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Original Research Paper

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ASSOCIATION BETWEEN ABNORMAL THYMIC HASSALL'S BODIES AND CONGENITAL HEART DEFECTS IN THE CHILDREN

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ABSTRACT

Background: The development of heart and thymus are closely related. During embyogenesis changes in the microenvironment of the thymic medulla are associated with disrupted migration of neural crest cells which are important in the normogenesis of both heart and thymus.

Objectives: To examine the association between congenital heart defects and thymic microstructure.

Patients and Methods: Thymic microstructures of patients with congenital heart defects were studied. Twenty nine patients with congenital heart defects were divided into two groups according to the age. Fourteen patients were below 6 years of age formed paediatric group and rest fell in the adult group. Five micro-meter thick sections of thymus were stained with hematoxylin and eosin and the microscopic examination was focused on the structure of Hassall's bodies.

Results: The Hassall's bodies showed considerable variation in size and detail. In most children with congenital heart defects the Hassall's bodies were large with heterogenous amorphous material enclosed in cystic dilatations, which are typically seen in adult thymuses.

Conclusion: children with complex congenital cardiac defects show adult type thymic Hassall's bodies.

KEYWORDS : Thymus, Hassall bodies, congenital heart defects

BACKGROUND:

The thymus is a primary lymphoid organ found in all vertibrates, except jawless fish. The thymus has a unique capacity to support the development of self-tolerant T-cells expressing a diverse repertoire of antigen receptor. Thymopoeisis involves reciprocal tissue interactions between the epithelial cells derived from endoderm of the embryonic pharynx (branchial region) and neural crest-derived mesenchyme. However , the contribution of mesenchymal cells to thymic epithelial cell proliferation and creation of the thymic microenvironment are still unclear[1-3]

The general microscopic description of human thymus is complicated because thymus is a very dynamic organ rapidly changing under exogenous influence and involuting with age[4].Thymus consists of multiple thymic lobules of variable shape,size and orientation. Each lobule contains central and peripheral zones representing the medulla and cortex, respectively. Histomorphologically these two zones are easily distinguished by lymphocyte density, which is characteristically more pronounced in the cortex. Between cortex and medulla, the cortico-medullary junction is recognized as an area rich in blood vessels and a site where connective tissue septa reach the medullary region.[5,6]

Hassall's bodies ,named after Dr Arthur Hill Hassall who described acidophilic squamous spherical structures in the thymic medulla, have been thought to be specific for this organ[7]. Hassall's bodies have been the subject of only few studies focused on both, morphological and functional aspects. Classical studies describe them as onion-like structures, variable in number and size, often displaying degenerative changes in the central area, such as necrosis, cellular detritus, sometimes extensive calcification, cystic alterations, and foamy macrophages [9, 10]. But the importance of Hassall's bodies residing in ensuring proper functioning of the immune system is also evident from the data relating to the effects of immunosuppressive treatment on the morphology of thymus (number of hassall's bodies decreased) [11, 12], and interesting associations between human immunodeficiency virus and hassall's bodies. The most accepted definition of hassall's corpuscles is according to bodey et al [8] who define it as a unique, antigenically distinct, functionally active, multicellular component of the lymphocytic cellular microenvironment of the thymic medulla. Hassall's bodies participate in physiological activities of thymus in both, prenatal and adult phases. Approximately 0.4 % up to 0.6 % of newborn infants are delivered with a moderate or severe congenital heart defects [14]. These congenital heart defects are etiologically heterogeneous, and the genetic and environmental causes have been proposed for many specific defects [15]. More than twenty-five years ago,the first paper showed the relationship of neural crest-cells with the development of the heart . The region of neural crest cells migrating to the heart was documented extensively using quail chick chimeras and experimental partial ablation of neural crest, and was called cardiac neural crest , not because the cells migrated exclusively to the heart but because they were found to be critical for normal heart development [17]. Pluripotent neural crest cells originating from the hind-brain migrate to the caudal three pharyngeal arches and become condensed in the mesenchymal subendocardial folds, known as the aorticopulmonary septation complex [18].

The cardiac neural crest ablation phenotype includes three distinct components [19, 2]: defective development of the cardiac outflow tract, abnormal myocardial function, defective development of the derivates of the caudal pharynx including arch arteries, parathyroid and thyroid glands, thymus and the secondary heart field.

Hassall's bodies are structurally organized from thymic epithelial cells, usually undergoing hypertrophy prior to their inclusion in the outer cell layer of the corpuscles [8]. Hassall's bodies have a secretory function (cytokines and growth factors) [22], as well as a function in communication between antigen-presenting cells and T cells [23]. Their number, size and morphological features depend mostly on age of the individual. Raica et al. [9] classified Hassall's corpuscles according to age, structure and immuno-histochemical features into four groups, namely

- juvenile,
- immature,
- mature and
- senescent types.

The mature and senescent types are found only in patients aged over six years [9] Ablation of a smaller area within the cardiac neural crest is thought to contribute to conotruncal anomalies including tetralogy of fallot and double-outlet right ventricle [20]. The transposition of large arteries occurs infrequently after cardiac neural crest ablation [21]. Since the development of thymus and heart are closely related, the association between the thymic microscopic structure of infants and congenital heart defects was observed especially the changes in the structure, size and number

of the hassall's bodies have been noticed. These changes need further evaluation in order to establish their association with congenital heart defects.

MATERIAL AND METHODS:

The study has been conducted jointly in the Departments of Cardiovascular & thoracic surgery and the Department of Pathology. It is a prospective study and included all the patients of congenital heart defects operated in the department of cardiovascular and thoracic surgery. These patients were divided into two groups according to the age. Patients below 6 years of age formed one group and rest fall in the other group. The general workup of the patients included a thorough history and physical examination. Baseline investigations viz. haemogram, renal function tests and liver function tests, were supplemented with Electrocardiograph , skiagram of the chest, Echocardiography, and cardiac catheterization in selected patients. Patients were operated either through the right antero-lateral thoracotomy or through median sternotomy. In all patients partial thymectomy was done at the time of operative repair of the defect. The fragments of thymic parenchyma were fixed with formalin and subjected to detailed histopathological examination by a single pathologist.

OBSERVATIONS AND RESULTS

Our study included 29 patients who were diagnosed with congenital heart defects and were operated in the department of CTVS.

	Male	Female
Patients	13	16

Fig. No.1: Sex distribution of patients

Out of 29 patients 16 were females and 13 were males.

Age	no. of patients
0-2 years	6
3-6 years	8
7-10 years	3
11-20 years	5
21-30 years	3
31-40 years	1
41-50 years	1
51-60 years	1
>60 years	1

Fig. no. 2: Age distribution of patients

Fourteen patients were below 6 years of age and formed the paediatric group. Rest of the patients (15) were in the adult group.

Type of cardiac defect	Paediatric group(Age<6 years)	Adult group(Age >6 years)
0-2 years	5	6
3-6 years	3	3
7-10 years	3	2
11-20 years	1	1
21-30 years	1	2
31-40 years	1	1

Fig. No. 3:Types of cardiac defect and their age distribution

The number of patients with various congenital heart defects is shown in table 3 and fig 3.

All observed thymuses were of normal structure, including the well-developed cortex as well as medulla..

In most cases, the Hassalls bodies were large with the heteroge neous amorphous material enclosed in a cystic dilatation. This type of Hassall's bodies is typical for adult thymuses.

In infants and small children, the Hassall s bodies are rather small formed by ovoid or irregular congregation of epithelial cells without prominent acidophilia, necrosis or cellular detritus.

This study revealed that the thymuses from patients above 6 years of age(n=15), irrespective of type of cardiac defect, have adult type large Hassall's bodies with the heterogeneous amorphous material enclosed in a cystic dilatation.

On examination of thymuses of 14 patients who were below 6 years of age, the Hassall's bodies showed considerable divergences in size as well as in quantity.

The thymuses of patients with diagnosis of Ventricular septal defects revealed sparse but giant Hassall's bodies in the medulla. Similar findings were seen in thymic medulla of the patients with Tetrology of Fallot.

Small Hassall s bodies corresponding with infant age were observed in cases with atrial septal defects and pulmonary valve.

DISCUSSION:

Hassall's bodies are structurally organized from thymic epithelial cells, usually undergoing hypertrophy prior to their inclusion in the outer cell layer of the corpuscles [8]. Hassall's bodies have a secretory function (cytokines and growth factors) [22], as well as a function in communication between antigen-presenting cells and T cells [23]. Their number, size and morphological features depend mostly on age of the individual. Raica et al. [9] classified Hassall's corpuscles according to age, structure and immuno-histochemical features.

The mature and senescent types are found only in patients aged over six years [9] Ablation of a smaller area within the cardiac neural crest is thought to contribute to conotruncal anomalies including tetralogy of fallot and double-outlet right ventricle. The transposition of large arteries occurs infrequently after cardiac neural crest ablation . Since the development of thymus and heart are closely related, the association between the thymic microscopic structure of infants and congenital heart defects was observed especially the changes in the structure, size and number of the hassall's bodies have been noticed. Contrary to this , in our study most of cases of patients with ventricular septal defect, tetralogy of Fallot and other defects, we found Hassall's bodies with cystic dilatation filled with abundant cellular debris and acidophilic necrotic material. These morphologic features are typical of senescent Hassall's bodies according to Raica et al.[9]. In one case, we described a lymphocyte-rich type of Hassall's bodies, originally depicted by Raica et al. It is possible that this type of Hassall's bodies could reflect a rapid involution of the thymus induced by preoperative stress

In the review of literature, we found only one hypothesis about the origin of cystic dilatations in thymuses, which we noticed in most of our cases. In this hypothesis, Ors et al suggested that the various types of cystic structures might represent maturational stages of classical Hassall s corpuscles. In other vertebrates, for example reptiles and amphibians, degenerative cysts were described by more research groups .

Changes of the thymic microscopic structure in infants with congenital heart defects are probably related to the embryonic development of both the organs. Thymic organogenesis depends on the interactions between cells of all three embryonic germ layers, namely endoderm-derived epithelium of pharyngeal pouches, neuroectoderm-derived neural crest mesenchyme and mesoderm-derived hematopoietic cells. The normal development of heart outflow tracts, development of great arteries and secondary heart-field development are also induced by neuroectoderm-derived neural crest. It is important to take into consideration that the changes in microscopic structure of thymus may reflect the stress caused by changes in circulation and oxygenation of blood or by repeating preoperative examination of the patient. This hypothesis seems to be less presumable. In cases of heart defect with none or

minimal influence of the migration of neural crest cells (for example atrial septal defect), structurally normal Hassall s bodies were found.

Congenital heart disease is one of the most common phenotypic manifestations of chromosome 22q11 deletion syndrome . More than 75 % of patients with a chromosome 22q11 deletion express some forms of cardiovascular anomalies. In our study ventricular septal defect cases were found to reveal the most prominent changes in thymic Hassall's corpuscles. Chromosome 22q11 deletions are often associated with extra-cardiac anomalies, typically affecting the neck and head and resulting in apparently different clinical syndromes including DiGeorge syndrome. These syndromes have been grouped together under an acronym CATCH 22 (Cardiac defects, Abnormal facial features, Thymus aplasia or hypoplasia, Cleft palate, Hypocalcaemia while 22 denotes the deletion on chromosome 22). The normal development and structure of thymus has important clinical implications, e. g. Chaoui et al stated that an absent or hypoplastic fetal thymus in ultrasound assessment can be a marker for cardiac defects and deletion 22q11.2.

Since the development of thymus and heart are closely related, the association between the thymic microscopic structure of infants and congenital heart defects was observed especially the changes in the structure, size and number of the hassall's bodies have been noticed.

CONCLUSION:

In our study, children with congenital heart defects like Ventricular septal defects and Tetrology of Fallot did show abnormal adult type thymic Hassall's bodies. These changes need further evaluation in order to establish their association with congenital heart defects.