Academic Sciences Asian Journal of Pharmaceutical and Clinical Research

Vol 5, Suppl 3, 2012 ISSN - 0974-2441

Review Article

REVIEW ON REACTIVE AIRWAYS DYSFUNCTION SYNDROME (RADS)

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Received:7 March 2012, Revised and Accepted:15 may 2012

ABSTRACT

Over the past twenty years, work-related asthma has been increasingly recognized to focus on reactive airways disease syndrome (RADS), but little is known about its impact on health. RADS is a controversial and poorly understood condition produced by inhalational injury from gas, vapors, or fumes. There was a general lack of adequate information on exposure, investigation and, in particular, outcome of reported cases or case series of RADS. In this review, it is our intent to summarize clinical presentation, diagnosis, pathology, management and case series of RADS.

Keywords: reactive airways dysfunction syndrome.

INTRODUCTION

Brooks et al' in 1985 coined the phrase "reactive airways dysfunction syndrome" (RADS) to denote the development of a persistent asthma-like condition with airway hyperresponsiveness developing in a previously healthy asymptomatic individual within 24 h of a single exposure to concentrated respiratory irritants. [1] As the symptoms of this condition and asthma are alike, people always confuse it to be asthma. However, RADS is different from asthma. In fact the symptoms of RADS come and go, while asthma symptoms are ongoing. [2] RADS initiated by exposure to high concentrations of irritant gases, fumes, or chemicals. The most commonly reported agent associated with RADS was chlorine, toluene di-isocyanate (TDI) and oxides of nitrogen. [3] Although there is lack of adequate information about RADS that can better explore it. A more structured approach to gathering information is required. We suggest that a web-based database of RADS cases be established which would allow continuous update and better analysis of outcome in these individuals. Here, studies were done by searching MEDLINE, EMBASE and CINAHL from 1985 to 2011 supplemented by review of references of recent review articles and original reports.

Epidemiology

RADS may occur after inhalational accidents at home, in the workplace, or in the general environment. Estimating the incidence of RADS is difficult for several reasons. Because it is estimated that 60,000 inhalational accidents occur in the home and lead to medical consultation yearly in the United States. [2] Industrial accidents also have the potential to expose nonemployees to noxious inhalants; the release of isocyanates at Bhopal, for example, led to more than 2000 deaths due to pulmonary edema, and caused RADS in many others. [4,5] The size of populations at risk after an incident can only be determined approximately in many cases. Precise, subject-specific information regarding the duration and magnitude of exposure at the time of an accident is rarely available. [6]

Clinical Presentation

In 1985, Brooks and colleagues [1] described ten patients who developed an asthma-like condition that persisted beyond the usual recovery period. The condition appeared after a single inhalational exposure to high levels of a toxic substance. The exposures were either brief (lasting just a few minutes) or for as long as 12 h. There was a short time interval between exposure and the development of symptoms of from several minutes to several hours. Most importantly, asthmatic symptoms were persistent, defined as lasting at least 3 months and averaging 3 years since the time of the initial exposure. Several points about RADS should be emphasized. First, RADS results from a high-level inhalation exposure to a toxic substance. Second, the asthma-like condition originates with the exposure. Individuals with preexisting asthma (and therefore preexisting bronchial hyperresponsiveness) may develop pronounced symptoms of cough, wheezing, and shortness of breath induced by a nonspecific irritant exposure. This is not RADS but a temporary exacerbation of a preexisting condition. Third, RADS is associated with persistent symptoms. Usually, those who survive a short-term toxic gas, fume, or aerosol exposure recover completely without significant clinical or physiologic sequel regardless of the severity of the initial clinical manifestations. [7] Finally, once RADS is established, because of the induced nonspecific bronchial hyperresponsiveness, the patient is then subject to bronchospastic responses from many and varied environmental stimuli, including cigarette smoke, cold air, traffic fumes, and common household chemicals such as hairsprays, perfumes, and bleaches.

Diagnosis

There is no "gold standard" objective test for the diagnosis. Patients with RADS do not develop recurrence of symptoms after reexposure to a low level of the substance that initiated the problem as might be expected with other forms of occupational asthma. Therefore, confirmation of the diagnosis by objective means, such as a fall in lung function on returning to work and improvement when away from work, is not possible. Results of specific bronchoprovocation challenge tests utilizing low-level exposures would be expected to be normal.[8] Therefore, accurate diagnosis depends on the compatible history and the demonstration of persistent nonspecific bronchial hyperresponsiveness. The criteria for the diagnosis of RADS as proposed by Brooks et al in 1985[1] appear in Table 1.

Table 1: Clinical criteria for diagnosis of reactive airways disease (RADS)

1.	A documented absence of preceding respiratory complaints.
2.	The onset of symptoms occurred occurred after a single exposure incident or accident.
3.	The exposure was a gas, smoke, fume or vapour which was present in very high concentrations and had irritant quantities to its nature.
4.	The onset of symptoms occurred within 24 hours after the exposure and persisted for at least three months.
5.	Symptoms simulated asthma with cough, wheezing and dyspnea predominating.
6.	Pulmonary function tests may show airflow obstruction.
7.	Other types of pulmonary disease were ruled out.
8.	Methacholine challenge testing was positive
9.	Requires immediate medical attention
10.	No atopic predisposition
11.	Bronchial biopsy specimen with mucosal damage and inflammation without eosinophilia.

Background

Some chemical agents may induce the asthmatic state both as a specific agent and as a toxic irritant depending on the level of exposure. For example, exposure to TDI may result in specific bronchial hyperresponsiveness after a period of symptomless

exposure. TDI has also been reported to cause RADS after a brief high-level exposure. [9] Case reports documenting a persistent asthma-like illness following a toxic inhalation exposure appeared in the literature prior to 1985. In retrospect, these cases most likely represented examples of RADS. In 1970, Gandevia [10] described four workers who developed new-onset asthma after exposure to excessive concentrations of gases and vapors such as hydrogen sulfide, diethylene diamine, fumes from overheated plastics, and smoke and fumes from combustion of a variety of materials. Harkonen et al and Charan and coworkers [11,12] noted persistent bronchial hyperresponsiveness or airways obstruction after high-level SO2 exposure. Flury et al[13] reported persistent symptoms of airflow obstruction after a significant exposure to concentrated ammonia. Similar reports documented persistent asthmatic states resulting from such exposures as agitated liquid manure,[14] a mixture of several drain cleaning agents, chlorine, and smoke. [15]Since 1985, a number of reports have documented RADS originating from a number of exposures such as sulfuric acid, locomotive exhaust, hydrochloric acid, floor sealant, anhydrous ammonia fumes, and intratracheal ignition of the ether vehicle used in free-basing cocaine[16,17] Examples of case reports of patients with RADS published since 1985 appear in Table.

Reports of patients with RADS

First author	Year	RADS exposures (No.)	Cases not meeting Brooks' criteria (No.)
Brooks [1]	1985	Uranium hexafluoride, floor sealant, spray paint (3), 35% hydrazine, heated acid, fumigating fog, metal coat remover, fire/smoke	
Afford [18]	1988	so2[1]	
Bergstrom [19]	1988	Firefighting[1]	
Boulet [20]	1988	Sulphuric acid, bleaching agent, perchloroethylene, TDI	
Lerman [21]	1988	Floor sealant[1]	
Stenton [22]	1988	Smoke inhalation[2]	
Bernstein [23]	1989	Toxic ammonia fumes	
Taylor [24]	1989	Cocaine[1]	
Tarlo [25]	1989		Acids, chlorine, sulphuric acid, sulphur dioxideb, burnt paint fume, spray paint without isocyanates, chlorine, TDI, diphenyl methane diisocyanate
Gilbert [26]	1989	Dust or mold in silo (fungus)	
Luo [27]	1990		TDI [2]
Promisloff [28]	1990	Sodium hydroxide, silicon tetrachloride, trichlorosilane b[2]	Sodium hydroxide, silicon tetrachloride, trichlorosilaneb
Donnelly [29]	1990	Chlorine gas[1]	
Demeter [30]	1990	Sulphuric acid, unknown	Lithium bromide, hydrogen chloride, cleaning solvent, zinc chloride [11]
Rajan [31]	1990	Acetic acid[1]	
George [32]	1990		Smoke [7]
Saric [33]	1991		Respiratory irritant such as hydrogen fluoride [30]
Kern [34]	1991	Acetic acid [4]	Acetic acid
Langley [35]	1991	Welding fumes[1]	
Moisan [36]	1991	Smoke inhalation[3]	
Moore [37]	1991	Chlorine gas[1]	
Angelillo [38]	1992	Chlorine [3]	
Deschamps [9]	1992	Ethylene oxide[1]	
Hu [39]	1992		*o*-chlorobenzylidene malononitrile
Snyder [40]	1992	Methylene chloride (phosgene)[1]	
Blanc [41]	1993	Sodium azide [2], epoxy resin, household cleaner containing morpholine	
Cone [42]	1994	Metam sodium[20]	
Deschamps [16]	1994	Sodium hypochlorite and hydrochloric[1]	
Palczynski [43]	1994	TDIs	
Chan-Yeung [44]	1994		Sulphur dioxide, hydrogen sulphide, acetic acid, hydrogen peroxide, chlorine, chlorine dioxide, hydrogen sulphide, methyl mercaptan, sulphur dioxide, hydrogen peroxideb[2]
Gautrin [45]	1994		Chlorine [12], nitrogen dioxide [3]
Palczynski [46]	1994		Freons and phosgene
Deschamps [16]	1994	Sodium hypochlorite and hydrochloric acid (chlorine)b	
Gadon [47]	1994	2-diethylaminoethanol[14]	
Tarlo [48]	1995		Isocyanates [8], acid [3], acrylate [2], fume [2]
Sallie [49]	1995		Chlorine[9], sulphur dioxide[4], oxides of nitrogen [3], phosphine [2], ammonia [2], hydrogen sulphide, hydrogen chloride gas, chloracetyl chloride, sodium fumes, hypochlorite, carboxylic acid, cleaning agents [3], combustion products [3], isocyanate[3], epoxy resin, glutaraldehyde, azodicarbonamide, aromatic amine, enzymes, trichloroethylene[3], methylene chloride, paint, pesticide, lubrication oil
Stanbury [50]	1996		Pentamidine
Piirila [51]	1996	Sulphur dioxide [4]	Sulphur dioxide
Weiss [52]	1996	Sodium azide and hydrozoic acidb [2]	
Schonhofer [53]	1996	Chlorine [3]	
Lemiere [54]	1996	Isocyanates mixed with organic solvent	

Yelon [55]	1996		Formic acid
Lemiere [56]	1997	Chlorine	
Burns [57]	1997	Bromine and hydrobromic acid [2]	
Provencher [58]	1997		Chlorine, isocyanates and acid were the most often reported causal agent
Forrester [59]	1997		Refractory ceramic fibre, phosphoric acid
Danielsen [60]	1998		Hydrogen peroxide [3]
Leroyer [61]	1998	Diphenylmethane diisocyanate	
Conrad [62]	1998	Dinitrogen tetroxide [5]	
Wheeler [63]	1998		General fume[4], solvent/hydrocarbon[2], corrosive agents[3], formaldehyde [3], irritant gas [2], other [4]
Chatkin [64]	1999	TDI [4], isocyanate, chlorine, spray paint	Methyl mercaptan, solvent, glueb, solvent, acrylateb, TDI, isocyanate
Woolf [65]	1999		Bromine
de la Hoz [66]	1999		Bromotrifluoromethane, hydrogen fluoride, hydrogen bromide, carbonyl fluoride, carbonyl bromide
Hill [67]	2000		*o*-chlorobenzylidene malononitrile (CS)
Meyer [68]	2001		Hydrogen fluoride, nitric acidb, aldehydes, acetic acid
Dube [69]	2002		Fume from an iron smelting process
Kopferschmitt-Kubler [70]	2002		Acid [4], chlorine [3], isocyanate [3]
Perfetti [71]	2003		Diphenylmethane diisocyanate
McLaughlin [72]	2003		Chlorine [2], rubber fume, sewerage gas, ammonia, propionic acid, NH4 and sorbic acidb, ethanol, isopropanol, gingerine
Piirila [73]	2003	Thermal decomposition products of CFC[2]	
Henneberger [74]	2003		Nickel, Petroleum fraction [2], smoke[3], diisocyanates [2], soldering fume, caustic acids, dry wall powder, solvents [5], glues, 2-butoxyethanol, styrene-maleic anhydride resin, isopropanol, herbicides, sulfur dioxide, Petroleum distillate, Copier toner, Safrotin, Chemicals (NOS) [4], Ethyl acrylate, Sewer cleaner chemicals, paint fumes, diesel fuel, sodium hydroxide, chlorine, diazonin, gasoline, diesel fuel, ethylene glycolb, ammonia, acids, bases, oxidizer (NOS)b, muriatic acid, ethanolamines, indoor air pollutant
Franzblau [75]	2003	Hydrofluoric acid	
Rosenman [76]	2003		Cleaning agent [42]
Banauch [77]	2003		World trade centre fume [20]
Matrat [78]	2004	Bromochlorodifluoromethane	Bromochlorodifluoromethane [2]
Gorguner [79]	2004		Sodium hypochlorite and hydrochloric acid (chlorine) [55]
Costa sola r [80]	2005	Chlorine and sulphur [18]	
Aslan S [81]	2006	Chlorine [44]	
Greven F [82]	2009	Fire [25]	
Aro L [83]	2009	Fire and irritant dusts [12]	
Khalid I [84]	2009		Household aerosol product [1]
Timo hannu1 [85]	2009	Mixed iodine compounds [1]	
Abbas Aghabiklooei [86]	2010	Dimethyl sulfate [1]	
Chung-li du [87]	2010		Expanded perlite [24]
Veronica A Varney [88]	2011	Ammonia spillage [1]	

Pathology

Few authors have reported histological findings of RADS. Examination showed evidence of airways inflammation with some, but not all, of the changes regarded as characteristic of asthma. The histopathological features like acute desquamation of the epithelium, with subepithelial haemorrhage and swelling, inflammatory infiltrate, and regeneration of the epithelium was noted. Eosinophils were not found. There was no evidence of mucus gland hypertrophy, basement membrane thickening, or smooth muscle hyperplasia.[45,56] Deschamps and colleagues showed mucus gland hyperplasia but only a mild inflammatory response with sparse lymphocytes and polymorphonuclear cells and no eosinophils. There was no thickening of the basal lamina and no alteration of tight junctions or of cilia. [16] Gautrin et al[45] showed that airway inflammation, thickening of the basement membrane, and subepithelial fibrosis were present when assessed 1 year after exposure. Bronchial biopsy specimens revealed fewer eosinophils but greater basement membrane thickening than seen in patients with asthma due to sensitizing agents. The reason for the discrepancy in histologic findings in patients with RADS is not known. It may be due to the type and extent of exposure, the treatment employed, and/or the period of time from the initial exposure to the diagnosis and biopsy. Larger populations and serial biopsy specimens may be illustrative. It is reasonable to state that the histopathologic state of RADS and the changes over time are not yet fully defined. Further study is necessary.

Mechanisms

Airway inflammation is the primary factor responsible for smooth muscle hyperresponsiveness, edema, and increased mucous production, resulting in increased work of breathing. A complex interaction occurs between inflammatory cells and airway epithelium. Mediators released from inflammatory cells induce edema, mucous secretion, and bronchospasm. The pathogenesis of RADS is not clear and to this point it is substantially speculative. Alberts and Brooks have speculated that the onset of RADS may be due to exposure of high-level irritant, causes massive epithelial damage and destruction that is followed by activation of nonadrenergic, noncholinergic pathways via axon reflexes and the onset of neurogenic inflammation.[90] Nonspecific macrophage

activation and mast cell degranulation may also occur with the release of proinflammatory chemotactic and toxic mediators. Secondary recruitment of inflammatory cells to the site of injury will then enhance and sustain the subsequent profound inflammatory response.[91]These combined effects not only induce changes in microvascular permeability but also cause increased mucus cell secretion. The chronic inflammatory process often noted in bronchial wall biopsy specimens is likely the end result of direct exposure to toxic inflammatory mediators released by alveolar macrophages, mast cells, and eosinophils or to the recruitment of lymphocytes with subsequent release of a complex cascade of cytokines that only enhance the inflammatory response. [92]

Management

There have been few developments in the management of this condition. The treatment of the patient with established RADS is no different from that of any other asthmatic. Traditional treatment is the same as that of conventional asthma, despite evidence that patients with RADS are less responsive to β2 agonists. [45] There is a paucity of data regarding therapeutic interventions for those with persistent symptoms. The condition appears to have an equal male/female incidence. In reviewing their approach to management, Palczynski and coworkers [46] suggest using inhaled ipratropium and corticosteroids for the first 1 to 3 months of therapy. Since patients with RADS are no more susceptible on reexposure to the causative agent than are other asthmatics, the worker may return to the workplace if measures are taken to limit subsequent exposures to less than the provocative threshold for that individual. Malo assessed mill workers following exposure to chlorine, and found that 29 of 51 still had bronchial hyper-responsiveness over a period of 24 months. [93] The long-term expected outcome for patients with RADS has not been well documented. Individuals with RADS generally continue to report bronchial irritability symptoms and demonstrate nonspecific bronchial hyperresponsiveness for years after the inciting event. Tarlo and coworkers [48] had reported that if symptoms of irritant-induced asthma do not clear within 6 months, they are likely to persist for several years. It is not yet possible to predict which patients will have persistent symptoms and permanent hyperresponsiveness on the basis of the agent or the circumstances of exposure. It is also not yet possible to assess the benefit of various treatment modalities (eg, corticosteroids) in the short-term setting on the likelihood of developing permanent changes (ie, RADS). Demeter and Cordasco reported that of 11 patients followed up for at least 2 years, 6 (55%) had a regression of symptoms, 3 (27%) remained in stable condition, and 2 (18%) progressed [30] Oral corticosteroids and bronchodilators commenced within the first 3 months have had the most favorable outcomes.(Alberts WM,1996) However, some reported case series suggest symptoms may be more persistent than originally thought. Nebulized sodium bicarbonate following chlorine gas exposure has been shown to improve quality of life and forced expiratory volume in 1 second (FEV1), [95] but not lead to a resolution of symptoms. Lung transplantation has been used for severe ongoing symptoms of RADS following the New York World Trade Center collapse. [97] Veronica and its collegues observed that high-dose oral vitamin D may use in treatment of RADS via its anti-inflammatory. [88]

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