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Editor-in-chief PULMON
Dr. Suraj K.P.
Professor,
Dept. of Pulmonary Medicine
Govt. Medical College,
Kozhikode, Kerala, India - 673008
E mail: drsurajkp@yahoo.com

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Head Office of Academy of Pulmonary and Critical Care Medicine

Dr. Kurian Oommen

Thottathil

Kavumbhagom PO

Thiruvalla -689102

Ph: 0469 2604796, 9847248015

drkurianoommen@gmail.com

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Editorial

Atmospheric Pollution and Lung Health

Raveendran Nair M.
Consultant Pulmonologist, Ray Mayo Clinic, Attingal.

Atmospheric pollution has long been recognized as a major health hazard. Atmospheric pollution indicates the presence of contaminants or substances in the air that interfere with human health and welfare or produce other harmful environmental effects. Breathing clean air is considered to be a basic requirement of human health and well being. In spite of the continued efforts at loco regional and global levels, air pollution continues to pose a major challenge to human health and well being.

WHO reports that in 2012 around 7 million people died as a result of air pollution. Air pollution has now become the world's largest single environmental health risk. Reducicng air pollution can save millions of lives. In April 2014, WHO has issued new information estimating that outdoor air pollution was responsible for about 3.7 million deaths of people under the age of 60 years in 2012. It is disheartening to note that half of the burden of air pollution is borne by the developing countries[1]. Both indoor and outdoor pollutions are equally harmful from a public health perspective. Indoor air pollution occurs mainly due to the burning of solid fuels in poorly ventilated dwellings. Indoor smoke can be 100 times more than the permissible levels for small particles. Exposure is particularly high among women and children who spend most of their times indoor.

Outdoor air pollution may be consequent to natural disasters and anthropogenic activities. Man made activities involve rapid urbanization, industrialization, wide spread construction activities, open burning of garbage and plastic materials, uncontrolled combustion of shredded tires and vehicular traffic related emissions. Hazardous chemicals and particles escape into the atmosphere by the aforementioned ways and may cause several adverse effects on human health and environment. Increased combustion of fossil fuels in the last century is responsible for the progressive change in the atmospheric composition. Air pollutants such as carbon monoxide, sulfur dioxide, oxides of Nitrogen (NOX), volatile organic compounds (VOCS), Ozone (O_3), heavy metals like zinc, iron, copper and Nickel and respirable particulate matter (PM 2.5 and PM10) may differ in their chemical composition, reaction properties, emissions, disintegration time and ability to diffuse to short or long distances.

Particulate matter (PM) represents a major family of air pollutants. Fine particulate matter with an aero dynamic diameter of 2.5 μm. (PM 2.5) and perhaps to a greater extent ultrafine particles (PM < 0.1 μm.) can penetrate into the innermost regions of the lung. These fine particles are composed of non organic compounds (sulphate, ammonium and hydrogen ions) certain metals, elemental carbon (black carbon), organic species including polycyclic aromatic hydrocarbons (PAH) and many other families. Black carbon (BC) is an incomplete combustion byproduct considered to be a proxy for all traffic related particles[2].

Vehicular traffic related pollutants are the major contributors to unhealthy air quality. Common transportation related air pollutants include carbon monoxide, oxides of Nitrogen (NOX), particulate matter and Ozone (O_3) that is formed when NO_2 interacts with volatile organic compounds in the presence of sunlight. PM 2.5 concentration and PM 2.5 absorbance are possible markers of traffic related pollution. More specifically PM 2.5 absorbance is a measure of the blackness of PM 2.5 which depends on the presence of elemental carbon in PM 2.5. Because elemental carbon represents a major fraction of diesel motor exhausts PM 2.5 absorbance is considered to be a sensitive index of air pollution due to diesel engines and truck traffic. PM 2.5 absorbance is considered to be a sensitive marker of traffic related pollution than PM 2.5 per se.

Petroleum refining products consist mainly of cyclo alkanes, straight and branched chain alkenes. They are continuous sources of air pollution in various occupational settings[3]. Benzene and Toluene are major monocyclic hydro carbons in petrol with nitropyrene in diesel exhaust emissions. Benzene is highly volatile and the most usual mode of exposure is inhalation of vapor[4]. In India, the percentage of benzene in automobile gasoline is only about 3 % whereas in other countries it may be as high as 30 %.

Air pollution has both acute and chronic effects on human health, affecting various organ systems of the body, but the brunt is borne by the cardiopulmonary system. The respiratory system is particularly vulnerable to air pollution because the lungs must move in large quantities of ambient air (over 400 million liters in a lifetime) in order to oxygenate the circulating blood efficiently. Air pollutants like ozone and PM can injure the lungs directly. They may trigger an inflammatory response in the lungs which may spill into the systemic circulation to affect the cardiovascular system and other organs of the body. The pulmonary consequences of air pollution may range from minor upper respiratory irritation to chronic respiratory and cardiovascular diseases, lung cancer, acute respiratory infections in children and chronic airway diseases in adults. Asthma is triggered by exposure to dust, smoke, pollens, volatile organic compounds, ozone, carbon monoxide, sulphur dioxide and oxides of Nitrogen. Ozone is a lung irritant, can aggravate preexisting asthma and COPD. Both short term and long term exposures to air pollution have also been linked to premature mortality and morbidity.

Numerous epidemiological and laboratory studies have documented a reduction in pulmonary function with both short and long term exposures to air pollution[5].Petroleum products and its exhaust can lead to significant respiratory symptoms like chronic cough, breathlessness and wheezing[6]. In high concentrations they cause significant systemic inflammatory response. The particles generated from petrol exhaust are extremely small and are present in the nuclei or accumulation modes with diameters of 0.02 nm and 0.2 nm respectively. Since their surface area being larger they are capable of carrying much larger fractions of toxic components such as hydrocarbons and metals in their surface. They can remain suspended in air for longer periods and deposit deep in the lungs in large numbers compared to larger particles. Transport of oxygen to the tissues is hindered by methHb, a byproduct of benzene metabolism in the body leading to functional anemia. As the levels of methHb rises, symptoms like dyspnoea, palpitation, anxiety and confusion occurs[7,8]. Carbon monoxide also has a stronger affinity for hemoglobin compared to oxygen (230 times more) leading to tissue hypoxia.

Effects of Sulphur dioxide in the respiratory system ranges from a reversible reduction in pulmonary function to constriction of bronchioles, severe airway obstruction, hypoxemia, pulmonary edema and death[9].

Nitric oxide impairs the lung's immune defense mechanisms thereby increasing the susceptibility to various infections and asthma attacks. It has also the potential to induce inflammatory response.

Solid particulate matter (PM) generated from emissions gets adsorbed onto soot particles which can penetrate the lungs thereby increasing the risk for pneumoconiosis and lung cancer[10].

Quality of breathing air plays a pivotal role in the growth and development of lungs during childhood and adolescence. This has been firmly demonstrated by the children's health study[11]. This has shown that lung growth as measured by the rise in FVC, FEV_1 and MMEF from the ages of 10-18 years exhibited a declining trend among the children exposed to ambient air pollution. The study concluded that most children are susceptible to the chronic respiratory effects of breathing polluted air[11]. Thus impaired lung growth and development during childhood and adolescence creates an additional risk factor for lung diseases in adult life.

Children are particularly vulnerable to the deleterious effects of air pollution. Children predominantly breath through their mouth there by bypassing the usual filtering effects of nasal passages and allow the pollutants to travel deeper into the lungs. More over children have a large surface area of the lungs relative to their weight and inhale relatively more air than the adult. They also spend more time outdoors.

There is a strong association between ambient fine particulate air pollution and elevated risk of both cardio pulmonary and lung cancer mortality[12]. Each 10 μm /m^3 elevation in long time average PM2.5 ambient concentrations was associated with approximately a 4%, 6 % and 8% increased risk of all cause, cardio pulmonary and lung cancer mortality respectively[12].

The detrimental effects are not uniformly seen among all individuals exposed to air pollution. Some individuals are genetically prone for the exaggerated harmful effects of air pollution. Recent results from the normative aging study (NAS) among a population of elderly men, linked long term exposure to black carbon (BC) with the rate of lung function decline. It is seen that oxidative stress is associated with lung function decline[13]. Traffic pollution including black carbon induce oxidative stress systemically and in the lungs[14,15]. There exists a strong association between long term black carbon exposure and rate of lung function decline among elderly men with relatively high oxidative stress risk profiles compared with men with a lower risk[16].

In this issue of Pulmon, Gayathri etal has looked at the occupational hazard of petrol pump workers in Trivandrum city. In their cross sectional study comprising of 30 petrol pump workers with age and sex matched control, they have measured FEV_1 and FEV_6. The study concluded that there is a significant reduction in pulmonary function among petrol pump workers compared with the control group. The observed lung function impairment is restrictive in nature. Though there are several studies of similar nature conducted at certain centers in India and abroad, this seems to be the first of its kind being published from the state of

Kerala. The authors certainly merit appreciation in this respect. In spite of certain limitations of the study it has clearly shown a link between the occupational exposure to fuel related pollutants and the declining lung function among the petrol pump workers. The petrol pump workers are actually exposed to the twin effects of the fuel related pollutants and traffic vehicular particulate matter. So the differential effects of these two exposures are worth studying. One possible way is to have a comparative study involving the petrol pump workers and the traffic police personals, who are constantly exposed predominantly to vehicular traffic pollutants. Equally important would be to do a study involving the residents in and around the petrol pumps who are constantly exposed to both traffic pollutants and fuel related exposure. A multi centric Cohort study can shed more light on these details.

The study results are in agreement with similar studies conducted elsewhere. Now it has become clear that the petrol pump workers are occupationally vulnerable to declining lung function which may increase with the duration of exposure. This should call for implementation of preventive measures including pre placement lung function screening and periodic surveillance. Control measures to reduce the benzene concentrations in the ambient air, evaporation controls, use of catalytic converters and reducing the benzene content of the fuel are to be adopted. Use of protective masks at work place, improvement in engine design, soot filters and fuel modification such as biodiesel are other measures which may minimize the exposure risk.

Clean ambient air is an essential pre-requisite for healthy living. To accomplish this an orchestrated and sustained effort should come from all concerned, the government, policy makers, NGOS, professional bodies and all responsible individuals at large. Attempts to minimize atmospheric pollution should ideally start at home by taking steps to reduce indoor air pollution and then participating in various activities to reduce outdoor pollution. Since motor vehicles contribute to more than 50 % of urban air pollution, attempts to reduce this alone can pay rich dividends. This may involve the designing of communities and transportation systems which may impact how often automobiles are used, how many automobile trips are taken, and how long these trips are. Reducing auto trips by increasing mass transit use, car pooling, walking and bicycling may help mitigate air pollution. During the 1994 summer Olympics in Atlanta, USA when peak morning traffic decreased by 23% and peak ozone level decreased by 28%, emergency visits for asthma events in children decreased by 42%. This observational study clearly suggests that efforts to reduce traffic congestion and thereby improving the air quality can improve the respiratory health of the community. Other measures to reduce vehicular emission may include reduction of lead and sulphur contents of fuels, retirement of older commercial vehicles, conversion of diesel and petrol run public transport vehicles to compressed natural gas. Changes in vehicular technology in autorickshaws and motorized two wheelers- change from two stroke to 4 strokes may also be beneficial. But the rising trend of NOX along with the presence of volatile organic compounds indicates an ever increasing tendency to form ground level ozone and as a result smog in that region. It is predicted that the current regimen of vehicle technology, fuel standards and high growth of private vehicles will nullify all the past emission reduction by the end of 2020. Our country is now in the “Swatch Bharath” movement initiated by the honorable Prime Minister of India Sri. Narendra Modi. This movement calls for an earnest and concerted effort by each one of us towards accomplishing a clean environment. Many respiratory organisations in the world are already engaging themselves to accomplish clean air environment in their respective regions. With this prime objective in mind, APCCM had launched the “LUNG HEALTH DAY” , about seven years back. It is being observed on 2nd of December every year commomerating the

Bhopal gas tragedy of 1984. It is planned to observe the lung health day every year highlighting a particular theme about lung health.

We can win the fight against air pollution and reduce the number of people suffering from cardio respiratory diseases including lung cancer , said Dr. Maria Neira ,WHO director for public health, Environmental and social determinants of health. A good quality air can go hand in hand with economic development and over all prosperity of a nation. We cannot buy clean air in a bottle, but countries, states and regions can adopt stringent ,sustained and broad based measures that will clean the air and helps save lives of their people.

References

1. World Health Report 2002 : Reducing risks, promoting healthy life, Geneva world Health Organisation 2002.
2. Jansen N.A, Hoek G, Simic Lawson M etal Black carbon as an additional indicator of the adverse health effects of air borne particles compared with PM 10 and PM 2.5 Environ Health perspect. 2011; 119:1691-9
3. Yadav JS, Seth N Cytogenetical damage in petrol pump workers. IJ HG 2001: 1(2): 145-50
4. Niazi GA, Fleming AF Blood dyscrasia in unofficial vendors of petrol and heavy oil and motor mechanics of Nigeria.Tropical doctor 1989; 19: 55-58.
5. Gamble J, Jones W, Minshall S Epidemiological environmental study of Diesel bus garage workers. Acute effects of No2 and respirable particles in the respiratory system. Environ.Res: 1987 Feb 42(1) : 201-14
6. Uzma N, Salar BM, Kumar BS et al Impact of organic solvents and environmental pollutants on the physiologic function in petrol filling workers. Int. J Res. public health 2008 Sep. 5(3) : 139-46
7. DL Lee, AV Tuyi Methhemoglobin www.emedicine.com
8. M. Donshaw, Burlce J, Schoffstall.P et al Methhemoglobin www.emedicine.com
9. Cotes JC Lung function assessment and application in medicine.5th edition OxFord Black Wel Scientific Publications. 1993 P122
10. Lewis TR, Campbell KL , Vaughan TR. Jr. Effects on canine pulmonary function via induced No2 Impairment , particulate interaction and subsequent S0X. Archive Environ Health Vol 18 issue4 1969 p 596-601, 29 April 2013
11. Gauderman W J, Edward Avol , Gillilands F etal. The effect of Air pollution in lung development from 10-18 years of age.NEJM 35: 1057-1067 Sept. 2004
12. Arden pope C, Richard T, Burnett etal. Lung cancer , cardio pulmonary mortality and long term exposure to air pollution. JAMA. vol 287:No. 9, March 6, 2002
13. Ochs Balcom HM, Grant BJ, Muti P etal. Antioxidants, oxidative stress and pulmonary function in individuals diagnosed with asthma and COPD. EurJ Clin. Nutr 2006 ; 60: 991-9
14. Evelson P, Gonzalez-Flecha B. Time course and quantitive analysis of the adaptive responses to 85% oxygen in the rat lung and heart. Biochem Biophys Acta. 2000 ; 1523: 204-16
15. Neophytou AM, Hart JE, Cavallari etal.Traffic related exposures and biomarkers of systemic inflammation, endothelial activation and oxidative stress, a panel study on the US trucking industry. Envior Health . 2013; 12:105
16. Mordukhovich I, Lepeule J, Brent A Coull etal. The effect of oxidative stress polymorphism on the association between long term black carbon exposure and lung function among elderly men. Thorax 2015: 70:130-137

Review Article

Obesity Hypoventilation Syndrome

Kiran Vishnu Narayan
Assistant Professor in Pulmonary Medicine, Govt Medical College, Kozhikode.

Abstract

The obesity pandemic has caught up even in developing nations. With this arises complications affecting all the major organs of the body. As a pulmonologists skewed view of obesity; the lungs,chest wall bellows and the respiratory controllers are all affected .Though obstructive sleep apnoea (OSA) among obese people are now well recognised among pulmonologists, OSA with hypoventilation or the Hypercapnic OSA gets unrecognized. This has important implications, because compared with eucapnic obese patients, those with Obesity Hypoventilation Syndrome (OHS) present with severe upper airway obstruction, a restrictive physiology, blunted central respiratory drive, pulmonary hypertension, increased health care utilisation and increased mortality. Therefore it is important to identify Obesity Hypoventilation syndrome which is slowly becoming a common condition in the OPD and the ICU. This review will focus on the epidemiology, basic pathophysiology and principles in diagnosis and management of OHS.

Introduction

Obesity hypoventilation syndrome or OHS is characterized by obesity (BMI ≥ 30 kg/m^2), daytime hypercapnia ($PaCO_2$ ≥ 45 mm Hg), and sleep-disordered breathing in the absence of other known causes of hypercapnia. The classical character in Charles Dickens "Posthumous papers of the Pickwick Club" in 1836, describes a plethoric, obese, sleepy boy Joe who used to sleep and snore always when idle. 120 years later, the term "Pickwickian syndrome "was thus adapted by Burwell and colleagues on seeing patients resembling Joe[1].

Epidemiology

By 2015, nearly 1 of 3 adults in the world are expected to be overweight (BMI ≥ 25 kg/m^2) and almost 1 in 10 adults will be obese (BMI ≥ 30 kg/m^2)[2]. As per the WHO fact sheet ,more than 1.4 billion adults, 20 and older were overweight. Of this around 200 million men and nearly 300 million women were obese. Ironically 65% of the world's population live in countries where overweight and obesity kills more people than underweight. The Overseas Development Institute (ODI), found that Indians form a massive chunk of the one in three adults now overweight or obese. Kerala, just second to Punjab leads this trend among states with a prevalence of 24.3% among males and 34% among females[3]. With this level of obesity, the prevalence of OHS is expectedly going to be high. Prevalence of OHS is also more among patients with a higher BMI[4,5]. The aggregate prevalence of OHS among OSA patients referred to sleep disorder centers is 17% (range 4%–50%). The considerable range in prevalence reflects varying patient populations assessed across studies. The estimated prevalence of OHS among the general adult population is 0.15 - 0.3%. Unfortunately the data regarding OHS is not available from India primarily due to under recognition[6]. In ICU admissions, Marik and Desai found that 8% of all admissions met diagnostic criteria for OHS. Though all

OHS patients got admitted with acute on chronic hypercapnic respiratory failure, nearly 75% were misdiagnosed and treated for obstructive lung disease despite having no evidence of obstruction on pulmonary function testing[7].

Morbidity and Quality of Life

Although obesity and severe OSA are associated with decreases in quality of life, OHS may contribute to further decrements in quality of life. Cardiovascular and metabolic comorbidites like Insulin resistance are more common in patients with OHS than in patients with eucapnic obesity. These may be present three or more years prior to a diagnosis of OHS[8,9]. A study revealed that the prevalence of Pulmonary hypertension among a cohort of 34 OHS patients was 58% compared with just 9% among age, sex and weight matched OSA patients[10]. Another study showed that OHS patients were 9 times more likely to have a diagnosis of both cor pulmonale and congestive heart failure. Quality of life among this group is also worse compared to normal obese, OSA and other respiratory disorders, such as obstructive lung disease[8,11]. As a consequence, the direct health costs like general healthcare visits, outpatient visits and medications per year of an OHS patient can reach twice that of an OSA or obese eucapnic patient, reach six times that of an age, gender and socioeconomic status matched control subject. In addition, labour income and employment rates are lower in OHS patients than in OSA or control subjects. There are increased hospital admissions including ICU admissions and thereby increased mortality as compared to age and weight matched controls[12,13].

Pathophysiology

The exact pathophysiology is unknown. OHS as compared to eucapnic obesity or simple OSA is mainly characterised by hypoventilation. The PCO_2 levels in blood are determined by the balance between CO_2 production and elimination. The hypercapnia in OHS is mainly due to hypoventilation. Obesity alone cannot be responsible for the development of hypercapnia because less than one third of morbid obese people develop hypercapnia. Mechanisms put forward for explaining hypoventilation include abnormal lung and chest wall mechanics due to obesity with an increased work of breathing, ventilation perfusion mismatch, disruption of the central respiratory control centres leading to an impaired response to hypoxia and hypercapnia and the presence of sleep disordered breathing with upper airway obstruction[14,15].

The increased adiposity load of obesity reduces chest wall compliance and lung volumes, including functional residual capacity. This low tidal volume breathing pattern reduces pulmonary compliance and also leads to expiratory flow limitation in the lower airways generating intrinsic positive end expiratory pressure and air trapping. These changes, together with upper airway resistance, further increase the load on the inspiratory muscles. As a result higher levels of ventilatory drive are required to maintain eucapnia and chemosensitivity is progressively impaired by rising carbon dioxide levels. The reduced ventilatory response in OHS to elevated CO_2 and low oxygen tensions compared to hypercapnic patients and obese control subjects has been demonstrated in studies[16,17].

During sleep, the partial pressure of carbon dioxide ($PC0_2$) rises during episodes of airflow obstruction and during episodes of impaired ventilation. In eucapnic individuals and those with OSA the acute hypercapnia which ensues from a brief apnoea or hypopnea episode is rapidly reversed by the increased tidal volumes in the successive few breaths(restorative breaths). Patients who develop OHS are unable to normalize the raised $PC0_2$ between such obstructive respiratory events. Studies have shown that if the obstructive event (apnoea) become 3 times longer than the intervening duration of restorative hyperpnoea, then such a patient will be unable to maintain eucapnea. So these intermittent cycles of hypercapnia continues. Daytime hypercapnia results from the inability to effectively eliminate carbon dioxide accumulated at night from sleep disordered breathing . Further the increased $PaC0_2$ causes a decrease in pH and leads to a compensatory increased renal bicarbonate retention. The bicarbonate levels often remain elevated, as the kidneys do not completely eliminate bicarbonate during the day. The kidneys retain bicarbonate to compensate for the elevated PCO_2 levels. Once CSF bicarbonate is elevated, ventilation is again depressed leading to elevated CO_2 levels. The elevated CO_2 levels cannot be then eliminated due to a blunted ventilatory response to hypercapnia while awake[18].

Physiological alterations that are seen in obese patients tend to reduce ventilation to the lower lobes ,with increased perfusion to the same areas because of increased pulmonary blood volume. This in turn produces a mismatch. Lastly there is also central leptin resistance. Leptin is normally produced from adipocytes as a satiety hormone acting on the hypothalamus to inhibit eating. It also acts as a ventilatory stimulant. Normally obese patients

have an increase in carbon dioxide production. This is countered by the presence of increased leptin levels which tend to stimulate ventilation and produce eucapnia. So the majority of severely obese patients are eucapnic. In OHS, there are elevated leptin levels but central leptin resistance. This appears to be responsible for the reduced ventilatory response and increased visceral fat. Fortunately the reduced ventilatory response is reversible with response to positive pressure ventilation[19,20].

Clinical features

As mentioned previously OHS is identified by the triad of obesity (BMI ≥ 30 kg/m^2),chronic awake alveolar hypoventilation(PCO_2 ≥ 45 mm Hg and $Pa0_2$ < 70 mm Hg), and sleep-disordered breathing. Severe obesity (BMI >50 kg/m^2) is one clue that OHS may be present, since nearly 50 percent of such individuals have OHS[4]. The symptoms and many of the physical findings are identical to obese OSA patients. Among OHS patients admitted to hospital, only 20% had previously received the diagnosis of OHS. A large proportion of patients are diagnosed with OHS only when presenting with acute respiratory failure. This highlights that OHS is underdiagnosed or that the diagnosis is dramatically delayed[21].

OHS has a similar prevalence among both sexes, but slightly higher among males with an age at diagnosis usually in the fifth or sixth decade of life. Majority(90%) of OHS have OSA, with an Apnoea Hypopnea Index(AHI) of >30. A minority of patients around 10% may have an AHI of <5 ie non obstructive sleep apnea which occurs during REM sleep[22]. Nonobstructive sleep hypoventilation is defined as an AHI <5 events/hour(ie non obstructive) with a $PaC0_2$ increase by ≥ 10 mm Hg during sleep or an oxygen saturation ≤ 88% for at least 5 min without obstructive respiratory events. As per the American Academy of Sleep Medicine scoring rules for respiratory events hypoventilation during sleep is defined as a

1) PCO_2 (transcutaneous or end-tidal carbon dioxide as surrogates) >55 mm Hg for 10 min or

2) An increase in $PC0_2$ of >10 mmHg from the awake supine value to a value exceeding 50 mm Hg for 10 min.

For those in the paediatric age range hypoventilation is scored when $PC0_2$ is > 50 mmHg for more than 25% of the total sleep time. All clinical features seen in OSA are commonly obtained like poor night time sleep, unrefreshing sleep, excessive daytime somnolence, morning headaches and fatigue. OHS patients experience excessive daytime sleepiness that could be related to the severity of nocturnal rapid eye movement (REM) sleep hypoventilation (i.e. if the the percentage of REM sleep spent in hypoventilation is higher, higher is the excessive daytime sleepiness)[23,24].

A diagnosis is usually made when the obese patient presents with dyspnoea and has evidence of polycythemia, pulmonary hypertension and Sleep disordered breathing. They may also present with severe dyspnoea and obtundation indicating acute on chronic type 2 respiratory failure.The history in addition should focus on ruling out other causes of hypoventilation like severe COPD with FEV_1 <35% or 1 Litre, excess sedatives, opioids, alcohol abuse, neuromuscular weakness like myasthenia gravis,muscular dystrophies,bilateral diaphragm palsy,severe kyphoscoliosis disorders of the central nervous system like stroke or spinal cord trauma, endocrine causes like severe hypothyroidism, peripheral causes like hypophosphatemia and severe hypokalemia and rarely congenital central hypoventilation syndrome.

Physical examination shows a drowsy, plethoric (due to polycythemia), obese patient with an enlarged neck circumference and a high mallampatti score. They are typically rapid shallow breathers but the rate increases during an exacerbation. Cyanosis may occur during exacerbations or in severe OHS. Paradoxical respiration may indicate diaphragm dysfunction or fatigue and impending failure. Cardiovascular examination may show systemic hypertension and evidence of Pulmonary hypertension with loud P2 and features of Right heart failure. Classically, mild to moderate Pulmonary hypertension is expected in OHS and this may persist even with therapy.

Several laboratory findings are supportive of OHS. One of the authority figures in this subject, Mokhlesi and colleagues first demonstrated that a threshold value of arterial bicarbonate of 27 mEq/L could be used as a screening tool to suggest chronic respiratory acidemia from hypoventilation. They showed that a value less than 27 mEq/L had a 97% negative predictive value for excluding a diagnosis of OHS[15,25]. Another study by Macavei and colleagues showed that a calculated serum bicarbonate level of ≥ 27 mEq/L had a sensitivity of 85% and a specificity of 89% for the diagnosis of OHS among their patient sample. An elevated bicarbonate is an indirect evidence of "chronic" respiratory acidosis with compensation[26].

Hypoxemia during awakening is unusual of either OSA or obesity. So an abnormal pulse oximetry during wakefulness should prompt evaluation for OHS among obese OSA patients[27]. Other tests include assessing for infection as a precipitant, checking for erythrocytosis, TSH, drugs and toxin levels like alcohol. Imaging may show evidence of right heart enlargement and prominent proximal pulmonary arteries. Once patient recovers from an exacerbation, a baseline spirometry can be done to exclude other causes for hypercapnia mentioned above. Common spirometry findings expected include a normal Forced expiratory ratio (FEV_1/FVC) with mild to moderate restriction. Additional pulmonary function testing may show reduction in maximum inspiratory and expiratory pressures due to abnormal respiratory mechanics and relative muscle weakness[28].

In a nutshell, clinically screen a obese patient by assessment of the SpO_2 and Serum HCO_3 levels. If there is hypoxemia with elevated bicarbonate, it may be a clue to further evaluation for OHS.

Management

In the Acute setting

As described earlier, OHS is frequently unrecognised until the individual presents with acute on chronic ventilatory decompensation. In the acute setting mentation, hemodynamic stability and asessment of the arterial pH helps triaging the patient admission. In general, a conscious or adequately responsive patient who is hemodynamically stable with pH greater than 7.30 can be managed with NIV in a step down unit with vigilant monitoring and good nursing. Patients who have altered mentation, is hemodynamically unstable, has multiorgan failure and those who are intolerant to an initial trial of NIV or if pH is less than 7.30 are directly admitted to the ICU and may need intubation and mechanical ventilation. The treatment of choice is positive pressure ventilation either by non invasive (bilevel or BIPAP) or invasive mechanical ventilation. Though most patients require supplemental oxygen at baseline, it alone as a treatment modality is not useful[29].

Non invasive ventilation in OHS

The goal of ventilation is to improve alveolar ventilation and relieve upper airway obstruction. Typically Bilevel Positive airway pressure ventilation or BIPAP is used. BIPAP consists of 2 independent pressure settings- Inspiratory positive airway pressure (IPAP) and an Expiratory positive airway pressure (EPAP) or PEEP. The EPAP is required to pneumatically splint up the airways, thereby releiving upper airway obstruction. The Pressure support or the difference between IPAP and EPAP provides degree of alveolar ventilation. In simple terms, higher the pressure support, greater are the tidal volumes achieved and greater the alveolar ventilation. Therefore in acute on chronic type 2 failure, the treatment of choice is bilevel positive airway pressure ventilation. The physiologic benefits of NIV include decreased work of breathing by unloading the respiratory muscles, improving central chemosensitivity after few days of use, opening the atelectatic lung regions, reduction of AHI with improvement in daytime sleepiness and improvement of right ventricular function.

Settings

NIV should be applied initially during sleep and wakefulness during the acute hospital setting. The interface(mask) selected should be of the proper size. An oronasal mask or a full face mask is recommended in the acute setting as higher pressures and thereby better tidal volumes can be generated and mouth breathing is tolerated. Nasal masks though more comfortable and tolerated may be ineffective due to mouth breathing. The interface can be later switched to a nasal mask once the patient is more stable. The straps should be just tight enough to allow two fingers to be passed beneath it. Early acclimitisation and better tolerance can be achieved by initiating with lower pressures and holding the mask without strapping. The pressures can be titrated up slowly and mask strapped on. Though each patient is different, and pressure settings have to be individualized, an initial starting pressure is usually 10 cm H_2O of IPAP and 5cm H_2O of EPAP. Strict and vigilant monitoring is required to observe for deterioration and complications. The first few hours of NIV are extremely important. Monitoring the level of consciousness, respiratory pattern and rate, presence of apneas and snoring, heart rate, blood pressure and SpO_2 will guide the physician in titrating pressure support. The EPAP can be gradually increased by 2 cm H_2O until apneas/ snoring and accompanying cycles of desaturation are abolished .The IPAP can be stepped up by 2cm H_2O to obtain adequate tidal volumes of atleast 8mL/kg to 10 mL/kg till the pulse oximeter reading shows a stable value with SpO_2>90%.This indicates adequate alveolar ventilation and oxygenation. It has been seen that OHS patients require a higher IPAP and EPAP as compared to COPD patients

because of the coexisting severe OSA[25]. Infact studies conducted among OHS patients have shown that high IPAP (mean of 18 cm H_2O with a range 12–30 cm H_2O) and EPAP (mean of 9 cm H_2O with range 5–13 cm H_2O) with the IPAP at least 8 to 10 cm H_2O greater than EPAP to achieve adequate ventilation were required to produce a significant improvement in hypercapnia and hypoxia[24,30,31]. Despite delivering high pressures many of these patients still remain hypoxic and may require the addition of supplemental oxygen.

Careful attention should be paid to air leak, nasal bridge/ facial skin breakdown, or discomfort from an improperly fitting mask. The patient should be given regular breaks every 2-4 hours and skin assessed for pressure effects. Breaks should be allowed for eating and communicating with bystanders. This will mitigate claustrophobia also. Improvement is seen by better mentation, reduction in respiratory rate to less than 25/minute ,more synchronous respiratory efforts and sustained improvement in $SpO_2 \geq 90\%$.The ABG should be repeated at 1 hour and at least 20 % decline in PCO_2 is expected. Some patients may never reach eucapnia reflecting the chronic respiratory acidosis. So the pH may be the best marker of acute clinical improvement. A sustained pH more than 7.35 indicates acid base stability, and then daytime NIV can be discontinued. The nocturnal support should be continued for 2 more days. Most patients improve within 1-3 hours of adequate NIV and a stable pH is reached in 12-24 hours. It has been seen that acute on chronic type 2 failure in patients who have OHS resolves more rapidly compared with patients who have COPD and congestive heart failure[30,32]. Other general care like head end elevation to 30 degrees, avoidance of sedative-hypnotics and narcotics, deep vein thromboprophylaxis and stress ulcer prophylaxis are also to be given.

NIV Failure

The need for vigilant monitoring by the physician and nursing staff is imperative for clinical success and for early detection of complications. Progressive deterioration of consciousness with cardiorespiratory arrest, vomiting with aspiration and even death can occur. Mouth breathing during acute respiratory failure results in gastric distension and the high IPAP applied may distend the gastroesophageal sphincter thereby producing vomiting. Early markers which should alert the clinician of impending respiratory failure (NIV failure) include a deteriorating mentation, persistent tachypnoea and accessory muscle overactivity, poor patient synchrony, persistent hypoxemia and refractory hypercapnia even after 1-2 hours of NIV. The best predictor of early NIV failure (ie within the first 1 to 3 hours) is the lack of improvement in pH and PCO_2 after 1 hour of NIV[33]. A prospective study done among 33 morbidly obese patients with acute respiratory failure from multiple causes reported a NIV failure rate of 36%. In this study, a higher BMI was predictive of failure (46.9 kg/m^2 in successful NIV versus 62.5 kg/m^2 in NIV failure)[34].

Carrilo et al carried out an interesting study comparing the use of NIV in acute exacerbations of COPD and OHS. Consecutive patients were treated with a similar NIV protocol based on the finding of respiratory acidosis, dyspnoea and respiratory rate of ≥ 25/minute. Initial settings were an inspiratory positive pressure of 12 cmH_2O, increasing by 2–3 cmH_2O as tolerated, and an expiratory positive pressure of 5 cmH_2O increased by 1–2 cmH_2O to improve hypoxaemia or comfort. OHS patients experienced less NIV failure (7% versus 13% in the COPD group), fewer ICU readmissions, and lower ICU and hospital mortality[35].

Invasive Ventilation

The clinical signs indicating early need for invasive mechanical ventilation have been described earlier. There are specific issues ubiquitous to the airway control of obese patients including bag and mask ventilation and intubation. Obesity itself is a risk factor for difficult bag and mask ventilation and intubation. Studies have shown that approximately 50% of morbidly obese patients with acute respiratory failure often have a difficult intubation defined as requiring more than two attempts with the same laryngoscope blade by an experienced laryngologist[34,36]. Difficulty lies not only due to the short neck with reduced mobility and crowded oropharynx, but also to the difficulty in oxygenation. The physiological changes exclusive to obesity like low thoracic compliance, atelectasis and diminished functional residual capacity (FRC) may cause development of severe hypoxemia and even periintubation cardiorespiratory arrest. So the physician should anticipate these issues and have adequate knowledge of alternate airway control techniques or have assistance of an anaesthetist. Preoxygenation with 6cm CPAP to improve FRC and intubation with fibreoptic bronchoscope is a useful method in difficult situations[37]. Mechanical ventilation is similair to conventional ventilation, except for accepting higher peak and plateau pressures needed to overcome poor chest wall compliance. High pla-

teau pressures may not indicate lung over distension because the pleural pressures are also elevated due to the stiff chest wall and hence transpulmonary pressures remain normal[38].

At discharge

Patients who are discharged from the ICU will require a formal Polysomnography, ABG and spirometry at follow up to assess severity of OSA and for CPAP titration. It is essential for these patients to be discharged from the ICU on adequate NIV therapy. Though OHS patients require BIPAP during the acute setting, most of them can be managed with CPAP at discharge. A prospective randomized study by Piper et al compared the long-term efficacy of BIPAP versus CPAP in OHS patients. This study showed that majority of OHS (80%) patients could be succesfuly titrated with CPAP. After 3 months of therapy, there was no significant difference between the groups in terms of adherence to PAP therapy or in improvement in daytime sleepiness, hypoxemia or hypercapnia. Therefore, BIPAP is not superior to CPAP and treatment should be individualized to each patient. But BIPAP should be used if the patient requires high CPAP pressures (>15 cm H_2O) and has difficulty in tolerating the high pressures, if hypoxemia persists despite resolution of obstructive respiratory events and lastly if the PCO_2 levels do not normalise after 3 months therapy with CPAP[39].

CPAP titration can be done to identify the pressure that will abolish apneas, hypopneas, Respiratory event related events and snoring both in supine and REM sleep. If oxygen saturation levels remain below 90% inspite of abolishment of obstructive events with CPAP, a BIPAP titration may be required. The IPAP is started at the identified CPAP level which abolished obstructive events and then titrated upwards till SpO_2 >90%.If the BIPAP is unable to maintain SpO_2 >90% inspite of a high IPAP(atleast 8-10cm higher than EPAP),then it is advisable to add supplemental oxygen along with positive airway pressure ventilation[5].

The role of newer modes - Volume Assured Pressure Support (VAPS)

VAPS is a hybrid mode of ventilation which combines the comfort of pressure support at the same time providing consistent Tidal volumes. Different manufacturers have given names for VAPS like Average VAPS (Respironics) and intelligent VAPS (Resmed), though the basic working mechanism remains the same. The underlying goal of these modes is to help in better adapting to the patient's own ventilatory pattern and requirements, which will clearly vary during different stages of sleep and with different activities during the day. In a randomised crossover trial of AVAPS versus standard pressure support in obesity hypoventilation patients a small improvement on nocturnal PCO_2 was seen, but no long-term quality of life improvement[40]. In another trial by Murphy et al, they showed that there was no long-term advantage in AVAPS over optimally titrated bilevel pressure support, so these ''intelligent'' modes do not seem to have a role in the general population of OHS patients. They may be useful sometimes as an aid in OHS patients who are starting NIV for the first time. The devices are also costlier than conventional CPAP or BIPAP machines[41].

Good outcomes are obtained only if the patient is adherent to Positive airway pressure therapy (PAP) whatever be the mode of non invasive ventilation. Adherence as in OSA may be defined as atleast 4.5 hours/day of continous CPAP usage. Early outpatient follow up is therefore mandatory with measurements of ABG and objective assesment of adherence to therapy. Improvement in blood gas values may be seen as early as one month after the institution of PAP therapy[42].

Medical Management - Adjuvants in Treatment

Long Term Oxygen Therapy (LTOT).

Studies have shown that oxygen therapy may be needed in up to 50% of patients with OHS in addition to PAP therapy to keep oxygen saturation levels above 90% in the absence of hypopneas and apneas. LTOT alone is not recommended in patients with nocturnal hypoventilation as it may worsen hypercapnia and abolish hypoxic ventilatory drive[43]. In a double-blind randomised crossover study involving OHS, participants breathed oxygen concentrations (FiO_2) 0.28 and 0.50, each for 20 min, separated by a 45 min washout period. Arterialised-venous PCO_2 ($PavCO_2$) and pH, Minute Ventilation (VE) and Dead space ventilation (Vd/Vt) were measured at baseline, then every 5 min. The authors showed that breathing at FiO_2 0.5 and 0.28 produced a fall in minute ventilation with elevation in CO_2 levels and acidemia only among the OHS patients compared to age and sex matched healthy controls. The effect was higher when breathing at higher FiO_2 (.5) and suggested that ventilatory responses were the key determinant of PCO_2 rises highlighting the potential dangers of higher oxygen treat-

ment in OHS patients[44]. Consistent usage of PAP therapy has shown to reduce the need for supplemental oxygen as seen in a retrospective cohort study by Mokhlesi etal.The need for daytime supplemental oxygen decreased from 30% to 6% in patients who were adherent to PAP therapy[42]. Therefore, patients should be reassessed for both diurnal and nocturnal oxygen requirements a few weeks to months after PAP therapy is instituted.

Phlebotomy

Secondary erthrocytosis is seen in hypoxemic patients as a compensatory physiological mechanism to increase oxygen carrying capacity and thereby oxygen delivery. But hyperviscosity impairs the beneficial effect of increased RBC numbers. Venesection is indicated in hypoxic lung disease when the hematocrit is >55% or features of hyperviscosity are present[45]. Ultimately PAP therapy improves the secondary erthrocytosis by releiving hypoxemia.

Weight Reduction

Borel et al. examined the effects of NIV in OHS on cardiovascular, metabolic and inflammatory variables. As expected the NIV group showed significant improvement in sleep and ABG measures. But level of inflammatory markers, endothelial function and arterial stiffness did not improve. Weight loss was shown to improve both obstructive events and REM related hypoventilation in OHS. Reversal of cardiovascular damage is related to the duration and severity of obesity as well as genetic factors and so NIV should be combined with weight loss to produce a beneficial cardiovascular profile[39,46].

Medroxyprogesterone

It acts as a respiratory stimulant and increases respiratory drive thereby improving daytime hypercapnia. Data showing improvements in PCO_2 levels have been limited. In a series of 10 men with OHS treated with high doses of oral medroxyprogesterone (60 mg/day) for one month, the $PaCO_2$ decreased from 51 mm Hg to 38 mm Hg and the PaO_2 increased from 49 mm Hg to 62 mm Hg. All these patients were able to normalize their $PaCO_2$ with 1–2 min of voluntary hyperventilation, suggesting that there was no limitation to ventilation[47]. Side effects include increased risk for deep vein thrombosis which is especially dangerous in an OHS patient who is mostly immobile with cor pulmonale and cardiac failure.It also produces break through uterine bleed,decreased libido,erectile dysfunction in males.

Acetazolamide

It induces metabolic acidosis through carbonic anhydrase inhibition.This stimulates respiration which increases minute ventilation in normal subjects[48].

In addition optimal management of cor pulmonale and failure with diuretics and inotropes may be required.

Surgical Management

Bariatric Surgery

It has variable long-term efficacy in treating OSA. Most studies available were conducted on OSA patients with majority of them showing short term improvement only following surgery. Most of the patients had recurrence of OSA symptoms inspite of minimal or no weight gain indicating factors other than obesity to be responsible[49]. There has been a single study which examined the impact of Bariatric surgery on OHS. In this study by Sugerman et al involving 31 OHS patients, an improvement in blood gases were noted initially. Preoperative PaO_2 increased from 53 mm Hg to 73 mm Hg one year after surgery, and $PaCO_2$ decreased from 53 mm Hg to 44 mm Hg. The patients were followed up and 5 years post surgery values had worsened, with the mean PaO_2 dropping to 68 mm Hg and $PaCO_2$ increasing to 47 mm Hg. The long term effects occurred despite a minimal increase in BMI postoperatively (38 kg/m^2 to 40 kg/m^2). The deterioration after an initial improvement indicates that factors other than obesity are involved and may be due to the reappearance of sleep disordered breathing[50]. Ideally, patients with OHS being planned for bariatric surgery should be treated with PAP therapy or tracheostomy, prior to surgery in order to decrease perioperative morbidity and mortality. PAP therapy should also be started immediately post extubation to avoid postoperative respiratory failure. There is no solid data to show that PAP therapy initiated postoperatively leads to ananastomotic disruption or leakage of the surgical site.

Tracheostomy

This was the most primitive therapy that was described for management of OHS. With the advent of PAP it is rarely used now. Tracheostomy is now indicated only in patients who do not tolerate or are non compliant with

PAP therapy, in patients who have severe corpulmonale and persistent hypercapnia despite optimal adherence to PAP and in a OHS patient who cannot be extubated from invasive mechanical ventilation. Tracheostomy is effective in OSA by bypassing the area of upper airway obstruction reducing dead space. It results in resolution of hypercapnia in the majority of patients due to reduction in the severity of obstructive sleep events. But the hypoventilation is not adressed and so a polysomnography with open tracheostomy is needed to decide whether nocturnal ventilation is required[51]. But tracheostomy can be technically difficult even among experienced ENT surgeons because of the anatomical abnormalities expected in obesity. A low lying larynx may result in accidental perforation of great vessels by the tracheostomy tube .An increased risk of stoma site bleeding and infection occurs because of the excess granulation tissue production stimulated by the adipose tissue.

Summarising, weight reduction along with Non invasive ventilation applied through a good interface is the best option available at present for managing sleep disordered breathing and the alveolar hypoventilation associated with OHS.

Conclusion

Obesity hypoventilation is a specific entity which combines the issues of obesity, sleep disordered breathing and hypoventilation.With the rising trends of obesity universally, the prevalence of OHS is expected to rise with increased morbidity and mortality.A chronically compensated respiratory acidosis is a clue to suspecting the diagnosis in an obese patient, after ruling out other causes of hypoventilation. Positive airway pressure ventilation is the treatment of choice along with weight reduction. Future research on the pathophysiology of OHS and newer treatment modalities in addition to PAP will help to improve the outcome.

References

1. Bickelmann AG, Burwell CS, Robin ED et al. Extreme obesity associated with alveolarhypoventilation : a Pickwickian syndrome. Am J Med 1956;21:811–8.

2. World Health Organization. Preventing chronic diseases: a vital investment. World Health Organization; Geneva: 2005.

3. International Institute for Population Sciences (IIPS) and Macro International. 2007. National Family Health Survey (NFHS-3), 2005–06: India: Volume I. Mumbai: IIPS.

4. Nowbar S, Burkart KM, Gonzales R. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med 2004; 116:1.

5. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care 2010; 55:1347.

6. Balachandran JS, Masa JF, Mokhlesi B. Obesity Hypoventilation Syndrome- Epidemiology and Diagnosis.Sleep Med Clin. 2014 September ; 9(3): 341–347

7. Marik PE, Desai H. Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. J Intensive Care Med. 2012; 28(2):124–30.

8. Basoglu OK, Tasbakan MS. Comparison of clinical characteristics in patients with obesity hypoventilation syndrome and obese obstructive sleep apnea syndrome: a case-control study. Clin Respir J 2014; 8:167.

9. Borel JC, Roux-Lombard P, Tamisier R. Endothelial dysfunction and specific inflammation in obesity hypoventilation syndrome. PLoS One 2009; 4:e6733.

10. Kessler R, Chaouat A, Schinkewitch P. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest. 2001; 120(2):369–76.

11. Budweiser S, Hitzl AP, Jörres RA. Health-related quality of life and long-term prognosis in chronic hypercapnic respiratory failure: a prospective survival analysis. Respir Res. 2007; 8:92.

12. Berg G, Delaive K, Manfreda J. The use of healthcare resources in obesity-hypoventilation syndrome. Chest. 2001; 120(2):377–83.

13. Jennum P, Kjellberg J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. Thorax 2011; 66: 560–6.

14. Laaban JP, Chailleux E. Daytime hypercapnia in adult patients with obstructive sleep apnea syndrome in France, before initiating nocturnal nasal continuous positive airway pressure therapy. Chest 2005;127:710–5.

15. Mokhlesi B, Tulaimat A, Faibussowitsch I. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath 2007;11:117–24.

16. Sampson MG, Grassino K .Neuromechanical properties in obese patients during carbon dioxide rebreathing, Am J Med 1983;75:81-90.

17. Han, F., Chen, E., Wei, H. Treatment effects on carbon dioxide retention in patients with obstructive sleep apnea-hypopnea syndrome. Chest. 2001;119:1814–1819.

18. Berger KI, Goldring RM, Rapoport DM. Obesity hypoventilation syndrome. Semin Respir Crit Care Med 2009; 30

19. Considine RV, Sinha MK, Heiman ML et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334(5):292-295.

20. Makinodan K, Yoshikawa M, Fukuoka A et al. Effect of serum leptin levels on hypercapnic ventilatory response in obstructive sleep apnea. Respiration 2008;75(3):257-264.

21. Quint JK, Ward L, Davison AG. Previously undiagnosed obesity hypoventilation syndrome. Thorax 2007; 62: 462–3.

22. Resta O, Foschino-Barbaro MP, Bonfitto P. Prevalence and mechanisms of diurnal hypercapnia in a sample of morbidlyobese subjects with obstructive sleep apnoea. Respir.Med. 2000;94: 240–6.

23. Chouri-Pontarollo N, Borel JC, Tamisier R. Impaired objective daytime vigilance in obesity-hypoventilation syndrome: Impact of noninvasive ventilation. Chest 2007; 131: 148–55.

24. Perez de Llano LA, Golpe R, Ortiz Piquer M. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest 2005;128:587–94.

25. Mokhlesi B, Tulaimat A. Recent advances in obesity hypoventilation syndrome. Chest 2007; 132:1322–36.

26. Macavei VM, Spurling KJ, Loft J. Diagnostic predictors of obesity-hypoventilation syndrome in patients suspected of having sleep disordered breathing. J Clin Sleep Med. 2013; 9(9):879–84.

27. Olson AL, Zwillich C. The obesity hypoventilation syndrome. Am J Med. 2005; 118(9):948–56.

28. Koenig SM. Pulmonary complications of obesity. Am J Med Sci 2001;321:249–79.

29. Masa JF, Celli BR, Riesco JA, et al. Noninvasive positive pressure ventilation and not oxygen may prevent overt ventilatory failure in patients with chest wall diseases. Chest 1997;112:207–13.

30. Ortega Gonzalez A, Peces-Barba Romero G, Fernandez Ormaechea I. Evolution of patients with chronic obstructive pulmonary disease, obesity hypoventilation syndrome or congestive heart failure in a respiratory monitoring unit. Arch Bronconeumol 2006;42:423–9.

31. Rabec C, Merati M, Baudouin N. Management of obesity and respiratory insufficiency.The value of dual-level pressure nasal ventilation. Rev Mal Respir 1998;15:269–78

32. Lee WY, Mokhlesi B .Diagnosis and Management of Obesity Hypoventilation Syndrome in the ICU. Crit Care Clin 2008(24) 533–549

33. Anton A, Guell R, Gomez J. Predicting the result of noninvasive ventilation in severe acute exacerbations of patients with chronic airflow limitation. Chest 2000;117:828–33.

34. Duarte AG, Justino E, Bigler T. Outcomes of morbidly obese patients requiring mechanical ventilation for acute respiratory failure. Crit Care Med 2007;35:732–7.

35. Carrillo A, Ferrer M, Gonzalez-Diaz G. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012; 186: 1279–1285

36. Crosby ET,Cooper RM,Douglas MJ. The unanticipated difficult airway with recommendations for management.Can J Anaesth.1998;45(8):757-776

37. Paix AD, Williamson JA, Runciman WB. Crisis management during anaesthesia: difficult intubation. Qual Saf Health Care 2005;14:e5–6.

38. Slutsky AS, Ranieri VM. Ventilator induced lung injury. N Engl J Med 2013;369:2126-36.

39. Piper AJ, Wang D, Yee BJ et al. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. Thorax 2008;63(5):395-401.

40. Storre JH, Seuthe B, Fiechter R. Average volume-assured pressure support ventilation in obseity hypoventilation: a randomised crossover trial. Chest 2006; 130: 815–821.

41. Murphy PB, Davidson CH, Hind MD. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax 2012; 67: 727–734.

42. Mokhlesi B, Tulaimat A, Evans AT et al. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. J Clin Sleep Med 2006;2(1):57-62.

43. Banerjee D, Yee BJ, Piper AJ et al. Obesity hypoventilation syndrome: hypoxemia during continuous positive airway pressure. Chest 2007;131(6):1678-1684.

44. Hollier CA, Harmer AR, Maxwell LJ et al. Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: a randomised crossover study. Thorax. 2014;69(4):346-53.

45. McMullin MF,Bareford D,Campbell et al. Guidelines for the diagnosis,investigation and management of polycythaemia.Br J Haematol. 2005; 130:174-95

46. Borel JC, Burel B, Tamisier R. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. PLoS ONE 2013; 8: e52006.

47. Sutton FD Jr, Zwillich CW, Creagh CE et al. Progesterone for outpatient treatment of Pickwickian syndrome.Ann Intern Med 1975;83(4):476-479.

48. Rapoport DM, Garay SM, Epstein H, Goldring RM. Hypercapnia in the obstructive sleep apnea syndrome: a reevaluation of the Pickwickian syndrome. Chest 1986;89(5):627-635.

49. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. Am J Med 2009;122(6):535-542.

50. Sugerman HJ, Fairman RP, Sood RK et al.Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. Am J Clin Nutr 1992;55(2 Suppl):597S-601S.

51. Kim SH, Eisele DW, Smith PL et al. Evaluation of patients with sleep apnea after tracheostomy. Arch Otolaryngol Head Neck Surg 1998;124(9):996-1000.

Original Article

The Outcome of Non Invasive Ventilation in Acute Exacerbation of COPD

Soumya V.K.*, Mohamed Musthafa A., Santhosh Kumar P.V.*****
*Senior Resident, **Assistant Professor, ***Additional Professor
Department of Pulmonary Medicine, Govt. Medical College, Kozhikode.

Correspondence : Dr. Soumya V. K.
Senior Resident, Dept. of Pulmonary Medicine, Govt. Medical College, Kozhikode.

Abstract

Background : Non invasive ventilation (NIV) is an excellent modality in the management of patients with acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD) with respiratory failure, which minimizes the need for invasive ventilation with its attendant complications to a great extent.
Aim of the study : To determine the effectiveness of NIV in acute exacerbation of COPD and to assess the factors determining the outcome of NIV.
Methodology : A prospective observational study was conducted in the Intensive Respiratory Care Unit of a tertiary care centre in North Kerala during January 2012 to August 2013. All patients admitted with acute exacerbation of COPD, with respiratory rate > 25/min, acidosis (pH < 7.35) and hypercapnia ($PaCO_2$ >45mm Hg) were included in the study. Those with contraindication for NIV were excluded. NIV was instituted in these patients via full face mask and monitored respiratory rate, SpO_2, pulse rate, blood pressure and arterial blood gas analysis (ABG) at 1hr, 12 hrs and 24 hrs. Statistical analysis was done using SPSS software version 16. Comparison of blood gas parameters pre and post NIV, quantitative variables and qualitative variables were done with paired t test, t test and chi square respectively.
Results : Out of total 79 patients 70.9% were successfully treated with NIV. The mean body mass index (BMI) was 23.69 and 21.23 in NIV success group and NIV failure group respectively. The mean pH was 7.28 and 7.23 in NIV success group and NIV failure group. The mean $PaCO_2$ fell from the baseline of 85 ± 16.5 mm of Hg to 77.3 ± 14.7 mm of Hg at 1 hour. Thirty five percent of patients with NIV failure had evidence of infection and only 11% had evidence of infection in patients with NIV success.
Conclusion : Non Invasive ventilation as an early treatment modality can significantly improve hypercapnea in acute respiratory failure in COPD. The factors determining the outcome are baseline pH, evidence of infection and BMI.
Keywords : COPD, NIV, ARF(Acute respiratory failure)

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major health problem and leading cause of morbidity and mortality worldwide[1]. Acute exacerbation of chronic obstructive pulmonary disease(AECOPD) are periods of acute worsening which greatly affect the health status of patients with an increase in hospital admission and mortality[2]. Estimates of in-patient mortality range from 4% to 30%, but patients admitted due to acute respiratory failure (ARF) experience a higher rate, in particular elderly patients with co-morbidities (up to 50%) and those requir-

ing intensive care unit (ICU) admission (11%–26%)[3-7]. Noninvasive ventilation(NIV), which refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway, has been shown to reduce intubation rates, mortality, and duration of hospital stay in several studies[8-13]. Although its clinical efficacy has been demonstrated in the management of patients with acute exacerbation of COPD from the west, there are few studies from this part of the country. This study was done to assess the effectiveness of NIV as a therapeutic modality in acute exacerbation of COPD and to assess various factors determining its outcome in south Indian population.

Materials and Methods

This study was prospective observational study, conducted in the Intensive Respiratory Care Unit of a major tertiary hospital in North Kerala. The study was conducted during January 2012 to August 2013 after ethical clearance from institutional ethics committee.

All patients admitted with COPD acute exacerbation, not improving with standard medical treatment with respiratory rate > 25/min, acidosis (pH < 7.35) and hypercapnia ($PaCO_2$>6.0kPa, 45mm Hg) were included in the study. Patients with life-threatening hypoxaemia, severe co-morbidity, confusion, agitation, severe cognitive impairment, facial burns or trauma, recent facial or upper airway surgery, vomiting, fixed upper airway obstruction, undrained pneumothorax, upper gastrointestinal surgery, patients with inability to protect the airway, copious respiratory secretions, moribund patient and patients with bowel obstruction were excluded.

Detailed history, complete physical examination including anthropometry were done and all patients were subjected to routine blood investigation, Chest X Ray (CXR), 12 lead surface electrocardiogram and Arterial Blood Gas Analysis(ABG).

NIV was instituted using either Resmed VPAP IV or Resmed Stellar 100 devices, via full face mask of appropriate size with initial ventilator settings of Inspiratory Positive Airway pressure (IPAP) of 10 cmH_2O and Expiratory Positive Airway pressure (EPAP) of 4 cmH_2O. Monitoring of respiratory rate, SpO_2, pulse rate, blood pressure and ABG at 1hr, 12 hrs and 24 hrs was done. Other parameters monitored were level of consciousness, patient comfort, chest wall movement, presence of leak and accessory muscle use. IPAP was increased by 2 cm of H_2O increments during the first hour according to patient tolerance, achievement of effortless breathing and SpO_2 improvement, up to a maximum of 20 cm H_2O.

Any deterioration in terms of patient's respiratory effort- respiratory rate, level of consciousness, intolerance to NIV, worsening blood gas parameters were indicators of switch over to invasive ventilation. The NIV was used as much as possible in the first 48 hours and subsequently weaned off according to clinical improvement and ABG results.

NIV failure was considered when there was failure to improve or deterioration in arterial blood gas tensions, development of new symptoms or complications such as pneumothorax, sputum retention, nasal bridge erosion, intolerance or failure of coordination with the ventilator, deteriorating consciousness level, patient and carer wish to withdraw treatment.

The factors studied were age, body mass index (BMI), COPD duration, presence of comorbidities, premorbid status-dyspnoea on exertion (DOE), smoking score, Anthonisens classification, leucocyte count, serum electrolytes, serum albumin, respiratory rate prior to NIV, IPAP and EPAP levels, pre NIV and post NIV blood gas parameters, total duration of NIV use and development of complication.

Statistical analysis was done using SPSS software version 16. Comparison of blood gas parameters pre and post NIV was done with paired t test. Comparison of quantitative variables were done with t test and that of qualitative variables were done with chi square test.

Observations

A total of 79 patients were enrolled in the study. Out of these, 56 (70.9%) were successfully treated with NIV and 23 (29.1%) were NIV failures. All were males, with 40 patients between the age group of 40-59 years and 39 patients above 60 years. Thirty patients were hypertensive, 30 diabetic and 12 had coronary heart disease. There was one patient with history of chronic kidney disease and 3 had bronchiectasis.

Out of 79 patients 64 (81%) had a premorbid DOE Grade – 3, cor pulmonale was present in 42(53.2%) and 43(54.4%) patients were admitted with Type 3 Anthonisen class of acute exacerbation of COPD.

Table 1 :

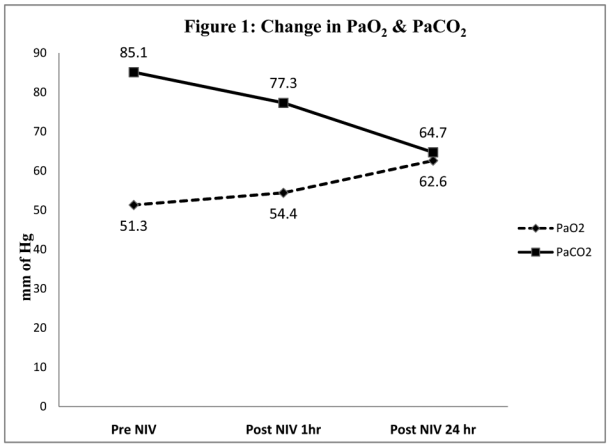
The baseline characteristics of the study population

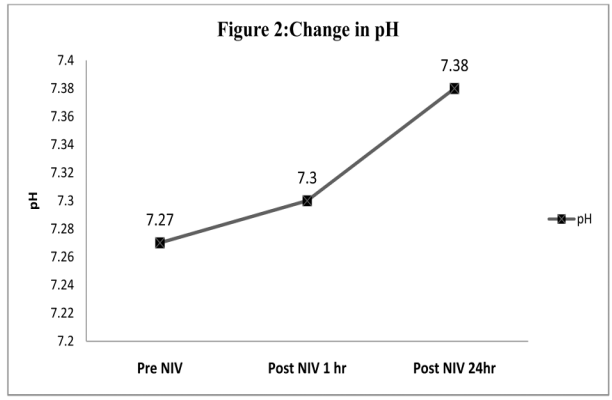
Characteristic	Minimum	Maximum	Mean	Std Deviation
COPD Duration (Years)	2	25	8	3.7
Smoking Score	125	3800	1093	718.8
Duration of exacerbation (Days)	2	20	8	4.3
Total leukocyte count (cu/mm)	1000	40500	12353.8	5526.2
Serum Na (mEq/L)	117	144	131	6.2
Serum K (mEq/L)	2.3	6.3	4	1
Serum Albumin (g/dl)	2.3	4.4	3.3	0.4
Glagow Coma scale	12	15	14	1.1
Respiratory Rate	25	50	34	4.9
PaO_2 (mmHg)	28	95	51.3	12.5
$PaCO_2$ (mmHg)	63	125	85	16.4
pH	7.12	7.35	7.27	0.1
HCO_3 (mmEq/L)	24	60.2	36.2	9.4

Mean IPAP was 14.3 ± 2.4 cm of H_2O and EPAP was 7.1 ± 1.1 cm of H2O. Maximum IPAP used was 20 cm of H_2O and EPAP was 8 cm of H_2O .

The mean SpO_2 rose from the baseline of 51.3± 12.5 mm of Hg to 54.4 ± 10.8 mm of Hg and 62.6 ± 9.5 mm of Hg at 1hour and 24 hours respectively (p <0.05) and mean $PaCO_2$ fell from the baseline of 85.1 ± 16.5 mm of Hg to 77.3 ± 14.7 mm of Hg and 64.7 ± 13.3 mm of Hg at 1 hour and 24 hours respectively (p <0.05) as in figure 1

The mean pH rose from the baseline of 7.27 ± 0.06 to 7.3 ± 0.07 and 7.38 ± 0.07 at 1 hour and 24 hours respectively (p <0.05) as in figure 2.





The mean duration of NIV use was 110.2 hours and mean hospital stay was 15 days. In the study population 32 (41%) patients developed complications, most common being eye irritation 14 (17%). Other complications include ear pain, skin irritation, hypotension, oronasal dryness, gastric distension and nasal congestion.

The mean age in NIV Success group was 58.64 yrs whereas that in the NIV Failure group was slightly higher 62.48yrs and this difference was not statistically significant (p value 0.066).

The mean BMI in NIV success group was 23.69 and that in the NIV failure group was 21.23 and this difference was statistically significant (p value 0.001).

The mean duration of COPD in NIV success group and NIV failure group were 7 ± 3.4 years and 8.7 ± 4.1 years respectively, with a p value of 0.065. The majority of patients had grade 3 DOE in premorbid state. Only 3 patients had grade 4 DOE and all of them had unfavourable outcome (p 0.007).

Another parameter which showed significant difference between the NIV success group and NIV failure group was the evidence of infection - mean leucocyte count and presence of fever. The mean leucocyte count was 11,175 and 15,224 in NIV success and NIV failure group respectively (p 0.003). In NIV success group only 6 (11%) patients were febrile whereas in NIV failure group 8 (35%) were febrile (p 0.0011).

The respiratory rate of the patients at time of commencement of NIV in the two groups was compared. It was found that the mean respiratory rate in the NIV success group was 33/minute whereas in the NIV failure group was 36/minute.

Table 2 :

Pretreatment respiratory rate and blood gas parameters

	NIV Success	NIV Failure	p Value
Respiratory Rate (per minute)	33	36	0.01
pH	7.28	7.23	0.004
PaO_2 (mm Hg)	51.8	50.1	0.59
$PaCO_2$ (mm Hg)	83.6	88.6	0.22

The ABG parameters at the time of commencement of NIV in the two groups were compared. It was found that the mean pH was 7.28 and 7.23 in NIV success group and NIV failure group respectively with the p value of 0.004, mean PaO_2 was 51.8mm of Hg and 50.1mm of Hg in NIV success group and NIV failure group respectively with the p value of 0.59, and mean $PaCO_2$ was 83.6mm of Hg and 88.6mm of Hg in NIV Success group and NIV Failure group respectively with the p value of 0.219.

There was no statistically significant correlation seen between the outcome and smoking score, serum electrolytes and serum albumin.

Table 3 :

Comparing the pretreatment and post treatment Blood gas parameters

	Mean	Std Deviation	Significance
Change in PaO_2 at 1hr	3.12	9.89	0.006
Change in PaO_2 at 24hrs	10.93	12.06	0.00
Change in $PaCO_2$ at 1 hr	7.74	8.24	0.00
Change in $PaCO_2$ at 24hrs	19.85	13.71	0.00
Change in pH at 1 hr	0.03	0.037	0.00
Change in pH at 24hrs	0.10	0.068	0.00

Discussion

Non-invasive ventilation is well established treatment option in the management of acute hypercapnic respiratory failure in acute exacerbations of COPD. The present study proved that the use of NIV in patients admitted for AECOPD with respiratory failure can obviate the need for intubation. About 80% of patients enrolled in the study were successfully treated with NIV.

BMI is a strong independent predictor of mortality in both stable COPD and acute exacerbation of COPD. We found that higher the BMI probability of NIV success was greater. Similar observation was found by Ambrosino et al[14], who studied the effect of nutrition expressed as % ideal body weight in NIV outcome in patients with acute respiratory failure due to COPD.

In contrast to previous studies[14] it was observed that high initial $PaCO_2$ had no bearing in the poor outcome of NIV in COPD acute exacerbation. Thus patients with initial high $PaCO_2$ can be given NIV trial before invasive ventilation.

In stable COPD, the co morbidity burden (usually measured by Charlson Index) is an established predictor of mortality [15]. In acute exacerbation of COPD, co morbidities like ischemic heart disease, congestive cardiac failure, chronic liver disease, chronic renal failure and diabetes are liable to decompensate and hence increase mortality. We found no statistical significance in outcome in relation to the presence of co morbidity. This may be due to small number of patients in NIV failure group. An-

other reason may be, because the study was conducted in an ICU setting, where continuous monitoring and timely appropriate measures were instituted in case of deterioration of co morbidities.

Patients with premorbid DOE grade 4 had unfavourable outcome, which implies that higher degree of physiological dysfunction during the stable state has poorer outcome. The presence of corpulmonale, higher smoking score, longer COPD duration, longer duration of present exacerbation or Anthonisens class had no bearing on the outcome in the present study. We found that evidence of infection viz presence of fever, leucocytosis had a negative impact on the outcome, similar to previous studies[16].

The best marker of severity of COPD acute exacerbation is the pH which reflects acute deterioration in alveolar hypoventilation [17,18]. In the present study mean pH was 7.28 and 7.23 in NIV success group and NIV failure group respectively which was comparable with the previous study results. Thus baseline pH is a significant predictor for successful NIV. This implies the fact that non invasive mechanical ventilation should be instituted early in every patient before a severe acidosis ensues.

Conclusion

1. Non invasive ventilation as an early treatment modality can significantly improve hypercapnia in acute respiratory failure in COPD, thereby avoiding the need for invasive mechanical ventilation and its complications

2. The factors determining the outcome are baseline pH, evidence of infection and BMI.

References

1. Hurd S. The impact of COPD on lung health worldwide: Epidemiology and incidence. Chest 2000; 117(2 Suppl):1S-4S.

2. Donaldson GC, Wedzicha JA. COPD exacerbations– 1: Epidemiology. Thorax 2006;61(2):164–8.

3. American Thoracic Society Statement Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152(5 Pt 2):S77–121.

4. Seneff MG, Wagner DP, Wagner RP, et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 1995;274(23):1852–7

5. Connors AF, Dawson NV, Thomas C, et al. For the SUPPORT investigators Outcomes following acute exacerbations of chronic bronchitis. Am J Respir Crit Care Med 1996;154(4 Pt 1):958–67.

6. Bach PB, Brown C, Gelfand SE, et al. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001;134(7):600–20.

7. Patil SP, Krishnan JA, Lechtzin N, et al. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. Arch Intern Med 2003; 163(10): 1180–6.

8. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonay disease. N Engl J Med 1995; 333(13):817–822.

9. Kramer N, Meyer TJ, Meharg J, et al. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 1995; 151(6):1799–1806.

10. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 1993; 341(8860):1555–1557.

11. Celikel T, Sungur M, Ceyhan B, et al. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest 1998; 114(6):1636–1642.

12. Plant PK, Owen JL, Elliott MW. A multicentre randomised controlled trial of the early use of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards. Lancet 2000; 355(9219):1931–1935.

13. Agarwal R, Gupta R, Aggarwal AN, Gupta D. Noninvasive positive pressure ventilation in acute respiratory failure due to COPD vs other causes:

Effectiveness and predictors of failure in a respiratory ICU in North India. Int J Chron Obstruct Pulmon Dis 2008;3(4):737-43

14. Ambrosino N, Foglio K, Rubini F, et al. Non-invasive mechanical ventilation in acute respiratory failure due to chronic airways disease: correlates for success. Thorax 1995;50(7):755–7

15. Marti S, Munoz X, Rios J et al. Body weight and comorbidity predict mortality in COPD patients treated with oxygen therapy. Eur Respir J 2006;27(4) :689-96.

16. Jolliet P, Abajo B, Pasquina P, et al. Non-invasive pressure support ventilation in severe community acquired pneumonia. Intensive Care Med 2001;27(5):812–21.

17. Hussain S.F., Irfan M., Naqi Y.S. Acute respiratory failure in Pakistani patients: risk factors associated with mortality . J Coll Physicians Surg Pak 2006 ;16(4): 287-290.

18. Juan G, Calverley P, Talamo C, et al. Effect of carbon dioxide on diaphragmatic function in human beings. N Engl J Med 1984;310(14): 874–9.

Original Article

Low Pulmonary Function in Petrol Pump Workers in Trivandrum City

Gayatri B. Nair [1], Nila Surendran [1], Anjaly Mohan [1], Sanjeev Nair [2], Vijayakumar K. [3], Anitha Kumari K. [2]

1 MBBS Student, Government Medical College, Trivandrum
2 Department of Pulmonary Medicine, Government Medical College, Trivandrum
3 Department of Community Medicine, SMCSI Medical College, Trivandrum

Correspondence : Gayatri B Nair, 186/A, Swathi Nagar 5, Pippinmoodu, Trivandrum - 695005

Key words : Petrol pump workers, Pulmonary function, Trivandrum, Kerala

Abstract

Background : Petrol pump employees are constantly exposed to petroleum vapours and vehicular exhaust. This causes various health problems, particularly in the lungs. Although studies have been conducted in other parts of the country on lung function in petrol pump workers, none have been published from Kerala. This study aims at determining whether these workers in Kerala have any abnormality in pulmonary function.

Objective : To determine whether the pulmonary function (as measured by Forced Expiratory Volume in 6 seconds (FEV_6)-% predicted, Forced expiratory volume in first second(FEV_1)-%predicted and ratio of FEV_1 to FEV_6 (FEV_1/ FEV_6 ratio)) is different in petrol pump workers as compared to age-sex matched controls in Trivandrum.

Method : Cross sectional study. Study population consisted of 30 petrol pump workers who have been working for more than one year and 30 age-sex matched individuals from various residential areas in Trivandrum. Height, weight, smoking index, history of asthma were recorded. The parameters, FEV_6%-predicted, FEV_1%-predicted and the FEV_1/FEV_6 ratio were assessed using a handheld spirometer. The study was conducted from July to October 2013.

Result : Petrol pump workers and controls selected from general population were comparable for height, weight, smoking index and history of asthma. The median values (with inter quartile range) of FEV_6%-predicted in petrol pump workers and general population were 77.5(67-87) and 87(82-91) respectively; of FEV_1%-predicted were 78 (66-88) and 86 (78.6-89.7) respectively and FEV_1/FEV_6% were 82.5 (80-87) and 82.5(79-86) respectively. The difference in the median FEV_1%-predicted and FEV_6%-predicted between petrol pump workers and general population were statistically significant. Proportion of Petrol pump workers with FEV_1%-predicted and FEV_6%-predicted below 80% and FEV_1/FEV_6% below 70% were higher and the difference in proportions was statistically significant.

Conclusion : Petrol pump workers have a lower lung function in terms of FEV_1%-predicted and FEV_6%-predicted. The FEV_1/FEV_6 ratio was not statistically significantly different between petrol pump workers and general population even though the proportion with a FEV_1/FEV_6 ratio less than 70% was significantly higher in petrol pump workers.

Introduction

With urbanisation and rapidly increasing number of automobiles in most of the towns and cities, there is an increase in air pollution.Health effects of occupational exposure to petroleum vapours and air pollution from vehicular sources is less explored among petrol pump workers. Petrol or gasoline is a complex combination of hydrocarbons. 95% of components in petrol vapour are aliphatic and acyclic compounds and less than 2% are aromatics. The benzene content of petrol is in the range 1–5%[1].

Petrol pump is a place where workers are exposed to both petroleum vapours and the vehicular exhaust. The combined effects of the two may result in impairment in pulmonary function.

Petrol pumps in India rather than being self serviced, employ workers, increasing the opportunity for exposure. Long-term exposure to petrol vapour has shown to affect the different physiological systems in the body. To meet the present day requirement, there are many petrol pumps getting established and there is an increased recruitment of workers. Because of the predominant role of petrol (gasoline) as a motor vehicle fuel, the effects of gasoline engine emissions pose even greater problems.

Similar studies have been done in other states of India, but no studies have been published yet from Kerala. Since Kerala is a highly literate state, with greater heath awareness, the authors wanted to determine if the petrol pump workers in Kerala had any abnormality in their pulmonary function. The present study attempts to evaluate the changes in Pulmonary Function Test (PFT) of petrol pump workers as compared to age and sex matched individuals in Trivandrum City.

Specific objectives of the study were to determine whether the following pulmonary function tests - FEV_1 as percent of predicted, FEV_6 as percent of predicted and FEV_1/ FEV_6 ratio is different in petrol pump workers as compared to age and sex matched individuals in Trivandrum.

Materials and Methods

The study was a cross sectional study. Study setting was petrol pumps and residential neighborhoods in Trivandrum. The study period was from July to October 2013. The sample size was calculated using the formula for difference in means (with results of similar studies done previously) and was found to be 13. However, as per the statistician's advice, the sample size was fixed as 30 petrol pump workers and 30 age-sex matched individuals, amounting to a total of 60.Petrol pump workers who have been working for more than one year were included in the study.Those not willing to give consent were excluded. Age-sex matched individuals were recruited from various residential areas in Trivandrum. Departmental ethics clearance was obtained from the Department of Community Medicine, Trivandrum Medical College as per institutional ethics committee norms. Verbal informed consent was obtained from all the participants of the study. Subject confidentiality was ensured.

Data Collection

Study tool used was a handheld portable computerised spirometer. The subjects were familiarised with the setup and detailed instructions were given. Tests were performed in a standing position. The subjects were asked to breathe forcefully following deep inspiration into the mouthpiece attached to the spirometer. Expiration was maintained for a minimum period of 6 seconds, at least three acceptable trials were made and the highest reading obtained was taken for analysis. The absolute values of Forced Expiratory Volume in six seconds(FEV_6) (taken as surrogate for Forced Vital Capacity), Forced Expiratory Volume in the first second (FEV_1) and FEV_1/FEV_6; and the percentage of predicted for the first two were recorded.

The instrument used was Vitalograph COPD-6, model 4000. The instrument was validated in the Trivandrum scenario and Cronbach's alpha value was found to be 0.81 and 0.75 for the parameters FEV_1 and FEV_6 when compared to a full spirometer[2].

Statistical Analysis

Data was entered into Microsoft Excel and analyzed using EpiInfo 7 (©CDC Atlanta).Quantitative variables were expressed as mean (SD) and qualitative variables as proportions. The 'percent of predicted' values of FEV_1, FEV_6 and the absolute values of FEV_1 / FEV_6 were compared between the petrol pump workers and the controls. These variables were tested for significance using the Kruskal-Wallis H test. The other quantitative variables like age, height, weight and smoking index were compared using the student t test and the chi square test was used to compare qualitative variables (proportions). A p-value of less than 0.05 was considered significant.

Results

Petrol pump workers and controls from general population were found to have no difference in parameters like age, sex, height, weight, history of asthma and smoking and shown to be adequately matched. [Table no 1]. The median percent of predicted values for FEV_1 and FEV_6 were statistically significantly lower in petrol pump workers as compared to controls whereas the median FEV_1/FEV_6 ratio was not significantly lower [Table no 2]. Proportions of patients with percent of predicted values for FEV_1 and FEV_6 below 80% and FEV_1/FEV_6 ratio below 70% which could indicate obstructive lung pattern were determined. [Table no 3]. Relative risk for Percentage-predicted-FEV_1 and Percentage-predicted-FEV6 less than 80% was 1.83 (95%CI 1.1, 3.04) and 2.43 (95%CI 1.49, 3.96) respectively and for proportion of FEV_1/FEV_6 less than 70% was significant (p value 0.01). Logistic regression was done for factors associated with low FEV_1, and low FEV_6, including age, sex, height, weight, past history of Asthma and smoking in the models and the adjusted odds were still found to be statistically significant.

Table 1 :

Baseline Characteristics of petrol pump workers and general population

Baseline Characteristic	Petrol Pump Workers (30)	General Population (30)	p Value
Age (yrs)	42.27 (±14.68)	40.57(±14.69)	0.66
Sex (F)	7 (23%)	8 (26%)	0.77
Height (cm)	165.07(±7.45)	165.57(±6.85)	0.79
Weight (kg)	65.07(±8.79)	66.72(±6.65)	0.41
History of asthma (Y)	2 (6%)	1 (3%)	0.55
History of smoking(Y)	9 (30%)	6 (20%)	0.37
Smoking Index (pack years)	0.71(±1.54)	0.72(±1.79)	0.99

* Numerical variables expressed as mean (± standard deviation) and categorical variables expressed as number (%).

* Numerical variables tested for significance using students t test and categorical variables compared using chi square test.

Table 2 :

Lung function of petrol pump workers and general population

Pulmonary Function parameter	Petrol Pump Workers (30)	General Population (30)	p Value*
FEV_1% predicted	78 (66-88)	86 (78.6-89.7)	0.005
FEV_6% predicted	77.5 (67-87)	87 (82-91)	0.003
FEV_1/FEV_6%	82.5 (80-87)	82.5 (79-86)	0.739

* Values in %, expressed as median (Inter-quartile range)

* Kruskal-Wallis H test

Table 3 :

Proportion of subjects with abnormal values of lung function parameters

PFT Value	Petrol Pump Workers (30)	General Population (30)	p Value*	RR (95% CI)*
FEV_1% predicted <80%	17(56.67%)	8(26.67%)	0.018	1.83 (1.1, 3.04)
FEV_6% predicted <80%	17(56.67%)	4(13.33%)	<0.001	2.43 (1.49, 3.96)
FEV_1/FEV_6% <70%	6(20%)	0(0%)	0.011	Undefined

* OR – Relative risk; 95% CI – (95% confidence interval)

* Chi square test was used for comparison

Discussion

Similar studies were conducted in petrol pump workers and general population of Mysore, Kancheepuram, Delhi and Jammu[3,4,5,6]. These studies also showed significant lowering of PFT values except FEV_1/FEV_6 ratio in petrol pump workers.We have obtained similar results in Trivandrum i.e. both the FEV_6%predicted and FEV_1% predicted are significantly lower in petrol pump workers as compared to the general population but the absolute val-

ues of FEV_1/FEV_6 ratio were not statistically significantly different in petrol pump workers as compared to controls. However 20% of petrol pump workers were seen to have obstructive lung pattern i.e. FEV_1/FEV_6 ratio < 70% whereas none among the general population had FEV_1/FEV_6 ratio <70%, this difference in proportions was statistically significant (p=0.011). This obstructive pattern among the petrol pump workers (20%) is possibly explainable by the vehicular exhaust and fumes [7,8]. Automobile emissions are known to enhance airway response to inhaled allergens in suceptible subjects and vehicular fumes can also result in COPD in such subjects.

Petrol constituents (hydrocarbons) are the source of exhaust. However petroleum hydrocarbons have been shown to have a different effect on the lung. They cause an increase in lung tissue malondialdehyde (MDA), an index of lipid peroxidation. They also cause decrease in glutathione content and activities of superoxide dismutase. Hence a lowering of antioxidant activity is seen. All these cause oxidative stress which causes loss of cell and tissue integrity. This could explain the edema and hemorrhagic necrosis of lung tissue following exposure to petroleum hydrocarbons. Studies have reported that exposure to petroleum hydrocarbons impairs type II pneumocytes resulting in a decreased production of surfactant and consequent alveolar collapse, ventilation-perfusion mismatch, and hypoxemia. This ultimately leads to hemorrhagic alveolitis, interstitial inflammation, intra-alveolar hemorrhage and edema, hyperemia, bronchial necrosis, and vascular necrosis which leads to defective lung parenchyma and causes a restrictive pattern[9].

In this study also FEV_1 and FEV_6 percentage of predicted values are statistically significantly lowered. FEV_1/FEV_6 values did not show any statistically significant lowering, even though the porportion of those with values less than 70% was different between the two groups.About 20% of petrol pump workers had obstructive pattern on spirometry. Workers have exposure to vehicle fumes thereby leading to probable COPD.The restrictive changes indicate some form of parenchymal lung damage, which needs to be further evaluated. Further tests including body plethysmography, DLCO measurement and HRCT in cases with higher degree of restriction, may provide further information on the pattern of lung damage in these patients and whether these changes indicate early interstitial lung disease. Such evaluation would also lead to findings which will lead to providing information on safety measures needed for the petrol pump workers.

Recommendations

Obstructive and restrictive lung pattern suggest that workers may be given protective masks to escape petrol vapour and vehicular exhausts. However further studies, as described above need to be done to determine if dust masks, which provide protection against fine particulate matter or half/full facepiece gas masks/chemical cartridge respirators, which filter and clean chemical gases and particles out of the air, are more appropriate for these workers[10]. Periodic health checkups of workers may be planned to identify those at risk early and provide them with alternative career options. Also, they can be educated about additive risk factors (like smoking) that may aggravate their risk of developing lung pathologies[11].

Limitations

Lung function was measured using a portable hand held spirometer. The community controls were not chosen from the same community as that of the petrol pump workers, so there could be potential confounders. While a history of Asthma was elicited, detailed clinical examination for other diseases like COPD or other respiratory illnesses, were not done and other investigations like a chest skiagram were not obtained.

Conclusion

FEV_1%-predicted and FEV_6%-predicted are significantly lower in petrol pump workers compared to age and sex matched controls whereas FEV_1/FEV_6 ratio was not significantly lower even though the proportion of those with FEV_1/FEV_6 ratio less than 70% was higher.The proportion of those with subnormal lung function were more in petrol pump workers and the difference was statistically significant between the two groups for all three parameters.

Acknowledgement

Our sincere gratitude to the Association of petrol pumps owners for giving us permission to conduct our study in the petrol pumps. We also acknowledge the research training provided by the Department of Community Medicine, Medical College, Trivandrum, which lead to this research being taken up and to the Department of Pulmonary Medicine, Medical College, Trivandrum for providing technical and clinical support.

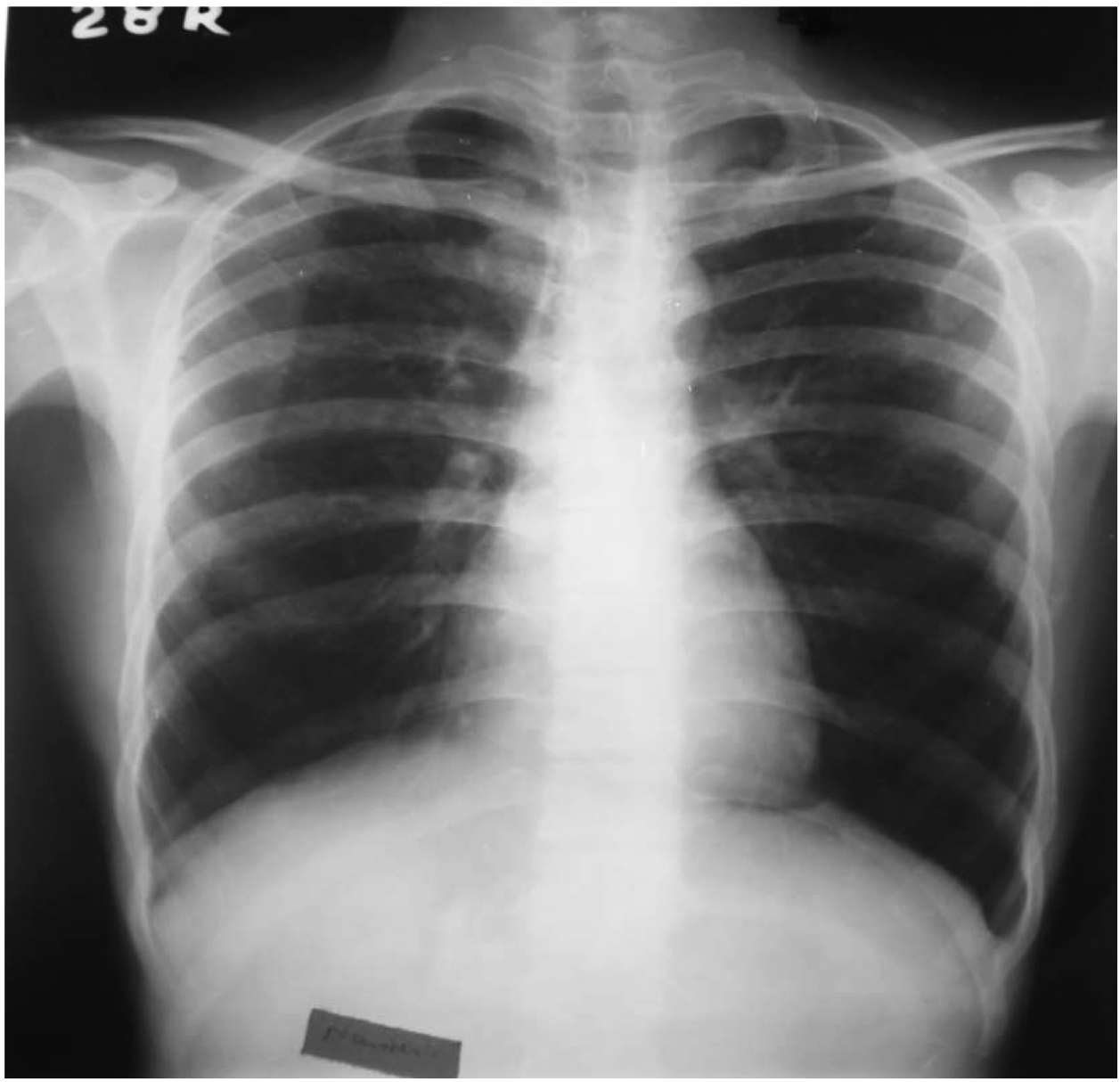
References

1. Chilcott Petrol – Toxicological overview. Version 2. Chemical Hazards and Poisons Division, Chilton, Didcot, Oxfordshire, United Kingdom; 2007.
2. Kavithai P. Unpublished data – Personal communication. Prevalence of obstructive lung diseases among school children; 2014.
3. Madhuri BA, Chandrashekhar M, Kondam A, et al. A study on pulmonary function tests in petrol pump workers in Kancheepuram population. Int J Biol Med Res 2012; 3(2):1712-1714.
4. Begum S, Ratna MB.Pulmonary function tests in petrol filling workers in Mysore city. Pak J Physiol 2012; 8(1): 12-14.
5. Singhal M, Khaliq F, Singhal S,et al. Pulmonary functions in petrol pump workers : A preliminary study. Indian J Physiol Pharmacol 2007; 51 (3) : 244–248.
6. Sharma N, Gupta N, Gupta R. Ventilatory Impairment In Petrol Pump Workers. JK Science January-March 2012; 14(1) : 5-8.
7. PihlavaT, UuppoM,Niemmi S.Health effects of exhaust particles. University of VAASA, Finland; 2012.
8. Environment and human health, Inc. North Haven, Connecticut. The harmful effects of vehicle exhaust: A Case for Policy Change 2006; 14-16.
9. Azeez OM,AkhigbeRE, AnigboguCN. Exposure to petroleum hydrocarbon : Implications in lung lipid peroxidation and antioxidant defense system in rat. Toxicol Int 2012; 19(3): 306-309.
10. Occupational Safety and health administration. Respiratory Protection (Revised)U.S. Department of Labor; 2002.
11. Action on Smoking and health. Smoking and respiratory disease. ASH, UK; February 2011.

Radiology Pearl

Rare Presentation of a Common Disease

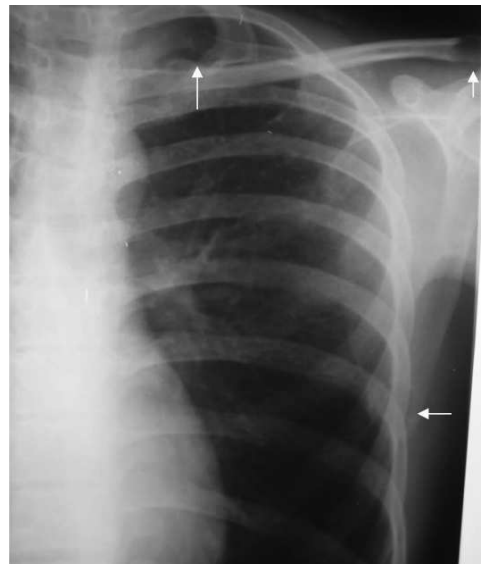
Soumya V. K.*, Sabir M. C.**
*Senior Resident, Dept. of Pulmonary Medicine, Govt. Medical College, Kozhikode.
**Consultant Pulmonologist, BMH, Kozhikode



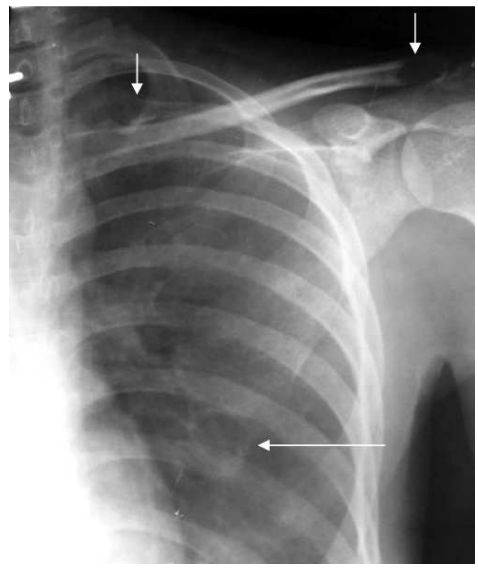
This 20 years old male patient was under evaluation in Orthopedic department for arthritis Left knee and Right wrist. He was referred to Pulmonary Medicine OPD for evaluation of recurrent cough, dyspnoea on exertion grade II and low grade fever of 1 month duration. Any clue in chest X ray pointing to the diagnosis.

Answer

Chest X ray showed lytic lesions in lateral end of left clavicle, left 3rd rib posterior end and inferior angle of left scapula.



X Ray PA – close up focusing lesion



AP view- clearly delineate lesion

On evaluation Tuberculin test was positive with an induration of 18 mm and ESR was 110 mm in 1 hr. CT Thorax confirmed lytic lesion in left 3rd rib, scapula and clavicle with random nodules bilateral upper lobes, ground glass opacity and paraaortic lymphadenopathy. Synovial biopsy from Left knee joint revealed granuloma and synovial fluid AFB culture (BACTEC) showed growth of tubercle bacilli. Patient was diagnosed to have disseminated tuberculosis and was started on anti-tuberculosis treatment. There was good response to treatment.

Case Report

Lung Cancer presenting as Central Diabetes Insipidus

Arjun P. [1], Ajithkumar B.V. [2], Roshni Syam [3], Madhavan Unni [4], Biji K. A. [5], Mathew Thomas [6]

1. Sr. Consultant & Coordinator, Pulmonary Medicine, 2. Consultant Endocrinologist, 4. Professor & Head, Dept. of Radiodiagnosis, 5. Consultant Pathologist, 6. Professor & Head, Dept of Internal Medicine, Kerala Institute of Medical Sciences (KIMS) Trivandrum, Kerala. 3. Consultant, Chest & Gastro Oncology, Regional Cancer Centre, Trivandrum, Kerala

Abstract

A 62 year old smoker on evaluation of polyuria was detected to have central diabetes insipidus. On detailed workup he was diagnosed to have a mass lesion in the lung, although he did not report as having any respiratory symptoms. Further workup confirmed the diagnosis of Non Small Cell Lung Cancer (Adenocarcinoma). An extensive metastatic workup was done which revealed that apart from the loco-regional spread, the only extra thoracic metastasis was to the posterior pituitary. This is a very rare presentation of an isolated secondary malignant deposit of adenocarcinoma of lung to the posterior pituitary.

Key words : Diabetes Insipidus, Bronchogenic Carcinoma

Introduction

Diabetes insipidus is a very rare presentation of lung cancer. Herein we present the case of a 62 year old smoker, who presented with polyuria, and on evaluation was found to have central diabetes insipidus due to metastasis to the posterior pituitary from a non-small cell lung cancer from the right upper lobe of the lung. There are two unique features in this case: the only metastatic deposit outside the thoracic cavity was in the pituitary and despite having a mass in the lung, he was totally asymptomatic. This case is being reported to highlight these two aspects. To the best of our knowledge no similar case has been reported in the literature.

Case Report

A 62 yr old man presented to the urology OP of our hospital with symptoms of polyuria and increased thirst of two months duration. He had normal renal functions, electrolytes and a stag horn calculus in the right kidney revealed by tests done from outside. The post void residual urine was 80ml. He was referred to the endocrinologist for further evaluation. There was no history of diabetes mellitus, systemic hypertension or psychiatric illness. He was a smoker (20 pack years) and used to take alcohol three days a week. There was no history of head ache or visual symptoms. There were no symptoms pertaining to any other system.

On examination he was euvolumic. General examination did not reveal any abnormality. His pulse rate was 76/minute and the blood pressure was 140/90 mmHg. There was no goiter. His cardiovascular and respiratory systems were normal on examination. Abdomen was soft, no mass was palpable. Neurological examination was also normal. There were no visual defects. Basic investigations including complete blood count, urine and stool examination, hepatic and renal parameters were normal. TSH, sodium, potassium, calcium, phosphorus, and bicarbonate were also normal. The urine specific gravity was normal. Urine osmolarity was 105 milli osmol/kg of water. Serum osmolarity was 296m osm/kg water. In view of the pres-

ence of a stag horn calculus, a nephrogenic diabetes insipidus was considered as the clinical probability and hydrochlorothiazide was started at a dose of 12.5 mg and later increased to 25mg/day. He was followed up in the endocrinology clinic. He was asked to measure the intake of fluids and urine volume at home.

After two weeks of hydrochlorothiazide therapy, he was still symptomatic with polyuria and polydipsia persisting. His blood pressure was 120/84 mmHg. Serum sodium was 146mmol/L. In view of the persisting polyuria he was admitted for reassessment, and considering central diabetes insipidus as a possibility, a water deprivation test was planned. (Table1). He was admitted in the evening of the day before the test and fluid intake was avoided from midnight to promote overnight dehydration.

(Fig 1). The pituitary was also bulky. The bright spot was missing. There was also an altered tissue signal intensity of the posterior pituitary.

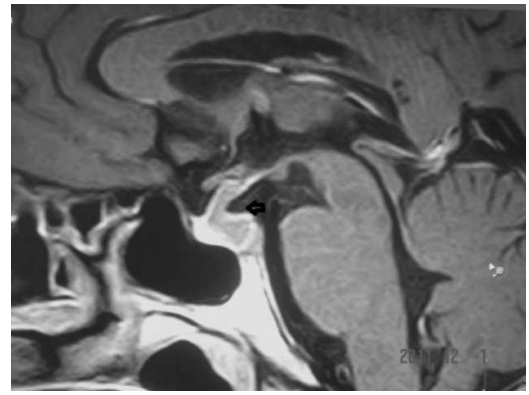


Fig 1 : Magnetic resonance Imaging showing thickening of the pituitary stalk and absence of the bright spot (Arrow head).

Table 1 :

	12 am	8 am	9 am	10 am	11 am	12 pm	1 pm	2 pm
Wt	73	70	70	72	72	72	74	74
BP	140/80	130/80	130/90	130//80	120/70	120/70	120/70	126/70
Urine Output (ml)	200	80	100	500	300	50	200	100
Urine osmol	139		305	295	327	557	591	-
Serum osmol	296	304	-	316	-	-	-	-
Serum Na	136	150	-	150	151	148	146	141

The urine output was 2030 ml between 12 am and 8 am on that day, without any fluid intake which resulted in hypertonic dehydration. In the morning he complained of extreme thirst, with weight loss of ~2% but remained hemodynamically stable. Investigations revealed hypertonic dehydration (Serum Na of 150 mmol/L, Serum osmolarity of 316 milliosmol/Kg of water), with dilute urine (osmolarity of 295 milliosmol/Kg of water). After confirmation of the presence of hypertonic dehydration, he was given injection Argenine Vasopressin (AVP): 5 units subcutaneously at 10:20 am and there was resultant rise of urine osmolarity of approximately 100%. This established the diagnosis of central diabetes insipidus. He was started on DDAVP nasal spray 1 puff (10 micro grams) twice daily, after which his symptoms and urine output dramatically improved and reached normal. Magnetic resonance imaging of the brain revealed thickening of the pituitary stalk

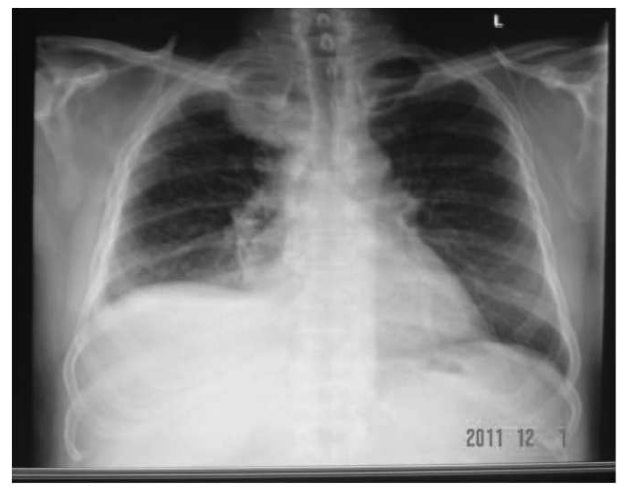


Fig 2: Chest X Ray PA view showing a mass lesion in the right upper lobe

He was worked up for all possible causes of central diabetes insipidus. A chest X Ray PA view (Fig 2) revealed the presence of a mass lesion in the right upper lobe although he denied having any symptom pertaining to the respiratory system. 3 consecutive smears for acid-fast bacilli were negative as were 5 consecutive smears for malignant cells in sputum. A tuberculin test was done which did not show any induration after 48 hours of administration. Further workup included thoracic imaging by a Computerised Tomogram, which in addition to the right upper lobe mass, showed the presence of multiple mediastinal nodes and ipsilateral pleural effusion (Fig 3

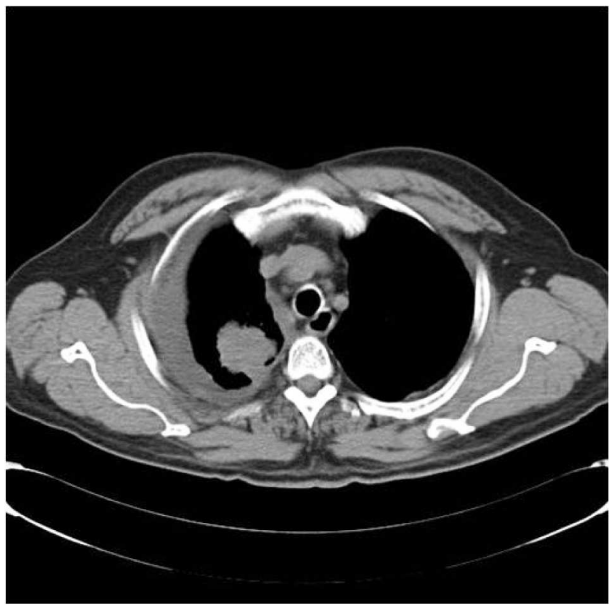


Fig 3: CT thorax showing the presence of a right upper lobe mass and pleural effusion

He underwent a flexible bronchoscopy, which did not show any intraluminal pathology. Specimen obtained from bronchial brushings and broncho-alveolar lavage (BAL) from the right upper lobe were all negative for malignant cells and acid fast bacilli. A transbronchial biopsy was attempted from the right upper lobe bronchus but yielded only normal lung tissue. Transbronchial needle aspiration was attempted from two sites – right lower paratracheal (Station 4) and sub-carinal lymph nodes (station 7). The material obtained from these sites showed presence of occasional atypical cells. A pleural tap was done, which yielded about 15 ml of hemorrhagic fluid, which satisfied the criteria for an exudative effusion (protein 5.5g%, sugar 90mg%). Pleural fluid cytology revealed the presence of adenocarcinoma cells (Fig 4). Immunohistochemistry with TTF1 was done on the cell block prepared from the sediments of pleural fluid after centrifuging. TTF-1 (Thyroid transcription factor-1) is a highly specific marker for primary pulmonary adenocarcinoma and thyroid malignancy. TTF1 was strongly positive on the cell-block sections. As there was no features of thyroid malignancy even after detailed evaluation the primary in our patient should be from the lungs. A final diagnosis of Non Small Cell Lung Cancer with posterior pituitary metastasis producing central diabetes insipidus was made. A complete metastatic work up was done including bone scan and abdomen scan, which did not show the presence of any metastatic deposit elsewhere. He was referred to Regional cancer Centre, Trivandrum for further management. He was started on whole brain radiation and was advised chemotherapy. Within a week, he developed intense breathlessness and was found to have developed a massive right sided pleural effusion. The fluid was drained using an intercostal drain and subsequently pleurodesis was done using bleomycin. He was then started on chemotherapy with carboplatin and gemcitabine. Two months later on follow up he has shown significant improvement in terms of reduction of polyuria and breathlessness.

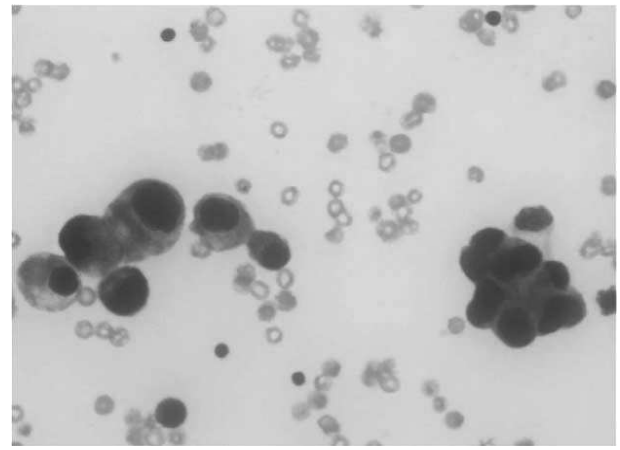


Fig 4: Pleural fluid cytology showing presence of adenocarcinoma cells (May Grunwald Giemsa, 40X)

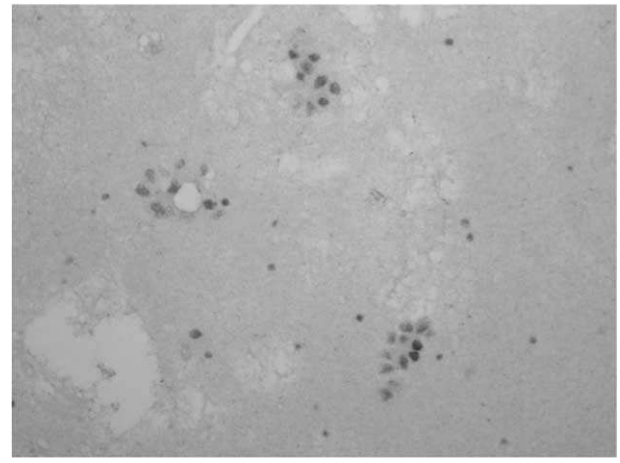


Fig 5: Immunohistochemistry on pleural fluid cell block showing Thyroid Transcription Factor-1 (TTF-1) positivity (20X)

Discussion

Tumour metastasis to the pituitary gland is a very rare phenomenon in systemic malignancy[1]. It has been documented in 1 – 3.6% of patients with malignancy[2]. Breast cancer and lung cancer are the most common malignancies that are described to metastazise to the pituitary. In lung cancer, it is the Non small cell lung cancer (NSCLC) that has a propensity to metastzise to the pituitary[3]. Metastasis are more frequently seen in the posterior pituitary than anterior and this posterior localization is attributed to the fact that the posterior lobe receives direct blood supply from the systemic circulation, whereas the anterior lobe is supplied by the hypophysial portal system[1].

Pituitary metastasis are usually asymptomatic, and symptoms are seen in only less than 10% cases[4]. Patients usually remain asymptomatic since they die from advanced complications of the primary neoplasm. Most common symptoms include diabetes insipidus, headache, visual defects, ophthalmoplegia, retro-orbital pain and anterior hypopituitarism. Of these the most frequent presentation is with diabetes insipidus since the posterior pituitary is predominantly involved[1] . The incidence of metastasis producing diabetes insipidus is 5-14% [5]. In contrast, diabetes insipidus is seen only in 1-2% of patients with pituitary adenoma and this forms an important criterion to distinguish between these two[6]. Involvement of posterior pituitary is usually seen as part of disseminated disease and patients usually have evidence of metastasis elsewhere, in particular osseous metastasis by the time they develop diabetes insipidus.

Magnetic Resonance Imaging (MRI) along with clinical findings forms the basis of diagnosing pituitary metastasis. MRI also helps to differentiate metastasis from adenomas. Radiological features suggestive of metastasis include (a) Thickening of the pituitary stalk (b) loss of a high intensity signal from the posterior pituitary (c) isointensity on T1 and T2 weighted MRI images (d) invasion of the cavernous sinus and (e) sclerotic changes around the sella tursica[2].

Treatment options for patients with pituitary metastasis include surgical resection, chemotherapy and radiotherapy[2]. There is no difference in survival between surgical and non-surgical treatment. The overall prognosis is poor since the primary tumour is very aggressive and mean survival time is usually 6-7 months depending on the primary tumour[1].

In our case, there are two distinct standout features. Firstly, although the patient had a mass lesion in the lung, he surprisingly did not have any symptom pertaining to that at all. Secondly, apart from spread to adjacent mediastinal nodes and to the pleura, the only other area to where the tumour had metastasized was to the posterior pituitary. There were no bony or intra-abdominal metastatic deposits. To our knowledge, no such case has been documented in literature. Also no cases of lung carcinoma with posterior pituitary metastasis have been reported from India till date. All these features make our case very unique indeed.

References

1. Chen CW, Chiang YH, Chen CY et al: Pituitary metastasis from bronchogenic carcinoma. J.Med Sci, 25:153-156,2005

2. Fasset DR, Couldwell WT: Metastasis to the pituitary gland. Neurosurg Focus, 12:1-4,2004.

3. Murren JR, Turrisi AT, Pass HI: Small cell lung cancer. In: Cancer: Principles and practice of oncology, 7th ed, DeVita VT, Hellman S, Rosenberg SA (Eds), p 812, Lippincott-Williams & Wilkins, Philadelphia, 2005.

4. Karamouzis MV, Melachrinou M, Fratzoglou M et al: Hepatocellular carcinoma metastasis in the pituitary gland: case report and review of the literature. J Neurooncol, 63: 173-177, 2003.

5. Houck WA, Olson KB, Horton J: Clinical features of tumor metastasis to the pituitary. Cancer 26: 656-659,1970.

6. Schubiger O, Haller D. Metastases to the pituitary-hypothalamic axis. An MR study of 7 symptomatic patients. Neuroradiology 1992;34:131-134.

Case Report

An Unusual Cause of Dysphagia

Shamini P. H. [1], Santhosh Kumar P. V. [2], Anandan P. T. [3], Sunny George [3]
1. Junior Resident, 2. Additional Professor, 3. Associate Professor; Dept. of Pulmonary Medicine, Govt. Medical College, Kozhikode.

A forty nine year old female housewife, presented to us with cough, dyspnoea on exertion, right sided chest pain, dysphagia of 3 weeks duration and hemoptysis of 5 days duration. Her complaints started as cough, which was productive with moderate amount of mucoid sputum, with no postural or diurnal variation. She had dyspnoea, which was grade 2 in severity and non progressive with right sided continuous, dull aching type of pain which gets radiated to back of upper chest. She found it difficult to swallow liquids more than solids for the past 3 weeks. She was having hemoptysis, about 30 ml of blood with clots for the initial 2 days and later became streaky. She did not give any history of fever, loss of weight, hematemesis, melena, hoarseness of voice or stridor. She had history of pulmonary tuberculosis 20 years back, for which she took anti-tuberculosis treatment. She also gave history of allergic symptoms with recurrent respiratory tract infections for the last 15 years, with 1 episode of hemoptysis 10 months back. There was no previous history of diabetes mellitus, hypertension or coronary artery disease.

On examination, she was moderately built and nourished, vitals were stable. On respiratory system examination, there was tracheal deviation to right side with apex beat in normal position, increased tactile vocal fremitus over right supraclavicular, infraclavicular and suprascapular areas, with an impaired note on percussion, increased vocal resonance and a bronchial breath sound heard over above said areas. Other system examination was within normal limits.

Her routine blood investigations showed a hemoglobin of 9.8 gm% , with a raised ESR of 62mm/hr. Her sputum AFB was negative and Tuberculin skin test with 5 TU was non-reactive. Chest X-ray revealed a homogenous opacity in the right upper zone with well-defined upper, lateral and lower borders and medial border not clearly demarcated (fig 1) with an air-crescent. So we suspected cavity with fungal ball and proceeded with CT Thorax, which showed bronchiectasis in anterior basal segment of left upper lobe and posterior segment of right upper lobe, dilated esophagus in the upper thoracic region and right apical fibrosis – post tuberculosis sequelae (fig 2). In view of her dysphagia, a barium swallow X ray was obtained, which revealed a wide-mouthed traction diverticuli with air-fluid level arising from posterolateral wall of esophagus, which is seen to fill with orally administered contrast, from the level of T1 to T4 vertebra. Contrast is seen to empty partially. No evidence of free spillage into tracheobronchial tree, pleural space and mediastinum (Fig 3).

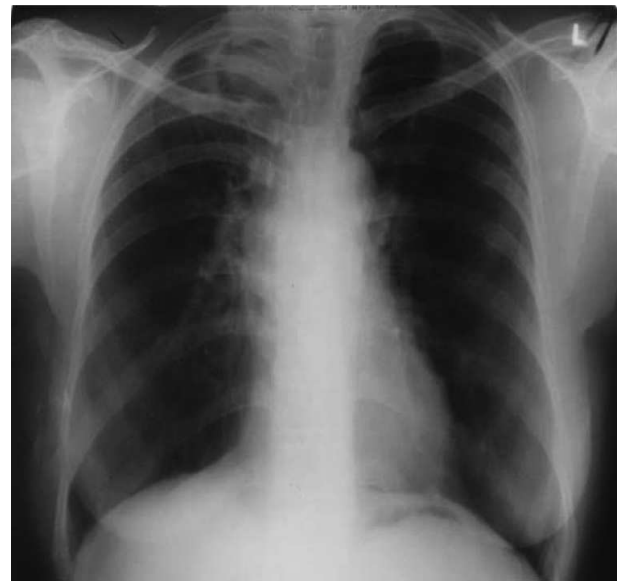


Fig 1 : Chest Xray

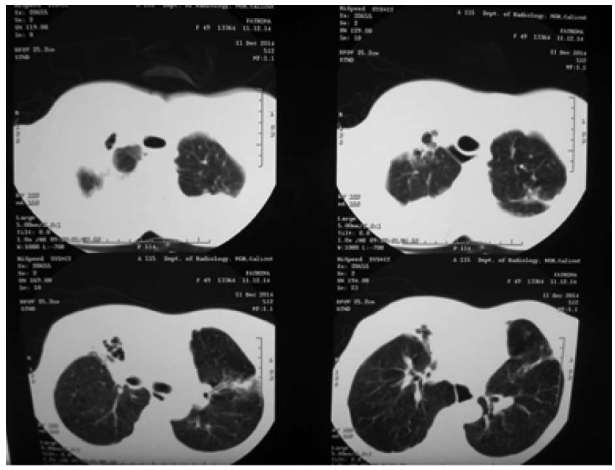


Fig 2 : CT Thorax

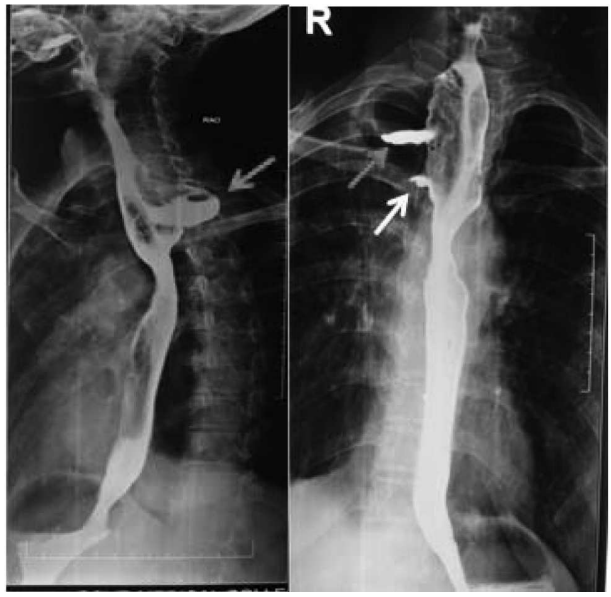


Fig 3 & 4 : Barium swallow

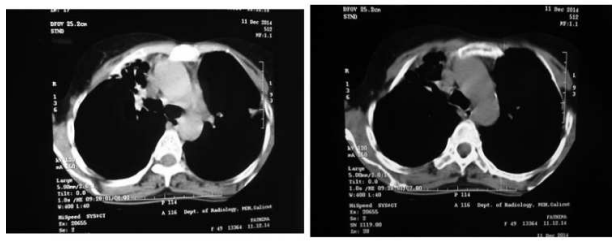


Fig 5 & 6 : CT Thorax

We proceeded with a gastrosurgery consultation and was advised conservative management only. So we came to a final diagnosis of bilateral bronchiectasis – secondary infection, right apical fibrosis, traction diverticuli esophagus, post tubercular sequelae. She was managed with antibiotics, bronchodilators and other supportive measures. She responded to the treatment and got discharged after 1 week.

Discussion

A diverticulum is a sac or pouch arising from a tubular organ. An out pouching of mucosa through muscular layer of esophagus is known as esophageal diverticulum. It can be classified into

- Congenital / acquired.
- True / false
- Pharyngoesophageal / midesophageal/ epiphrenic

Acquired diverticulum

Pulsion : Due to high intraluminal pressures against weakness in the GI tract wall leading to herniation of mucosa through defects in muscular layer. It is a false diverticulum.

Eg :Zenker's diverticulum

Traction : Due to pulling forces on the outside of esophagus from an adjacent inflammatory process. It is a true diverticulum.

Eg : TB , Histoplasmosis.

Mid esophageal diverticulum

Also known as Parabronchial diverticulum. It was first described in 19th century. Historically inflamed mediastinal lymphnodes from an infection with TB accounted for most cases. Most common in the middle 1/3rd of thoracic esophagus. Other causes include histoplasmosis, fibrosing mediastinitis. Resultant desmoplastic reaction in para-esophageal tissue causes full thickness pinching on esophageal wall, producing a conical, broad-mouthed true diverticulum. It often project to right side because subcarinal lymph nodes in this area are closely associated with right anterior wall of esophagus and because of over abundance of structures in mid thoracic region of left chest. This type is commonly seen in middle aged adults and elderly. Dysphagia, postural regurgitation, belching, retrosternal pain, heartburn and epigastric pain are the usual symptoms. Pulmonary symptoms include mild nocturnal cough to life threatening massive aspiration.

Diagnostic Evaluation

- It includes Chest X ray, Barium esophagogram, CT Thorax, Esophagocopy and Manometry.
- It is an incidental finding in routine imaging stud-

ies. Chest X-ray and CT thorax may show air –filled & / or fluid-filled structures communicating with esophagus. CT thorax also helps to identify mediastinal lymphadenopathy and may help to localize the sac. Barium radiography is the diagnostic procedure of choice. Esophagoscopy is done to rule out mucosal abnormalities, including cancer and identifying a fistula. Manometry helps in identifying a primary motor disorder.

Management

- Determining cause is critical. Asymptomatic with inflamed mediastinal lymph nodes from Tuberculosis/Histoplasmosis needs treatment with Anti tuberculous treatment/ Antifungal agents. If the size is <2cm, observation is the rule. If symptomatic or size ≥ 2cm, we may go for surgical intervention. The options include-Diverticulopexy / Diverticulectomy / Long esophagomyotomy.

References

1. Pearson F G , Cooper J D , Deslauriers J et al : Esophageal Surgery – 2nd edition , Churchill Livingstone Publications , Chapter 31 (507-514).

2. Brunicardi F C , Andersen D K , Billiar T R et al : Schwartz's Principles of Surgery – 9th edition , McGraw Hill Publications , Chapter 25 (803-887).

3. Townsend C M , Beauchamp R D , Evers B M , Mattox K L : Sabiston Textbook of Surgery : The Biological Basis of Modern Surgical Practice – 19th edition , volume 2 (1012-1066).

Case Report

Lung Nodules with a Saddle nose-A happy ending to a stormy course

Priya J. [1], Soumya V. K. [2], Kiran V. N. [3], Jyothi E. [4]
1. Junior Resident, 2. Senior Resident, 3. Assistant Professor, 4. Associate Professor,
Dept. of Pulmonary Medicine, Govt. Medical College, Kozhikode.

Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG), is a systemic disorder that involves both granulomatosis and polyangiitis. It is a form of vasculitis that affects small- and medium-size vessels in many organs. Here we report a case of a middle aged female who presented to us with cough, fever and dyspnoea on exertion and was diagnosed with Wegener's granulomatosis

Case Report

A 50 year old female, housewife, diabetic on oral hypoglycaemic agents presented to our department with complaints of cough with scanty mucoid expectoration, intermittent low grade fever of 2 months duration and insidious onset, progressive grade I to grade II dyspnoea on exertion(DOE) of 1 month duration. There was associated myalgia and eye pain and redness. She had loss of appetite with no documented loss of weight. Past history revealed history of recurrent episodes of mucopurulent discharge from nose with 2 episodes of epistaxis for the last 6 years. Recurrent episodes of eye pain and redness were present since 1year, the recent episode since 1 month.

On examination she was moderately built and nourished. There was no pallor, icterus, cyanosis, clubbing, lymphadenopathy, pedal oedema or elevated JVP, afebrile with stable vitals. Both eyes showed conjunctival congestion with thinned sclera and a bluish hue with developing staphyloma (Figure 1). On auscultation, bilateral fine mid to late inspiratory crackles in mammary, infra axillary and infra scapular areas were heard.

Her CXR (Figure 2) revealed bilateral nodular shadow predominantly in right mid and lower zone with both hemidiaphragms at same level. Her hemogram showed leucocytosis-12200/cumm, hemoglobin- 12.1gm% with elevated ESR 120/1st hr. She was referred to our department with a contrast enhanced computerised tomography(CECT) thorax (Figure 3) which showed bilateral nodules in the middle and lower lobes with feeding vessel sign, with no pleural effusion or mediastinal adenopathy and was referred as a case of angioinvasive metastasis/ septic emboli.

Patient was admitted and started on parenteral antibiotics, and she was worked up for connective tissue disorder and sarcoidosis. An opthalmology and ENT opinion were obtained and CT Paranasal sinus (PNS) was ordered. Her Antinuclear antibody (ANA) and Creatine phosphokinase (CPK) were negative, Rheumatoid factor was borderline elevated (47IU/mL), serum calcium – 8.4mg/dl, serum Angiotensin converting enzyme(ACE)-65U/L. There was no evidence of proteinuria, with normal renal function tests (RFT) and liver function tests (LFT). She could not raise phlegm for testing and her mantoux was 22 mm. Her DLco was 56.9ml/min/mm Hg. Fiberoptic bronchoscopy showed normal bronchial tree and transbronchial lung biopsy(TBLB) was done from Right lower lobe basal segments.

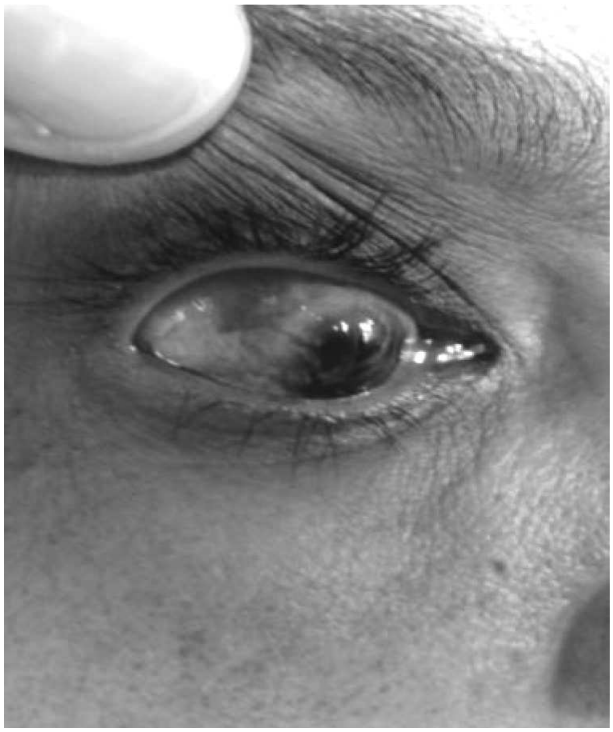


Figure 1 : Episcleritis with staphyloma

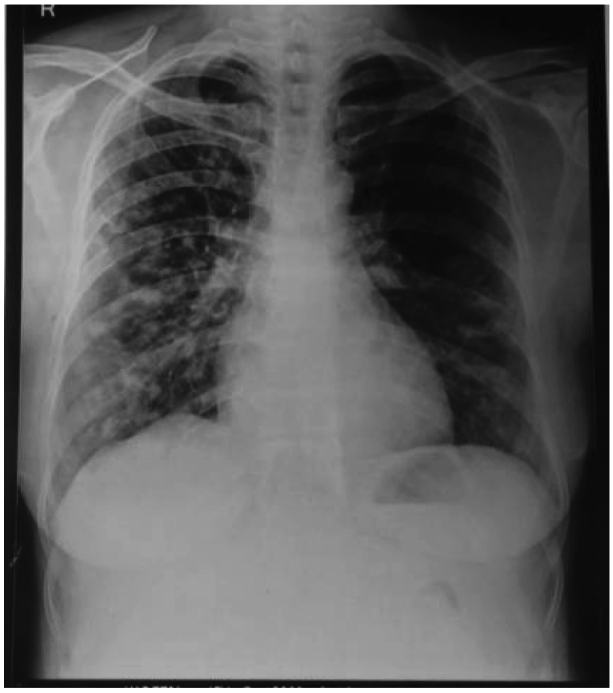


Figure 2 : Chest X ray showing multiple nodular shadows

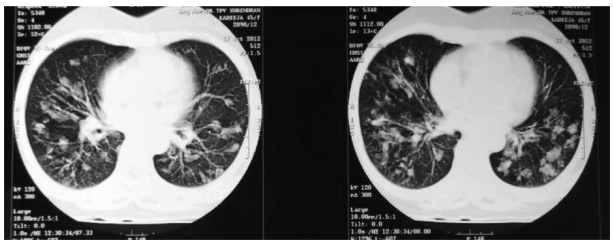


Figure 3 : CECT Thorax-Lung window

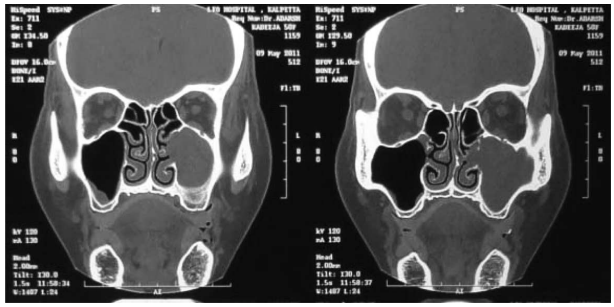


Figure 4 : CT Paranasal sinus

Ultrasound abdomen was within normal limits. Ophthalmologist suggested the possibility of connective tissue disorder in view of recurrent episcleritis. CT PNS (Figure 4) showed bilateral maxillary sinus polyps with sinusitis, bilateral frontal sinusitis and hypoplastic nasal bone. She had noticed her nasal deformity (Figure 5) for the last one and a half years.

Her recurrent episcleritis, pan sinusitis and nasal deformities with nodular shadows in the lung prompted us to do an ANCA evaluation. The reports revealed a positive c- ANCA (6.37u/ml) and negative p ANCA(1.93u/ml). TBLB showed lymphocyte infiltrate with no definite granuloma. The otolaryngologist did a Direct nasal endoscopy which showed irregular granulation like area in the posterosuperior part of nasal septal mucosa, with histopathology of the biopsy specimen revealing granulomatous inflammation.

Our patient who had nasal mucosa ulcers, saddle nose deformity, bilateral sinusitis with nasal polyp, scleritis, bilateral lung nodules with granulomatous inflammation on nasal mucosa biopsy and positive c ANCA was diagnosed to have Wegeners granulomatosis. As there was life threatening organ involvement in the form of vision impairment it was a severe form.

As she had severe life threatening disease, she was started on high dose steroids, Cotrimoxazole 960 mg OD thrice a week and pulse Cyclophosphamide infusion was suggested. Dramatically as the patient was being hydrated for cyclophosphamide infusion she collapsed in the ward with bradycardia and hypotension. Noting an elevated JVP with no increase in the distribution of crackles a right heart infarction was clinically diagnosed with the Electrocardiogram (ECG) showing inferior wall myocardial infarction (IWMI) with Right Ventricular Infarction and Complete heart block (CHB). All emergency and supportive treatment was started and in view of a short window period, she was immediately considered for primary Percutanous transluminal coronary angioplasty(PTCA) by

the cardiologists. A coronary angiogram showed mid total occlusion of Right coronary artery(RCA) and PTCA was done with Bare metal stent (BMS). Post procedure period was uneventful, with normal sinus rhythm in ECG. Considering vasculitis as a precipitant for coronary stenosis, she was given Pulse cyclophosphamide therapy along with Prednisolone from the cardiology department. Thereafter patient was discharged with dual antiplatelets, Methotrexate and Prednisolone with a final diagnosis of Severe Wegeners Granulomatosis, Acute coronary syndrome- ST elevation Myocardial infarction- IW with CHB and Type II Diabetes Mellitus.

Patient was under our follow up, Prednisolone was tapered after 6 months and she is presently on maintenance dose Prednisolone. Patient improved symptomatically and radiologically with disappearance of the nodules completely on follow up skiagrams.

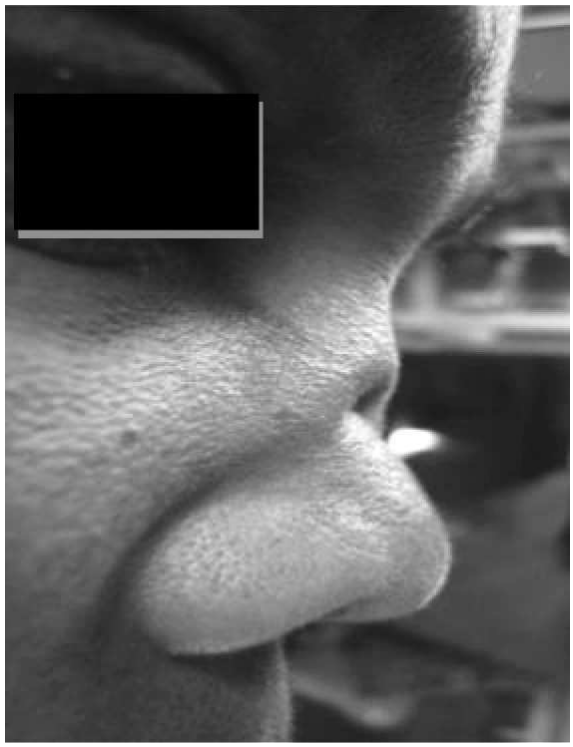


Figure 5 : Saddle nose deformity

Discussion

Wegener's granulomatosis is a distinct clinicopathological entity characterised by granulomatous vasculitis of upper and lower respiratory tract together with glomerulonephritis. It is the most common pulmonary vasculitidis with an estimated prevalence of 3 in 1,00,000 and with a male to female ratio of 1:1. Mean age of onset is 40 years.

Lung involvement typically appear as multiple bilateral nodular cavitating infiltrates which on biopsy reveal typical necrotising granulomatous vasculitis[1]. Immunopathogenesis is not clear; however it is proposed to be due to an abnormal cell mediated immune response to an exogenous or even endogenous antigen that enters through or resides in the upper airway.

Clinical manifestations

Involvement of upper airway occurs in 95% of patients. They often present with severe upper respiratory tract findings such as paranasal sinus pain, tenderness and purulent or bloody nasal discharge, with or without nasal mucosal ulceration. Nasal septal perforation may follow leading to saddle nose deformity.

Pulmonary involvement may be manifested as asymptomatic infiltrates or as cough, hemoptysis, dyspnoea and chest discomfort. Endobronchial disease may lead to obstruction with atelectasis.

Eye involvement may range from conjunctivitis to dacryocystitis, episcleritis, scleritis and retroorbital mass lesions.

Renal disease may occur as either mild glomerulitis with proteinuria, hematuria and red blood cell casts or as rapidly progressive renal failure. Skin and cardiac manifestations are also seen.

Lab findings include

Elevated ESR

Mild anaemia and leukocytosis

Mild hypergammaglobulinemia

Slightly elevated rheumatoid factor

Elevated c ANCA

ACR Criteria for classification[2]

1. Nasal or oral inflammation

2. Abnormal chest Xray

3. Active urinary sediment

4. Granulomatous inflammation on biopsy

Two or more of these if present is suggestive of Wegener's granulomtosis.

cANCA have been detected in more than 90% patients with active generalised WG and in 40 to 70 % with active regional WG[3].

Treatment

Oral cyclophosphamide (2 mg/kg/day) and prednisolone is the initial treatment of choice for Wegener's granulomatosis. By 3 to 6 months, assuming complete remission is achieved, azathioprine or methotrexate can be substituted for cyclophosphamide. Treatment should be continued for a minimum of 12 to 18 months. Relapse can be treated with cyclophosphamide and prednisolone.

References

1. Longo DL,Fauci AS. The Vasculitis Syndromes. Harrison's Principle of Internal Medicine. 18th Edition. The McGraw-Hill Companies

2. Leavitt RY, Fauci AS, Bloch DA, et al. The American college of rheumatology 1990. Criteria for the classification of Wegener's granulomatosis. Arthritis Rheum.1990;33(8);1101-7

3. Alfred P.Fishman, Jack A.Elias, et al. Alveolar Hemorrhage Syndromes. Fishman's Pulmonary Diseases and Disorders. 4th edition. The McGraw-Hill Companies

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3.Books and other Monographs

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