Prevalence and Treatment Outcomes of Marine-Lenhart Syndrome in Japan

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Keywords

Graves' disease · Hyperthyroidism · Marine-Lenhart syndrome · Thyroid nodule · Toxic adenoma

Abstract

Introduction: Marine-Lenhart syndrome (MLS) is now understood to be a combination of Graves' disease and autonomously functioning thyroid nodule(s) (AFTNs). The prevalence of the syndrome and suitable treatments for those living in iodine-sufficient areas are uncertain. **Objectives:** We aimed to investigate the prevalence, treatment, and prognosis of MLS in Japan, an iodine-sufficient area. **Methods:** This study involved patients who visited our hospital between February 2005 and August 2019. Among patients with both thyrotoxicosis and thyroid nodule(s) larger than 10 mm, MLS and isolated AFTNs were diagnosed based on serum thyroid-stimulating hormone receptor antibody levels and scintigraphy using radioiodine or technetium-99m and thyroid uptake. **Results:** Twenty-two patients were found to have MLS, compared to 372 with isolated AFTNs and 8,343 with Graves' disease, during the period. Therefore, the rate of MLS cases was 0.26% among all patients with Graves' disease (22/8,343). Treatments and outcomes were assessed for cases of MLS ($n = 18$) and isolated AFTNs ($n = 269$). Antithyroid drugs (ATDs) were withdrawn in 27.8% of cases in the MLS group and

10.3% in the isolated AFTN group. There was no significant difference in the clinical outcome after ATD withdrawal between the 2 groups. However, the rate of hypothyroidism after radioactive iodine (RAI) administration was significantly higher in the MLS group than in the isolated AFTN group (42.9 vs. 9.0%, $p = 0.005$) despite similar doses of RAI. **Conclusions:** The prevalence of MLS among patients with Graves' disease was 0.26% in Japan. RAI therapy induces hypothyroidism more frequently than in those with AFTNs probably because RAI is taken up in the surrounding Graves' tissues.

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Introduction

The Marine-Lenhart syndrome (MLS), first described by Charkes in 1972 [1], is now commonly defined as “a combination of Graves' disease and autonomous functioning thyroid nodule(s) (AFTN)” [2–4]. Typical scintigraphic images include both increased uptake in the affected nodule(s) and diffuse uptake in the extranodular tissue. In contrast, AFTN (solitary toxic adenoma or toxic multinodular goitre) is defined as single or scattered hot nodule(s) with suppressed extranodular tissue.

AFTNs are common in iodine-deficient areas, accounting for up to 60% of cases of thyrotoxicosis. However, it is rare (3–10% of cases of thyrotoxicosis) in regions with sufficient iodine supply [5]. The prevalence of AFTNs in iodine-sufficient areas is unclear.

Regarding treatment of MLS, radioactive iodine (RAI) comprising 13–26 mCi and 13–40 mCi resulted in euthyroidism [6–8] and hypothyroidism [6, 8–10], respectively. Some cases of thyroidectomy (Tx) have been reported [2, 11–18], and others showed normalization of thyroid function with antithyroid drugs (ATDs) [2, 6, 7, 19]. However, none of these reports were conclusive regarding the most suitable treatment partly due to the short observation periods after treatment. To investigate the clinical significance of MLS, we assessed the frequency, treatment, and prognosis of the syndrome at a hospital with thyroid specialists in Japan, an iodine-sufficient country with an average daily iodine intake of 1.2 mg [20].

Materials and Methods

Patients

This study involved patients who visited our hospital between February 2005 and August 2019. Thyrotoxicosis was diagnosed when the thyroid-stimulating hormone (TSH) concentration was ≤ 0.1 $\mu\text{U/mL}$, and FT4 and/or FT3 level was high. Graves' disease was diagnosed based on the following criteria: (i) thyrotoxicosis, (ii) positive TSH receptor antibody (TRAb), and (iii) non-suppressed radioiodine or technetium-99m thyroid uptake [21]. AFTN (solitary toxic adenoma or toxic multinodular goitre) was diagnosed when patients had both thyrotoxicosis and nodule(s) > 10 mm in diameter and for which the radioisotope accumulated (hot nodule). MLS was diagnosed when a combination of Graves' disease and AFTN was confirmed. Treatments and outcomes of patients with MLS and AFTN only were assessed retrospectively by follow-up for > 12 months after treatment.

Laboratory Methods

Between February 2005 and December 2018, serum TSH, FT4, and FT3 levels were measured using chemiluminescence immunoassays with Architect kits (Abbott, Japan) (normal ranges of TSH, 0.3–5.0 $\mu\text{U/mL}$; FT4, 0.7–1.6 ng/dL; and FT3, 1.7–3.7 pg/mL). After January 2019, serum levels of these markers were measured using electrochemiluminescence immunoassays with ECLusys kits (Roche Diagnostics, Japan) (normal ranges of TSH, 0.5–5.0 $\mu\text{U/mL}$; FT4, 0.9–1.7 ng/dL; and FT3, 2.3–4.0 pg/mL). Serum TRAb levels were measured via ELISA using TRAb-ELISA (Cosmic Corp., Tokyo, Japan) (normal range $< 15\%$) before July 2008 and via electrochemiluminescence immunoassays using ECLusys kits (Roche Diagnostics, Japan) (normal range < 2.0 IU/L) after August 2008. Thyroid scintigraphy (planar image) was performed using radioiodine in 1,026 patients (81.9%) and technetium (Tc)-99m in 227 patients (18.1%) as tracers. The normal lower limits of radioiodine uptake were 5% for 3 h and 10% for 24 h and that of Tc-99m uptake was 0.5% for 20 min. Ultrasound examination was per-

formed by well-trained registered medical sonographers using TOSHIBA Aplio SSA-700A or SSA-770A systems with PLT-805AT (8 MHz) and PLT-1204AX (12 MHz) linear probes between February 2005 and July 2012, and TOSHIBA Aplio TUS-A500 (versions 3.0, 5.0, and 6.0) systems with PLT-805AT (8 MHz) and PLT-1005BT (10 MHz) linear probes after August 2012.

Treatment Protocol

ATD, RI, and Tx were performed as treatments. Methimazole was the first choice for ATD, with an initial dose of 10–30 mg depending on the FT4 level. The starting dose was gradually reduced as thyrotoxicosis improved [21]. Methimazole was switched to propylthiouracil or potassium iodide when adverse reactions occurred. The initial dose of radioiodine-131 was based on 13 mCi and determined by each physician with reference to thyroid size and function. If hyperthyroidism continued after a single dose of radioiodine, additional doses were given. Total Tx, lobectomy, and lobectomy with isthmectomy were performed as surgical techniques.

Statistical Analysis

The Mann-Whitney U test was used to compare ages, RAI doses, and nodule sizes between the MLS and AFTN groups. Pearson's χ^2 test was used to compare sex differences. Bonferroni methods were used to adjust for multiple testing. The contingency table was analysed using Fisher's exact test (in less than 20 cases) and Pearson's χ^2 test (in equal or more than 20 cases) for independence and residual analysis. Analysis items with a two-sided $p < 0.05$ were considered statistically significant. Statistical analyses were performed using StatFlex version 6.0 (Artech Co. Ltd., Tokyo, Japan).

Results

Frequency Analysis

Of 202,778 new outpatients during the study period, 25,913 patients were diagnosed with thyrotoxicosis and underwent ultrasonography. Of these, 1,253 patients had one or more nodule(s) larger than 10 mm and were further evaluated by TRAb levels and scintigraphy (Fig. 1). Of 579 patients with positive TRAb test results, 22 patients had hot nodule(s) and non-suppressed uptake of the extranodular thyroid gland. These patients were diagnosed with Graves' disease with AFTN, or MLS. The isolated AFTN group consisted of 372 patients with negative TRAb test results and hot nodule(s) (Fig. 1). Representative scintigraphic images are shown in Figure 2. The total number of patients with Graves' disease was 8,343. Thus, the proportion of all patients with Graves' disease with MLS was 0.26% (22/8,343). In addition, the proportion of the patients with MLS to those with thyrotoxicosis with nodule(s) was 1.8% (22/1,253), and that of MLS to Graves' disease with nodule(s) was 3.8% (22/[22 + 557]) (Fig. 1).

The median age was 57 (range 20–81) years in the MLS group and 53 (range 13–89) years in the AFTN group;

Fig. 1. Study flowchart of the identification of patients with MLS (Graves' disease + AFTN) and isolated AFTN. † No patients showed positive TRAb with suppressed thyroid uptake or negative TRAb with non-suppressed thyroid uptake. AFTN, autonomously functioning thyroid nodule; TRAb, TSH receptor antibody; MLS, Marine-Lenhart syndrome; TSH, thyroid-stimulating hormone.

there was no significant difference between the 2 groups ($p = 0.23$). Women comprised 86.4% of patients in the MLS group and 90.8% in the AFTN group; there was no significant difference between the 2 groups ($p = 0.48$).

Treatment

Treatments and outcomes were analysed among those with MLS ($n = 18$) and AFTN ($n = 269$) who were followed up for more than 12 months after treatment (Table 1). ATD constituted a significantly higher proportion at 44.1% (8/18) in the MLS group than in the AFTN group (10.8% [29/269], $p < 0.001$). In contrast, the rates of RAI were similar ($p = 0.596$), but Tx constituted a significantly higher proportion at 43.9% (118/269) in the AFTN group than in the MLS group (16.7% [3/18], $p = 0.024$).

The maximum diameter of nodule(s) was significantly smaller in the MLS group than in the AFTN group (median 27.0 vs. 38.0 mm, $p < 0.01$). In the AFTN group, the mean maximum diameter of the nodule(s) was larger in the Tx group than in the ATD and RAI groups (median 41.0 vs. 31.6 mm, $p < 0.001$ and 41.0 vs. 34.0 mm, $p < 0.001$, respectively). Although not significantly different,

a similar trend was observed in the MLS group (55.0 vs. 23.0 mm, $p = 0.09$ and 55.0 vs. 31.0 mm, $p = 0.072$, respectively). There was no statistically significant difference in the maximum diameter of the nodule(s) between the MLS and AFTN groups or in the RAI and Tx groups, but the ATD group had significantly smaller nodule(s) than did the MLS group (23.0 vs. 31.6 mm, $p = 0.027$).

Table 2 shows the distribution of thyroid function after ATD withdrawal in the MLS and AFTN groups. ATDs were withdrawn in 5 of 18 patients (27.8%) in the MLS group and 3 of 29 (10.3%) patients in the AFTN group, with no significant difference between the 2 groups ($p = 0.23$). All patients presented with euthyroidism, and all patients in the MLS group were TRAb negative before ATD withdrawal. Subclinical hyperthyroidism (low TSH levels with normal FT4 and FT3 levels) occurred in 2 patients in the MLS group and 2 in the AFTN group after ATD withdrawal. Three patients in the MLS group and one in the AFTN group remained euthyroid after ATD withdrawal. There was no significant difference in clinical outcomes between the 2 groups ($p = 0.571$).

Fig. 2. Representative scintigraphic images of Graves' disease, MLS, Graves' disease + cold nodule, and AFTN. Iodine-131 thyroid uptake at 3 h was 67.8% (normal 5–15%) in (a). Iodine-131 thyroid uptake at 24 h was 35.5% (normal 10–40%) in (b), 21.0% in (c), and 31.1% in (d). + represents suprasternal notch. **a** Graves' disease: thyroid scan shows increased diffuse uptake in both thyroid lobes. **b** MLS: thyroid scan demonstrates a hot area in the isthmus consistent with hyperfunctioning nodule (arrowhead). The remaining tissue showed a slightly increased uptake as expected in Graves' disease. **c** Graves' disease + cold nodule: there is a photopenic area (arrowhead) in the right thyroid lobe with increased uptake in the remaining tissue. **d** AFTN (solitary toxic adenoma): thyroid scintigraphy shows a functioning hot nodule in the left lobe. No background tracer accumulates. AFTN, autonomously functioning thyroid nodule; MLS, Marine-Lenhart syndrome.

Table 1. Details of treatment (data indicate number of patients and nodule size)

	MLS		AFTN	
	patients, <i>n</i>	maximum diameter of nodule(s), mm	patients, <i>n</i>	maximum diameter of nodule(s), mm
ATD	8 [†]	23.0 (13.0–39.0)	29 ^{††}	31.6 (17.0–56.0)
RAI	7	31.0 (21.0–35.0)	122	34.0 (10.0–82.0)
Tx	3	55.0 (34.0–59.0)	118	41.0 (10.0–115.0)
Total	18	27.0 (13.0–59.0)	269	38.0 (10.0–115.0)

In the case of multiple autonomously functioning thyroid nodules (3 cases in the MLS group, 68 cases in the AFTN group), the largest nodule was measured. Data regarding nodule size are reported as medians (ranges). The surgical technique for MLS was total thyroidectomy ($n = 3$) and for AFTN, lobectomy or lobectomy with isthmectomy ($n = 80$) or total thyroidectomy ($n = 38$). [†] One patient received potassium iodide, one patient received propylthiouracil, others received methimazole. ^{††} All patients received methimazole. MLS, Marine-Lenhart syndrome; AFTN, autonomously functioning thyroid nodule; ATD, antithyroid drug; RAI, radioactive iodine; Tx, thyroidectomy.

Table 2. Comparison of thyroid function after ATD withdrawal between MLS and AFTN groups

	Subclinical hyperthyroidism patients, <i>n</i> [duration of normal thyroid function after ATD withdrawal, months]	Euthyroidism patients, <i>n</i> [follow-up period after ATD withdrawal, months]
MLS (<i>n</i> = 5)	2 [2.2 (1.4–3.0)] [†]	3 [9.9 (2.5–18.1)] [†]
AFTN (<i>n</i> = 3)	2 [11.4 (9.5–13.3)] [†]	1 [46.1]

Fisher's exact test was used to compare the distributions of hyperthyroidism and euthyroidism after ATD withdrawal between the MLS and AFTN groups. The test showed no significant difference in thyroid function after ATD withdrawal between both groups ($p = 0.571$). The median ATD treatment durations for the MLS and AFTN groups were 21.7 (range, 9.7–46.2) and 34.5 (range, 33.1–56.4) months, respectively. [†] Numbers in brackets indicate medians (ranges). ATD, antithyroid drug (methimazole or propylthiouracil); MLS, Marine-Lenhart syndrome; AFTN, autonomously functioning thyroid nodule.

Table 3 shows the distribution of thyroid function after RAI in the MLS and AFTN groups. Thyroid function was assessed on the last visit, 12–139.6 months after RAI administration. The rate of hypothyroidism after RAI was significantly higher in the MLS group than in the AFTN group (42.9% [3/7] vs. 9.0% [11/122], $p = 0.005$). The median dose of radioiodine-131 in both groups was 13 (interquartile range 13–13) mCi.

Discussion

The original paper published by Marine and Lenhart in 1911 dealt with 8 patients in whom the thyroid pathology revealed the presence of adenoma with an iodine content lower than the level in the extranodular tissue [22]. Charkes [1] later reported, in 1972, ten patients with Graves' disease with incidental functioning nodules and named the disease as MLS. Chandramouly et al. [23] defined this syndrome as a variant of Graves' disease with TSH-dependent functional nodule(s), that is, poorly functioning nodule(s) that acquired functionality via TSH stimulation. Konno et al. [11] referred to this syndrome as the coexistence of Graves' disease and AFTN. Thereafter, the coexistence of thyroid functioning nodule(s) and Graves' disease has been called MLS. Thus, the definition and concept of this syndrome have changed with time: "TSH-dependent functional nodule(s)" [8, 24, 25] and "coexistence of Graves' disease and AFTN" [2, 6, 7, 9, 10, 12–19, 26–29]. However, most of the previous reports emanated from studies conducted in iodine-defi-

Table 3. Comparison of thyroid functions after RAI between the MLS and AFTN groups

	Hyperthyroidism	Euthyroidism	Hypothyroidism
MLS (<i>n</i> = 7)	0	4 [57.1%]	3 [42.9%]
AFTN (<i>n</i> = 122)	4 [3.3%]	107 [87.7%]	11 [9.0%]

The median follow-up durations after RAI in the MLS and AFTN groups were 46.9 (range, 19.5–140) and 44.6 (range, 12.0–134) months, respectively. Pearson's χ^2 test was used to compare thyroid functions after RAI between the MLS and AFTN groups. The test showed a significant difference in thyroid function after RAI between both groups ($p = 0.019$). Data indicate the numbers of patients (proportion in the group). MLS, Marine-Lenhart syndrome; AFTN, autonomously functioning thyroid nodule; RAI, radioactive iodine.

cient areas. Here, to investigate the clinical significance of the current definition of MLS, we analysed the frequency, treatment, and prognosis of the syndrome at a hospital that specializes in diseases of the thyroid in Japan, an iodine-sufficient country.

Although 0.8–4.3% of patients with Graves' disease were reported to have TSH-dependent functional nodule(s) [1, 8, 30], the prevalence of AFTN in those with Graves' disease has not been reported. Sasaki et al. [6], who included only a small number of patients in their study, suggested that 0.42% of patients with Graves' disease had AFTN. Here, we systematically analysed patients with thyrotoxicosis and coexisting nodules and showed that the prevalence of the syndrome was 0.26% of patients with Graves' disease. Thus, the prevalence of MLS in Japan is assumed to be 0.26–0.42% of all Graves' disease. The proportion of patients with MLS to those with thyrotoxicosis with nodule(s) was 1.8% and that of MLS to Graves' disease with nodule(s) was 3.8%.

The frequency of AFTN is low in iodine-sufficient areas but high with about half the degree of the frequency of Graves' disease in the presence of the nodules. Several studies identified that 30–50% of AFTN cases are associated with normal TSH levels [31–33]. Belfiore et al. [34] reported the correlation between nodule size and prevalence of thyrotoxicosis among 740 patients with AFTNs in an iodine-sufficient area. Thyrotoxicosis was present in 43.3% of nodules larger than 30 mm, whereas it was present in 10.0% of nodules smaller than 25 mm. Thus, TSH suppression tended to occur when the nodule exceeded 30 mm. In this

study, the median diameter of nodules in the MLS group was 27 mm (less than 30 mm) and significantly smaller than that in the AFTN group. Among cases with small nodules, AFTNs might not suppress TSH, whereas MLS cases presented with overt hyperthyroidism due to Graves' disease.

TRAb may be positive in some patients with AFTNs [35]. Differential diagnosis between these patients and those with MLS is based on thyroid scan findings. In patients with AFTNs, increased tracer uptake is seen in the areas of nodule(s) identified on ultrasonography, and the rest of the thyroid gland is suppressed. In contrast, in MLS, the area of the nodule(s) is particularly intense, with diffuse uptake in the thyroid gland [12]. No TRAb-positive AFTN was detected in this study.

In this study, the median age was 41 (range 5–94) years in the Graves' disease group and 53 (range 13–89) years in the AFTN group, and women comprised 81.0 and 90.8% in each group, respectively, which were close to the previous reports in Japan [36–40]. Therefore, the population of patients with hyperthyroidism in this study is considered representative of the Japanese population. We found that there was no difference in the clinical course after ATD withdrawal between the MLS and AFTN groups. Regarding RAI therapy, interestingly, more patients with MLS than those with AFTNs became hypothyroid despite similar nodular sizes and RAI doses. It is reasonable that RAI is trapped in the tissue of patients with Graves' disease in addition to functional nodules in MLS under suppression with serum TSH. Assuming that is the case, RAI therapy could be a good choice of treatment for MLS. As inducing hypothyroidism is a treatment goal among patients with Graves' disease, Tx including the nodule(s) is another choice of treatment for MLS.

One limitation of this study is that the timing of thyroid function evaluation after RAI was different in each case. Another limitation is that it is difficult to compare the frequency of thyroid nodules in this study with previous reports because of the improved diagnostic accuracy of recent ultrasonography. Lastly, some cases of Graves'

disease and AFTNs were difficult to diagnose. "Undetermined thyrotoxicosis" would include "TRAb-negative Graves' disease" and "AFTN without sufficient accumulation on scintigraphy."

In conclusion, the rate of MLS among patients with Graves' disease was 0.26% in Japan. Although this syndrome is treated in accordance with AFTNs, RAI therapy induces hypothyroidism more frequently than in patients with AFTNs probably because RAI is taken up in the surrounding Graves' tissues.

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Statement of Ethics

The protocol was approved by the Ethics Committee of Kuma Hospital (approval number: 20200213-6). Informed consent was obtained from each patient prior to the initiation of this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study design and discussed the results and conclusions of this work. H.D. collected and analysed the data and wrote the manuscript with support from M.N. E.N. conceived the original idea and supervised the project.

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