

THE CURRENT DEBATE

PRELIMINARY REPORT ON AEROTOXIC SYNDROME (AS) AND THE NEED FOR DIAGNOSTIC NEUROPHYSIOLOGICAL TESTS

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Abstract

Researchers have found, in studies carried out over several years, that many passengers and crew, following their recent flights in commercial jet aeroplanes, have become unwell, with a range of symptoms in common. This condition, which has not yet been officially recognised, is called *Aerotoxic Syndrome (AS)*. It seems to be caused, primarily, by neurotoxic organophosphates contaminating the air circulating in jet cabins. Patients with such symptoms may visit their GPs, who then arrange diagnostic tests. Some of their symptoms fall within the jurisdiction of diagnostic neurophysiological investigations, but neurophysiology practitioners may be unaware of this syndrome. Until AS is officially recognised as an illness, and guidelines for diagnostic procedures established, patients requiring specific investigations may not be appropriately referred, or tests may be performed unnecessarily. This report seeks to stimulate debate within the field, and facilitate studies, if needed, to help define the diagnostic criteria.

Key words: *Aerotoxic syndrome (AS), chronic fatigue syndrome (CFS), continuous positive airways pressure (CPAP), sleep apnoea, neurotoxins, pyrolised air, organophosphates (OP), tri-cresyl phosphate (TCP), tri-ortho cresylphosphate (TOCP).*

Aims

This paper has evolved from a single case study. The authors have attempted to highlight several issues – many of which are outside the remit of practitioners in clinical neurophysiology, but which put this syndrome into context. However, as some departments may be seeing patients with a potential diagnosis of aerotoxic syndrome (AS), practitioners need to be aware of the condition, and the relevance of neurophysiological tests in such cases. A brief overview of the wider issues has been included, with a bibliography, in the hope that readers may find the topic of sufficient interest and importance to consider investigating further, especially with an increasingly multidisciplinary approach to diagnostic investigations. Due to the complexities of the condition, national guidelines for the diagnostic process may be required, and the authors hope that this article may facilitate debate and further studies within and beyond the field.

Introduction

There have been increasing numbers of reports, in both the mass media (Clarke, 2005; Bennis, 2007a, 2007b; Lean, 2007; Toxic Free Airlines, 2007; Aerotoxic Association, 2007; Brehany, 2008; Hogg, 2008) and academic journals (Abeyratne, 2002; USNAS, 2001; Winder and Balouet, 2001; Winder, Fonteyn, et al., 2002) about airline pilots suffering from ill health due to air pollution inside their cockpits. Some were so severely affected that they had to take early retirement on grounds of ill health (Hoyte, 2007; TFA, 2007). There is a growing body of evidence that the problem is widespread and global, and has not only affected pilots, but cabin staff and passengers too (Michaelis, 2007; TFA, 2007; SoRaSS, 2008). The condition has been called *Aerotoxic Syndrome (AS)*, although this is not well known amongst healthcare practitioners, and reports indicate that very few doctors have expertise in this field (Myhill, 2007).

Symptoms vary, according to the toxic components of the air pollution and duration of exposure, and may include fatigue, sleep disorders, blackouts, seizures, neuromuscular pain and weakness (Winder and Balouet, 2001; Winder and Michaelis, 2005). It is, therefore, quite feasible that some patients, having been referred to departments of clinical neurophysiology for investigation of these symptoms, may have aerotoxic syndrome. Until this is recognised, sufferers may not be asked appropriate questions when medical histories are being

taken, as a result referrals for inappropriate diagnostic investigations may be made and inadequate or irrelevant treatment provided.

Literature Review

A preliminary Internet literature search was undertaken, to establish the factual basis for this condition. It soon became clear that a significant amount of work has already been published by experts in various fields (Abeyratne, 2002; AFAP, 2003; AOPIS, 2008; CAT, AMA, 1953; COT, 2006; Heuser, et al., 2005; HoL, 2007; HoLSaTC, 2000; Montgomery, et al., 1977; Sigmund, 2007; Winder, 2002). Many papers and reports were available, facilitating cross-referencing, and a picture of the evolution of this condition quickly emerged. Studies have been carried out by academics in university departments, for example University College, London, UK (Mackenzie Ross, 2008a) and University of New South Wales, Sydney, Australia (SoRaSS, UNSW, (2008); Winder, 2005), with their findings presented to various governments and their agencies (COT, 2007c; HoLSaTC, 2000; HoL, 2007, 2008; Mackenzie Ross, 2006).

The term 'Aerotoxic Syndrome' was first proposed in 1999 (Winder, et al., 2002), and many people believe this condition is caused by contaminated air circulating in the cabins of jet aeroplanes (Winder, 2002; Michaelis, 2007; Mackenzie Ross, 2006). So far, the earliest relevant article identified was published in 1951 (Sigmund, 2007). A review of 89 cases was published in 1973 (the earliest clinical study located), and a peer-reviewed case study in 1977 (Montgomery, et al., 1977). The subject was a 34-year-old flight navigator who was exposed to contaminated air and incapacitated during a flight. He suffered disturbances of both neuromuscular and cognitive function, requiring medical attention. This incident warranted further investigations to ascertain its cause (Montgomery, et al., 1977). The recommended enquiries were not initiated or carried out at that time (TFA, 2007). Over the subsequent 30 years, and with a growing awareness of this problem amongst flight crews, it seems little has been done to thoroughly investigate the problem, and resolve the matter (Gill, 2006; Michaelis, 2008b).

The Background to Aerotoxic Syndrome

A growing number of pilots and cabin crew, as well as passengers, claim to have been affected by air pollution whilst flying, and several anecdotal reports are available (AA, 2008; TFA, 2008). A major retrospective study was carried out by Susan Michaelis, which is reported to be the most comprehensive to date (Michaelis, 2007; TFA, 2008). It has been highly acclaimed by several professionals, including medical practitioners (Singh, 2007). Described as the 'definitive manual', it covers the design and function of the air systems in aeroplanes, the risks and problems, the contaminants and their effect on health, the range of symptoms experienced by exposed people, and the short and long-term health problems encountered (Michaelis, 2007).

Air Supplies in Conventional Passenger Aircrafts

Contamination of the air supplies, used by passengers and crew on aeroplanes, is said to be caused by the use of lubricating oils and hydraulic fluids in jet engines, and an inappropriate design of the air intake air mechanisms (Myhill, 2007). Air from outside the aeroplane is sucked in through the engines, and is 'bled off' then used within the cabin, for a) pressurisation and b) the oxygen supply for crew and passengers. This bleed air is very hot, and requires cooling in an air conditioning pack before being circulated. Contamination can occur from either of these two sources (the cooling system or the engine); for example, when the engine sealing system leaks, droplets of oil can be sucked in with the air, and subsequently circulated within the cabin. This is a common cause of air contamination, as no seals are 100% effective. Some types of seal actually use a controlled air leak, therefore some oil contamination will usually be present in bleed air (Myhill, 2007; Brennan, 2008).

The pyrolised (heated) air contains various chemicals, and it depends on the nature of the fault as to which chemical, or combination of chemicals, will be transmitted into the cabin. The contaminants may include organophosphates (OPs), which are known neurotoxins (Winder, et al., 2002; Shell, 2003; Mackenzie Ross, 2006). Each has different effects on humans, depending on the individual's susceptibility, the strength of the contaminant and exposure time, the effects of which may also vary when chemicals are combined (Myhill, 2007).

The Health and Safety at Work Regulations of 1992 require employers to identify and evaluate risks to health, carry out a full risk assessment, and implement appropriate measures to eliminate or minimise those risks.

Tri-cresyl phosphate (TCP) is frequently cited in the literature as one of the chemicals used in engine oil (Myhill, 2007; Winder, 2002). This chemical is listed on the data sheet as one of the ingredients of one particular product used in aeroplane engines. Its potential risks are described, with clear information for users. "Tri-cresyl phosphate is neurotoxic in animals and man. These effects are delayed and may be permanent depending upon the degree of exposure." Where respiratory problems may occur, precautions are advised including the use of breathing equipment, masks and filters (Shell, 2003).

Neurotoxicity of Organophosphates

There has been increasing awareness of the adverse effects of organophosphates (OPs) on human health for over 50 years and they are well documented (MAFF, 1951; CAT, AMA, 1953; Stephens, et al., 1995; Mackenzie, 2006; Myhill, 2007). The detrimental effects of OPs have been extensively studied by several researchers, for example Dr Sarah Mackenzie Ross at University College, London. Her research includes studies on the effect of OPs on the farming community when, some years ago, a compulsory governmental programme required the use of chemicals containing OPs in 'sheep dip' (Mackenzie Ross, 2008b; Stephens, et al., 1995; DEFRA, 2008a). Many farmers developed illnesses which, later, were attributed to their exposure to OPs. Other pesticides and weedkillers also contained OPs and, due to the known adverse effects to human health, regulations were introduced for the withdrawal of these OPs, with a legal requirement for their replacement by other, less toxic agents (Sigmund, 2007; Steenland, 1996). However, the authors of a report prepared for the Ministry of Agriculture, Food and Fisheries (MAFF), in 1951, presented the hazards of OPs to humans, and made safety recommendations, which still have not been fully implemented (Sigmund, 2007).

Other examples of organophosphate poisoning, with neurotoxicity, include an epidemic of 'Ginger Jake', which occurred in the USA, in 1930, when people ingested 'Ginger Jake', a headache remedy contaminated with tri-ortho-cresyl phosphate (TOCP)¹. Thousands of people were neurologically impaired, with a delayed neuropathy, some with persistent and severe effects (Steenland, 1996). A similar problem occurred, in Sri Lanka, where cooking oil contaminated with TCP was ingested, causing a toxic polyneuropathy (Vasconcellos, et al., 2002). Another reported incident occurred in 1995, when Japanese underground passengers were exposed to Sarin (Nishiwaki, et al., 2001), twelve people were killed and over 5,500 needed emergency medical care.

Reports have been published on the disabling symptoms experienced by Gulf War soldiers, their condition came to be known as Gulf War Syndrome (GVA, 2002; Myhill, 2007; Rainer, et al., 2008). Specific conditions caused by organophosphates have been named, such as organophosphate-induced delayed neuropathy (OPIDN) (Vasconcellos, et al., 2002; COT 2006), chronic organophosphate-induced neuropsychological disorder (COPIND), and organophosphate ester-induced chronic neurotoxicity (OPICN) (COT, 2007). Possible links have also been found between toxic substances, including OPs, and motor neurone disease (Rainier, Fink, et al., 2008), Alzheimer's Disease, Parkinson's Disease (Bekarovski and Radulovic, 2001; DEFRA, 2007; Myhill, 2007), and genetic damage in susceptible patients (Myhill, 2007).

Dr Mackenzie Ross is currently engaged in a 3-year study of airline pilots, 2006-9, funded by the Department for Environment, Food and Rural Affairs (DEFRA). In her capacity as an independent expert, she gave evidence, in 2007, to a House of Lords inquiry into Air Travel and Health (Mackenzie Ross, 2006, 2008a). The Organophosphate Information Network (OPIN) is coordinated by Elizabeth Sigmund, who has collected a significant amount of data on this subject (DEFRA, 2003; Gill, 2006).

Symptoms

The symptoms of aerotoxic syndrome have been classified into two sections: single, or short-term exposure and long-term low level exposure (Winder and Balouet, 2001; Winder and Michaelis, 2005).

After short-term exposure, patients may complain of:

- **neurotoxic symptoms:** blurred or tunnel vision, nystagmus, disorientation, shaking and tremors, loss of balance and vertigo, seizures, loss of consciousness, parasthaesias

¹ Other OPs mentioned in the literature include mono-cresyl phosphate (MCP), di-cresyl phosphate (DCP), tri-aryl phosphate (TAP), tri-butyl phosphate (TBP), tri-ortho phosphate (TOP), tri-phenyl phosphate (TPP) and ortho-cresyl phosphate (OCP).

- **neuropsychological symptoms:** memory impairment, headache, light-headedness, dizziness, confusion and feeling intoxicated
- **gastro-intestinal symptoms:** nausea, vomiting
- **respiratory symptoms:** cough, breathing difficulties (shortness of breath), tightness in chest, respiratory failure requiring oxygen
- **cardiovascular symptoms:** increased heart rate and palpitations
- **irritation:** of eyes, nose and upper airways

After long-term exposure, patients may complain of:

- **neurotoxic symptoms:** numbness (fingers, lips and limbs)
- **neuropsychological symptoms:** memory impairment, forgetfulness, lack of co-ordination, severe headaches, dizziness, depression, sleep disorders
- **gastro-intestinal symptoms:** salivation, nausea, vomiting, diarrhoea
- **respiratory symptoms:** breathing difficulties (shortness of breath), tightness in chest, respiratory failure, susceptibility to upper respiratory tract infections
- **cardiovascular symptoms:** chest pain, increased heart rate and palpitations
- **skin symptoms:** skin itching and rashes, skin blisters (on uncovered body parts), hair loss
- **irritation:** of eyes, nose and upper airways
- **sensitivity:** signs of immunosuppression, chemical sensitivity leading to acquired or multiple chemical sensitivity
- **general:** weakness and fatigue (leading to chronic fatigue), exhaustion, hot flushes, joint pain, muscle weakness and pain

The Diagnostic Process and Clinical Neurophysiological Investigations

Patients who present with either short or long-term symptoms, such as those described above, will probably seek advice, in the first instance, from their GP. They may have an initial clinical examination and routine blood tests and, if symptoms persist, be referred to specialist consultants from a variety of disciplines, including cardiology, respiratory physiology, gastro-enterology and neurology, for further opinion and investigations as documented later, in the case study.

Within neurophysiology departments, patient referrals would most probably come from a neurologist. Some patients may require baseline, sleep deprived or long-term ambulatory electroencephalographic (EEG) recordings for blackouts or seizures; a sleep EEG/polysomnograph for fatigue, excessive daytime sleepiness (EDS), difficulty sleeping, or sleep apnoea; evoked potentials (EPs), nerve conduction studies (NCS) and electromyography (EMG) for parasthaesiae in limbs, aching muscles, reduced motor function and weakness.

The Department of Health (DH) recently introduced a policy targeting waiting times, whereby patients should be treated within 18 weeks, from the date of the initial GP referral (DH, 2008a). Preparatory discussions were taking place in 2004, with full implementation planned by 2008 (Dunn, 2004). Nationally, most of the clinical physiology services (including audiology, cardiology, neurophysiology and respiratory physiology) had waiting lists, in breach of the 18-week limit specified by the DH (DH, 2008a). Patients with symptoms such as those described above were likely to have long waits for some investigations. However, exclusion factors were built in to these waiting time targets; for example, when tests were required in different disciplines the 18-week process could be applied separately to each (DH 2008).

Case Study: One Patient's Report – A Traveller's Tale

“This is the tale of a fabulous holiday and its aftermath. In the spring of 2005, my eldest son and I decided to visit my youngest son, during his gap year in Sydney. So, off to Australia we went and, whilst there, also visited my godson in New Zealand. We came home via Hong Kong, where we saw another friend (who knows when we might have another opportunity to visit the Far East!). Hong Kong was wet, hot and humid outside, damp and cold inside. After a three-day visit, we went off to catch the plane home to the UK. Our plane, due from Sydney, arrived very late but, eventually, we boarded. Then, we sat in the plane, on the runway, for six hours - the sun rose, it became rather hot in the cabin, but the air conditioning was on. We noticed droplets of ‘water’ being sprayed over us, but didn’t think anything of it, at the time. After landing at Heathrow, several hours late, we continued home - the weather here was very wet, but warm.

“So far so good, but the fun started about ten days later, when I became very breathless, had generalised aches and pains, and some difficulty walking. So off I went to my GP, who diagnosed a chest infection and gave me some antibiotics. Some days later, although not getting any worse, I did not seem to be getting any better, so back to my GP I went. He sent me straight to A&E, as he suspected a pulmonary embolism (PE) was causing the chest pain. I then had a scan, lung function tests, and chest X-ray, all normal.

“Unfortunately, I did not get any better and, over a 2-year period, saw a cardiologist, who ordered an angiogram, echocardiogram, and walking tests, all normal. She then referred me to a chest physician who ordered a high resolution computerised tomography (HRCT) scan, this was normal. I was then referred to a neurologist who ordered more investigations, including nerve conduction studies, electromyography with repetitive stimulation, and sleep studies, which were all normal, plus further respiratory tests, including another sleep study, and a lactic acid test. Eventually I had to give up work, on the grounds of ill health, and retire earlier than planned. Friends were very kind, but one trip a week to the supermarket suddenly became my main social event. Reading labels on products was a very good way of getting a rest, as I couldn’t walk very far (why, oh why, is the bread always in the far corner?). A local embroidery group invited me to join them, providing a nice, sedentary, social activity (and my embroidery skills improved enormously over that time!).

“Even after the passage of time, I was still getting breathless, had chest pain, plus general aching in the whole of my body. Also, I was still getting very tired, and unable to walk any distance (to someone who had played three rounds of golf each week, this was devastating!). My concentration was poor, memory bad, at times I was rather confused, and getting really fed up. This was, in part, because every time I saw a new consultant I went to the bottom of his/her outpatient waiting list, as my condition was not considered urgent.

“Eventually there were some positive results, the second sleep study and lactic acid tests were abnormal. As a result of the first, a diagnosis of sleep apnoea was given, and the second indicated a possible myopathy, for which a muscle biopsy was considered although this has not yet been carried out. Unfortunately, the words ‘sleep apnoea’ were put on a form and, although I had never fallen asleep during the daytime or while driving, I was not allowed to drive. For someone who could no longer even walk to the bus stop, it meant isolation. It was decided I should have a continuous positive airways pressure (CPAP) machine and plod on. Then, another blow - getting access to a CPAP machine, as there was a nine-month waiting list. So, after a lot of phone calls, I eventually obtained one. As soon as I received my machine, I was able to resume driving! Still I could not walk very far, even after treatment had started. I continued to have pains in my chest and general weariness, but I could now get out and about as long as I could park near my destination. After several visits to the respiratory physiology department, and much patience on the part of the staff, the machine was eventually adjusted to my needs. Apparently, my lung capacity was too large for my age, height and weight but, as I have never smoked, had done a lot of underwater swimming, and also sang in the local choir, it was hardly surprising. Also, as a radiographer, we had had lung function tests every year, as well as numerous other health and safety checks (always normal).

“I’ve had my CPAP machine for over a year now and, while I am still not able to play golf or swim, I can now get around the supermarket, my memory is a lot better, and the chest pains less frequent. My legs still ache, progress with walking is very slow, and I still have a reduced quality of life.

“In all, it has taken well over three years, six hospital consultants, an occupational health doctor, several other members of NHS staff including neurophysiologists, the loss of my job, a temporary loss of my driving licence and, most recently, letters to the hospital Chief Executive, to see if the whole saga could have been made a little quicker. He was very good, and replied to all the letters, but did not see how this problem could be rectified. However, although the various members of hospital staff were very helpful, it leaves me wondering why it has taken so long for me to go through the diagnostic process.

Table 1

Date	Specific Symptoms	Department	Test	Results	Treatment
12/04	Occupational Test	Respiratory	Spirometry	Normal	N/A
Spring 05			Holiday		
After Holiday	Unwell, tired, Chest pain	GP	Clinical examination	?Chest infection	Antibiotics
06/05	Chest pain (?PE), Short of breath, Ongoing fatigue and walking difficulties	GP > A&E Respiratory Respiratory Cardiology X-ray Dept	Various: VQ Scan Lung Function Tests Echocardiogram Chest X-ray	Normal Normal Normal Normal	
11/05		Cardiology	Angiography	Normal	
11/05		Haematology	Bloods	Normal	
12/05		Respiratory	Lung Function Tests	Normal	
03/06	Tiredness	Neurophys	Sleep EEG	Normal	
03/06	Weakness	Neurophys	NCS	Normal	
		Neurophys	EMG	Normal	
		Neurophys	Repetitive Stim	Normal	
07/07	Tiredness	Respiratory	Sleep Studies	Sleep Apnoea	CPAP machine
	Weakness		Lactic Acid Test	? Myopathy	None
07/08	Slowly Improving				

Summary of Results from the 3-year Diagnostic Process of the Traveller’s Tale

“From my own preliminary research, the onset and presentation of my symptoms have been similar to many others who fly, including airline pilots, cabin staff and passengers (AA, 2008; Hoyte, 2007; TFA, 2007). It has taken many years for their symptoms to be recognised as an ‘entity’, although AS is still not regarded as a disorder linked to time spent in aeroplanes. Using the term ‘Aerotoxic Syndrome’, an internet Google search identified over 5,000 links, whereas a specific search carried out on the web sites of the Department for Environment, Food and Rural Affairs, the Department of Health, NHS Direct and the National Institute of Health and Clinical Excellence, reaped no information (DEFRA, 2008b; DH, 2008b; NHS Direct 2008; NICE, 2008). However, a general search on the Internet, using the terms Neurotoxicity, Myalgic Encephalopathy (ME), Chronic Fatigue Syndrome (CFS), Fibromyalgia, Mitochondrial Myopathy and Organophosphate Poisoning, identified many relevant papers, some of which have been included in the bibliography (COT, 2007b; MEA, 2008; Myhill, 2007; Sigmund, 2007).

“I still do not have a definitive diagnosis to explain all the symptoms. Treatment for sleep apnoea has helped and, with the passage of time, the severity of my symptoms has subsided, the incapacity has reduced. At a recent visit to the neurologist, he felt that a second diagnosis of Chronic Fatigue Syndrome (CFS) may now be appropriate. It was of interest to read that one of the causes of CFS is exposure to organophosphates (MEA, 2008), and many of the affected airline crews have also been diagnosed with CFS (Myhill, 2007; AA, 2008). Anyhow, if you have the opportunity to visit Australia or New Zealand, do go, but I suggest you come back on the boat, and think of me going to bed every night hooked up to my CPAP machine, looking a little bit like Nellie the Elephant!”

Results of the Literature Search

a) Clinical Studies

The preliminary literature review of aerotoxic syndrome yielded several clinical studies. In one report, the Committee on Toxicology of Chemicals in Food, Consumer Products and the Environment (COT) reviewed eight independent clinical studies by different authors, carried out between 1973 and 2005, on groups of affected patients, totalling 367 subjects, in at least six countries (COT, 2007b). Several other reports have been cited in the literature (Montgomery, et al., 1977; Winder et al., 2002; COT, 2007c; Mackenzie Ross, 2008b), with cases also being reported in the media (Benns, 2007a,b; AA, 2008). In many cases, involving both aircrew and passengers, there are descriptions of several symptoms, similar to those noted earlier, including muscle pain, cognitive impairment, fatigue and sleep disorders (TFA, 2007).

There is limited published evidence of clinical neurophysiological (CN) investigations being carried out in suspected cases of aerotoxic syndrome, although Myhill reported that nerve conduction studies (NCS), performed within 2 years of the most recent toxic fume exposure, may be abnormal (Myhill, 2007). In another study, of the fifty responding aircrew, approximately 17% reported impaired nerve conduction studies (the only CN tests mentioned), 12% admitted having seizures or blackouts, and 8% reported sleep problems following exposure to contaminated air (Winder et al., 2002). There were, however, reports of CN tests being performed in other types of organophosphate poisoning (OP), for example Duffy and colleagues reported the long-term effects of OP poisoning on the EEG (Duffy, et al., 1979). In 1981, Senanayake reported the findings of a study in which a patient had TCP-induced neuropathy. He had carried out nerve conduction studies (NCS) and electromyography (EMG), in a 3-year follow-up of his case. In another paper, motor and sensory NCS contributed to the diagnosis of a case of organophosphate-induced delayed polyneuropathy (OPIDP). The authors concluded that as exposure to OPs can cause neuropathies, this should always be considered, even if symptoms are not well defined (Vasconcellos, et al., 2002).

No evidence has yet been found of diagnostic guidelines or procedural pathways for suspected cases of AS, nor of sleep apnoea being a feature of AS. However, sleep apnoea was listed as a feature of Fibromyalgia Syndrome (FS) (Bennett, 2008), and it was reported that some patients diagnosed with FS may actually have aerotoxic syndrome (Myhill, 2007). Investigations on AS sufferers were mostly reported as normal when investigated using NHS facilities (Myhill, 2007) and, unless chemical poisoning was suspected, toxicology procedures were not usually requested. Some patients with suspected AS had been investigated using diagnostic procedures not routinely available to the NHS. Such tests were more sensitive, and positive results had been obtained, with neurotoxic chemicals being identified in fat tissue sampled by biopsy and also in blood tests. Low levels of melatonin had also been found (Myhill, 2007).

b) Responses by Airlines and Governments

Many government discussion documents and reports on airline cabin pollution are available on various web sites (COT 2006, 2007a,b,c; HoL, 2007, 2008; HoLSaTC, 2000), although some available draft reports cannot be quoted, cited or reproduced (COT 2007a). Most reports state that studies are inconclusive (COT, 2007c).

No objective documentary evidence has yet been found to verify air quality, or compliance with safety procedures to maintain this air quality, to substantiate claims, made by the airline companies and government agencies, that the cabin air is safe (Loraine, 2007a). Reports have, however, been published stating that neither is the quality of cabin air being monitored (Loraine, 2007a; AA, 2008) nor is it being adequately filtered to avoid the risk of pollution (Winder, et al., 2002; Loraine, 2007a).

c) Developing Public Awareness

As a direct consequence of the apparent reluctance by the relevant authorities to resolve the problem of contaminated air in jet aeroplanes, a strategy to heighten awareness of aerotoxic syndrome and its causal factors has, in recent years, started to gain momentum. Some of the pilots affected by AS have embarked upon a campaign to educate the public, who may also be affected by the problem, highlighting the lack of government action, worldwide. Two web sites have been set up, by pilots who had to take early retirement on the grounds of poor health due to AS: *toxicfreeairlines.com* by Captains Tristan Loraine and Susan Michaelis, and *aerotoxicassociation.com* by Captain John Hoyte (TFA, 2007; AA, 2007). The problem of contaminated air is deemed the 'Asbestos of the Aviation Industry' (TFA, 2008). Captain Tristan Loraine has produced a documentary film 'Welcome Aboard Toxic Airlines' (Loraine 2008a), written a fact-based novel (Loraine, 2007b) which is soon to be made into a film - 'Shadows From the Sky', scheduled for distribution in 2010 (Loraine 2008b). A song for the soundtrack has already been composed and recorded (Garbutt 2008). Other campaigns are also developing momentum, such as within the travel industry, due to concerns about the safety

of the paying public, and signatures have been collected for a petition (Brehany, 2008). Most recently, and in not dissimilar circumstances, Georgina Down, an individual with impaired health due to toxic chemical crop spraying too close to her rural home, has achieved a legal victory, after several years of personal campaigning. The high court judge ruled in her favour, with resultant crop spraying restrictions due to be enforced in the UK (CT, 2008). This campaign has received considerable publicity and Georgina is now regarded as the British 'Erin Brockovich' (Brockovich, 2008).

Discussion

a) Questions Raised by This Study

As it may be some time before any conclusions can be drawn from the evidence surrounding aerotoxic syndrome, some questions arise now: Are clinical neurophysiology (CN) departments receiving requests for investigations on patients with a potential diagnosis of AS and, if so, which tests? Are pertinent questions being asked of patients when taking a medical history? Have CN tests contributed to the diagnostic process? Is there more evidence of AS in the medical literature? If so, have CN procedures been carried out in these studies, and were they helpful? Is sleep apnoea (obstructive, central, or mixed) a common finding in AS? What is the incidence? Have AS patients with other sleep disorders been referred for investigation? Have the other clinical physiology services been investigating patients with possible AS? Are specific blood tests and tissue sampling the most appropriate investigations to support the diagnosis? In the interests of patient care, how can the diagnostic process be facilitated? What other diagnoses have been suggested for patients with this cluster of symptoms? In an evidence-based environment, where is the evidence to confirm that airline cabin air is toxin free, and there is no risk to human health? What is being done to safeguard airline crews and the paying public? Airline companies have a duty of care to all, so would aircrews and passengers alike have legal redress in the proven absence of such duty of care?

b) Responses by Airlines and Governments

It has been claimed that airline passengers and crews will be at risk from toxic fumes until the design of the cabin air supply system is changed (Michaelis, 2007). However, if there is no proven risk to health, why change the design? Recommendations for robust, evidence-based studies have been made repeatedly, by many researchers and committees (Mackenzie-Ross, 2008; Michaelis, 2007, 2008b; Sigmund, 2007), as the validity of existing studies is not accepted by all parties (Lorraine, 2007a; COT, 2007c). The matter was discussed in the House of Lords as long ago as 2000 (HoLSaTC, 2000), questions have been raised in the House from time to time and another study commissioned (HoL, 2007, 2008). Governments and airline companies have acknowledged that cabin fume episodes do occur, but have yet to be convinced that the cabin air can be sufficiently polluted to cause illness, or that aerotoxic syndrome actually exists, perhaps because there is '... insufficient evidence to justify epidemiological research focussing specifically on exposure to organophosphates' (COT, 2007c). However, government investigations are continuing, albeit rather slowly (COT, 2007a,b,c; HoL, 2007, 2008). This leaves the responsibility to others to try and establish the facts, as it is considered a major risk to safety (Winder, 2002; Gill, 2006; GCAQE, 2008).

From a legal aspect, it would seem that airline companies may not be in compliance with the manufacturer's recommended safety procedures when using engine oils (Shell, 2003), potentially putting airline crews and the public at risk. As a consequence, airlines are contravening international aviation legislation by not ensuring all possible safety measures have been put in place for their staff and passengers (Winder et al., 2002). Many studies have been carried out over several years. One report, for example, cites 443 references, including those of earlier reports submitted to governments in other countries (COT, 2007c). The apparent lack of action by the authorities is deemed to be a conspiracy by the international airline industry, in collusion with governments, to protect commercial interests (Lorraine, 2007a). However, like other industrial public health and safety issues, when enough information becomes available, and companies or governments have failed to implement their 'duty of care', lawsuits may follow. Indeed, it has been reported that this process has already begun (Winder, 2002; AA, 2007; Sigmund, 2007).

c) Official Recognition of Aerotoxic Syndrome

The term 'syndrome' is used for a specific cluster of symptoms, in this case when found in patients after flying (Winder, et al., 2002). When new clusters of symptoms appear, under what circumstances do they become recognised as a syndrome? What criteria need to be addressed to facilitate this? Which organisation makes the decision? Has the National Institute for Health and Clinical Excellence (NICE) been made aware of the symptoms some people experience following air travel, sought expert opinion, or carried out any studies? – no relevant reports have yet been found. When will AS be classed as a condition in its own right? If it is not a valid 'condition' what is the cause of all the similar symptoms reported by so many people after flying? If

evidence from current studies is rejected, due to flawed study design, then surely, considering the large-scale potential risk, it is in the public's interest, and the authorities have a duty of care, to seek independent expert advice, as quickly as possible, with a view to designing and funding appropriate large-scale studies.

d) Diagnostic Tests, Protocols and Costs

Diagnostic tests are requested by clinicians to try and find the cause of symptoms, with or without a provisional diagnosis, based upon a clinical history, plus the signs and symptoms presented by each patient. When a syndrome is not officially recognised or defined, how can it be diagnosed? It would seem, from the literature reviewed so far, that specific diagnostic protocols for aerotoxic syndrome do not exist, probably because the condition has not yet been recognised. Without an official name, a set of symptoms may continue to be investigated on an ad hoc basis, and diagnostic services may not be used cost-effectively.

It has been reported that some patients have been investigated more effectively in non-NHS facilities (Myhill, 2007). Does this mean that NHS staff members are less well informed than those in the independent sector? Are the required tests too expensive to be carried out in NHS departments? Either way, it would seem that NHS patients are not getting a minimum standard of care, especially if patients have to spend many months waiting for tests, results and assessment, like the subject of the case study, with no treatment or support for over 2 years. One author suggests symptoms are being investigated without considering the possibility of a toxic cause (Myhill, 2007). Without an appropriate diagnostic protocol there is the potential for arranging unnecessary tests. This is not only detrimental to the patients and investigating staff, but also potentially costly to the taxpayer, and a waste of limited resources, both in health care facilities and government agencies. This scenario is multiplied when assessing the global picture, and further studies are warranted.

e) The Use of Clinical Neurophysiological Tests in Aerotoxic Syndrome

As there was little mention of AS sufferers having tests in departments of clinical neurophysiology, this lack of documentary evidence does not mean that CN tests were not performed. For example, in the study where 12% of respondents admitting to having seizures or blackouts (Winder et al., 2002), it is quite feasible that at least some may have had EEGs. Also, it was reported that NCS may be abnormal if performed within two years of a toxic fume exposure (Myhill, 2007). Information concerning the relevance of such CN investigations needs to be obtained. Are practitioners asking appropriate questions regarding air travel when taking a clinical history? Unless patients volunteer the information, GPs and hospital staff won't know the amount of time these patients spent in aircraft cabins. With such large passenger numbers currently travelling by air, might it be prudent to ask all patients?

f) Case Study – The Tale of the Traveller's Long Journey

From this case study, it is apparent that the various symptoms warranted investigations in a variety of diagnostic departments, and the whole process was not completed within 18 weeks. The investigations were started in 2005, before the new DH 18-week pathway policy was implemented (DH, 2008). Had this policy been in force, a diagnosis with appropriate treatment might have been implemented within 54 weeks (allowing for a maximum 18-week pathway for each of the three disciplines of cardiology, neurophysiology and respiratory physiology), rather than the ongoing investigations and assessments taking over three years.

Recommendations

From this preliminary review, the authors hope to have demonstrated that exposure to neurotoxic organophosphates in a variety of circumstances, including toxic fume exposure in aeroplanes, can cause neurological impairment which, in some cases, may warrant specific diagnostic investigations in departments of clinical neurophysiology. Insufficient evidence has yet been found to clarify the extent to which CN tests are useful for patients with suspected AS, but it is suggested that such information may contribute to the development of relevant diagnostic protocols. The authors recommend a more extensive literature search to ascertain the range and frequency of neurophysiological investigations in patients deemed to have aerotoxic syndrome, and the role of such tests in the diagnostic process. It would be useful to publish such findings. It would also be of interest to determine a) to what extent departments of clinical neurophysiology have been involved, performing tests on patients with possible aerotoxic syndrome or other organophosphate-induced symptoms; b) the extent and range of tests performed on patients with such referrals by other clinical physiology disciplines (particularly cardiology and respiratory physiology); and c) whether or not any other cases of obstructive sleep apnoea have been linked to AS or other organophosphate exposure.

This may be an appropriate topic to be reviewed by the ANS Research and Development Special Interest Group, for recommendations on how best to take this study forward within the field of neurophysiology and

beyond, since the symptoms cross the boundaries of clinical physiology disciplines. ANS Council might like to consider providing a bursary to help fund a suitable student through a research programme, to further investigate this syndrome and the role of clinical neurophysiology in the diagnostic process.

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