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Marine-Lenhart Syndrome: Current Perspectives on Diagnosis and Management

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Abstract

Marine-Lenhart syndrome (MLS) is an uncommon disorder characterised by the concurrent presence of Graves' disease and hyperfunctioning thyroid nodules. Its global prevalence ranges between 2.7- 4.1% of Graves' disease cases, presenting significant challenges in diagnosis and management. MLS is often difficult to detect due to limitations in autoimmune serology tests, thyroid ultrasonography, and access to nuclear medicine facilities. Diagnosis relies on a combination of clinical hyperthyroidism symptoms, the presence of specific thyroid antibodies, and scintigraphy findings that reveal "hot" or "cold" nodules. The primary therapeutic options for MLS include antithyroid drugs, radioactive iodine (RAI) therapy, and surgery. RAI is commonly employed as definitive treatment, often requiring higher doses to address the resistance of hyperfunctioning nodules. Surgery is indicated in cases involving large nodules, compressive symptoms, or suspected malignancies. Treatment strategies should be tailored to the individual clinical characteristics of each patient to minimize complications and ensure optimal outcomes. Advancing the diagnosis and management of MLS requires enhanced access to advanced diagnostic technologies and improved healthcare provider proficiency in identifying and treating the syndrome. A multidisciplinary and integrated approach is essential for achieving favorable clinical outcomes for MLS patients.

Keywords*: Marine-Lenhart Syndrome, Diagnosis, Management.*

I. INTRODUCTION

Marine-Lenhart syndrome (MLS) is an uncommon condition characterised by the coexistence of Graves' disease and hyperfunctioning thyroid nodules.[1] The term "Marine-Lenhart syndrome" was first introduced by David Charkes in 1972, when he described 10 patients with Graves' disease and functionally active nodules.[2] Worldwide, the prevalence of MLS is estimated to range from 2.7% to 4.1% among all cases of Graves' disease, whereas in Japan it is lower, at approximately 0.26% to 0.42%.[1,3] In Indonesia, no national publication has yet reported the prevalence of MLS.

This disease poses significant challenges in both diagnosis and management due to various limitations encountered in clinical practice. The diagnosis of MLS can be difficult because autoimmune serological testing is not available in all healthcare facilities, access to radiological modalities such as thyroid ultrasonography is limited, and nuclear medicine facilities remain scarce in many regions. Another challenge is the limited awareness and understanding of MLS among healthcare providers, which hinders optimal patient management.

Due to limited diagnostic and therapeutic modalities, the management of MLS is often suboptimal, potentially increasing the risk of complications if not addressed promptly. MLS can have serious consequences for patient health if not appropriately treated. Hence, nuclear medicine plays a crucial role in providing effective diagnostic and therapeutic options for the management of Marine-Lenhart syndrome.

II. DEFINITION

The coexistence of a functioning thyroid nodule with Graves' disease is referred to as Marine-Lenhart syndrome (MLS).[3] This syndrome affects around 0.8-2.7% of Graves' disease patients and is infrequently recorded. The syndrome is named in honour of David Marine and Carl H. Lenhart for their early research on adenomas in goiter with exophthalmos.[2]

Its characteristics include: (1) the nodule demonstrates increased radioiodine uptake when stimulated by thyroid-stimulating hormone (TSH), in contrast to the autonomous nodules seen in Plummer's disease; (2) the nodule appears "cold" on scintigraphy, with lower radioiodine accumulation than the surrounding tissue; (3) the nodule is more resistant to radioiodine therapy, requiring higher doses of I-131; (4) following successful therapy, the nodule shows a relative increase in radioiodine uptake; and (5) pathologically, the nodule is an adenoma.[2]

III. DIAGNOSIS

History Taking and Physical Examination1

Marine-Lenhart syndrome (MLS) describes the coexistence of Graves' disease with hyperfunctioning nodules, such as toxic adenoma or toxic multinodular goiter. Patients with Graves' disease typically present with classical symptoms of hyperthyroidism and features specific to Graves' disease, such as orbitopathy, dermopathy, and acropachy. The symptoms of hyperthyroidism vary depending on age, severity, and duration of disease. Symptoms and signs can be evaluated using the Wayne index.[4]

In patients with MLS, the majority of nodules are hypoactive (>95%), and only a small proportion are hyperactive based on scintigraphy findings. In patients with hyperactive nodules, thyrotoxicosis results from the combined effects of Graves' disease and toxic nodular goiter.[5] Most autonomous adenomas are benign, while functional thyroid carcinomas are uncommon. Well-differentiated papillary carcinoma is often detected in patients with Graves' disease

who undergo surgery, with a reported prevalence of about 7.8%. The carcinoma often occurs in Graves' disease with palpable nodular lesions, with an incidence of up to 35%. Although most of these carcinomas are microcarcinomas (88%), palpable nodules require evaluation and periodic follow-up to detect potential malignancy.[6]

Laboratory Examination

The initial test for diagnosing hyperthyroidism is the measurement of thyroid-stimulating hormone (TSH). If TSH is low, free thyroxine (FT4) and free triiodothyronine (FT3) levels should be checked. If free hormone tests are not available, total T4 and T3 can be employed. Hyperthyroidism is diagnosed when TSH levels are low but FT4 and/or FT3 levels are high. Measurement of thyrotropin receptor antibody (TRAb) or thyroid-stimulating immunoglobulin (TSI) is important for confirming autoimmune aetiology. Third-generation TRAb assays have a sensitivity of 97% and specificity of 99% for the diagnosis of Graves' disease.[4,7]

In patients with thyroid nodules, TSH measurement should be performed as a guide. Normal or elevated TSH often indicates an increased risk of malignancy, whereas low TSH usually suggests a benign nodule. If TSH is low, the next step is radionuclide scanning with technetium-99m pertechnetate, iodine-131, or iodine-123 to detect hyperfunctioning thyroid nodules, which are usually benign and rarely require further evaluation.[8]

Imaging

Thyroid ultrasonography is effective in evaluating patients with Graves' disease, nodular goiter, or toxic multinodular goiter. In Graves' disease, ultrasound typically reveals thyroid enlargement with a hypoechoic pattern, either diffuse or occasionally with associated nodules. Marked vascularity on colour Doppler is often observed, which aids in differentiating from destructive thyroiditis. In patients with thyroid nodules, ultrasound provides information on nodule size, echogenicity, and vascularity assessed using colour Doppler imaging.[9]

In 2023, the European Thyroid Association advised performing neck ultrasonography for all patients with suspected thyroid nodules. The assessment should document the size, location, and characteristics of the nodules, and estimate the risk of malignancy in accordance with the EU-TIRADS classification system. In cases with multiple nodules, details of all suspicious nodules should be documented. Additional modalities, including Doppler, elastosonography, and contrast-enhanced ultrasound (CEUS), may be employed, with CEUS being particularly valuable for delineating the size and boundaries of the ablation zone after minimally invasive procedures. In patients with MLS, ultrasound findings may reveal features of Graves' disease along with the presence of nodules.[10,11]

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB), ideally performed under ultrasonographic guidance, is the recommended initial step in evaluating thyroid nodules. FNAB should be performed according to size criteria and ultrasonographic characteristics as outlined in the American Thyroid Association (ATA) guidelines.[2] FNAB findings in Marine-Lenhart syndrome typically reveal follicular adenoma or hyperplastic lesions.[1]

Marine-Lenhart syndrome can coexist with papillary thyroid carcinoma, and this association has been documented in several case reports. [1,14] Although FNAB is generally not recommended for hyperfunctioning nodules, it remains indicated in cases of Marine-Lenhart syndrome. Thyroid nodules

>1–1.5 cm in patients with Graves' disease should be evaluated.[12,13]

Nuclear Medicine

Thyroid scintigraphy is an important diagnostic modality for confirming this syndrome, as Marine-Lenhart syndrome exhibits three principal scintigraphic patterns.[14] Type 1 is characterised by increased uptake in the thyroid gland with a single hyperfunctioning nodule; type 2 presents with increased uptake in the thyroid gland accompanied by multiple hyperfunctioning nodules; and type 3 exhibits a similar pattern to type 2, but with the presence of an additional cold nodule.[14]

Thyroid scintigraphy with technetium-99m (Tc-99m) pertechnetate is a valuable nuclear medicine technique for distinguishing between different causes of thyrotoxicosis. Pertechnetate is taken up via sodium-iodide symporters (NIS) situated in the thyroid follicular cells. In Graves' disease, NIS expression is upregulated through stimulation by TSH receptor antibodies (TSHR-Ab), which act independently of endogenous TSH, leading to increased tracer uptake within the thyroid gland.[15]

In most cases, initial scintigraphy demonstrates hyperactivity in the extranodular parenchyma with relative hypoactivity within the nodule, which is suppressed by the high overall glandular activity. Following treatment with antithyroid drugs or radioiodine (RAI), there is increased radiotracer accumulation within the nodule, resulting in either an apparent increase in radioiodine uptake (RAIU) or the appearance of a hot nodule as serum TSH levels begin to rise. In some cases of Marine-Lenhart syndrome, homogeneous increased uptake is observed in the extranodular tissue with intense focal uptake in the nodule, whereas in others, the activity within the nodule is similar to that of the extranodular tissue.[6,12]

Scintigraphy patterns in Graves' disease, Marine-Lenhart syndrome, Graves' disease with a cold nodule, and autonomously functioning thyroid nodule (AFTN) demonstrate distinct radioiodine uptake characteristics. In Graves' disease, there is diffuse increased uptake in both thyroid lobes, with an I-131 uptake of 67.8%. In Marine-Lenhart syndrome, a "hot" area corresponding to a hyperfunctioning nodule is observed, with an I-131 uptake of 35.5%. In Graves' disease with a cold nodule, a photopenic area is present in the right lobe, with an I-131 uptake of 21.0%. In AFTN, scintigraphy shows a "hot" nodule in the left lobe, with an I-131 uptake of 31.1%.[3]

Based on these thyroid scintigraphy findings, the diagnosis of AFTN can be differentiated from Marine-Lenhart syndrome. In AFTN, tracer uptake is increased in the nodule identified on ultrasonography, while the remaining thyroid tissue demonstrates suppressed activity. Conversely, in Marine-Lenhart syndrome, the nodule exhibits intense uptake accompanied by diffuse tracer uptake throughout the thyroid gland.[3]

Diagnostic Approach

Marine-Lenhart syndrome has been described as a variant of Graves' disease with the following criteria: (1) computed tomography (CT) scan of the thyroid reveals an enlarged gland with one or two nonfunctioning nodules; (2) the nodules are TSH-dependent, whereas the paranodular tissue is TSH-independent; (3) restoration of nodule function can be demonstrated following endogenous or exogenous TSH stimulation; and (4) the nodules are histologically benign.[6,16]

To standardise the definition of Marine-Lenhart syndrome, clear diagnostic criteria have been proposed for patients with Graves' disease and active thyroid nodules. Diagnosis involves thyroid function tests

demonstrating hyperthyroidism and positive serological results for Graves' disease (TRAb or TSI). Increased radioiodine uptake, along with the presence of a "cold" or "hot" nodule, should be confirmed by ultrasonography. Fine-needle aspiration biopsy (FNAB) of the thyroid nodule is required to detect hyperplastic lesions or follicular adenomas, with diagnostic surgery performed if necessary to exclude follicular carcinoma. Cytological evaluation is generally unnecessary for hyperfunctioning nodules; however, biopsy is indicated for "hot" nodules not proven to be hyperfunctioning. Based on history-taking, physical examination, and supportive investigations, several guidelines have proposed diagnostic flowcharts for Marine-Lenhart syndrome.[2]

IV. MANAGEMENT

Antithyroid Drugs

Antithyroid drugs, such as thionamides (propylthiouracil, carbimazole, and methimazole), are used to treat hyperthyroidism. Propylthiouracil is preferred in severe thyrotoxicosis because it inhibits the peripheral conversion of T4 to T3, although it has a shorter half-life. The initial dose of carbimazole or methimazole is 10–20 mg every 8–12 hours, which can be reduced once euthyroidism is achieved. Propylthiouracil is usually administered at 100–200 mg every 6–8 hours. Dosage can be tapered gradually (titration regimen) or given in high doses alongside levothyroxine (block-and-replace regimen). Monitoring is performed every 3–4 weeks, with euthyroidism typically achieved within 6–8 weeks. Common side effects include rash, fever, and arthralgia, while more serious adverse events, such as hepatitis or agranulocytosis, require immediate drug discontinuation and blood testing, although these are rare.[17]

Radioactive Iodine (RAI)

Radioactive iodine (RAI) therapy is an effective treatment option for hyperthyroidism, either as an initial therapy or for relapse following antithyroid drug use. It is particularly recommended for elderly patients or those with cardiac comorbidities. Pre-treatment with antithyroid drugs such as carbimazole or methimazole is advised to reduce the risk of thyroid storm. However, RAI is contraindicated in pregnant and lactating women, and pregnancy should be deferred until at least six months post-treatment.[6]

Radioiodine (RAI) therapy is regarded as the first-line treatment in the following circumstances: (i) the presence of a solitary hyperfunctioning nodule; (ii) one or more hyperfunctioning nodules within a multinodular goitre without suspicion or confirmation of thyroid malignancy; (iii) advanced age; (iv) comorbidities (e.g., cardiovascular or cerebrovascular disease, systemic or pulmonary hypertension) that increase surgical risk; (v) a history of neck surgery or previous radiation exposure; and (vi) limited or no access to experienced thyroid surgeons.[11]

The typical RAI dose for hyperthyroidism ranges from 185 to 555 MBq (5–15 mCi), adjusted based on the severity of thyrotoxicosis, thyroid size, and iodine uptake. Higher doses are often chosen for complete ablation, with subsequent hypothyroidism managed using levothyroxine. In Marine–Lenhart syndrome, higher doses are required because functioning nodules are more radioresistant compared to Graves' disease without nodules.[12] Extraneous (non-nodular) thyroid tissue is more susceptible to RAI-induced damage.[15] By comparison, RAI is the first-line treatment for autonomously functioning thyroid nodules (AFTN).[18]

Thyroid function should be monitored annually, particularly during the first 5–10 years after therapy, to detect hypothyroidism. During the first 2–3 months, β-blockers or antithyroid drugs may be used to control hyperthyroid symptoms. If symptoms persist, a second RAI dose can be administered after six months. Adverse effects may include hypothyroidism (10–20% in the first year, increasing by 5% annually) and mild pain from radiation thyroiditis.[6] RAI therapy may also exacerbate Graves' ophthalmopathy.[6,12] Careful assessment and pre-treatment with corticosteroids can reduce this risk.[19]

Therefore, radioactive iodine using iodine-131 (I-131) is considered one of the main treatment options for Marine–Lenhart syndrome, as the coexistence of Graves' disease and hyperfunctioning nodules responds well to this therapy. However, because initial scintigraphy in Marine–Lenhart syndrome may reveal a "cold" nodule, it is important to exclude malignancy using ultrasonography and fine-needle aspiration biopsy (FNAB) prior to RAI administration. In patients with Graves' disease, the most common thyroid malignancy is papillary thyroid carcinoma.[15]

Agrawal et al (2021) shows scintigraphy from a previously published case report of Marine-Lenhart syndrome. Pre-ablation thyroid scintigraphy with Tc-99m demonstrated diffusely increased uptake in both enlarged thyroid lobes (27.7% uptake at 20 minutes) with a large cold nodule in the lower pole of the left lobe, consistent with Graves' disease with a cold nodule. Post-radioiodine ablation scintigraphy revealed normalization of tracer uptake in the previously cold nodule. Fine-needle aspiration cytology of the nodule indicated benign pathology.[15]

In the same study, another case demonstrated increased tracer uptake in both enlarged thyroid lobes (19.7% uptake within 20 minutes), with cold nodules identified in the upper and lower poles of the right thyroid lobe. These findings were consistent with Graves' disease accompanied by cold nodules in the right thyroid lobe. Following radioiodine ablation, tracer uptake in both the cold nodules and the residual thyroid tissue returned to normal.[15]

The third case report is illustrated by Neuman et al (2018), involving a 60-year-old female patient with Marine-Lenhart syndrome (MLS) and Graves' ophthalmopathy. A technetium-99m pertechnetate thyroid scan demonstrating increased uptake in both thyroid lobes, with a more focal "hot nodule" in the upper to mid-right lobe, corresponding to the nodule detected on ultrasonography. The patient was treated with methimazole and, after achieving a euthyroid state, underwent total thyroidectomy, followed by bilateral orbital decompression one month later. Histopathological examination confirmed hyperplastic thyroid tissue consistent with Graves' disease.[2]

Radioiodine therapy offers the advantage of permanent cure, although higher doses are required in MLS.[20] In the management of Marine-Lenhart syndrome, radioiodine (RAI) therapy with doses of 13–26 mCi has been effective in achieving euthyroidism, while doses ranging from 13–40 mCi are more likely to result in hypothyroidism.[3] Low-dose RAI at 10 mCi has also been reported as effective for MLS management.[21]

Surgical management

For malignant nodules, the primary treatment is surgery.[15] Surgical procedures either hemithyroidectomy or total thyroidectomy may be considered as first-line therapy depending on the patient's specific condition. Surgery is recommended for: (i) women planning pregnancy within six months, (ii) patients with large goitres (≥ 80 g) or compressive symptoms, (iii) patients with low radioactive iodine uptake (RAIU),

(iv) patients diagnosed with or suspected of having thyroid cancer (including those with indeterminate nodule cytology) or large (≥ 4 cm) non-functioning nodules, and (v) patients with Graves' disease and moderate-to-severe Graves' ophthalmopathy.[22]

In patients with Graves' disease and moderate-to-severe ophthalmopathy, some experts recommend RAI therapy with rhTSH assistance after thyroidectomy to achieve total thyroid ablation, which is considered more effective in improving Graves' ophthalmopathy than thyroidectomy alone.[11] Surgery also provides permanent cure but carries risks such as iatrogenic hypoparathyroidism and recurrent laryngeal nerve injury.[20] In certain circumstances, surgery is preferred due to the risk of RAI resistance.[22]

The patient was treated with methimazole, and after achieving a euthyroid state, underwent total thyroidectomy. Histopathological examination revealed papillary microcarcinoma with a follicular variant. The patient subsequently received radioactive iodine ablation therapy with a dose of 100 mCi.[12]

Accordingly, several considerations must be taken into account when determining the optimal management for Marine-Lenhart syndrome. Table 1 presents the therapeutic modalities that may be offered to patients based on specific clinical considerations.[13]

Table 1. Therapeutic Modalities Options[13]

Clinical Condition	RAI	ATD	Surgery
Pregnancy	X	√√ / !	√ / !
Elderly patients with comorbidities increasing surgical risk and/or limited life expectancy	√√	√	X
History of previous neck surgery or anterior neck scar tissue	√√	√	!
Limited access to thyroid surgeons	√√	√	!
Symptoms or signs of neck compression	√	-	√√
Confirmed or suspected thyroid malignancy	X	-	√√
Large nodule/goiter (> 80 g)	√	-	√√
Nodule/goiter with substernal or retrosternal extension	√	-	√√
Concomitant hyperparathyroidism requiring surgery	-	-	√√

V. Conclusion

Marine-Lenhart syndrome is a rare condition characterised by the coexistence of Graves' disease with a functioning thyroid nodule. The presence of Graves' disease in this syndrome can be confirmed through the clinical manifestations of hyperthyroidism, the typical features of Graves' disease, and the detection of TRAb or TSI. The functioning nodule in this syndrome may present as either a hot or a cold nodule, which subsequently demonstrates increased radiotracer uptake following therapy. Although malignancy is an uncommon coincidence in this syndrome, histological evaluation of the nodule is still recommended. Definitive management for Marine-Lenhart syndrome involves either radioactive iodine (RAI) therapy or thyroidectomy, with the choice guided by the patient's specific clinical circumstances.

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