Congenital Anomalies of Thymic Origin in the Neck

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Rationale: A symptomatic mass in the thymus is due to anomalies in the development of the pharyngeal pouches and is also an unusual cause of consultation. These anomalies may be found anywhere along the natural path of the embryonic thymus, from the angle of the jaw to the upper mediastinum.

Aim: To review the epidemiology, pathogenesis, diagnosis, and management of congenital anomalies of thymic origin

Material and method: A MEDLINE search was carried out, using the Cochrane methodology, for articles published from January 1980 to January 2007 using the terms "thymus gland," "cervical mass." Following this bibliographical search, the texts considered most relevant by the authors were selected.

Conclusions: While this anomaly is relatively common, its level of presentation is very low and it should always be considered in the differential diagnosis of congenital masses in the neck. New diagnostic imaging techniques provide an early and more accurate diagnosis, thus allowing a better outcome in these patients.

Key words: Thymus. Neck. Mass. Congenital (source: MeSH).

Anomalías congénitas de origen tímico en el cuello

Justificación: La masa tímica sintomática en el cuello se debe a anomalías en el desarrollo de las bolsas faríngeas y es una causa inusual de consulta. Estas anomalías se pueden encontrar a lo largo de la vía embriológica de descenso del timo, desde el ángulo de la mandíbula hasta el mediastino superior.

Objetivo: Realizar una revisión estructurada de la epidemiología, la patogenia, el diagnóstico y el tratamiento de las masas congénitas de origen tímico en el cuello.

Material y método: Se realizó una búsqueda en MED-LINE, según la metodología Cochrane, de artículos publicados desde enero de 1980 a enero de 2007 usando los términos "thymus gland" y "cervical mass"; los autores seleccionaron de esta búsqueda los manuscritos que consideraron relevantes.

Conclusiones: Aunque esta anomalía es relativamente común, su presentación clínica es poco frecuente; siempre se debe considerar en el diagnóstico diferencial de las masas congénitas en el cuello. Las nuevas técnicas de imágenes facilitan un diagnóstico precoz y más preciso, lo que permite un mejor pronóstico para estos pacientes.

Palabras clave: Timo. Cuello. Masa. Congénito (fuente: DeCS).

INTRODUCTION

Thymic remnants are often found in the neck. Nonetheless, they are an infrequent cause of patient presentation at the clinic so there is little experience with this anomaly. These remnants are due to alterations in the embryonic development of the third and fourth pharyngeal pouches^{1,2} and can be found throughout the route for the embryonic descent of the thymus, from the angle of the jaw to the upper

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Received November 20, 2007. Accepted for publication January 30, 2008. mediastinum.3-5 The diagnosis is difficult to achieve in a presurgical work-up,6 despite the notable advances in the understanding of their characteristics.⁷ for the above reasons, a structured review has been carried out of the epidemiology, pathogenesis, diagnosis, and treatment of congenital anomalies of thymic origin in the neck.

Search Strategy and Selection Criteria

A search was made on MEDLINE, using the Cochrane methodology, for articles published between January 1980, and December 2006, using the expressions "thymus gland" and "cervical mass." The initial search gave results from articles published in various languages, of which those published in English and Spanish were chosen. Of these, the available abstracts were reviewed to select the literature finally considered relevant by the authors to prepare this text.

HISTORY

According to its etymology, the name thymus derives from the Greek word thymos which means soul or spirit.8 Despite being anatomically easy to recognize, its function had been a mystery until recent times. Galen (2nd century AD) defined a role for this organ in the purification of the nervous system^{8,9}; subsequently, Vesalius (15th century) posited the theory that the thymus acted as a damper to protect the major vessels in the mediastinum located behind the sternum. In the 18th century, it was generally believed that the thymus somehow regulated the foetal and neonatal pulmonary function, and was known as the vicarious respiratory organ.^{8,9} In 1777, William Hewson was the first to identify correctly the thymus as a lymphmodifying gland and in 1832 Sir Astley Cooper devoted an entire book to the anatomy of the thymic gland with detailed dissections of corpses.¹⁰ In 1846, a crucial development occurred in our understanding of the thymus when Hassall and Vanarsdale used improvements in compound microscopy to study it in greater depth and describe the differences between the thymus and other lymphoid organs, specifically the histological characteristic known as Hassall's corpuscles.^{8,11} Nonetheless, it was only in 1961 that the Australian immunologist Miller, by demonstrating the devastating effect of thymectomy on the immune system, was able to give a clear idea of its true function. 9,10 More recently, the role of the thymus has been clarified as an essential organ for the maturing of lymphocytes and the elimination of autoreactive lymphocytes in papers published by Kappler et al¹¹ in 1987. Over the last 20 years, a lot of progress has been made in our awareness of the mechanisms for regulating the immune response and the role of cytokines. The first attempt to remove a mass of thymic origin in the neck was performed by Polloson and Piery in 1901, when they performed a partial excision of a thymic cyst. 12 The literature includes reports of at least 100 cases of symptomatic thymic masses in the neck.^{1,12,13}

EPIDEMIOLOGY OF CONGENITAL ANOMALIES OF THYMIC ORIGIN

The exact incidence of masses of thymic origin in the neck is uncertain,^{1,2} since it is usually an asymptomatic anomaly, therefore it may be more frequent than has been reported.^{1,3} This premiss is reached after reviewing such studies as those of Wagner et al,13 who reported in 1988 on the presence of asymptomatic ectopic thymic tissue in 30% of the autopsies performed on children, or Pages et al, 14 who studied 763 autopsies of different ages and surgical samples from 8 children and adults and found 72 cases (9.2%) of ectopic thymic tissue in the neck, and Tabatabaie et al, 15 who reported on 4 cases (4.45%) of thymic tissue in the neck of 90 patients subjected to thyroidectomy without thymic disease. On the basis of the foregoing data, it is possible to infer that thymic remnants are common in the neck, but their symptomatic presentation is highly unusual.

This anomaly is more frequent in males, with a proportion of 3:1, and is most commonly located on the left side of the neck.^{1,4} As for the age at presentation, two thirds of these lesions are diagnosed in the first decade of life and 75% of the patients are under 20 years of age at the moment of presentation⁵; however, there have been reports of cases in adults, with the eldest being a 71-year-old male. 16

DEVELOPMENT OF THE THYMUS

The thymus is a bilobular gland mainly deriving from the ventrolateral surface of the third pharyngeal pouch.^{5,8} In addition, a minimal portion originates on the ventral aspect of the fourth pharyngeal pouch⁵ (Figure 1).

During the sixth week of gestation, the third pharyngeal pouch divides into 2: a dorsal portion which gives rise to the inferior parathyroid glands and a ventral portion which gives rise to the primordial thymus.

In the seventh week, each primordial thymus migrates caudally and medially from the angle of the jaw to the anterosuperior mediastinum, forming a tubular structure called thymopharyngeal tract or duct. This tract begins in the pyriform sinus, perforates the thyrohyoid membrane and emerges between the common carotid artery and the vagus nerve. It runs behind the glossopharyngeal nerve and alongside the thyroid gland to enter the mediastinum (Figure 2).

Towards the eighth week, the primordial thymuses merge along the midline and descend to adopt their characteristic position on the anterosuperior mediastinum; the cephalic portion usually regresses.

The tenth week sees the start of the invasion of lymphocytes forming the thymic lymphoid tissue.

Around the thirteenth week of foetal life, the thymus already has a cortex and a medulla, and Hassall's corpuscles can be seen.

By the age of 4 years, the thymus has reached an approximate weight of 12 to 15 g and it continues growing until puberty, when it attains its maximum weight (30-40 g). 17,18 After puberty, the lymphoid tissue in the thymus reduces and is replaced by fat or connective tissue, whereas Hassall's corpuscles remain longer. In adult life, the thymus regresses to an approximate weight of 15 g; nonetheless, the organ does not disappear¹⁸ (Figure 3).

PHYSIOLOGY OF THE THYMUS

The thymic gland has several functions, mainly in the development of the immune function in new-born and infant children.3 It is involved in the maturation of immunocompetent Tcells, implying the differentiation of the 2 sub-types of T cells: CD4 and CD8. It also allows the proliferation of clones of mature T cells, which then enter the lymph flow and participate in the development of immune tolerance, the prevention of autoimmune diseases, 9 as well as in the secretion of hormones and other factors, such as thymolin, thymopentin, and thymosin alpha 1.9-11

A	Maxillary Process	B Maxillary Process	
Mandibular Process Pharyngeal Slits 1	Pharyngeal Pouches 1 2	External Auditory Canal	Primitive Tympanic Cavity Eustachian Tube Palatine Tonsils Parathyroid Gland (Inferior) Thymus
4 Epicardial Relief	4	Cervical Sinus	Parathyroid Gland (Superior) Ultimobranchial Body

Figure 1. The slits and pharyngeal pouches give rise to different structures, including the thymic gland, which originates from the ventrolateral surface of the third pharyngeal pouch and from the ventral portion of the fourth pharyngeal pouch.

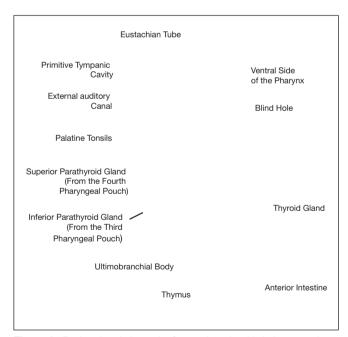


Figure 2. During the sixth week of gestation, the third pharyngeal pouch divides into 2: a dorsal portion which gives rise to the inferior parathyroid gland and a ventral portion which gives rise to the thymic primordial thymus. Then, in the seventh week, each primordial thymus migrates caudally and medially from the angle of the jaw to the anterosuperior mediastinum, forming a tubular structure called thymopharyngeal tract or duct. This tract begins in the pyriform sinus, perforates the thyrohyoid membrane and emerges between the common carotid artery and the vagus nerve. It runs behind the glossopharyngeal nerve and alongside the thyroid gland to enter the mediastinum.

PATHOGENY OF THYMIC MASSES IN THE NECK

The pathogeny of cervical thymic tissue has not been completely clarified. 19,20 In 1938, Speer²¹ put forward 5 theories for its development: a) remnants of the branchial slits or a thymopharyngeal tract; b) neoplasic changes in the lymphoid, cytoreticular or connective tissues; c) sequestering of thymic tissue during migration; d) cystic degeneration of Hassall's corpuscles; and *e*) derived from the lymphoid tissue of the thymic gland in various stages of its development. Other abnormalities have also been proposed as theories explaining its genesis, such as a cervical thymus that has not descended, the persistence of a thymic cord directly linked to the mediastinal thymus and the cervical extension of the mediastinal thymus.20

CLINICAL PRESENTATION

Remnants of thymic tissue may persist all along the descent of the primordial thymus.³⁻⁵ This accessory tissue, similar to the thymic gland, suffers hyperplasia during the early years of life and may present as a cervical mass of varying dimensions.²² Ectopic thymic tissue may be either cystic or solid. The cystic form represents 90% of cases while the solid form constitutes the remainder. 15,16 Cervical thymoma is extremely rare, with only 20 cases published.

In 1983, Zarbo et al²³ classified all the varieties of thymic abnormalities in the neck into 7 categories, depending on their anatomic location and their nature, ie, cystic or solid.

Cervical thymic cyst is the most frequent variety. It generally presents progressive growth²⁴ and may result from remnants of the thymopharyngeal duct, the cystic degeneration of Hassall's corpuscles, or the cystic degeneration of a solid thymic tissue, either by infection or tumour.²³ Most cysts are located on the left side of the neck (68%), followed by the right side (25%), and less commonly on the midline (7%).²⁵ Other locations include the trachea, the posterior pharynx, and the pyriform sinus.²⁴ Mikal²⁶ classified thymic cysts as true, mixed, or false. A true cyst corresponds to anomalies in the thymopharyngeal duct, which usually communicates with the pyriform sinus; a mixed thymic cyst refers to a thymic fistula containing ectodermal tissue from the second brachial slit and endodermis from the third pharyngeal pouch whereas a false cyst corresponds to the cysts of the brachial slits incidentally containing thymic tissue.

The solid presentation of cervical thymic tissue is an even more unusual cause of cervical thymic mass and since there are no differences in the symptomatology between the cystic and the solid varieties, some authors have indicated that the solid variant represents an early stage of the development of the thymus. The scientific literature includes reports of multiple combinations of these 2 presentations, including accessory cervical thymus, cervical thymic cyst, a thymus incompletely descended, persistent thymopharyngeal duct, and persistent thymic cord. In addition, half of the cervical thymic cysts are connected to the normal thymic tissue of the mediastinum, through fibrous cords, cystic masses, or by a solid thymic mass. 16,20,24,25

The most common symptom, present in 80%-90% of patients, is a painless mass, followed, in 6% to 13% of patients, by an obstructive symptom such as dysphagia, dyspnoea, stridor, or dysphonia. 1-3 The sudden-onset form of presentation is less frequent, and is usually secondary to an infection or haemorrhage.^{5,25}

Most of the cases reported have involved newborns, in which respiratory impairment is usually more severe due to extrinsic compression or displacement of cervical structures.^{5,6} There are other variants, such as intra-thyroid ectopic thymic tissue, that are rarely found.²⁶ Gilmour, and then Bale and Sotelo Avila found this intra-thyroid thymus in infant autopsies.^{27,28} All these variants may suffer a malignant transformation, and for this reason cases of thymomas have been described in different locations of the neck.²⁹ In the cases reported by Mayauchi et al,³⁰ the symptoms were masses in the neck and goitre. A thymoma located adjacent to or displacing the thyroid may appear as a mass in the thyroid or as a carcinoma of the thyroid in nuclear imaging tests.^{29,30}

DIAGNOSTIC STUDY

The diagnosis of cervical masses is based on a good clinical history and the physical examination. Most cases of thymic abnormalities are not diagnosed prior to surgery because their rarity means this possibility is not taken into consideration. Pre-operative diagnosis of this kind of lesion

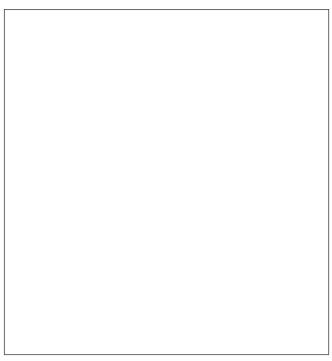


Figure 3. Macroscopic image showing the relationship between the thymus and the lungs, heart and large vessels in a 52-year-old woman whose autopsy was performed at the Hospital Universitario de Santander

with confirmation of a normal thymus in the mediastinum is essential to prevent an unnoticed total thymectomy and subsequent immunodeficiency, especially in infants and children.³ Pre-operative diagnosis is both rare and difficult, not to mention the lack of an optimal study to assess thymic masses in the neck.⁴⁻⁶ An ultrasound examination is useful to establish differences between cystic and solid lesions in the neck³¹; in addition, advances in high resolution ultrasonography allow a detailed description of morphology and vascularization. This kind of study is cost-effective and non-invasive. The characteristic appearance in an ultrasound scan is the finding of a remnant between the thyroid gland and the neck muscles, with multiple linear structures and echogenic foci that give it a starry sky appearance,32 probably due to the presence of Hassall's corpuscles. This is, however, variable, as it has been shown that the thymic parenchyma may sometimes be hypoechoic and less characteristic. Some authors have described the echogenicity of the thymus as very similar to hepatic parenchyma. 31,32

In computerized tomography (CT), cervical thymic masses are observed to be homogeneous with a non-specific attenuation of the soft tissues, closely related to the carotid sheath. Magnetic resonance (MR) testing is superior to CT in the definition of the characteristics and is frequently capable of demonstrating whether the cervical mass is connected to the mediastinal thymus or defining if the density of the mass is similar to normal thymic tissue.³³ In MR imaging, the thymus is slightly more intense than the muscle in T1-weighted image and relatively isointense with adipose tissue in T2-weighted image.³⁴

The cytological study of samples obtained by fine needle aspiration biopsy usually allow a pre-surgical diagnosis to be made and it should be considered in the initial assessment of cervical masses of thymic origin. Nonetheless, its sensitivity and specificity have not been well studied in the paediatric population.35

PATHOLOGY STUDY

As has been mentioned, most of these lesions are multiloculated cysts containing inside a clear yellowish liquid; less frequently there have been cases in which solid lesions have been observed and these may be accompanied by necrotic remains, cholesterol crystals, and haemorrhage. ³⁶ Cystic lesions are coated with an epithelium that may be ciliate, non-ciliate, stratified, pseudo-stratified, cuboidal, or columnar. The walls of the cyst can measure from less than 1 mm to over 1 cm.^{20,22,24} The pathognomonic findings considered for diagnosing both forms of presentation, ie, cystic and solid, are the presence of thymic parenchyma, lymphoid tissue of thymic origin, and Hassall's corpuscles.²⁰⁻²⁹

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of tumours of thymic origin must consider congenital masses in the neck (including brachial cysts, cysts of the thyroglossal duct, vascular malformations, cystic hygroma) as well as acquired lesions, such as thyroid adenomas, cervical adenopathies, dermoid or epidermoid cysts, inflammatory, and neoplasic lesions.^{5,6}

TREATMENT

For diagnostic and therapeutic reasons, surgery is the treatment of choice for symptomatic cervical masses originating in the thymic gland. Although the natural history of the masses containing thymic tissue is not yet known, it is accepted that this tissue may have the same pathological spectrum as the tissue in normal locations, and for this reason surgical handling of cervical ectopic thymus entails complete surgical resection, due to the possibility of neoplasic transformation that may go unnoticed due to the scant suspicion and frequency of its presentation^{20,29}; cases of malignant transformation have been reported in solid ectopic thymic tissue, squamous cell carcinoma in a thymic cyst, and thymoma in cervical ectopic thymus.30,37

In children, confirmation must always be obtained of the existence of a mediastinal thymus before proceeding with a thymectomy in order to avoid the risk of an athymic patient. Although the long-term consequences of thymectomy at an early age are not known, there is evidence of alterations in some immunity parameters among children subjected to total thymectomy during early-age heart surgery.³⁸ In surgery, despite being well adhered to the main vessels and the nerves of the neck, thymic tissue can be resected with careful dissection. Some authors believe that, when dealing with a

benign lesion, it is possible to treat the patient conservatively without surgery but, if subsequent studies reveal any change, a decision must be made on whether to perform a thymectomy. 20,39 In the case of life-threatening ectopic, due to compression of the trachea, in the absence of any mediastinal thymic gland, it is recommended to perform a partial excision to release the obstruction and maintain normal immune function.^{25,40} With cervical thymic cyst, total excision must always be performed, since the thymic cyst lacks any active thymic tissue.

In conclusion, although this anomaly is relatively common, it presents very rarely; consideration must always be given to this possibility when facing a congenital mass in the neck. New imaging techniques have made it easier to achieve early diagnosis and improved treatment, thus allowing a better course in these patients.

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