

Thymus gland and thymic dysfunctions in children

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ABSTRACT

The thymus is the organ that has gained significant awareness in the last two centuries, being considered the main donor of cells for the lymphatic system, much like the bone marrow is the donor of cells for the cardiovascular system. Currently, knowledge regarding the thymus gland has considerably improved. Thymic dysfunctions encompass congenital and acquired conditions, which manifest through organ hypoplasia or hyperplasia, as well as formations/tumors of the anterior mediastinum.

Keywords: thymus, dysfunction, children

INTRODUCTION

Guiding physicians with changes in the thymus gland to identify pathology/normal changes in thymic appearance. Monitoring patients with early detection of complications, initiating treatment and improving quality of life is the goal of the study.

MATERIALS AND METHODS

In preparing this article, we intended to summarize the current literature data, with searches on PubMed and Google Scholar, using the keywords thymus and thymic dysfunction. The anatomy, physiology, functions of the thymus gland, and its dysfunctions were elucidated, emphasizing attention to organ hyperplasia. Likewise, imaging immunohistopathological methods and immuno-histopathological methods used in the paraclinical diagnosis of thymic pathology were described and the principles of monitoring patients. Imaging and immuno-histopathological methods used in the paraclinical diagnosis of thymic pathology, and the principles of monitoring patients were elucidated.

RESULTS

Anatomy of the thymus gland

The thymus gland is a bilobed, pyramidal organ in the anterior mediastinum. An isthmus connects

the two lobes of the thymus. The horns of the thymus extend superiorly to the lower poles of the thyroid gland, connecting with it by strands of connective tissue. The anterior surface is connected to the sternum, the four upper costal cartilages, and the point of insertion of the stern-hyoid and sternothyroid muscles. The thymus at the front of the neck relates to the infra-hyoid muscles. The posterior surface is related to the superior pericardium, the aortic arch with branches, the left brachiocephalic vein, and the trachea. Laterally, the thymus is connected to the mediastinal pleura, the lungs, and the phrenic nerves, especially the left one. The organ is covered by a connective tissue capsule, the septa of which penetrate the tissue and divide it into incomplete lobules. Each lobe has a peripheral area, called the cortex, and a middle area, called the medulla, and is where most of the negative and positive thymocyte selection processes take place, undergoing rearrangement [1,11,17]. The thymus is composed of two types of cells: lymphocytes (mainly T cells, B cells and natural killer cells) and reticular cells. There is a close anatomical and functional correlation between the thymic cells [18].

The immune function of the thymus

Throughout life, the immune system must balance responses against various pathogens, while preventing damage to its own organ systems and tissues. The thymus serves as the central organ of self-

non-self-immune tolerance, through the mechanism of peripheral and central tolerance. The cells involved in regulating the immune response are mature T lymphocytes in the thymus. [14]

Endocrine function of the thymus

The endocrine influence of the thymus also relates to the function of the hypothalamic-pituitary axis, indirectly participating in the regulation of tissue metabolism, which is directly controlled by the peripheral endocrine organs: thyroid, pancreas and adrenals [14]. Physiological involution of the thymus, as a function of age, results in significant loss of its ability to generate *de novo* immunocompetent T cells. With age, the atrophied thymus decreases in its ability to establish central tolerance, thereby causing the growth of auto-reactive T cells at the periphery, with persistence of the autoinflammatory and autoimmune process. [5,7,16]

Congenital pathology of the thymus

Congenital thymic diseases refer to thymic flattening and hypoplasia, congenital thymic hypertrophy and positional abnormalities - ectopic thymus. Orofaciocervical syndrome type 2 (OTFCS) is characterized by short stature, facial dimorphism (long face, narrow jaw), scapular girdle abnormalities, hearing loss and mild intellectual disability. CHARGE syndrome (acronym from: coloboma, cardiac malformations, choanae atresia, growth retardation, genital and urinary tract abnormalities, ear abnormalities) is characterized by varying degrees of thymic alterations and even complete thymic aplasia, resulting in combined immune deficiency. Congenital athymia is first identified by newborn screening for severe combined immunodeficiency, which assesses immune function by quantification of cortical thymic epithelial cells (cTrec) by polymerase chain reaction using DNA isolated from dried blood spots [12,13].

Congenital hyperplasia of the thymus

Congenital thymic hyperplasia is characterized as a distinct increase in both the size and weight of the thymus and is the most common cause of anterior mediastinal enlargement. Congenital thyphomegaly is considered a dysfunction of the hypothalamic-pituitary system, manifested by polyglandular endocrinopathy and congenital immunodeficiency, associated with the thymus-dependent group of immunodeficiencies. The radiological diagnosis of thymic hyperplasia is characterized by an increased cardio-thymicthoracic index-the ratio of the width of the cardio-thymic shadow at the tracheal bifurcation to the transverse dimension of the thorax at the level of the diaphragmatic cupula. [6,15,18].

Ectopia and shape abnormalities of the thymus gland

The main cause of thymus gland ectopia is migration abnormalities, a rare, frequently benign pediatric condition in which the thymic tissue is in an unusual place. It frequently occurs in the cervical region; therefore, it is called cervical ectopic thymus [3]. Clinically, ectopic thymus of the neck in children presents as a firm, asymptomatic mass of the neck, without specific clinical features, which usually appears at the age of 2-13 years. Ultrasonography in the diagnosis of cervical ectopic thymus, which is characterized by the presence of hyperechogenic inclusions, on a hypoechoic background, known as “the sky-stellar appearance at”

Ductal pathology of the thymus gland

Hyperplasia of the thymus gland is the abnormal development of the thymus, which causes the gland to increase in size. It is not always pathological, but enlargement of the thymus to an extent unexpected for the patient's age raises a red flag and should lead to further investigation. Thymic hyperplasia with hypofunctioning thymus, would lead to immune deficiency. Hyperfunctional thymic hyperplasia leads to autoimmune diseases, most commonly myasthenia Gravis, but the relationship has also been found with Graves disease, and collagen vascular disorders [2].

Morphologically, there are two types of thymic hyperplasia: true hyperplasia and lympho-follicular hyperplasia.

True thymic hyperplasia has three different clinicopathological forms:

1. Massive thymic hyperplasia. Usually defined as hypertrophy of the cortex and medulla of the thymus, without histological abnormalities, associated with an increase in thymus mass, greater than the cardiac shadow on the radiological frontal teleheart, and/or a thymus weight greater than 2% of body mass. The cause is unknown, it may be due to thymic hyperfunction, or dysfunction related to endocrine activity of the gland. Patients usually present with symptoms of irritation of mediastinal structures, symptoms can range from none to respiratory distress.
2. Rebound hyperplasia is common in a number of conditions, such as recovery from severe stress, severe infections, heart surgery, after steroid administration, after remission of Cushing's syndrome, after treatment of malignant tumours.
3. Hyperplasia in association with endocrine abnormalities (Graves' disease, acromegaly, thyrotoxicosis, hypothyroidism and Addison's disease), sarcoidosis and Beckwith-Wiedeman syndrome [15,18].

True/rebound hyperplasia of the thymus gland (TTH). It is the most common cause of diffuse enlarged thymus and represents a rebound phenomenon in patients who have previously undergone a stressful pathology/medical intervention, such as an acute illness (pneumonia or other severe respiratory infections), surgery (more common in congenital heart malformations), corticosteroid therapy, radiotherapy, chemotherapy, burns, after long-term steroid administration, after remission of Cushing's syndrome, after treatment of malignant tumors, causes a rapid decrease, starting in the first days of illness, in the size of the thymus gland to 40% of its original volume (depending on the severity and duration of the stress).

Recent studies have shown that synthetic corticosteroids, including dexamethasone, deteriorate the architecture and cellularity of the thymus gland, with apoptosis of thymocytes and progressive depletion of CD4+CD8+ double positive T cells. In acute thymic involution, the primary effect is a decrease in the number of cortical thymocytes, leading to a decrease in the number of peripheral T lymphocytes with all its effects. During the recovery phase, it may increase back to its original size or even larger (up to 50% larger). This "rebound effect" is known as thymic rebound hyperplasia.

Thymic lymphofollicular hyperplasia (thymitis). It is characterized by histological appearance, with an increased number of hyperplastic lymphofollicular follicles, with germinal centres, similar to those in the medullary lymph nodes, also known as autoimmune thymitis. The main feature of thymic lymphofollicular hyperplasia is the development of ectopic germinal centers and neo-angiogenesis. It has been described in chronic disseminated infections, endocrinopathies, autoimmune diseases (myasthenia gravis, systemic lupus erythematosus, scleroderma, rheumatoid arthritis, periarteritis nodosa, Hashimoto's thyroiditis, autoimmune anemia, Behcet's disease, ulcerative colitis and multiple sclerosis). Positive diagnosis is based on specific features on CT and histological examination [18].

Thymus tumors are of epithelial origin, occurring in the anterior mediastinum and account for 0.2-1.5% of all malignancies with an incidence of 0.15 per 100,000 population and 20% of all mediastinal tumors as well as 50% of all anterior mediastinal tumors.

According to the 2021 WHO classification, tumors of the thymus gland are:

1. Thymomas: Thymoma unspecified, thymoma type A, thymoma type AB, thymoma type B1, thymoma type B2, thymoma type B3, micronodular thymoma with lymphoid stroma, metaplastic thymoma, lipofibroadenoma.

2. Carcinomas: squamous cell carcinoma, basaloid squamous cell carcinoma, lymphoepithelioma adenocarcinoma NOS, poorly differentiated papillary carcinoma, ACC-like thymic carcinoma, enteric-type adenosquamous adenocarcinoma, mucoepidermoid carcinoma, clear cell carcinoma, sarcomatoid carcinoma, or undifferentiated carcinoma [4,8].
3. Thymic neuroendocrine neoplasms: non-specific/neuroendocrine carcinoma, typical neuroendocrine carcinoma, grade I, atypical neuroendocrine carcinoma, grade II, large cell neuroendocrine carcinoma, small cell carcinoma, combined small cell carcinoma, non-specific/neuroendocrine carcinoma, typical neuroendocrine carcinoma, grade I, atypical neuroendocrine carcinoma, grade II. The initial diagnosis of thymic neoplasm is suspected on chest X-ray [9,12].

Paraclinical diagnosis of thymic pathology

In the most common cases, indications for a thorough examination are the extension of the mediastinal shadow, detected on chest X-ray, severe pathologies with atypical evolution, local signs of tumor invasion, cases of sudden death in childhood among the child's relatives.

Ultrasound of the thymus gland is the first line for the evaluation of the anatomical position, shape and structure of the thymus gland, as well as the presence of volume formations and for guided aspiration or biopsy of thymic masses with immunological and histological confirmation.

Ultrasonography of the fetal thymus is now widely performed, its dimensions being used as a predictive factor for intrauterine growth restriction, preterm birth, pre-eclampsia, chorioamnionitis or neonatal sepsis.

18F-fluorodeoxyglucose positron emission tomography/CT has excellent diagnostic value in thymic rebound and can differentiate thymic hyperplasia, thymoma and thymic carcinoma.

MRI is more sensitive in defining tumor contour, capsule invasion, intra tumor signals and vascular involvement allows the possibility of assessing the size of the thymus gland. Due to better contrast resolution, it is possible to differentiate microscopic lipid inclusions from an infiltrative process.

Immunological diagnosis is used for the evaluation of thymus gland function in various pathological conditions, including confirmation of congenital thymic aplasia/hypoplasia, differential diagnosis, SCID, impaired immunological function in thymic hyperplasia and thymic tumors.

Neonatal screening for SCID, assesses immune function by quantifying TRECs, by polymerase chain reaction, using DNA isolated from dried blood spots.

Low or undetectable TRECs are considered a positive finding during SCID screening, as they represent excision products of epizomal DNA, formed during T-cell receptor rearrangement in the thymus. All positive patients subsequently undergo a complete haemolucogram and lymphocyte phenotyping by flow cytometry, which is the 'gold standard' in oncohaematological diagnosis, including immunodeficiency.

Management of thymus gland dysfunction

The approach to hyperplastic thymus is multidisciplinary to establish a definitive diagnosis with appropriate treatment. Asymptomatic patients should be monitored by the family physician and pediatrician.

Those with severe manifestations, such as superior vena cava syndrome or myasthenia gravis, require consultation with the thoracic surgeon to differentiate thymic hyperplasia from thymoma, or other malignant conditions and choose treatment tactics. The priority treatment of massive thymic hyperplasia is surgical resection.

In the case of myasthenia gravis, associated with hyperplasia of the thymus gland and clinical signs present, acetyl cholinesterase inhibitors such as physostigmine or pyridostigmine should be used. Platelet therapy helps to improve the symptoms of the disease. There is evidence that thymectomy leads to remission of the disease if drugs and plasma therapy do not improve symptoms. Graves' disease-associated thymic hyperplasia resolves as hyperthyroidism is treated. Differential diagnosis will be made with thymolipoma, thymoma, thymic cysts, malignant thymoma, thymic carcinoma, thymic germ cell tumors [2].

Monitoring of the patient with thymic pathology varies according to the form and severity of the dysfunction and requires the involvement of the multidisciplinary team.

The first step is to start prenatally, by assessing ultrasonography of the fetal thymus in fetuses with a positive family history of primary immunodeficiency, congenital athymia or thymic hypoplasia, cardiac pathology, which is an absolute indication for thymus size monitoring. Particular attention should be paid to the group of fetuses in whom, in several ultrasound measurements, the thymus size does not fall within the nomograms for a given gestational age, should a perinatal immunological consultation, with decision on BCG vaccination and subsequent postnatal diagnosis. Information about thymus hypoplasia is noted in the child's health book. In case of thymic hyperplasia asymptomatic patients should be monitored by family doctor and

pediatrician. Patients with pronounced thymus enlargement are dynamically monitored by pediatrician, allergist immunologist, endocrinologist, undergo annual laboratory and instrumental examination, to rule out possible mediastinal neoplasms, development of polyglandular insufficiency syndrome of different grades. These will include detailed clinical examination, ultrasonography/chest X-ray or CT, MRI of the chest, immunological examination, or immuno histopathological examination, depending on need.

Thymoma patients are indicated to be followed up by a physician-oncologist and a CT scan every 6 months for the first few years, then annually from 5 to 10 years. In myasthenia gravis dynamic imaging evaluation is recommended to monitor thymus dimensions and the need for future surgery in case of massive thymic hyperplasia. In Gravis disease dynamic imaging monitoring of the rib cage with monitoring of thymus dimensions is recommended to reassess the need for future biopsy or thymectomy.

In thymic hyperplasia associated with severe hyperthyroidism, the hyperplasia will resolve if the hyperthyroidism is controlled. Children with Di George syndrome, the most common variant of congenital thymic hypoplasia, require rigorous multidisciplinary follow-up - cardiologist, endocrinologist, otolaryngologist or oral and maxillofacial surgeon, speech pathologist, immunologist.

The immune function of all patients with DGS will be monitored every 6-12 months. This will include flow cytometry for enumeration of immune cells, in vitro proliferation tests to assess T-cell function, serum immunoglobulins and specific antibody typing. The decision for vaccination is made on an individual basis, depending on the child's immune status.

Most patients will not be vaccinated with live vaccines (measles, mumps, rubella, varicella, live polio vaccine). Genetic testing of parents is indicated. Close monitoring of these patients will allow early detection of complications, initiation of treatment and improvement of quality of life.

CONCLUSIONS

1. Thymus enlargement to a certain extent, unexpected for the patient's age, raises an alarm and requires further investigation.

2. The approach to the patient with thymus gland dysfunction is multidisciplinary.

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