Irritant-Induced Asthma and Reactive Airways Dysfunction Syndrome (RADS)

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Abstract

Irritant-induced asthma affects about one-fifth of workers with the diagnosis of 'occupational asthma'. There are believed to be two types of irritant-induced asthma. Single exposure-type of irritant-induced asthma occurs when a person inhales a very high concentration of an irritant gas, vapor or fume to manifest newly-developed asthma symptoms plus nonspecific airway hyperresponsiveness within 24-hours following the exposure. In contrast, repeated exposure irritant-induced asthma evolves when a purportedly genetically predisposed individual is repeatedly exposed to non-massive levels of an irritant gas, vapor or fume (or as a mixture) over a few days, weeks or months and eventually develops clinical asthma. The treatment of RADS is similar to the treatment afforded patients suffering from an acute inhalational injury. Aerosolized bronchodilators are essential for treating acute bronchoconstriction. Likely, oral corticosteroids are not effective. There is no human study showing efficacy of oral corticosteroids in the treatment of RADS. Inhaled steroids have been found effective in reducing airway hyperresponsiveness in a case considered to be RADS.

Keywords: Irritant-induced asthma; Reactive airways dysfunction syndrome; Non-allergic asthma

Abbreviations:

SENSOR: Sentinel Event Notification System for Occupational Risks; RADS: Reactive Airways Dysfunction Syndrome; RAD: Reactive Airways Disease; LICEDS: Low-Intensity Chronic Exposure Dysfunction Syndrome

Introduction

Irritant-induced asthma affects less than one-fifth of workers with the diagnosis of 'occupational asthma' [1-7]. Between 1993 to 2003, the Sentinel Event Notification System for Occupational Risks (SENSOR) collected data from four states (California, Massachusetts, Michigan, and New Jersey); 445 cases of Reactive Airways Dysfunction Syndrome (RADS) represents 9% of work-related asthma events [**1**]. Data published by SWORD (Surveillance of Work-Related and Occupational Respiratory Diseases) and OPRA (Occupational Physicians Reporting Activity) for the years, between 1992 and 2001, emphasizes that RADS comprises between 13.7% and 29% of incident work-related respiratory diseases depending on whether cases are reported by chest physicians or occupational physicians [8]. When comparing subjects with inhalation injuries to those with immunological occupational asthma, there is a predominance of men [8,9] and smoking whereas atopy is less frequent.

Brooks et al. establish two models of irritant-induced asthma without latency [10]. Single exposure-type of irritant-induced asthma occurs when a person inhales a very high concentration of an irritant gas, vapour or fume to manifest newly-developed asthma symptoms plus nonspecific airway hyperresponsiveness within 24-hours following the exposure. In contrast, repeated exposure irritant-induced asthma evolves when a purportedly genetically predisposedindividualis repeatedly exposed to non-massive levels of

an irritant gas, vapour or fume (or as a mixture) over a few days, weeks or months and eventually develops clinical asthma.

Single Exposure Irritant-Induced Occupational Asthma

Reactive Airways Dysfunction Syndrome (RADS) materializes as new-onset asthma without immunological sensitization within 24-hours subsequent to a single, massive irritant gas, vapor or fume exposure [11-14]. Acute irritant-induced asthma and Reactive Airways Dysfunction Syndrome (RADS) are synonymous with single exposure irritant-induced occupational asthma. Usually, it is not possible to accurately gauge the precise concentration of the irritant exposure since almost all cases are accidental and occur without warning such as with an unanticipated explosion, accidental release of irritant(s) held under pressure, when there are activities taking place in a confined space having reduced exchange ventilation rate and/or reduced fresh air make-up and when there are emissions of airborne smoke and irritant gases accompanying a fire. Presumably in some poorly understood manner, a massive irritant exposure leads to persistent airway inflammation, altered airway remodeling, sustained airway hyperresponsiveness and asthmatic symptoms. It must be stressed that the reference of Reactive Airways Dysfunction Syndrome ('RADS') is not the same as the designation Reactive Airways Disease ('RAD') [15].

The latter is a code word for the general term of 'asthma' while RADS refers specifically to acute irritant-induced asthma caused by a high-level irritant exposure. Initially in the ensuing minutes after the exposure, the person experiencing RADS may note burning of their eyes, nose and throat due to the characteristic irritant nature of the exposure. Typically, symptoms begin with immediate-onset coughing. Both shortness of breath and chest discomfort can represent early complaints but wheezing usually takes longer to evolve. Within a few hours or possibly the next morning (and always within 24 hours after the accidental exposure) the affected individual seeks treatment in an

emergency facility or a physician's office. In some cases respiratory symptoms associated with RADS are transient and resolve within 12 weeks or less [6]. In other cases of RADS, continuing asthma-type symptoms and nonspecific airway hyperresponsiveness persist for years following the inciting exposure [16]. The reason for the differences is unknown. One review of RADS cases reported a median duration of symptoms lasting 13 months [17]. The routine chest x-ray is characteristically interpreted as being 'negative' without acute infiltrates or pleural changes. When performed, spirometric tests often display 'normal' or 'mild' airflow limitation with no 'significant' response to an inhaled bronchodilator.

Among the 10 subjects originally described by Brooks and co-workers, four had a reduced Tiffeneau index [18]. Persistent airflow limitation occurs only in a small percentage of persons with RADS. Bhérer and coworkers showed airflow obstruction in 31/51 (60%) subjects assessed 18 to 24 months after inhalational accidents due to chlorine [19]. Some patients demonstrate a mixed spirometric pattern reflecting combined central and peripheral involvement [20,21].

The hallmark of RADS is persistent airway hyperresponsiveness as defined by a "positive' methacholine challenge test (e.g., PC20 for methacholine is <8 mg/ml). However, the level of bronchial hyperresponsiveness to methacholine tends to be mild or even borderline in some cases [22].It is important that other pulmonary conditions, that simulate RADS, are excluded including vocal cord dysfunction. Table 1 provides the diagnostic criteria for RADS.

1. Absence of pre-existing respiratory disorder, asthma symptomatology or a history of asthma in remission and exclusion of conditions that can simulate asthma
2. Onset of asthma after a single exposure or accident.
3. Exposure is to an irritant vapor, gas, fumes or smoke in very high concentrations.
4. Onset of asthma occurs within minutes to hours and always less than 24 hours after the exposure.
5. Finding of a positive methacholine challenge test (<8 mg/ml) following the exposure.
6. Possible airflow obstruction on pulmonary function testing.
7. Another pulmonary disorder to explain the symptoms and findings is excluded

Table 1: Diagnostic Criteria for RADS

Repeated Exposure Irritant-Induced Occupational Asthma

Repeated exposure-type of irritant-induced asthma has been classified under different names including: Repeated Exposure Irritant-Induced Asthma; 'Atypical RADS'; 'Low-Dose RADS'; Low-Intensity Chronic Exposure Dysfunction Syndrome (LICEDS); 'Not-So-Sudden 'Irritant-Induced Asthma; and, 'Chronic Irritant-Induced Asthma [1,4,5,10,14,21,23-25]. In the repeated exposures-type of irritant-induced asthma, the clinical appearance of asthma takes longer to evolve and only after repeated irritant exposures. Table 2 proposes the diagnostic criteria necessary for establishing the diagnosis of repeated exposure irritant-induced asthma [26].

Numerous epidemiological surveys are conducted in workers repeatedly exposed to both low and high levels of chlorine, sulphur dioxide and/or ozone in pulp and paper mills [16,19,27-31]. Persistent

asthmatic symptoms and presence of nonspecific bronchial hyperresponsiveness and/or variable airflow obstruction are reported among three pulp mill workers experiencing repeated chlorine "gassing" episodes occurring over several years [27]. Mild increases in bronchial responsiveness and other clinical associations appear during a two-year follow-up of Canadian workers undergoing repeated chlorine 'puff' exposures [32]. Among 25 subjects, the onset of asthma symptoms takes longer to materialized following repeated irritant exposures taking place over days, weeks or months [10]. When analyzed, 88%of subjects were considered "atopic" and 40% developed new-onset asthma in the setting of underlying pre-existing asthma clinically quiescent for at least one year before the exposure [10].

1. There is no preceding latency but asthma symptoms commence during repeated intermittent or continuous inhalational exposures to non-massive, moderate, lower intensity but tolerable concentrations of an irritant vapor, gas, fumes or smoke.
2. Asthma symptoms start during the time repeated irritant exposures take place and not after cessation of exposure.
3. The duration of the repeated exposures is always more than 24 hours and typically does not last longer than 4 months of repeated exposures before asthma symptoms begin. Rarely does the irritant exposure last ≥1-year before the initiation of asthma symptoms.
4. There is the absence of pre-existing asthma symptomatology for the previous 1-year or there may be a past history of childhood asthma that resolved or there was a past history of adult asthma in remission for at least 1-year. There may have also been a diagnosis and/or treatment of bronchial asthma instituted by a previous physician.
5. Typical irritant-induced asthma symptoms include episodic coughing, wheezing and symptoms of "bronchial irritability", (i.e., acute respiratory complaints that follow exposures to various nonspecific irritants, physical factors and odors). There also may be intermittent chest tightness and nocturnal episodes of coughing, wheezing and breathlessness.
6. Spirometry may be normal, show airflow limitation and/or demonstrate a positive response (≥12%) to an inhaled bronchodilator.
7. There is a positive methacholine challenge test (<8 mg/ml) that confirms the presence of nonspecific airway hyperresponsiveness.
8. There must be exclusion of alternative conditions that simulate asthma including vocal cord dysfunction. The possibility of occupational asthma caused by a workplace sensitizer is also eliminated.

Table 2: Diagnostic Criteria for Repeated Exposure Irritant-Induced Asthma

(Also, Not-So-Sudden Irritant-Induced Asthma, 'Low-Dose RADS' Or 'Low Intensity Chronic Exposure Dysfunction Syndrome, 'LICEDS')

Etiological Agents

Cases of inhalation accidents, reported to Surveillance Of Work-Related and Occupational Respiratory Disease (SWORD) and the Open Public Records Act (OPRA) between 1992 and 2001,classified the offending agents into five categories. The most frequently reported agents were irritant gases (42%) followed by solvent vapors (18%), metallic fumes (11%) acid mists (9%) and other (18%) [8]. The originally reported causative agents of RADS include: uranium hexafluoride gas, floor sealant, spray paint containing significant concentrations of ammonia, heated acid, 35-percent hydrazine, fumigating fog, metal coating remover, and smoke [12].

Table 3 lists reported causes of irritant-induced asthma and RADS.

Exposure	Agent or Process
Acids	Glacial acetic, sulfuric, hydrochloric, hydrofluoric acid
Alkali	Ammonia, bleach, calcium oxide, sodium hydroxide, World Trade Center dust, air bag emissions
Gases	Chlorine, sulfur dioxide, mustard, ozone, hydrogen sulfide, phosgene, nitrogen dioxide; dinitrogen tetroxide
Spraying	Spraying of paints and coatings
Explosion	Irritant gases, vapors and fume releases under pressure; uranium hexafluoride; World Trade Center disaster
Fire/pyrolysis	Combustion and pyrolysis products of fires, burning paint fumes, pyrolysis products of polyvinylchloride (PVC) meat wrapping film; smoke inhalation, Chlorofluorocarbons degradation, urea fumes
Confined spaces	Epichlorhydrin, acrolein, floor sealant, metal coating remover, biocides, fumigating aerosol, cleaning aerosol sprays, mixture of drain cleaning agents
Environment & Workplace	SO_2 gas in a pyrite dust explosion; locomotive and diesel exhaust; Dunsmuir Metam Sodium Spill; aerosols of metalworking fluids including aldehyde and formaldehyde; aluminum smelter workers exposed to pot-room fumes; metal processing plant and c chlorine gas exposures; bleachery workers with ozone and chlorine dioxide/SO_2 gassings; chlorine gas "puffs" among pulp mill workers & chlorine gassing incidents; sodium persulfate; inorganic salts used as oxidizing agents in hair bleaches & hair-coloring preparation; shoe and leather workers exposed to the organic solvents ; workers exposed to SO_2 from apricot sulfurization tunnel construction workers, cleaning and disinfecting workers in the food industry, chili pepper pickers; dust exposure in Norwegian smelters; 2-hydroxyethyl methacrylate and methyl methacrylate in dentists; synthetic leather workers exposed to organic solvents toluene, xylene and methyl ethyl ketone; eucalyptus; fragranced aerosol products; gases from liquid manure; steam system additive 2-diethylaminoethanolamine; irritant gas containing chromate at a chrome pellet manufacturing plant; bromochlorodifluoromethane and bromotrifluoromethane.

Table 3: Causes of Irritant-Induced Asthma and RADS

Cigarette Smoking and RADS

Cigarette smoking is opined as a risk factor for occupational asthma even though its effect on the development of occupational asthma is still unclear [33]. As to date, there is no recognized association between cigarette smoking and non-allergic irritant-induced asthma or RADS [34,35]. Conceivably, a better distinction can be made after splitting allergic-occupational asthma from non-allergic occupational asthma/RADS. A proposed mechanism to explain the connection between cigarette smoking and allergic sensitization could be that inhalation of cigarette smoke injures the bronchial epithelium of certain workers leading to the widening of the tight junctions between epithelial cells; the change heightens bronchial epithelial permeability and permits greater penetration of antigen through the epithelial layer [36]. It is also possible that there may be the release of different mediators in smokers compared to non-smokers.

Perhaps in some cases, cigarette smoking predisposes individuals to allergic sensitization [37,38].Tobacco smoke provokes an increase in serum IgE and enhances respiratory sensitization to ovalbumin in animals studies [39]. A higher total IgE concentration has been noted in cigarette smokers' serum [40]. An association between atopy, cigarette smoking, and allergic sensitization to a workplace exposure is reported for workers exposed to green coffee beans, tetrachlorophthalic anhydride and platinum salts [37,38,41]. Both smoking and the intensity of platinum salts exposure were associated with development of platinum salt sensitivity among South African platinum refinery workers [37].Accordingly, evidence emerges of an increased risk of allergic occupational sensitization in cigarette smoking workers exposed to certain high and low molecular weight agents [33].

Pathology of RADS and Irritant-Induced Asthma

The pathological features of RADS showing mononuclear cell inflammation, denuded epithelium and edematous mucosa [12,42-45]. Additional pathological findings reveal mucosal squamous cell metaplasia, thickening of the basement membrane and reticular and collagen-associated bronchial wall fibrosis [43,44,46]. A subject suffering from RADS following a single exposure to a mixture containing an isocyanate disclosed mainly aT-lymphocytes inflammatory response [47]. Purportedly, a case of RADS in a worker exposed to chlorine gas showed asequence of pathological changes [22]. Serial bronchial biopsies acquired at 3 and 15 days and then 3 and 5 months after the inhalational accident demonstrated Initial bronchial mucosal denudation, sloughing of epithelial cells and infiltration of a submucosal fibrinohemorrhagic exudate. Subsequent changes unveiled subepithelial edema and cellular regeneration of the basal and parabasal cells; even later, there was deposition of collagen. In another human investigation studied approximately 11 years after the inhalational accident suggested the key cellular role of the eosinophil [48]. A rat model describedmaximalepithelial flattening and necrosis arisingbetween 1 and 3 days after a single high-level exposure to chlorine gas. Bronchoalveolar lavage documented neutrophilic inflammation [49]. With time and after further goblet cells and smooth muscle cells appeared, there was reduction in the amount of epithelial flattening and cellular necrosis. Some rats showed persistent epithelial aberrations [49].

Possible Mechanisms Explaining Irritant-Induced Asthma and RADS

Geneticfactors

Molecular variation in a gene sequencemightinflict greater host susceptibilityfor lung injury [50-62]. A mouse model of chlorine-induced pulmonary injury supports the hypothesis that some of the functional and pathological airways changes in asthma relate to induction of oxidative stress [63]. Inadequate antioxidant defense and genetic factors have been implicated in the pathogenesis of isocyanate-induced asthma [62,64,65]. Polymorphic variant in the class π glutathione-S-transferase locus confers susceptibility to developing Toluene Di-Isocyanate (TDI) asthma; and, the homozygosity for the Val105-encoding alleles confers protection [66]. Achange in gene structure may causean inability to efficiently detoxify Reactive Oxygen Species (ROS) that serve as subcellular messengers for many genetic pathways [57,67]. The cellular damage perpetuated by a persistent oxidant stress couldoverwhelm the pulmonary antioxidant defenses leading to ensuing airway inflammation, airway hyperresponsiveness and other features of irritant-induced asthma [68]. Among lung antioxidants, glutathione is considered to be a potential susceptibility factor for asthma [59,66,69-71]. Theoretically, glutathione S-transferase influences how an individual handles an inflammatory-

derived ROS burden. Intermediate metabolites can damage cells and generate oxidative stress, and therefore contribute to the pathogenesis of asthma. In some manner, the intermediate electrophilic metabolites arising in the first phase of detoxification, might not be metabolized and/or excreted by glutathione transferase enzymes in asthmatic patients.

Ionic channels

Irritant exposures may alter pulmonary ionic channels such as the transient receptor potential vanilloid-1 (TRPV1) and TRPA$_1$ [2,72-82]. (Normally, these channels are primed to recognize irritant chemical and to counter with appropriate neurogenic and biochemical rejoinders [Brooks SM, 2008 #2677]. When there is significant cellular damagefrom a high-level irritant exposure, cellsrelease inflammatory products such as bradykinin, ATP, prostaglandin E2, Nerve Growth Factor, proteases andserotonin that sustainand potentiate the responsiveness of TRPV1 and TRPA1receptors/channels [83-86]. TRPV1 and TRPA1 channels manifest much higher neuronal Ca2+ responsiveness to irritant chemicals, in such a sustained and potentiated state, and introduce changes leading to irritant-induced asthma. Previously unresponsive neuronal tissues can gainhigher sensitivity and display more prolonged neuronal signalling [87]. Neuropeptides released from activated nerve endings lead to localized neurogenic inflammation (see below). The finality of the various alterations leads to sustained airway inflammation, neural plasticity, airway remodeling, persistent airway hyperresponsiveness and clinical asthma symptoms.

Tachykinins and Neurotrophins

The release and subsequent actions of tachykinins and neurotrophins submit an another explanation for airway inflammation and hyperresponsiveness afterirritant-induced airway epithelial injury [88,89]. Neuropeptides released from nerve endings evoke neurogenic inflammation [72,90-96]. For example, Nerve Growth Factor (NGF), accumulating in inflamed tissue, can induce different cells to release pro-inflammatory mediators. In part, sustained neurogenic inflammation evokes a release of cytokines and pro-inflammatory molecules thatfunction in both an autocrine and paracrine manner to create a feedback mechanism causing more NGFrelease [97]. Under the influence of inflammation, nerves undergo remodeling (i.e. neural plasticity) [98]. Neural plasticity appearing in an inflamed airway may both increase synthesis of tachykinins and facilitate its release [98,99]. Neural plasticity induces nervoushyperactivity that translates as bronchial hyperresponsiveness [98].

Airway smooth muscle

Airway Smooth Muscle (ASM) cells regulate airway tone in asthma through the release and response to various cytokines, growth factors and mediators of airway inflammation [100,101]. Borger et al proposed that the pathogenesis of asthma could relate to an abnormal phenotype of airway smooth muscle where there is faster proliferation of ASM cells; the quickening might contribute to the increase in ASM mass found in patients with asthma [102]. Increases in ASM mass, epithelial goblet cell hyperplasia, bronchial epithelial abnormalities, lamina reticularis thickening, proliferation of airway blood vessels and nerves are key structural changes in the airways of asthmatics. Cultured ASM cells of patients with asthma produce less prostaglandin E2 but show greater number of E-prostanoid receptors on the cell membrane [102]. PGE2 is the major prostanoid produced by ASM

cells and can lead to the inhibition of ASM cellular proliferation. Both PGE2 and PGF2α directly activate lung C-fibers.

Abnormal airway remodelling

The initiation of an abnormal Epithelial-Mesenchymal Trophic Unit (EMTU) in response to an irritant may be because the bronchial epithelial cells of asthmatics are more responsive to environmental irritants [103].

Subclinical asthma

Severe early-onset asthma, appearing first during childhood, is associated with a strong allergic component, eosinophilic inflammation and diminished anti-inflammatory response to corticosteroid resistance. Adult-onset asthma without airway eosinophilia may signify a distinct clinical type of asthma [104]. Feasibly, the asymptomatic individual with roots of childhood asthma may have their asthma exacerbated or aggravated by accidental single or repeated irritant exposures [10,105,106]. The reason for this conclusion is because the type of asthma originating in infancy or childhood was believed to have an encouraging future prognosis. Presumably, many cases went into "remission" or displayed a reduction in asthma symptoms between the ages of 10 and 20 years [107]. It is now recognized that this assumption is not always correct. While the severity of asthma symptoms fluctuates with time, the inherited tendency towards respiratory symptoms never disappears; and,a majority of young adults who seem to be free of asthmatic symptoms do, in fact, have persistent asthma symptoms [108-111]. Even in the absence of current asthma symptoms, asymptomatic asthmatic subjects can still demonstratesubstantial air flow limitation and show increases in bronchial hyperresponsiveness [112-115].

Asthma clinical phenotype

Perhaps, repeated exposure-type irritant-induced asthma exemplifies a distinct asthma phenotype dependent on the type of airway cellular inflammation and the airway's unique response to environmental stimuli [116-118]. Bronchoscopic evaluation of the types of airways' cells has been utilized to investigate difficult-to-treat asthma and define asthma phenotypes [118-120].

Prognosisof Irritant-Induced Asthma and RADS

The long-term outcome of irritant-induced asthma was examined in a follow-up study of 35 subjects reassessed nearly 14 years after their inhalational accident [16]. The type of causal agent, the interval since the accident, and a visit to an emergency room or a hospitalization were not predictors of prognosis. In this investigation, asthma symptoms persisted in all subjects and more than two thirds required inhaled corticosteroids. Nearly 50% revealed bronchial obstruction and 75% showed bronchial hyperresponsiveness. One quarter of the sample of subjects manifested bronchial eosinophilic inflammation. Workers often reported impaired smell after the inhalational accidents. It seems that the long-term outcome of subjects with irritant-induced asthma is similar to subjects with allergic occupational asthma. As for allergic-type occupational asthma, approximately 25% of subjects show a disappearance of bronchial hyperresponsiveness two years after the inhalational accident with a plateau afterwards [121].

Treatment of Irritant-Induced Asthma

The treatment of RADS is similar to the treatment afforded patients suffering from an acute inhalational injury. Aerosolized bronchodilators are essential for treating bronchoconstriction (as measured by spirometry) or bronchospasm (as determined by auscultation finding of wheezing). The beneficial effect of parenteral steroids has been shown in an animal model of RADS in which dexamethasone was administered immediately before chlorine inhalation [49]. There are no human study showing efficacy of oral corticosteroids in the treatment of RADS cases; and, possibly oral steroids may not be effective. Inhaled steroids have been found effective in reducing airway hyperresponsiveness in a case considered to be RADS [22]. A substantial number of patients with RADS show biopsy findings of eosinophilic inflammation many years after the acute inhalational accident [16]. These findings are used as a justification for employing inhaled steroids to treat RADS.

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