Original Communication

SOME ASPECTS OF EARLY DEVELOPMENT OF THE THYMUS: EMBRYOLOGICAL BASIS FOR ECTOPIC THYMUS AND THYMOPHARYNGEAL DUCT CYST

Ivan Varga [1, 2]*, Paulina Galfiova[1, 2], Veronika Jablonska-Mestanova [3], Stefan Polak [1, 2], Marian Adamkov [4]

[1] Institute of Histology and Embryology, Faculty of Medicine, Comenius University in Bratislava, Bratislava, Slovakia, Europe
[2] University Centrum of Reproductive Medicine of the 1st Department of Gynecology and Obstetrics, University Hospital, Bratislava, Slovakia, Europe
[3] Institute of Anthropology, Faculty of Natural Sciences, Comenius University in Bratislava, Bratislava, Slovakia, Europe
[4] Institute of Histology and Embryology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovakia, Europe

RESUMEN

Introducción. El objetivo principal de nuestro trabajo es el estudio histológico del desarrollo del timo humano entre la 5ª y la 8ª semana de gestación. Describimos varios términos embriológicos poco usados como: *timo secundus*, *descensus thymi* (la base embriológica para situar el timo en la garganta), *ductus timicus* (la base embriológica para el defecto innato llamado *conducto* timofaríngeo con posibilidad de formar un quiste). **Material y método.** Nuestras observaciones se basan en la investigación de 18 embriones humanos entre la 6ª y la 8ª semana de gestación. **Resultados.** La base del timo es común con la base de las glándulas paratiroideas. Es comparable con las bolsas faríngeas (*saccus pharyngeus*) en los embriones largos de 8 a 9 mm. La proliferación endodermal del epitelio en el tercer foco faríngeo (*focus faringeus 3*) es muy visible. La parte craneal y la parte dorsal son la base de origen de las glándulas paratiroideas inferiores. La parte caudal y la parte ventral son la base para el timo. Hemos observado también la notable proliferación del epitelio en la segunda bolsa faríngea, llamado por algunos autores *Timo secundus*. En nuestra opinión, en el ser humano no se forma un timo funcional en este lugar y la proliferación del epitelio en la mayoría de los casos, se detiene pronto. **Conclusión.** En este trabajo ofrecemos una vista general sobre la importancia clínica del desarrollo del timo y la descripción de los defectos innatos más frecuentes del mismo.

Palabras clave: *timo, foco faríngeo, ectopía tímica, conducto timofaríngeo*

ABSTRACT

Introduction. The aim of our morphological study is to describe the development of human thymus from 5th up to 8th week after fertilization in the context of its phylogenesis. We explicate some of the "forgotten" embryological terms with respect to their functions in thymic development, such as "*thymus secundus*", "*descensus thymi*" (an embryological basis for cervical thymus) and "*ductus thymicus*" (an embryologic basis for a congenital anomaly called thymopharyngeal duct with possible thymic cyst). **Material and methods.** Our findings are based on the study of 18 human embryos from 6th to 8th week of development. **Results.** The first primordia of the thymus and parathyroid glands within the endoderm of pharyngeal pouches can be seen in 8 to 9 mm crown-to-rump-length stages. The most evident epithelial proliferation is visible in the paired third pharyngeal pouch (*saccus pharyngeus tertius*): the cranial dorsal part of pharyngeal pouch initiates the inferior parathyroid gland and the caudal ventral part of the pouch gives rise to the epithelial thymus. We found an obvious endodermal epithelial proliferation also in the second pharyngeal pouch. Some authors depict this proliferation as "*thymus secundus*", but the proliferation of endoderm close down and the functional second thymus does not develop in human embryos. **Conclusion.** In our work we also review the clinical significance of early thymus development, as well as the most common developmental anomalies of thymus.

Key words: *thymus, pharyngeal pouches, ectopic thymus, thymopharyngeal duct*

* *Correspondence to*: **Dr. Ivan Varga**, PhD., Deputy Head of Institute of Histology and Embryology, Faculty of Medicine, Comenius University in Bratislava, Sasinkova Street 4, SK-811 08 Bratislava, Slovakia (Europe).
ivan.varga@fmed.uniba.sk

Received: 16 January, 2011. **Revised**: 30 January, 2011. **Accepted**: 20 February, 2011.

INTRODUCTION

In vertebrates, the pharyngeal apparatus develops from a transient series of segmental structures appearing as bulges on the cranial lateral side of the embryo, named the pharyngeal (phylogenetically so-called branchial) arches (*arcus pharyngei*). The pharyngeal arches are composed of tissues derived from all three embryonic germ layers. Indeed, each arch is covered by ectoderm on the outside and endoderm on its inside. Its core is of mesodermal origin and is surrounded by mesenchyme derived from neural crest (ectomesenchyme). As development proceeds, a lateral wall of the pharynx invades the arches forming an endodermal out-pocketing known as the pharyngeal pouch (*saccus pharyngeus*), whereas externally, the overlying ectoderm depresses forming a groove termed pharyngeal cleft (*sulcus pharyngeus*) (Grevellec and Tucker, 2010). The question regarding the development of organs derived from the pharyngeal region in different vertebrates belongs to one of the most complicated embryological problems. A number of studies have tried to answer the question regarding the origin of structures of the oral, pharyngeal and laryngeal cavities, original pharyngeal arches, clefts and pouches as well as organs of head and neck (Pospíšilová and Slípka, 2000; Graham, 2001; Graham, 2003; Gordon et al, 2004). The results of these studies are sometimes considerably different, because during the early ontogenesis of vertebrates not only the localization and function of pharyngeal arches, but also of ectodermal clefts and endodermal pouches change substantially (Varga et al, 2008). Phylogenetically, the pharyngeal region was the place, where the gills of aquatic vertebrates developed. The respiratory and osmoregulatory functions of gills have lost their importance in the process of evolutionary transition of animals from aquatic to terrestrial way of life. The pharyngeal (branchial) region has become adapted to the new endocrine (developing of parathyroid glands and calcitonin-producing cells of thyroid gland) and immune functions (thymus and palatine tonsil) (Slípka et al, 1998). One of the genetically determined consequences of a disrupted formation of pharyngeal apparatus is the DiGeorge´s syndrome (*aplasia thymoparathyroidea*) caused by a multigene-deletion from chromosome 22 (Wurdak et al, 2006).

Majority of recently published manuscripts about thymus development describe its development in mice (Müller et al, 2008; Foster et al, 2008; Itoi et al, 2006), whereas classical morphological studies on human embryos and fetuses are occasional (for example Repetto et al, 2010). The aim of our morphological study is to describe the development of human thymus from 5th up to 8th week after fertilization in the context of its phylogenesis. We explicate some of the "forgotten" embryological terms with respect to their functions in thymic development, such as "*thymus secundus*", "*descensus thymi*" (an embryological basis for cervical thymus) and "*ductus thymicus*" (*ductus medullaris thymi*; an embryologic basis for a congenital anomaly called thymopharygeal duct with possible thymic cyst). The paired epithelial primordia of thymus derived from the third pharyngeal pouch descend together with the inferior parathyroid primordia. Influenced by "*descensus thymi*", the epithelial primordium detaches from the pharyngeal wall and at the beginning of the 7th week, it may have a fissure formed in the center which can be designated as "*ductus thymicus*".

MATERIAL AND METHODS

Our findings are based on the study of 18 human embryos from 6th to 8th week of development (six embryos in each developmental week). The studied embryos belong to the collections of the Departments of Histology and Embryology of the Faculty of Medicine, Comenius University in Bratislava, Slovakia. We used serially sectioned slides, in sagittal and transversal sections. Paraffin sections (approximately seven micro-meters thick) were stained with hematoxylin and eosin and with Masson´s trichrome (staining for collagen fibers). The reticular fibers were visualized by using the modified Lillie´s impregnation method (Lillie, 1965). The presence of glycogen was demonstrated by the combination of Periodoc Acid Schiff (PAS)-reaction, Celestine blue and Orange G.

RESULTS

The first primordia of the thymus and parathyroid glands within the endoderm of pharyngeal pouches can be seen in 8 to 9 mm crown-to-rump-length stages. The most evident epithelial proliferation is visible in the third pharyngeal pouch: the cranial dorsal part of the pharyngeal pouch initiates inferior parathyroid gland and the

caudal ventral part of the pouch gives rise to the epithelial thymus (see Fig. 1a and 1b). The differences between these two endodermal epithelial proliferations are evident: the cells of future parathyroid gland are larger and lighter (Fig. 2 and 3) and contain more glycogen inclusions (PAS-positive substance, Fig. 4) than the epithelial cells of developing thymus.

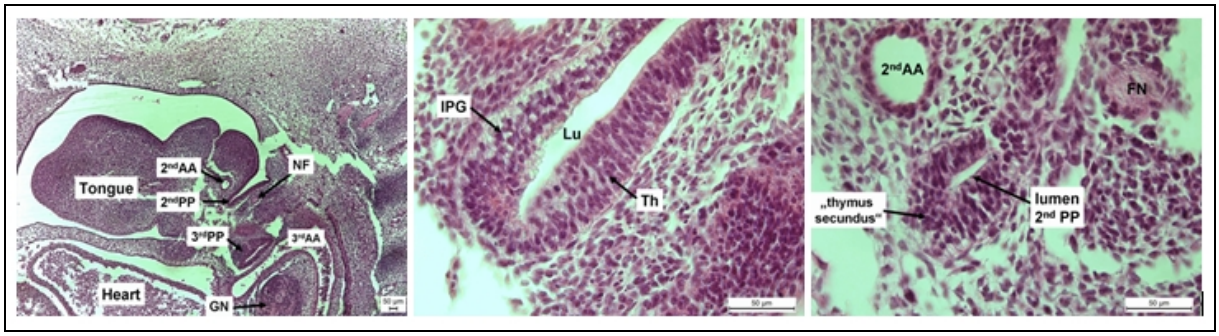

Figure 1a (left)**-** Sagittal section of human embryo at the beginning of 6th week of development (36 days). Nearby second pharyngeal pouch (2ndPP) is the second aortic arch (2ndAA) and facial nerve (NF); nearby third pharyngeal pouch (3rdPP) is the third aortic arch (3rdAA) and glossopharyngeaus nerve (GN). The developing tongue and heart are visible, too (Hematoxylin & Eosin, Orig. Magn. 50x). **Figure 1b** (middle)- Detail view of the third pharyngeal pouch (the same embryo as in Fig. 1a, but 75 sections; 0.5mm laterally). The endodermal proliferations of thymus (Th) and inferior parathyroid gland (IPG) are visible. Lu – lumen of the third pharyngeal pouch (Hematoxylin & Eosin, Orig. Magn. 400x). **Figure 1c** (right)- Detail view of the second pharyngeal pouch (the same embryo as in Fig. 1a, but 6 sections; 40µm laterally). The endodermal epithelial proliferation of the second pharyngeal pouch (2ndPP) is so-called "thymus secundus". 2ndAA – second aortic arch, FN – facial nerve (Hematoxylin & Eosin, Orig. Magn. 400x).

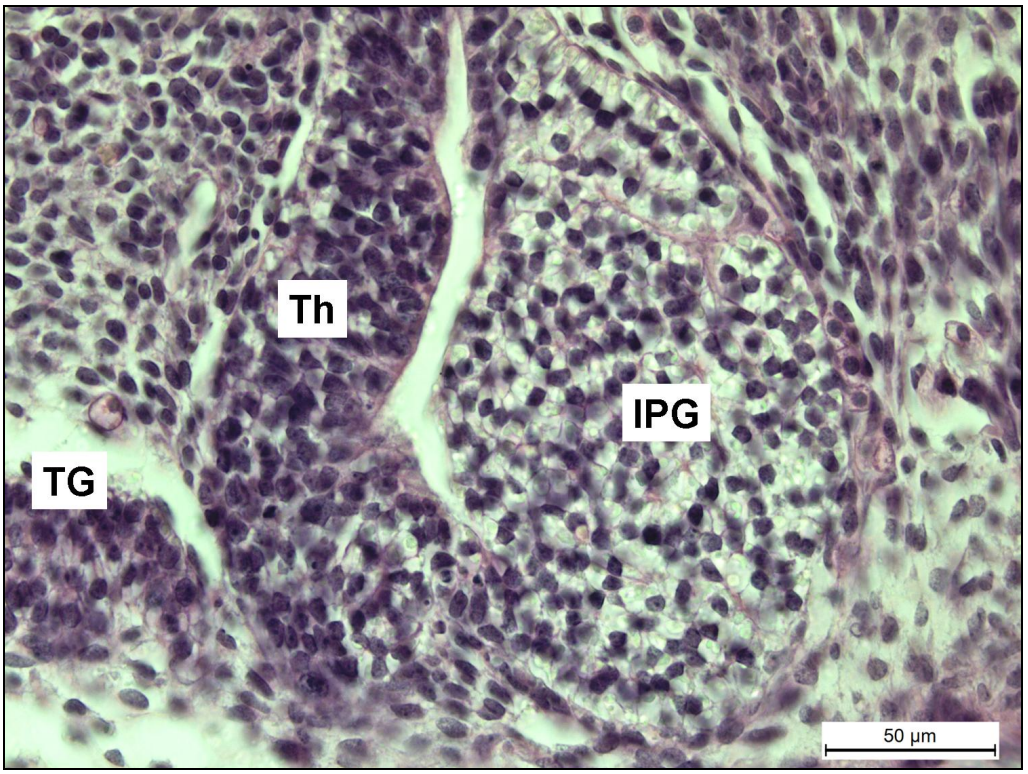

Figure 2- Sagittal section of human embryo at the middle of 7th week of development – detail view of the third pharyngeal pouch. Th – thymus, IPG – inferior parathyroid gland, TG –thyroid gland (Hematoxylin & Eosin, Orig. Magn. 400x).

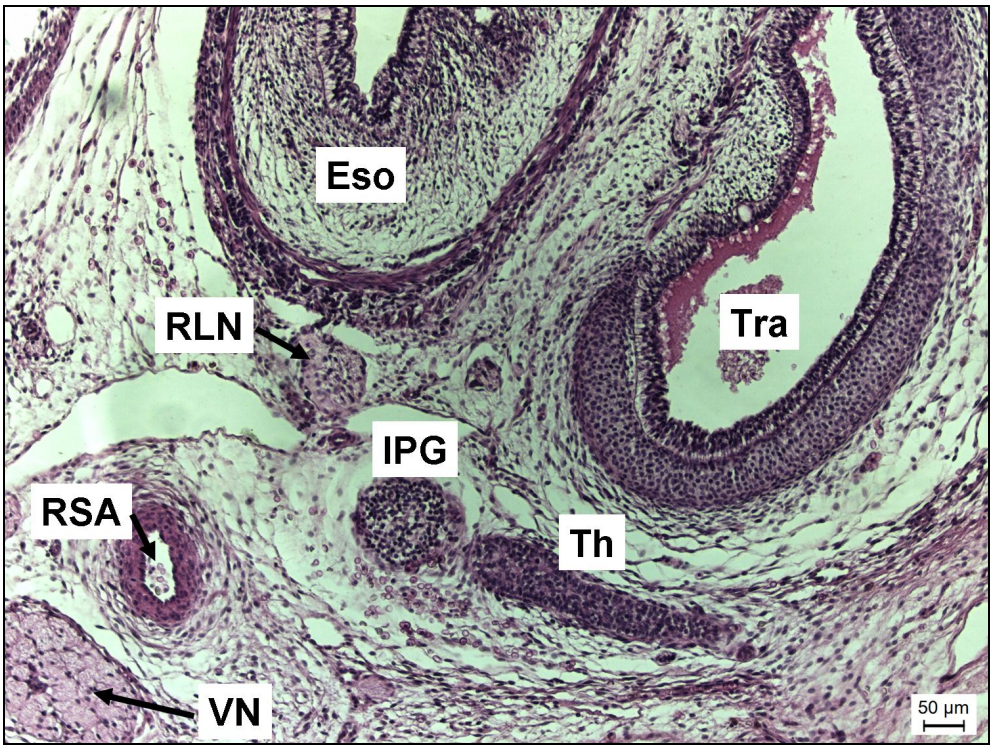

Figure 3- Transversal section of human embryo at the end of 7th week. Th – thymus, IPG – inferior parathyroid gland, Eso – esophagus, Tra – trachea, RLN – recurrent laryngeal nerve, RSA – right subclavian artery, VN – vagus nerve (Hematoxylin & Eosin, Orig. Magn. 100x).

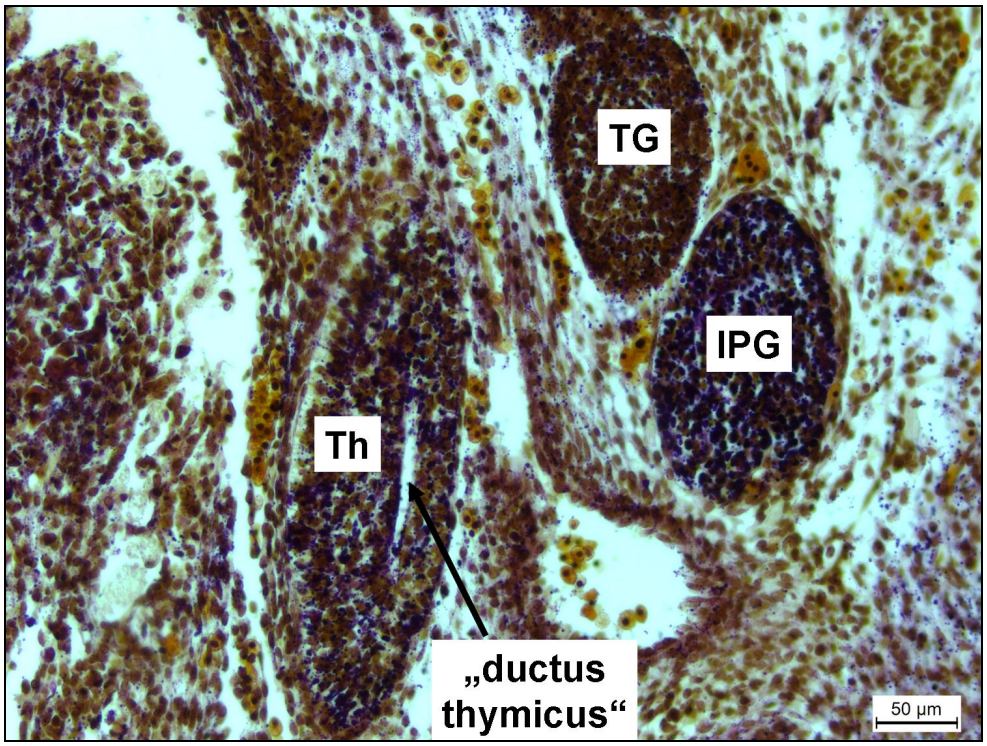

Figure 4- Sagittal section of human embryo at the end of 7th week. Th – thymus with ductus thymicus, TG – thyroid gland, IPG – inferior parathyroid gland (containing PAS-positive substance) (PAS + orange G + celestine blue, Orig. Magn. 200x).

We found a quite obvious endodermal epithelial proliferation also in the second pharyngeal pouch (*saccus pharyngeus secundus*, Fig. 1c) in early human development (beginning of the 6th week), but we did not find a marked epithelial proliferation in the fourth pouch (*saccus pharyngeus quartus*).

The paired epithelial primordia of thymus derived from the third pharyngeal pouches descend together with the third parathyroid primordia. Influenced by "*descensus thymi*", the epithelial primordium detaches from the pharyngeal wall and at the beginning of the 7th week, it may have a fissure formed in the center which could be labeled as "*ductus thymicus*" (*ductus medullaris thymi*, Fig. 4).

The thymus primordia at the 7th and 8th week of development contain almost exclusively epithelial cells. These epithelial cells are arranged at the periphery as a row of prismatic cells, as can be seen at the light microscopic level (Fig. 5). A basal lamina separates these epithelial cells from the surrounding mesenchyme, derived from neural crest (*textus cristae neuralis*, *mesectoderma*, Fig. 6). The rapid growth of embryo causes the paired thymus primordia come close to each other and lay in front of the pericardium at the 7th and 8th week of development (Fig. 7 and 8). They stay separated by a layer of connective tissue and never fuse together. In this period, the epithelial primordia of thymus ("*thymus epithelialis*") develop into a primary lymphoid organ ("*thymus lymphaticus*").

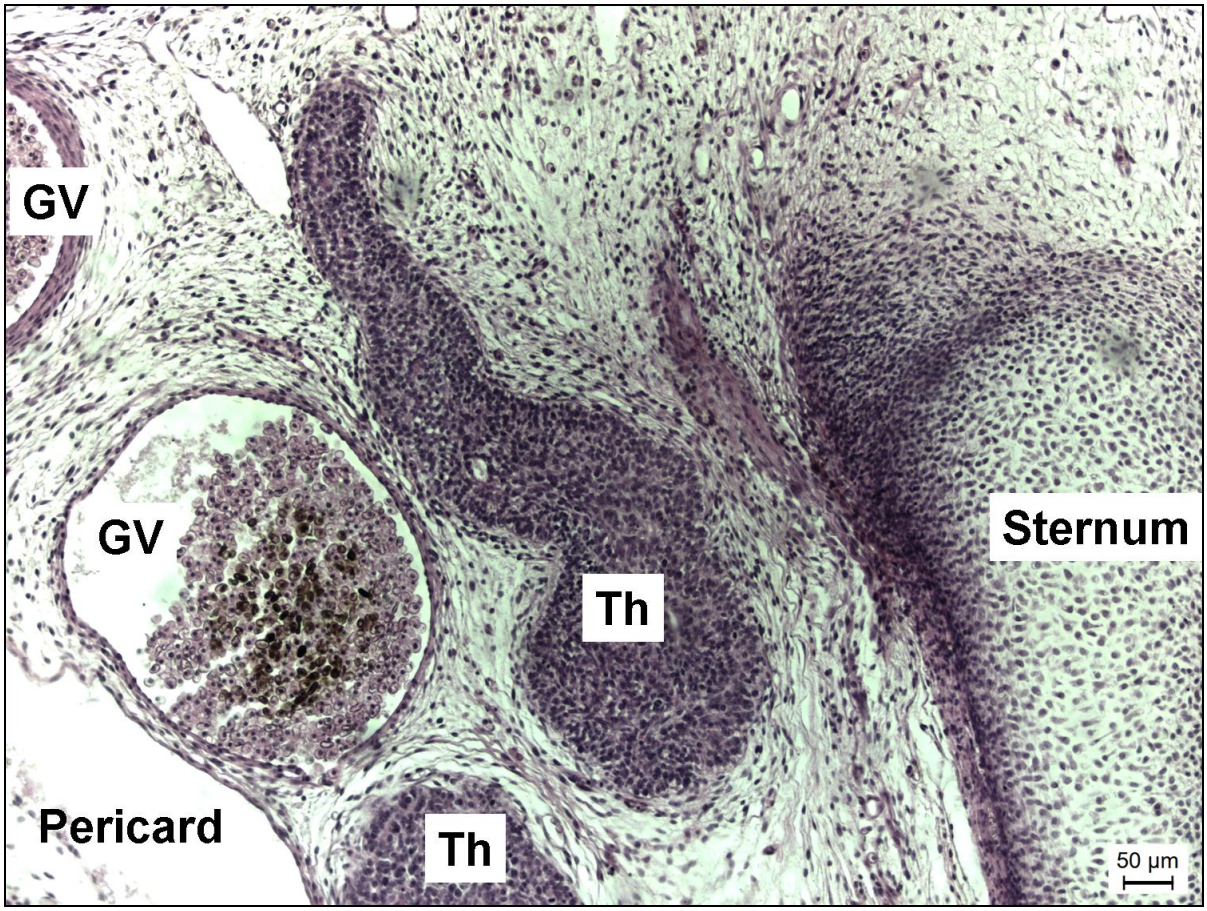

Figure 5- Sagittal section of human embryo at the middle of 8th week. Th – epithelial thymus, GV – developing great vessels (Hematoxylin & Eosin, Orig. Magn. 100x).

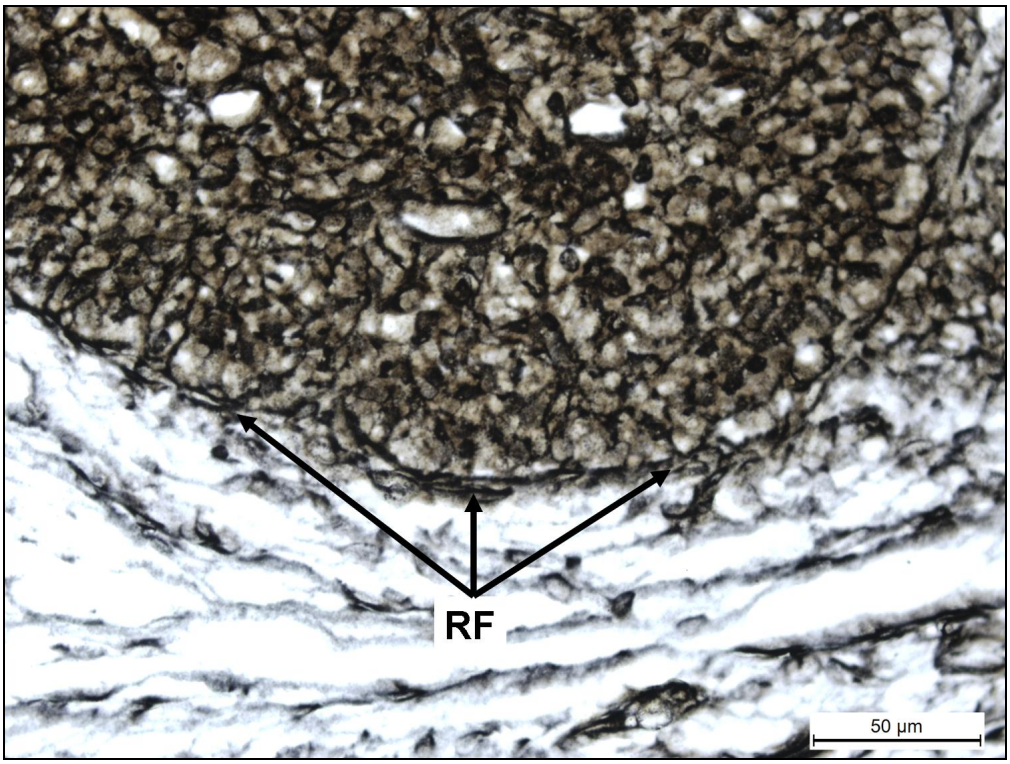

Figure 6- Visualization of reticular fibers of thymus of the same embryo as in Fig. 5. Reticular fibers (RF) surround the epithelial thymus (impregnation method according to Lillie, Orig. Magn. 400x).

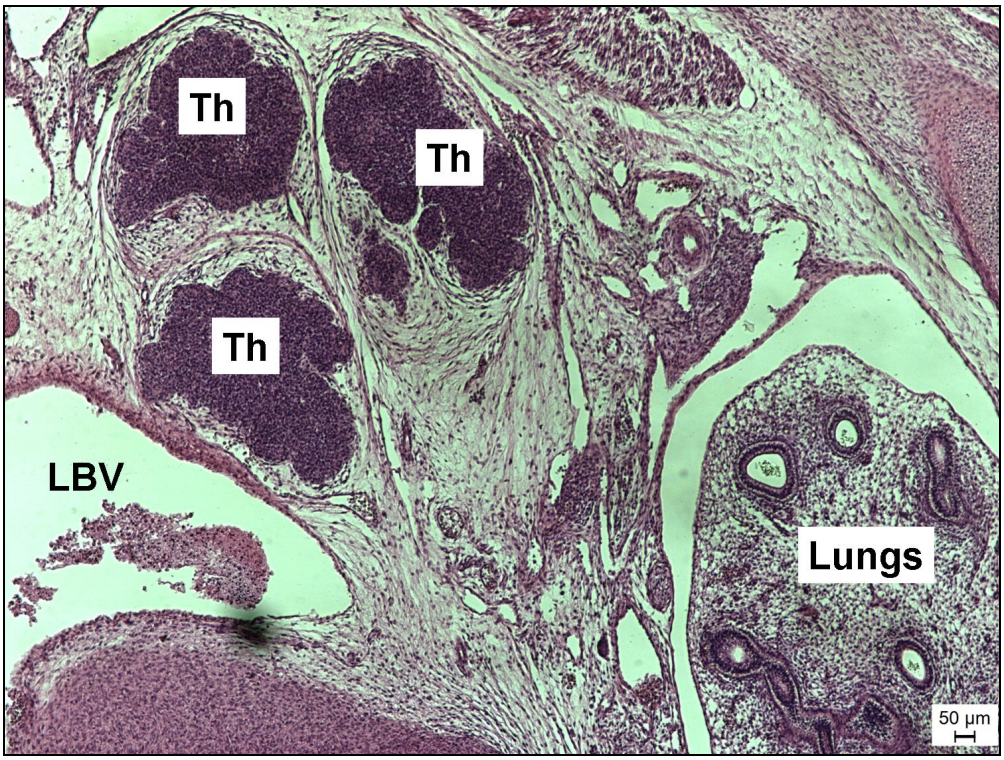

Figure 7- Transversal section of human embryo at the end of 8th week. Th – thymus, LBV – left brachiocephalic vein (Hematoxylin & Eosin, Orig. Magn. 50x).

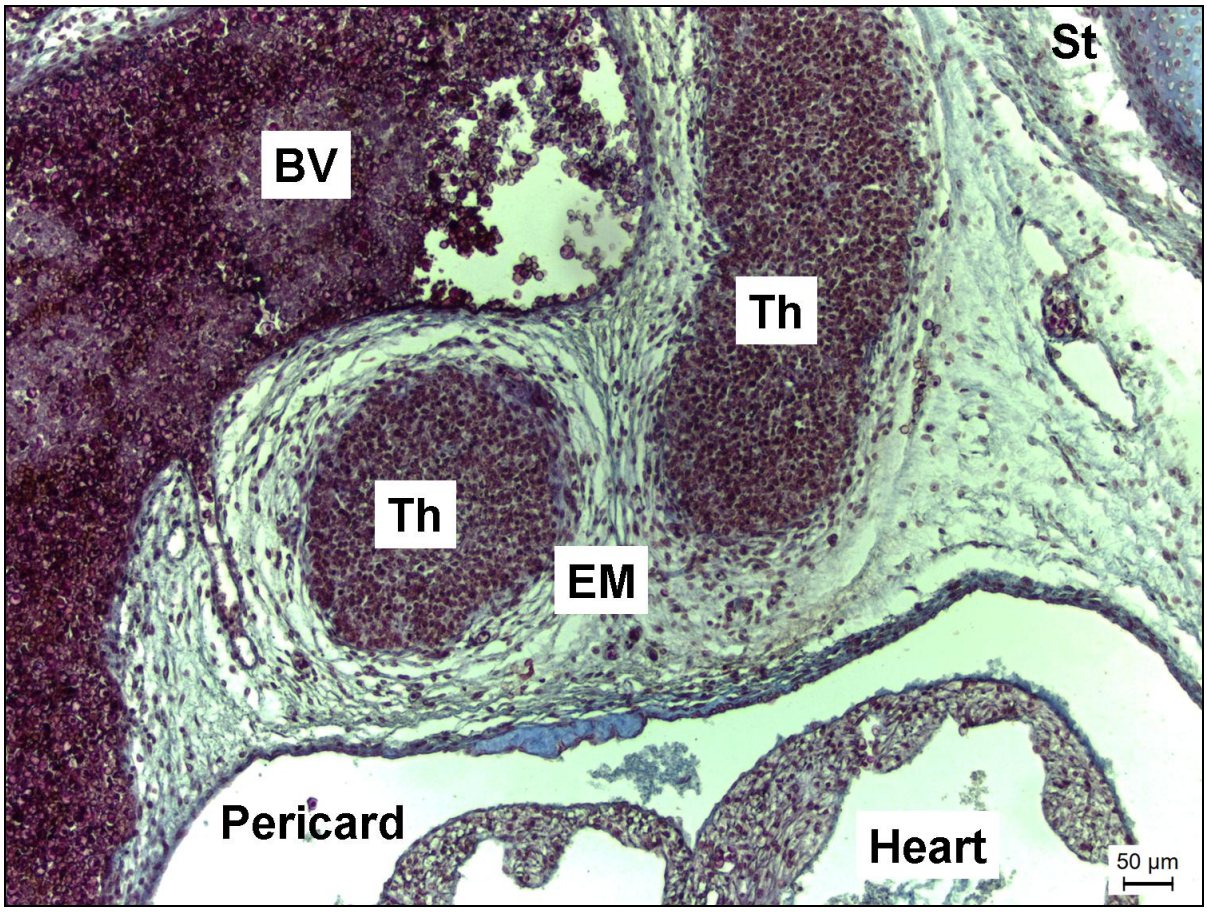

Figure 8- Sagittal section of human embryo at the end of the 8th week. Th – thymus, EM – ectomesenchyme, BV – brachiocephalic vein, St – cartilage of developing sternum (Masson´s trichrome, Orig. Magn. 100x).

DISCUSSION

The embryonic pharynx is very important for the development of many organs, including the thyroid and parathyroid glands, palatine tonsil as well as the thymus. An epithelial proliferation of a distal part of the second, third and fourth pharyngeal pouches in the cranio-caudal sequence starts at the beginning of the sixth week of development (6 to 8 mm crown-to-rump-length).

We found a quite obvious endodermal epithelial proliferation not only in the third pharyngeal pouch, but also in the second pharyngeal pouch. Some authors depict this proliferation as "*thymus secundus*", but the proliferation of the endoderm close down and the functional second thymus does not develop in human embryos at all (Pospíšilová and Slípka, 1994; Slípka and Pospíšilová, 1995). We assume that the thymus-developing potency of the second pharyngeal pouch is probably evolutionary encoded. For example, in sharks, when a thymus develops for the first time from the evolutionary point of view, the thymuses appear in all branchial clefts, except the first and the last one (Pospíšilová et al, 1999). In the process of vertebrate evolution a gradual reduction of gills together with the thymic primordia occurs. Finally, in humans, thymic primordia have been reduced usually only to the paired third pharyngeal pouch. However, according to some authors (Gasser, 1975; Van Dyke, 1941), part of thymus (thymus IV) develops from the epithelial proliferation of the fourth pharyngeal pouch. In our sections, we did not find a marked epithelial proliferation in the fourth pouch. According to Pospíšilová et al (1999), the early thymic primordia in the second and fourth pouch stop their differentiation, because they cannot fuse with the ectodermal proliferation mass of the pharyngeal clefts. This hypothesis, which supports the dual endo- and ectodermal

origin of epithelial thymus, was confirmed also by Rezzani et al (2008). Nevertheless, confirmed experimentally, a single pharyngeal endoderm can generate a functional thymus, too (after ectopic transplantation of pharyngeal endoderm in mice; Gordon et al, 2004).

The epithelial primordium detaches from the pharyngeal wall and at the beginning of the 7th week, it may have a "fissure" or "duct" formed in the center. This "duct" may be a reminiscence of an evolutionary stage in thymic phylogenesis in sharks *Notorynchus cepedianus*. In this species, all of the seven hollow thymic primordia are claimed to be joined with the branchial clefts by means of epithelial ducts. This structure confirms that at certain point the thymus had an excretory character (Slípka, 1986).

The thymus primordia at the 7th and 8th week of development contain almost exclusively epithelial cells. The ultrastructural appearance indicates different types of epithelial cells at the periphery in comparison to those in the center of this early thymic primordium (von Gaudecker, 1986). Mass of epithelial cells that constitutes the primordial thymus attracts lymphoid precursor cells to this region from the blood-stream. The lymphoid precursor cells leave the blood vessels and migrate through the neural crest-derived mesenchyme into a primitive epithelial organ (Bockman, 1997).

The disruption of thymic descent can result in an ectopic thymus (*ectopia thymi*) or cervical extension of thymus (*textus thymicus accessorius, lobuli thymici accessorii*) localized anywhere from the mandibular angle to the upper mediastinum. An ectopic thymus localized in the cervix is often called also "*thymus cervicalis*". The cervical thymus is a distinct entity from cervical extension of thymus. The basic difference is that in a case of ectopic thymus there is no thymus gland localized in its normal position.

An ectopic thymus does not usually cause severe clinical symptoms. On the other hand, cervical remnants of thymic tissue have been found in up to 30% of infants studied at autopsy (Wagner et al, 1988). Genetic research has confirmed theory that the migration of thymic primordia is controlled by neural crest-derived cells, which are present as an ectomesenchyme on the surface of these primordia. Patients with a deletion in the HOX family of transcription factors (expressed by neural crest cells) have a normal sized thymus, but in general, it is located above its normal position (Manley and Blackburn, 2003). Various types of cervical thymus may be present as a neck mass, usually laterally, from the angle of the mandible to the manubrium. Since it is rare to diagnose this entity before its surgical removal, the differential diagnosis includes the more common pharyngeal cleft cyst, thyroglossal duct cyst, cystic hygroma, cystic dermoid and lesions of the salivary gland as well as thyroid and parathyroid glands and cervical lymph nodes (Zarbo et al, 1983).

Review of literature reveals relatively few records concerning anomalies in shape and location of thymus. More than 100 cases have been described in the literature, ten percent of which occurred in neonates. Among the most severe clinical symptoms of ectopic cervical thymus belong:

- Severe dyspnoe, stridor or dysphagia (Bistritzer et al, 1985; Shah et al, 2001);
- Mimicking thyroid gland enlargement (Conwell and Batch, 2004) or subglottic mass as congenital haemangioma (Pai et al, 2005);
- Causing snoring at sleep (Prasad et al, 2006).

When *ductus thymicus* persists, it can be present clinically as a mass in the neck, and can develop into thymopharyngeal duct cyst – a special variant of ectopic thymic tissue (Zarbo et al, 1983). Congenital thymic cysts are uncommon and often misdiagnosed as either pharyngeal cleft cysts or cystic hygromas. However, they may have a characteristic appearance on CT. The course of the embryologic thymic tissue descent from the neck to the mediastinum indicates the potential site of deposition of an ectopic cervical thymic cyst. In a child, a cystic lesion that has an intimate relationship to the carotid sheath is likely to be a thymic cyst. Approximately 100 cases of vestigial cervical thymus or thymic cysts have been reported in children, only five of them with a persistent thymopharyngeal duct cyst (Burton et al, 1995). Other hypothesis for thymopharyngeal duct cyst development is a cystic degeneration of Hassall´s corpuscles of ectopic cervical thymus (Kaufman et al, 2001), but from an embryological point of view this hypothesis is, in our opinion, not so relevant.

Thymic cysts have been described as asymptomatic and of little clinical consequence. Recent reports have stressed the possibility of respiratory compromise associated with these lesions (Wagner et al, 1988). They are usually present in the 1st decade of life, after the age of two years, possibly because thymus reaches its greatest development before puberty. The lesions, mentioned above, may be found anywhere along the normal descent route of the thymus gland from the mandible to the *manubrium sterni*; 50% of them extend into the mediastinum (De Caluwé et al, 2002; Cigliano et

al, 2007). The most frequent immunodeficient conditions caused by abnormal development of thymus (thymic aplasia or hypoplasia) are reviewed in Table 1.

We confirm the previous findings that the most evident epithelial proliferation is visible in the third pharyngeal pouch and gives rise to inferior parathyroid glands as well as to the epithelial thymus. We found a quite obvious endodermal epithelial proliferation in the second pharyngeal pouch, too, which is probably evolutionary encoded. But we did not find a marked epithelial proliferation in the fourth pouch in our sections. According to the difficult thymic development, we summed up some of the clinical diseases related to its disruption.

Syndrome	Thymus	Humoral immunity	Cellular immunity	Lymfocytes (in blood)	Immunoglo-bulins	Genetic
DiGeorge syndrome	Aplasia	Normal	Deficient	Normal or reduced	Normal	-
Nezelof syndrome	Hypoplasia	Normal or slightly deficient	Deficient	Reduced	Normal or slightly deficient	Autosomal recessive
Reticular dysgenesis	Hypoplasia	Deficient	Deficient	Reduced	Deficient	-
Agamaglo-bulinaemia (Swiss type)	Hypoplasia	Markedly reduced	Absent or deficient	Markedly reduced	Deficient	Autosomal recessive
Thymic alymphoplasia	Hypoplasia	Deficient	Absent or deficient	Reduced	Deficient	Male only, recessive
Louis-Barr syndrome (ataxia telangiectasia)	Hypoplasia	Slightly deficient	Deficient	Variable	Normal or slight IgA deficiency	Autosomal recessive
Agamaglo-bulinaemia with thymom	„spindle cell“ tumor	Deficient	Deficient	Reduced	Deficient	-

Table 1- Immunodeficient consequences caused by abnormal development of thymus (according to Day and Gedgaudas, 1984).

ACKNOWLEDGEMENT

The study was supported by the Grant VEGA of Ministry of Education of Slovakia “Thymus in human ontogenesis - the changes in structure and ultrastructure of thymus in children with congenital heart defects”

REFERENCES

Bistritzer T, Tamir A, Oland J, Varsano D, Manor A, Gall R, Aladjem M. 1985. Severe dyspnea and dysphagia resulting from an aberrant cervical thymus. Eur J Pediatr 144: 86-7.

Bockman DE. 1997. Development of the thymus. Microsc Res Techn 38: 209-15.

Boyd J, Templer J, Havey A, Walls J, Decker J. 1993. Persistent thymopharyngeal duct cyst. Otolaryngol Head Neck Surg 109: 135-9.

Burton EM, Mercado-Deane MG, Howell CG, Hatley R, Pfeifer EA, Pantazis CG, Chung C, Lorenzo RL. 1995. Cervical thymic cysts: CT appearance of two cases including a persistent thymopharyngeal duct cyst. Pediatr Radiol 25: 363-5.

Cigliano B, Baltogiannis N, De Marco M, Faviou E, Antoniou D, De Luca U, Soutis M, Settimi A. 2007. Cervical thymic cysts. Pediatr Surg Int 23: 1219-25.

Conwell LS, Batch JA. 2004. Aberrant cervical thymus mimicking a cervical mass. J Paediatr Child Health 40: 579-80.

Day DL, Gedgaudas E. 1984. Symposium on nonpulmonary aspects in chest radiology. The thymus. Radiol Clin North Am 22: 519–538.

De Caluwé D, Ahmed M, Puri P. 2002. Cervical thymic cysts. Pediatr Surg Int 18: 477-9.

Foster K, Sheridan J, Veiga-Fernandes H, Roderick K, Pachnis V, Adams R, Blackburn C, Kioussis D, *Coles M.* 2008. Contribution of neural crest-derived cells in the embryonic and adult thymus. J Immunol 180: 3183-9.

Gasser RF. 1975. Atlas of Human Embryos. Hagerstown: Harper & Row, 1-318.

Gordon J, Wilson VA, Blair NF, Sheridan J, Farley A, Wilson L, Manley NR, Blackburn CC. 2004. Functional evidence for a single endodermal origin for the thymic epithelium. Nature Immunol 5: 546-53.

Graham A. 2001. The development and evolution of the pharyngeal arches. J Anat 199: 133-41.

Graham A. 2003. Development of the pharyngeal arches. Am J Med Gen 119A: 251-6.

Grevellec A, Tucker AS. 2010. The pharyngeal pouches and clefts: Development, evolution, structure and derivates. Sem Cell Dev Biol 21: 325-32.

Itoi M, Tsukamoto, Yoshida H, Amagai T. 2006. Mesenchymal cells are required for functional development of thymic epithelial cells. Int Immunol 19: 953-64.

Kaufman MR, Smith S, Rothschild MA, Som P. 2001. Thymopharyngeal duct cyst: an unusual variant of cervical thymic anomalies. Arch Otolaryngol Head Neck Surg 127: 1357-60.

Lillie RD. 1965. Histopathologic Technic and Practical Histochemistry. 3rd edition. New York: McGraw-Hill Book Company, 1-715.

Manley NR, Blackburn CC. 2003. A development look at thymus organogenesis: where do the non-hematopoietic cells in the thymus come from? Curr Opin Immunol 15: 225-32.

Müller SM, Stolt CC, Terszowski G, Blum C, Amagai T, Kessaris N, Iannarelli P, Richardson WD, Wegner M, Rodewald HR. 2008. Neural crest origin of perivascular mesenchyme in the adult thymus. J Immunol 180: 5344-51.

Pai I, Hegde V, Wilson POG, Ancliff P, Ramsay AD, Daya H. 2005. Ectopic thymus presenting as a subglottic mass: diagnostic and management dilemmas. Int J Ped Otorhinolaryng 69: 573-6.

Pospíšilová V, Slípka J. 1994. Does the thymus develop in the third branchial pouch only? Funct Develop Morphol 4: 247-8.

Pospíšilová V, Slípka J, Zlatoš J, Kočová J. 1999. Contribution to the thymus evolutionary morphology. Plzen Lek Sborn 72: 205-7.

Pospíšilová V, Slípka J. 2000. Pharyngeal region derivates in early human development. Plzen Lek Sborn 74: 93-8.

Prasad TRS, Chui CH, Ong CL, Meenakshi A. 2006. Cervical ectopic thymus in an infant. Singapore Med J 47: 68-70.

Repetto E, Aliendo MM, Biasutto SN. 2010. Morphological changes of the thymus in the fetal stage and its clinical significance. Rev Arg de Anat Clin 2: 7-15.

Rezzani R, Bonomini F, Rodella LF. 2008. Histochemical and molecular overview of the thymus as site fot T-cells development. Prog Histochem Cytochem 43: 73-120.

Shah SS, Lai SY, Ruchelli E, Kazahaya K, Mahboudi S. 2001. Retropharyngeal aberrant thymus. Pediatrics 108: 94-7.

Slípka J. 1986. Evolutionary morphology of the branchial region as the reflection of environmental changes. In: Novák VJA, Vančata V, Vančatová MA (eds.) Behaviour, Adaptation and Evolution. Praha, ČSAV, 203-211.

Slípka J, Pospíšilová V. 1995. „Thymus secundus“ beim Menschen. Ann Anat 177: 386.

Slípka J, Pospíšilová V, Slípka JJr. 1998. Evolution, development and involution of the thymus. Folia Microbiol 43: 527-30.

Van Dyke JH. 1941. On the origin of accessory thymic tissue, thymus IV: the occurrence in man. Anat Rec 79: 179-209.

Von Gaudecker B. 1986. The development of the human thymus microenviroment. In: Müller-Hermelink HK (ed) The human thymus. Histophysiology and pathology. Berlin, Springer-Verlag, 1-41.

Wagner CW, Vinocur CD, Weintraub WH. 1988. Respiratory complication in cervical thymic cysts. J Pediatr Surg 23: 657-60.

Wurdak H, Ittner LM, Sommer L. 2006. DiGeorge syndrome and pharyngeal apparatus development. BioEssays 28: 1078-86.

Zarbo RJ, McClatchey KD, Areen RG, Baker SB. 1983. Thymopharyngeal duct cyst: a form of cervical thymus. Ann Otol Rhinol Laryngol 92: 284-9.