REVIEW ARTICLE

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Congenital esophageal stenosis: a rare malformation of the foregut

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ABSTRACT

Congenital esophageal stenosis (CES) is a type of esophageal stenosis, and three histological subtypes (tracheobronchial remnants, fibromuscular thickening or fibromuscular stenosis, and membranous webbing or esophageal membrane) are described. Symptoms of CES usually appears with the introduction of the semisolid alimentation. Dysphagia is the most common symptom, but esophageal food impaction, respiratory distress or failure to thrive can be clinical manifestations of CES. Wide spectrum of differential diagnoses leads to delayed definitive diagnosis and appropriate treatment. Depends on hystological subtype of CES, some treatment procedures (dilation or segmental esophageal resection) are recommended, but individually approach is still important in terms of frequency and type of dilation procedures or type of the surgical treatment. Dysphagia can persist after the treatment and a long follow-up period is recommended. In 33% of patients with CES, a different malformations in the digestive system, but also in the other systems, are described.

Keywords: congenital esophageal stenosis, esophageal stricture, esophageal dilatation, infant, dysphagia

Abbreviations:
CES: congenital esophageal stenosis
TBR: tracheobronchial remnants
FMS: fibromuscular stenosis or fibromuscular thickening
EM: esophageal membrane or membranous webbing
EA: esophageal atresia

INTRODUCTION

Esophageal stenosis is a clinical condition defined as a fixed narrowing of the esophagus.

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This condition can be congenital or acquired. Congenital esophageal stenosis (CES) is manifested as an intrinsic narrowing of the esophagus present at birth.[1,2] Acquired esophageal strictures in children can be divided into the following categories: traumatic, inflammatory, peptic, and after surgery.[3,4] The incidence of CES is approximately 1 in 25000–50000 live births[5] with a slight predominance in males.[6] This congenital condition can be isolated[7] or associated with a different malformations.[1,6,8-23]

In order to examine this condition, we searched in both the library archive of our Faculty of Medicine and electronic medical and general databases, including the following keywords: "congenital esophageal stenosis", "esophageal stricture", "esophageal dilatation" in combination with "infant" and "child".

Development of the esophagus

The formation of the primitive digestive system is initiated by the establishment of the entodermal layer within the blastocyst (12 days of gestation). The primitive gut has a double layer (18–19 days of gestation) because the mesoderm divided into somatic and splanchnic mesoderm, becomes closely associated with the entoderm. In the 22nd day of gestation, two depressions are formed. One of them is located on the ventral side of the head (future oral region) and the other is caudally in the future anal region. Caudal to the oral opening and the future oral cavity, the foregut forms pharynx from which four pairs of diverticula (the pharyngeal pouches) arise laterally. By the end of the 1st month of gestation, digestive tube becomes narrowed distal to the pharynx and this segment forms the esophagus. Local dilation at the end of the primitive esophagus is the future stomach. The primitive esophagus is very short, but the stomach moves caudally during the development, and thus, the esophagus becomes longer. The tracheal outgrowth appears in the primitive foregut, at the level of the 4th pair of the pharyngeal pouch. By this concept, trachea and esophagus become separated organs after longitudinal dividing of tracheoesophageal foregut from caudal to cranial direction. Trachea extends from the common foregut tube as the lung buds grow, by one explanation, or both the trachea and esophagus elongate from the common foregut tube, by the other one. The most tracheoesophageal malformations could be explained by this interpretation.[24,25]

Nowadays, this theory is changed. The saddle-shaped ridge that separated the primitive esophagus from tracheal segment remains fixed at the level of the 1st vertebral body. From that point, the trachea and the future esophagus grow rapidly in a caudal direction.[26-28] Some methods of computer-assisted serial reconstruction of human developmental process, confirmed this concept.[29] (Fig. 1)

Kluth and Fiegel investigated the development of the foregut in the Adryamicin animal model and cited mechanical theories that emphasized the role of deviations of the septum between primitive esophagus and trachea, as well as inadequate recanalization after the "physiological occlusion" of the primitive esophagus, in some congenital malformations of the foregut.[30] Although theories and new animal models exist, the development of the foregut malformations has not been completely defined.

Types of CES and associated malformations

The first case report of distal esophageal membrane was described by Rossi in 1826[10] and two years later, Abel described the successful treatment of the congenital esophageal membrane.[31] The first report of tracheobronchial remnants in congenital esophageal stenosis (CES) was described when they were found at autopsy of a 19-year-old girl with the diagnosis of achalasia in 1936.[32] The first case of CES associated with esophageal atresia (EA) was reported in 1958.[33]

CES is divided into 3 pathohistological types: tracheobronchial remnants (TBR); fibromuscular

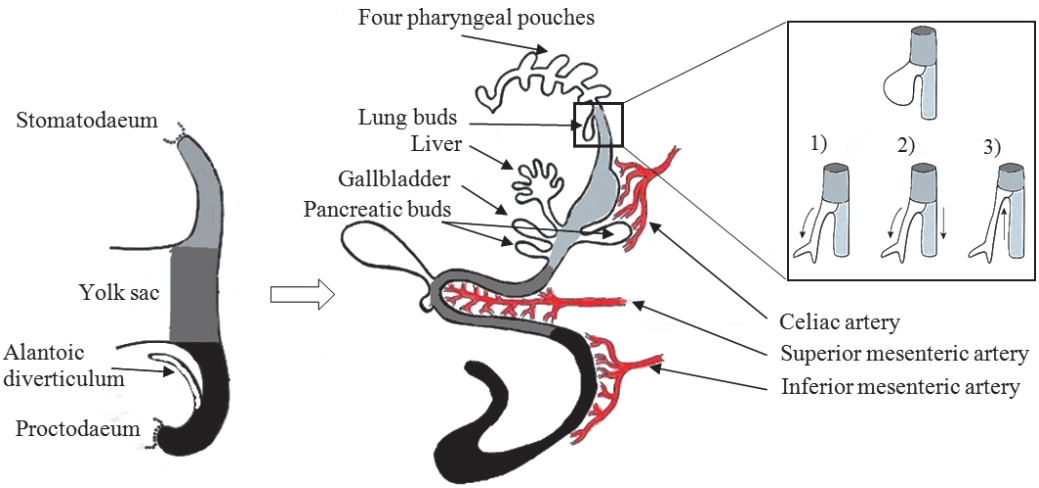

Fig. 1 Development of the esophagus in the primitive digestive tube (light grey – foregut; dark grey – midgut; black – hindgut)
1) Trachea extends from the common foregut tube as the lung buds grow 2) Both the trachea and the esophagus elongate from the common foregut tube and are separated by a mesenchymal septum; 3) Separation of the trachea and the esophagus starts from the level where the lung grows out and moves rostrally.

thickening or fibromuscular stenosis (FMS); and membranous webbing or esophageal membrane (EM).[34,35] The FMS and EM can be found together.[36]

There is no gender predisposition,[1,12,37] but some authors noted a slight predominance in males.[6] A higher incidence of CES has been observed in white populations.[5] There is only one report of familiar CES.[38]

CES resulting from TBR (choristoma or heterotopy[40]) is the most frequent cause of lower CES.[9,11,13,16,17,19,34] An ectopic cartilaginous ring or its part can be found in the upper esophagus, but in studies from Japan, cartilage was found usually within 3 cm of the cardia.[12,37,41-43] Singaram et al[44] noted the reduction of myenteric nitrinergic neurons in cases with TBR. Amae et al[34] speculated about related muscle layer disorders because of the muscular proliferation and disarrangement of the esophageal muscle fibers in TBR cases. They suggested classification of TBR as bronchopulmonary foregut malformation. Although authors speculate about TBR as a result of inadequate separation of the primitive esophagus of the foregut,[1,11,15,16,23,34,37,45] the exact mechanism for the occurrence of this disorder has not been fully clarified, especially after new insight into early esophageal development.

Histologically, TBR may contain cartilage, respiratory epithelium, or seromucous glands. In cases without cartilage, stenosis will not develop.[23,45] Ectopic respiratory epithelium (ciliated columnar epithelium) must be present in deep structures of the esophageal wall, and frequently, non-inflammatory lymphoid tissue ("lymphoepithelial bronchogenic tissue" by Ishida[37]) is found. Drainage through the esophagus in TBR may be mechanically obstructed by cartilage or significant lymphoepithelial tissue, or functionally by an aperistaltic segment.[12,37,45]

FMS is less frequent than TBR. It is a segmental hypertrophy of muscular and submucosal layers with a diffuse fibrosis.[1] Takayanagi[46] reports a case of FMS only with significantly thickened muscular layer and without other histological features of FMS. The stenotic segment is with dysmotility.[38,47] It is presumed that FMS may represent a disease linked to achalasia of the esophagus or Hirschsprung's disease. The reduction of myenteric nitrinergic neurons is described

in two cases of FMS. Prominent neutrophilic infiltrates as a potential cause of myenteric neural destruction, postulating that the FMS may be due to an autoimmune process. These suggestions have not been confirmed either in animal models or in human studies.[44]

EM has a normal squamous epithelium and muscular layer.[48-50] Webs are generally single, less frequently multiple,[48,50] associated with segmental stenosis.[36,49] Tedesco and Morlon[51] defined criteria for EM and differentiated it from other types of CES.

Only a few cases of multiple CES have been reported.[6,39] In 2001, Ramesh et al[52] suggested a new classification based on the type of stenosis and the association of esophageal stenosis with other anomalies of the foregut separation. By this classification, multiple stenoses were included, as the rarest type of CES.

EM mainly involves the upper or middle third of the esophagus, FMS the middle or lower third, and TBR mainly the lower third (within 1cm of the gastroesophageal junction).[2]

The reported incidence of CES associated anomalies is up to 33%.[1,13] Different congenital malformations associated with CES have been noted, but the most frequent one was EA with or without tracheoesophageal fistula.[1,8,9,11,13-23] Other malformations described in CES cases were: cardiac anomalies, microgastria, diaphragmatic hernia, intestinal atresia, duodenal duplication, Meckel's diverticulum, anorectal malformations, celiac disease, tracheoesophageal fistula, tracheomalacia, chromosomal anomalies (trisomy 21), vesicoureteral reflux, microphthalmus, Apert syndrome, palatal cleft, and hemangioma.[1,6,10-15,17,21,22]

Clinical manifestations and diagnosis of CES

Vasudevan et al[21] described an intrinsic stenosis in the middle part of the esophagus, duodenal atresia, duodenal web, ventricular septal defect and atrial septal defect diagnosed by a prenatal ultrasound scan. It is the earliest incidentally established diagnosis of CES.

Infants with CES usually tolerate breastfeeding, and start to present dysphagia (regurgitation and vomiting) with the introduction of semisolid or solid alimentation. This data is suspicion of some obstructive disorder.[1,5,12,17,36,47,49,53] Symptoms usually begin at the age of 4 to 10 months, but it depends on the severity of stenosis. Diagnosis is generally delayed and CES can be misdiagnosed until the second year of life.[7,35] Clinical sign of CES can be failure to thrive (Z-score weight for height < -2 SD[54]) or foreign body impaction,[5,7,15,49] but in some cases severe stenosis, hypersalivation, respiratory distress, stridor during feeding, chronic "allergic" cough, developmental deficits, regurgitation of liquids, aspiration pneumonia, even lethal pneumonia, can be noted.[5,22,23,43,55] During the follow-up of EA surgery, CES can be an incidental finding on esophagogram or during esophagoscopy.[2] Less frequently, CES may be suspected in neonates[1,5,36,38,47,56] or in adults.[47,48]

Atypical clinical presentation of CES is a diagnostic challenge. Pediatric dysphagia represents a wide spectrum of differential diagnoses (structural deficits, neurologic diseases, respiratory compromise, feeder-child interaction dysfunction, psychological problems, a numerous genetic, metabolic, and degenerative diseases).[3,57-59] The differential diagnosis of the esophageal stenosis, in general, includes gastroesophageal reflux disease, eosinophilic esophagitis, caustic ingestion, mediastinal irradiation, candidiasis, achalasia, longterm nasogastric intubation, and bullous skin disorders.[2]

In the study of Michaud et al,[54] patients with CES associated with EA were significantly younger at the time of diagnosis than were patients with isolated CES (7 vs 126 months). One third of patients with CES did not have any symptoms at the time of diagnosis, and the diagnosis was established during the surgical repair of EA or postoperatively, or the finding of CES was incidental. Vomiting, food impaction, and impaired growth were significantly more frequently observed in the group with isolated CES than in patients with CES associated with EA.

As the first diagnostic step, Savino et al[53] suggested to exclude the oropharyngeal causes of dysphagia. For this reason they primarily performed otorhinolaryngeal and neurologic evaluations. An indicative finding leads further to investigation through esophagography, endoscopy, pH probes, and esophageal manometry. The definitive diagnosis of CES and its types is possible by histopathology.[2,60]

In CES, the contrast study demonstrates segmental, concentric, usually short (0.5–1 cm) and smooth narrowing of the esophagus with a variable dilatation of its proximal part. Before this diagnostic method is employed, extrinsic compression, foreign body, and fistula should be excluded.[1,2] This method can identify 90% of esophageal stenosis.[54] The lateral view can be necessary sometimes.[48,49]

More than one radiological method is required because the barium swallow can miss the diagnosis or it can be misinterpreted. Mild CES can be interpreted as transient spasm, dysmotility, or esophageal narrowing due to reflux, so an additional diagnostic investigation should be performed if a clinical suspicion is present.[39]

The inability to pass the endoscope through the esophagus indicates stenosis,[6,61] but EM can be missed because small caliber endoscope can go through the web without noticing it.[48,62] The absence of signs of esophagitis (mucosal alterations) exclude causes as achalasia, peptic stricture or stenosis by caustic ingestion. The monitoring of pH and the esophageal manometry can differ stenosis from peptic strictures.[1,23,34,61,63]

Barium study can suggest the presence of TBR or FMS.[1] The endoscopic ultrasound can be used to differentiate FMS from TBR stenosis.[1,6,22] Nowadays, the endoscopic ultrasonography (EUS) is available for use in small children. Miniprobe performes through the endoscope, and evaluation of the esophageal wall at the stenotic level can distinguish FMS from TBR.[64,65] Takamizawa et al[6] used EUS in 5 cases of CES to distinguish TBR from FMS. In ultrasound findings cartilaginous structures were visualized as hypoechoic structures. Usui et al[64] described that, while the inside of a homogenous cartilage layer should be hypoechoic, the interface with other tissues may be hyperechoic. These differences may be caused by differences in the thickness of the cartilaginous structures and its interaction with surrounding tissues. In general, EUS finding of CES is presented as focal circumferential, hypoechoic wall thickening of the esophagus in the region of the stricture with disruption of the normal wall layers at this level[66] and can visualize a sonolucent area in the fourth layer that shows a cartilaginous component in the muscle layer. EUS may be useful diagnostically in confirming the diagnosis and differential diagnosis of CES, because biopsy of the esophageal wall may not be practical.

In a study of Michaud et al,[54] 8 out of 61 patients with CES underwent CT scanning and this method confirmed CES, but did not show any signs of TBR. CT scans may not always demonstrate the presence of the cartilage.

Histopathology confirms definitive diagnosis, but it is necessary to emphasize that resected esophageal tissue is not thick enough in every single case, for exclusion of TBR.[1,67] In TBR, this analysis should describe the presence of mature or immature cartilage, seromucous glands, and pseudostratified ciliated columnar epithelium, alone or in combination.[23,54] EM can be diagnosed by endoscopy. Histopathological finding in FMS is circumferential proliferation of the smooth muscle fibers and fibromuscular thickening. Besides this, in cases where TBR and EM are not confirmed, diagnosis of FMS is usually retained. It can lead to the overestimation of the FMS cases.[54]

In a study of Zhao et al[22] a delay of 2–2.5 years between the onset of symptoms and the diagnosis of TBR has been observed. The early diagnostic differentiation is very important because of the definitive appropriate treatment.

In the postoperative follow-up of atresia, special attention should be given to the control

contrasted study that may reveal CES early.[21] It should be emphasized that the absence of pathological esophagography finding does not exclude CES.[23,39]

Treatment of CES

During the diagnostic procedures, histological analysis is not always available. Due to the lack of histological verification of CES, most authors could not determine exact relationship between the treatment (dilation or surgery) and the type of CES.[1,7,9,11,13,14,16,17,19,20,34,37,42,46,54,61,62,68-78]

Both dilatation and surgery are treatments for CES. The possibility to carry out some procedure and effect of the chosen treatment depends on the pathologic features of the stenosis – its pathohistological type and severity of the CES.[34]

In patients with TBR, the resection of the esophageal stenotic segment followed by end-to-end anastomosis is the treatment of choice. Coloplasty was also used, but this treatment is not recommended anymore.[6,21,22,34,60] In this type of CES, dilation may be ineffective or result in esophageal perforation with serious complications[1,21,22,34] or lethal outcome.[11] Surgical treatment implies enucleation of the remaining cartilage, myotomy, and myectomy.[6,79,80] Diab et al described the resection of esophageal segment as long as 3 vertebrae with end-to-end anastomosis.[62] During the surgical procedure, the vagus nerve must be isolated to prevent its damage. Another important step is the identification of the cartilage ring by palpation or by endoscopic ultrasound. A balloon catheter is very useful in defining the boundaries of resection, that is, the distance between the teeth and the site of the stenosis, because the intraoperative macroscopic inspection or the palpation cannot locate the stenosis in every case.[6,7,34,79]

Recently, thoracoscopic resections of CES have been reported. Besides all benefits of the minimally invasive procedures, minimized esophageal dissection could prevent gastroesophageal reflux. It is reported that oral feeding started on postoperative days 6–7.[81]

In cases with CES located in the distal esophagus, (Nissen) fundoplication is recommended and it was associated to the procedure to prevent gastroesophageal reflux and protect the suture.[34] Nowadays the preference is more towards partial fundoplication, if indicated. Surgical treatment has low morbidity and mortality in comparison with dilation.[22]

The endoscopic dilation should be the first-line treatment in CES without cartilage.[1,16,23] Patients with EM (the rarest type of CES) are treated successfully with dilatation.[5,48,75-78] In the study of Michaud et al,[54] dilation was effective in 38% of patients without the need for surgery and without causing any complications. Authors emphasized that they did not perform histological analysis, so they could not exclude the possibility of patients with TBR being among the patients who underwent dilation. Savary bougienage and balloon dilation, as dilation methods, were performed under general anesthesia. The choice of dilation technique depends on personal experience and preference of a specialist. The range of the number of dilation procedures number was 1 to 11. They noted 66% of patients with persistent symptoms even after surgery. Dysphagia was persistent in the period of as long as 1–18 years. The authors suggested that patients with CES should be followed over the long term.

For the purpose of finding the appropriate balloon catheter size, the "rule of thumb" guide (the size of the patient's esophagus is approximately the size of the patient's own thumb) is used.[82] Lan et al[83] empirically adopted the rule of not increasing the diameter of the balloon catheter by more than one catheter size up (2–3 mm in diameter) for each next dilation. This rule reduced their treatment failure rate to less than 3%, while this rate in other series was up to 33%. By using an uniform radial force, balloon dilatation can provide a more effective and less traumatic dilatation of esophageal stenotic segment, compared with bougienage.[84] The frequency of dilation procedures is individualized, as well as optimal period between procedures. The endoscopic balloon dilation has many advantages: the esophageal mucosa and stenotic segment can be visualized

directly; the catheter can be inserted to assess the effectiveness of dilation; the possible bleeding can be evaluated; and exposure to radiation is avoided. The complications of dilation methods as recurrent stenosis, bleeding, sepsis, mediastinitis, esophageal perforation, aspiration pneumonia, and cardiac arrest, were reported.[1,19,72,83,85-92] Unnecessary or overenthusiastic repetition of dilation may be a cause of complications, and Amae at al.[34] suggested that surgical intervention should be considered if the first dilation failed to achieve expected results. Persistent dysphagia may be consequence of dilation failure, but it can also be related to esophageal dysmotility observed in patients with CES regardless the type or associated EA.[54,63]

According to Terui et al,[93] efficacy of endoscopic dilation with radial incision of the web, in cases of EM, has been reported. Instruments for incision include electrocoagulation, high-frequency-wave and laser. Nose et al[94] used balloon catheter for pulling up the web from the distal part during incision. Complications during these procedures have not been reported.

Takamizawa et al[6] emphasized that balloon dilation is the treatment of choice for patients with EM and that esophageal dilation is effective for most patients with FMS. Besides that, they recommended that if dilations are required within 6-month intervals and remain ineffective after 3 years, surgical intervention should be undertaken. Suzuhigashi et al[95] noted that all cases of perforation by balloon dilatation were recognized in FMS patients.

Bacteremia was noted after esophageal dilation in some studies.[96-100] Not common, but serious complication of dilation procedures can be brain abscess. Isolated organisms belong to the normal oropharyngeal flora in these cases.[101] Peri-esophageal venules interconnect with vertebral veins so that blood may be forced into the brain in a retrograde direction.[102] Transient bacteremia can be induced by disruption of the esophageal mucosa with arterial seeding into the brain.[103] In children, immunosuppresion due to steroid therapy and state of chronic dehydration because of decreased fluid intake due to the esophageal stricture, facilitate the formation of abscess.[101]

Recent studies described using of Mitomycin C for the treatment of esophageal stenosis. Mitomycin C is an alkylating antibiotic used as an antineoplastic and antiproliferative agent.[104] Local application in duration of 2 min, in concentration from 0.1 to 1 mg/ml, and with repetition up to 12 times (mean 3.5) was noted. If Mitomycin C was applied more than once, interval periods ranged from 1 to 12 weeks. The treatment is very successful (over a 80% success rate) but it is noted only in acquired esophageal stenosis, particularly in postoperative strictures after surgery of the foregut malformations.[105] Local or systemic side effects of Mitomycin C are not described,[106] but also no randomized controlled trials and no prospective studies were found.[105]

Stenting of esophageal stenosis should be considered in children with fixed esophageal strictures that have failed medical and endoscopic treatment and by 2005, the use of silicon-coated nitinol stents had reached the pediatric population.[107] A case report of the use of a biodegradable esophageal stent in the treatment of a corrosive esophageal stenosis was published.[108] Esophageal stenting is combined with dilations, as a treatment. Migration of the stent was the most commonly cited complication of placement, reported in 5% to 29% of patients. Minimizing the risk for stent migration in the lowest part of esophagus could be achieved by allowing the bottom of the stent to protrude into the stomach. The decision to proceed with stenting as a therapeutic option depends on a variety of factors, including location of the stricture, frequency of required dilations, number of strictures present, age/size of the child, and maturity of the stricture, in cases of acquired stenoses. Manufacturer guidelines generally recommend stent removal in 4 to 6 weeks. In patients with acquired esophageal stenosis, corticosteroid injection and use of mitomycin C application at the stricture site may have been attempted in order to decrease or eliminate the need for repeated dilations during the treatment with stent.[109]

Stenting can reduce both the number of dilations and the treatment length. In many cases, this strategy is effective when either metallic or plastic stents are utilized. Treatment complications,

such as esophageal perforations, can be conservatively managed, considering surgery only in cases with severe complications.

Recommendation

CES is condition with undefined incidence. Some case reports or review articles do not emphasize pathohistological types of described CES. It is necessary to start with systematical monitoring of this condition. Because of the rarity, possibility of CES is often neglected that leads to delayed diagnosis and treatment. Cases with fewer clinical symptoms may remain undiagnosed. Only multicenter systematic analysis of CES, from diagnosis to treatment, with detailed description of follow-up period, could help in standardization of protocol for the most successful treatment. Nowadays the treatment of CES mostly depends on experience and personal opinion of specialists. Individual approach could be applied in some exceptions, but standard protocol for early diagnosing and treatment of CES could improve the patient's condition after the treatment.

In order to easier achieve standard protocol for diagnosing and treatment of CES, the most important facts about CES from available literature are summarized in Fig. 2.

CONCLUSION

The diagnosis of CES is delayed because the disease is a very rare condition. Every single case suspicious of CES, even from prenatal examinations, should be analyzed in the center of expertise. Keeping in mind the possibility of CES when an infant suffers from repeated vomiting, dysphagia, respiratory distress, or has a failure to thrive, is very important. Conducting contrast studies of the upper gastrointestinal tracts is helpful in making a differential diagnosis. The definitive diagnosis of CES and its types is necessary for appropriate treatment, but also because of the possibility of different concomitant malformation findings. Minimally invasive surgery for TBR cases should be performed at competent centers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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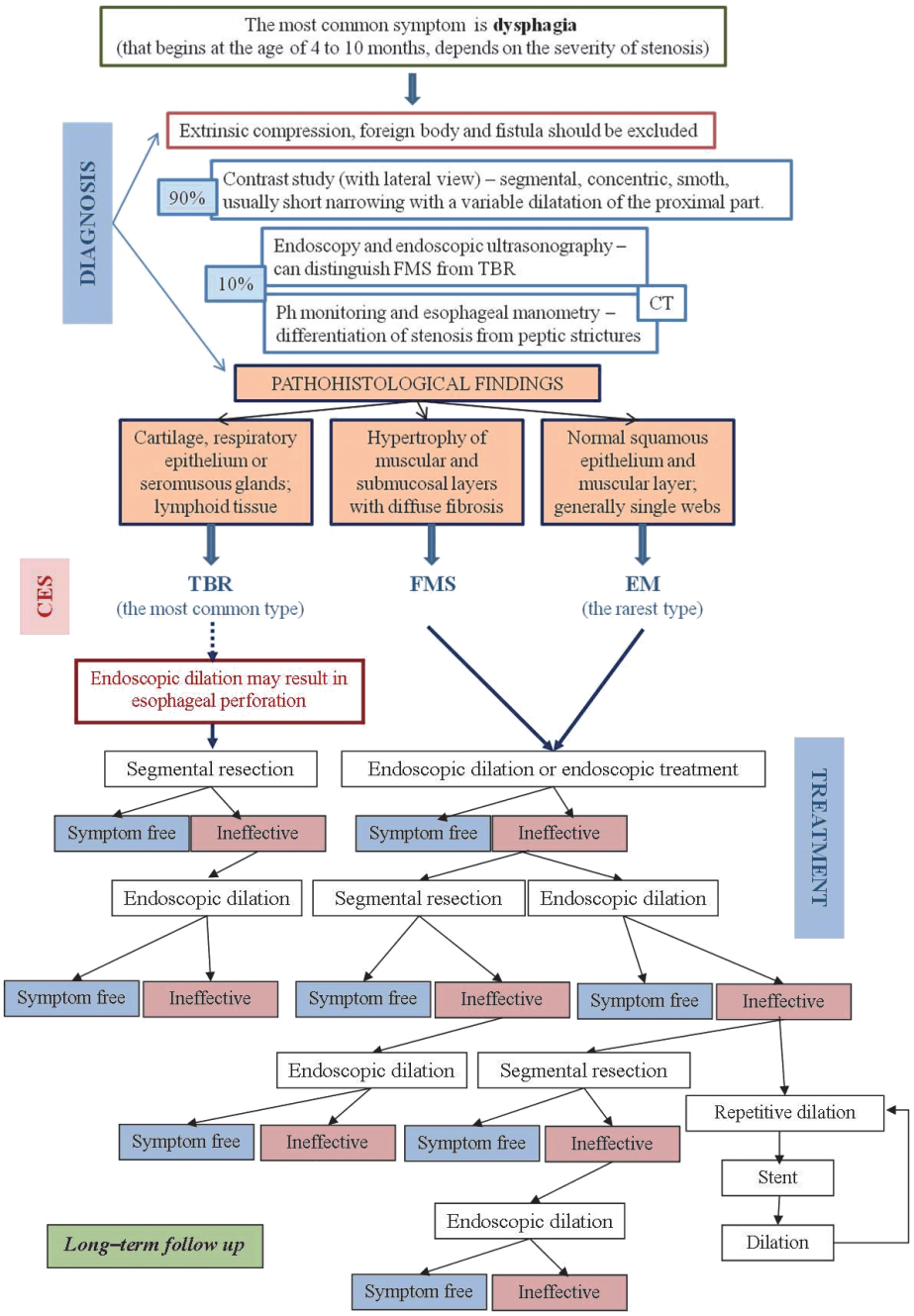

Fig. 2 The most important facts about congenital esophageal stenosis (CES) – from symptoms to treatment, with flow chart of CES treatment

TBR: tracheobronchial remnants, FMS: fibromuscular thickening or fibromuscular stenosis, EM: membranous webbing or esophageal membrane.

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