Workshop booklet

FIRST INTERNATIONAL WORKSHOP ON ESOPHAGEAL ATRESIA

May 27-28, 2010 - LILLE, France

Auditorium
Le Nouveau Siècle
8, Place Pierre Mendès France

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Acknowledgements

The organizing committee wants to thank for their supports:

Conseil régional Nord-Pas-de-Calais

RÉGION Nord-Pas de Calais

Ville de Lille

Ville de Lille

Université de Lille 2

Ministère santé DHOS

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Welcoming message

We are pleased to welcome you to the 1st International Workshop on Esophageal Atresia in Lille. In the framework of the French National Plan for Rare Diseases, our centre has been appointed as the French Reference Centre for Congenital and Malformative Diseases of the Esophagus in 2006. Rare diseases are also one of the priorities in the second program of Community action in the field of Health (2008-2013) of the European Union that promotes exchange of information and transnational cooperation.

Esophageal atresia is indeed a rare disease with an incidence of 1/3000.
Recent advances in surgery and neonatal care have provided a better prognosis, the survival rate of infants born with esophageal atresia has dramatically improved over the last decade, increasing from 80% to more than 95%. Esophageal atresia is definitely not only a neonatal surgical issue but a long lasting disease through adulthood since many problems (growth, respiratory, digestive, feeding difficulties) persist on the long term.

The aim of this workshop is to address the most recent questions and challenges for the future. It will gather among the best European and North American specialists in the field who will cover a wide range of themes from epidemiology, neonatal screening, surgical challenges, digestive and ENT/respiratory aspects to psychosocial aspects and roles of patients' associations. We will save time for discussion and presentation of original studies.

The workshop will be held in Lille, a city which is ideally located in the heart of Europe (Brussels airport is at 35 minutes by train, Paris Charles de Gaulle Airport at 50 minutes, London 2 hours by train, Frankfurt 5 hours). Lille is also a historical city under medieval and Flemish influence, rich in museums, theatres and restaurants. The congress will take place in the very centre of the city close to all the facilities.

We hope you will enjoy the meeting.

Frédéric Gottrand,
President of the organizing committee

Summary

May 27th

9:00 Welcome address, introduction

F. Gottrand, Department of Pediatrics, University of Lille 2
Pr D. Gosset, Dean of the Faculty of medicine, University of Lille 2, Madame C. Faye et Mr R. Bertrand, Jeanne de Flandre Hospital, Lille France

Embryology - environmental factors Chairs: *R. Besson and S. Lyonnet*

9:30 Molecular embryology of the foregut
P. De Santa Barbara, Muscles and pathologies – INSERM - Montpellier France

10:00 Environmental factors in the etiology of esophageal atresia
J. Oddsberg, Unit of Esophageal and Gastric Research – Karolinska Institute - Stockholm Sweden

10:30-11:00 Coffee break - Visit of exhibition and epidemiology, genetics posters

Genetics - prenatal diagnosis Chairs: *A. Coran and M. Holder*

11:00 Genetic factors in isolated and syndromic esophageal atresia
S. Lyonnet, Department of Genetics, University Paris Descartes, Necker Hospital - Paris France

11:30 Ultrasound and MRI prenatal diagnosis of OA: impact on management
V. Houfflin Debarge & J. Bigot, Departments of Obstetrics and Radiology, Jeanne de Flandre Hospital, Lille France

Conference Chair: *R. Sfeir*

12:00-12:30 Esophageal atresia treatment: a perspective in the 21st century
L Spitz, Department of Pediatric Surgery, Institute of Child Health, London UK.

12:30-13:30 Lunch

13:30-14:00 Visit of exhibition and surgery posters

Challenges in surgical procedures-anastomotic strictures

Chairs: *E. Hassal and S. Sarnacki*

14:00 Challenges in surgery: thoracoscopic treatment and long gap
DC. Van der Zee, Department of Pediatric Surgery, Wihelmina Children's Hospital, Utrecht Netherlands

14:30 Tissue engineering
P. Cattan, Department of Digestive and Endocrine Surgery, Saint-Louis Hospital, Paris France

15:00 Anastomotic strictures: conservative treatment
F. Gottrand & L. Michaud, Department of Pediatrics, Jeanne de Flandre Children's Hospital, Lille France

15:30-16:00 Coffee break - Visit of exhibition and gastroenterology posters

Endoscopic features-gastro-esophageal reflux Chairs: *T. Lamireau and G. Podevin*

16:00 Endoscopic features in EA patients, birth to adulthood
C. Faure, Department of Pediatrics, St Justine Hospital, Montreal Canada

16:30 The new definitions of Barrett's esophagus: different types of columnar metaplasia, identification and significance in EA
E. Hassall, Division of Gastroenterology, British Columbia Children's Hospital, Vancouver Canada

17:00 Gastro-esophageal reflux: surgical options
P. de Lagausie, Department of Pediatric Surgery, La Timone Children's Hospital, Marseilles France

May 28th

Extra-digestive complications Chairs: *R. Epaud and MD. Lamblin*

8:30 Abnormal pharyngo-oesophageal function in infants and young children: diagnosis with high resolution manometry
N. Rommel, Neurogastroenterology Clinic, Gasthuisberg University Hospital, Leuven, Dept Neurosciences, Exp ORL, University of Leuven, Belgium

9:00 Pulmonary outcome
C. Delacourt, Unit of Pediatric Pulmonology, Necker Hospital, Paris, France

9:30 Management of severe tracheomalacia
P. Fayoux & R. Sfeir, Departments of ENT and Pediatric Surgery, Jeanne de Flandre Children's Hospital, Lille France

10:00-10:30 Coffee break - **Visit of exhibition and ENT, pneumology and fistula posters**

10:30-12:00 Oral presentation of selected posters Chairs: *P. de Lagausie and C. Faure*

12:00-13:00 Lunch

13:00-13:30 Visit of exhibition and outcome posters

Outcome Chairs: *L. Storme and D. Seguy*

13:30 Outcomes of esophageal atresia beyond childhood
RJ. Rintala, Department of Pediatric Surgery, Hospital for Children and Adolescents, Helsinki, Finland

14:00 Multidisciplinary clinics: how to improve the follow-up of the patients?
D. Lévesque, department of pediatrics,Gastroenterology service, Montreal Children's Hospital, Montreal University Health Center, Canada

14:30 Family support groups: an essential contribution to follow-up care
European and Australian family support groups

15:15-15:45 Summary of the workshop and perspectives Chair: *F. Gottrand*
A. Coran, Professor of Surgery, University of Michigan Medical School and C.S.Mott Children's Hospital, Ann Arbor, Michigan, USA

May 27th

Embryology - environmental factors

Molecular embryology of the foregut

P. de Santa Barbara, Muscles and pathologies – INSERM ERI 25- 34295 Montpellier France.

The gastrointestinal (GI) tract is a remarkably complex, three dimensional, specialized and vital organ system derived from a simple tubal structure. The vertebrate GI tract includes the luminal digestive system of the oesophagus, stomach, intestines, and colon (which we will designate as «gut») and the GI tract derivatives - thyroid, lungs, liver, and pancreas. The gut is composed of the three germ layers - mesoderm (which forms the smooth muscle layer), endoderm (which forms the epithelial lining), and ectoderm (which includes the enteric nervous system). Originally, the gut develops from two invaginations at the anterior (anterior intestinal portal, AIP) and posterior (caudal intestinal portal, CIP) end of the embryo, which elongate and fuse to form a straight tube. The primitive gut tube is initially patterned into three broad domains along its anterior-posterior (AP) axis: the fore-, mid- and hindgut. As they develop, each region of the gut is characterized by unique mesodermal and endodermal morphology, which can easily be discerned by gross and microscopic examination. These tissues show regionally specific differentiation along the AP axis designating the pharynx, esophagus, and stomach (the foregut), small intestines (the midgut), and large intestines (hindgut). This regionalization that are maintained throughout life is essential and necessary for the normal adult gut function. These patterning events are remarkably conserved across species (Roberts, 2000); anomalies in these events are likely to be to be responsible for many of the human gut malformation syndromes (as tracheoesophagal atresia, infantile hypertrophic pyloric stenosis or anal atresia) (Geneviève et al., 2007; de Santa Barbara et al., 2002).

The lung and the gut are two independent systems that originated from one common embryonic organ, the foregut. The development of the foregut is not well-documented compare to the other part of the digestive system. We know that the origin of the respiratory system comes from the formation of an endodermal diverticulum in the ventral wall of the foregut, whereas the esophagus forms from the dorsal wall. At first stage, the trachea and the esophagus separate by a process of septation and elongation. After the formation of the mesenchymal septum, the separation of the respiratory tract from the esophagus is definitive. Finally, the formation of full trachea seems to form from a process of tracheal budding and endodermal proliferation.

Candidate factors for foregut development include known pattern formation genes first identified in Drosophila. These include nuclear homeotic transcription factors (HOX, SOX and NKX factors) and secreted factors (BMP and Hedgehog factors) (Smith et al., 2000; Ramalho-Santos et al., 2000; Moniot et al., 2004; Que et al., 2007; Que et al., 2009). Genetic evidence from different animal models indicate that these factors play multiple and crucial roles in the development and the septation of the trachea and esophagus.
To better understand the molecular basis of human malformation and syndromes as tracheoesophagal atresia, it is essential to better understand normal development at the molecular level and to develop translational research between scientists and clinicians.

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Environmental factors in the etiology of esophageal atresia

J. Oddsberg, Unit of Esophageal and Gastric Research – Karolinska Institute - Stockholm Sweden

The etiology of EA is mainly unknown. Data from family and twin studies suggest that hereditary factors do not play a major role in the etiology of EA.1 Environmental risk factors thus seem to be important. Only a few environmental exposures of the pregnant mother have been investigated in relation to the risk of EA. They are summarized as follows:

Parity Several studies have shown that low maternal parity increases the risk of EA in the offspring.2 It has been speculated whether an increased risk of EA with low parity might be linked with fertility problems.3
Maternal age Very contradictory results have been reported regarding the correlation of maternal age to the risk of EA in the child. Our group has conducted a large, population-based study providing support for an increased risk of EA with older maternal age. The association remained when the analysis was restricted to cases without chromosomal abnormalities.2 Both age and parity may be indicators of a role of endocrine or other biological mechanisms in the etiology of EA.

Ethnicity Maternal ethnicity seems to influence the risk of having an infant with EA, with an increased risk among Caucasian women.2 An increased risk in this ethnic group might reflect differences in environmental risk exposures, as well as differences in genetic predispositions, triggered by environmental risk factors.
Drugs Few studies have assessed the role of drugs in the etiology of EA. A relation between maternal use of exogenous sex hormones during early pregnancy and risk of EA in the infant has been suggested.4 A potential link between maternal exposure to the hyperthyreosis medication methimazole and EA has also been reported, 5 but except for one smaller cohort study, 6 this potential association is mainly addressed in case reports. Further studies with more valid study design have to be undertaken to investigate this potential association.
Herbicides or insecticides One study has shown an association of borderline significance between contact with herbicides or insecticides during pregnancy and risk of EA in the infant.7

Tobacco smoking and alcohol There are three case-control studies addressing the role of maternal tobacco smoking in the risk of EA. No increased risk of EA with maternal smoking was found overall. 7-9 In one of the studies, an increased risk of EA with associated anomalies was found in a subgroup of smokers. Combined exposure of maternal tobacco smoking and alcohol further elevated some of the relative risks.8

Obesity A systematic review and meta-analysis has been published showing an increased risk for a range of birth defects with maternal obesity. Regarding EA, however, no association was found in an analysis based on 222 cases.10 During the same time period we conducted a large population-based study supporting the lack of any association between maternal obesity and risk of EA.9

Socioeconomic status The literature describing socioeconomic status inequalities with respect to EA have been sparse and hampered by limited statistical power. We conducted a study using educational level as a marker of socioeconomic status, that contradicts an increased risk of EA in women of low socioeconomic status.9

Diabetes Associations between diabetes and gastrointestinal malformations have been seen in some studies, but not in others.11 Results of a recent, larger, case-control study suggested that women with pre-existing diabetes had an increased risk of delivering a child with EA associated with other malformations, but not isolated EA.12 We have conducted a large, population-based case-control study including 780 infants with EA born in Sweden during the period 1982-2007, in which there was a 70% higher risk of EA in infants of women with any type of diabetes (preexisting or gestational) during pregnancy compared to those of women without diabetes (unpublished data).

Epidemiological studies of exposures during pregnancy and the risk of birth defects in the infant often reveal weak to moderate associations. Weak relative risks could be the result of the occurrence of biological interactions.13 A first step is to identify exposures that increase the risk to subsequently identify other factors that explain why only some of those exposed are affected. There remains much to be known about environmental risk exposures affecting the risk of EA in the infant. Studies of interactions between different environmental exposures might be a second step. Gene-environment interaction studies for birth defects are evolving. Collaboration between geneticists and epidemiologists with an interest in environmental risk factors could be the future that could make true progress in our knowledge in the etiology of EA.

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An overview of isolated and syndromic œsophageal atresia

Geneviève D, de Pontual L, Amiel J, Sarnacki S, Lyonnet S. An overview of isolated and syndromic oesophageal atresia.Clin Genet 2007: 71: 392–399. © Blackwell Munksgaard, 2007

Oesophageal atresia (OA) and/or tracheo-oesophageal fistula (TOF) are frequent malformations observed in approximately one in 3500 births. OA/TOF can be divided clinically into isolated OA (IOA) and syndromic OA (SOA) when associated with other features, the most frequent being cardiac, limb and vertebral malformations or anal atresia. SOA is observed in 50% of patients and can be subdivided into several causative groups comprising environmental agents, chromosomal disorders, malformative associations (CHARGE syndrome and VATER/VACTERL association), and other multiple congenital anomaly disorders. The observation of chromosomal disorders with SOA, as well as mouse models of OA provide support for the involvement of genetic factors in OA. Yet, epidemiological data (twin and family studies) do not support the major role of genetic factors in the majority of cases of IOA but rather a multifactorial model. However, several genes involved in SOA have been recently identified, namely N-MYC, SOX2, and CHD7 involved in Feingold (MIM 164280), anophthalmia-oesophageal-genital (MIM 600992) and CHARGE syndromes respectively (MIM 214800), suggesting that OA/TOF, at least in their syndromic forms, may be a highly genetically heterogeneous group.

Oesophageal atresia (OA) is a frequent congenital malformation (1/3500 births) characterized by a discontinuity of the lumen of the oesophagus. OA is distinct from oesophageal stenosis that usually occurs in childhood or early after birth in dyskeratosis congenita (MIM 127550, 305000 and 224230) and epidermolysis bullosa (MIM 226730). Tracheo-oesophageal fistulae (TOFs abnormal connection between the oesophagus and the tracheobronchial tree) should be also considered as an incomplete form of OA. Embryological studies have shown that the respiratory diverticulum appears at 4 weeks postconception in the ventral wall of the foregut and is then split into a ventral portion (from which the respiratory tract develops) and a dorsal portion that gives rise to the oesophagus. How the tracheo-oesophageal cleavage occurs remains questionable, as it may involve either an apoptotic fusion of the lateral walls of the foregut (1, 2) or the formation of a tracheo-oesophageal septum arising from fusion of longitudinal ridges within the lumen of the foregut (3).
OA is divided into five anatomical subtypes based on the location and type of anastomosis between trachea and oesophagus (Fig. 1) (4). To our knowledge, no difference in developmental origin could be identified for each of the five subtypes (5). OA type C is by far the most frequent (around 85% of OA) (6). No developmental explanation for the overrepresentation of type C has been identified yet and to date, no correlation between a clinical subtype of OA and specific genetic disorders has been established.
OA has been divided into two different forms: isolated OA (IOA, 50%) and syndromic OA (SOA, 50%). The most frequent associated malformations are cardiac (13–34%), limb (5–19%), renal (5–14%) and vertebral malformations (6–21%), as well as anal atresia (10–16%) (7–9). Epidemiological studies do not support the existence of strong genetic factors in IOA [for review, see Shaw-Smith (10)]. In IOA, recurrence risk is estimated to 1% and twin concordance rate is low inOA(2.5%). In SOA, however, first-degree relatives are more likely to present malformations of the VACTERL spectrum (11). Several disease genes involved have been recently identified namely N-MYC, SOX2, and CHD7 in Feingold syndrome (FS, MIM 164280), anophthalmiaoesophageal-genital (AEG, MIM 600992) syndrome and CHARGE syndrome, respectively (MIM 214800). Moreover, mouse models (12) and chromosomal anomalies support the involvement of genetic factors in OA. In this review, we focus on clinical presenting symptoms as entries into syndromic forms of OA. We also discuss on the molecular mechanisms involved in OA.

Isolated oesophageal atresia In IOA, the sex ratio is balanced with a mild excess of men (7–9). Offspring risk studied in a series of 79 patients with OA averages 1% and the recurrence risk in sibs is low [1/130 affected sib in a series of 79 patients with OA/TOF (13)]. Very little is known regarding the cause of IOA. It has been observed rarely as an isolated feature in maternofoetal intoxication such as maternal diabetes and to our knowledge, no murine model has been hitherto described. Taken together, these scarce data do not support heritability of

IOA. Syndromic oesophageal atresia Aetiologies of SOA are summarized in Table 1. Conditions frequently associated with OA Chromosomal anomalies The incidence of trisomies and other chromosomal rearrangements averages 6–10% in SOA. Interestingly, the most frequent chromosomal anomalies observed in OA/TOF are complete (trisomy 13, 18, 21,mosaic trisomy 8 and triploidy) (7–14) or partial trisomies (dup 1q32-qter, dup 2q, dup 5q, dup 7p and dup 12q) (14). A few recurrent chromosomal deletions are reportedly associated with OA/TOF, namely 17q21.3-q23 and 22q11.2 deletions (15–17) and rarely 13q13-qter and 5p deletions (14). Patients with the 13q13-qter deletion present with multiple congenital anomaly (MCA) resembling the VACTERL association (cf VATER/VACTERL section). An interstitial 17q21.3-q23 deletion has been reported in three patients with OA with microcephaly, mental retardation, facial features, minor hand anomalies (symphalangism and proximal thumbs) and abnormal cranial imaging (15). OA/TOF has also been occasionally observed in patients with an interstitial 22q11.2 deletion (DiGeorge syndrome) (16, 17). Finally, the recent observation of a reciprocal 6;15 translocation in a patient with OA and mental retardation points towards the likely involvement of the BPAG-1 gene, coding for a hemidesmosomal protein (belonging to the plakin family originally identified as one of the major autoantigens of bullous pemphigoid) and suggests BPAG-1 as a candidate gene in OA (18).

VATER/VACTERL association

OA/TOF is a frequent feature in VACTERL syndrome. The VATER/VACTERL association (MIM 214800) is a non-random condition including vertebral defects, anal atresia, TOF and radial aplasia (Fig. 2) (19, 20). This acronym has been extended to VACTERL, to include cardiac, renal and limb (radial ray) defects with an upper' subtype when heart malformations are present and a lower' subtype when renal malformation are present (21). The difficulty of this diagnosis consists in the absence of specific features or solid diagnostic criteria. Another pitfall is the existence of several well-known genetic disorders mimicking or partly overlapping, the VATER/VACTERL phenotype, especially the 13qter and 22q11.2 deletions, maternal diabetes, mitochondrial DNA mutations (22, 23), the oculo-auriculo-vertebral spectrum (OAVS), the Fanconi anaemia (FA), the Opitz G/BBB syndrome or Mullerian duct aplasia, unilateral renal aplasia, and cervicothoracic somite dysplasia association (24, 25).

Feingold syndrome

OA is a frequent feature in FS (also named oculo-digito-oesophago-duodenal syndrome,MIM 164280), an autosomal dominant condition characterized by the association of OA to microcephaly, mild life-long learning disability and brachymesophalangy of the second and fifth fingers (Fig. 3) (26). The disease is caused bymutations of the third exon of the MYCN gene (27), a member of the myelocytomatosis viral oncogene (MYC) transcription factor family involved in the regulation of transcription, cell cycle, and cell differentiation and metabolism (by regulation of all three RNA polymerases). Moreover, MYCN coordinates morphogenesis by acting as a downstream target of the SHH, WNT, TGF and FGF signalling pathways [see Hurlin (28) for review].

Rogers/AEG syndrome

OA is also frequently observed in Rogers syndrome, also named AEG syndrome (MIM 600992), a rare autosomal dominant disorder characterized by the association of OA to ocular anomalies (anophthalmia, microphtalmia, lens abnormalities, and optic nerve malformation), genital abnormalities, vertebral defects and cerebral malformations. Mutations in the SOX2 gene are responsible for this condition (29) as well as for some cases of isolated microphtalmia, anophtalmia or coloboma (30).

Maternal diabetes. Children born to insulindependent diabetic mothers have a twofold to threefold increased risk of congenital malformations including OA (31). OA is a rare feature in maternal diabetes and is occasionally observed as a malformation on its own. Similarly, the Foetal alcohol syndrome (FAS) is a frequent cause of mental and growth retardation. It has been estimated that 1/30 pregnant women abuse alcohol and that largely 6% of them have children with recognizable FAS (32). OA is occasionally observed in FAS (33). Other frequent features observed in FAS are microcephaly, hyperactivity and irritability in infancy, heart malformations and characteristic facial features. The malformations in FAS have been correlated to pre-mature cell death because of inhibition of the sonic hedgehog (SHH) pathway. (34, 35).

Maternal phenylketonuria (MIM 261600). Phenylketonuria (PKU) is an inborn error of metabolism resulting from a deficiency of phenylalanine hydroxylase and characterized by mental retardation. Maternal PKU is usually because of mild undiagnosed PKU in pregnant mothers. Patients born to affected mothers present with intrauterine and postnatal growth retardation, microcephaly, congenital heart disease, craniofacial abnormalities, and minor hand malformations. OA is a rare feature of maternal PKU. Similarly, foetuses exposed to methymazole (carbimazole) during pregnancy present with aplasia cutis, absent nipples, choanal atresia and occasionally OA (36).

CHARGE syndrome

The CHARGE syndrome (MIM 214800) refers to an association of MCA including ocular coloboma (C), heart disease (H), choanal atresia (A), retarded growth and/or anomalies of the central nervous system (R), genitourinary defects and/or hypogonadism (G), and ear anomalies and/or deafness (E). Other diagnostic criteria include semicircular canal agenesis which is now regarded as major diagnostic criteria in CHARGE syndrome (37). OA is not a frequent feature in CHARGE syndrome and is observed in between 10% to 17% of patients (38, 39). Mutations in CHD7 are responsible for this condition (40). CHD7 belongs to a large family of evolutionarily conserved helicaseDNA-binding proteins, thought to play a role in chromatin organization. It has been hypothesized that this family of proteins protects the chromatin fibre from changing its epigenetic state (41).

Opitz G/BBB syndrome

Opitz G syndrome (MIM 300000) is characterized by the association of midline abnormalities (such as cleft lip/plate, hypertelorism, laryngotracheal cleft, heart defects, and hypospadias) with mental retardation and agenesis of the corpus callosum. Two modes of inheritance have been described in Opitz G syndrome. Mutations in the MID1 gene are responsible for the Xlinked form, whereas the autosomal dominant form has been mapped to chromosome 22q11.2 (42). OA is a rare feature of G syndrome (43). Among G/BBB syndrome patients, few have been described with 22q11.2 deletion (44–46). Molecular studies in these patients demonstrate that the size of the deletion does not differ from the deletion observed in DiGeorge syndrome and velocardiofacial syndrome (44). To date, molecular studies could neither explain the clinical variability in patients with 22q11.2 deletion nor the apparent random presence of the OA/TOF.

Fanconi anaemia

FA (MIM 227650) is a rare autosomal recessive disorder affecting all bone marrow elements and associated with cardiac, renal and limb malformations as well as dermal pigmentary changes. Gastrointestinal atresia has been reported in 14% patients with FA (47). However, OA is a rare feature of FA and is usually observed when FA presents as VACTERL in association with hydrocephalus (VACTERL1H). Both Xlinked and recessive forms of FA/VACTERL1H have been described (48, 49). Chromosome breakage studies should be performed in patients with VACTERL1H phenotype or when OA is associated with features resembling FA (i.e. cafe´ au lait spot, microcephaly, and growth retardation), especially because of the susceptibility to cancer in such patients (50). An X-Linked gene (FANCB) and 10 autosomal recessive complementation group genes have been described in FA (FANCA, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCJ, FANCL, and FANCM). The VACTERL phenotype appears to be overrepresented in the FA complementation groups D1, E, and F (50). In addition, mutations in the FANCB gene have been recently identified in patients with the Xlinked VACTERL1H (51).

Oculo-auriculo-vertebral spectrum

The OAVS (MIM %164210) is a clinically heterogeneous group belonging to the wide spectrum of hemifacial microsomias and involving the first and second branchial arch derivatives. OAVS is characterized by the association of hemifacial microsomia and ear deformities (ranging from pre-auricular tags of cartilaginous masses to atresia of the external auditory canal, anomalies in the size and shape of the external auricle, and even to anotia) to vertebral anomalies and congenital heart defects (52, 53). It has been estimated that 5% of OAVS patients present with OA/TOF (53). Autosomal dominant, autosomal recessive and X-linked mode of inheritances have been observed in OAVS. Recently, Fischer et al. (54) proposed that epigenetic dysregulation of BAPX1 may play an important role in OAVS.

Bartsocas–Papas syndrome

Bartsocas–Papas syndrome (or lethal popliteal pterygium syndrome–MIM 263650) is a rare autosomal recessive disorder characterized by extensive popliteal pterygia, absent digits, facial features including facial cleft and genital malformations. Rare features include microphtalmia, absent kidney, digestive atresia namely anal atresia and occasionally OA/TOF (55).

Fryns syndrome

Fryns syndrome (MIM 229850) is an autosomal recessive MCA syndrome, usually lethal in the neonatal period, and characterized by diaphragmatic defects, lung hypoplasia, distal limb hypoplasia, cleft lip and palate, cardiac defects, abnormal genitalia, renal cysts, and cerebral and/ or urinary tract malformations. Digestive atresias including OA are occasionally observed in Fryns syndrome (56).

Discussion

OA/TOF is a frequent yet aetiologically heterogeneous malformation. The systematic search for associated features should help to decide whether one is dealing with an isolated or a syndromic form of OA. This step is essential to recognize known SOA and offer genetic counselling and prenatal diagnosis. The causes of SOA are summarized in Table 2. Pregnancy history is important, in particular if exposures to teratogens or maternal diabetes are noted. The observation of a dominantly inherited OA with microcephaly and brachymesophalangism of the second and fifth fingers is suggestive of FS, while semicircular canal agenesis is highly suggestive of CHARGE syndrome. Likewise, the observation of anophthalmia/ microphthalmia is suggestive of AEG syndrome. Among these monogenic conditions, several genes have been identified providing a hitherto unknown clue to the understanding of the physiopathology of OA/TOF: MYCN (FS) involved in cell cycle and cell differentiation and CHD7 (CHARGE syndrome) involved in chromatin organization. Recently, Hales (57) suggested that agent checking DNA damages and regulating DNA repair, cell cycle checkpoints and apoptosis during development, may act as teratogen suppressors, protecting the conceptus against insults from DNA-damaging teratogens even in the absence of exogenous DNA-damaging agents. For instance, administration of adriamicine, an inhibitor of topoisomerase II and an anticancer agent, results in OA and other malformations including vertebral defects in rats at embryonic day 10.5 (58). Exposures to substances such as ethanol, phenytoin, thalidomide, hyperglycemia, and anticancer drugs produce DNA damage, either directly or as a result of oxidative stress (59, 60). The observation of OA in FAS, maternal diabetes and exposure to adriamicine, associated with the recent identification of MYCN mutations in FS, strongly support the view that DNA repair and cell cycle checkpoint genes play a key role in OA. How OA could be caused by mutations in CHD7, the CHARGE syndrome gene, involved in chromatin organization, is still questionable. However, the MYCN protein broadly affects transcription after dimerization with MYCassociated factor X (Max). The Myc–Max protein complex binds several proteins involved in ATP-dependent chromatin regulation, namely cAMP-response element-binding protein and p300, which possesses histone acetyl transferase activity such as SNF5 (a member of the Swi/Snf family) and Tip 48 [see Hurlin (28) for review]. These observations suggest that abnormal epigenetic control during development may produce OA. This hypothesis is supported by the recent report of abnormal histone acetylation of BAXP1 in OAVS, a rare cause of SOA (54). Yet, DNA repair/cell cycle checkpoint genes are not the only group of targeted genes in OA. Indeed, developmental genes may also be involved in the pathophysiology of OA (i.e. SOX2 and AEG syndrome). In fact, several knockout mouse models of developmental genes also present with OA including mice knocked out for the SHH pathway genes (Shh, Gli2 and Gli3, Foxf1) (61–65) and other homeobox-containing transcription factors such as hoxc4 (66).Moreover, a direct link between MYCN and SHH has been observed, suggesting common physiopathological mechanisms between DNA repair/cell cycle checkpoint and development [see Hurlin (28) for review]. It is very likely (as demonstrated in CHARGE syndrome) (40) that new genetic tools, such as array-based comparative genomic hybridization and/or oligonucleotide/single-nucleotide polymorphism microarrays, will contribute to the identification of submicroscopic deletions–duplications and novel genes involved in the physiopathogenesis of OA.

Acknowledgements

We are very thankful to the families and the AFAO (French oesophageal atresia association) and to Dr Ravi Savarirayan for his critical review.

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Ultrasound and MRI prenatal diagnosis of esophageal atresia: impact on management

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Antenatal diagnosis of esophageal atresia (EA) is still hazardous. Detection rate ranges between 9,2 and 31% in prenatal ultrasound scan but most of the series described cases of the 90's and prenatal detection rate seems to have improved in some recent publications [1-4]. Prenatal diagnosis is difficult as normal esophagus is usuallly not seen in routine ultrasound examination. However, Malinger, recently report visualization of normal esophagus using a high resolution linear transducer with complete visualization in 86,7% of cases and partial visualization in 96,7% [5]. Diagnosis of EA is usually suspected in the third trimester because of indirect signs: association of hydramnios and absent or small stomach bubble. Isolated, these signs are poor predictors of EA. Moreover, most of the EA have a tracheo-esophageal fistula (90%) with visualization of the fetal stomach because of amniotic fluid passing in the stomach through the fistula. The predictive positive value of combination of these two signs is low between 40 % and 56 %, with many infants suspected prenatally to have EA with a normal esophagus at birth [1, 2, 6]. Several reports described an improvement in prenatal diagnosis by the visualization of a blind ending pouch in the fetal neck or upper mediatinum during fetal swallowing. This sign has a high specificity for EA. However, its identification depends on fetal position, gestational age (rare before 26 weeks) and on the presence of fetal swallowing during examination [7, 8]. Research of the pouch sign implies a longer examination period (15-30 min) [9, 10]. Consequently, failure to identify a pouch in the fetal neck does not exclude esophageal atresia [11]. The association of these 3 signs (hydramnios, absence or small stomach and presence of a pouch), especially if they persist in successive examinations increases the likelihood of EA. The positive predictive value of this association ranges from 60 to 100 % with 80-100 % sensitivity [1, 5, 9]. MRI might improve prenatal diagnosis. The location of the midline sagittal plane might be easier in MRI, indeed it avoids the difficulties due to fetal position or mother echogenicity. In T2 weighted MRI, the criterion for EA is for Langer, non visualization of the intra thoracic portion of the esophagus (100% sensitivity in a serie of 10 ultrasound suspected EA) [1]. However, Levine noted that esophagus is not identified in 64% of fetuses in MRI [12]. Therefore, non visualization of the esophagus as only criteria for EA would lead to many false positive diagnosis; this fact is concordant with our experience. Some improvement of MRI prenatal diagnosis might be possible using Fast Imaging Employing Steady-state Acquisition (FIESTA, BFFE). Salomon was able to visualize the esophageal pouch during fetal swallowing movements in two cases [11]. However, as in ultrasound examination, fetal swallowing in necessary to visualize the pouch. Very few studies evaluate prenatal prognostic factors in ultrasound or MRI. The location of the pouch has been described as a good pronostic factor. A neck pouch is more likely to be associated with a long atretic gap. Conversely, a mediastinal pouch is associated with EA with distal tracheoesophageal fistula and primary esophageal repair [8, 9]. However, infants with prenatal diagnosis had a worse prognosis in Sparey study with more prolonged mechanical ventilation, longer hospital stay and long term gastrointestinal problems, may be because EA diagnosed prenatally are more often associated with others malformations [2].

Even difficult and hazardous, prenatal diagnosis is perceived to be advantageous for several reasons. Prenatal suspicion of EA alert the sonographer to look for other malformations (cardiac, renal, vertebral …) encountered in 50 to 60% of EA [2]. Many of these malformations could be missed prenatally. Fetal caryotyping can be offered when EA is suspected during pregnancy (2-8% aneuploïdies) [2]. Prenatal diagnosis also permits optimal neonatal management with delivery in a tertiary center with paediatric surgeons. It avoids the institution of

oral feeding. The parents could be prepared to the birth of an affected infant, informed of the possible association with prenatally unrecognized structural anomalies and are given the opportunity to meet the surgeons before birth. However, the high false positive rate of prenatal diagnosis means that unnecessary anxiety might be induced in parents.

Counseling parents after antenatal suspicion of EA is difficult and an appropriate balance between information and unnecessary parental anxiety must be the objective of fetal medecine teams.

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Esophageal atresia treatment: a perspective in the 21st century

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Firstly, three general aphorisms of importance:
1. There is a well defined and clear relationship between volume (of cases), management outcome and research output.
2. Most medical and surgical procedures have a better outcome when performed in hospitals that do a lot of the procedure in question.
3. Increased hospital specialisation is associated with improved patient outcomes.

A clear example of the effect of centralisation of care is the outcome for biliary atresia in the U.K. Prior to 1995, 15 centres were undertaking surgery for biliary atresia. The 5- year native liver survival in the two centres with "high" volume was 61% compared with 14% in the 13 centres operating on less than 5 cases per year. This led the NHS to legislate that in the future only 3 centres would be designated to carry out surgery on biliary atresia. Since then 6 other paediatric surgical conditions have been allocated supraregional status. The common theme for all of them is volume, specialisation and the team approach.

Oesophageal atresia is a relatively uncommon condition. Each regional centre, serving a population of 2.5 m, will manage on average 8 – 10 cases per year. With 5 paediatric surgeons per centre, each surgeon will operate on 1 – 3 cases of oesophageal atresia per year. For isolated atresias, surgeons will manage only 1 case every 5 – 10 years. This is clearly unacceptable.

The management of long-gap atresia is complex and can be divided into 3 stages, a) at the initial procedure, b) delayed primary repair,and c) replacement procedures.

Every effort should be made to retain the patient's oesophagus, but
"persistent attempts to retain the native oesophagus can have disastrous effects on the child and the family."

Gastric transposition is now accepted as the replacement procedure of choice in many centres. We have carried out the procedure in 192 cases (1980 -2005) with a 4.6% mortality, leak rate of 12% and stricture of 20% (mostly following caustic ingestion). A highly satisfactory outcome was achieved in 90 % of cases and there was no deterioration of function over time.

Recurrent fistula occurs in 5 – 8% of cases so that any one centre will only see 1 or 2 cases in 10 years. The repair of the recurrent fistula can be challenging and the re-recurrence rate is 10%.

How can we improve the outcome for oesophageal atresia in the future?
I would propose the following:
1. centralisation particularly for
    a) pure and long-gap atresia
    b) replacement procedures
    c) recurrent fistula
    d) associated major cardiac defects
2. recognising the value of team work and specialisation
3. careful and long term follow-up
4. promoting the work of parent support groups

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Challenges in surgical procedures-anastomotic strictures

Long gap esophageal atresia – where a wise man knows to stop (Chinese verb)

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Introduction

Esophageal atresia always is a challenge for pediatric surgeons, a long gap esophageal atresia even so more1. In the past many alternative technique has been presented to overcome the distance between the two esophageal ends. More recently Foker et al.2 have advocated an elongation technique with traction sutures. Although successful outcome has been reported in several publications, the procedure is cumbersome and not without substantial morbidity2,3. With the advent of minimal invasive pediatric surgery, it has become clear that endoscopic procedures have less morbidity and is better endured than open surgery4. This presentation will describe the thoracoscopic approach of long gap esophageal atresia and define its limits.

Patients

Between 2007 and 2009 four patients presented with long gap esophageal atresia. Two of them were referred from other centers. The first child was born at 30 week of gestation with a birth weight of 1500 gr. She underwent the thoracoscopic elongation procedure at the age of 4 weeks and 2400 gr. The second child was born term and was operated at the third day of life. The third child was born extremely pre- and dysmature and came from abroad at the age of 5 months. The fourth child was two years of age, also came from abroad and had undergone approximately 20 previous operations without success.

Technique

The technique was published earlier5 and will be described only in short. The approach is similar for primary thoracoscopic esophageal atresia repair with a 5mm trocar for the endoscope and two 3mm trocars for manipulation. First the proximal and distal esophagus are mobilized as far as possible. When is determined that a primary anastomosis is not possible, Vicryl®4x0 sutures are introduced with the use of an Endoclose® introducer, hooking up the esophageal ends in four quarters, and withdrawing the sutures with the use of the Endoclose® a little distant from the introduction site. In this way the proximal and distal esophagus can be stretched cross like. Outside the skin the sutures are pulled through a small piece of silicone tube and traction is applied with mosquitos. At the tip of the proximal and distal esophagus a clip is applied to follow the approximation of the esophageal ends over the days. Every day the sutures are tested for further traction and an X-ray indicates the progression of the stretching. When the ends have approached sufficiently, during a new thoracoscopy both ends of the esophagus will be opened and a delayed primary anastomosis will be performed over transanastomotic 6F gastric tube.

Results

In the first child in a first procedure a proximal fistula was closed thoracoscopically shortly after birth. At the age of 4 weeks she underwent the thoracoscopic Foker procedure. There was a four vertebrae gap after maximal traction. After three days the proximal sutures came loose and she underwent thoracoscopic replacement of the sutures. At that time the esophageal ends had approached leaving a two vertebrae gap. After another three days the ends had approached sufficiently to undertake a thoracoscopic delayed primary anastomosis. In the postoperative period there was a small leakage that healed spontaneously under a placed chest tube. She required dilation of the esophagus twice. One month later she underwent a laparoscopic antireflux procedure. She is now three years old, eating everything and no further sequelae.

The second child was a term boy with a pure esophageal atresia. He underwent a thoracoscopic Foker procedure on day three. The distal esophagus was small and vulnerable. After three days the sutures from the distal esophagus came out. At thoracoscopy a rupture had occurred at the top of the distal esophagus. Therefore the rupture was closed and the procedure was abandoned. He underwent a jejunal interposition

two weeks later without complications. He is now almost three years and eats what is served to the family.
The third child came from abroad at the age of five months with a weight of 3.8 kg and a gastrostomy. She underwent a thoracoscopic Foker procedure subsequently. The postoperative course was complicated by an anastomotic leakage for which a chest tube was placed for one week. She was temporarily fed by gastrostomy. At the age of one month a laparoscopic antireflux procedure was performed after which oral feedings were slowly introduced. Because she was not used to swallowing the introduction took some time, but eventually she is eating everything by mouth. She is now almost two years of age. A small residing sinus after the anastomotic leakage is followed conservatively.
The fourth child came to us at the age of two years, after having undergone approximately 20 surgical procedures elsewhere of open Foker elongation in combination with Kimura technique for elongation of the proximal esophagus. At thoracoscopic exploration the esophagus had completely scarred and was not usable. It was therefore converted to a thoracotomy and a jejunal interposition was used for restoration of continuity. He is now one year after the operation and doing well, eating spaghetti, and play backing before the television.

Discussion

Thoracoscopic repair of esophageal atresia is becoming more widespread nowadays.
Long gap esophageal atresia is much more infrequent and in a recent survey it was already suggested that this type of esophageal atresia should be cared for in only a limited number of centers of expertise1.
Thoracoscopic repair of long gap esophageal atresia was first described by our group in 20075, and although mentioned on several occasions, has not been described elsewhere.
As described above the technique is feasible, even in the very small, and with good ultimate outcome, but the procedure should be monitored very critically from beginning to the end, and there should be a low threshold for changing to an alternative technique in case of adverse events and/or complications. Therefore such procedures should be restricted to centers with extensive experience of not only endoscopic techniques, but they should also have an armamentarium of alternative techniques available in case one technique does not succeed. The Department of Pediatric Surgery in Utrecht is such a "Center of expertise", but:

"Long gap esophageal atresia – where a wise man knows to stop".

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Tissue Engineering

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Abstract

Surgical repair and bridging of the esophagus in newborns with esophageal atresia by primary anastomosis is successful in the majority of cases; however, bridging of long-gap esophageal atresia is still a surgical challenge. In theses situations, delayed repair (primary hitching of the esophagus end to the prevertebral fascia or the Foker technique), myotomy, and esophageal replacement with either gastric, jejunum, or colon transposition are possible therapeutic options. However, these techniques result in high morbidity and mortality rates. Moreover disabling symptoms related to late complications such as anastomotic strictrures, reflux, and delayed conduit emptying impair the patient's quality of life. Immediate or late failure of oesophageal reconstruction with these techniques may lead to the critical situation in which another reconstructive attempt can not be performed due to the lack of an appropriate esophageal substitute. Alternative techniques for esophageal reconstruction would be of great benefit for these patients who have a definitive esophagostoma. Attempts of esophageal replacement by artificial materials have not been successful because of their lack of biocompatibility leading to chronic infection, anastomotic leakage, migration, and stenosis. In a preliminary study in a pig model, we established, that short circumferential replacement of the cervical esophagus by a fresh aortic allograft allowed long-term patency of the esophageal lumen and nutritional autonomy.1 Limits of this approach were: 1. the need for a stent calibration for at least 6 months to avoid stricture formation; 2. potential higher morbidity and mortality rates when performing the technique at the thoracic level, due to the less confined nature of the graft site, compared to the cervical region; 3. the absence of contractility and propulsive capacity of the fibrotic graft area, which limits the application of this technique to short segmental defect replacement (<4cm)).

Tissue engineering is an interdisciplinary field which applies the principles of engineering and life sciences to the development of biological substitutes that restore, maintain or improve tissue function.2 The underlying principle of tissue engineering involves using isolated cells combined with complex biomaterials and cultivating new tissues and organs in vitro and in vivo.

The ideal esophageal substitute issued from tissue engineering would have the following characteristics: a.) propulsive peristalisis; b) elasticity; c) capacity to resist to reflux of gastric juices; d) colonization by mucous secreting cells for lubricating the esophagus. In experimental models, replacement of the esophagus in vivo has been performed with patch or circumferential implantation using synthetic as well as natural scaffolds: polyglycolic acid, small intestine submucosa, and a silicone/collagen hybrid, either alone or seeded with autologous cells.3, 4 Studies using patch grafts have reported better results than studies using circumferential scaffolds that were associated with higher rates of stricture and lack of muscle regeneration in these implants. However, when autologous epithelial cells were seeded onto the scaffolds, an increased regeneration of mesenchymal tissue was observed.5 Moreover, early epithelialisation was associated with a lower risk of stricture formation and an increased distensibility of the neo-esophagus, after circumferential replacement.6 Based on these observations, the hybrid approach of assembling individual tissue components in vitro and later mixing them to form composite tissue is currently one of the most promising approaches in tissue engineering of the esophagus.7 Another successful approach has consisted in transplanting esophageal organoid units (mesenchymal cores surrounded by epithelial cells), seeded on biodegradable polymer tubes. While restoring a normal esophageal histology in a rat model, this approach allowed, a gain weight after circumferential 2 cm-long esophageal replacement.8

Inability to provide oxygen and nutrients to neo-tissues both in vitro and immediately after implantation is still, a major limitation. Advances in scaffolds composition and design, in bioreactor technology and in the use of pro-angiogenic factors may all help to overcome this difficulty.
We are currently investigating the in situ tissue assembly of an acellular matrix seeded with autologous myoblats and autologous epithelial cells seeded on human amniotic membrane, as well as the creation of pre-capillary and vessels networks in biological scaffold.

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Anastomotic strictures: conservative treatment

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Recent advances in surgery and neonatal care have provided a better prognosis for EA [1]. Indeed, the survival rate of infants born with esophageal atresia (EA), with or without tracheoesophageal fistula, has dramatically improved over the last decade increasing from 80% to more than 95% [2]. However, anastomotic stricture remains a frequent complication occurring in 18–50% of patients with EA that have been surgically repaired [3]. Several predisposing factors have been identified including nature of the suture materials, anastomotic tension, anastomotic leakage, fistula, gap length, and gastroesophageal reflux. Anastomotic tension, which is highly correlated with gap length, plays probably the most important role in the development of subsequent stricture [4].

Initial treatment: Balloon or bougie dilations remain the treatment of choice for symptomatic esophageal strictures. Dilation with a balloon is theoretically more efficient because the expansive force is applied uniformly and radially at the site of the stricture, whereas a bougie exerts a shearing axial force that results in a greater degree of trauma and thereby increases the risk of perforation [5]. In a retrospective study, Lang et al. showed that balloon esophageal dilation is superior to bougie in term of safety and efficacy [6]. However, no prospective study on the efficacy and safety of Savary-Gilliard bougie dilation compared to balloon in an homogenous population of patients with EA has been reported.
The success rate of bougie dilations vary from 58% to 96% depending upon stricture etiology. For uncomplicated esophageal strictures, the perforation rates for balloon dilation and bougienage are 0–2.8% and 8–9%, respectively.
Altogether data from literature suggest that, more than the technique (balloon or Savary-Gilliard bougie), a trained operator is required to reduce complications occurrence following esophageal dilations.

Recurrent stenosis: In some patients, stricture remains without a substantial symptom-free-interval or recurs despite an initial successful dilation. The cause of recurrent stenosis is unknown, but intense fibrogenesis during healing and after the trauma induced by the dilation procedure may be responsible. Esophageal strictures refractory to conservative treatment (balloon dilation or bouginage) are difficult to manage. Iterative dilations increase the risk of complications such as perforations (perforations occur in 5–8% of dilations). Repeated dilations may cause psychological problems in children because of repeated anesthesia. Moreover, repeated mechanical irritation at the site of stricture may increase the risk of carcinoma. For recurrent stenosis, conservative treatment is preferable to surgical treatment. Esophageal replacement is the usual procedure, but it carries high risks of morbidity especially on the long term [7]. To avoid repeated dilations, many agents have been used experimentally to inhibit new collagen formation directly or indirectly and to prevent stricture formation (e.g., steroids plus antibiotics, vitamin E, vitamin A, and pentoxifylline), but only a few have gained acceptance for clinical application [9].
Esophageal stenting, a routine treatment for esophageal strictures caused by neoplasms in adults, was recently used to prevent stricture formation in children [10, 11], but the morbidity rate (nausea, vomiting, pain, migration of the stent, and induction of gastroesophageal reflux) is high. Several issues are raised by this procedure and remain unsolved: requirement for a second stent in some patients after slippage of the first one, prevention of induced gastroesophageal reflux by systematic antacid treatment, retrograde migration of the stent into the larynx, and consequences of stenting in a rapidly growing child.

A therapeutic option recently described is the topical application of mitomycin-C to the stricture's intraluminal surface after dilation. Mitomycin-C is an antibiotic used as an antineoplastic agent, that inhibits DNA synthesis and reduces fibroblastic collagen synthesis by inhibiting DNA-dependent RNA synthesis. Mitomycin-C can suppress cellular proliferation during the late G1 and S phases. It has been successfully used as an antifibrotic agent to prevent scar formation when treating childhood glaucoma, lacrimal duct stenosis, laryngeal and tracheal stenosis. There have been a few small series and case report all reporting some effectiveness in the treatment of refractory esophageal strictures [8]. In our experience of 6 children, local application of mitomycin-C to refractory esophageal stenoses was beneficial for 4 years thereafter in terms of digestive symptoms and radiographic and endoscopic findings. However, biopsies revealed a de novo gastric metaplasia at the site of the stenosis in two of the six cases. This suggests that long term follow-up with esophageal biopsies is required in such patients.

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Endoscopic features-gastro-esophageal reflux

Endoscopic Features in Esophageal Atresia: from Birth to Adulthood

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Since the first successful surgery in 1941, the survival of patients with esophageal atresia (EA) has improved greatly. Consequently, the follow-up of these patients has revealed gastrointestinal (GI) complications unrecognized 60 years ago, such as gastroesophageal reflux and esophagitis with their related consequences.2 Among these complications, one of the major concerns in the long-term GI follow-up is the increased incidence of gastric metaplasia of the esophagus 3-5, intestinal metaplasia 6, 7 and esophageal adenocarcinoma 8-10 that have indeed all been reported in young adults with EA 7- 9. However, the exact incidence and natural history of these complications are unknown in EA patients and whether systematic upper GI endoscopic screening and surveillance in the follow-up of patients with EA is recommended is not yet established. In this presentation, we will not address the problem of congenital stenosis, anastomotic and peptic strictures. We will rather discuss:

1- The specificities of upper GI endoscopy in EA
• Do we need to scope the patients? When? How often? (Is there any clinical symptom predictive of endoscopic appearance?) Performing a systematic endoscopic assessment in patients with EA is largely debated in the pediatric 5, 11, 12 and more recently adult literature.13,14 The predictive value of an early (<3 years of age) normal UGI endoscopy is unknown regarding development of peptic esophagitis and Barrett esophagus later in life. In a study designed to determine if clinical symptoms may predict endoscopical lesions15, 63 patients with EA have been recruited. Eighteen had dysphagia related to an esophageal stricture needing dilatation and were not included in the analysis. Forty-five patients (26 girls) with a median age of 7.3 years (range 0.4 to 17.9) were evaluated. Mucosal abnormalities at endoscopy were observed in 19 out of 45 patients (42%). Symptoms were reported by 62%, but none could be identified as statistically associated with an abnormal endoscopy. Furthermore, 6 asymptomatic patients had abnormal endoscopies, reflecting the difficulty in adequately deciding which patients need to be investigated.15 • Pitfalls: Of the importance of correct landmarks in patients with EA. Hiatal hernia or gastric pull-up can complicate landmark recognition and lead to erroneous diagnosis of gastric metaplasia 16, mostly in patients with a long gap atresia. In this regard, the esophageal mucosa should be determined by carefully delimiting the gastroesophageal junction, identified as the proximal margin of the gastric mucosal folds, as defined by Prague C & M criteria.17
2- What is actually observed in patients with EA?
• Esophagitis. Peptic esophagitis3, 12, Barrett esophagus 3, 12 and eosinophilic esophagitis18 have been reported in children and more recently in adults with repaired EA. We report a systematic cross-sectional endoscopic evaluation in 45 EA patients (median age of 7.3 years, range 0.4 - 17.9).
Twenty-six patients (58%) had a normal endoscopy, 14 (31%), esophagitis, and 16 (36%) gastric metaplasia. No intestinal metaplasia or adenocarcinoma was detected similar to other reports.12 Data in adults are sparse. Maynard et al. report in the present meeting preliminary results of a systematic endoscopic screening in 21 adults aged 27 ± 7 years born with EA.14 Esophagitis was found in 29% patients (n=6), Barrett endoscopically suspected in 24% patients (n=5) in whom intestinal metaplasia was documented in 3 cases. All together, these data demonstrate that EA, even in childhood, is a significant risk factor for the development of esophagitis and Barrett esophagus.
• Miscellaneous. Various anecdotic features can also be observed in patients with EA. Some of them may have clinical consequences (diverticulum, "mucosal bridge") and may be related to symptoms. Others such as a high incidence of heterotopic pancreas19 could lead to a new pathophysiological hypothesis if this association between EA and heterotopic pancreas is related to the same developmental mechanisms. Conclusion and perspectives: The present data demonstrate the high incidence of esophageal mucosal lesions in pediatric and adult patients with EA without any predictive clinical symptom.

This argues for a systematic screening of endoscopic lesions in all patients with EA even in the absence of upper GI symptoms. However, the evaluation of systematic endoscopic follow-up with esophageal biopsies in EA patients to accurately evaluate the complications, the response to treatment and the outcome are urgently warranted. The predictive value of a normal endoscopy should also be assessed. Finally, a close collaboration should be established with pathologists, the lesions should be described according to standardized landmarks, and biopsy samples should be taken with special care.

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The new definitions of Barrett's esophagus: Different types of columnar metaplasia, identification and significance in esophageal atresia

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Statements from the Pediatric Global Consensus on Definition of GERD1
41. In the pediatric age group, Barrett's esophagus mainly occurs in individuals with hiatal hernia, and in those with certain underlying disorders that predispose to severe GERD. Agree: 100% (A+, 25%; A, 62.5%; A-, 12.5%; Grade: low)

42. The term 'Endoscopically Suspected Esophageal Metaplasia' (ESEM) describes endoscopic findings consistent with Barrett's esophagus that await histological confirmation. Agree: 100% (A+, 25%; A, 75%; Grade: not applicable)

43. Documentation of esophagogastric landmarks together with multiple biopsies are necessary to characterize endoscopically suspected esophageal metaplasia. Agree: 87.5% (A+, 12.5%; A, 62.5%; A, 12.5%; D-, 12.5%; Grade: moderate)

44. When biopsies from endoscopically suspected esophageal metaplasia show columnar epithelium it should be called Barrett's esophagus and the presence or absence of intestinal metaplasia specified. Agree: 100% A+, 50%; A, 37.5%; A-, 12.5%; Grade: not applicable)

Introduction: As in adults,2 in children the term Barrett's esophagus (BE) has been variably interpreted3, 4 and therefore lacked clarity needed for clinical and scientific communication about columnar metaplasia of the esophageal mucosa. Therefore, recently a pediatric consensus group sought to rectify this.1 The same new approach has been adopted by a European-North American Clinical Practice Guidelines Committee on Pediatric GERD.5
While the prevalence of Barrett's esophagus (BE) is much lower in children than adults, columnar metaplasia with goblet cells occurs in some 5% of children with severe chronic GERD, and in another 5% without goblet cell metaplasia.6 In adults and children, Barrett's esophagus (BE) is an acquired condition, due to chronic, severe GERD.7
Terminology: Metaplasia vs Heterotopia v Dysplasia. These will be discussed and illustrated.
Importance of BE: It is a marker for the presence of severe GERD, and it has malignant potential. Although adenocarcinoma of the esophagus occurs only rarely within childhood,8 the diagnosis nevertheless has consequences for long-term follow-up and for longevity.
Endoscopy, histology: Recent studies in adults have shown that there may be a marked disparity between endoscopic and biopsy findings.9 These data support the need for histologic confirmation of endoscopically suspected BE. For this reason, a term that acknowledges the possibility that the endoscopic appearance may not be diagnostic was therefore chosen, ie, 'endoscopically suspected esophageal metaplasia'.1, 2 Another advantage of this term is that it does not carry the same implications as does 'Barrett's esophagus' for life or health insurance.

Landmarks Accurate diagnosis of BE begins with identification and documentation of the key endoscopic landmarks of the gastroesophageal junction. These are: the Z-line, the lower esophageal sphincter (LES) zone, the diaphragmatic pinchcock, and the top of the gastric folds. This is the first and most basic «process of care» criterion for accurate diagnosis of BE.10 Landmarks are not always easily identifiable, especially in the operated

esophagus (e.g., repaired esophageal atresia), or when hiatal hernia is present. Hiatal hernia is highly prevalent in adults with severe reflux disease as it is in 40% of children with the most severe reflux disease,6 and in almost all patients with long-segment BE.3, 11 Marked inflammation or pus may also make landmark identification difficult. In this circumstance, endoscopy should be repeated after 12 weeks or so of high dose PPI treatment, enabling identification of landmarks.

Another caveat regarding the nature of the columnar lining on biopsy is the risk of sampling error, i.e., that focal areas of goblet cell metaplasia can be missed, either by inadequate tissue sampling, or failure to stain the biopsies with Alcian blue at pH2.5. These are also «process of care» criteria for diagnosis.10 The purpose of taking multiple closely-spaced biopsies is to most accurately characterize the mucosa as purely gastric columnar, i.e., cardia-type, or columnar with intestinal metaplasia, and to detect the presence of dysplasia.2, 4 The highest yield of goblet cell metaplasia is proximal, both in children and adults.4, 12, 13

Cardia-type metaplasia without goblet cells While goblet cell metaplasia is felt to represent the end-point of a GERD-induced chronic mucosal injury, at least in benign mucosa,14, recent reports in adults15 and children4 have shown that esophageal metaplasia can occur in the form of cardia-type columnar metaplasia without goblet cells. Peitz et al15 prospectively observed the development of cephalad extensions of cardiac-type metaplasia in 10 of 13 adults with previous distal esophageal resections and a neoanastamosis. The tongues were 0.3-7cm in length at 3-88 months post-operatively, and intestinal metaplasia was present in only 3. Thus, it is apparent that metaplasia can manifest as columnar epithelium without goblet cells, i.e., cardia-type mucosa. Another issue of concern, and reason for adoption of the new definition, is that there is now some doubt whether only mucosa containing goblet cell metaplasia is premaligant. This added to the rationale for a more flexible approach to diagnosis.

Children at greatest risk for development of BE Certain disorders predispose children to the most severe and chronic GERD, and therefore to Barrett's esophagus. These include children with repaired esophageal atresia or congenital diaphragmatic hernia; significant neurological impairment, such as cerebral palsy, or syndromes such as chromosomal disorders, Cornelia de Lange syndrome, Down's syndrome, and those with chronic lung disease, such as cystic fibrosis.6, 16-18 Children without these disorders, but with hiatal hernia, or with a strong family history of GERD or Barrett's esophagus or adenocarcinoma, also have a higher prevalence of BE.3, 17, 19 Issues especially pertaining to Esophageal Atresia

Esophageal atresia (EA) is relatively common in childhood, and it predisposes to chronic severe GE reflux. In most cases, children with repaired EA have a normal longevity. For these reasons, there is a general consensus in the literature that patients with EA should be followed carefully.
There have been several reports of BE occurring in children17, 20-23 or adults24-26 with repaired EA including patients who developed adenocarcinoma or squamous carcinoma.27-31
Barrett's in EA has been overdiagnosed in many reported cases, but it almost certainly is also missed. The reasons for inaccuracy of diagnosis are that few of the published reports consistently used rigorous diagnostic approaches. With uniform approaches to landmark identification, biopsy protocols, and definitions, EA can be studied in a uniform manner between centers.
Implications of the new definition of Barrett's for EA patients:
- Increased frequency of diagnosis of 'Barrett's' – with or without intestinal metaplasia
- More need to follow these patients

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