Communicación breve / Short communication

Characterization of autopsy-proven fatal asthma patients in São Paulo, Brazil

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ABSTRACT   *Few data are available on autopsy-proven fatal asthma patients in São Paulo, Brazil. We characterized 73 asthma patients who were autopsied at the Serviço de Verificação de Óbitos da Universidade de São Paulo between 1996 and 2004. An interview with the next of kin assessed socioeconomic status, history, and treatment of asthma. There were 42 women and 31 men. Fifty-six (76.7%) of them were older than 34 years. Sixty-three percent were Caucasians, 77.3% had < 8 years of schooling, and the median income was 1.6 times the minimum wage. Twenty-two patients (30.1%) were smokers and 14 (19.2%) were ex-smokers. Only 25 (34.2%) patients were regularly followed by a doctor. Only 12.3% received inhaled steroids. Thirty-five patients (47.9%) had moderate-to-severe asthma. Fifty-five (75.3%) deaths took place outside a hospital. We conclude that this population shares characteristics of severe or poorly controlled asthma, low educational and socioeconomic levels, and lack of medical care and of inhaled steroid use.*

Key words   Asthma, autopsy, socioeconomic factors, Brazil.

Death due to asthma is considered a preventable event. Nevertheless, it is estimated that 1 in every 250 deaths worldwide is due to this disease (1). In the 1980s, the term asthma paradox was introduced to refer to the observation that, despite significant advances in the understanding of asthma pathogenesis and treatment, asthma mortality had increased in countries like Australia and New Zealand in the previous 20 years (2). More recently, asthma mortality has been decreasing or stabilizing, with the decrease more prominent in countries where the use of inhaled steroids has increased (3–5).

In Latin America, asthma carries a heavy burden, with Brazil having a disease prevalence of 11.4%, comparable to that in countries such as Australia and the United Kingdom. In 2004, asthma was the fourth leading cause of hospitalization in Brazilian public hospitals (6). The Asthma Insights and Reality in Latin America survey revealed that more than half of the Latin American patients with asthma who were surveyed had daily symptoms, had been hospitalized, had attended a hospital emergency service, or had made unscheduled emergency visits to other healthcare facilities during the previous year because of their disease; only 6% received inhaled steroids (7).

In addition to incidence and severity, asthma mortality is high in Latin America, especially in countries like Uruguay and Mexico, reaching overall

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mortality rates of 4.1 and 5.6 per 100 000 inhabitants, respectively (3, 8). Brazil has an intermediate position, with a mean mortality rate of 2.04 per 100 000 inhabitants or approximately 2 000 deaths/year (8). Fatal asthma episodes are linked to several risk factors, including disease severity, previous near-fatal asthma episodes, hypersensitivities, underuse of medical services, and low socioeconomic status (9–13).

There are no previous data on autopsy-proven fatal asthma patients in São Paulo, Brazil. Over the last 9 years, autopsy samples were collected from 73 fatal cases of asthma at the Faculdade de Medicina da Universidade de São Paulo, São Paulo city, Brazil. To better characterize these patients, we retrospectively analyzed their demographics and clinical history, including asthma treatment and events surrounding deaths due to asthma. We anticipated that socioeconomic factors and lack of access to regular medical care or adequate treatment would be frequently associated with asthma deaths in Brazil.

We consulted the files of PRO-AIM, a municipal organ where all death certificates of São Paulo city are registered. We retrieved data related to the total number of deaths and the total number of deaths having asthma as the underlying cause (International Classification of Diseases, 10th revision, J45 and J46) from 1996 to 2004. We also determined the São Paulo total population and the number of patients submitted to autopsy in the Serviço de Verificação de Óbitos da Capital da Universidade de São Paulo (SVOC-USP). Approximately 13 000 autopsies performed for other than legal reasons are carried out yearly in this institution, the largest service of this kind in Latin America. In this large autopsy service, São Paulo inhabitants who died in natural circumstances but without a clear cause of death are submitted to an autopsy to determine the death cause, based mostly on gross examination of the organs. From this population, we analyzed a subset of patients whose lungs were collected for the purpose of his-

tological studies (14–16), based on the availability of a researcher from our group during the autopsy. These patients died due to asthma; the diagnosis was confirmed by macro- and microscopic examination at autopsy and by an interview with the next of kin. This study was approved by the local ethical committee board.

All included subjects had a history of asthma and died in an acute crisis. All deaths were ascribed to status asthmaticus by pathologists. The autopsies showed gross findings compatible with fatal asthma such as mucus plugs and hyperinflation. Histological findings included eosinophilic or noneosinophilic inflammation, muscle hypertrophy, and mucus hypersecretion (14–16).

Interviews with the next of kin were performed at variable intervals after death by social workers who contacted the relatives of the deceased via telephone or telegram. Written informed consent was obtained with the next of kin for both the interview and assessment of the clinical chart, if available. The questionnaire upon which the interview was based was drafted by a physician expert in asthma. Additionally, treatment in the academic hospital was offered for the relatives of the deceased who had asthma.

The interview assessed demographics, per capita income, living conditions, school education, and smoking habits. Ethnicity was defined by the next of kin. Body mass index was obtained from the autopsy records. The past history of asthma was characterized by age at onset of symptoms, parental history of asthma, use of regular medical care, and type of medication received in the last 6 months. Early onset of asthma was defined when asthma symptoms started before the age of 12 years (17). Relatives were asked whether the deceased had been hospitalized because of asthma in the last year and whether the patient had ever been admitted to an intensive care unit for an asthma exacerbation. Associated history of rhinitis was also investigated. For patients who had received regular medical care in a hospi-

tal, the institution was contacted to obtain medical information.

Data related to the last crisis consisted of duration of asthma symptoms until death. Sudden-onset fatal asthma was considered to be death that occurred < 2 hours after the onset of the fatal attack (18). Slow-onset fatal asthma was divided into two categories: (1) duration of symptoms > 2 hours and < 1 day, and (2) > 1 day. We also specified the location of death.

The São Paulo population increased from 10 040 370 to 10 679 760 inhabitants during the study period (1996–2004), with a mean of 224 (207–257) deaths due to asthma per year. Figures 1 and 2 show the general and age-adjusted mortality rates for asthma deaths. During the study period there were a mean of 84 (62–118) asthma autopsies in the SVOC-USP yearly. The median age of these individuals was 49 years (0–92 years), with an average of 57.8% women and 42.2% men autopsied each year. The ethnic distribution was 65.23% Caucasians, 32.57% African descendants (blacks and mulattos), and 2.2% Asian descendants.

A complete autopsy, with microscopic confirmation of the diagnosis of fatal asthma was performed by our research group in 97 cases during this period. From these cases, we obtained interviews with 73 families. In the remaining cases, either it was not possible to find relatives or the family member refused to participate. The interview with the next of kin was performed a median of 11 months (range 1–59 months) after death.

Demographic data are presented in Table 1.

Age at onset of symptoms was obtained for 68 patients. Thirty-three (48.5%) patients had early-onset asthma and 35 (51.5%) had late-onset asthma, with no significant difference between males (54.8% early-onset, 45.2% late-onset) and females (50% early-onset, 50% late-onset). Information on parental history of asthma was obtained in 44 interviews; 16 (36.4%) individuals had at least one parent with asthma. Twenty-eight patients (38.4%) had a previous diagnosis of rhinitis or symptoms of rhinitis.

FIGURE 1. Overall asthma mortality rates (asthma deaths per 100 000 inhabitants) in São Paulo city, 1996–2004
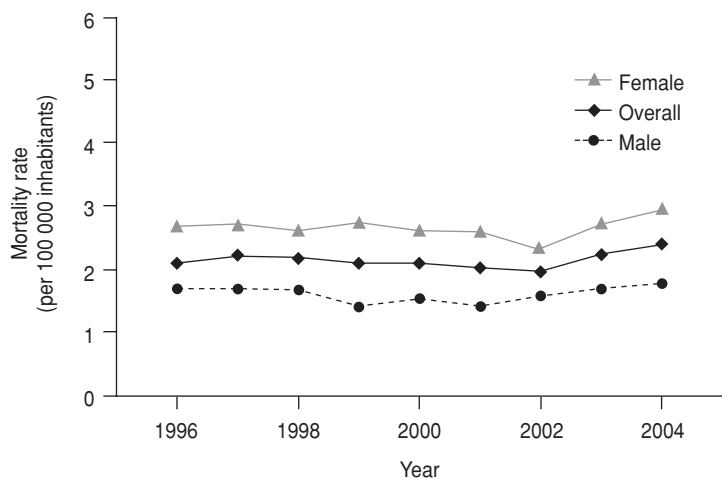
FIGURE 2. Age-adjusted (5–34 years) asthma mortality rates (asthma deaths per 100 000 inhabitants) in São Paulo city, 1996–2004
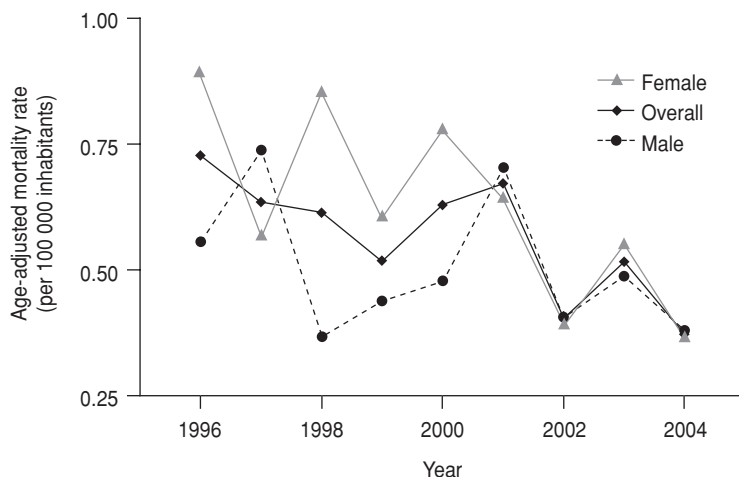
Twenty-five patients (34.2%) were regularly followed by a doctor and 12 of them had been seen by a respiratory doctor or attended a specialized center for the care of asthma.

Anti-asthma medication was analyzed in two categories: controllers (oral and inhaled corticosteroids, long-acting inhaled beta-agonists and methylxanthines) and relievers (short-acting beta-agonists and anticholinergics). Forty-one percent of the patients received no controller medication. Only 9 of 73 (12.3%) patients received an inhaled steroid regularly. Twenty-one patients (28.8%) received oral steroids regularly. Thirty-five (47.9%) patients received methylxanthine as a controller medication. Table 2 shows the controllers and associations used by the patients. Most of the patients—71 (97.3%)—used reliever medication.

Overall, 35 patients (47.9%) presented at least one of the following characteristics associated with severe asthma: hospitalizations due to asthma in the previous year, previous admission to the intensive care unit due to severe asthma exacerbations, forced expiratory volume in 1 second (FEV_1) < 60% of predicted, regular use of high-dose inhaled corticosteroid, or regular use of oral corticosteroid.

Sudden-onset fatal asthma occurred in 11 of 66 (16.7%) patients; 17 of 66 (25.7%) patients had slow-onset fatal asthma for > 2 hours and < 1 day and 38 of 66 (57.6%) had slow-onset fatal asthma for > 1 day. Fifty-five (75.3%) patients died at home, at work, in the street, or en route to the hospital.

In this study, we characterized 73 patients with autopsy-proven fatal asthma in São Paulo city, Brazil, in the period 1996–2004. An earlier survey described mortality rates in Latin American countries (8), but to our knowledge this is the first study to characterize autopsy-proven fatal asthma patients in Brazil and in Latin America.

As expected, many subjects of this study who died from asthma were undertreated for their disease. Only 12.3% of the patients were taking inhaled steroids on a regular basis, despite the use of reliever medication by 97% of the patients in the 6 months before death. A subgroup of 35 patients (47.9%) could be classified as having moderate-to-severe asthma, based on hospitalizations for asthma in the previous year, previous admission to the intensive care unit due to severe asthma exacerbations, FEV_1 data, and controller medications used. Despite this fact, only one-third of the patients were seen regularly by a doctor.

Although these data are not sufficient to conclude that the lack of adequate anti-inflammatory therapy and regular medical care contributed to death in these subjects, evidence from several countries (3–5) suggests that the introduction of asthma management plans that encourage more frequent use of inhaled steroids is associated with decreased mortality rates.

Asthma death rates in the general population in São Paulo remained stable at around 2.0 deaths per 100 000 inhabitants during the study period, although age-adjusted (5–34 years) mortality rates appear to have decreased in the last 3 years of the study period. Interestingly, oscillations by gender in the 5- to 34-year-old population occurred from 1996 to 1999, with a

TABLE 1. Demographic data on 73 autopsy-proven fatal asthma subjects in São Paulo city, 1996–2004[a]

	Age group			
	0–5 years	5–34 years	34–78 years	Total
Number of subjects	2	15	56	73
Gender				
Female	1	9	32	42
Male	1	6	24	31
Race				
Caucasian	2	9	35	46
African	0	5	19	24
Asian	0	1	2	3
Smoking status				
Smoker	NA[b]	6	16	22
Nonsmoker	NA	9	26	35
Ex-smoker	NA	0	14	14
Body mass index, kg/m^2	NA	19.8 (12.8–24.8)	23.6 (20.1–35.8)	23.1
Education				
Illiterate	NA	0	11	11
< 8 years of education	NA	8[c]	32	40
> 8 years of education	NA	5	10	15
Per capita income (times minimum wage)	1.7	1.3 (0.3–8.9)	1.2 (0.3–7.7)	1.6
Basic sanitary conditions				
Yes	2	15	51	68
No	0	0	5	5

[a] Body mass index and per capita income data are presented as medians and ranges. Two individuals in the 5- to 34-year group and three individuals in the 34- to 78-year age group had no information available on education.
[b] NA, not applicable.
[c] Seven of the eight patients were old enough to have received at least 8 years of education.

TABLE 2. Types and associations of controllers used by patients

Number of controllers	Number of patients	OS[a]	MX[b]	LABA[c]	IS[d]
1	1				X
	6	X			
	17		X		
2	1		X	X	
	2		X		X
	10	X	X		
3	1		X	X	X
	1	X		X	X
	3	X	X		X
4	1	X	X	X	X

[a] OS, oral steroid.
[b] MX, methylXanthine.
[c] LABA, long-acting beta-agonist.
[d] IS, inhaled steroid.

mirror image by sex. However, we believe there is no epidemiologic reason for this finding. A trend in decreased asthma mortality similar to that observed in several other countries was not observed in São Paulo (4, 5, 19, 20) during the study period.

Data indicate that asthma mortality is higher in the population older than 34 years (21). In the autopsied popula-

tion, 76% (56 of 73) of the subjects were older than 34 years. Most epidemiologic studies are based on the 5- to 34-year age range because of the lack of accuracy in the asthma diagnosis on death certificates for younger and older subjects. In this study, we had the opportunity to confirm asthma diagnosis in an older population with histopathological analysis and interviews. Previ-

ous data suggest that asthma mortality in persons older than 65 years is 11 times higher than in patients aged 15 to 34 (21). Because of several confounding factors, such as heart failure, smoking, and chronic obstructive pulmonary disease (COPD), it has been suggested that asthma in the elderly is underdiagnosed and undertreated (22); increasing awareness of asthma in the elderly is therefore very important.

There was a slight predominance of women in this population, as observed in another series analyzing asthma deaths (23). Recent surveys indicate that severe asthma in adults is more common in middle-aged women (24). Demographic data indicate that race/color of the 73 individuals who died from asthma was not different from that of the overall population of São Paulo city (25).

Recent data estimate that approximately 60% of the Brazilian population formally employed earns 1 to 4 times the minimum wage (26). Although not strictly different from the mean Brazilian incomes, our data indicated that these subjects had low incomes (median 1.6 times minimum wage) and fewer than 8 years of education in a large proportion of cases. Low socioeconomic status is a well-known indirect risk factor associated with fatal asthma. The increase in risks associated with low socioeconomic levels relates to a poor home and psychosocial environment, home crowding, low access to medical care, and inadequate continuity and quality of medical care (27). In addition, low educational levels are related to discontinuity of medical care, repeated failure to contact physicians during exacerbations, failure to recognize disease severity or deterioration, and difficulties in understanding the appropriate technique for using inhaled medication devices (27).

Smoking is considered an independent risk factor for fatal asthma. Smoking prevalence in São Paulo is 23% for men and 17% for women (28). In the population we studied, smoking rates exceeded the city rates (45.2% of men and 19.1% of women). It has been shown that asthmatics are unaware of the increased risks of

asthma deterioration posed by cigarette smoking (29). Also, there is evidence that active smoking may decrease steroid efficacy in people with asthma (30, 31). Although there were elderly patients who smoked among the studied subjects, they all presented histological alterations consistent with fatal asthma. Because of the lack of medical data, we cannot exclude the coexistence of COPD in some of these elderly smokers.

This study has important limitations. It was carried out with relatives of the deceased many months after death, so the reliability of the data obtained is certainly limited and may contribute to the lack of information for some patients. First, there was a mourning period to be respected. Second, especially in the first years of the study, it was difficult to track relatives because many did not have a telephone or lived in areas not served by mail services or not present on city maps, such as the slums. The objective of this study was to characterize a subset of autopsied patients; therefore, we cannot extrapolate our findings to all of São Paulo's fatal asthma population. A control group of people with severe or near-fatal asthma with the same demographic characteristics would be desirable to identify risk factors, but it was beyond the scope of this study.

A previous study correlated lesser use of primary care services and increased risk for fatal asthma (23). Because of their socioeconomic characteristics, these individuals probably rely on the public health system for asthma care (in São Paulo state it was estimated that 38.2% of the population has private health insurance) (32). In our study, it is difficult to ascertain whether the absence of regular medical care and underuse of anti-inflammatory drugs are patient- or doctor-related factors. Holanda (33) reported a survey among the main coordinators of asthma management in 10 capitals of Brazil. All the participants reported that no inhaled drugs were available in the primary care units, that there was an unmet demand for anti-asthma drugs, and that few specialized asthma outpatient services existed in the nonacademic public health services. The author concluded that management of low-income patients with asthma was behind the most recent international asthma management guidelines (33).

Almost half the individuals were receiving methylxanthines, representing most of the patients who received only one controller medication. One possible explanation is that methylxanthines are available in the public health system. Similarly, this fact may also explain the greater frequency of use of oral steroids than of inhaled steroids, because the latter were not universally available for low-income people in the public health system during the study period.

There were signs of asthma-related deterioration many days before the fatal attack. This was previously shown in one study, where 80% of the patients admitted to the hospital with acute severe asthma had worsening asthma symptoms for more than 2 days before hospitalization (34). It has been suggested that patients with near-fatal asthma fail to take action when asthma is worsening. In another study analyzing characteristics of patients who died of asthma, 80% of the patients were reportedly on inhaled steroids with good compliance, but the mode of onset of the last attack was sudden in 16 of 20 patients (11). The final events leading to a fatal asthma attack are not yet understood, are most likely protean, and may be related to the asthma phenotype. Most subjects of this study died at home or en route to the hospital, an observation confirmed by previous studies (8, 11).

In summary, we presented the characterization of 73 autopsy-proven fatal asthma cases in São Paulo city showing that these individuals share characteristics of severe or poorly controlled asthma, low educational and socioeconomic status, low frequency of use of inhaled steroids, and lack of regular medical care. It has been previously argued that more asthma research in Latin America is needed to better understand local characteristics (35). We also believe that it is the appropriate way to encourage efforts to improve asthma management programs in this part of the world.

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RESUMEN

Caracterización de los pacientes fallecidos por asma certificada por autopsia en São Paulo, Brasil

Se cuenta con poca información acerca de los pacientes fallecidos por asma certificada por autopsia en São Paulo, Brasil. Se caracterizaron 73 pacientes de asma sometidos a autopsia en el Serviço de Verificação de Óbitos da Universidade de São Paulo entre 1996 y 2004. Mediante entrevistas con sus parientes se estableció el nivel socioeconómico, los antecedentes de asma y el tratamiento seguido. Del los 73 pacientes (42 mujeres y 31 hombres), 56 (76,7%) eran mayores de 34 años; 63,0% eran caucásicos y 77,3% tenían menos de 8 años de escolaridad. La mediana de los ingresos era de 1,6 veces el salario mínimo. De los pacientes, 22 (30,1%) eran fumadores y 14 (19,2%) lo habían sido. Solamente 25 (34,2%) pacientes tenían seguimiento médico regular y solo 12,3% usaba inhaladores de esteroides; 35 (47,9%) presentaban asma moderada o intensa; 55 (75,3%) de las muertes ocurrieron fuera de los hospitales. Se concluye que esta población se caracterizaba por padecer de asma intensa o poco controlada, bajo nivel educacional y socioeconómico, carecía de atención médica y no usaba inhaladores de esteroides.

Palabras clave

Asma, mortalidad, autopsia, características de la población, factores socioeconómicos, esteroides, Brasil.