REVIEW ARTICLE

LAMB Syndrome

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Abstract

Lentigines, atrial myxoma, and blue nevi (LAMB) syndrome/Carney syndrome is a very rare, autosomal dominant, and hereditary syndrome. Seventy percent of individuals with LAMB syndrome have germline inactivating or deleting mutations of the *LAMB SYNDROME1* gene [currently known as protein kinase cyclic adenosine monophosphate (cAMP)-dependent type I regulatory subunit α (PRKAR1A), located at the 17q22-24 chromosome level], a member of the lentiginosis family. Dermatological features include skin pigmentation and cutaneous/mucosal myxomas, usually diagnosed by the age of 20 years (neonatal presentation is exceptional, requiring a meticulous differential diagnosis). Melanocyte-derived tumors such as epithelioid blue nevi (with different levels of pigmentation) and pigmented epithelioid melanocytoma (previously "animal-type melanoma") are often found. Myxomas, mesenchymal tumors with mostly a benign pattern, may be recurrent. Primary cutaneous melanotic schwannoma is atypical, while nonskin sites are frequent. Corticotropinomas or somatotropinomas are part of the hereditary syndrome-related pituitary adenomas (representing 5% of all). The primary pigmented nodular adrenocortical disease involves bilateral cortical hyperplasia causing Cushing's syndrome (CS) at an earlier age than non-LAMB syndrome cases; osteoporotic fractures seem more prevalent compared to other etiologies. Typically benign, a few cases of adrenocortical carcinoma have been identified. A total of 5% of familial nonmedullary thyroid cancer are syndromic, also including LAMB. Lentigines, atrial myxoma, and blue nevi syndrome-related thyroid frame include hyperthyroidism, follicular hyperplasia/adenomas, and follicular carcinoma (usually aggressive, bilateral, or multifocal). Large-cell calcifying Sertoli cell tumors (LCCSCTs) of the testes have malignant behavior in adults; in children, these may induce precocious puberty. Two particular mammary tumors are found: myxoid fibroadenomas and breast myxomatosis. Cutaneous/subcutaneous lesions, pigmented or not, or any focal swelling of nonidentified cause needs careful examination since dermatological elements are among the earliest and most discernible by which to detect lesions in LAMB syndrome, a systemic condition with multilevel endocrine involvement.

Keywords: Benign, Children, Cushing's disease, Cushing's syndrome, Cutaneous lesions, Fibroadenoma, Lentigines, atrial myxoma, and blue nevi syndrome, Malignant, Primary pigmented adrenocortical disease.

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Introduction

The LAMB syndrome was discovered in 1985; however, the related mutations weren't yet known 20 years earlier. An elevated risk of numerous different tumor forms is a characteristic of the LAMB. J. Aiden Carney is the person who identified the LAMB syndrome. In 1985, which is a mix of myxoma, pigmented skin lesions, and endocrine axis hyperactivity. It stands for a condition of numerous neoplasms that include both endocrine and nonendocrine tumors. While the complex only emerges intermittently in the remaining cases, 70% of LAMB syndrome patients show an autosomal dominant hereditary characteristic with complete penetrance. Those who are affected typically experience changes in their skin tone (pigmentation). Typically, this condition's signs and symptoms start in adolescence or early adulthood.[1] The LAMB syndrome is an extremely uncommon autosomal-dominant hereditary syndrome with a high penetrance and underlying endocrine elements, such as primary pigmented nodular adrenocortical disease at the level of the adrenal cortex, pituitary adenomas secreting adrenocorticotropic hormone (ACTH), and growth hormone (GH), causing Cushing's disease. The corresponding gigantism or acro-myxomas that are found in the skin, mucosa, heart, and breast are among those that are more frequently linked to the illness. Additionally, pigmented cutaneous lesions, also known as lentiginosis, can be found at the skin's surface. The syndrome is also linked to schwannomas of the psammomatous melanotic kind. Several tumors, like osteochondromyxoma and some adult testicular tumor forms, have a high propensity for malignancy. These cases include Sertoli cell tumors with massive, calcifying cells.

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The LAMB syndrome has also been referred to as LAMB (lentigines, atrial myxoma, blue nevi) syndrome and nevi, atrial myxoma, ephelides (NAME) syndrome. Contrary to popular belief, it is distinct from the Carney triad, which consists of pulmonary chondromas, stomach stromal tumors, and paragangliomas.[2]

Genetic Mutations in LAMB Syndrome

Since the initial description of the LAMB syndrome and the identification of the mutations traditionally associated with the disease, a number of genetic and clinical variants have been discovered. The *LAMB SYNDROME1* gene, which is positioned at the 17q22–24 chromosome level and encodes a PRKAR1A, is germline mutated in 70% of people. The gene codes for cyclic AMP-dependent protein kinase.[3] A has mutations of the inactivating type or substantial deletions. In *PRKAR1A* gene mutations, genotype–phenotype associations have been established. Adrenal hyperplasia is associated with defects in catalytic subunits (PRKACA), whereas myxomas, pigmented skin lesions, and hypophyseal tumors are

associated with defects in PRKACB, another catalytic subunit. In people with LAMB syndrome, these genetic factors may be connected to certain adrenal tumors and testicular neoplasia.[4]

Definition of LAMB Syndrome

The LAMB syndrome is a rare genetic disorder associated with one of the multiple endocrine neoplasia syndromes. Multiple glands in the body, including the pituitary, thyroid, and adrenal glands, are impacted by the Carney complex. In addition, it has been linked to testicular tumors, breast myxomatosis, aberrant pigmentation, heart myxomas, and cutaneous myxomas.[5]

Epidemiology of LAMB Syndrome

Unknown is the precise prevalence of the LAMB syndrome. Since 1985, 750 instances from various ethnic backgrounds have been reported globally. Because it's difficult to diagnose and the medical community isn't sufficiently aware of this uncommon and complex condition, and the prevalence can be overestimated.

Etiology of LAMB Syndrome

De novo mutations cause around 25% of cases to arise spontaneously. Initially believed to be autosomal dominant, the LAMB syndrome has since been linked to two genetic loci. About two-thirds of LAMB syndrome patients have a germline mutation in the *LAMB SYNDROME* gene 1, which affects the regulatory subunit 1A of protein kinase A PRKAR1A, which is located at 17q22–24.

On chromosome 2p16, the second locus has been observed, although no particular gene has been found. Patients with *PRKAR1A* gene mutations have been documented to have changes at a location on 2p16.

Patients with isolated micronodular pigmented primary pigmented adrenocortical disease, (PPNAD) or nonpigmented hyperplasia have also been shown to carry inactivating mutations of the phosphodiesterase genes *PDE11A* and, less frequently, *PDE8B*. These mutations cause the protein's catalytic domain to change just one nucleotide, producing a Carney complex, or they cause premature stop codon production.[6]

Histopathological Analysis

Unless there is a suspicion of cancer, lentiginous pigmentation is often not treated with a skin biopsy. Lentigines are defined histologically by elongated epidermal ridges and enhanced basal layer pigmentation.

In a loose, mucinous stroma in the dermis, cutaneous myxomas show a nonencapsulated proliferation of spindled or stellate dermal fibroblasts. It is possible to witness bizarre multinucleated cells as well as typical mitotic figures.

The superficial and reticular dermis of blue nevi typically exhibits strongly pigmented melanocytes. The epithelioid blue nevus is characterized by large, epithelioid cells with little pigmentation and plenty of cytoplasm organized in nests in the dermis.[7]

LAMB Syndrome and Endocrine Manifestations

Cushing's Syndrome and Nodular Primary Pigmented Adrenocortical Disease

Young individuals and women are more likely to develop CS as a result of PPNAD. The second and third decades of life are when the incidence peaks. Clinical symptoms are comparable to those seen in people who have other reasons of elevated cortisol levels.

Primary Pigmented Adrenocortical Disease

Cushing's syndrome without a need for ACTH. Only 60–70% of patients with the LAMB syndrome display CS when there is histological proof of PPNAD. The condition was given its name after the macroscopic features of the adrenal cortex, which are tiny, pigmented nodules less than 10 mm in diameter, most frequently encircled by atrophic cortex. Because both adrenal glands are mostly affected, the condition is bilateral.

Pituitary

Acromegaly is often brought on by pituitary tumors, which also affect the cells that make GH. In the LAMB, acromegaly progresses gradually. Not until the third decade of life does it start to show up. Clinical acromegaly is a rare condition that affects 10–15% of people.[8]

Thyroid

Patients with the LAMB syndrome frequently have thyroid nodules. On ultrasound, cystic or multinodular illness is discovered in over 75% of patients. Most thyroid nodules are benign, harmless follicular type adenomas. Thyroid cancer is seen in about 3% of the patients. Most frequently, it is papillary carcinoma, which can be numerous and occasionally highly aggressive, necessitating ongoing thyroid monitoring.

Gonadal Tumors (Testicular and Ovarian Lesions)

Testicular Lesions

Gonadotrophic Tumors (Testicular and Ovarian Lesions) Tumors in the Testicles: The most prevalent varieties are Leydig cell tumors, nodular adrenocortical rests, and LCCSCTs. One of the tumors is seen in 20–50% of Carney patients. Large-cell calcifying Sertoli cell tumor, a benign stromal tumor, is one of the rarest lesion tumors, yet it usually affects male LAMB syndrome patients. About 50% of patients may have bilateral and multifocal LCCSCT. They eventually replace the healthy testicular tissue as people age. They may be the source of the decreased fertility seen in men with LAMB syndrome because they have the potential to replace and clog seminiferous tubules. Rarely have malignant alterations been reported, especially when the initial tumor is big and has a diameter more than 6 cm. Less frequently seen are documented. These masses are frequently asymptomatic and not perceptible; however, Carney complicated sperm abnormalities have been described in these masses.[9]

Nonendocrine Manifestions

Cardiac

In the heart (cardiac myxoma) and other areas of the body, noncancerous (benign) tumors known as myxomas are more common in people with Carney complex. Cardiac myxomas can appear in many chambers of the heart and can occur in any of the four chambers. These tumors may obstruct blood flow to the heart, which could result in major consequences or instantaneous demise.

Cardiac Myxomas

Benign tumors affect people of all ages and genders equally. They are seen in 20–40% of people with Carney complex. Any heart

chamber may include several Carney complex-associated myxomas, which must be surgically removed. Because of cardiac weakness and embolism, they may be the cause of stroke. Although they may have been sufficiently removed, they can occur again, making surgical treatment difficult. The majority of deaths in patients with the LAMB syndrome are caused by these tumors, either directly or as a result of complications during or after surgery. The high rate of sudden mortality recorded in people with the LAMB syndrome is probably due to it.

Integumentary

Additionally, internal organs and the skin may develop myxomas. Skin myxomas can show up as little lumps on the skin's surface or deep within the skin. Myxomas in the LAMB syndrome frequently come back after being removed. All LAMB syndrome patients have patches of atypical skin pigmentation. Lentigines are brown skin lesions that can develop anywhere on the body, but they usually form around the lips, eyes, or genitalia. Additionally, some affected people have one or more blue–black moles known as blue nevi.

In patients with the LAMB syndrome, the three most typical skin symptoms are quite prevalent and present at an early stage.

In between 50% and 80% of patients with the LAMB syndrome, lentiginosis is present. Usually flat, ill-defined, brownish to black macules, lentiginosis is found around the lips, eyelids, ears, and genital region. They often don't change when exposed to sunlight and are small (less than 5 mm). Few lesions to profuse pigmentation are examples of the density range of pigmented patches. It occasionally manifests before birth and is frequently seen during childhood and the prepubertal stage. Until the early adolescent era, lentigines typically do not develop their normal intensity and distribution. It is challenging to discriminate between solar- and LAMB-complicated lentigines. However, lentigines linked with the LAMB syndrome tend to disappear with age, in contrast to age-related skin lesions. In patients with the LAMB, blue nevi are, after lentigines, the second most common cutaneous lesions, occurring in roughly 40% of patients. They appear as ovoid or star-shaped marks of bluish-black color with a varied distribution.

About 20–55% of individuals have been found to have cutaneous myxoma, the third most prevalent skin manifestation of the Carney complex. They frequently occur before the age of 18 and frequently repeat. The lesions range in size from microscopic, sessile, opalescent or dark pink papules that rarely exceed 1 cm in diameter to enormous, finger-like, pedunculated lesions. Although they can happen everywhere, they frequently impact the perineum, eyelids, ears, nipples, and external ear canal. The dermatological criterion for Carney-complicated diagnosis, which is the most precise, is myxoma.[10]

Breast Lesions

Myxoid fibroadenomas, ductal adenomas, and lobular or nodular myxomatosis are examples of lesions. About 20% of female patients experience them, and they are frequently bilateral.

Melanotic Schwannoma

They are found in 5–10% of individuals, and they might be misinterpreted for malignant melanomas because they show schwannoma-like clinical features but show spindle cell architecture. They typically exhibit multicentricity and frequent calcifications. They can be seen everywhere, but the paraspinal sympathetic chain and the gastrointestinal tract (esophagus, stomach, and rectum) are where they are most frequently seen. In 10% of cases, malignancy may be seen, and it frequently metastasizes to the lung, liver, or brain.

Osteochondromyxoma

Early in childhood, generally before the age of two, when spontaneous bone tumors are uncommon, they have been observed to occur. Clinically, the tumors are painless masses that have developed in little flat bones and distal long bones (diaphyseal) (nasal). Even though osteochondromyxoma is often benign, local invasiveness has been documented.[11]

Other Lesions

Other lesions, such as hepatocellular carcinoma, an intraductal papillary mucinous pancreatic tumor, or numerous fusiform myxomatous cerebral aneurysms, can be related to the LAMB syndrome but are less common.

Diagnostic Evaluation of LAMB Syndrome

When two or more of the cardinal symptoms are present and are supported by imaging, biochemical testing, or histology, a diagnosis is made by a clinician. A single symptom is enough to make the diagnosis if the patient has a proven germline PRKAR1A mutation and/or a first-degree relative who has the condition. Once the diagnosis has been established, the patient will need ongoing monitoring. All patients should undergo a clinical work-up for every LAMB syndrome manifestation at least once per year. For certain manifestations, these tests should begin in infancy.

Adrenal

Although it can vary, urinary cortisol is typically higher in most people. Even after high doses, the dexamethasone suppression test is unable to reduce cortisol release. The majority of patients react to dexamethasone by producing more cortisol, which is paradoxical. Even in patients with normal baseline cortisol levels and no clinical signs of CS, the dexamethasone suppression test may be utilized as a diagnostic tool to identify PPNAD. One out of three individuals has normal-looking adrenals on a CT scan and often low plasma ACTH levels, whereas the other two have micro- or, less frequently, macro-nodules larger than 10 mm. The adrenal glands are often normal in size and weight and are dotted with black or brown nodules set in a cortex that is frequently atrophic, according to path reports.

Pituitary

If patients are carefully screened, biochemical anomalies of the GH axis as well as changes in the rhythm of GH secretion may be found in up to 80% of cases. These biochemical problems appear before radiological signs of a pituitary tumor and may be caused by GH cell hyperplasia, which is seen on pathological inspection as regions with irregular borders and increased cellularity. The majority of the remaining individuals respond abnormally to the oral glucose tolerance test, although their pituitary imaging and insulin-like growth factor type 1 (IGF-1) levels are normal. Oral glucose tolerance testing and magnetic resonance imaging can be used to monitor these patients. If a tumor forms, it is surgically removed; however, if IGF-1 levels rise without a tumor being apparent, therapy options such as somatostatin analogs or GH receptor antagonists may be considered.

Thyroid

Usually, a cystic or multinodular illness is observed in about 75% of individuals. It is advised to perform a thyroid ultrasound every year as part of a clinical assessment of post-pubertal pediatric and adult patients. The thyroid nodule is examined with a fine needle to aid in the diagnosis.

Gonadal

Microcalcifications and hypoechogenic lesions are visible on sonographic examination of the testes and ovaries.

Cardiac Myxoma

The first 6 months of life should be used to begin the early diagnosis of these tumors, followed by yearly cardiac ultrasound screening. Every six months, patients with cardiac myxoma should be screened. Transesophageal ultrasonography and cardiac magnetic resonance imaging can be beneficial in challenging situations.

Breast Lesions

Breast magnetic resonance imaging was done on individuals who had previously been diagnosed with lesions even though regular mammograms did not reveal any obvious evidence. Not enough standards are in place for treatment and aftercare.

Management of the LAMB Syndrome

The hereditary complex of disorders has not been specifically treated; gene testing is advised after the mutation is determined starting with any form of lesion. To effectively assess and address additional aspects of the LAMB syndrome that are more likely to manifest later in life, a multidisciplinary team is required.

To manage the effects of cortisol oversecretion, CS caused by PPNAD must be treated. Although mitotane or ketoconazole have been utilized as anticortisol medications in some cases, bilateral adrenalectomy is the most typical treatment. For people with thyroid nodules, fine needle aspiration is advised. Patients who have lesions that seem cancerous should be referred for surgery.

Few Carney patients with acromegaly have tumors that are rapidly growing and will need surgery, whether or not it is followed by radiation therapy.[12] Somatostatin analogs may be used to treat acromegaly either as a stand-alone therapy or as an adjunct to trans-sphenoidal surgery. When bilateral, LCCSCTs are benign and just need imaging surveillance. Testicle-sparing surgery may be an option for tiny tumors to enable histopathologic analysis if measurements of tumor markers or imaging features point to a suspicion of malignancy. Several papers describe the use of aromatase inhibitors in treating prepubescent boys with LCCSCT.

Typically, malignant LCCSCTs only affect elderly patients and those with unilateral or unifocal illness. The preferred course of treatment for malignant LCCSCTs is orchiectomy.

Cardiac Myxoma

The preferred course of treatment for cardiac myxomas is surgical resection. They may recur in affected patients. Follow-up with meticulous monitoring is included in the plan of care of the patient.

Surgery is used to completely remove psammomatous melanotic schwannomas (PMS) with tumor-free margins. For malignant tumors, chemotherapy and radiation therapy may be necessary.

Other possibly impacted family members of patients with the LAMB syndrome should undergo genetic testing for mutations in the PRKAR1A. Even in the absence of a PRKAR1A pathogenic variation, clinical surveillance for at-risk family members is advised.

When neither parent of a person with LAMB syndrome possesses the pathogenic gene variant or any of the clinical characteristics associated with the condition, the patient is most likely suffering from a de novo mutation.[13]

Differential Diagnosis of LAMB Syndrome

- Adrenal carcinoma
- Adrenal incidentaloma
- Breast cancer
- Intracardiac thrombus
- Lentigo
- Melanocytic nevi
- Primary cardiac neoplasms
- Rhabdomyomas

Management of LAMB Syndrome

A systemic medical treatment that targets the cAMP/ protein kinase A (PKA) signaling in condensation nuclei counter (CNC) or was created in response to a hereditary abnormality is not yet available. Every manifestation is handled separately. Surgery is typically explored in a multidisciplinary environment for the majority of symptoms, especially cardiac myxomas, PPNAD, thyroid carcinomas, PMS, and frequently acromegaly. In the absence of symptoms or patient complaint, therapeutic abstention and simple monitoring are frequently suggested instead of surgical removal for the other clinical criteria.

For any patient presenting with CNC diagnostic criteria without a family history of CNC, as well as for every first-degree relative, PRKAR1A sequencing and copy-number variation analysis are recommended. Analysis of the PRKACA, PRKACB, and phosphodiesterases genes can be explored, particularly in isolated PPNAD, for patients without any known PRKAR1A mutation. In order to properly arrange the follow-up since CNC manifestations may manifest before the age of three, genetic analysis should be made available to and discussed with first-degree relatives of mutant carriers during the first two years of life in children.[14]

Prognosis

Cardiovascular illness, notably cardiac myxomas and complications from cardiac surgery, is associated with the highest risk of mortality in the LAMB syndrome (57%). Metastatic or intracranial psammomatous melanotic schwannoma (14%), carcinoma or metastatic tumor (14%), and no-cardiac postoperative complications (12%) are other leading causes of death.[7]

Conclusion

Skin myxomas and pigmented lesions, among other cutaneous symptoms, are crucial markers for the Carney complex. Pituitary, adrenal, and thyroid glands, as well as testicular tumors and breast deformities in women, are only a few of the endocrine panel's manifestations. Despite being a rare entity, ongoing multidisciplinary care is necessary, and early tumor detection improves the prognosis overall. An uncommon autosomal dominant hereditary condition is the Carney complex. It is

crucial to do genetic research on index cases and first-degree relatives. In order to gain a deeper understanding of the parts of this condition that are yet unknown, it is crucial to clinically monitor the patients and look into the molecular foundation of the problem through multicenter research, as is the case with all uncommon disorders.[15]

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