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JAMA. 2001;286(15):1879-1881 (doi:10.1001/jama.286.15.1879)

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Meningiomas in Lymphangiomyomatosis

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LYMPHANGIOLEIOMYOMATOSIS (LAM), a multisystem disorder occurring predominantly in women of childbearing age, is characterized by cystic lung disease, abdominal tumors (eg, angiomyolipomas), and other mass lesions in the chest, thorax, and brain.¹⁻⁴ It is estimated that the prevalence of LAM is no greater than 3 cases per 100 000 in the US population.¹ In some affected individuals, progressive lung destruction leads to respiratory failure.¹⁻⁶ In view of the overwhelming predominance of women among those with LAM,¹ it has been postulated that disease progression is influenced by hormonal factors, leading to the use of oophorectomy, tamoxifen, and progesterone as potential therapeutic modalities.^{7,8} Although none of these treatments has been subjected to a controlled trial to determine efficacy, progesterone is commonly used in the treatment of LAM.

Both sporadic and inherited forms of LAM have been described.⁹ A suggested genetic influence on LAM is based on its association with tuberous sclerosis complex (TSC), an autosomal dominant disorder with variable penetrance that is associated with neurologic (eg, tubers, astrocytomas), renal (eg, angiomyolipomas), and dermatologic (eg, facial angiofibromata) manifestations.¹⁰ The estimated prevalence of TSC is 1 in 10 000 to 15 000 in the US population.¹¹ Because lesions common in TSC are found in LAM (eg,

Context Lymphangiomyomatosis (LAM), a cystic lung disease associated with progressive respiratory failure, is found predominantly in women of childbearing age and therefore has been treated with progesterone and other hormonal agents. However, meningiomas have progesterone receptors, and progesterone is believed to be a mitogen for meningioma cells in culture. Since 30% to 40% of patients with tuberous sclerosis complex (TSC) have LAM, we routinely screen patients with LAM for brain lesions found in TSC.

Objective To determine the prevalence of meningiomas in women with LAM.

Design and Setting Analysis of results from ongoing routine screening protocols initiated in December 1995 at the National Heart, Lung, and Blood Institute.

Patients Two hundred fifty women with sporadic LAM who were referred for screening by magnetic resonance imaging (MRI) and/or computed tomography (CT) of the brain.

Main Outcome Measures Presence of meningiomas on MRI and/or CT scans.

Results Eight women with LAM (3 with and 5 without a diagnosis of TSC) had lesions on MRI scans compatible with meningiomas. Five of the patients had been treated with progesterone. Multiple meningiomas were observed in 2 patients.

Conclusions Women with LAM appear to have a high prevalence of meningiomas. We recommend that patients with LAM be screened for meningiomas regardless of diagnosis of TSC. In view of the lack of a documented effect of progesterone on progression of lung disease in LAM and the reported mitogenic response of meningiomas to progesterone, we recommend that the drug not be given to LAM patients with an MRI result consistent with diagnosis of meningioma.

JAMA. 2001;286:1879-1881

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angiomyolipomas), the latter has been thought to represent a forme fruste of TSC.^{12,13} Mutations in 2 genes, *TSC1* and *TSC2*, are associated with TSC,¹⁴⁻¹⁶ although the molecular basis for the clinical manifestations has not been determined. In sporadic LAM, mutations as well as loss of heterozygosity affecting the TSC genes have been found in the abnormal smooth muscle cells ("LAM cells") that proliferate in the disease, consistent with a common genetic basis for disease in both sporadic and inherited LAM.¹⁷⁻¹⁹

In a retrospective study as well as in a prospective screening study, LAM was found in 30% of patients with TSC and no overt clinical disease.^{20,21} In view of the relatively high frequency of LAM in patients with TSC, we began routine

screening of the brain with magnetic resonance imaging (MRI) and computed tomography (CT) for evidence of TSC (eg, tubers) in patients with LAM. In patients with documented TSC, MRI and/or CT are used also to detect and follow other cerebral lesions, such as astrocytomas.²² This study was undertaken to document the prevalence of meningiomas in patients with LAM. A high prevalence of meningiomas in patients with LAM

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Table 1. Description of Patients With LAM and Meningiomas*

Patient No.	No. of Meningiomas	TSC Diagnosis†	Oophorectomy	Received Progesterone	Received BCPs	Received HRT
1	7	No	Yes	Yes	Yes	No
2	2	Tubers, AML	Yes	Yes	No	No
3	1	Tubers, AML, family history, dermatologic findings	No	Yes	Yes	Yes
4	1	No	No	Yes	Yes	Yes
5	1	No	Yes	No	Yes	Yes
6	1	No	No	No	No	No
7	1	Tubers, AML, dermatologic findings	No	No	No	Yes
8	1	No	Yes	Yes	No	Yes

*LAM indicates lymphangioleiomyomatosis; BCPs, birth control pills; HRT, hormone replacement therapy; NA, not applicable; and AML, angiomyolipoma.

†Tuberous sclerosis complex (TSC) present in 3 patients.

Table 2. Neurologic and Neuroimaging Findings in 250 Women With LAM*

Findings	Sporadic LAM (n = 198)	TSC and LAM (n = 52)
Normal clinical neurologic findings	188	48
Meningiomas	4	2
Astrocytomas	0	2
Cortical/subependymal tubers	0	48
Sensorimotor abnormalities	10	4
Meningiomas	1†	0
Astrocytomas	0	1
Cortical/subependymal tubers	0	4
Seizures‡	3	18
Meningiomas	1†	1
Astrocytomas	0	0
Cortical/subependymal tubers	0	14

*LAM indicates lymphangioleiomyomatosis; TSC, tuberous sclerosis complex. A total of 47 patients (35 with LAM and 12 with TSC) had miscellaneous or nonspecific neuroimaging findings.

†This patient had both seizures and focal neurologic findings.

‡Of the 3 patients with sporadic LAM and seizures, 2 had normal neurologic findings and 1 had sensorimotor abnormalities. Of the 18 patients with TSC and LAM, all those with a history of seizures had normal neurologic findings.

whose lung disease is often treated with progesterone would be of concern because meningiomas are progesterone-sensitive tumors.²³⁻²⁶

METHODS

Two hundred fifty women with the diagnosis of LAM, of whom 52 were

known to also have TSC, were referred to the National Institutes of Health for participation in LAM protocols (Protocols 82-H-0032 and 95-H-0186) approved by the institutional review board of the National Heart, Lung, and Blood Institute, beginning in December 1995. In addition to self-referral or referral through individual physicians, subjects were informed of the study by the LAM Foundation and the Tuberous Sclerosis Alliance/National Tuberous Sclerosis Association. All subjects gave informed consent before enrollment. All persons with LAM were eligible for the study and were screened for TSC.

The diagnosis of LAM was made by tissue biopsy in 220 subjects and by CT of the chest in the remaining women. Subjects with LAM exhibited characteristic thin-walled cystic lesions in the lung parenchyma on high-resolution CT.²⁷ Patients diagnosed as having TSC met established criteria.²² Patients with a diagnosis of LAM underwent MRI and/or CT of the brain as part of the clinical evaluation for TSC. Those individuals found to have mass lesions were subject to repeated scans, as medically indicated. MRI scans were performed using a 1.5-T magnet. T1-weighted (repetition time in milliseconds/echo time in milliseconds, 400-600/8-22) and T2-weighted (2000-4384/94-104) spin-echo images were obtained,

with a 5-mm section thickness. The T1-weighted scans were repeated after the administration of 0.1 mmol of gadopentetate dimeglumine per kilogram of body weight (Magnevist; Berlex Laboratories, Wayne, NJ). All MRI studies were evaluated by a neuroradiologist. Lesions within the cranial cavity and brain parenchyma were identified. Their morphological characteristics and enhancing features were recorded and their probable histology classified using established imaging criteria. Conventional precontrast CT scans at 5-mm thickness were also performed in most subjects and postcontrast CT was performed only when deemed necessary.

RESULTS

Of the 250 women with LAM, extra-axial tumor masses with morphological characteristics of meningiomas were found in 8 (TABLE 1), 2 of whom had multiple lesions and 3 of whom exhibited manifestations of TSC. Three women, 1 of whom had a diagnosis of TSC, had never received progesterone. Other neurologic findings, including astrocytomas and tubers, as expected in patients with TSC, are summarized in TABLE 2.

COMMENT

The frequency of meningiomas in LAM far exceeds that expected in the general population (1:20000), with women more commonly affected than men (2:1),^{28,29} consistent with the possibility that meningiomas may be associated with the underlying LAM or with treatments for it. With regard to the latter, progesterone has been reported to have a mitogenic effect on meningiomas,²³⁻²⁵ and progesterone receptors are found in meningiomas.²⁴ Indeed, anti-progestins have been used as a treatment for meningiomas.³⁰ The abnormal smooth muscle cells found in LAM have been implicated in the production of growth factors, including insulin-like growth factor 1 and platelet-derived growth factor.^{31,32} Growth factors are believed to be mitogenic for meningiomas,³³ consistent with the pos-

sibility that secretory products of LAM cells might enhance proliferation of meningiomas.

One of the concerns engendered by our study is the possible involvement of progesterone in the formation or progression of meningiomas. Although some of the women had never been exposed to progesterone, low doses in contraceptive agents or hormone replacement therapy could have played a part in initiation or progression of meningiomas. We cannot exclude the possibility that the high prevalence of meningiomas may be a result of both LAM and progesterone therapy.

Progesterone has been used as a potential therapeutic agent in LAM,⁷ although its efficacy has not been tested in a randomized, double-blind clinical trial. Preliminary data from the natural history study at the National Insti-

tutes of Health are not consistent with a beneficial effect of progesterone analogues in LAM. In view of the potential mitogenic effect of progesterone on meningiomas, it appears prudent for patients with LAM and meningiomas to avoid this agent.

At present, our standard procedures for screening and monitoring patients with sporadic LAM include evaluation of the chest for pulmonary disease and abdomen for angiomyolipomas and lymphangioleiomyomas, but do not include routine MRI of the head. Screening by abdominal CT has shown that 54% of the patients with LAM had angiomyolipomas.²⁷ Based on our findings, we recommend using MRI to screen patients with LAM for meningiomas and no progesterone administration to patients with meningiomas. Follow-up for LAM patients with me-

ningiomas should include, in addition to the standard chest and abdominal CT scans, a yearly MRI of the brain to evaluate tumor growth or development of new tumors.

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Funding/Support: This work was supported by the Intramural Research Program, National Heart, Lung, and Blood Institute, National Institutes of Health.

Acknowledgment: We thank Martha Vaughan, MD, and Vincent Maganiello, MD, PhD, for discussion and critical review of the manuscript. Pauline M. Barnes, RN, Ruth Litzenger, RN, the LAM Foundation, and the National Tuberous Sclerosis Association/Tuberous Sclerosis Alliance assisted with recruitment of patients.

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