Review Article

Death due to asthma

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ABSTRACT

The prevalence and fatality rate of asthma have increased worldwide. Underdiagnosis and undertreatment of asthma are central to the occurrence of fatal asthma. Atopy is the principal risk factor associated with asthma. However, consideration of the epidemiologic, physiologic, pharmacologic, pathologic and clinical parameters of asthma assessment may provide valuable insight into death due to asthma. Psychologic and socioeconomic factors may further aggravate the asthma status. Ethnic minorities are at increased risk of asthma. The perception of dyspnea may be blunted in asthma sufferers. Slow-onset fatal asthma may be associated with submucosal eosinophilia, whereas sudden-onset may be associated with submucosal neutrophilia. Fatal asthma occurs in patients abusing regular β2-agonist therapy. Peak flow assessment often provides insight into asthma deterioration prior to signs of respiratory distress. Markers of risk of death due to asthma further identify the fatality-prone asthma patient.

Key words: fatal asthma, poor perception, underdiagnosis, undertreatment

INTRODUCTION

Underdiagnosis, including inadequate assessment of asthma severity and undertreatment of the asthma sufferer, is central to the occurrence of near-death or fatal asthma. That asthma morbidity can be reduced, in fact that asthma mortality can be prevented, is not generally appreciated by the community as well as many medical practitioners. Many physicians address less serious disorders occurring less frequently than asthma with more dexterity and dedication than that with which they address asthma.

The prevalence and fatality rate of asthma has increased worldwide with nearly 100 million individuals now affected by asthma. In the USA, asthma mortality has plateaued at nearly 6000 deaths annually. Inadequate assessment of respiratory disability with inadequate treatment is responsible for the significant asthma fatality rate. Frequently the severity of asthma is appreciated by neither the patient nor the clinician. Most asthma deaths are preventable by prompt diagnosis of asthma and early introduction of an appropriate therapeutic program including repeated evaluation with close medical supervision. Any asthma sufferer may be fatality-prone, particularly if the medical evaluation, treatment and follow-up are inadequate.

Factors identified with increased risk of fatal asthma have been attributed to the pathologic changes in the Airways and the management of asthma by the physician as well as the patient. Atopy is the principal risk factor associated with asthma. However, consideration of the epidemiologic, physiologic, pharmacologic, pathologic and clinical parameters of asthma assessment may provide valuable insight into asthma deaths. Psychologic and socioeconomic factors may further aggravate the asthma status, but such factors usually are not primary risk contributors.

PARAMETERS OF ASTHMA ASSESSMENT

Epidemiologic

Although there have been many epidemiologic studies of fatal or near-fatal asthma, there have been few assessments of the mechanisms underlying a life-threatening attack. Asthma prevalence in the USA has increased in the under-18 and over-65-year-old age groups, whereas mortality involves mainly the 5-34 and the over-50-year-old groups. Ethnic minorities are at particular risk. In the USA, asthma sufferers of African-American and Hispanic background are more prone to fatal asthma than their Caucasian counterparts. In New Zealand, the Maoris (indigenous Polynesians) have a significantly greater fatality rate than the national average for that country. However, in all instances, living in a socioeconomically deprived, crowded city center area may be a common predisposing factor. Such areas have an over-abundance of sensitizing antigens such as dust mite, cockroach and animal allergens. In certain ethnic communities, seeking routine health assessment is not condoned. Individuals use the emergency room for asthma treatment only during serious asthma attacks. They often have inadequately controlled asthma.
which exacerbates abruptly with a possible fatal outcome if appropriate therapy is not readily available. Other precipitants of life-threatening asthma may include respiratory infection or even allergen overload including mold spores and pollen antigens.

**Physiologic**

The perception of dyspnea and chemosensitivity may be reduced, in spite of hypoxia and hypercapnia, in patients with near-fatal asthma, compared with normal subjects with no asthma history. Such lower hypoxic responses have been associated with a blunted perception of asthma severity and even impaired chemosensitivity to hypercapnia. These observations were further correlated with reductions in the mean hypoxic ventilatory response and airway occlusion pressure in patients with near-fatal asthma. This is particularly noted when compared with non-asthma or asthma patients who never experienced a near-fatal attack.

There were three patterns of respiratory decompensation observed in 34 patients intubated and mechanically ventilated for severe near-fatal asthma. Group I deteriorated rapidly after the onset of symptoms with endotracheal intubation in <3h. Group II experienced a gradual onset of respiratory failure over days, i.e. 9.2±7.7 days, and Group III experienced acute exacerbation during unstable asthma, i.e. 4.2±3.5 days. It was felt by these authors that acute bronchodilatation was central to the sudden asphyxic asthma.

The mean hypoxic ventilatory response (0.14±0.12L/min/cent of arterial oxygen saturation) and airway occlusion pressure (0.05±0.95 cm of water/cent of arterial oxygen saturation) were significantly lower in the patients with near-fatal asthma than in normal subjects and the patients with asthma who had not had near-fatal attacks. Patients with near-fatal asthma had a lower hypoxic response that coupled with a blunted perception of dyspnea when compared with normal subjects. Therefore, some patients may have a hereditary lower sensitivity to hypoxia which becomes apparent only if severe hypoxia develops during an exacerbation of asthma. So an impaired hypoxic response associated with a reduced perception of dyspnea may result in a delay to seek, and therefore institute, appropriate care.

**Pathologic**

Pathologic assessment of post-mortem tissues obtained from subjects with fatal asthma episodes has yielded several striking observations. It is possible to differentiate two types of fatal asthma. Slow-onset fatal asthma was associated with submucosal eosinophilia, whereas sudden-onset fatal asthma was associated with mucosal eosinophilia and submucosal neutrophils. Thus, submucosal eosinophil assessment correlated significantly with the time interval between onset and death resulting from asthma.

Autopsy evaluation of airway dimensions was conducted in asthmatic subjects with death due to asthma (fatal asthma), asthmatic subjects with death not due to asthma (non-fatal asthma) and subjects without asthma (controls). Large central and small peripheral airway diameters were measured and then grouped according to the basement membrane diameter. Area was expressed as area/mm² of basement membrane. In cartilaginous airways, fatal asthma subjects had greater total wall, inner wall, outer wall, smooth muscle, mucous gland and cartilage areas than controls (P<0.05). Non-fatal (P<0.05) asthma subjects had greater small cartilage airways and membranous bronchioles than controls. In the large membranous bronchioles, the area of smooth muscle was greater in fatal and non-fatal asthma subjects than in the controls (P<0.05). It was the authors’ opinion that structural changes contributing to airway responsiveness occurred in large and small airways in fatal asthma. However, such changes were observed in the small airways in non-fatal asthma cases. Pulmonary functional changes consistent with large and small airway dysfunction may suggest airway hyper-responsiveness and in turn fatality-prone asthma.

Airway wall measurements of post-mortem tissue revealed increased diameter in fatal asthma compared with either non-fatal or normal subjects. The fatal asthma subjects all died suddenly out of the hospital and had not received mechanical ventilation. They had long histories of asthma and had required prior hospitalizations for frequent episodic attacks with sustained periods of airflow impairment.

Pathologic studies such as these provide appreciation of the pathochemical correlates relating to fatal asthma. The hypertrophied smooth muscle allows for greater shortening in response to bronchoconstrictor response to allergen challenge, whereas the increase in outer wall diameter may permit uncoupling of the distending force of parenchymal recoil from the forces contributing to airway recovery.

Narrowing of the airway may be further compromised by mucous gland hypertrophy with excessive mucus production and inner-wall thickening by muscle hypertrophy. With the increased recognition of early asthma airway remodelling and airway tissue response to therapy, assessment of the pathologic changes is critical to understanding fatal asthma.

The characteristic pathologic changes occurring in fatal asthma usually consist of mucus-inspissated bronchi and bronchioles. Usually eosinophils and desquamated epithelial cells occupy the airways, which may be distended with emphysematous changes and thickened basement membrane, now recognized to be the results of airway remodelling. Occasional post-mortem examination is devoid of inflammatory changes but complicated by pneumothorax, cor pulmonale, aspiration, pneumonia and/or pulmonary edema. There usually is an inflammatory component, further substantiating inadequate treatment.

**Pharmacologic**

Fatal asthma has occurred when patients use regular β₂-agonist therapy. In some instances these patients were not administer-
ing concomitant anti-inflammatory therapy. The role of regular versus intermittent (on-demand) β₂-agonist therapy remains controversial.²¹ β₂-agonist-induced protection against induced bronchospasm is attenuated with long-term regular abbreviated therapy.²² Regular administration of inhaled terbutaline for 7 days lost the protective effect of a single dose of inhaled terbutaline against the bronchoconstriction induced by adenosine monophosphate and methacholine. In these studies, the inhibition of the bronchoconstricting agent was reduced by 2.1 and 1.5 doubling doses respectively. Salmeterol affords significant protection against methacholine-induced bronchoconstriction which is diminished after 4–8 weeks of treatment.²³

Repeated use of inhaled β₂-agonists may be associated with deterioration in control of asthma with an increase in airway hyper-responsiveness.²⁴⁻²⁶ Regularly scheduled or frequent use of short-acting β₂-agonists for prolonged management of asthma fails to adequately control asthma symptoms, peak flow variability and/or airway hyper-responsiveness.²¹ Regular administration of β₂-agonists to mild asthma sufferers was associated with an increase in peak expiratory flow variability. After cessation of treatment there was a 10% fall in forced expiratory volume in one second (FEV₁) and an increase in bronchial reactivity to histamine. Such changes occur with terbutaline,²⁴⁻²⁶ fenoterol,²¹ and albuterol.²⁷

The mechanism contributing to the increase in bronchial reactivity and deterioration in asthma control after β₂-agonist therapy is unclear. Desensitization of β₂-receptor has been postulated,²⁴⁻²⁶ with smooth muscle relaxation and enhanced mediator release.

Fenoterol has been associated with an increase in fatal asthma when administered regularly.³⁹ Assessment of fatal and near-fatal asthma in a nested case control study in Saskatchewan, Canada, confirmed the relationship of fatal asthma to β₂-agonist abuse.³⁰ The risk of asthma increased when 1.4 canisters or more of β₂-agonist were consumed. It is yet to be determined whether the increased use of β₂-agonist in fatal or near-fatal asthma contributes to mortality or is merely a marker of severe disease.³⁰

At least one study of near-fatal asthma suggests such exacerbations are related to severe asphyxia rather than cardiac arrhythmia,³¹ making undertreatment a significant contribution to asthma mortality.³² Psychotropic drug administrations were also associated with an increased risk of death, whereas corticosteroids were only slightly associated with subsequent death, more strongly associated with readmission.³⁹

Clinical

Can the fatality-prone asthma sufferer be identified? If so, what are the markers for the risk of asthma death? In thirty-nine deaths due to asthma in patients not prescribed fenoterol,³⁰,³² hospital admission in the previous year for asthma treatment was the strongest indicator of subsequent risk of death and a strong marker for increased readmission for asthma. The risk of death was increased with the number of previous admissions.

Ascertaining asthma severity by historical evidence or peak flow evaluation provides additional insights into the increased risk of death due to asthma. A peak expiratory flow rate (PEFR) < 100 L/min caused a 2-fold risk of subsequent death or readmission. A Pco₂ > 45 mmHg was associated with an increased risk of death.³² It is critical to classify asthma by severity: mild, moderate and severe.¹¹ This is now the basis of the zonal step-wise therapy initially proposed in the National Heart, Lung and Blood Institute (NHLBI) International Consensus for the Diagnosis and Treatment of Asthma, and further refined by the World Health Organization/NHLBI Global Strategy for Asthma (GSA).¹¹

Patients with severe asthma requiring three or more admissions/year and who had a very severe attack within the same year are highly susceptible to fatal attacks of asthma.¹ A history of previous life-threatening attacks is associated with a 3-fold risk of death when compared with individuals whose asthma is treated on an outpatient basis. A previous life-threatening attack is associated with a 14-fold increased risk of death, whereas a previous hospital admission is associated with a 7-fold increased risk.¹¹

Therefore there are three markers which indicate the risk of death due to asthma. First, a hospital admission for asthma in the previous 12 months is the most consistent predictor of a fatal asthma attack.¹¹ Second, multiple hospital admissions for asthma in the previous year are associated with an even greater increased risk. Third, the chronic use of three or more categories of asthma drugs has an increased risk of asthma fatality.¹¹ Oral corticosteroid drug administration had only a weak association with subsequent risk of death. As markers of a severe attack, Pco₂ > 45 mmHg and PEFR 100 L/min are consistent with a life-threatening attack.³²

Other clinical factors contributing to fatal asthma attacks include inadequate assessment of asthma severity by the clinician as well as the patient, i.e. underdiagnosis with resulting undertreatment.¹¹ Therefore, assessment must include evaluation by objective parameters with a peak flow meter correlated with the clinical manifestations. This is particularly true of fatality-prone asthmatics who may have a poor or inadequate understanding of their asthma severity.

Evaluation of such a fatality-prone asthma sufferer should include response to therapy, i.e. beneficial, no change, worse, in reference to the clinical status as well as appraisal of lung function after therapeutic intervention.

Undertreatment, or more specifically inappropriate treatment, occurs when pulmonary functional assessment is infrequently obtained and with over-reliance on frequently administered bronchodilation therapy to treat the underlying pathophysiologic changes, i.e. inflammation, of fatal asthma.¹¹ Other management factors contributing to fatal asthma risk factors include discontinuity of medical care and delays in seeking medical attention. Delays in seeking care are often related to the absence
of a written prepared plan for treating asthma exacerbations as well as inadequate access to emergency medical care. Chronic disability due to asthma, as in other long-term disorders, may lead to aberrant behaviour and depression. Children may be particularly afflicted by a false sense of hopelessness. Asthma cannot be cured, but it can be controlled. Although information linking depression and increased asthma fatalities is derived principally from clinical reports, the association is striking in a review of cases where children died suddenly and unexpectedly of asthma. There is clinical evidence that these children had expressed despair, hopelessness, even a desire to die, and other evidence of depression.

Occasionally, patients who have experienced life-threatening asthma exacerbations have been observed to deny that they are at risk of death. Often after a near-fatal exacerbation of asthma, such affected children tend to develop decompensating psychiatric disorders, symptoms of extreme anxiety or even high levels of denial. Other patients minimize their symptoms and avoid appropriate health care. Therefore, as a result of the physiologic and psychologic interactions leading to anxiety, depression and possible fatal asthma episodes, such affected patients require specific professional intervention."

**CONCLUSION**

Fatal asthma results from underdiagnosis and undertreatment. Although those suffering from severe persistent asthma, or even those with mild intermittent asthma, may suffer from a life-threatening or even fatal exacerbation of asthma. To prevent such fatal occurrences, it is critical to identify and correct those factors that accentuate risk of death from asthma. There are several parameters to identify patients at high risk of fatal asthma. The greatest risk to the individual with asthma is complacency or underestimation of the severity of asthma by the patient, the patient’s family, or even the patient’s physician. The risk can be mitigated by appropriate identification of the patient at high risk for fatal asthma through careful assessment of the risk factors (Table 1).

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