LETTER TO THE EDITOR

The functional morphology of the thymus – new views on this forgotten organ

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Dear Editor-in-Chief, Bratislava Medical Journal,

We have been highly interested in the topical review “The role of ascorbic acid and monosodium glutamate in thymocyte apoptosis” from Serbian authors Pavlovic and Sarac (1). We congratulate the authors for their interest and actual paper on the one of the most mysterious organ of human body, the thymus. The aim of our paper is to shortly summarize the recent knowledge about factors affecting morphology of the thymus gland, especially focused on Slovak studies.

The thymus is lymphoepithelial organ with immune and endocrine functions. It is the crossroad between immune and neuroendocrine systems (2). Interactions between nervous, endocrine, and immune systems might represent the anatomical and functional basis for the understanding of the pathways and mechanisms that enable the brain to modulate the progression of disease (3). From the phylogenetical point of view, thymus played a key role in the evolution of animals during development of an adaptive immune system; therefore it is an important feature separating higher vertebrates from other animals (4). The development of thymus gland is extremely complex. The thymus is derived from pharyngeal region; a region from which, in case of aquatic vertebrates, the gills develop (5, 6). The development of the pharyngeal region, as well as its derivatives (connective tissue, bone and muscles of head and neck, thymus, parathyroid and thyroid glands) involves the interactions between a numbers of disparate embryonic cell types derived from all germ layers: ectoderm (including neural crest-derived cells), endoderm, and mesoderm (7–9).

For centuries, thymus remained an enigmatic organ with unknown functions. The first demonstration of its crucial role in establishing the development of normal immune system was provided in 1961. It was shown that mice thymectomized immedia-
ately after birth had poorly developed lymphoid tissues, impaired immune responses and inordinate susceptibility to intercurrent infections (10–12).

Due to the knowledge of the normal development and microscopic structure, thymus gets a new importance this time. The human thymus is an organ, which interests specialists from many branches: theoretical and clinical. As a primary lymphoid organ and the place of maturation of T-lymphocyte subpopulation, thymus presents the biggest interest for immunologists. It’s the only lymphatic organ, in which the epithelial cells form the carrying framework (13). That is predetermined by its incomparable properties, which are also reflected in many pathological states. Thymus develops from the interaction of all three germinal layers (14). During human ontogenesis, thymus undergoes major morphological changes including a rapid prenatal growth and postnatal progressive (age-related) involution (15).

Both radiologists and other clinicians interested in the neck region (for example 16–18) frequently get into touch with congenital development defects and remnant embryonal descent of thymus. Migration of the neural crest cells, which is also important for the development of heart, is closely connected to the ordinary development of thymus. For example, it brings up the question of congenital immunodeficiency by various heart defects (19), chromosomal anomalies such as the DiGeorge’s syndrome (for example 20–23). Based on the knowledge of thymic normogenesis, some authors question the prenatal diagnostic of congenital heart defects by examining the thymus by some acceptable, non-invasive imaging technology (24). The question of thymus transplantation in its congenital agenesis is becoming very actually at this place (25). The thymic size can be an important indicator of the function of immune system (26), nutrition status (27, 28), and also the general health status of child in the pediatric praxis (29, 30). In medical literature, some authors also expected the relationship between the thymic normogenesis and development of atopy or allergy (31, 32). The changes in T-lymphocyte population (on the cellular and molecular level) and thymus involution are also connected to the aging of the immune system. Early aging of the immune system can thereby contribute to the genesis of autoimmune disease and also expressively affect the overall ageing of the organism (33, 34).
Human thymus reaches its biggest size in proportion to body weight at birth. Under normal circumstances, the thymus commences age-related involution soon after birth. The thymus undergoes a progressive reduction in size due to profound changes in its anatomy associated with the loss of thymic epithelial cells and decrease in thymopoiesis (35–37). Age-related involution is reversible. For example, castration in old rats and mice resulted in the regeneration of the atrophied thymuses (38, 39). In various stressful conditions, the thymus is subjected to stress-related involution. These progressive, but reversible processes take place within a few days of stress. This involution is intensive especially in newborns and infants who normally have a large volume of thymus tissue. An increased levels of endogenous steroids (conspicuous in newborns and infants who normally have a large volume of thymus) within a few days of stress. This involution is intensive especially in newborns and infants who normally have a large volume of thymus tissue. An increased levels of endogenous steroids (conspicuous according to Hans Selye theory by stress) causes atrophy of thymus tissue. An increased levels of endogenous steroids (conspicuous in newborns and infants who normally have a large volume of thymus) within a few days of stress. This involution is intensive especially in newborns and infants who normally have a large volume of thymus tissue. An increased levels of endogenous steroids (conspicuous according to Hans Selye theory by stress) causes atrophy of thymus cortex and thereby its preterm aging. Consequently, a special chapter of thymus studies is the research of factors influencing its function, whereas not all exogenous factors are known by now.

A chronic stress in the experiment (in laboratory rats evoked by cyclical and forced swimming) caused the reduction of the thymus volume, decreased the number of lymphocytes and simultaneously also increased the number of apoptotic lymphocytes in thymus (40).

Also, infections in pregnancy, for example chorioamnionitis, cause structural changes in thymus of fetus and newborn (41). De Felice et al (42) proved the reduction of thymus in newborns with chorioamnionitis by the X-ray studies of thorax. Their results affirmed the importance of prenatal examination of the size of thymus for precocious diagnostics and successful treatment of gravidity with chorioamnionitis. By a preterm ageing, thymus also reacts to common infections of the upper airways. Children of HIV-positive mothers had also small thymus (43). Some studies pointed out the connection between small thymus and children mortality. The size of this organ is in much closer relation with mortality than the birth weight (44).

In 1903, it was found out that infant thymus is sensitive to X-ray irradiation. Bodey et al (45) described the experiment on dogs and mice, which were exposed to a single application of whole body irradiation. The so-called “thymic cysts” were found in the cortex of thymus. Their secretory product, probably thymic hormones, presented the components of micro-environment for developing thymocytes in the phase of an acute thymus involution.

Fatality in the Chernobyl Nuclear Power Plant (Ukraine) was one of the biggest radiation “experiments” in history. Dramatic reduction of the number of CD3+CD4+ a CD5+CD8+ lymphocytes, as well as thymosin α1 level in blood was noted in humans working within 30km from nuclear accident (46).

Thymic size can also be affected by hormonal treatment. The impact of corticosteroids on the size of thymus has not been yet well examined. According to Fletcher et al (47), antenatal administration of exogenous steroids causes a significant reduction of the thymic size in premature infant. On the other hand, Chen et al (48) didn’t find any statistically significant difference in the thymic size in newborn after antenatal therapy by dexamethazone.

Thymic size is very sensitive to chemotherapy; after chemotherapy of patient with malign disease, thymus volume has been reduced on the average by 43 %. Nevertheless, consequently between the first and the second chemotherapy thymus volume increased by 36 % (49).

The influence of the nutrition on the size and function of thymus is also interesting, specially its particular components, eventually exogenous substances (for example pesticide, food dopes) received by food (1). For example, an absence of biotin in mice food affects not only the bone metabolism, but it also causes an early involution of thymus (50). From an ubiquitous environmental toxicants to negative influence on the thymic size thereby also on their function have, for example, bendiocarbamate (52) and polychlorinated biphenyls (53, 54).

Collinson et al (27) confirmed the relation between nutrition and the size of thymus in newborns. They found out that in Gambia, the size of newborns thymus was smaller in period between July till December – in months of so-called “hungry season”. On the other hand, research of the thymus size by specific sub-population, Roma newborns living in Slovakia, hasn’t shown any difference between the thymic sizes compared to majority (non-Roma) population (28). At the same time, if we take into consideration their nutrition deficient (for example they receive only 44 % of the recommended daily dose of vitamin C), suboptimal hygienic norm, higher unemployment, lower education, more common occurrence of contagious diseases, higher ratio of smoker and alcohol consumers (55–58), we would expect markedly smaller thymus in the case of Roma people. Park et al (53) even discovered bigger thymus in Roma newborns in comparison to non-Roma population. However, they couldn’t explain this difference.

Thymic involution and thus related variance of thymic function in children, conditional by virtue of external or internal factors, may have a diagnostic as well as therapeutic sense. It presents the acceleration of age-related involution of thymus. The consequence is an increase of apoptotic cells and inhibition of thymopoiesis. A fast decrease in the size of thymus leads to drop of its function. The exact mechanism of an early involution as well as the possible use of this knowledge in everyday clinical praxis has not been explored deeply enough by now (15).

References


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