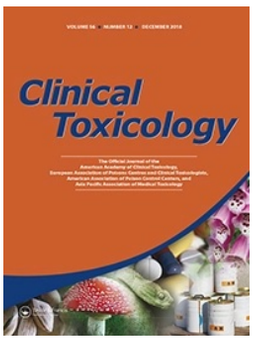

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SHORT COMMUNICATION

Aerotoxic syndrome, discussion of possible diagnostic criteria

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ABSTRACT

Introduction: The term aerotoxic syndrome (ATS) was proposed 20 years ago to describe a constellation of symptoms reported by pilots and cabin crew following exposure to hydraulic fluids, engine oil, and pyrolysis products during flight. Hydraulic fluids and engine oil contain a large number of potentially toxic chemicals, including various organophosphate compounds (OPCs). However, ATS is not yet recognised as a valid diagnosis in aviation or general medicine, because the incidence and aetiology continues to be debated.

Discussion: Early studies report findings from symptom surveys or cognitive assessments of small samples of self-selected aircrew, but objective measures of exposure were lacking. Over the last decade, researchers have used more sophisticated techniques to measure exposure, such as on board monitoring studies and biomarkers of exposure (e.g., reduced levels of serum butyrylcholinesterases [BChE]) and more sophisticated techniques to detect nervous system injuries such as fMRI and auto-antibody testing. Consideration has also been given to inter-individual differences in the ability to metabolise certain chemical compounds as a result of genetic polymorphisms and exclusion of other potential causes of ill health.

Conclusions: We discuss factors which suggest a diagnosis of probable ATS; recommend an assessment protocol which incorporates the aforementioned techniques; and propose diagnostic criteria for probable ATS, based on our previously reported findings in aircrew and the results of recent studies.

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KEYWORDS
Aerotoxic syndrome; organophosphates; pilots and cabin crew; contaminated air

Introduction

The term "Aerotoxic Syndrome" (ATS) was proposed in 1999 to describe a constellation of symptoms reported by cabin crew [1]. On most commercial aircraft, cabin air is drawn from outside and then circulated around the engine before being pumped into the cabin ("bleed air"). Cabin air sometimes becomes contaminated by hydraulic fluids or jet engine oils because of faulty seals or following the overfilling of oil reservoirs. Hydraulic fluids and engine oils contain a number of potentially neurotoxic organophosphate compounds (OPC) including tricresyl phosphate (TCP), but also contain other neurotoxins such as toluene and xylenes.

Over the last decade, air monitoring studies detected small amounts of contaminants in cabin air during normal operating conditions. A recent cabin air quality study, carried out on 177 flights of 61 bleed air supplied aircraft and eight B787 (bleed air free) aircraft, quantified approximately 100 individual compounds [2]. Mean concentrations of volatile organic compounds and aldehydes in the B787 aircraft were lower than in the bleed air aircraft. Tri-n-butyl- phosphate, which originates from the hydraulic system, was the most prominent OPC. OPC mean concentrations were in the range of 0.74–5.36 μg/m^3. Only a small fraction of organophosphates could be attributed to TCP, which concentrations were low and in agreement with previous studies [3]. Regulatory authorities estimate fume events happen on 0.2–0.5% of flights, but in this study, 18 cases of increased TCP concentrations, which is considered as indication of oil leakage, were detected during 177 flights. TCP concentrations increased to 0.56–1.67 μg/m^3, especially in the take-off phase of two A321 and one A380 flight [2].

Airlines and regulatory authorities use these findings to argue that the level of chemical substances in cabin air fall within safe exposure limits and cannot be responsible for ill health reported by aircrew. However, the type and quantity of chemicals that enter the cabin air following an engine oil leak remains uncertain and consideration has not been given to the possibility that cumulative low-level exposure over time could be responsible for ill health and/or the synergistic effects of chemical combinations may increase toxicity several fold.

In this article, we discuss factors which suggest a diagnosis of ATS, the application of brain MRI techniques, and serum auto-antibody and genetic testing in suspected cases, and we propose diagnostic criteria for "Aerotoxic Syndrome".

Reported symptoms

Symptoms reported by aircrew following exposure to contaminated air can be divided into acute symptoms, which occur

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within 48 h following exposure, such as eye, skin and respiratory irritation, headaches, nausea, vomiting, gastrointestinal symptoms, and chronic symptoms, persisting for more than 1 or 2 months, including cognitive impairment, gastrointestinal problems, myalgias, palpitations and fatigue [4].

Symptoms correlate with flying hours

In most cases, symptoms appear to onset during the flying career and show a temporal relationship with time spent on board aircraft as they onset or worsen when flying and reduce or resolve during holidays and days off. Winder et al. (2002) undertook a survey of 50 Australian aircrews. Most of the respondents reported that their symptoms occurred after exposure to fumes in the cabin. Some recovered once they vacated the plane, but 41 aircrews reported symptoms persisted for 1–6 months leading to hospitalisation in 8 of them [5].

Consistency and specificity of symptoms

Symptoms should occur repeatedly after flying and not occur under other circumstances.

Objective evidence of exposure

Commercial aircraft do not have air quality monitoring systems on board so previous studies have used a number of different measures of exposure. These include proxy measures such as aircraft type flown and duration of employment as a pilot or flight attendant and more direct measures such as engineering reports of oil leaks, wipe samples of the cabin and flight deck walls and biomarkers of exposure in blood and urine such as butyrylcholinesterase (BChE)(a biomarker of exposure to OPC). In one case, a pilot had a 50% reduction of BChE values, gradually increasing to normal in the first five consecutive days following a flight [6]. Smell events, odour in the cabin (old socks, wet dog) do not necessarily indicate the presence of harmful contaminants, they can be caused by a number of different factors such as de-icing chemicals, cosmetics, cleaning products, food and beverages, and frequently the source of a smell event cannot be identified [2].

Inter-individual differences in the ability to metabolise certain chemicals may explain why not all aircrew are equally affected following exposure to contaminated air. For example, a genetic susceptibility to organophosphates poisoning has been reported in other occupational groups involving the Paraoxonase (PON)-1 enzyme, which is involved in the detoxification of organophosphates. People differ in terms of PON-1 activity due to genetic polymorphisms and a blood test can determine whether an individual has high, intermediate or low PON-1 activity [7]. Cytochrome P450 enzymes mediate the conversion of organophosphates to its reactive metabolites. Genetically based diverging levels of cytochrome P450 indicate a difference in individual hepatic activity of 50–100-fold [8]. In a worst-case scenario, a 4000-fold difference in sensitivity can be postulated for individuals expressing a very high P450 activity and very low PON 1 activity.

Objective evidence of nervous system injury

Routine neurological examination is frequently reported to be normal in many cases, or reveals only mild abnormalities. Nerve conduction velocities, electromyography, autonomic nervous system tests and brain MRI, SPECT and PET have been reported in many case studies, but are also normal in many individual cases. Neuropsychological studies of pilots and flight attendants consistently demonstrate reduced performance on tests of psychomotor speed, executive functioning, and attention [9], but cannot determine causation.

Recent studies have measured immunoglobin (IgG) levels using Western blotting against neurofilament triplet proteins (NFP), tubulin, microtubule-associated tau proteins, microtubule-associated protein-2 (MAP-2), myelin basic protein (MBP), glial fibrillary acidic protein (GFAP), and glial S100B protein [6,10] and find evidence of central nervous system (CNS) injury. For example, 34 flight crew with CNS related complaints, were found to have higher auto-antibody-levels than matched controls [6], but again, causation cannot be determined.

Magnetic resonance imaging (MRI) of 12 aircrew with cognitive complaints, including diffusion tensor imaging, spectroscopy, and functional MRI revealed a reduction of white matter microstructure in small brain regions, correlating with severity of cognitive impairment, but not flying hours, and reduced brain activation on a executive function task [11]). Further MRI studies of aircrew are necessary to confirm these findings.

Other causes of ill health excluded

The symptoms reported by aircrew are relatively non-specific, making it important that other causes of ill health are excluded by medical history, physical and neurological examination, laboratory investigation, brain MRI and psychological assessment. Neuropsychological assessment not only detects cognitive impairment, but also can exclude a depressive disorder, somatisation disorder and malingering [9]. Psychological factors such as mass hysteria, stress-induced hyperventilation, nocebo effects or psychosomatic conditions; or other aspects of working in the aviation industry such as shift work, jet lag, pressure changes, exposure to cosmic radiation and ozone may be responsible for the onset of ill health.

Conclusions

We propose criteria to diagnose and recognise ATS, based on the cases we have examined, see Table 1 [6]. Future studies need to obtain objective measures of exposure such as engineering reports and air quality analysis and correlate these with symptom onset. Specialised tests should be undertaken to provide objective evidence of nervous system injury and to determine whether there are subgroups of

Table 1. Proposal of diagnostic criteria of probable aerotoxic syndrome.

1. Reported symptoms include: headache, loss of balance, gastro-intestinal complaints, palpitations, and cognitive complaints
2. Symptoms correlate with flying hours. Symptoms onset shortly after a fume event or directly after flying and improve after cessation of flying
3. Consistency and specificity of symptoms. Symptoms should occur repeatedly after flying and not occur under other circumstances
4. Objective evidence of exposure is available such as air incident reports, engineering records, on-board air monitoring or swipe/sample measurements of chemical contaminants. Biomarkers of exposure are available such as reductions in serum-butyrylcholinesterases activity; and/or other supportive findings such as a high P450 activity and/or low PON-1 activity
5. Objective evidence of nervous system injury is available following medical tests, brain imaging and/or elevated serum neuronal and glial autoantibodies are detected
6. Other causes of ill health are excluded by medical history, physical and neurological examination, laboratory investigation and brain imaging. Neuropsychological tests should exclude a depressive disorder, somatisation disorder, and malingering

people at increased risk of developing ill health following exposure to engine oil fumes in commercial aircraft. We suggest that if an individual meets all 6 criteria of probable ATS, genetic susceptibility should be assessed in a (pharmaco)genetic lab.

Disclosure statement

No potential conflict of interest was reported by the authors.

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