BRITTLE ASTHMA A REPORT OF 2 CASES

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ABSTRACT

Brittle asthma, even though it is thought to be a rare form of Asthma, may form the bulk of our difficult to treat asthma and frequently unresponsive exacerbation. Brittle Asthma. Brittle asthma is a rare form of severe asthma characterized by a wide variation of Peak Expiratory Flow (PEF),[1] in spite of high doses of inhaled steroids and bronchodilator therapy. Brittle asthmatic patients have very serious and often, life threatening, attacks. There are two forms of brittle asthma.

CASE PRESENTATION

We present the cases of a 45yr old Nurse anesthetics who was diagnosed >5yrs ago and a 56yr old unemployed who was diagnosed >15yrs ago. Both have been stable for years on add on maintenance therapy with high doses of inhaled corticosteroid and β_2 agonist as oral salbutamol and an inhaler therapy during exacerbation. Recently, both patients noticed worsening of symptoms despite high dose therapy, They have been in and out of hospital recently for uncontrolled asthma. They later had to be admitted in ICU because of respiratory insufficiency. These two lapsed into brittle asthma with recurrent bronchospasm, due to repeated exposure to anesthetic agents and environmental exposure at home respectively.

KEY WORD: Brittle Asthma, Peak Expiratory Flow (PEF), Respiratory Insufficiency, environmental exposure.

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INTRODUCTION

Asthma is a chronic inflammatory disease of the airways. It is characterized by variable airflow obstruction which is reversible either spontaneously or with treatment. The chronic inflammation of airways causes an increase of bronchial hyper responsiveness in response to variety of stimuli.
Asthma causes recurrent episodes of coughing, wheezing, chest tightness and breathlessness. Brittle asthma is very difficult to recognize and to treat, it is a rare form of severe asthma that the clinicians may recognize and treat strictly, because of high morbidity and mortality associated with it. [1]

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Asthma is a heterogeneous disease. Since 1977, the term brittle asthma has been used in different ways by different physicians, leading to some confusion over whether such a group is truly separable from other patients at the severe end of the asthma spectrum. In order to try and clarify this area a classification of brittle asthma into two types based on its distinct phenotypes were made.[2] It merely accounts for 0.05% of asthmatic population.[2] It is characterized by wide variability of PEF despite taking high dose of corticosteroids. Patients with variation of PEF are on increased risk of mortality. The exact mortality of brittle asthma is not known,[3, 4]. Depending upon peak expiratory flow rate, it is classified into two types namely type 1 and type 2:
Type 1 brittle asthma is characterized by a maintained wide PEF variability (> 40% diurnal variation for > 50% of the time over a period of at least 150 days) despite considerable medical therapy including a dose of inhaled steroids of at

least 1500 pg of beclomethasone or equivalent. [3]
It is common between the age of 15 and 55 years, with more females to males ratio (F2.5:M1) (Table 1). It is associated with positive skin prick tests and intolerance to some food items e.g wheat and dairy products (Table 2) Several studies have shown some degree of relationship between Brittle asthma and personality disorders. Type 2 brittle asthma is characterized by acute attacks that are very severe and could lead to mortality or admission into intensive care unit (ICU) and use of mechanical ventilation as a result of respiratory insufficiency. [4]

Table 1: Patients' characteristics with brittle asthma

	Type 1	Type 2
Sex (F/M)	2.5 F: 1M	1 F: 1M
Age (years)	15 – 55	No specific age
Atopy	Yes	No
Food intolerance	Yes	No
Psychological Factors	Yes	No
Morbidity	High	-
Mortality	-	High

Table 2. Positive food challenge in Brittle Asthma

Food	% Positive Response
Dairy Product	50
Wheat	50
Fish	37
Citrus	34
Egg	34
Potato	26
Soya	23
Pea nut	13
Yeast	16

Type 1 brittle asthma has increase in hospital visit for admissions or assessment and stabilization of asthma. The patients with type 1 brittle asthma are taking a considerable amount of medications, such as inhaled steroid and bronchodilator, or oral steroids, with attendant adverse effects. They have increase rate of developing esophageal reflux, osteoporosis, weight gain, that increase their morbidity. [3,5]

Type 2 brittle asthma is associated with increase in hospital admission for acute severe attack, and is associated with a high mortality. The patients with type 2 normally remain stable for a long period, but when they have an attack, it is very severe, and may require assisted ventilation. [3]
The diagnosis of brittle asthma involves PEF monitoring and assessment for the factors responsible for poor control of asthma. Majority (60%) of most patients with type 1 brittle asthma are intolerant to wheat and diary product[5] however, psychosocial factors, co- morbid condition like congestive cardiac failure, COPD, low socio economy, poor quality of life and asthma related events are commonly associated with brittle asthma among patients [6, 7, 8]. Immunoglobulin deficiency, autonomic imbalance and relative resistance to anti inflammatory action of steroids are also considered to be associated factors[9].

Identifying and avoiding the allergen exposure is critical in the management and treatment of brittle asthma. Long term subcutaneous β2 agonist has often resulted in improvement in symptoms and variation of PEF in 50% patients [10]. Effectiveness of alternative immunomodulatory treatment in steroid resistant brittle asthmatic patients has not been elucidated so far.[10,11]

Type 1 brittle asthma is associated with Atopy, demonstrated by a skin prick test positivity for cat, horse, wheat and chocolate. The reaction to *Dermatophagoidespteronyssinus* is greater in type 1, but seen only in varying frequencies. Many patients in this group report history of intolerance, to peanuts, fish and wheat. Type 2 brittle asthma may worsen after exposure to fungal spores such as *Alternaria.* [11]

Both patients with type 1 and 2 brittle asthma have a reduced perception of worsening airways obstruction, and a reduced hypoxic drive. [11,12]
An important mechanism in brittle asthma is airway smooth muscle contraction that is activated rapidly by a cholinergic reflex, and by local release of bradykinins, substance P. bronco constrictor and inflammatory peptides. Many allergens might enhance this mechanism, also edema formation due to vasodilatation, plasma exudation could lead to acute airway narrowing in brittle asthma.[12] The smooth muscle is also remodeled in severe asthma and is seen much in bronchial walls of patients that died from asthmatic attack. Bronchial biopsy shows thickening of the subbasement membrane, irreversible changes in smooth muscle, and glandular componentscontribute to stable and irreversible obstruction of airways. Neutrophils predominance over eosinophils as early changes has also been observed. [12] Altered steroid response is also considered in brittle asthma. [13]

CASE 1

A 45yr old male nurse anesthetic who was diagnosed 5years ago with asthma and was on controller therapy. He was admitted into the Emergency Room (ER) with history of cough, shortness of breath, chest tightness, wheeze. His symptoms have worsened over the last 2 days despite been on high dose of corticosteroid (oral prednisolone 20mg twice a day) and β_2 agonist (salbutamol 4mg twice a day), he has been admitted in the hospital for ecxercabation about 12 times in the last 6 months.

Patient is an anesthetic nurse who has been working in the hospital theatre for 10 years, he puts in an average 10 hours per day and attend to average of 10 surgery cases 3 times every week.

Patient admits repeated exposure to anesthetic agents.

About 4months prior to this admission he was treated for acute ecxercabation with 100% O_2, intravenous fluid (normal saline) and 10mg nebulized salbutamol over 2 hours and IV Hydrocortisone 100mg stat then daily for 72 hours in addition to macrolide antibiotics Erythromycin 500mg thrice daily for 5 days. He did well and was discharged from emergency room, patient was maintained on inhaled corticosteroid and long acting $\beta_2$agonist as maintenance therapy, Patient was advised on avoidance of smoke, dusty environment including reduction in number of hours exposed to anesthetic agent. He had remained stable except for occasional ecxercabation during rainy season and Hamattan periods and winter periods.

On Physical examination the patient was alert, conscious, tachypnic and anxious. The blood pressure was 140/90mmhg with a respiratory rate of 30bpm. Cardiovascular function was recorded to be normal. Lung examination showed generalized rhonchi, prolong expiratory phase, bronchial breath sound and coarse crepitation. $SPO_2$of 78%.

White blood count was 9.5 x 10^9/µL with eosinophilia (30%) and high neutrophil count (68%) suggesting allergen hypersensitivity due to environmental exposure and respiratory tract infection as the possible predisposing factors for acute asthmatic episode. Peak Expiratory Flow (PEFR) was 250L which was far less for his predicted age and height (160cm) of 590l/min. serum electrolyte, urea and createnine were within normal range, Chest Xray shows hyperinflation and hyper lucent lung fields.

CASE 2

A 56yr old unemployed who was diagnosed >15yrs ago, has been stable for years on add on maintenance therapy with high doses of inhaled corticosteroid and β_2 agonist as (salbutamol) and salbutamol inhaler for use during exacerbation (PRN). He presented at the Emergency Room with sudden onset of breathlessness, tachypnea, fever and restlessness. He has been having repeated episode of attack in recent past with daily exacerbation of symptoms despite been on a high dose inhaled corticosteroid/ Long acting β_2 agonist (Fluticasone/ salmeterol) 250µg twice daily.

Physical examination reveals an acutely ill looking restless middle aged man who was dyspneic, febrile (t-37.8°C), he was dehydrated, cyanosed and anxious.

Chest examinations revealed a wide spread expiratory wheeze with evidence of consolidation at the right infra mammary areas.
He had an SPO_2 of 65% at room air, Respiratory-silent chest, PR 120bpm, BP 150/90mmhg, HR 105 bpm

Chest X-ray revealed a hyper inflated with hyper lucent lungs with homogenous opacities at the right lung base. Complete Blood count shows RBC 5.6 X 10^9, PCV 35%, WBC 11.0 X 10^9, Neutrophils count was 68% with toxic granulocytosis, and Eosinophils was 16%.

Clinical and examination findings were consistent with Brittle Asthma presenting in life threatening state precipitated by Respiratory tract infection
Patient was admitted to ICU and was given 100% O_2 at 4l/min, IVF 5%destrose saline, he was also place on nebulised salbutamol 10mg and intravenous hydrocortisone 200mg stat and Ceftriaxone 2g stat the 12 hourly for 72 hours

DISCUSSION

These cases represent Brittle asthma with recurrent bronchospasm, severe acute exacerbation of bronchial asthma secondary to repeated exposure to anesthetic agents and repeated respiratory tract infection/environmental exposure to dust and particulate matter at home respectively.

Brittle asthma even though it is thought to be rare form of Asthma, a lot of our difficult to treat asthma and frequent unresponsive exacerbation might just be hidden face of Brittle Asthma. It is very difficult to treat and often carries high mortality rates among Asthmatics. The patients with brittle asthma have poor adherence to the treatment and have to be monitored closely. The standard guidelines for asthma are not applicable, because the brittle asthmatic patients are taking high doses of inhaled steroids and bronchodilators, so when their conditions are worsening, they have to take oral steroids.[14]

The treatment for type1 brittle asthma begins with reduced allergen exposure, and avoidance foods for which the patients are intolerant to. Mineral supplements such as selenium, magnesium, anti-oxidant and vitamins A, C, B have been found to reduce incidence of brittle asthma. [15]

The therapy is essentially based on high doses of inhaled corticosteroid, during acute attacks it is desirable to prescribe oral steroids and increase dose of β_2-agonist. Subcutaneous infusion of β_2-agonist, such as terbutaline at 6 and 15mg per day through a battery-powered syringe driver (CSIT). Adverse effects such as changes in serum potassium or glucose concentrations might abounds. Using this technique, around half of patients with type I brittle asthma show marked improvements in symptoms, variation in PEF and use of other asthma medication, including oral steroid use. Around 25 % show some improvement in symptoms but less improvement in PEF while the remaining does not respond. Chronic steroid-dependent asthmatics without intrinsic PEF variability do not respond to this form of therapy.[16]

Salmeterol has no proven efficacy in these patients for reasons that are not clear. Whether formeterol, which is a full agonist may be more useful than salmeterol, a partial agonist, remains to be determined.

The treatment of patients with type 2 brittle asthma, that are relatively symptom free, consists of avoidance of allergen exposure, identification of the triggers, self-management, and to treat the acute attacks with injection of adrenaline in a preloaded syringe. These patients have unexpected attacks, that requires emergency hospital admission, for acute respiratory insufficiency and they may require assisted respiration through mechanical ventilation devices. Adrenaline may have theoretical advantages over selective 132 agonists, because of its action as an alpha adrenoceptor against reducing airway oedema as discussed in the section on acute airway narrowing above.

Preloaded syringes (Epi-Pen, ALK, UK; Ana Pen, Allerayde, UK) should be provided for emergency treatment. Inhaled adrenaline may be more effective than a selective 132 agonist inhaler. Once adrenaline has been injected the patient should be placed on a dose of nebulized salbutamol or terbutaline. Rapid onset attacks such as these are often equally quick to resolve leading to the opportunity for inadequate assessment of severity in these cases. [16]

New therapy such as leukotriene receptor antagonists and 5-liposygenase inhibitors oral cyclosporine or methotrexate, or intra-venous immunoglobulin, may help the treatment in brittle asthma.

A good attention of physicians may help for psychological components of asthma and especially in brittle asthma, could influence the disease. Environmental exposure to triggers like dust, chemical agents, working environment and chronic respiratory tract infection could explain why the two patients have developed Brittle asthma over time as a result of repeated exposure and treatment cycles. Respiratory tract infections are important triggers for asthma exacerbations in adults and children. [17,18]

Between 14% to 45 % acute exacerbation of asthma are thought to be associated with respiratory tract infection in children.[19, 20] Patients with hospital acquired pneumonia may remain totally asymptomatic.[21] Chronic respiratory tract infection may well be the most likely reason behind the patient recent asthma exacerbation. Early diagnosis and aggressively treating respiratory tract infection can reduce risk of asthma exacerbation.

CONCLUSION

Diagnosis is based on the analysis of specific symptoms, role of triggers, personal or family history, measurement of lung function and PEF

monitoring. Pharmacological treatment of type 1 brittle asthma in addition to the high doses of inhaled and/or oral steroids and bronchodilators includes subcutaneous injections of beta2 agonist and inhalation of long acting beta2 agonist. The treatment of patients with type 2 brittle asthma includes exclusion of allergen exposure, identification of triggers, self-management and management of acute attacks. The patient was treated with multiple drug therapy and was advised to change working place and modify leaving environment

Patients with brittle asthma, whether type 1 or type 2, pose difficult and complex management problems. Trying to classify these severe patients will help to determine the differing factors involved and, while this classification will not embrace all patients with severe asthma, but can help to identify the possible causality and treatment of this high morbidity group. Individualized treatment approach is always advocated keeping in view the possible triggers and previous drug therapy, diet, psychological and environmental exposures.

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