UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Mémoire de Maîtrise en médecine No 3407

Voyages aériens et risque de pneumothorax dans la lymphangioléiomyomatose pulmonaire

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30.01.2017

PNEUMOTHORAX RELATED TO AIR TRAVEL IN PULMONARY LYMPHANGIOLEIOMYOMATOSIS

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ABSTRACT

Introduction

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease affecting almost exclusively women and characterized by abnormal proliferation of smooth muscle cells (LAM cells) in the lungs, kidneys and axial lymphatics. In the lungs, LAM cell proliferation leads to the development of multiple thin-walled cysts resulting in the gradual onset of respiratory insufficiency and frequent pneumothorax (PT). Air travel (AT) could further increase the risk of PT in LAM through rupture of subpleural cysts induced by changes in atmospheric pressure in aircraft cabin.

Methods

To assess whether AT increases the risk of PT in LAM, we performed a retrospective surveyed of women members of European LAM patient associations. Data were collected through a questionnaire regarding the occurrence of PT episodes, including dates, affected side, and therapeutic modalities, as well as a list of AT after disease onset. A post-flight PT was defined as a PT diagnosed by a physician ≤ 30 days after AT. Flights performed after lung transplantation were withdrawn from the analysis.

Results

A total of 145 women responded to the survey. Their mean age was 48 ± 12 years. 207 episodes of PT were reported with a mean ± SD number of 2.5 ± 1.3 per patient. 128 patients with available dates allowed us to calculate the annual incidence of PT since the first symptoms attributable to LAM, and since LAM diagnosis which were respectively 7% and 5% (versus 0.006% in the general women population). 83 (57%) patients travelled by air. 75 patients with evaluable data performed a total of 191 AT. A PT occurred within 30 days after AT in 5/75 patients. One had bilateral PT. The probability of PT within 30 days after AT was 5/191 (2.6%) per patient, and 6/382 (1.6%) per lung. As compared to the 30 days before AT, the incidence of PT per lung was significantly higher during the 30 days after AT (RR 6, CI 1.02-113). In contrast, no difference in PT incidence was observed when comparing 2 other 30-days periods before and after AT.

Conclusions

The incidence of PT in LAM is 1000 higher than in the general women population. The occurrence of PT increases significantly within 30 days after AT as compared to the 30 days before AT, suggesting that AT per se is a risk factor for PT occurrence in LAM.

Keywords

Air travel, lymphangioleiomyomatosis, incidence, pneumothorax.

INTRODUCTION

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease almost exclusively affecting women in their reproductive age (1). It is characterized by the proliferation of abnormal smooth muscle-like cells (LAM cells) in the lungs and lymphatic system (2), and is currently seen as benign metastazing neoplasm (1). LAM occurs either sporadically or in association with tuberous sclerosis (3; 4). In the lungs, LAM cell proliferation leads to the development of multiple thin-walled cysts and progressive destruction of the parenchyma resulting in dyspnea, obstructive ventilatory defect, reduced carbon monoxide transfer factor, and hypoxemia. Another typical feature of pulmonary LAM is the occurrence of pneumothorax (PT), which occurs in more than half of patients during disease course (5). Extra-thoracic involvement includes renal angiomyolipomas, thoraco-abdominal lymphangiomas and chylous effusions (1-2; 5-7).

Air travel (AT) is a matter of concern in patients with LAM (8). During commercial flights, the cabin is pressurised to a level corresponding to an altitude of about 8000 ft (2438 m) above sea level. The resulting decrease in alveolar oxygen partial pressure may worsen pre-existing hypoxemia in patients with respiratory diseases. In addition, following Boyle's law, when barometric pressure decreases, the air eventually trapped in a non-communicating space such as a pulmonary cyst will increase in volume, and could lead to cyst overinflation and rupture, with consecutive PT. (9-11). The occurrence of a PT during flight may have serious consequences in patients with impaired respiratory function, and the treatment of PT in such circumstances may be delayed.

In two recent retrospective studies specifically addressing the issue of AT in patients with LAM, the reported frequency of pneumothorax after AT was respectively 2.2 % and 1.1 % (8; 12). However, although suggesting that the occurrence of PT related to AT was uncommon, these studies did not determine whether AT *per se* constitutes a risk factor for the occurrence of PT in LAM. Hence, as compared to healthy subjects, patients with LAM are at increased risk of PT at all times, and whether the risk of PT is further increased by AT in these patients is unknown.

To explore this issue, we undertook a retrospective survey of LAM patients from several European countries focused on PT occurrence and AT. The main objectives were to calculate the incidence of pneumothorax in LAM, and to determine whether AT increases the risk of PT in this population.

METHODS

Patient recruitment

Patients with pulmonary LAM were recruited through European LAM patient associations in France, Germany, Italy, Spain, United Kingdom, and through a rare lung disease registry in Switzerland. Data were collected retrospectively though a questionnaire available in the language of each country. Patients provided informed consent to participate.

Data collection

Patients were asked to provide detailed information regarding the date of the first symptoms attributable to LAM, date of LAM diagnosis, current forced expiratory volume in one second (FEV1) if known, and the occurrence, date and side of lung transplantation. They were also asked to report details on each episode of PT which occurred since the first symptoms of LAM, including date of PT diagnosis, affected side, and treatment received according to pre-specified categories (spontaneous healing, needle aspiration, chest tube, chemical pleurodesis, and surgical pleurodesis). Patients were also asked to report with the best possible accuracy the 4 first AT which took place since the occurrence of the first symptoms of LAM including date, origin and destination, travel duration, occurrence of respiratory symptoms, occurrence of PT during or after AT, and whether it occurred on a lung previously treated for PT. The French patient association FLAM performed data collection and capture. An anonymized database was provided to the investigators. For patients who reported a flight-related PT as defined below, a telephone interview was conducted through the patient association to check the data and obtain additional details.

Data analysis

In a first set of analyses, we determined the overall incidence of PT in the study population. The beginning of the exposure period to the risk of PT was defined as the date of the first symptoms attributable to LAM or the date of LAM diagnosis, respectively. The end of the exposure period to the risk of PT was defined as the date of completion of the survey, or the occurrence of unilateral or bilateral lung transplantation. Transplanted lungs were not considered at higher risk for PT and were withdraw from the calculation. When a PT was the first symptom attributable to LAM, it was included in the calculation of PT incidence during the exposure period which started with first symptoms. We considered two different hypotheses to compute the PT incidence: 1) the risk of PT is constant across the whole LAM population, 2) the risk of PT is variable from one patient to another. A standard Poisson regression (model 1) was used to compute the incidence according to the first hypothesis. In order to compute the PT incidence according to the second hypothesis, we used two different

regressions to model the variable risk (13): a negative binomial regression (model 2) and a Poisson regression with a random intercept (model 3). In each of these models, only an intercept was considered (mean model). Model 1 is equivalent to calculate the ratio of the total number of observed PT and the sum of all the exposure period. In model 2, we supposed that the incidence was distributed as a gamma distribution (the negative binomial distribution can be view as a Poisson distribution where the parameter is itself a random variable distributed as a gamma distribution). In this model, the estimation of the intercept leads to an estimation of the mean incidence rate (over the patients). In model 3, we supposed that intercept was normally distributed and therefore the incidence was distributed as log-normal distribution. In this model, the estimation of the intercept leads to an estimation of the median incidence rate. Patients were withdrawn from the analysis if the date of the first symptoms, the date of LAM diagnosis, or any date of PT were missing.

In a second set of analyses, we aimed to determine whether AT increases the risk of PT occurrence in LAM. A PT was arbitrarily defined as related to AT if it was diagnosed by a physician within 30 days after AT. This time interval was defined before the survey. We considered that cyst rupture and consecutive PT may not occur immediately during a flight, or that a patient with mild respiratory symptoms may seek medical attention only after several days. An interval of 1 month was also used in another study on the occurrence of PT due to AT in the Birt-Hogg-Dubé syndrome (14). Each lung was considered as an independent observation. Patients were withdrawn from the analyses if any date of PT, the affected side, or any date of AT were missing. Transplanted lungs were withdrawn from analysis. Lungs treated with chemical or surgical pleurodesis were still considered at risk of PT and were included. AT was defined as both an outbound and a return trip, each of which may have consisted of one or more stops, i.e. one or more episodes of ascent and descent. Given the retrospective nature of this study, we reasoned that it would be difficult for patients to recall each episode of ascent and descent. In addition, as we intended to compare the incidence of PT between pre-AT and post-AT periods, the time periods between 2 episodes of ascent and descent, or between an outbound and a return trip would be overlapping, thus leading to count events twice. The time interval between outbound and return trip was not recorded, but we reasoned that in the vast majority of AT, the duration of a trip would be less than 15 days. According to European statistics, the average duration of trips performed by European citizen is 5.4 days (15), and 94% of trips last <14 days (16). Thus, an interval of 30 days was considered appropriate to observe the occurrence of PT related to an episode of AT. The date of AT, defined as the date of the first outbound flight, was considered as day 0. To determine whether AT increases the risk of PT occurrence, we compared the frequency of PT during the 30 days preceding AT (days -30 to -1) and during the 30 days following AT (days 0 to +29). In additional analyses, we also compared two other 30-days periods preceding and following AT, i.e. period -60 to -31 days with period +30 to +59 days, and period -90 to -61 days with period +60 to +89 days. A standard Poisson regression was used for these analyses. Quantitative data were expressed as mean ± standard deviation. Statistical analyses were performed with R 3.2.3.

RESULTS

Study population

145 filled questionnaires were available. All patients were women. Their countries of origin were France (31.7%), Germany (23.4%), United Kingdom (17.2%) Italy (15.2%), Spain (5.5%), Switzerland (4.1%), Australia (0.7%), Belgium (0.7%), Ireland (0.7%) and Turkey (0.7%). The mean age at time of survey was 48 ± 12 years. The mean age at first symptoms attributable to LAM and at LAM diagnosis were respectively 36 ± 11 and 42 ± 11 years. The mean FEV_1 was 58 ±24 % predicted (n = 71).

Incidence of pneumothorax in LAM

Among the 145 patients, 6 had missing dates of first symptoms of LAM, and 11 had missing one or more dates of PT. The mean follow-up duration per patient since the first symptoms attributable to LAM was 11.4 years, and the cumulated follow-up duration was 1454 patient-years (n = 128 patients). The mean of follow-up duration per patient since LAM diagnosis was 6.4 years, with a cumulated follow-up duration of 817 patient-years (n = 128 patients).

The 145 patients reported a total of 207 PT. Eighty-three (57.2 %) had at least one PT, and fifty-six (38.6 %) had 2 or more PT. The mean number of PT per patient was 2.5 ± 1.3. The mean number of PT per lung was 1.3 ± 1.5.

The annual incidence of PT in the study population since the first symptoms of LAM and since LAM diagnosis according to the 3 statistical models are shown in Table 1.

Table 1 Annual incidence of pneumothorax in the study population

Start of exposure period	Model 1	Model 2	Model 3
First symptoms of LAM	0.12 (0.1, 0.14)	0.18 (0.13, 0.24)	0.07 (0.05, 0.11)
Diagnosis of LAM	0.09 (0.07, 0.11)	0.10 (0.07, 0.15)	0.05 (0.03, 0.08)

Data were calculated from three models: Model 1: constant risk of PT across the whole LAM population, standard Poisson regression. Model 2: variable risk from one patient to another, negative binomial regression. Model 3: variable risk from one patient to another, Poisson regression with random intercept. Results are expressed as incidence per patient per year (2.5% and 97.5% confidence intervals).

Risk of pneumothorax after air travel

Eighty-three out of 145 patients (57%) travelled by air and reported a total of 209 flights (mean 1.4 ± 1.6). After the diagnosis of LAM, only 58 patients (40%) travelled again by air. Among the patients who did not fly after the diagnosis of LAM, the main reasons not to fly were personal

convenience (38%), personal decision following the explanation of the possible risks of air travel in LAM (21%) and physician's advice to avoid air travel (41%).

Among the 83 women who flew, 3 (cases 26, 36, and 141) had missing dates for AT, 3 (cases 38, 53, and 89) had missing dates of PT, and 4 (cases 11, 38, 89, and 93) had missing side of PT. Thus, a population of 75 patients was used to determine the risk of PT associated with AT. These patients reported a total of 191 AT. Considering each lung as an independent observation, 150 lungs performed a total of 382 AT. Sixteen percent of them experienced dyspnea and/or chest pain on at least one occasion during AT.

Six PT diagnosed by a physician occurred in 5 patients within 30 days after AT (Table 2). One patient (case 143) had bilateral PT which was the first symptom of the disease. Four patients (cases 25, 84, 142, and 143) experienced their first PT at this occasion. One patient (case 102) had had 3 PT previously, and had had chemical pleurodesis on the same side. No patient had respiratory distress during AT associated with the occurrence of PT, but 2 of them felt short of breath or had thoracic pain within the 30 days following AT whereas the other 3 did not report these symptoms. Three patients were treated with surgical pleurodesis (cases 25, 142, and 143), one had chemical pleurodesis (case 84), and in one the PT was treated conservatively (case 102). Three other patients (cases 27, 98, and 107) reported the occurrence of PT within 30 days after AT, but since the precise dates of PT were not available, these PT were not counted. In one other patient (case 141), the dates of AT and PT were considered erroneous and this case was also removed. Based on the above data, the risk of PT within 30 days after AT was 5/191= 2.6% per patient and 6/382 = 1.6% per lung.

Table 2 Characteristics of patients who presented PT within 90 days before and after AT

Patient number	Age [years]	Number of previous PT	Side of current PT	Delay between AT and PT [days]	time of PT occurrence relative to AT	Perceived relationship between AT and PT occurrence	PT Treatment
90	34	0	L	-70	Before	no	Chemical pleurodesis
104	27	0	L	-65	Before	no	Chest tube
104	29	2	R	-61	Before	no	Spontaneous healing
102	44	1	R	-32	Before	no	Spontaneous healing
44	46	3	R	-31	Before	no	Chest tube and surgical pleurodesis
102	44	2	R	-1	Before	no	Chemical pleurodesis

143	26	0	R	0	After	yes	Surgical pleurodesis
143	26	0	L	0	After	yes	Surgical pleurodesis
84	64	0	R	19	After	yes	Chemical pleurodesis
25	26	0	L	24	After	yes	Surgical pleurodesis
102	44	3	R	29	After	no	Spontaneous healing
142	59	0	R	29	After	yes	Surgical pleurodesis
25	26	1	L	80	After	yes	Chemical pleurodesis

PT = Pneumothorax; AT: air travel, Perceived relationship between AT and PT = The pneumothorax occurred before or after air travel; PT mention = If the patient mentioned or not in the survey the presence of the pneumothorax after the air travel; L = Left; R = Right.

The number of PT occurring within 30 days after AT was compared to the number of PT within 30 days before AT, and expressed as a relative risk (Table 3). The risk to have a PT between days 0 to 29 after AT was 6 times higher than the risk to have a PT between days -1 to -30 before AT. This difference was significant. The risk to have a PT between days 30 to 59 and days 60 to 89 after AT compared to the risk to have PT between days -31 to -60 and days -61 to – 90 days was not significantly increased. There was no overlap between periods before AT and periods after AT in the patients who had performed several AT, so no event was counted twice.

Table 3 Risk of Pneumothorax according to exposure period before and after air travel

Exposure period before AT [days]	Number of PT during exposure period before AT	Exposure period after AT [days]	Number of PT during exposure period after AT	Relative risk	Lower limit of confidence interval (2,5%)	Upper limit of confidence interval (97,5%)
-30 to -1	1	0 to 29	6	6	1.025	113
-60 to -31	3	30 to 59	0	0	0	∞
-90 to -61	3	60 to 89	1	0.333	0.016	2.603

Data were calculated with a Poisson regression, each lung was considered as an independent observation. 382 AT were considered. Exposure: expressed as days before or after AT, with day 0 being the day of AT.

DISCUSSION

In this retrospective survey of 145 patients with LAM, we analysed the incidence of PT during disease course, and the relationship between AT and PT, an important concern for patients affected by this disease. We determined for the first time the overall incidence of PT in LAM. We confirmed previous observations regarding the frequency of PT after AT. Additionally, we showed for the first time that AT *per se* may increase the risk of PT occurrence in LAM.

Several series have reported that 50 to 80% of LAM patients experience PT during disease course (2-6; 17-23), but the true incidence of PT occurrence in LAM has not been determined so far. Based on clinical experience, we considered that the risk of PT was variable from one patient to another (as some do not experience PT at all) and as the median is more robust to outliers than the mean, model 3 was considered the most appropriate. With this model, the incidence of PT in the LAM population was 7% per year from the first symptoms of LAM, and 5% per from LAM diagnosis. The incidence of spontaneous PT in the general population has been estimated to 1 to 6/100'000 per year in healthy women and 7 to 18/100'000 per year in healthy males (21). This means that the incidence of PT in LAM is about 1000 times higher than in the general female population.

During commercial flights, the cruising altitude varies between 4'534 and 14'630 meters. Aircraft cabin is pressurized to approximately 753 hPa (565 mmHg), corresponding to an altitude of 2438 meters above sea level (9). During the ascent, a non-communicating volume such as a subpleural bullae or a pulmonary cyst may increase its initial volume by 30% (11), which may theoretically lead to cyst rupture and cause a PT. Previous epidemiological studies have examined the effect of atmospheric pressure changes on the incidence of spontaneous PT. Bense *et al* found that during a fall of 10 hPa or more over a 24-hour period, a significant increase in hospital admissions for pneumothorax was observed within 48 hours after this drop in atmospheric pressure (24). Scott G.C *et al* found that the incidence of PT was significantly higher than expected by chance when patients with chronic obstructive pulmonary disease (COPD) or in absence of COPD were exposed several times (4 or more times) to an unusual variation of atmospheric pressure during the four days prior to the occurrence of their PT (25). Haga T. *et al* reported that during the days when spontaneous PT occurred, there was a significant difference of atmospheric pressure of 0.6 hPa with the days before these PT appeared in comparison to the days without PT (26). Araki K. *et al* reported the case of a young healthy man who experienced an episode of spontaneous PT at the age of 19, which was treated by chest tube insertion. At the age of 22, he developed a PT just after a visit to the Tokyo Skytree during which a high-speed lift took him from sea level to an altitude of 350 meter within 50 seconds. This speed of ascent represented a rate change of barometric pressure of 42 hPa/min, which is more marked than the one occurring in an aircraft cabin (6.6-13.3 hPa/min) during ascent (27; 28). Altogether, these data suggest that atmospheric pressure changes may lead to the occurrence of PT in some subjects. Therefore, changes of cabin pressure during AT could theoretically lead to occurrence of PT, especially in patients with pre-existing lung condition already predisposing to PT occurrence.

The mechanisms and incidence of PT aboard aircrafts has been studied in the 50's and 60's for pilots of military aircrafts. These healthy subjects were submitted to changes of atmospheric pressure and strong acceleration which could favour the occurrence of PT. Indeed, the incidence of PT in this particular population was estimated to 47-78/100'000/yr. However, these flights conditions could not be compared to those of commercial aircrafts and an extrapolation of these figures is not possible. The risk of PT during AT aboard commercial aircrafts is unknown. Only 0.003% of passengers have an in-flight medical problem requiring emergency intervention, and PT has been reported to constitute only 0.095% of in-flight emergencies (29). There are only anecdotal reports of in-flight PT (30-33).

Two previous studies have analysed the occurrence of PT related to AT in LAM patients (8; 12). The first study surveyed patient's members of the LAM Foundation (USA) and the LAM Action registry (UK) who travelled by air during disease course. The risk of PT during flight was estimated to 2.2% per flight and to 4% per women who flew (8). Another study examined patients with LAM, sarcoidosis and idiopathic pulmonary fibrosis who travelled by air or by ground to the National Institutes of Health (NIH) Clinical Research Center to be included in research protocols. 281 LAM patients travelled to the NIH center. A PT was diagnosed in 14/204 patients who travelled by air, but only 6 patients had no evidence of PT before the trip and PT could be potentially related to AT. The incidence of PT during flight was 2.9 % per patient and 1.1% per flight. These incidences were higher than those of patients who travelled to the NIH by car or train, which were respectively 1.3% per patient and 0.5% per ground trip (12), suggesting a possible effect of AT on PT incidence. In the present study, we found a risk of PT of 2.6% per patient per flight, and 1.5% per lung per flight, which is well within the range of the two previous studies.

To determine whether AT *per se* is a risk factor for PT occurrence in LAM, in the context of an elevated baseline risk of PT at all times, we compared the incidence of PT during 30 days periods before and after AT. The only significant increase of risk was observed in the 30 days following AT (RR= 6). No significant difference was observed between other 30-days periods preceding and following AT. This suggests that AT by itself may be a risk factor for PT in LAM, in a population in which PT incidence is extremely high at all times. Although a RR of 6 was significant, the total number of events was small and we consider that this study does not allow a definite determination of the relative risk. In the study by Taveira da Silva (12), there was only a two-fold difference in PT incidence between AT and ground travel, although no statistical comparison was performed. A prospective study with a larger number of patients would be needed to further explore this issue.

To what extent pleurodesis protects against PT recurrence in LAM, especially during AT, is unclear. In one study (18), the recurrence rate of PT in LAM was 66% after conservative therapy, 27% after chemical pleurodesis and 32% after surgical pleurodesis. Although the recurrence rate was reduced approximately two-fold by pleurodesis in this study, the overall

risk of recurrence remained elevated. In comparison, a recent metaanalysis showed that the risk of recurrence of spontaneous PT was between 0% and 3.2%, after surgical pleurodesis with bleb resection, and between 2.5% and 10% after thoracoscopic talc poudrage (35). Based on these data, and for the purpose of this analysis, we considered that LAM patients who underwent pleurodesis remain at risk of PT, and we did not exclude post-pleurodesis periods from calculations. Indeed, among the 5 LAM patients who reported a PT within 30 days after AT, one had had previously pleurodesis on the affected side.

The 2010 European Respiratory Society guidelines on LAM provided recommendations for LAM patients regarding AT (36). Patients with minimal respiratory manifestations of LAM were not discouraged to fly, unless they present new respiratory symptoms which have not been evaluated by a physician. Patients with a known untreated PT or a PT treated within the previous month were advised not to travel by air. We do not consider that the present study should lead to revise these recommendations, but a larger prospective study should be performed to confirm these findings.

Recently, Johannesma P.C. *et all* had evaluated the risk of spontaneous PT due to AT or diving in patients with Birt-Hogg-Dubé syndrome (BHDS), an autosomal genetic disease characterised by cutaneous lesions, renal tumors and pulmonary cysts. Questionnaires were send to 190 BHD patients, of whom 158 responded to the survey. From the 145 patients who flew, 13 presented a PT confirmed by chest X-ray in a period ≤ 1 month after AT. The risk was estimated to 0.63% per flight which is lower than the figures reported in LAM in previous studies and our data (14; 8; 12). Consistent with these data, the frequency of PT during disease course is lower in BHDS (35-38 %) as compared to LAM (50-80 %) (2-6; 17-23; 33; 34). This difference could be due to the fact that cysts are less numerous in BHDS than in LAM, or because they are less prone to rupture (14).

The present study has several strengths. We studied a large cohort of patients with LAM from various European countries. We restricted the analyses to cases with available dates of events and excluded those with missing data, even if PT after AT was mentioned by the patient in the survey. We considered each lung as an independent observation, thus allowing to analyse appropriately particular situations such as bilateral PT or reduced risk of PT due to unilateral lung transplantation.

Our study has several limitations, mainly due to its retrospective nature. Recall bias and errors in filling the questionnaires might have occurred and the fact that we explored the history of only 4 events for AT and PT episodes is a bias. However, for the patients identified as having a PT within 30 days of AT, a telephone interview was conducted to check the data. As the study was a patient survey, we did not check the accuracy of LAM diagnosis. However, since all patients were members of LAM associations, we assumed that LAM was the correct diagnosis in all. Patients who replied to the survey, and more generally members of LAM

patient associations, may not be fully representative of the whole LAM population. Furthermore, patients who experienced symptoms during AT or feared the occurrence of PT may have been more prone to respond to the survey, and thus lead to an overestimation of the effect size. Despite the relatively large study population, the number of PT related to AT was small, and the relative risk may be overestimated. Some patients may have had an asymptomatic PT before AT which may have been revealed only after AT. To address this potential bias, a prospective study should include a chest X-ray before and after AT. In addition, other causes of decrease of barometric pressure, such sudden meteorological changes or ascent at high altitude by cable car were not accounted in our study. The number of PT before AT may have been underestimated since some patients may have cancelled their AT after the occurrence of AT, as recommended by some guidelines.

In summary, the annual incidence of PT in the LAM population was 7% per year since the first symptoms and 5% since LAM diagnosis, i.e. 1000 times higher than the risk of spontaneous primary PT in the general female population. The risk of having a PT within 30 days after AT was 2.6% per patient and 1.6% per lung. The probability of PT within 30 days after AT was significantly increased (RR=6) as compared to similar period before AT, suggesting that AT *per se* is a risk factor or a trigger for PT occurrence in this particular situation. This study also illustrates the role of patient associations in research on rare diseases and the value of studying patient-related outcomes which have a practical impact on their everyday life.

ACKNOWLEDGEMENTS

The authors acknowledge L. Falconer, D. Faure, S. Geilling, E. Miano, V. Reptova, A. Valdevieso, J. Lacronique, T. Nicolosi, T. Urban, and Junior Trad (Institut Supérieur d'interprétation et de Traduction, Paris), for their contribution to the review, translation, and diffusion of the questionnaires of this survey. Patients who replied to the questionnaires are also warmly acknowledged. The following entities participated to patient recruitment: Association France Lymphangioléiomyomatose (FLAM), 31 rue de Fénetrange, 57930 Gosselming, France; LAM-Selbsthilfe Deutschland, Postfach 31 07 39 - D-04211, Leipzig, Germany; LAM Action, Division of Respiratory Medicine - Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham NG5 1PB, United Kingdom; Associazione Italiana Linfangioleiomiomatosi (A.I.LAM), Ospedaliera Cannizaro, via Messina 829, 95126 Catania, Italy; Asociación Española de Linfangioleiomiomatosis (AELAM), C./ La Fragua 16, SP 28260 - Galapagar, Madrid, Spain; Swiss pulmonary physicians participating to the Swiss Registries for Interstitial and Orphan Lung Diseases (SIOLD). This study is dedicated to M. Goncalves (deceased) and C. Durand (deceased), the first two presidents of FLAM.

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