Not all COPD is caused by cigarette smoking

According to the World Health Organization (WHO), passive smoking carries serious risks, especially for children and those chronically exposed. The WHO estimates that passive smoking is associated with a 10 - 43% increase in risk of COPD in adults.

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Case history

A 48-year-old black African woman presented with a history of shortness of breath that had progressed over the past 5 years (Fig. 1). She was treated at her local clinic for asthma. Her admission was precipitated by an episode of acute bronchitis. She was reviewed in the respiratory clinic 6 weeks later when she was in a stable state. She was found to have clinical evidence of severe airflow limitation, a hyperinflated chest and a bilateral wheeze. A severe, obstructive ventilatory defect was confirmed on spirometry. The airway obstruction could not be reversed with inhalation of 200 µg salbutamol and a standard oral corticosteroid trial (prednisone 40 mg daily for 14 days).

This implied a diagnosis of chronic obstructive pulmonary disease (COPD) and was supported by a reduced transfer factor for carbon monoxide (diffusion test). She had never smoked and was a housewife, which prompted speculation about the aetiology of her COPD. Review of the history revealed that she spent most of her life in a rural environment and was in charge of cooking food over an open wood fire in the communal hut in which she lived with her family of 6 children and her husband who smoked tobacco indoors. She did not have a history of tuberculosis, asthma or childhood respiratory disease before the onset of her respiratory symptoms. She had lived under similar circumstances during her childood. The diagnosis of COPD was not considered because she was a lifetime non-smoker. Exposure to burning of biomass (BM) fuels since childhood would probably explain a diagnosis of COPD. Fig. 2 illustrates the type of exposure to which she was subjected. This case highlights the issues related to non-smoking causes of COPD.

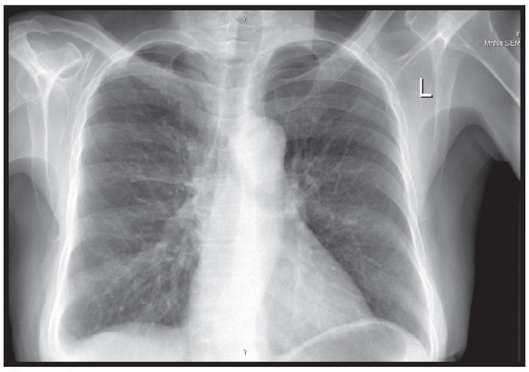

Fig. 1. Posteroanterior chest radiograph.

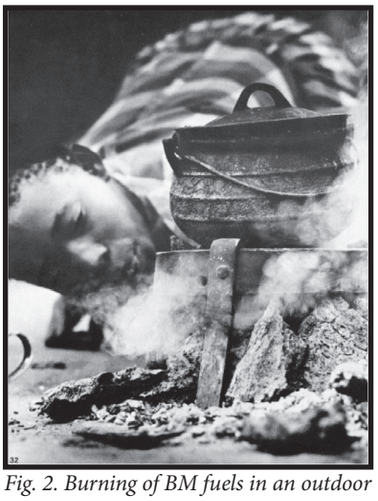

Fig. 2. Burning of BM fuels in an outdoor fire.

Introduction

Deaths caused by chronic non-communicable diseases are projected to rise dramatically in developing regions of the world. It is estimated that about 338 million people worldwide will die of one or more non-communicable diseases in the next decade. In 2005 COPD was the 4th leading cause of death in the world, surpassing HIV/AIDS. The World Bank and the WHO ranked COPD as the 12th leading cause of disease burden in the world and it is expected to rank 5th in 2020. While tobacco smoking is the leading cause of COPD in all regions of the world, attention to the non-smoking causes of COPD is critical as part of the global strategy to combat this disease. For example, the WHO estimates that, although smoking is the leading cause of COPD, about 400 000 deaths per year occur from exposure to BM fuel pollution. Table I lists the non-smoking causes of COPD. This review presents evidence for non-smoking causes of COPD, discusses the pathophysiology of each of these causes, and emphasises the role of education in prevention of the disease.

Table I. Non-smoking causes of COPD

Non-specific occupational dust exposure
Byssinosis
Cannabis exposure
Indoor pollution
Burning of biomass fuels
Liquids
Solids
Gases
Outdoor and environmental pollution
Homozygous alpha-1-antitrypsin deficiency
Pulmonary tuberculosis

Occupational exposure and COPD

Cigarette smoking is undoubtedly the leading cause of COPD in the workplace. The association between workplace exposure and COPD has been debated for many decades. Awareness of the link between dusty trades and chronic bronchitis, termed industrial bronchitis, can be traced back to the 19th century. In 1984, the US Surgeon General's report concluded that the only accepted cause of COPD was cigarette smoking. Occupational exposure was then considered to be putative as opposed to an established cause of COPD.

Occupation-related COPD is not a clinical subcategory, mainly because the chronicity and insidious nature of the airflow limitation do not reverse when exposure is discontinued. Therefore, a clinical diagnosis of occupational COPD, using methods similar to those employed for occupational asthma, is not feasible.

Some individuals with occupational COPD may be misclassified as having occupational asthma because they may demonstrate variable airflow limitation. A good example is byssinosis, where the airflow limitation is variable in the early part of the natural history of the disorder, which may be misdiagnosed as asthma. Conversely, occupational asthma that has progressed to fixed airway obstruction may be misclassified as COPD.

There is growing evidence from large population-based studies suggesting that a significant proportion of COPD is related to occupational exposure. This includes exposure to dusts, gases, vapours and fumes (DGVF), the so-called occupational COPD effect. The American Thoracic Society (ATS) published a consensus statement on the population-attributable risk (PAR) of COPD and asthma, based on a number of large-scale general population studies. From these studies it was calculated that the PAR for COPD is about 15%. These studies did not specifically identify risk factors for COPD in the workplace.

Occupations linked to increased prevalence of COPD include construction, mining, working with leather, manufacturing of plastics, rubber, textiles, and food products, spray painting and welding. Specific substances have been linked to higher prevalences, including quartz, welding fumes, wood dust, sawdust, asbestos and solvents. DGVF remains the common factor in all these exposures.

The genetic susceptibility to COPD with regard to exposure to DGVF is still poorly understood, but certain data suggest a genetic influence on the causation of the disease.

There now appears to be reasonable evidence for harmful occupational exposures as an independent cause of COPD. Occupational health administrators now need to consider which strategies will result in a reduced exposure rate. Indeed, in some cases, these strategies may be practically easier than smoking cessation strategies. More data are required with regard to the situation in South Africa, which is further compounded by under-reporting, a high prevalence of pulmonary tuberculosis and its sequelae, and other confounders such as domestic combustion of BM fuel.

Biomass fuel burning and COPD

Almost 3 billion people worldwide use BM and coal as their main sources of fuel for cooking, heating and other household needs. Wood, crop residue, dung and coal burnt in open fires or in poorly functioning stoves may lead to a high level of indoor pollution. There is currently a growing body of evidence in the form of case control and other robust studies that BM fuel is an important risk factor in the development of COPD, especially in women in developing countries. BM fuel accounts for the high prevalence of COPD in non-smoking women in parts of Africa, the Middle East and Asia. Exposure to BM fuels has also been linked to an increased risk of tuberculosis. Annually, 2 million deaths of women and children are attributable to indoor pollution.

BM fuel (sometimes referred to as biofuels) is an organic non-fossil material of biological origin. It is derived from recently living organisms or their metabolic byproducts. Table II is a summary of the classes of BM fuels.

BM fuels are renewable forms of energy, unlike fossil fuels such as coal, petroleum and nuclear energy, and are burned to release stored chemical energy. Numerous research projects are underway to produce BM fuels in a cost-effective and environmentally safe manner. Burning of wood and cow dung is the commonest form of domestic BM fuel in developing countries, invariably in poorly ventilated environments.

Burning of BM results in emissions referred to as BM smoke, comprised of a diverse number of compounds associated with adverse health effects. These are particulate and gaseous. Gaseous compounds include carbon monoxide, aldehydes, ozone, nitric oxide and acrolein. Particulates are organic and inorganic matter such as polycyclic aromatic hydrocarbons, elemental carbon and trace metals. Benzo[a]pyrene is a polycyclic aromatic hydrocarbon with probable carcinogenic effects in humans. At least 200 organic compounds are identifiable in wood smoke, mostly wood polymers and resins. Controversy still exists with regard to the precise substances in BM fuel combustion that cause adverse health effects, and many of the identifiable compounds therefore serve as useful surrogates of exposure.

Burning of BM fuel therefore results in BM pollution, which occurs in many settings. High concentrations have been measured during forest fires and indoors in developing countries. Contrary to popular belief, the highest concentration occurs indoors after combustion for cooking and heating. Such indoor kitchens are usually poorly ventilated and attached to the rest of the living area. The homes are therefore turned into potential death traps for the inhabitants. The stoves are simple and lead to inefficient combustion of fuels.

Exposure to burning of BM fuels is generally assessed through surveys and questionnaires. Some studies have used personal, environmental and biological monitoring. The last includes measurement of blood carbon monoxide monitoring.

Table II. Classes of available BM fuels and their origins

Solids – wood, charcoal, animal dung and dried compressed peat
Liquid – ethanol from sugar cane (automotive fuel in Brazil); corn (gasoline additive in the USA); methanol from BM (not currently economically viable); straight vegetable oils (in diesel engines); waste vegetable oils (in diesel engines); and biodiesel from trans-esterification of animal fats and vegetable oil
Gases – methane from the natural decay of garbage or agricultural manure; hydrogen from the cracking of any hydrocarbon fuel in a reformer or by the electrolysis of water and gasification

Exposure to pollutants from the combustion of BM fuels is a global problem. Together with coal, BM fuels form the primary source of energy for about 3 billion people worldwide, although they account for about 13% of the world's energy use. The main BM fuels used are wood, charcoal, crop residues and dung. About 50% of the world's population relies on BM fuels for cooking and heating, mainly in rural areas in developing countries, but also in urban areas with burgeoning informal settlements. For example, South Africa has the 5th largest electricity utility in the world, but 30% of its residents in informal urban settlements are not connected to the electricity supply and rely on other fuels, including BM fuels. Residents of non-recognised settlements such as illegal slums in India are either illegally connected to an electricity supply or rely on dangerous sources of energy such as BM fuels in poorly ventilated and overcrowded conditions. The most exposed regions in the world are South and Central America, sub-Saharan Africa and South Asia. Wood provides 75% of energy needs in tropical Africa. While global energy from BM fuel has fallen from 50% to 13%, there is evidence of growing dependence on this type of fuel in poorer parts of the world. Based on current trends, an extra 200 million people will rely on BM fuel by 2030.

Estimation of personal exposure is difficult because of the complex nature of indoor activities that lead to BM pollution. The factors that influence exposure are summarised in Table III.

Table III. Factors influencing personal exposure to BM pollution

1. Type of fuel and cooking/heating device
2. Status of fire
   - Starting or off
   - Burning
   - Smouldering
   - Moisture content of fuel
3. Ventilation characteristics of dwelling and site of device
4. Ambient conditions of dwelling
   - Humidity
   - Airflow
5. Proximity of individual to device
   - Women who do the cooking are closest
   - Children may be strapped to the mother's back and have high exposure
6. Activity of individual and aggregate time spent in proximity of fire
   - Lighting of stove
   - Cooking over the fire and physical activity that influences breathing pattern. This is also related to type of food being prepared
   - Adding or moving the fuel, stirring the food

Numerous studies from developing countries have documented high levels of exposure to indoor BM pollution related to adverse respiratory health outcomes. Without exception, these studies provide evidence that exposures are in excess of several orders of magnitude of any international norm. For instance, particulate matter in kitchens in India is 30 times higher than the WHO standard.

Mechanism of disease

There is a paucity of studies on the pathophysiological mechanisms of BM pollution-induced adverse health effects. The particulate phase appears to have the greatest health-damaging potential. Small particles less than 10 µm in diameter (PM10) and, in particular, particles less than 2.5 µm are able to penetrate deeper into the lungs.

The gaseous phase is said to interfere with local defences, stimulate inflammation in the airways by irritant properties, increase bronchoalveolar permeability, and impair macrophage function. Nitrogen dioxide adversely affects mucociliary apparatus and humoral and cell-mediated immunity. This leads to impaired respiratory defences and decreased clearance of organisms. Daily exposure leads to increased cytokine release and an inflammatory airways response. Acute exposure can lead to increased bronchial reactivity and exacerbation of asthma. Long-term exposure can lead to chronic inflammation, and make the lungs more susceptible to infections and vulnerable to greater damage by infectious and other noxious agents. Studies in mice indicate that short-term exposure leads to epithelial damage, decreased mucin expression and increased airway reactivity. Sulphur dioxide is known to impair host defences against microbial agents. Like nitrogen dioxide, it also increases airway reactivity, interfering with asthma control. Sulphur dioxide is also cytotoxic to epithelial cells.

Formaldehyde irritates the airway and nasopharyngeal mucosa and may predispose to infections, leading to increased allergic sensitisation. Carbon monoxide exposure results in increased carboxyhaemoglobin, leading to a reduction in placental oxygen delivery, and causes low birth weight and an increase in perinatal death.

Particulate matter has major pro-inflammatory properties and is known to worsen asthma. Metallic particles and ultrafine particles of PM_{10} are the most important agents leading to oxidative stress and cytokine induction. Ultrafine particles induce oxidative stress and increased IL-8 production from epithelial cells. PM_{10}r has been shown to stimulate an influx of neutrophils into the airspaces of rat lung. Transition metals generate hydroxyl radicals, which are capable of inducing oxidative stress and cellular damage.

PM_{10} also activates the nuclear translocation of transcription of nuclear factor kappa B, which is known to upregulate the transcription of genes encoding pro-inflammatory molecules, e.g. TNFα + IL8.

Alpha-1-antitrypsin deficiency (AATD) and COPD

Epidemiological and family studies provide evidence for genetic factors contributing to COPD susceptibility. In COPD, many recent studies have been underpowered or have not been extensive enough to provide the full extent of genetic variation. The strongest association of COPD and genetics exists with AATD – a genetic disorder manifesting as pulmonary emphysema, liver cirrhosis and, rarely, as panniculitis of the skin, and characterised by low serum levels of AAT, the main protease inhibitor (PI) in human serum. The prevalence in western Europe and the USA is estimated at approximately 1 in 2 500 and 1 in 5 000 newborns, respectively. Type ZZ (homozygous deficiency) and type SZ AATD are risk factors for the development of respiratory symptoms, early-onset emphysema, and airflow obstruction early in adult life. Factors such as cigarette smoking and dust exposure are additional risks linked to an accelerated progression of this condition. Estimates suggest that 75 - 85% of patients with severe AATD will develop emphysema. Smoking appears to be the most important risk factor for the development of emphysema among AAT-deficient persons. Among smokers, mild to moderate reductions in AAT levels may be associated with a more rapid decline in lung function. AATD is diagnosed by measuring serum levels of AAT and, if reduced, an effort should be made to identify the genetic abnormality responsible for the reduction. Augmentation with an intravenous form of

purified, pooled human plasma has been shown to increase the serum levels of AAT among deficient patients. Its use appears to have an impact on the rate of lung function decline and overall survival. To date, no confirmatory, large, prospective, randomised trials are available.

Cannabis exposure and COPD

Recently there has been considerable interest in the impact of cannabis exposure on lung disease. It is estimated that smoking 3 - 4 joints of cannabis per day is equivalent to smoking 20 cigarettes per day with regard to damage to the bronchial mucosa. Furthermore, modern cannabis joints may contain very high concentrations of the active ingredient, tetrahydrocannibol, compared with previously (300 mg v. 60 mg). There is good evidence that cannabis smoking is associated with acute and chronic bronchitis. The association with emphysema is less clear and better epidemiological studies are needed to answer this question. Cannabis smokers frequently smoke cigarettes as well, making it difficult to ascertain the burden of COPD caused by cannabis smoking.

Pulmonary tuberculosis (PTB) and COPD

PTB is both a parenchymal and an endobronchial disease. Few studies have formally investigated the contribution of TB to the burden of COPD. These have shown that, after healing, PTB results in significant chronic airways obstruction. Pathophysiologically, PTB can therefore result in damage to the airways and lead to airway obstruction. The extent and severity of the obstruction are related to the extent of PTB in the individual patient. In countries such as South Africa, where there is a high incidence of TB, a significant number of COPD cases are likely to be due to healed PTB. Epidemiological studies to systematically document the prevalence of post-TB COPD have not been conducted. Furthermore, the pathophysiology of TB-related COPD may be quite different to that of smoking and BM pollution exposure-related COPD. For example, it is not known if there is a persistent neutrophilic inflammation of the airways or whether the airway obstruction is solely due to fibrosis. This has important implications for treatment. It is likely that the obstruction is not reversible, rendering bronchodilator treatment relatively ineffective. Cigarette smokers are at higher risk of developing PTB. Many patients with PTB-related COPD also smoke, making it difficult to define the relative contribution of TB to the airway obstruction.

Conclusion

Non-smoking causes of COPD largely remain an underdiagnosed clinical entity. Several of the reasons are presented in this review. Although the vast majority of COPD cases are accounted for by cigarette smoking, the non-smoking causes of COPD still result in a significant amount of morbidity and mortality. This review aims to highlight these causes and to provide the burden of proof, thus allowing the primary health care practitioner to draw attention to the possibility of COPD in the absence of exposure to cigarette smoking. As many of the non-smoking causes of COPD are concentrated in resource-limited settings, where education with regard to risk is limited, it is hoped that many preventive strategies will run parallel with the primary prevention of cigarette smoking, thus creating greater awareness of the entity.

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In a nutshell

- Personal cigarette smoking is estimated to account for about 95% of all cases of COPD.
- This may be an overestimate of the burden of COPD caused by cigarette smoking as non-smoking causes of COPD are under-recognised.
- Many people with COPD due to non-smoking causes, such as biomass pollution, atmospheric pollution, pulmonary tuberculosis and nonspecific occupational dust may be underdiagnosed or misclassified as 'fixed' airway obstruction asthma or bronchiolitis.
- The reasons are ignorance of the non-smoking causes of COPD by the medical community.
- These causes of COPD predominantly affect people living in resource-limited settings where clinical expertise and access to spirometry are limited.
- Women are predominantly affected.
- The problem is further compounded by the fact that many individuals exposed to these causes also smoke, making it difficult to determine the contribution of these factors to the burden of COPD.
- This review presents the burden of proof for non-occupational causes of COPD and alerts attending physicians to these possibilities.
- As much as there is a need to ban cigarette smoking, attention to the non-smoking causes of COPD and their prevention must also be part of the global strategy to reduce the burden of COPD.