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„CAROL DAVILA", BUCHAREST

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Long-term outcomes in the surgical treatment of esophageal atresia: complications and quality of life beyond childhood

PhD THESIS ABSTRACT

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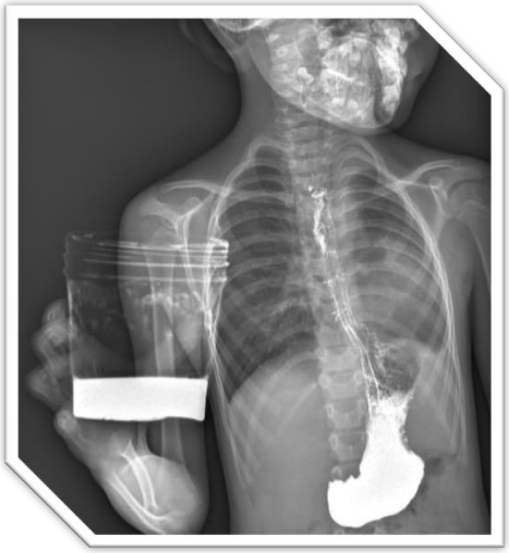

„Looking for gastro-esophageal reflux”, intro image

(retrieved from the gallery of Emergency Clinical Hospital for Children „Marie S. Curie” Bucharest)

Esophageal atresia, unlike other diseases, will always bring a touch of exclusivity and authenticity to pediatric surgery, throughout its particularities of diagnosis, treatment and evolution according to the patient’s specific growth and development.

Revolution of pediatric has occurred at the same time to the evolution of neonatal intensive care. Improvements in the esophageal atresia prognosis of survival led to a greater burden of residual clinical manifestations related to the spectrum of the disease. Moreover, incidence of some intermediate and long-term complications started to grow.

The reasoning for choosing this topic to study starts from the remark that long-term follow-up in esophageal atresia in Romania is currently lining up to international standards. The pathology left over to the post-surgical age of the esophageal atresia has a great potential to alter the patient’s and its family quality of life. Therefore, I believe that this issue is inciting towards several research directions looking to improve the medical, surgical or endoscopic procedures.

General part

Importance of esophageal atresia surgery history in understanding its actual long-term morbidity

The survival of newborns with esophageal atresia could not have been possible without the advances made in neonatal intensive care. Subsequently, a revolution in surgical principles and techniques took place, and one of the emblematic problems of the surgical treatment of esophageal atresia that has always challenged surgeons is how to manage the situation in which the distance between the esophageal ends is too wide to allow the anastomosis to be performed. This initially led to the emergence of several technical artifices to lengthen the two segments of the esophagus and, initially, colonic interposition became the dominant procedure if the primary anastomosis could not be performed.

Puri P supports the statement that soon became a therapeutic principle in the modern surgical treatment of AE: "the best esophagus for the patient is his own esophagus, and every effort should be made to preserve it by a delayed primary anastomosis". Thus, the challenge that the distance between the esophageal ends provides in conjunction with the stubbornness of the surgeon to methodically apply Puri's principle will form the origin of the large-scale emergence of gastroesophageal reflux disease and primary anastomosis associated esophageal strictures.

Gastro-esophageal reflux disease in postoperative evolution of the modern esophageal atresia treatment

"Gastroesophageal reflux should be considered part of esophageal atresia because of its frequency in association with it", state Tovar and Fragoso in the European Journal of Pediatric Surgery (2013). Symptoms associated with gastroesophageal reflux disease after treatment of esophageal atresia have a very high prevalence and a very high variability, data that can easily lead to questioning the quality of screening or the level of awareness given the high adaptability of these patients to which they are subdued from the first day of life. Moreover, gastroesophageal reflux, analysed through the dynamics of esophageal atresia,

seems to present some etiopathogenetic particularities of anatomy that make it more difficult to be managed comparing to the "physiological" one in newborns and infants or the one secondary to conditions other than esophageal atresia.

The North American and European Pediatric Gastroenterology, Hepatology and Nutrition Associations (NASPGHAN-ESPGHAN) have published in 2016 the first guidelines of good practice in the approach to gastroesophageal reflux disease in patients with a history of esophageal atresia/congenital esotracheal fistula in the pediatric population. This represents a huge step towards standardizing the treatment of these children and, at the same time, a request from the authors to deepen the research in this direction, considering that the level of evidence for some recommendations is very low and lacks support from randomized studies.

The traditional tool in detecting of gastroesophageal reflux is the esophageal barium swallow. This can have a significant diagnostic value if performed correctly, in a good general shape of the patient and by an experienced radiologist. pH-metry is very popular in the diagnosis of gastro-oesophageal reflux. This represents a gold standard in the diagnosis and characterization of the pathophysiological behaviour of gastroesophageal reflux and in tracking the effectiveness of anti-acid treatment. Digestive endoscopy has its first purpose to identify any macroscopic signs of reflux esophagitis. In the absence of endoscopic signs, biopsies should be systematically made from the entire esophagus, both distal and proximal, as well as nearby the anastomosis to identify microscopic signs of reflux esophagitis. Moreover, digestive endoscopy directly helps to exclude conditions that - clinically - mimic gastro-oesophageal reflux.

Dysphagia is the most common symptom associated with gastroesophageal reflux disease. It is very commonly found in esophageal atresia as independent of gastroesophageal reflux disease, and this feature must be carefully taken into account. Untreated dysphagia over time leads to vicious behavioural changes in children that tend to adapt its eating habits to its swallowing difficulties. Moreover, dysphagia should always be specifically addressed and evaluated when interviewing the patient with a history of esophageal atresia, because in many times it can be ignored because of the adaptation to it.

Symptomatology has no predictive value for endoscopic evaluation findings, therefore reflux esophagitis may be identified in countless cases, even in the absence of symptoms.

Thus, it is emphasized that the insidious nature of reflux esophagitis esophageal atresia evolution and that the presence/nature of the symptoms is not the aspect that motivates further investigation in the follow-up of patients with esophageal atresia. From the point of view of endoscopic or histopathological imaging, reflux esophagitis is divided into an erosive form (in which the lesions caused by gastro-oesophageal reflux can be visualized) and a non-erosive one (in which the mucosa is apparently normal). Erosive esophagitis knows 3 classification systems: Hetzel-Dent, Savary-Miller and Los Angeles, the latter being universally accepted.

In the NBI visualization mode, the blood capillaries and the microscopic configuration of the mucous surfaces are magnified, acquire a dark-red/brown colour and the blood vessels with an increased caliber become cyan. This proves to be very useful in identifying the squamo-columnar junction in children and in the diagnosis of esophagitis.

Esophageal strictures represent one of the greatest challenges in the modern treatment of esophageal atresia. Most doctors prefer balloon dilatations, followed by Savary-Gillard dilators, esophageal stents and revision of the anastomosis. Regarding the adjuvant treatment adopted in the case of recurrent strictures, most doctors prefer intralesional steroid injection, mitomycin C injection, esophageal stenting, and incisional therapy (endoscopic sectioning) – in this order.

The conservative approach is currently the most accepted method in the treatment of gastroesophageal reflux disease, and proton pump inhibitors, respectively H-2 receptor antagonists, have been shown to be successful pharmacological means in alleviating digestive/respiratory symptoms and in obtaining a satisfactory weight gain. Because there is a high chance that gastroesophageal reflux symptoms will persist postoperatively in patients with a history of esophageal atresia, and the positive effects of fundoplication are transient in a large proportion of patients, the indication for antireflux surgery, timing of the surgery and the technique used in esophageal atresia associated gastroesophageal reflux is a controversial topic in current esophageal atresia surgery.

The clinical manifestations of high gastro-esophageal reflux often coincide with those of an isolated esophago-tracheal fistula (in H). At the same time, these two pathological entities can coexist. The "rush" to perform an antireflux procedure and differential diagnosis

errors can lead to unnecessary surgical interventions with potentially significant impact over the patient.

Quality of life concept in health care

Quality of life can be seen as a descriptive tool of human physical and psycho-social variables, covering a wide variety of specific concepts such as: health status, living conditions, material circumstances, perceptions and behaviour, well-being, happiness, lifestyle, all of them closely interconnected. Introducing the idea of quality of life into medical practice seems to be a challenge, but doctors must realize that this concern is not a sign of weakness, but an essential part of the concept of "care" in the definition of their profession.

The evaluation of the quality of life related to health is done differently in the case of children, compared to the approach method in the case of adult patients. Questioning by proxy (addressed to relatives) is preferable in the case of children, even if after the age of 5 it is considered that it can also be done directly, but with questionable results.

There is a growing interest in the quality of life of patients with esophageal atresia following the increase in their survival rate. They carry on the burden of associated complications, either associated with the previous surgical interventions, or associated with other malformations. The literature shows a reduced global quality of life in patients with esophageal atresia, regardless of age. Numerous studies need to be carried out to observe to what extent social integration, physical and mental functions are affected. At the same time, cross-cultural studies, comparisons between the youngest and the oldest patients and methods of specific approach to health-related quality of life in esophageal atresia would lead to new observations and possible changes in the therapeutic approach of patients with esophageal atresia on long term. Reporting the quality of life related to health in the case of patients with esophageal atresia could be the basis of attitude revisions in clinical practice, development of coping techniques or for changes in the health policies.

Special part

Personal contributions

There is an increasing number of primary anastomoses, therefore the dynamics and complexity of postoperative gastroesophageal reflux disease has increased, and this paper's aim is to consolidate the ideas surrounding the associated comorbidities in this situation. Another purpose is to lay the foundations for modern mid- and long-term follow-up of patients with esophageal atresia from Romania through a study that reflects the current stage of knowledge and the burden of complications associated with gastro-oesophageal reflux disease, in the case of children and adolescents that have been operated in the Emergency Clinical Hospital for Children "Marie S. Curie" for 15 years.

On the other hand, my inclusion in European research programs throughout the residency and as a specialist doctor in the early years introduced me to a Europe where clinical psychology and the concept of quality of life related to health plays an essential role in health policy making and in influencing clinical practice, while in Romania these aspects are most often ignored.

Thus, my personal contribution wants to be an applied scientific research paper whose aim is to define a first overview in the "Marie S. Curie" Emergency Clinical Hospital for Children in Bucharest, Romania, on the complications of gastro-reflux disease and the quality of life perspective that modern treatment of esophageal atresia entails.

The present research paper is divided into two cross-sectional descriptive studies, both aiming to objectify the current situation beyond the first childhood age, both from a medico-surgical and psycho-social point of view, of patients with a background of esophageal atresia. By combining the two studies, I want to raise awareness over the importance of tracking and adjusting the follow-up methods of esophageal atresia, especially gastro-oesophageal reflux disease, in medical centers in Romania.

Surgical treatment of esophageal atresia: outcomes beyond childhood

If not treated, reflux esophagitis - besides the specific sequence of complications (Barrett's esophagus, respectively esophageal adenocarcinoma) - manifests symptoms starting with early childhood. These are often well tolerated and children adapt excellently without considering a problem since their existence lasts from birth: episodes of heartburn, odynophagia, dysphagia, non-specific retrosternal pain, etc. Often, even when mentioned by children, the relatives of these patients ignore these problems stating them only if they are asked directly, considering that these are part of from the natural burden of the surgical intervention on the congenital malformation and do not know its evolution over time.

The present study was carried out between January 2020 and July 2022. During this period, I conducted a descriptive cross-sectional study among a group of patients operated for esophageal atresia in the Pediatric Surgery Clinic of the "Marie S. Curie" Emergency Clinical Hospital for Children from Bucharest. At the same time, we studied aspects of medical or surgical history, clinical, imaging and endoscopic data in an attempt to draw appropiate observations. The specific objectives of the present study are to outline a clinical profile and long-term identification of reflux esophagitis in a group of patients operated in the first years of life in which the preservation of the native esophagus was chosen, regardless of the type of esophageal atresia.

Inclusion criteria were: age older than 3 years and the fact that primary esophageal-esophageal anastomosis was performed as the surgical treatment of esophageal atresia. 49 potential candidates were identified of which only 14 could be coagulated for evaluation in the study. One of the biggest difficulties encountered was obtaining their contact details from the medical records and the reluctance of their relatives to the call for examination.

- Male:female ratio was 1:1.
- Average age of the patients was 6 years and 4 months, median age 5 years and 6 months. Youngest patients were 3 years of age and the oldest was 13.
- All of the patients have had type C esophageal atresia (Gross' classification).
- Average birthweight is 2567 g, the lowest value recorded being a female patient of 1200 g.
- Regarding the associated digestive malformations, I recorded two patients: one male newborn presenting with duodenal malformation another with microgastria diagnosed intraoperatively.

- 7 children out 14 (50%) presented esophageal dilatations for an esophageal anastomotic stricture in the first two years of life. In one case, revision of the anastomosis was done twice. Regarding the anti-reflux procedure, these were adopted in 3 cases and each time Nissen was the chosen fundoplication type. Among these 3, wrap failure is reported in one case and in one other its hiatal herniation.
- 3 patients (21%) had some form of esophageal stenosis at the time of evaluation, of which: 2 had not presented for esophageal dilatations for more than 3 years, one presented to the clinic for esophageal dilatations in the last month.
- 2 cases (14%) of histopathologically normal esophagus, 3 cases (22%) of non-erosive reflux esophagitis, 8 cases (57%) of erosive reflux esophagitis and 1 case of columnar metaplasia, with intestinal mucosa type (Barrett's esophagus).
- According to the Los Angeles classification, the cases of erosive esophagitis were divided as follows: A (1 patient), B (1 patient), C (2 patients), D (4 patients).
- Eso-gastro-duodenal barium swallow identified gastro-esophageal reflux (following provocation maneuvers or not) in 11 out of 14 cases. On the other hand, out of the 3 situations in which gastro-oesophageal reflux was not objectified in this way, in the case of one patient Barrett's esophagus was identified endoscopically.
- Dysphagia is the most frequent manifestation accused, (71%), followed regurgitation or vomiting (35%), epigastralgia (21%), retrosternal pain/heartburn (21%), odynophagia (14%). A case of gr. D reflux esophagitis also manifested by periodic episodes of hematemesis, associated with dysphagia and frequent regurgitation.
- For the entire group, an average pediatric BMI of 15.7 was obtained, the average being at the 38.6th percentile with an average Z-score of -0.85.
- In the case of height, the batch average position is noted at the 28.6th percentile and an average Z-score of -0.92, while in the case of weight, the batch average position is calculated at the 29.6th percentile and an average Z-score of -1.04 .

Gastro-esophageal reflux disease remains an insidious pathology in esophageal atresia. Born with the inability to swallow, often going through weeks or months of oro-tracheal intubation and *nil per os*, these children understand that dysphagia along with other digestive symptoms are a part of "normal" life, therefore it must always be carefully investigated even if the patients or their relatives do not systematically mention it in their history. In any patient with reflux esophagitis, the onset of Barrett's esophagus can become a matter of time in the

presence of life adaptation to distressing digestive symptoms and in the absence of periodic demanding evaluation and antacid treatment.

The prevention plan for reflux esophagitis, respectively Barrett's esophagus, must be initiated in childhood, by informing patients about GERD manifestations and their importance and their follow-up must be done systematically. In the present cohort, there is a relatively high incidence of reflux esophagitis, respectively of its advanced stages and this phenomenon can be correlated with the adherence of the patients to the postoperative follow-up.

Quality of life and health perception: questionnaire of esophageal atresia patients from Romania

Often, although the main (surgical) time in the treatment of esophageal atresia and its side effects are medically controlled, certain clinical manifestations make their presence felt sporadically throughout the rest of life: dysphagia, odynophagia, heartburn, abdominal pain, chest deformations, scars visible, respiratory disorders, low weight gain etc. These are often difficulties to which the patient adapts by developing specific, avoidant behaviours (eg: excluding a certain type of food) or psychological complexes once he becomes aware of the visible differences from the rest of the children.

The study of the quality of life is an emerging phenomenon that knows a rapid rise in medical systems around the world, especially where the demands of the health care system are very high. The quality of life of patients is insufficiently studied and known in Romanian hospitals, especially in pediatric centers where access to subjects is done indirectly through parents or relatives.

The hypothesis I am starting from is that the pathology related to esophageal atresia, its evolution, the chronic clinical manifestations, precipitated more or less by the medical system, have an impact on certain psychological and social aspects of the children and their families' lives. I believe that the resulting observations could be a first step towards generating awareness over the needs of these patients and improving the therapeutic approach to esophageal atresia in the long-term.

We created an analysis questionnaire regarding the quality of life of children with a history of esophageal atresia in Romania (55 questions). Its aim is the qualitative-comprehensive measurement from the parents' perspective of the clinical, medical-functional component, the emotional area, the adaptive behaviours and "problem behaviours" manifested by the child in the family, social, educational and relational context.

From a number of approx. 240 members registered on the online parents of children with esophageal atresia support group, 38 of them fully responded to the entire questionnaire.

- The evaluated patients' ages vary between 5 and 17 years, with an average of 9 years and a median of 8 years. The 75th percentile is at 12 years, and the 25th percentile is at 5 years.
- The weight gain of children with a history of AE is obviously deficient compared to those in the general population.
- Parents' knowledge of associated anomalies in the context of AE seems to be questionable, 57% answering that their son/daughter does not associate other malformations, and of the entire group only 8% declare that they know of a congenital cardiovascular condition.
- More than half of the respondents (61%) report that the native esophagus was preserved in the reconstruction procedure for the malformation.
- 30% of patients had their primary esophageal reconstruction procedure performed in a country other than Romania.
- 39% of patients underwent an anti-reflux procedure at the time of the survey.
- A significant number of patients (26%) did not receive an endoscopic evaluation by this age.
- 43% of parents/relatives declare at the time of the interview that they no longer struggle with gastro-esophageal reflux disease (confirmed by a medical professional), and 13% do not know whether their son/daughter has gastro-esophageal reflux disease.
- 5% of children were diagnosed with asthma by the time of assessment.
- 31% of children have been hospitalized in the last 2 years for the treatment of pneumonia and 40% of parents state that their patient son/daughter "gets a cold" at least 4 times a year.
- 34% of parents report teeth erosions.

- 42% of parents say that they have to be careful what to feed their child to avoid choking.
- More than 10% still have an esophageal stenosis after 5 years of age.
- More than 15% of children complain of abdominal pain and more than 10% regurgitate or vomit at least once a month.
- In the studied population, there is a moderate-increased intensity of problems in the spectrum of anxiety, depression, parents and children coping with the condition, interpersonal relationships, self-esteem, stress, somatization, emotional control problems.
- The school performance score seems to have been a favourable result, but the dominant distribution of the preschool segment (5-7 years) in the studied group must be taken into account.
- The most affected psycho-social aspect of these children seems to be efficiency. This quantifies the implicative-emotional behaviour. The high score obtained in this aspect demonstrates that these children do not cope with the responsibilities of their chronological age at the level of socio-educational functionality. More than 70% of children say at least occasionally that they cannot complete an assigned task. This is a problem that could be deepened, and could easily be the expression of a difficult future socio-professional insertion.

The medical-surgical history that esophageal atresia entails, expressed by prolonged and repeated contact with the hospital, represents a major source of stress for children from the first day of life. In addition to the manifestations in the medical pathological sphere, their adaptation efforts can also be precipitated by the relationship with the family, respectively by the family's relationship with the doctor. Moreover, as children advance in age, they become increasingly aware of their surroundings and of the fact that they are "different from the rest", this being for sure a request for psychological observation of their development to avoid the occurrence of emotional disorders, behaviours, respectively a difficult socio-professional insertion. Undoubtedly, the evolution of childhood and adolescence of patients with a history of esophageal atresia is significantly loaded with several stress factors, associated with complications or anatomical traits in the malformation’s spectrum. The family, society, school or hospital seem to play a fundamental role in shaping the adaptive mechanisms that these children develop. These lead the patients - children, to the adopting adaptive mechanisms, their families playing a fundamental role in shaping them.

Case studies

Along this PhD thesis, certain messages are supported by case studies. By this, I wish this work to have also have a teaching side.

Four cases are brought into discussion:

1. Error in evaluation of the two esophageal ends
2. Kinking of the graft in the colon interposition esophageal reconstruction
3. Proximal esophagus esophagitis in esophageal-colic anastomoses made in the substitutive treatment of esophageal atresia
4. Delayed diagnosis of the trachea-esophageal fistula recurrence
5. Esophageal atresia associating duodenal atresia
6. Esophageal atresia associating congenital microgastria

Conclusions and personal contributions

Reflux esophagitis has an insidious character, being masked by children's adaptation to symptoms and the absence of a well-standardized follow-up system. In the absence of an early diagnosis, it becomes increasingly difficult to treat and predisposes to Barrett's esophagus in the long term, respectively an increased neoplastic risk whose causes are sealed from the moment of the primary esophageal anastomosis in the first days of life.

Multidisciplinarity and super-specialty are fundamental principles in the modern treatment of long-term esophageal atresia, but difficult to achieve in the absence of human resources.

Pediatric surgery, also in Romania, has passed into an era where access to medical information is done with great facility and speed, and the transport of patients to centers from all corners of the world can often be done easily. Today, most parents of children with complex malformations can obtain a significant amount of medical information from the Internet. Most of them do not have the necessary training to filter and discern information, although their demands are increasing. Thus, I have noticed more and more often a conflict between two different positions: the "traditional" doctor who is aware of the gravity of the disease, wants to save the child's life and avoid long-term complications, and the relative,

the parent who wants the best quality of life for the child, refusing from the start that he might or might remain "different" for a long time or for the rest of his life.

I believe that the doctor must know the limits to which his interventions with the aim of ameliorating certain residual clinical manifestations of esophageal atresia could be more harmful than good and I suggest a psychotherapeutic approach with the aim of feeding some adaptive and stress management mechanisms. All this, of course, alongside with meticulous long-term follow-up of potential health-altering complications.

This work could constitute an impetus for new research directions and for the creation of guidelines for complex and multidisciplinary postoperative monitoring of patients operated for esophageal atresia, with the aim of early detection of complications, and could be used as an essential argument for changing some methods of both medical-surgical approach and regarding the doctor-patient relationship.

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