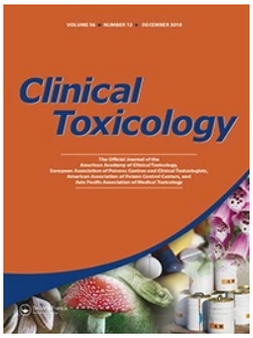

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SHORT COMMUNICATION

Three patients with probable aerotoxic syndrome

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ABSTRACT

Introduction: "Aerotoxic syndrome" is a debated entity. Regulatory authorities consider long-term health effects to be an unlikely consequence of exposure to contaminated air because several air quality monitoring studies report low concentrations of toxic chemicals in cabin air. We describe two pilots and one flight attendant, who developed ill health during their flying career which improved after cessation of flying.

Case details: The most frequently reported symptoms were headache, balance problems, fatigue, gastro-intestinal complaints and cognitive impairment. One of these patients had reduced levels of butyrylcholinesterase after a flight suggesting exposure to organophosphate compounds had occurred. All three were found to have elevated neuronal and glial auto-antibodies, biomarkers of central nervous system injury, and all three had genetic polymorphisms of paraoxonase (PON-1) and two of cytochrome P450, leading to a reduced ability to metabolize organophosphate compound (OPs).

Discussion: A similar constellation of symptoms has been described in other studies of aircrew, although objective evidence of exposure is lacking in most of these studies. Reduced levels of butyrylcholinesterases in one of our cases is suggestive of causation and elevated neuronal and glial autoantibodies provide objective evidence of damage to the central nervous system. We consider further research is warranted.

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CNS/Psychological; aerotoxic syndrome; cabin crew; organophosphates; contaminated cabin air

Introduction

Over the last two decades, several case studies and health surveys have been published describing health effects of aircrew and passengers, attributed to exposure to contaminated air [1]. Hydraulic fluids and engine oils contain a large number of toxic chemicals, including various organophosphates. The term "aerotoxic syndrome" (ATS) was proposed in 2000 to describe the short- and long-term health effects associated with breathing contaminated cabin air. However, reported symptoms are nonspecific and cabin air quality studies indicate contaminant levels are below occupational exposure limits and of no concern to human health [2]. Furthermore, objective evidence of exposure is frequently lacking in previous case studies and surveys and findings from routine medical and neurological examination (including brain imaging) are often reported to be normal in symptomatic aircrew. In this paper, we describe two pilots and one flight attendant, with neurological, respiratory and gastro-intestinal symptoms which onset during their flying career and report the findings of more specialized tests of nervous system injury, metabolic capacity and biomarkers of exposure to OP compounds.

Case reports

Patient A is a 50-year-old pilot, who worked for two (Dutch) commercial airline companies for more than 20 years, with 16 years of intercontinental flights. This patient was one of a case series of 34 flight crew members published in 2013, in which results of assays to detect auto-antibodies were described [3]. He was subsequently referred to our department for further evaluation of his complaints which onset gradually over a period of around 14 years. Initial complaints were burning eyes, migraine-like headaches with visual aura, position-dependent vertigo, loss of balance, tightness of chest and hyperventilation. Over time he developed various gastrointestinal complaints, deterioration of memory and concentration, confusional episodes and fatigue. Symptoms improved when he was not at work and worsened when he returned to flying. He suffered a cardiac dysrythmia following an intercontinental flight and was admitted to an intensive care unit and thoroughly investigated (Tables 1–3).

Patient B is a 31-year-old flight attendant. She worked for 4 years on both European and intercontinental flights. Sometimes she noticed noxious smells in the cabin but she did not report any fume events. Symptoms onset after 3 years of flying and interfered with her ability to perform her duties. After 10 months of alternative employment she felt well enough to return to flying, but her symptoms re-occurred within a few months of flying and she was referred to our department for further investigations. Results from a comprehensive neuropsychological assessment were in the normal range. Six months after her last flight, complaints persisted, (Tables 1–3).

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Patient C is a 30-year-old pilot, who has flown Boeing 737 aircraft for about 3500 hours and whose symptoms onset after 3 years of flying. After a six month period of sick leave she started flying again and almost immediately her complaints returned. Following an incident in which oil reservoirs were overfilled, her symptoms worsened. A cardiologist recorded periods of tachycardia (>100 b/min), but electro-cardiography and echocardiography were normal. Over the next six months of flying her condition deteriorated and she was forced to retire on ill health grounds. Extensive blood tests, including serology of Cytomegalovirus and Epstein–Barr virus were normal. Anti-thyroid peroxidase (TPO) antibodies were mildly elevated, but there were no signs of hypothyroidism or Hashimoto's disease. The only abnormality detected on neuropsychological tests were below average scores on tests of concentration (Tables 1–3 for further results). Brain MRI was not performed. Four years later, an inquiry by telephone revealed that her condition had improved considerably.

Discussion

The symptoms reported by patients have much in common with those reported in other case-series and surveys of aircrew, thought to have been exposed to contaminated air [1]. In patients A and B complaints persisted, in patient C complaints improved. The most frequently reported symptoms were headache, fatigue, gastro-intestinal complaints, cognitive impairment and balance problems. In patient A onset of complaints was gradual over a prolonged period of 14 years of flying, which may seem unusual, but is not uncommon in neurotoxicological disorders (e.g. painter's disease) and has been reported in a previous study of aircrew exposed to contaminated air [4]. Delayed onset of symptoms may reflect the cumulative effects of low level exposure or infrequent exposure to contaminated air. Patient A had reduced levels of butyrylcholinesterase (BChE) suggesting exposure to OPs had occurred. None of our cases reported fume events, but they did report noxious smells in the aircraft cabin. However, noxious smells are not necessarily indicative of engine oil contamination and can be caused by other factors such as de-icing procedures, insecticides and cleaning products. Frequently, the source of smell events cannot be identified [2].

Neuropsychological investigation of aircrew following exposure to contaminated air demonstrated lower scores on tests of working memory, processing speed, reaction time and mental flexibility, not attributable to mood disorder or malingering [5]. In our case series, only one patient showed

Table 1. Patient data, medical and flying history.

	Patient A	Patient B	Patient C
M/F	M	F	F
Age in years	50	31	30
Pilot/cabincrew	pilot	flight attendant	pilot
Medical history	–	–	–
Medication	no	no	no
Use of alcohol	occasionally	no	no
Flying history	20 years, 10,000 hours	4 years, 2600 hours	4 years, 3500 hours
Aircraft type	Dornier 228, Boeing 737, MD-11	Boeing 737 and 747, Airbus A330	Boeing 737
Fume events	–	–	–
Smell events	++	++	++
Onset of symptoms	after 14 years	after 3 years	after 3 years
Exposure time-related	++	++	++

Table 2. Symptoms and diagnostic tests.

Symptoms	Patient A	Patient B	Patient C
Fatigue	✓	✓	✓
Headache	✓	✓	✓
GI complaints	✓	✓	✓
Cognitive impairment	✓	✓	✓
Balance problems	✓	✓	✓
Vertigo	✓	✓	x
Chest tightness	✓	x	x
SOB/HV	✓	x	✓
Palpitations	x	x	✓
Muscle pain/cramp	x	✓	✓
Tingling in limbs	x	x	✓
E,T irritation	✓	x	✓
Tremor	x	✓	x
AChE	normal	n.a.	n.a.
BChE	↓	n.a.	n.a.
PON1 activity	↓	↓	↓
P450 activity	↑	↑	n.a.
Neuropsychology	NES screening: normal	normal	Concentration impaired
MRI Brain Imaging	normal	normal	n.a
Neurophysiology	EEG, autonomic testing and conduction velocities of peripheral nerves normal	EEG normal	Skin biopsy: no small fibre neuropathy

n.a.: not assessed; GI: gastrointestinal; SOB: shortness of breath.
AChE: acetylcholinesterase; BChE: butyrylcholinesterase.
NES: neuroevaluation system.

Table 3. Results of blood and genetic testing.

Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) patient A		
Day after flight	AChE (Normal value 26.7–50.9 U/l)	BChE (Normal value 2300–7000 U/l)
1	30.7	1189
2	32.5	1799
3	30.2	2138
4	33.1	2154
5	38.8	3106

Auto-antibodies to brain specific proteins, compared to healthy controls (Abou-Donia et al., 2013).			
	Patient A[a]	Patient B	Patient C
NFP	↑	↑↑	n
Tau	n	↑↑	↑
Tubulin	↑	n	n
MBP	↑	↑	↑
MAP-2	↑	↑↑	↑
GFAP	↑	↑	↑↑
S100-B	n	n	n

Genetic testing: (1) paraoxonase (PON-1) gene (patients A, B and C).	
Results	Effect
PON-1[M55L] and PON-1[Q192R] polymorphisms	reduced ability to metabolise organophosphates

Genetic testing: (2) analysis of cytochrome P450 (patients A and B).	
Results	Effect
CYP1A1*2A and CYP 1A2*C and F polymorphisms	overexpression of the enzymes mediating the conversion of organophosphates to its reactive metabolites.

Methods: Red blood cell AChE and plasma BChE were tested using a portable tester (Securetec). Sera samples of our patients were send to prof. M.B. Abou-Donia, Durham, North Carolina, to measure immunoglobin (IgG) using Western blotting against brain-specific proteins (Abou-Donia et al, 2013). PON-1 192 and 55 determination was performed by PCR amplification and restriction enzyme digestion. Genotyping assays were used to detect single nucleotide CYP 450 polymorphisms.
n: normal; ↑: increased; ↑↑: markedly increased.
[a]In patient A, in addition four serum samples were taken to test again for neuronal and glial auto-antibodies at four different time periods, before, during and after exposure, and showed a temporal relationship with exposure (3).

signs of cognitive impairment. Cholinergic symptoms in our cases may be gastro-intestinal complaints (A, B and C), palpitations (C), muscle pain and cramp (B and C) and tremor (B). However, various delayed neurological conditions have been reported following OP exposure, after the cholinergic symptoms have resolved, including cognitive impairment and increased neuropsychiatric morbidity [6] and several other noncholinergic mechanisms of OP toxicity have been proposed to account for these such as oxidative stress, impaired axonal transport, neuroinflammation, release of the neurotransmitter L-glutamate, and altered levels of dopamine and serotonin [7].

Acetylcholinesterase (AChE) was not found to be inhibited after a fume event in a study of eleven crew members [8]; however, BChE inhibition has been demonstrated in several case series and surveys, especially in blood samples obtained 24–48 hours after completing a flight [9]. BChE inhibition is the standard biological test used for OP monitoring, but should only be considered as a marker of acute exposure. BChE levels were measured in Patient A in the first 5 days after a long flight (Table 3) and were noted to be reduced on days 1 and 2.

A reduced ability to metabolize OPs due to genetic polymorphisms may explain why some individuals report ill health following exposure to contaminated air whilst others do not. Paraoxonase 1 (PON-1) and Cytochrome P450 are enzymes involved in the detoxification of OPs and lower activity levels are associated with specific genetic polymorphisms. Blood tests in our three patients showed PON-1 192- and 55-polymorphisms [10] and Cytochrome P450 polymorphisms were identified in patient A and B [11].

Brain reactive autoantibodies are independent of disease and are present in the vast majority of human sera [12], but some auto-antibody profiles appear disease-specific. In our patients MBP, MAP-2 and GFAP were increased in all three, whereas S-100ß was normal in all. Our findings were consistent with those reported in a study of 34 flight crew members in which auto-antibodies against MAP-2, tubulin, MBP, tau and GFAP were markedly elevated, whereas auto-antibodies against S-100 ß (a biomarker for traumatic brain injury) were (almost) normal, as in our cases [3]. Sera of the 12 healthy controls had no or low levels of circulating auto-antibodies. Our findings provide objective evidence of damage to the central nervous system, but not of causation. Whether the autoantibody profile is specific to engine oil emissions needs to be addressed in future studies.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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