Several times/day
Regurgitation	None	occasional	daily	Each meal

3. Length of hospital stay

In our study, patients were admitted in our facility for an average duration of 5.53 days.

This outcome matches the results of studies that similarly used Open Heller Myotomy via laparotomy as a surgical treatment of choice.

TableXXV: Length of hospital stay post-OHM reported in literature

Author	Number of patients	Length of hospital stay (days)
Erginel& al[27]	22	6
Wakhlu& al[26]	40	5 ± 0.43
Idrissa& al[31]	14	4 ± 1.5
Our case study	15	5 ± 0.53

4. Recurrence of symptoms

The recurrence of symptoms after surgical treatment by Heller Myotomy, particularly dysphagia, has been documented in studies to range from 0% to 20% (Mattioli &al[208]) (Patti &al[211]) (Esposito &al[194]), confronted to a higher ranged from 6% to 23% among adults[221].

It is hard to conclude if the dysphagia after the surgery is a direct result of the surgery's failure or due to a natural motility disorder of the lower part of the esophagus.

In our group of patients, the re-occurrence of symptoms was within the range in published studies with a rate of 3 out of 15 treated patients (20%).

5. Redo-surgery:

The best initial treatment for patients who have failed surgical treatment as the first-line option remains a controversial issue, as there is no consensus on the most effective approach.

When a patient who has undergone Heller's myotomy for achalasia experiences dysphagia, it's likely that the myotomy was not complete[222].

A thorough clinical evaluation and additional tests are needed to determine if the dysphagia is due to the myotomy failure or other causes. 7% of complications from achalasia surgery are related to the anti-reflux procedure and it can be difficult to differentiate the symptoms caused by myotomy failure and those caused by tight fundoplication[223,224]. In these cases, surgical revision to correct the anatomy is the best option.

If dysphagia is due to post-myotomy peptic stricture, the first treatment is usually proton pump inhibitors (PPIs). If this is ineffective, a reassessment of the anti-reflux procedure or modification of the existing one should be done[225].

To confirm the diagnosis of myotomy failure, paraclinical exams such as esophagogastroscopy, esophageal manometry, and an esophagram exam are necessary.

Esophageal manometry can compare the LES pattern before and after surgery but has limited value in diagnosing myotomy failure.

In a Loviscek & al study with patients' ages ranging from 13 to 78 years, Upper gastrointestinal transit series were considered the most useful test and can predict the outcome in patients who require re-intervention[226].

In our study 2 patients presented with recurrent dysphagia and regurgitation. The diagnosis of failed myotomy was supported by esophagram and endoscopy findings objectifying an incompetent cardia and a persistent esophagus dilation.

Table XXVI: Literature review of studies in children with recorded repeat heller myotomy and their indications.

Author	Year	Number of patients	Number of repeat HM	Repeat HM indication
Azizkhan &al[167]	1980	11	1	Recurrent dysphagia, regurgitation, and weight loss
Nihoul-Fékété &al[52]	1989	35	1	Recurrent dysphagia
Garzi &al[227]	2007	14	1	Pain due to insufficient myotomy
Paidas &al[87]	2007	14	2	Persistent chest pain
Vaos & al[85]	2008	15	1	Persistent dysphagia
Askegard-Giesmann &al[228]	2009	9	3	Recurrent dysphagia and regurgitation
Corda& al[229]	2010	26	2	Persistent dysphagia and recurrent regurgitation
Zagory &al[161]	2016	9	2	Persistent dysphagia
Duggan &al[212]	2019	31	1	Persistent dysphagia
Our study	2023	15	2	Persistent regurgitation and recurrent dysphagia

6. Assessment of Long-term Quality of Life[230,231]

There is limited literature on the long-term impact of surgical intervention on the Quality of Life of individuals with Esophageal Achalasia. In fact, to the best of our knowledge, no North African study has ventured into the evaluation of Quality of Life of pediatric Esophageal Achalasia patients and as of now very few published works analyze this impact[28,30,18,12].

The PedsQL (Pediatric Quality of Life Inventory) is a modular instrument developed at the Children's Hospital and Health Center in San Diego, California, which measures the health-related quality of life of children and adolescents aged 2 to 18.

The PedsQL 4.0 Generic Core Scales are a multidimensional set of scales that measure various aspects of a child's quality of life. They are designed to be integrated with the PedsQL Disease-Specific Modules, which are used to assess the HRQOL of children with specific medical conditions including but not limited to the Gastrointestinal Symptoms Scales and Module.

The PedsQL 4.0 Generic Core Scales, consisting of 23 items, cover four aspects of a child's quality of life: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). These scales were created through a combination of focus groups and cognitive interviews and are designed to be used with both school and community populations.

On the other hand, the PedsQL Gastrointestinal Symptoms Scales and Module for patients with functional gastrointestinal disorders (FGIDs) and organic GI diseases contains the following scales: stomach pain and hurt (6 items), stomach discomfort when eating (5 items), food and drink limits (6 items), trouble swallowing (3 items), heartburn and reflux (4 items), nausea and vomiting (4 items), gas and bloating (7 items), constipation (14 items), blood in poop (2 items), diarrhea (7 items). It has been validated for use in various gastrointestinal diseases such as Crohn's, GERD, and functional gastrointestinal disorders. However, it has not yet been validated for use in children with Esophageal Achalasia. Despite this, we chose implementing it due to its proven usefulness in chronic gastrointestinal illnesses[232,233].

Both questionnaires come in two formats, a child self-report and a parent proxy-report. The child self-report is for children aged 5 to 7, 8 to 12, and 13 to 18, while the parent proxy-report is for parents of children aged 2 to 4, 5 to 7, 8 to 12, and 13 to 18. This format assesses the parent's perception of their child's health-related quality of life. Both formats contain identical items, with only the language being age-appropriate and the tense being either first or third person.

The PedsQL and GI-PedsQL questionnaires were answered on a five-point Likert scale (three-point for ages 5-7) and score were later transformed to give a value from 0 to 100. Additionally, a higher score is indicative of a higher QoL in both.

To our knowledge, the PedsQL inventory is the only pediatric QoL measuring tool that has been adapted to children with Esophageal Achalasia while also having a validated Arabic version in 2011 by Arabiat &al[234] with proven reliability. These facts prompted our choice of QoL assessment tool.

In our study, we were able to assess the Quality of Life of 13 patients after a median elapsed time of 2.9 years ensuing last follow-up.

The overall PedsQL score was 72/100 (± 17) with a notably higher established scores in physical and emotional functioning but lower functioning score in both social settings and school performance compared to data from a control group of Esophageal Achalasia patients outlined by Marlais &al[235].

Meanwhile, we compared our patients' GI-PedsQL score results with a control group of children presenting with Gastroesophageal reflux disease (GERD) amidst the lack of a published Esophageal Achalasia one. The outcome showed that our patients performed significantly lower in the dimensions: Foods and drinks limitations, difficulty swallowing, heartburn and vomiting, however, they maintained a higher score in the remaining sections.

In the polish experience of Jarzębicka& al[30] appraising the long-term QoL of patients 12 years after Heller myotomy similar outcomes to our study were emphasized with patients reporting unsatisfaction with their health and a limitation of lifestyle because of EA.

Additionally, Meyer & al[28] reported a substantial negative impact of the QoL of 5 out of 8 children and their families after a Heller myotomy interval of 43 months.

Furthermore, Marlais & al[235] remarked in their extensive series that children with achalasia have a significantly lower quality of life (QOL) compared to both children with inflammatory bowel disease and healthy children.

The outcome of our Quality-of-Life investigation suggests that although the treatment of Esophageal Achalasia does alleviate chronic symptoms, a decrement of QoL is frequent in long-term assessments.

Table XXVII: PedsQL Generic core scale parent proxy-report results with historical controls from Marlais & al. (Journal of Paediatrics and Child Health, 2011)[235].

PedsQL Generic score dimensions	Mean SD	Score range	Historical control: healthy patients/remission	Historical control: achalasia patients
Physical functioning	79 ± 18	0-100	91 ± 6	73 ± 20
Emotional functioning	67 ± 10	0-100	76 ± 14	66 ± 18
Social functioning	78 ± 18	0-100	92 ± 13	87 ± 13
School functioning	62 ± 20	0-100	75 ± 12	64 ± 23
Overall score	72 ± 17	0-100	84 ± 8	73 ± 17

Table XXVIII: PedsQL Gastrointestinal Symptoms Scales and Module Parent proxy-report results with historical controls from Varni & al.

GI-PedsQL Section	Mean ± SD	Score range	Historical control: healthypatients	Historical control: GERD patients Mean ±SD
Stomach Pain	76.3 ± 22	0-100	79.1 ±20.3	51.3 ± 26.5
Stomach discomfort when eating	78.8 ±20.9	0-100	88.6 ±17.7	66 ±26.8
Food and Drink Limits	61.5 ± 11	0-100	91.0 ±15.6	68.2 ±29.5
Trouble Swallowing	41.66 ±19.5	0-100	96.5 ±11.3	68.2 ±29.5
Heartburn/Reflux	66.8 ±16.1	0-100	93.3 ±13.0	92.2 ±15.3
Nausea/Vomiting	66.6 ±19.2	0-100	92.1 ±15.2	80.8 ±20.8
Gas/bloating	77.0 ±21	0-100	86.9 ±18.9	78.3 ±24.9
Constipating	98.07 ±6.9	0-100	89.3 ±16.0	62.9 ± 25.3
Blood in poop	98.07 ±6.9	0-100	96.3 ±12.7	66.5 ±26
Diarrhea	95.63 ± 5	0-100	90.0 ±12.7	77.4 ±22.6
Symptom total score	76.0 ± 14.9	0-100	90 ± 12.7	70.0 ± 17.1

VIII. LIMITATIONS VS STRENGHTS OF OUR STUDY

Our study proved the long-term positive outcomes of patients who underwent partial Heller Myotomy during the surgical closure of their Esophageal Achalasia.

Nevertheless, we faced some limitations that restricted the power of our study:

- ♣ The retrospective design: in evidence-based medicine, the benefits and disadvantages of a treatment are best assessed with prospective double-blinded studies. However, those kinds of studies are very hard to undertake given the rarity of Esophageal Achalasia as a disease.
- ♣ The limited sample size in our study prevents us from making a conclusive statement on this matter.
- ♣ The absence of a comparison groups of patients who underwent other surgical techniques.
- ♣ The use of Eckardt Score, a subjective tool prone to bias as an assessment of our surgical success assessment and the limitation of objective postoperative radiological follow-up to patients with persistent or recurrent symptoms.
- ♣ Another constraint of the study was the incapability to demonstrate the manometry outcomes based on the Chicago classification.
- ♣ Our results may not be fully accurate as a considerable number of patients were either transferred to local care or did not attend follow-up appointments after three months, which creates a bias.

On the other hand, our study presents multiple strengths counting:

- ♣ The assessment of the long-term QoL performed by direct contact with patients' families.
- ♣ A subgroup of patients with AAA syndrome that adds to the current literature evidence

- ♣ Identification of two rare associations of esophageal achalasia: achalasia microcephaly syndrome and Down's syndrome.
- ♣ Our findings are in line with previous studies that confirm the safety and effectiveness of Heller's myotomy.

IX. Recommendations:

Our work has given us an elaborate insight to the modalities of Esophageal Achalasia management in our center, ergo the following science-based recommendations that will provide an alleviated quality of EA care if implemented:

- ♣ Due to the uncommon nature of this disease, it is suggested that individuals with achalasia receive care at facilities equipped with proper diagnostic tools and treatment options and that treatment choices should be made by a multidisciplinary team of expert specialists.
- ♣ A persuasive argument can be established for the frequent examination of physiological function in children after undergoing achalasia treatment, with the purpose of informing and directing future actions, particularly for high-risk clinical subtypes.
- ♣ It is preferrable for HREM to be adopted in the diagnosis process of pediatric esophageal achalasia as it has the capability to enhance treatment management.
- ♣ The need for standardized life-long regular follow-up regimes given the high rate of symptom relapse during adulthood hence the risk of serious late complications (i.e., megaesophagus or squamous cell carcinoma)
- ♣ Transitioning to a Laparoscopic approach to Heller's myotomy if no contradictions are present allowing for smaller incisions, less pain, shorter surgical duration, decreased blood loss during the procedure, shorter hospital stays and fewer postoperative complications.

CONCLUSION

Esophageal Achalasia (EA) is a rare condition affecting esophageal motility in children. It is characterized by an increased basal resting pressure and failure of complete relaxation of the lower esophageal sphincter, combined with an absence of normal esophageal peristalsis.

The precise pathogenesis of this condition is poorly understood so far.

Nonetheless, recent evidence suggests a possible role of an autoimmune reaction triggered by a viral infection that leads to an inflammatory process and consequent disruption of inhibitory neurons within the myenteric plexus, releasing nitric oxide.

The common symptoms of achalasia include dysphagia, regurgitation of undigested food, vomiting, and weight loss, while less typical symptoms include heartburn, chest pain, cough, and choking.

With the introduction of high-resolution manometry and the subsequent development of the Chicago Classification, the diagnosis of achalasia has undergone a significant transformation in the last decade. However, the contributions of upper gastro-intestinal barium/gastrografin transit and endoscopy in the diagnosis process as well as the follow-up assessments are undeniable.

There are several treatment options available for managing achalasia in children, including pharmacological therapies, pneumatic dilatation, Heller's myotomy, and peroral endoscopic myotomy. While none of these treatments provide a cure, they can offer relief from symptoms by decreasing LES pressure and EGJ outflow obstruction. Further research is needed to determine the most effective treatment approach for curing esophageal achalasia in children through prospective studies.

However, currently, surgical management using Heller's Myotomy, with or without fundoplication, is the preferred initial treatment approach for childhood esophageal achalasia. This approach may lead to a higher remission rate, a longer symptom-free period, and a more favorable long-term outcome.

There are no significant prognostic factors affecting the results of the treatment. However, worse outcomes may correlate with a delayed diagnosis and in most patients, Heller's Myotomy alleviates symptoms, although an impaired QoL is common in long-term follow ups.

APPENDIX

APPENDIX I: Medical sheet summary (Patient's information summary):

I. Demographic characteristics:

1. Medical record number:.....
2. Full name: .....
3. Age:.....
4. Gender: female □ male □
5. Residency: rural□ urban□
6. Consanguinity: no □ yes□(precise the degree):.....
7. Siblings:no □ yes□(precise the number):.....
8. Educational status: illiterate□primary□secondary□
9. Date of admission: .....
10. Date of discharge:.....

II. Past medical history:

A. Patient's medical history:

- Neonatal InfectionNO □ YES□
- Allgrove syndromeNO □ YES□
- Down's syndromeNO □ YES□
- Hirschsprung's disease NO □ YES□
- Endocrinopathy NO □ YES□

If yes, precise type:

□Diabetes mellitus
□Addison's disease
□Other (precise) .....

- Congenital central hypoventilation syndromeNO □ YES□
- Viral infection NO □ YES□

If yes, precise type of virus:

□ Herpes simplex virus 1
□ human papillomavirus
□ Measles
□ Chickenpox
□ Other (precise).....

- Autoimmune disease: NO □ YES□

If yes, precise type of disease:.....

- Medications and allergies: NO □
  YES□(precise):.....

B. Family medical history:

- Similar cases in family: **NO ☐ YES☐ (precise relationship):**……

C. Surgical history: NO ☐ YES ☐ (precise):

……

……..

III. Clinical presentation:

IV. Early-onset symptoms

1) Age at diagnostic:……

2) Type:

- **Weight loss NO ☐ YES☐**
- if yes, precise:

a) Percent weight loss: ……

b) Current Body Mass Index: ……

c) Duration: ……

- **Failure to thrive NO ☐ YES☐**
- if yes, precise percentile: ……

- **Regurgitation NO ☐ YES☐**
- if yes, precise:

1) Onset of symptoms:

☐Abrupt

☐Insidious, if yes, precise duration: ……

2) Timing of symptoms:

- ☐ Daily
- ☐ Occasional
- ☐ Each meal

3) Nature of vomited matter:

- ☐ Undigested food
- ☐ Partially digested food
- ☐ Hematemesis
- ☐ Bile
- ☐ Coffee-ground vomit

- **Dysphagia NO ☐ YES☐**
  - if yes, precise type:
  - Liquids
  - Solid food
  - Solid and liquid food
  - Paradoxical
  - Daily
  - Occasional
  - Each meal

- **Retrosternal pain NO ☐ YES☐**
  - if yes, precise intensity:
  - Daily
  - Occasional
  - Each meal

- **Regurgitation NO ☐ YES☐**
  - if yes, precise intensity:
  - Daily
  - Occasional
  - Each meal

- **HeartburnNO ☐ YES☐**
- **Respiratory symptoms:NO ☐ YES☐**
  - if yes, precise type:
  - Cough
  - Choking in supine position
  - Hoarseness
  - Aspiration
  - Pneumonia
  - Wheezing
  - Asthma

2) Duration:

3) Clinical Eckardt score:……. /12

Score	Weight loss (kg)	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None	None
1	<5	Occasional	Occasional	Occasional
2	5–10	Daily	Daily	Daily
3	>10	Each meal	Each meal	Each meal

V. **Paraclinical investigations:**

1. **Imaging:**

a) **Esophageal ManometryNO☐YES☐**

if yes, precisetype per Chicago Classification:

- **Type I: without contractility☐**
- **Type II: ≥ 20% of pan-esophageal pressure☐**
- **Type III: ≥ 20% of spastic waves (DL < 4.5s)☐**

b) **Upper GastrointestinalEndoscopy NO☐ YES☐**

if yes, precise:

1. **Endoscopy findings:**

- Esophagus: .....
- Stomach:
  - Cardia: .....
  - Fundus: .....
  - Body: .....
  - Pylorus: .....
- Duodenal bulb: .....

2. **If complementary biopsy done, precise findings:**

.....

.....

.....

.....

.....

.....

c) **Upper gastrointestinal tract radiography (UGI): NO ☐ YES☐**

If yes precise:

- Findings before gastrografin swallow:
  - .....

.....

.....

.....

- Findings after gastrografin swallow:
  - Esophagus: .....
  - Cardia:.....
  - Stomach body:.....
  - Duodenum:.....
  - Jejunum:.....
  - Other findings: .....

d) **Pulmonary X-rays:** NO ☐ YES☐ (precise findings):……

e) **Others (precise)**:☐……

2. **Biological tests:**

- **Complete blood count:**Hb: …….Hte…..WBC……Platelets……..
- **U&Es (Urea and Electrolytes):** NA+……..
  K+……..Urea……..Creatinine…….
- **LFTs (liver function tests):**ALT……AST……ALP……Bilirubin……Albumin……..
- **C-reactive protein (CRP):** ……..
- **ACTH stimulation test:**……
- **Other biochemical abnormalities:**……..

VI. MANAGEMENT:

A. Medical treatment: NO ☐ YES☐

If yes, precise type:

1) Beta-agonists☐
2) Anticholinergic☐
3) Phosphodiesterase inhibitors☐
4) Nitrates☐
5) Calcium channel blockers☐

B. Endoscopic treatment: NO ☐ YES☐

If yes, precise type:

1) Sclerosing agents☐
2) Neurotoxin☐
3) Stent☐

Surgical treatment:

a) **Age at surgical treatment**

b) **Technique:**

- Heller myotomy: - Open Heller myotomy ☐
  -Laparoscopic Heller myotomy ☐
- fundoplication: Nissen☐
  Dor ☐
  Toupet☐

c) **Per operative complication: NO ☐ YES☐(precise):**……

d) **Operating time length:** ……

VII. Postoperative management:

A. Gastrostomy tube: NO ☐ YES☐ (precise duration):.....

B. Medication:

1. Antibiotics:
   - Type:.....
   - Dose:.....
   - Duration:.....
2. Proton-pump inhibitors (PPIs):.....

C. Postoperative immediate complications:NO ☐ YES☐ (precise):

Complication	Management	Follow-up

D. Postoperative stay length:.....

VIII. Follow up

A. Results:

1. Mortality NO ☐ YES☐ (precise):
2. Symptoms relief:NO ☐ YES☐
3. Symptoms persistence:NO ☐ YES☐ (precise):

Symptom type	Intensity (i.e.: Mild, Moderate, Severe)

4. Postoperative early and late sequela: NO ☐ YES☐ (precise):

Sequela type	Time of occurrence in postoperative	Intensity (i.e.: Mild, Moderate, Severe)	Treatment

B. Follow up length: .....

C. Follow up paraclinical exams: .....

D. Post-operative Clinical Eckardt Score:

E. Redo-surgery: NO ☐ YES☐ (precise):

1. Cause: .....
2. Age at redo surgery: .....
3. Type of surgical act: .....
4. Treatment received between the initial and redo-surgery:

NO ☐ YES☐ (precise):

5. Redo-surgery follow-up length: ……..
6. Redo-surgery evolution (precise):

……

……

APPENDIX II: PedsQL Generic and GI-PedsQL questionnaires by parent-proxy in Arabic:

I. PedsQL Generic core scale parent proxy-report example:

*خلال **الأيام الـ 7** الماضية، ما حجم **المشكلة** الناتجة لطفلك/طفلتك عن كل مما يلي...*

الآلام والأوجاع في البطن *(مشاكل بخصوص...)*	ليست مشكلة أبدا	ليست مشكلة في معظم الأحيان	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة في معظم الأحيان
1. يشعر/تشعر بآلام أو أوجاع في البطن	0	1	2	3	4
2. تنشأ لديه/ا أوجاع في البطن	0	1	2	3	4
3. بطنه/ا تؤلمه/ا	0	1	2	3	4
4. يستيقظ/تستيقظ ليلًا لشعوره/ا بأوجاع البطن	0	1	2	3	4
5. يشعر/تشعر بانزعاج في بطنه/ا	0	1	2	3	4
6. يشعر/تشعر بعدم ارتياح في البطن	0	1	2	3	4

الانزعاج في البطن عند الأكل *(مشاكل بخصوص...)*	ليست مشكلة أبدا	ليست مشكلة في معظم الأحيان	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة في معظم الأحيان
1. عند الأكل، يشعر/تشعر بانزعاج في بطنه/ا	0	1	2	3	4
2. الأكل يسبب له/ا شعورًا سيئًا في البطن	0	1	2	3	4
3. بطنه/ا تؤلمه/ا عند الأكل	0	1	2	3	4
4. يشعر/تشعر بثقل في بطنه/ا عند الأكل	0	1	2	3	4
5. يشعر/تشعر بأن بطنه/ا ممتلئة بمجرد أن يبدأ/تبدأ بالأكل	0	1	2	3	4

قيود الأكل والشرب *(مشاكل بخصوص...)*	ليست مشكلة أبدا	ليست مشكلة في معظم الأحيان	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة في معظم الأحيان
1. لا يستطيع/تستطيع تناول بعض الأطعمة	0	1	2	3	4
2. لا يستطيع/تستطيع شرب بعض المشروبات	0	1	2	3	4
3. غير قادر/قادرة على أكل ما يريد/تريد	0	1	2	3	4
4. غير قادر/قادرة على شرب ما يريد/تريد	0	1	2	3	4
5. لا يستطيع/تستطيع تناول بعض الأطعمة لأنها تسبب له/ا الانزعاج في البطن	0	1	2	3	4
6. لا يستطيع/تستطيع تناول الأطعمة التي يتناولها أصدقاؤه/ا	0	1	2	3	4

صعوبة البلع *(مشاكل بخصوص...)*	ليست مشكلة أبدا	ليست مشكلة في معظم الأحيان	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة في معظم الأحيان
1. يصعب عليه/ا بلع الطعام	0	1	2	3	4
2. يشعر/تشعر بألم عند البلع	0	1	2	3	4
3. يعلق الطعام عند نزوله (إلى المعدة)	0	1	2	3	4

*خلال **الأيام الـ 7** الماضية، ما حجم **المشكلة** الناتجة لطفلك/طفلتك عن كل مما يلي...*

حرقة المعدة وارتجاع السائل المعدي *(مشاكل بخصوص...)*	ليست مشكلة أبدا	ليست مشكلة في معظم الأحيان	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة في معظم الأحيان
1. يشعر/تشعر بالحرقة في الحلق	0	1	2	3	4
2. يشعر/تشعر بألم أو وجع في الصدر	0	1	2	3	4
3. يتجشأ/تتجشأ كثيرًا (إخراج الهواء من المعدة من خلال الفم)	0	1	2	3	4
4. يعود الطعام إلى فمه/ا بعد الأكل	0	1	2	3	4

الغثيان والتقيؤ *(مشاكل بخصوص...)*	ليست مشكلة أبدا	ليست مشكلة في معظم الأحيان	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة في معظم الأحيان
1. يشعر/تشعر بالرغبة في التقيؤ	0	1	2	3	4
2. يشعر/تشعر بالرغبة في التقيؤ عند الأكل	0	1	2	3	4
3. يشعر/تشعر بالرغبة في التقيؤ بعد الأكل	0	1	2	3	4
4. يتقيأ/تتقيأ	0	1	2	3	4

الغازات وانتفاخ البطن *(مشاكل بخصوص...)*	ليست مشكلة أبدا	ليست مشكلة في معظم الأحيان	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة في معظم الأحيان
1. الشعور بامتلاء البطن بالغازات	0	1	2	3	4
2. الشعور بأن البطن ممتلئة جدًا	0	1	2	3	4
3. تصبح البطن كبيرة وصلبة	0	1	2	3	4
4. لديه/ا الكثير من الغازات	0	1	2	3	4
5. يخرج/تخرج الكثير من الغازات	0	1	2	3	4
6. يشعر/تشعر بأن بطنه/ا منتفخة	0	1	2	3	4
7. تصدر أصواتًا من البطن	0	1	2	3	4

II. PedsQL Gastrointestinal Symptoms scales parent proxy-report example:

*خلال **الشهر الماضي**، ما حجم **المشكلة** الناتجة لطفلك|طفلتك عن كل مما يلي...*

الصحة الجسمانية والأنشطة *(مشاكل بخصوص...)*	ليست مشكلة أبدا	نادراً ما تكون مشكلة	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة بشكل شبه دائم
1. المشي لمسافة تزيد عن 100 متر	0	1	2	3	4
2. الركض	0	1	2	3	4
3. المشاركة في الأنشطة الرياضية أو التمارين	0	1	2	3	4
4. رفع شيء ثقيل	0	1	2	3	4
5. الاستحمام بدون مساعدة الآخرين	0	1	2	3	4
6. القيام بأعمال المنزل	0	1	2	3	4
7. حدوث آلام أو أوجاع	0	1	2	3	4
8. إنخفاض مستوى الطاقة	0	1	2	3	4

الحالة العاطفية *(مشاكل بخصوص...)*	ليست مشكلة أبدا	نادراً ما تكون مشكلة	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة بشكل شبه دائم
1. الشعور بالخوف	0	1	2	3	4
2. الشعور بالحزن	0	1	2	3	4
3. الشعور بالغضب	0	1	2	3	4
4. صعوبة في النوم	0	1	2	3	4
5. القلق مما سيحدث له أو لها	0	1	2	3	4

الوظائف الاجتماعية *(مشاكل بخصوص...)*	ليست مشكلة أبدا	نادراً ما تكون مشكلة	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة بشكل شبه دائم
1. الانسجام مع الأطفال الآخرين	0	1	2	3	4
2. عدم رغبة الأطفال الآخرين في اللعب معه أو معها	0	1	2	3	4
3. التعرُّض للمضايقة والسخرية من الأطفال الآخرين	0	1	2	3	4
4. عدم القدرة على عمل الأشياء التي يستطيع الأطفال الآخرون في مثل سنه أو سنها أن يعملوها	0	1	2	3	4
5. مجاراة الأطفال الآخرين خلال اللعب	0	1	2	3	4

الأنشطة المدرسية *(مشاكل بخصوص...)*	ليست مشكلة أبدا	نادراً ما تكون مشكلة	هي مشكلة في بعض الأحيان	هي مشكلة في أحيان كثيرة	هي مشكلة بشكل شبه دائم
1. الانتباه في الصف	0	1	2	3	4
2. نسيان الأشياء	0	1	2	3	4
3. مجاراة الاطفال الآخرين في الواجبات المدرسية	0	1	2	3	4
4. التغيُّب عن المدرسة بسبب الشعور بالمرض	0	1	2	3	4
5. التغيّب عن المدرسة للذهاب إلى الطبيب أو إلى المستشفى	0	1	2	3	4

ABSTRACT

ABSTRACT

Introduction: Achalasia is a motility disorder of the esophagus characterized by absence of peristalsis and impaired relaxation of the lower esophageal sphincter. In childhood, symptoms are often atypical and vary with age.

Material & methods: We conducted a retrospective analysis following 15 cases of Esophageal achalasia in children at the Paediatric surgical department "B" of the Mohammed VI Marrakech teaching hospital during a 15-year period, from 2008 to 2022. Long term impact of the diagnosis on the patients' Quality of Life was assessed by questionnaires.

The objective of this study is to evaluate incidence and clinical course of diagnosed Esophageal Achalasia patients, to review the surgical management approach in our department as well as the current impact of this disease on our patients' Quality of Life.

Results: We identified 15 children including 7 with an Allgrove syndrome association, 1 with Down's syndrome and 1 association of Achalasia-Microcephaly syndrome. The median overall age at diagnosis was 6 years and patients developed symptoms earlier, but had delayed diagnosis with a mean duration of 2 years and 9 months of symptoms. The most frequent symptom detected was regurgitation and median follow-up was 11.62 months.

All patients benefited from a Timed esophagram that proved a dilated esophageal body, Bird's beak appearance of LES, and narrowing of the esophagogastric junction. Meanwhile endoscopy was performed in 11 patients with mainly an objectified resistance at the EGJ (n=9) and dilated esophagus (n=8).

Laparatomy was used to perform Heller's myotomy in all 15 cases and with a concomitant fundoplication procedure. Clinical evolution was overall satisfactory, with disappearance of initial symptoms in 13 patients. Two out of our 15 patients who underwent myotomy required a repeat-surgery.

Quality of life questionnaires' results outlined a low social and school functioning with patients' parents conveying a hindrance adjusting to their peers in addition to long-term food

and drinks limitations with difficulty swallowing bringing deleterious impact on the quality of life of children and their families.

Conclusion: Esophageal Achalasia is a rare but an irrevocably present disorder in our population. Amidst the era of novel management methods, a development of resources both human and technological is needed to ensure a higher postoperative palliative outcome. Additionally, further indulgence in the long-term Quality of Life of patients is imperative to factually evaluate EA management and enrich any future research into this disease.

Our study is the first of its kind assessing QOL in children with Esophageal Achalasia in Morocco. Furthermore, it is also, based on our extensive research, the first report in the North African region.

RESUME

Introduction: L'achalasie œsophagienne est un trouble de la motilité de l'œsophage caractérisé par l'absence de péristaltisme de plus d'une altération de la relaxation du sphincter œsophagien inférieur. Dans l'enfance, les symptômes sont souvent irréguliers et varient avec l'âge.

Matériel et méthodes: Nous rapportons une analyse rétrospective de 15 cas d'achalasie œsophagienne chez l'enfant recueillis au service de chirurgie pédiatrique " B " du CHU Mohammed VI de Marrakech durant une période de 15 ans, de 2008 à 2022. L'impact à long terme du diagnostic sur la qualité de vie des patients a été évalué par des questionnaires.

L'objectif de cette étude est d'évaluer l'incidence et l'évolution clinique des patients atteints d'achalasie œsophagienne, de revoir l'approche de la prise en charge chirurgicale dans notre service ainsi que l'impact actuel de cette maladie sur la qualité de vie de nos patients.

Résultats: Nous avons identifié 15 enfants dont 7 avec une association de syndrome d'Allgrove, 1 avec le syndrome de Down et 1 association de syndrome d'Achalasie-Microcéphalie. L'âge médian global au moment du diagnostic était de 6 ans et les patients ont développé des symptômes plus tôt, mais ont eu un diagnostic tardif avec une durée moyenne de 2 ans et 9 mois de symptômes. Le symptôme le plus fréquent était la régurgitation et le suivi médian était de 9,95 mois.

Tous les patients ont bénéficié d'un transit œso-gastro-duodénal qui a montré une dilatation du corps œsophagien, un aspect en bec d'oiseau du du sphincter inférieur de l'œsophage et un rétrécissement de la jonction œsophagogastrique (JOG). Parallèlement, une endoscopie a été réalisée chez 11 patients avec principalement une résistance objectivée au niveau de la JOG (n=9) et un œsophage dilaté (n=8).

La laparotomie a été utilisée pour réaliser l'intervention de Heller dans les 15 cas et avec une procédure concomitante de fundoplication. Les résultats cliniques ont été globalement

considérés comme satisfaisants, avec une disparition des symptômes initiaux chez 13 patients. Deux de nos 15 patients ayant subi une myotomie ont dû subir une nouvelle intervention.

Les résultats des questionnaires sur la qualité de vie ont mis en évidence un faible fonctionnement social et scolaire, les patients faisant état d'une difficulté à s'adapter à leurs pairs, ainsi que des limitations à long terme de choix d'aliments et des boissons avec des difficultés de déglutition, ce qui a un impact délétère sur la qualité de vie des enfants et de leurs familles.

Conclusion: L'achalasie œsophagienne est un trouble rare mais irrévocablement présent dans notre population. A l'ère des nouvelles méthodes de prise en charge, un développement des ressources humaines et technologiques est nécessaire pour assurer un meilleur résultat palliatif postopératoire. En outre, il est impératif de s'intéresser davantage à la qualité de vie à long terme des patients pour évaluer de manière factuelle la prise en charge de l'achalasie œsophagienne et enrichir toute recherche future sur cette maladie.

Notre étude est la première du genre à évaluer la qualité de vie chez les enfants atteints d'achalasie œsophagienne au Maroc. En outre, il s'agit également, sur la base de nos recherches approfondies, de la première étude dans la région de l'Afrique du Nord.

ملخص

مقدمة: تعذر الارتخاء المريئي هو اضطراب حركي اولي في المريء يتميز بغياب تمعج المريء وضعف في ارتخاء العضلة السفلى العاصرة للمريء. غالبًا ما تكون الأعراض في مرحلة الطفولة غير نمطية وتختلف مع تقدم العمر.

المواد والأساليب : أبلغنا عن تحليل بأثر رجعي لـ 15 حالة من حالات تعذر الارتخاء المريئي لدى الأطفال التي تمت معالجتها في قسم جراحة الأطفال "ب" بمستشفى محمد السادس بمراكش التعليمي خلال فترة 15 عامًا ، من 2008 إلى 2022. تم كذلك تقييم تأثير التشخيص على جودة حياة المرضى من خلال الاستبيانات.

الهدف من هذه الدراسة هو تقييم نسبة الإصابة والمسار السريري لمرضى تعذر الارتخاء المريئي الذين تم تشخيصهم، لمراجعة منهج التدخل الجراحي المتبع في قسمنا بالإضافة إلى التأثير الحالي لهذا المرض على جودة حياة مرضانا.

النتائج: تتبعنا 15 طفلاً من بينهم 7 مصابين بمتلازمة ألجروف ، وطفل مصاب بمتلازمة داون ، وحالة واحدة لمتلازمة تعذر الارتخاء-صغر الرأس. كان متوسط العمر الإجمالي عند التشخيص 6 سنوات وظهرت الأعراض على المرضى في وقت سابق، لكنهم تأخروا في التشخيص بمتوسط عامين و 9 أشهر من الأعراض. كان أكثر الأعراض شيوعًا هو القلس وكان متوسط المتابعة 9.95 شهرًا.

خضع جميع مرضى الدراسة لابتلاع الباريوم المريئي التي أظهرت اتساع جسم المريء، وظهور العضلة السفلى العاصرة للمريء على شكل منقار الطائر، وتضييق الموصل المريئي المعدي. وفي الوقت نفسه، تم إجراء التنظير الداخلي من اجل 11 مريضًا حيث اتضح لديهم مقاومة موضوعية في الموصل المريئي المعدي (ن = 9) والمريء المتوسع (ن = 8).

تم إجراء تدخل جراحة هيلر عن طريق فتح البطن في جميع الحالات الـ 15 وما يصاحب ذلك من إجراء نظام مضاد للجزر. اعتبرت النتائج السريرية مرضية بشكل عام، مع اختفاء الأعراض الأولية في 13 مريضًا. اثنان من أصل 15 مريضًا خضعوا لإعادة اجراء للعملية الجراحية.

أوضحت نتائج استبيانات جودة الحياة تدني الأداء الاجتماعي والمدرسي مع ابلاغ من طرف آباء المرضى عن عائق في التكيف مع أقرانهم بالإضافة إلى قيود طويلة الأجل على الطعام والشراب مع صعوبة في البلع مما يؤدي إلى إحداث تأثير ضار على نوعية حياة الأطفال وأسرهم.

الخلاصة: تعذر الارتخاء المريئي هو اضطراب نادر ولكنه موجود بشكل فعال في بلدنا. في خضم عصر أساليب النهج الطبي الجديدة، هناك حاجة إلى تطوير الموارد البشرية والتكنولوجية لضمان نتيجة أعلى بعد الجراحة.

بالإضافة إلى ذلك، فإن المزيد من الانغماس في جودة حياة المرضى على المدى الطويل أمر ضروري لتقييم إدارة مرضى الارتخاء المريئي بشكل واقعي وإثراء أي بحث مستقبلي حول هذا المرض.

دراستنا هي الأولى من نوعها التي تقيم جودة الحياة عند الأطفال المصابين بتعذر المريء في المغرب. علاوة على ذلك، فهو أيضًا، استنادًا إلى بحثنا المكثف، التقرير الأول في منطقة شمال إفريقيا.

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قسم الطبيب

أقْسِم بِالله العَظِيم

أن أراقبَ الله في مِهْنَتِي.

وأن أصُونَ حياة الإنسان في كآفّةِ أطوَارهَا في كل الظروف والأحَوال باذلة وسْعِي في إنقاذها مِن الهَلاكِ والمرَضِ والألَم والقَلَق.

وأن أحفَظَ لِلنَاسِ كرَامَتهُم، وأسْتر عَوْرَتهُم، وأكتمَ سِرَّهُمْ.

وأن أكونَ عَلى الدوَام من وسائِل رحمة الله، باذلة رِعَايَتي الطبية للقريب والبعيد، للصالح والطالح، والصديق والعدو.

وأن أثابر على طلب العلم، وأسَخِّرَه لِنَفْعِ الإنْسَان لا لأذَاه.

وأن أُوَقّرَ مَن عَلَّمَني، وأُعَلّمَ مَن يَصْغرَني، وأكون أخـًا لِكُلِّ زَميلٍ في المِهنَةِ الطِّبِّيَة مُتعَاونِينَ عَلى البرِّ والتقوى.

وأن تكون حياتي مِصْدَاق إيمَاني في سِرّي وَعَلانيَتي، نَقِيَّة مِمّا يُشينهَا تجَاهَ الله وَرَسُولِهِ وَالمؤمِنين.

والله على ما أقول شهيدا

كليـــــــة الـطـب
و الصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH
MARRAKECH
جامعة القاضي عياض
UNIVERSITÉ CADI AYYAD

سنة 2023 أطروحة رقم 073.

تعذر الارتخاء المريئي عند الاطفال

الأطروحة

قدمت ونوقشت علانية يوم **2023/02/22**

من طرف

السيدة نعمى رياض

المزدادة في بني ملال 3 دجنبر 1994

لنيل شهادة الدكتوراه في الطب

الكلمات الأساسية:

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