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Which agents cause reactive airways dysfunction syndrome (RADS)? A systematic review

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Aim	To identify those agents reported as being associated with reactive airways dysfunction syndrome (RADS).
Methods	A systematic review was undertaken. Abstracts were screened and those selected reviewed against pre-determined diagnostic criteria for RADS.
Results	Significant information gaps were identified for all measures of interest. In some articles, even the causative agent was not reported. The most commonly reported agents were chlorine (nine subjects), toluene di-isocyanate (TDI) (n = 6) and oxides of nitrogen (n = 5). Most exposures occurred in the workplace (n = 51) and affected men (60%). Dyspnoea (71%) and cough (65%) were the commonest symptoms. Median symptom duration was 13 months (interquartile range = 6.5–43.5) for RADS.
Conclusions	Although the most commonly reported agent associated with RADS was chlorine, the main finding of a general lack of adequate information on exposure, investigation and outcome suggests that to better explore RADS a more structured approach to gathering information is required. A minimum data set for reporting RADS cases is proposed.
Key words	Asthma; irritant-induced asthma; reactive airways dysfunction.

Background

Twenty years ago, Brooks coined the term 'reactive airway dysfunction syndrome' (RADS) [1] which he defined as symptoms simulating asthma within 24 h of a single, massive, chemical exposure. The United Kingdom surveillance of work-related and occupational respiratory disease (SWORD) survey found that the prevalence of asthma in those who had had an acute irritant exposure varied, apparently affected by the intensity and length of acute exposure, the duration of follow-up and the suspected agent [2]. As the agent involved in RADS may affect prognosis, the authors aimed to assess the range of agents implicated in RADS.

Methods

A systematic review of RADS using Brooks' criteria (see Figure 1) was undertaken. Studies were included if subjects suffered from RADS as defined by Brooks. Reactive airways dysfunction was defined (see Figure 1) as requiring a documented absence of preceding respiratory complaint with symptom onset occurring after a single specific exposure incident to a gas, smoke, fume or vapour present in very high concentrations which had irritant qualities to its nature. Further, Brooks required that the onset of symptoms occurred within 24 h after the exposure and persisted for at least 3 months, that symptoms simulated asthma (cough, wheezing, chest tightness and dyspnoea) and that while pulmonary function tests might show airflow obstruction, methacholine challenge testing was positive and other types of pulmonary disease were ruled out. Studies were excluded if they contained no cases meeting Brooks' RADS criteria or were duplicate publications or follow-up studies.

Studies were identified by searching MEDLINE, EMBASE and CINAHL from 1985 to 2005 (limited to English language and further limited to human research for EMBASE and MEDLINE) supplemented by review of references of recent review articles and original reports. The search was complemented by hand-searching conference abstracts published in the American Review of Respiratory and Critical Care Medicine, European Respiratory Journal and Thorax from 1985 onwards. Keyword search terms included reactive airways dysfunction

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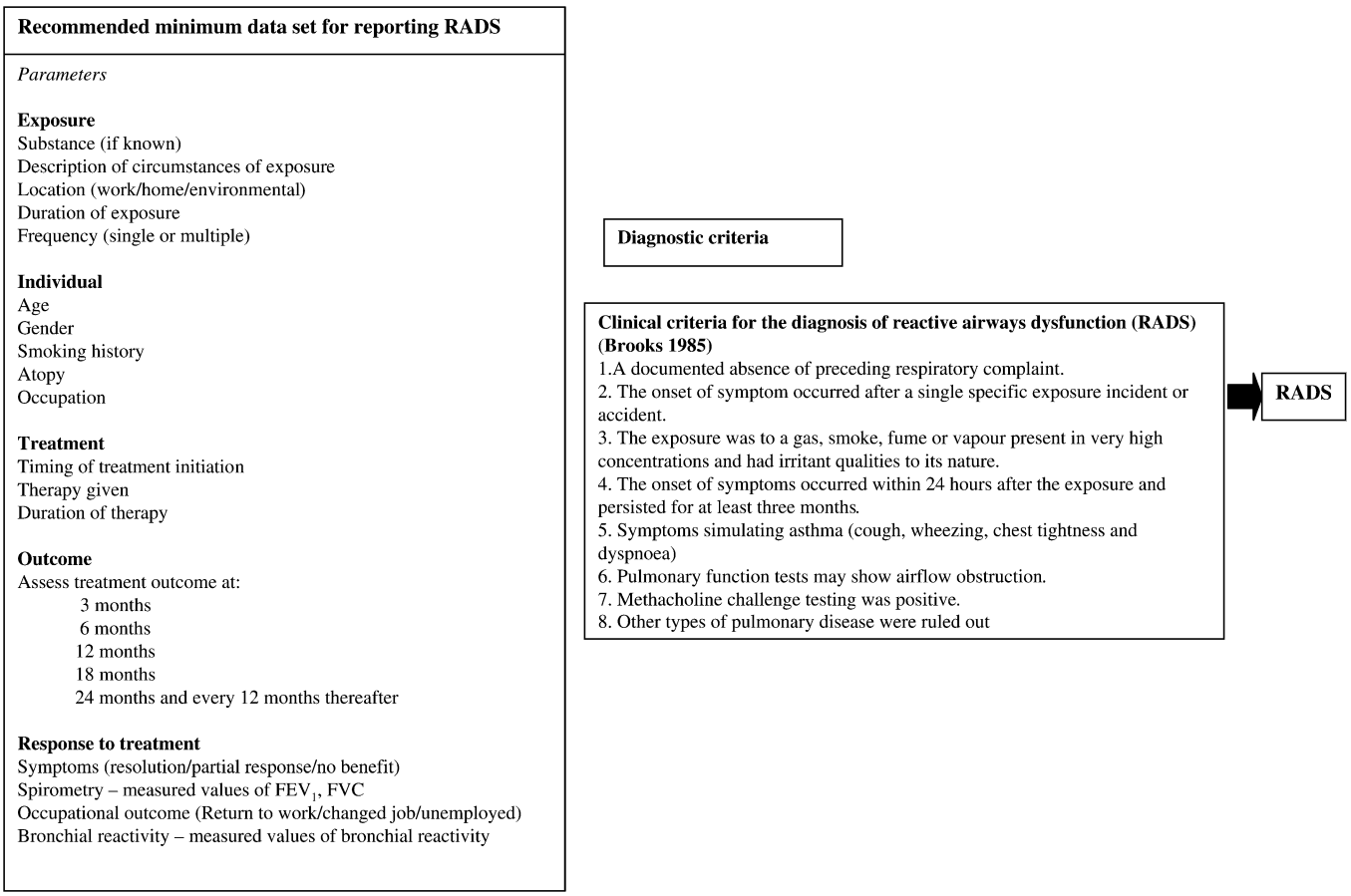

Figure 1. Flow chart showing on the left the suggested minimum data set for reporting any case of reactive airways dysfunction and on the right Brook's diagnostic criteria referred to in this review.

syndrome, irritant-induced asthma, toxic gas inhalation, non-immunologic asthma or irritant gas.

Two people (M.S.S. and F.D.D.) reviewed all titles and abstracts to exclude studies that failed to meet inclusion criteria. Full texts selected were reviewed to exclude studies where the patient did not have RADS. Disagreements on three cases were resolved by discussion. A single reviewer (M.S.S.) extracted data on the causative agent or agents, exposure level, duration of overexposure, location of accident, number of cases, symptom onset, symptoms, symptom duration, the provocation concentration causing a 20% fall (PC_{20}) in forced expiratory volume in 1 s after inhalation of methacholine or histamine, forced expiratory volume in 1 s (FEV_1%), FEV_1/forced vital capacity ratio (FVC), variation of peak expiratory flow, treatment onset, treatment type, treatment response, atopy and, where undertaken, biopsy results. After data extraction, results were entered on separate tables for each category of data (e.g. PC_{20}, FEV_1%) extracted.

Results

Eighty-four articles and abstracts were found but 25 of the articles identified either contained no cases meeting RADS criteria or were duplicate publications or follow-up studies and so were excluded. Among the 633 cases described in the 59 articles selected, 63 cases met Brooks' criteria and 570 had insufficient data for allocation to RADS (Appendix 1). Of the 63 RADS cases, 38 (60%) were male, 12 (19%) female and in 13 (21%) gender was not reported. The mean age in this group was 37.8 (SD 11.6) years but age was not reported for seven people.

The most common agents in patients who met Brooks' criteria were chlorine (nine subjects), TDI (six subjects), oxides of nitrogen (five subjects), acetic acid (four subjects), sulphur dioxide (four subjects) and paint (four subjects) [1].

The most frequent location of exposure episode in those with RADS (n = 63) was the workplace (n = 51) with others occurring in the environment (eight subjects), home (three subjects) and not reported (one subject). The proportion of non-atopic patients was higher than atopic patients but for 41% of RADS group atopic status was not reported.

The onset of symptoms in Brooks' group occurred immediately (within 1 h) in 29 patients and within 24 h in 34 patients. In one article that reported 20 cases [3], the onset of symptoms in 17 cases occurred within 24 h

and in three cases within 1 week. It is unclear in which of those cases symptoms began within 1 week. As it was not possible to categorize these 20 patients, they were excluded.

Dyspnoea, cough and wheeze were the most common symptoms. Seventy-one per cent of RADS subjects had dyspnoea ($n = 45$), 65% cough ($n = 41$), 43% wheeze ($n = 31$), 43% chest tightness ($n = 27$), 29% upper respiratory irritation ($n = 18$), 25% eye irritation ($n = 16$), 16% mucus production ($n = 10$) and 6% cyanosis ($n = 4$). In the RADS group, symptom duration was recorded in all cases. The median and interquartile range (IQR) for symptom duration in patients who met Brooks' criteria was 13 (6.5–43.5) months.

Of 63 patients who met Brooks' criteria, 19 (30%) were smokers with a median (IQR) consumption of 11 (7–18) pack-years, 7 patients (11%) were ex-smokers with a median (IQR) consumption 5 (5–10.8) pack-years and 21 (33%) patients were non-smokers. In 16 subjects with RADS (25%), no information was given about smoking.

Information regarding FEV_1% was available for 49 of the 63 (78%) subjects with RADS. Among these 49 subjects, 16 subjects (33%) had an FEV_1% <80%, the median (IQR) for FEV_1% being 63% (55.5–75). FEV_1/FVC ratios were available for 44 of the 63 patients (70%) meeting Brooks' criteria and in 23 of these 44 cases (52%), the ratio was <80%. The median FEV_1/FVC ratio was 69% (64.3–71.8).

Discussion

The most commonly reported agents in the literature associated with a diagnosis of RADS were chlorine, TDI and oxides of nitrogen. The agents most frequently implicated in RADS were as anticipated although this list is likely to be incomplete as many cases of RADS may go unreported. It is possible that a degree of publication bias exists as once an agent has been first reported thereafter single case studies are less likely to be published and so the relative contribution of some agents to the overall burden of RADS may be underestimated. As these reports are essentially descriptive papers such suspected publication bias cannot be formally tested. However, the main finding was the remarkable inconsistency in the information provided, which in many cases did not permit a diagnosis of RADS despite being reported as such. In >40% of all cases, data were missing. In five articles, the causative agents were not stated.

Information on outcomes in relation to exposures needs to be collected formally and in a structured way if better advice and understanding of these conditions is to be gained. It is proposed that the data listed in Figure 1 constitute a minimum data set for reporting of RADS cases in the medical literature. A web-based reporting system with a database that could be updated online to permit the reporting and follow-up of cases would be of benefit and would deal to some extent with the issue of publication bias.

In summary, a systematic review of agents reported as being associated with RADS has been undertaken. The key finding is a lack of complete reporting of relevant information which limits generalization from, or summary of, these reports. As a consequence, a minimum data set for reporting RADS in the literature is proposed.

Key points

- There was a general lack of adequate information on exposure, investigation and, in particular, outcome of reported cases or case series of RADS.
- The most commonly reported agent associated with RADS was chlorine with TDI and oxides of nitrogen next most common.
- We suggest that a web-based database of RADS (and irritant-induced asthma) cases be established which would allow continuous update and better analysis of outcome in these individuals.

Conflicts of interest

None declared.

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Appendix 1: Papers included in systematic review and agents implicated in RADS

First author	Year	RADS exposures (No.)[a]	Cases not meeting Brooks' criteria (No.)[a]
Brooks [1]	1985	Uranium hexafluoride, floor sealant, spray paint (3), 35% hydrazine, heated acid, fumigating fog, metal coat remover, fire/smoke	
Boulet [21]	1988	Sulphuric acid, bleaching agent, perchloroethylene, TDI	
Tarlo [5]	1989		Acids, chlorine, sulphuric acid, sulphur dioxide[b], burnt paint fume, spray paint without isocyanates, chlorine, TDI, diphenyl methane diisocyanate
Gilbert [28]	1989	Dust or mold in silo (fungus)	
Luo [12]	1990		TDI (2)
Promisloff [20]	1990	Sodium hydroxide, silicon tetrachloride, trichlorosilane [b](2)	Sodium hydroxide, silicon tetrachloride, trichlorosilane[b]

Appendix 1: (*Continued*)

First author	Year	RADS exposures (No.)[a]	Cases not meeting Brooks' criteria (No.)[a]
Demeter [29]	1990	Sulphuric acid, unknown	Lithium bromide, hydrogen chloride, cleaning solvent, zinc chloride (11)
George [30]	1990		Smoke (7)
Saric [31]	1991		Respiratory irritant such as hydrogen fluoride (30)
Kern [32]	1991	Acetic acid (4)	Acetic acid
Angelillo [17]	1992	Chlorine (3)	
Hu [33]	1992		*o*-chlorobenzylidene malononitrile
Blanc [34]	1993	Sodium azide (2), epoxy resin, household cleaner containing morpholine	
Palczynski [35]	1994	TDIs	
Chan-Yeung [36]	1994		Sulphur dioxide, hydrogen sulphide, acetic acid, hydrogen peroxide, chlorine, chlorine dioxide, hydrogen sulphide, methyl mercaptan, sulphur dioxide, hydrogen peroxide[b](2)
Gautrin [37]	1994		Chlorine (12), nitrogen dioxide (3)
Palczynski [38]	1994		Freons and phosgene[b]
Deschamps [39]	1994	Sodium hypochlorite and hydrochloric acid (chlorine)[b]	
Tarlo [40]	1995		Isocyanates (8), acid (3), acrylate (2), solvents, fume (2)
Sallie [41]	1995		Chlorine (9), sulphur dioxide (4), oxides of nitrogen (3), phosphine (2), ammonia (2), hydrogen sulphide, hydrogen chloride gas, sodium hydroxide, sulphuric acid, 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, unknown chemical
Stanbury [42]	1996		Pentamidine
Piirila [15]	1996	Sulphur dioxide (4)	Sulphur dioxide
Cormier [43]	1996	Hydrogen sulfide	
Weiss [18]	1996	Sodium azide and hydrozoic acid[b] (2)	
Schonhofer [19]	1996	Chlorine (3)	
Lemiere [44]	1996	Isocyanates mixed with organic solvent	
Yelon [45]	1996		Formic acid
Lemiere [46]	1997	Chlorine	
Burns [47]	1997	Bromine and hydrobromic acid (2)	
Provencher [48]	1997		Chlorine, isocyanates and acid were the most often reported causal agent
Danielsen [49]	1998		Hydrogen peroxide (3)
Forrester [16]	1997		Refractory ceramic fibre, phosphoric acid[b]
Leroyer [50]	1998	Diphenylmethane diisocyanate	
Conrad [51]	1998	Dinitrogen tetroxide (5)	
Wheeler [52]	1998		General fume (4), solvent/hydrocarbon (2), corrosive agents (3), formaldehyde (3), irritant gas (2), other (4)

Appendix 1: (*Continued*)

First author	Year	RADS exposures (No.)[a]	Cases not meeting Brooks' criteria (No.)[a]
Chatkin [6]	1999	TDI (4), isocyanate, chlorine, spray paint	Methyl mercaptan, solvent, glue[b], solvent, acrylate[b], TDI, isocyanate
Woolf [53]	1999		Bromine
de la Hoz [13]	1999		Bromotrifluoromethane, hydrogen fluoride, hydrogen bromide, carbonyl fluoride, carbonyl bromide[b]
Langley [54]	1999		Welding fume
Hill [55]	2000		*o*-chlorobenzylidene malononitrile (CS)
Meyer [56]	2001		Hydrogen fluoride, nitric acid[b], aldehydes, acetic acid[b]
Dube [57]	2002		Fume from an iron smelting process
Kopferschmitt-Kubler [58]	2002		Acid (4), chlorine (3), isocyanate (3)
Perfetti [59]	2003		Diphenylmethane diisocyanate
McLaughlin [60]	2003		Chlorine (2), rubber fume, sewerage gas, ammonia, propionic acid, NH4 and sorbic acid[b], ethanol, isopropanol, gingerine[b]
Piirila [22]	2003	Thermal decomposition products of CFC(2)	
Henneberger [61] Some selected agents	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 glycol[b], ammonia, acids, bases, oxidizer (NOS)[b], muriatic acid, ethanolamines, indoor air pollutant
Franzblau [14]	2003	Hydrofluoric acid	
Rosenman [62]	2003		Cleaning agent (42)
Banauch [63]	2003		World trade centre fume (20)
Matrat [11]	2004	Bromochlorodifluoromethane	Bromochlorodifluoromethane (2)
Gorguner [64]	2004		Sodium hypochlorite and hydrochloric acid (chlorine) (55)[b]

[a] $n = 1$ except where otherwise indicated.

[b] Indicates exposure to multiple agents.