

Ph.D Thesis

**The appearance and occurrence of the
embryonal remnants
in the pediatric surgical practice**

Tamás Józsa MD

Supervisor: György Balla MD, PhD, DsC

**Department of Pediatrics,
Medical and Health Science Center,
University of Debrecen
2007**

1. Introduction

The treatment of the congenital malformations is a developing field of the pediatric surgery. The persistent embryonal remnants are the special group of the congenital malformations. These remnants do not cause any symptoms or complications for a long term period in a lot of cases, but sometimes acute surgical treatment is required or malignant transformation develops. The most frequent embryonal structures are the persistent aberrant vessels of the fetal blood circulation, which give an uncommon blood supply to some organ. Besides of its, the primitive streak, the urachus, the omphaloenteric duct, the mesonephric duct, the paramesonephric duct, the thyreoglossal duct, the branchial clefts and the bronchopulmonary foregut can be the origin of persistent fetal structures, which lead complications. These remnants are considered in the medical literature as unnecessary structures, without any function. After the diagnosis, the remnants require total surgical excision.

I would like to survey of the occurrence and appearance of the embryonal remnants, except of aberrant vessels, in the patients of the Department of Pediatrics, Medical and Health Science Center, University of Debrecen, and to highlight to the appendix testis, which is the most common persistent embryonal remnant

2. Aims

1. The examinations of the occurrence and the appearance of the embryonal remnants in the patients of the Department of Pediatrics, Medical and Health Science Center, University of Debrecen from 1 January 1997 to 31 December 2006.
2. To observe of a special forms and symptoms of the embryonal remnants between our cases.
3. To determine the incidence of the most frequent embryonal remnant, the appendix testis (hydatid of Morgagni) with intraoperative survey and to compare the occurrence of appendix testis in patients with descended and undescended testes.
4. To determine these factors which can be influence the presence or absence of the appendix testis in the cases of undescended testis.
5. To examine the androgen and estrogen receptor pattern of the appendix testis in descended and undescended testis of children.
6. To examine the damage of the appendix testis in the cases of hydrocele, considering the epithelial destruction and the steroid receptor pattern.

3. Patients and methods

3.1 Examination of the appearance and occurrence of embryonal remnants

The patients with any type of persistent embryonal remnant were collected from the database of the Department of Pediatrics, Medical and Health Science Center, University of Debrecen from 1 January 1997 to 31 December 2006. The occurrence was given in the prevalence of these diseases, which were counted from the population of the children of the affected years in three country, Szabolcs-Szatmár-Bereg, Hajdú-Bihar and Jász-Nagykun-Szolnok. To calculate the prevalence we used the data of the Central Statistic Office (Központi Statisztikai Hivatal).

Reviewing of the medical history of our patients, we highlighted the very rare appearance of the persistent embryonal remnants and the previously undescribed symptoms.

3.2 The examination of the incidence of appendix testis

The presence of the appendix testis (i.e. a hydatid placed on the upper pole of testis that can be considered appendix testis) was retrospectively evaluated in 208 boys (ages from 2 months to 12 years, mean 4.5 years) who underwent orchiopexy, hydrocele or hernia repair admitted to the Surgical Ward of the Department of Pediatrics, University of Debrecen from May 2004 to Nov 2005. Included in our study there were 108 consecutive patients with undescended testis (125 orchiopexies) and 100 patients with groin hernia and testicular hydrocele (103 hernia and hydrocele repair) representing patients with descended testis. The diagnosis was made and the operation performed by two pediatric surgeons based on the same criterions. Patients with ectopic testis (testis placed outside the normal path of descent) or iatrogenic undescended testis (secunder retention after previous inguinal or scrotal operation) were excluded from this study. In orchiopexy cases the age of the patient at the time of operation, the appearance and form of the hernia sac, the side of the orchiopexy, testicular hypoplasia (i.e. when the undescended testis was softer and definitely smaller than the normal contralateral testis) and the appearance of the appendix testis were registered. In the cases of groin hernias and testicular hydroceles, when the testis was visible, only the appearance of appendix testis and the side of the surgical treatment were evaluated. The appearance other types of testicular appendages and appendix epididymidis were not examined in our study.

After reviewing these data we compared the occurrence of appendix testis in descended testes (patients who underwent inguinal hernia or hydrocele repair) and undescended testes, and analyzed the relationship between the occurrence of appendix testis and the undescended testes. Data were compared using Fisher's exact test and Chi-square test, p values less than 0.05 were considered significant.

3.3 The examination of the androgen and estrogen receptors of appendix testis

3.3.1 Patients

3.3.1.1 Examination of the role of appendix testis in the testicular descent

37 AT were collected from 34 boys (age 3 months – 9 years, mean 33 months) undergoing surgical exploration because of undescended testis and congenital inguinal hernia at the Surgical Ward of Department of Pediatrics, University of the Medical and Health Science Centre, University of Debrecen (MHSCUD). The testes were visible during operation. The study protocol was approved by the Human Ethics Committee of MHSCUD. Written informed consent was obtained from the parents or guardians before the children entered the study.

Classification: the testes that have failed to complete the migration phase to the scrotum were considered as congenital undescended testis (CU). The testis that was originally found in a scrotal position and, along with longitudinal growth, moved to an undescended position was considered as acquired undescended testis (AU).

Specimens were divided into three groups, Group AU (acquired undescended testis, n=14, age 20 months to 9 years mean 38 months), Group CU (congenital undescended testis, n=12, age 13 months to 4 years, mean 28 months), Group H (as a control group of descended testis, n=11, from boys undergoing inguinal hernioplasty, age 3 months to 7 years, mean 33 months), and the receptor status of AT was compared. Included in Group CU, there were 6 specimens from 3 patients (bilateral CU), who underwent previous human chorionic gonadotropin therapy - without a therapeutic effect.

3.3.1.2 Examination of the effects of hydrocele on appendix testis

23 AT were collected from boys who underwent surgical exploration because of hydrocele or congenital inguinal hernia at the Surgical Ward of Department of Pediatrics, University of

the Medical and Health Science Center, University of Debrecen (MHSCUD), during which the testis was visible. Patient's ages ranged from 13 months to 79 months (mean 40 months).

The patients were divided into three groups. Group A included 8 boys (mean age 41 months), who underwent hernioplasty due to groin hernia. Group B included 4 boys (mean age 35 months, mean interval between presentation of first symptom to operation was 3.8 months) operated on due to communicating hydrocele and Group C included 11 boys (mean age 41 months, mean interval between presentation of first symptom to operation was 5.2 month) operated on due to non-communicating hydroceles.

To categorize the hydroceles we used the following definitions: Communicating hydroceles: excessive fluid within the tunica vaginalis that did change in size on physical examination. Non-communicating hydroceles: excessive fluid within the tunica vaginalis that did not change in size and at the time of physical exam fluid could not be expressed from the scrotum.

The study protocol was approved by the local of human ethics committee of MHSCUD. Written informed consent was obtained from the parents or guardians before the children entered the study.

3.3.2 Methods

Formalin-fixed, paraffin-embedded tissue sections of the excised AT were haematoxylin-eosin (HE) stained and they were labelled for androgen receptors (AR) and estrogen receptors (ER) using immunohistochemical staining procedure. AR was labelled with BioGenex monoclonal mouse anti-human androgen receptor antibody (clone F39.4.1) and ER was labelled with DAKO monoclonal mouse anti-human estrogen receptor (clone 1D5) antibody, according to the method of Samnakay et al⁷. Visualization was performed using diaminobenzidine (DAB). Prostate cancer tissue was used as positive control for AR and breast cancer tissue for ER. In negative controls (serial sections of each sample), the primary antibody was omitted. The sections were evaluated under a light microscope with incorporated photography system (Leica DM 2500, DFC 480, Leica Microsystem, Heerbrugg, Switzerland) at 10x, and 40x magnifications. Brown staining for AR or ER of the investigated cells was considered as positive immunoreaction.

After incubation with the primary antibody, sections were stained with the fluorescein isothiocyanate (FITC)-conjugated goat anti-mouse secondary antibody (1:500, Vector Laboratories, Burlingame, USA), for 45 min in room temperature. Sections were counterstained with by 4,6-diamidino-2-phenylindole (DAPI, Vector Laboratories,

Burlingame, USA). As negative controls, the appropriate primary antibody was either omitted from the procedure or the specimens were preincubated with a synthetic blocking peptide. Receptors were imaged using LSM 510 laser scanning confocal microscope (Zeiss, Oberkochen, Germany) with a 63x water immersion objective (1.2 NA; Zeiss). Green fluorescence staining for AR or ER was considered as a positive reaction.

3.3.2.1 Haematoxylin-eosin staining

Formalin-fixed, paraffin-embedded tissue sections of the excised AT were stained with haematoxylin-eosin. Two blinded independent pathologists saw the haematoxylin-eosin staining in order to confirm the diagnosis of destruction of epithelial surface.

3.3.2.2 Light microscope immunohistochemistry

Formalin-fixed, paraffin-embedded tissue sections of the excised AT were stained for androgen and oestrogen receptors using immunohistochemical stains, BioGenex monoclonal mouse anti-human androgen receptor antibody (clone F39.4.1) and DAKO monoclonal mouse anti-human oestrogen receptor (clone 1D5) antibody, according to the method of Samnakay et al⁷, and visualization was performed using diaminobenzidine (DAB). Control sections were used for the determination of antibody reaction specificity: positive control was prostate cancer tissue for androgen receptor and breast cancer for oestrogen receptor and negative technique control (serial sections of each sample omitting the primary antibody). The sections were evaluated under a light microscope with incorporated photography system (Leica DM 2500, DFC 480, Leica Microsystem, Heerbrugg, Switzerland) at 10x, 20x and 40x magnifications. Brown nuclear staining for AR or ER in the epithelial surface and/or in the epithelial lining of the acini was considered positive immunostaining.

3.3.2.3 Fluorescence microscope immunohistochemistry

After incubation with the primary antibody, sections were stained with the fluorescein isothiocyanate (FITC)-conjugated goat anti-rabbit secondary antibody (1:500, Vector Laboratories, Burlingame, USA), for 45 min in room temperature. Sections were counterstained with 4,6-diamidino-2-phenylindole (DAPI, Vector Laboratories, Burlingame, USA). As negative controls, the appropriate primary antibody was either omitted from the procedure or was preincubated with a synthetic blocking peptide.

Receptors were imaged using LSM 510 laser scanning confocal microscope (Zeiss, Oberkochen, Germany) with a 63x water immersion objective (1.2 NA; Zeiss) Green fluorescence nuclear staining for AR or ER in the epithelial surface and/or in the epithelial lining of the acini were considered positive.

3.3.2.4 Methods

The presence of AR and ER with immunohistochemical and immunofluorescence staining was analyzed retrospectively in the procedure of examination the role of appendix testis in the process of testicular descent, and the presence of AR and ER with immunohistochemical and immunofluorescence staining and destruction of the epithelial surface of the AT with haematoxylin-eosin staining were analyzed in all groups of the examination of the effect of hydrocele on appendix testis.

3.3.2.5 Statistical analysis

Fisher's exact test and Chi-square test was used for all statistical analysis. $P < 0.05$ was considered statistically significant for all parameters.

4. Results and conclusions

4.1. The appearance and occurrence of embryonal remnants

The occurrence of embryonal remnants and the different type of the persisting anatomical structures in the patients of the Department of Pediatrics between 1. January 1997 and 31. December 2006 was demonstrated on Table 1.

These data show the very rare prevalence of the different types of persisting embryonal remnants. The early diagnosis of these entities are very important to perform the treatment, because there are several serious, sometimes life threatening complications of its. As we could see, the most frequent persist of the embryonal remnants is the appendix testis and we performed further examinations to determine the possible functions of it.

Table 1 shows the occurrence of embryonal remnants and the different type of the persisting anatomical structures in the patients of the Department of Pediatrics between 1. January 1997. and 31. December 2006.

The origin of the embryonal remnants	Form of appearance	Symptoms	Occurrence Patients Prevalence	
Primitiv streak	Sacrococcygeal teratoma	Visible mass	4	0.00013%
Bronchopulmonary foregut malformation	Extralobar pulmonary sequestration	Obstructive bronchitis	1	0.000066%
	Esophageal duplication	Esophageal obstruction	1	
Urachus	Cysta	Umbilical mass	2	0.00013%
	Vesicourachal diverticulum	Urinary tract infection	2	
Omphaloenteric duct	Cysta	Ileus	2	0.00093%
	Ductus omphaloentericus persistens	Ileus,	1	
		Bleeding	1	
	Meckel-diverticulum	Bleeding, invagination	6	
			2	
		Asmptomatic *	10	
Branchial remnants (II. brancial cleft)	Cysta	Inflammation	2	0.00065%
	Fistula	Inflammation,	4	
		Mucus	13	
Thyreoglossal duct	Cysta	Swallow,	12	0.00062%
		inflammation	6	
Mesonephric duct	Appendix epididymis**	Asimptomatic		
Paramesonephric duct	Appendix testis	Torsion	195	0.0066%
		asymptomatic ***		76%

* asymptomatic: appearing during the other operations

** the number of the appendix epididymis were not count in asymptomatic cases

*** the incidence ratio of the appendix testis in asymptomatic cases between 1.

May 2004. and 30. November 2005.

However, we have to point out two special appearance of persisting embryonal remnants between our cases. One of them is the extralobar pulmonary sequestration which is a very rare form of the bronchopulmonary foregut malformations and its blood supply arises from the right subclavian artery. The special localization of this type of malformation gives a very difficult differential diagnostic problem. We introduced the case of a 7 months old infant suffering recurrent bronchitis and right extralobar pulmonary sequestration was found. The surgical excision was successful.

We reported a case of a 2 years old girl with complete second branchial cleft fistula. The main symptom was the fetor ex ore, which was presented from early infancy. After the complete surgical excision of the fistula, the halitosis was resolved. That was the first reported case in the medical literature, which demonstrated, the fetor ex ore as the first sign of the persisting II. branchial cleft remnant.

The prevalence of the persisting embryonal remnants is very rare, but the early recognition and surgical excision of these structures are very important to avoid the inflammation or malignant transformation.

4.2 The incidence of the appendix testis

The incidence of appendix testis in the operated undescended testis cases was 30/125 (24%) and in those patient who underwent hernia or hydrocele repair was 78/103 (76%), i.e. significantly higher ($p < 0.05$) in the latter group of patients.

Undescended testes were associated in 83/125 (66%) with the presence of hernia sac.

There was no remarkable difference in the occurrence in the appendix testis between the right sided and the left sided undescended testes. The occurrence in the right side was 19/65 (29%), in the left side it was 11/60 (18%). Similarly, there was no significant difference ($p < 0.05$) in the occurrence of the appendix testis between the right and left sided cases in those boys, who underwent hernia or hydrocele repair and the testis was visible - the occurrence was 58/76 (76%) in the right side and 20/27 (74%) in the left side. Fifty of the 125 undescended testes (40%) were hypoplastic. The occurrence of the appendix testis in hypoplastic testes was 16/50 cases (32%).

The presence of appendix testis was similar in those patients with undescended testes who were found with patent processus vaginalis: 22/30 patients (73%) with and 61/95 patients (66%) without the presence of appendix testis were noted in patients who had an obvious hernia sac or a patent processus vaginalis.

The mean age with descended testis was 48 months at the time of operation. The mean age of all patients with undescended testis at the time of operation was 53 months. This value was 39 months in patients without appendix testis and 61 months in patients with the presence of the appendix testis.

Although the exact function of appendix testis has not yet been clarified, the clinical relevance of this structure is well known: pedicle-turned hydatids resulting in symptoms of acute scrotum and, rarely, neoplasms from Müllerian-type epithelium of the appendix testis have been identified. Recently, Samnakay et al. described that the human appendix testis was found to express both estrogen and androgen receptors. The significantly lower incidence of appendix testis in patients with undescended testes versus those with descended testes may suggest a physiological role of appendix testis, regulated by sexual steroids, in the process of testicular migration.

There were no differences between the side and the incidence of appendix testis in cases of undescended testes. Our findings demonstrated that testicular hypoplasia did not influence the appearance of appendix testis. Moreover, the incidence of appendix testis was equal in both hypoplastic and non-hypoplastic undescended testes, i.e. the testicular hypoplasia cannot be considered as a cause of appendix testis and, vice versa, the absence of appendix testis did not result in testicular hypoplasia.

The occurrence of associated hernia sac in the cases of undescended testes in our study was 66%, similar to that of McKiernan et al. There was no statistically significant association between the presence of hernia sac and the appearance of appendix testis: the incidences were similar in the cases of undescended testes, regardless whether it was or was not associated with a hernia sac.

However, to answer the question whether the absence of hydatid of Morgagni is a cause or the result of testicular maldescent is difficult. The differences in the age distribution of patients having undescended testis with and without the presence of appendix testis suggests that a causative role is more likely than the fast degradation or atrophy of appendix testis in undescended testes.

Mean age at orchiopexy was lower (39 months) in patients without appendix testis compared to those patients, who were found with appendix (61 months). Since children are being surveyed by pediatricians providing an appropriate and very effective primary care in Hungary, it is more likely that older patients with cryptorchidism had ascended testis (the testis originally was found to be in a scrotal position, and with longitudinal growth, the testis moves to an undescended position) rather than congenital undescended testis. Moreover,

congenital undescended testis is associated with a lower incidence of appendix testis than ascended testis.

4.3 The androgen and estrogen receptor status of the appendix testis in descended and undescended testis

In haematoxylin-eosin sections AT demonstrated a vascular stroma lined with pseudocolumnar epithelium. The stroma consisted of loose connective tissue containing blood vessels, fibroblasts and varying numbers of acini (gland-like structures), which were lined by nonciliated columnar epithelium.

AR positivity was observed as a brown staining of the cells of the surface epithelium and gland-like structures in immunohistochemistry sections. Stromal cells were stained variably. Immunofluorescence labelling showed a green, nuclear and cytoplasmic staining in the cells of the epithelial surface and gland-like structures.

ER positivity was observed as brown staining of the cells of the epithelial surface and gland-like structures. Stromal cells were stained variably in immunohistochemistry sections. Immunofluorescence labelling showed a green nuclear staining in the cells of the epithelial surface and gland-like structures.

The receptor pattern as evaluated both with immunohistochemistry and immunofluorescence staining in the examined groups showed that both AR and ER were positive in the 11/11 cases of Group H and in the 14/14 cases of Group AU 14/14. The specimens in Group CU were invariably negative for AR and positive 12/12 cases for ER.

The role of androgen hormones in the second or inguinoscrotal phase of the process of testicular descent has been described and there is evidence suggesting that androgens mediate the regression of the cranial suspensory ligament.

Samnakay et al. published the first study to confirm the presence of AR and ER in human AT investigating excised AT during scrotal exploration of testes of 10 patients because of acute scrotum. While AR was found in all cells of the epithelial layer, ER was presented only in the invaginations - like parts of this epithelial surface. In our study, in contrast with Samnakay's results, we did not find these marked regional differences. AR and ER were invariably expressed in the same epithelial cells of AT excised from patients with descended testis. These differences in the expression of the examined steroid receptors between the two studies suggest that the appearance of AR and ER depends on the age of the patients. While the range of the age of the investigated patients in our study was 3 months – 9 years (mean

33 months), in Samnakay et al investigated prepubertal and adolescent boys. Moreover, it should be noted, that the study of Samnakay et al did not represent a physiological situation of steroid receptor expression pattern, since the disorder mainly torsion of the appendix testis, resulting in an acute scrotum, might had influenced the expression pattern of both androgen and estrogen receptors in the investigated specimens.

Interestingly, we found 100 % AR expression in the specimens of patients with descended and acquired undescended testes. However, congenital undescended testes were invariably negative for AR both immunohistochemically and with immunofluorescence staining. Significantly, AR did not express in those 6 specimens, originated from 3 patients with bilateral undescended testis, who received a HCG treatment – without any improvement in the clinical condition. There was no difference in the expression of ER in Groups H, AU and CU. These receptors were found in all of the examined specimens.

The 100% presence of AR in the AT specimens of patients with acquired undescended testis and of patients with descended testes and its clear absence of these appendices of patients with congenitally undescended testes confirm the conclusion of our previous epidemiological investigative survey, that AR- positive AT may be one of the physiological requirements of the process of testicular descent. A fast secondary degradation of AR in the epithelial cells of the AT due to testicular non-descent per se seems to be unlikely as the epithelial layer of AT is AR-positive inquired forms of undescended testis.

In conclusion, testicular descent is a complex physiological-anatomical process regulated by multiple factors. According to our study, AR positivity of the epithelial layers of AT may significantly contribute to this complex process.

4.4 The androgen and estrogen receptor status and epithelial destruction of appendix testis in hydrocele

The presence of AR, OR and epithelial destruction are demonstrated in Table 2. The haematoxylin-eosin staining showed there was no epithelial destruction in either Group A or Group B, but the destruction was found to be significantly higher (67%) in Group C. The tissue sections of AT expressed both AR and OR in all patients in Group A and Group B and it was confirmed both immunohistochemical studies and immunofluorescence staining. The presence of AR and OR were significantly lower (androgen: 14%, $p < 0.001$, oestrogen: 33%, $p = 0.006$) in Group C demonstrates the negative immunohistochemical and immunofluorescence staining in the case of non-communicating hydrocele.

Table 2 Comparison of the presence of androgen and estrogen receptors and epithelial destruction in the different groups

	Presence of androgen receptor (p<0.001)		Presence of estrogen receptor (p=0.006)		Epithelial destruction (p=0.001)	
Congenital groin hernia (Group A)	14 (n=14)	100%	8 (n=8)	100%	0 (n=8)	0%
Communicating hydrocele (GroupB)	12 (n=12)	100%	7 (n=7)	100%	0 (n=7)	0%
Non-communicating hydrocele (Group C)	2 (n=15)	14%	5 (n=15)	33%	10 (n=15)	67%

Our results demonstrated the absence of AR in 86% of AT in cases of non-communicating hydrocele and OR in 67% of these patients, but there were no absence of these steroid receptors in patients with communicating hydrocele. Epithelial destruction was found in 67% in Group C, while there were no destructive changes in Group B. These findings suggest the role of the hydrostatic pressure of fluid between the layers of tunica vaginalis in the lesion of appendix testis.

To examine the effect of the hydrocele on the AR status of testis in children is difficult, as only a biopsy can determine the changes in the testis. If compared to the lesions caused by the AT, it highlights the serious harmful influence of the increased hydrostatic pressure on the testis. On the other hand, the damage of AT can possibly be a new surgical indication of the treatment of non-communicating hydrocele, but only after understanding the complete nature and function of AT.

In conclusion, the persistence of non-communicating hydrocele leads the lesion of appendix testis, indicated the absence of androgen and oestrogen receptors and epithelial destruction. The knowledge of the physiological role of appendix testis is important to complete the indications of surgical treatment.

5. Summary

1. Reviewing the patients data base of the Department of Pediatrics, Medical and Health Science Center, University of Debrecen from 1. January 1997 to 31. December 2006, we found and published a previously undescribed symptom of the second branchial cleft remnant. We introduced, that the fetor ex ore can be the first sign of a complete second branchial cleft fistula.
2. We described a special forms of the bronchopulmonary foregut malformations, the extralobar pulmonary sequestration and highlighted the unusual blood supply of this very rare entity.
3. We determined the incidence of appendix testis (hydatid of Morgagni) with the largest intraoperative survey in the medical literature, and found 76% incidence of these hydatides in the descended testes.
4. We demonstrated firstly in the medical literature, that the incidence of appendix testis is significantly lower in undescended testes than normally descended testes and the mean age at orchiopexy is also lower in patients without appendix testis compared to those patients, who were found with appendix. The side of manifestation, testicular hypoplasia and presence of associated hernia sac did not influence the appearance of appendix testis in cases of undescended testes. These findings suggest the possible physiological role of appendix testis in the process of testicular descent.
5. We determined the androgen and estrogen receptor pattern in the epithelial surface of appendix testis in patients with descended and undescended testis. Our findings, the 100% presence of AR in the AT specimens of patients with acquired undescended testis and of patients with descended testes and its clear absence of these appendices of patients with congenitally undescended testes confirm the conclusion of our previous epidemiological investigative survey, that AR- positive AT may be one of the physiological requirements of the process of testicular descent.
6. We demonstrated, that the persistence of non-communicating hydrocele more than one month, leads the lesion of appendix testis, indicated the absence of androgen and estrogen receptors and epithelial destruction.

6. Acknowledgement

I would like to express my gratitude to my supervisor Professor Dr. Balla György, the Director of DE OEC Pediatric Clinic, who helped my PhD dissertation with his ideas, useful pieces of advice and encouragement, and made it possible for me prepare the immunofluorescence pictures in his laboratory.

I am grateful to Professor Dr. Oláh Éva, the former Director of DE OEC Pediatric Clinic for her continuous support and helping my professional development in the past ten years at her clinic.

I am also indebted to Professor Dr. Kiss Csongor, who helped me with the planning, preparing, carrying out and assessing the results of the research and also provided help with the manuscripts. Without his help this appendix research project could not have been completed.

I wish to thank Dr. Kovács Ilona, who is the head of the Department of Pathology, Kenézy Gyula County Hospital, Debrecen, and her colleagues Dr. Hargitai Zoltán and Dr. Pór Ágnes for aiding my research with histological and immunohistochemical examinations. I also wish to thank Dr. Telek Andrea and Dr. Dienes Beatrix their help with the immunofluorescence work.

I would like to thank my pediatric surgeon colleagues Dr. Csízy István, who is the head of the department, Dr. Cserni Tamás, Dr. Kutasy Balázs and Dr. Magyar Ágnes and to the whole Department.

I highly appreciated Professor Dr. Kertai Pál's constructive remarks and friendly conversations.

Szécsiné Kerekes Margit, Barna Erika, Sósne Csik Andrea and Gyarmatiné Hadházy Gyöngyi provided all the necessary technical support for my research, which I am really grateful to them.

Last, but not least I wish to thank all my family the patience and understanding they showed all through my research and the completion of this dissertation.

7. List of own references

Józsa T: Retentio testis. In: Kornya L. szerk. Betegség enciklopédia. Springer 2002; 444-5

Józsa T: Tüdő sequestratio. In: Kornya L. szerk. Betegség enciklopédia. Springer 2002; 477-8

Józsa T: Bronchogen cysták. In: Kornya L. szerk. Betegség enciklopédia. Springer 2002; 217

Józsa T, Cserni T, Szikszay E, Csízy I, Oláh É: „Foetor ex ore”-t okozó lateralis nyaki cysta. Gyermekgyógyászat 2003; 54:593-5

Józsa T, Cserni T, Szikszay E, Csízy I, Oláh É: Fetor ex ore – a rare presenting symptom of a complete second branchial fistula. Clinical Pediatrics (Phila) 2004; 43:475-6. **IF: 0,692**

Józsa T, Cserni T, Kutasy B, Csízy I: Bianchi-féle transscrotalis orchidopexiával szerzett rövid távú tapasztalatok. Magyar Urológia 2006; 13:225-9

Cserni T, Kiss Á, **Józsa T,** Szőlősi Z, Nagy B: Extralobar pulmonary sequestration in the right upper thoracic region. Respiration 2007; 74:215-9 **IF:1,649**

Józsa T, Csízy I, Kutasy B, Cserni T, Fláskó T: Decreased incidence of appendix testis in cryptorchidism with intraoperative survey.

Urologia Internationalis 2007; in press. **IF: 0,709**

Impakt faktor: 3,05