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Transient Global Amnesia and Aeromedical Certification: Literature Review

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16. Abstract

Transient Global Amnesia (TGA) is a rare clinical syndrome of anterograde amnesia with potentially disastrous consequences should it occur to a pilot inflight. Since 1958, multiple investigations have been carried out with the objective of determining its etiology and long-term prognosis. Migraine, focal ischemia, venous flow abnormalities, epileptic phenomena, and personality traits have all been implicated as potential etiologic factors; however, there is no current consensus on the cause. TGA generally has a benign prognosis with a low recurrence rate, nevertheless, an acute episode of TGA presents an unacceptable risk of sudden incapacitation in flight. This unacceptable risk creates the need to familiarize aviation medicine practitioners with this condition and its pathophysiology. This paper summarizes the long-term prognosis of TGA, the long-term outcome for an airman experiencing this condition more than once, the long-term limitation(s) and neurological conditions associated with TGA, and the waiting period established by the FAA in consideration of an aeromedical certification applicant with this condition.

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INTRODUCTION

Transient Global Amnesia (TGA) is a rare clinical syndrome of anterograde amnesia with potentially disastrous consequences should it occur to a pilot inflight. Fischer and Adams were the first to use the term TGA in their publications in 1958 and 1964;[1,2] however, similar cases were published around the same time.[3,4] Since then, multiple investigations have been carried out with the objective of determining its etiology and long-term prognosis.

Migraine,[5,6] focal ischemia,[7] venous flow abnormalities,[8,9] epileptic phenomena,[10] and personality traits[11,12] have all been implicated as potential etiologic factors; however, there is no current consensus on the cause. TGA generally has a benign prognosis with a low recurrence rate,[13,14] nevertheless, an acute episode of TGA presents an unacceptable risk of sudden incapacitation in flight. This unacceptable risk creates the need to familiarize aviation medicine practitioners with this condition and its pathophysiology.

Background

To ensure an individual is medically fit to fly, the Federal Aviation Administration's (FAA) aeromedical certification process generally relies on the evaluation of an airman's application for a medical certificate and the physical examination by an Aviation Medical Examiner (AME). The goal of the aeromedical certification process is to reduce the risk of sudden inflight incapacitation or impairment, and protect the safety of other pilots, cabin crew, passengers, and persons on the ground.[15,16] As such, TGA presents a significant risk that must be mitigated.

The clinical characteristics of TGA have been known for over 60 years. It presents as an acute clinical syndrome characterized by sudden anterograde amnesia; however, some cases do present with retrograde memory loss. The abrupt onset of anterograde memory loss is generally accompanied by repetitive questioning and agitation as the individual struggles to understand what is happening. Characteristically, there is no alteration of consciousness, no diminished level of alertness, no loss of language function, and no alteration of executive functioning. The symptoms are short lived, resolving within 24 hours. Some recent memories may be regained, but it is not uncommon for a significant gap to exist in recalling memories for the period of impairment.[3,17,18]

Such acute impairment occurring during any phase of flight represents a significant risk, particularly if it occurs in single-pilot operations. As such, the FAA's Aerospace Medical Certification Division (AMCD) of the Civil Aerospace Medical Institute (CAMI) in Oklahoma City, OK, requested a review of the literature be conducted to assess the potential implications presented by TGA relative to the aeromedical certification of airmen. The AMCD was interested in answers to the following questions: (1) what is the long-term prognosis of TGA?;

(2) what is the long-term outcome for an airman experiencing this condition more than once?; (3) is there outcome data in the medical literature that suggests there are long term limitation(s) or new neurological condition(s) associated with TGA?; and (4) is the current post-TGA 6-month waiting period established by the FAA appropriate,[19, 103] or do different waiting periods and/or associated clinical follow-up need to be considered?.

The literature review focused on factors related to prognosis and long-term outcomes in individuals presenting with this pathology. The aim of the review was to gather information so as to attempt to answer the questions posed above.

METHODOLOGY

This review was based on information acquired in search of original research articles, clinical reviews, and case reports. The tool used to search for this information was Medline (via PubMed). Key words searched included: Transient Global Amnesia, TGA, epidemiology, prevalence, incidence, etiology, prognosis, treatment, risk factors, aerospace medicine, aviation medicine, aeromedical certification, medical certification, pilots, airman, incapacitation inflight, impairment inflight, special issuance, and a combination thereof.

The selection of the material was based according to its pertinence to the subject; bibliographical references of the publications found that were considered relevant was examined. Book chapters and recommendations of official sites of aeromedical certification were also cited.

Medical and Research Aspects

Epidemiology

The incidence of TGA has been reported in a limited number of population studies and has been very variable. A study in Rochester, Minnesota, of 277 TGA patients found an annual incidence of 5.2 per 100,000 per year and 23.5 per 100,000 per year in patients over 50 years.[20] In Finland, the incidence was reported as 10 per 100,000 per year and 32 per 100,000 per year in patients older than 50 years;[21] similar findings to those found in Italy where the rate was 10.4 per 100,000 per year.[22] In the United Kingdom was observed an incidence of 3 per 100,000 cases per year,[23] similar to the rate reported in Spain.[24] In Switzerland, the incidence was 6.8 per 100,000 per year,[25] with a general incidence annual between 3 to 10.4 per 100,000 cases per year.

TGA is more common in adults between the ages of 40 to 80 years, with average age onset at 60–65 years.[14,24,25] However, two cases involving a 16-year-old male and a 13-year-old female have been reported.[27]

No significant gender differences were found in a review of 1,333 cases.[26] Some studies have suggested a higher prevalence in men,[14,28] while other studies have found a higher prevalence in women.[22,25,26]

A correlation with time of day has been reported, with TGA episodes being more frequent in the morning.[6,12]

Risk Factors and Precipitating Events

Several different precipitating factors have been associated with the onset of a TGA episode. Depending on the series, specific precipitating factors have been identified in 28% to 89% of patients.[1,17,26,29-32] Physical activity, emotional disturbance, pain, sexual intercourse, exposure to cold water, or to large temperature changes, have been commonly associated events.[28,29,33]

Some precipitating factors have included an emotional disturbance, such as witnessing a motor vehicle accident; receiving bad news; anxiety associated with any surgical procedure; physical effort, such as work with heavy equipment; activities involving a Valsalva maneuver; straining with defecation; and excessive coughing or vomiting.[17,26,31,34] Other precipitating events for TGA have included acute myocardial infarction,[35,36] gastroscopy,[37] use of sildenafil,[38-40] brain tumors,[41] transatlantic flight,[42] high altitude exposure,[43,44] Epstein Barr virus reactivation,[45] post-anesthesia,[46,47] involvement in court-related or legal events,[48] and several other potentially stressful events have been reported. However, no studies showing a direct causal association of TGA with these triggers was found.

Cardiovascular risk factors have been associated with episodes of TGA, and vascular events are one of the main pathophysiological theories to explain the etiology of TGA. Several studies have been conducted to measure the relationship of atherosclerotic risk factors, such as hyperlipidemia, diabetes mellitus, and high blood pressure (HBP) in TGA patients compared to patients with transient ischemic attack (TIA).[26] Most studies have found that, generally, patients with TGA have similar prevalence of cardiovascular risk factors to the general population, but significantly lower than those with TIA.[7,12,17,26,30,32,49,50] Quinette et al., evaluated cardiovascular risk factors of 860 patients in studies and case reports from a literature review and found no more prevalence of these factors in the TGA cases and also analyzed their own series of 142 cases with findings similar to those reported previously.[26] A study found an odds ratio of 3.31 for patients who had HBP as a risk factor for TGA when compared to a control group with TIA.[51] Other studies did not find an increased prevalence of TGA with cardiovascular risk factors; some studies even suggest TGA patients have a lower prevalence than normal controls.[51] A study with 293 patients with TGA found high prevalence of hyperlipidemia and ischemic heart disease compared with normal controls but superior rates of HBP, diabetes, atrial fibrillation and previous ischemic stroke in TIA group.[52]

Migraine headaches have been the only risk factor with significant association identified in the majority of TGA studies.[6,26,30,49,51] A large cohort study in Taiwan found that migraine patients are more at risk of developing TGA than controls at a three-year follow-up, and this difference is greater among women with migraine in between 40–60 years.[5] TGA does not present as a migraine equivalent or migraine with aura event, although it has similar triggers.[6]

Family and personal history of psychiatric diseases, anxiety, depression, alcohol use, and certain phobic personality traits also have been associated with TGA.[11,26,53] A study by Quinette, et al., suggested that episodes in females were often associated with emotional events or a history of anxiety or personality disorders. In males, it was not uncommon for TGA to be associated with events involving physical exertion. In younger individuals, a history of migraine headache was often present.[26]

Despite all the associations mentioned above, no one factor has been found to satisfactorily explain the etiology of TGA.

Pathophysiology and Etiology

The precise pathophysiologic mechanisms in TGA are still unclear. It has been postulated that TGA originates from various causes that affect critical structures for memory.[18] Functional neuroimaging studies with positron emission tomography (PET) and diffusion-weighted image magnetic resonance imaging (DWI-MRI) have shown that the affected areas in TGA are the medial temporal lobe and the amygdala,[54-56] with a specific location in hippocampal CA-1 neurons of the *Cornu Ammonis*.[57] PET studies during a TGA episode have shown decreased oxygen consumption without alteration of cerebral blood flow[58] and with significant impairment of the hippocampus and its connections. With MRI studies, it has been found that these changes are bilateral and reversible.[59]

The arterial ischemia theory had been postulated by the common characteristics of TGA and TIA, i.e., sudden onset, short duration, and age range; however, no cardiovascular risk factors are shared, and patients with TGA have a better prognosis than patients with TIA.[7,12,17,26,30,32,49,50] No significant relationship with cerebral arterial vasoconstriction was found in TGA patients.[60]

Venous congestion has been raised as etiological theory by the association of TGA with the Valsalva maneuver, which reduces the venous return of the vena cava and increases the venous pressure in the medial temporal lobes.[8] A meta-analysis in 2012 of seven case-control studies, 312 TGA patients were compared to 261 controls. The analysis found higher internal jugular venous reflux (IVYR) in the TGA cases, but this finding does not completely explain the etiology of TGA; therefore, other causes must be considered.[61] It has been shown that there is no hemodynamic alteration in the intracranial venous circulation despite the presence of IVYR.[62]

It was previously mentioned that a potential relationship has been noted between TGA and migraine headaches. Although TGA and migraine present with an acute onset, gradual resolution of symptoms, similar symptoms during the episode, similar brain flow patterns and similar non-specific electroencephalographic findings, but unlike TGA, it tends to occur in younger patients and frequently recurs.[6,53] TGA could be related to the theory of cortical spreading depression, the same mechanism postulated in migraine.[63-65]

TGA does not appear to have an epileptogenic origin, although certain epileptic seizures may present with transient amnesia. Unlike seizures, TGA usually has a longer duration, absence of other cortical alterations, no alteration of consciousness, low recurrence, and there has been no evidence of abnormal electroencephalogram during a TGA event.[10,51,66]

Some psychogenic factors may be associated with TGA etiology due to the relationship the condition has with certain stressors, psychiatric disorders, and personality traits.[11,26,53]

Clinical Presentation

Anterograde amnesia, which affects the verbal and nonverbal components and retrieval memory impairment are the main cognitive alterations in TGA. Characteristically, patients present asking repetitive questions related to self-orientation, date, their situation, and/or location. Patients can store information momentarily, but it can be easily forgotten if patients are unfocused. There is no alteration of consciousness or in the ability to communicate or self-identify. Patients have no abnormalities related to walking, coordination, strength, sensitivity, or reflexes. Patients gradually recover the presenting amnesic gap of the event. Retrograde amnesia could be present in a TGA episode and varies in its duration; patients may not remember what happened at the beginning of the episode or certain events years ago.[18,67,68]

The episodic component of explicit memory is the main process affected in TGA. The semantic component and forms of implicit memory apparently are unaffected. Patients with TGA can perform complex motor tasks such as driving, cooking, teaching a physics class, and learning new skills.[2,58,68-70]

Neurological symptoms usually accompany the episode: headache, dizziness, and nausea/vomiting are present more frequently, but other symptoms have also been reported such as cold extremities, chills/flushes, sweating, paresthesia, chest pain, etc.[26,71]

It has been found that these patients, despite not being aware of their severe memory impairment, are concerned about what is happening and realize that something is wrong with them.[72] It has also been seen that patients can present anxious or depressed moods that can worsen memory deficit.[68]

The duration of the TGA episode is an important diagnostic criterion. An episode of TGA usually lasts between 4 and 6 hours. Most episodes do not exceed 10 hours, although cases lasting between 15 minutes and 24 hours have been reported.[17,26,71] An episode lasting less than one hour and/or presence of multiple episodes of TGA are major clinical predictors of epilepsy.[17]

Diagnosis

The diagnosis for definitive TGA is based on the criteria proposed by Caplan in 1985, later validated by Hodges and Warlow in 1990. The patient has to meet all the criteria for the diagnosis:[17,18]

1. The episode must be witnessed by an observer who is present for most of the attack.
2. There must be clear-cut presence of anterograde amnesia during attack.
3. There must be no alteration of consciousness.
4. There must be no loss of personal identity.
5. Cognitive impairment is limited to amnesia (no aphasia, apraxia, etc.).
6. There should be no presence of focal neurological symptoms or deficits during or after attack.
7. Epileptic features must be absent.
8. Memory impairment must resolve within 24 hours.
9. No other causes for amnesia must exist—patients with recent head injury or active epilepsy (medication or seizure in the previous two years) are excluded.

Associated symptoms (headache, nausea, dizziness) and some grade of retrograde amnesia may occur, although these are not required for diagnosis. As previously mentioned, the episode may or may not be associated with some triggering event.

Differential Diagnosis

The differential diagnosis of TGA must include other transient amnesic syndromes such as transient epileptic amnesia (TEA) and psychogenic amnesia or TIA. There are other causes of transient amnesia: intoxication, medications, exacerbation of depression, hypoglycemia, head injury, limbic encephalitis, and electroconvulsive therapy that should be taken into account when first examining the patient.[67]

Transient epileptic amnesia is considered rare and usually occurs in male patients in the sixth decade of life. The condition is characterized by short-term amnesic anterograde episodes with a median duration of 30 minutes to an hour, accompanied by recurrent questions and presenting usually as repetitive attacks—as many as 20 times in a year in untreated patients. It typically presents on awakening. The patients may have olfactory or gustatory hallucinations, as well as other convulsive phenomena such as complex partial seizures. Interictal EEG temporal lobe findings have been reported to be present in a third of patients, while non-specific findings have been seen in another third. The likelihood of EEG findings increases when recorded during sleep or in a sleep deprived state.[73-7]

Psychogenic amnesia is apparently less prevalent than TGA. Onset is associated with a stressful experience and the duration of episodes is longer than for TGA. Patients present neurobehavioral alterations such as loss of reading, writing, and use of devices (telephone) skills.[76] Alterations are seen more in retrograde than anterograde memory. Also, autobiographical memory and personal identity is impaired, the latter is the exclusion criterion of TGA.[67, 77]

As previously mentioned, patients with TIA have atherosclerotic risk factors that are significantly higher than patients with TGA. TGA is not accompanied by other neurological

deficits, so the clinical examination should emphasize the presence of associated neurological deficits. TIA also presents a higher cumulative risk of presenting stroke.[78]

Evaluation and Treatment

The diagnosis of TGA is clinical and there are no confirmation tests. Since few patients are seen in the clinical settings during their episode, the quality of the narrative provided by the witness or from alternative sources is important to clarify the situation. No definitive diagnosis should be made without the presence of a witness.[79]

A case that meets all the diagnostic criteria of TGA does not require additional studies. If the patient does not meet the criteria or presents with atypical characteristics, additional studies are recommended. Computed Tomography (CT) may be of value as part of eliminating other medical conditions. If the patient has an additional focal deficit after a complete neurological examination, TIA or stroke should be considered; if recurrent episodes or epileptic characteristics exists, TEA should be considered. If there are cognitive deficits, it becomes necessary to rule out toxic-metabolic causes or psychogenic amnesia, if there is loss of personal identity.[79]

Cerebrospinal fluid tests are not indicated if the diagnosis of TGA is clear, though it is a test of utility to rule out subarachnoid hemorrhage or neuroinfection.[79]

TGA does not require specific management other than clinical surveillance during the event. If the diagnosis of TGA is complete, a vascular evaluation or intensification of the management of risk factors for stroke is not necessary.[78]

Role of Neuroimaging

Functional neuroimaging studies with Single Photon Emission Computed Tomography (SPECT) shows temporal lobes hemodynamic changes in the acute presentation of TGA, and with Positron Emission Tomography (PET), alterations have been seen in hippocampal cavities and in the uptake of oxygen, without alteration of flow in critical areas of memory.[26,58] Functional MRI (fMRI) has allowed understanding of hippocampal pathophysiological processes during TGA although the opportunity of use in the acute moment is rarely accessible in emergency services.[56]

Computed Tomography findings in TGA are usually normal or show coincidental findings (cerebral atrophy, old stroke, tumors, etc.).[17,18] Computed Tomography, nevertheless, has been useful in ruling out conditions being considered in the differential diagnosis. Diffusion weighted magnetic resonance imaging (DWI-MRI) has shown unilateral or bilateral hippocampal high signal intensity. It is generally accepted that a large percentage of TGA cases may have small hyperintense punctate lesions;[80-84] however, the probability of finding these lesions is affected by the onset time of the symptoms. DWI-MRI has a low diagnostic value in the early stages and the best performance has been found when neuroimaging is performed between the first and third day of onset symptoms.[55,71,82,83] Long-term, it has been shown that these lesions are not permanent.[80,85] A negative DWI-MRI does

not rule out TGA.[71] DWI-MRI is useful to exclude some other process such as head injury or stroke.

Prognosis

When determining the long-term prognosis after a TGA episode, several factors need to be considered. These include persistent cognitive deficits, the possibility of a recurrent TGA episode, the risk of developing a seizure disorder, or of having a cerebrovascular event. Case series, case-control studies, and meta-analyses have been carried out to evaluate these potential outcomes.

Neuropsychological Aspects

During the acute episode, TGA patients lose anterograde episodic memory, with the possibility of some retrograde memory being lost. During recovery, patients regain memories lost in the retrograde amnesia first.[86]

A case-control study in 1991, involving a six-month follow-up of 41 patients, found that patients with TGA had altered performance in the tests of immediate verbal memory at 30 minutes, 24 hours, and had alterations in autobiographical memory. The findings suggested mild hippocampal diencephalic dysfunction.[87]

In another study of 34 patients, those with DWI-MRI lesions in the acute phase did not show significant improvements in neuropsychological testing at four and six months when compared to acute phase testing.[57] However, it should be noted that the deficits were mild. Another study with 14 patients evaluated with neuropsychological tests between 1 and 105 days following the TGA episode found that TGA patients presented selective cognitive dysfunctions after the clinical recovery of TGA.[88]

Borroni et al. found that in the long-term follow-up of 55 patients there was minimal alteration of the verbal and non-verbal components of memory with no impact on the activities of daily living. In this study, 18 of 55 patients fulfilled criteria of Mild Cognitive Impairment Amnesic.[89]

A study of 16 patients with TGA comparing with 15 healthy controls did not find difference in performance in neuropsychological tests with an average follow-up of 1082 days.[90] Pantoni et al. did not find significant differences in the Mini-Mental State Examination (MMSE) when comparing a TGA group with a TIA group.[12]

A meta-analysis in 2009 analyzed 25 studies and found significant alteration of anterograde memory and mild retrograde memory with non-amnesic executive functional impairment in the acute phase. It included a tendency to slow recovery in these alterations in the 5 days following the attack, with a complete recovery of the cognitive alterations in the long-term after 5 days until the 30 days after the attack.[91]

A recent study of 221 patients with TGA with an average follow-up of 12 years found no significant differences in survival curves at the time of appearance of a cognitive impairment (mild cognitive impairment and dementia) event when compared to controls.[30]

Recurrence

Several studies have estimated long-term recurrence at between 2.9% and 19%, with an annual recurrence rate of 2.5% to 5.8% (see table 1). There have been several cases involving two or more TGA episodes in the same patient.[20,26,92]

Table 1. Recurrence in TGA

Study	Patients in study (n)	Recurrence	Annual recurrence rate	Mean Follow-up
Hinge et al.,1986[93]	74	22%	4.7%	66.6 months
Miller et al., 1987[20]	277	14.4%*		80 months
Hodges and Warlow, 1990[17]	114	7.9%	3%	-
Melo et al., 1992[51]	48	6.25%		17.4 months
Gandolfo et al., 1992[92]	102	18.63%		82.2 months
Zorzon et al., 1995[49]	64	9.4%	2.5%	45.6 months
Lauria et al., 1997[22]	77	8.2%		-
Chen et al., 1999[32]	28	18%		42 months
Pantoni et al., 2005[12]	51	8%		6.8 years
Quinette et al., 2006[26]	142	3.5%	5.8%	-
Quientte et al., 2006[26] **	1259**	10.19%		-
Agosti et al., 2006[13]	85	14.11%		3 years***
Arena et al., 2017[30]	221	5.4%		4.21 years

* Included “probable episodes of TGA” recurrence of 23.8%
**Report based on author's literature review.
***Retrospective study where patients were recruited over a 3-year period.
-No data available.

One study involving 29 airmen in the United Kingdom with TGA reported an annual recurrence rate of zero for their series. However, the author’s review of ten articles involving 958 non-aviation patients found an annual recurrence of 2.8% and average recurrence in first year of 6.2%.[28]

TGA presents with a very low recurrence rate. If an individual with TGA develops a recurrent episode, the diagnostic criteria must be carefully reviewed to ensure the initial diagnosis was correct.[79, 94] Recurrence can be associated with TEA.[17] Patients with recurrent TGA have also been found to have a higher incidence of primary progressive aphasia. [95,96]

Neurological and Cardiovascular Outcomes in TGA

Several studies have shown no reported association of TGA with increased risk for mortality, neurological morbidity, such as stroke or epilepsy, or for cardiovascular sequelae.

A study in 1987 involving 227 patients found, despite the high recurrence of TGA, the condition did not increase the risk of developing stroke.[20] Another study in 1990 found that patients with TGA had a 0.6% annual rate of major vascular events (stroke, myocardial infarction or sudden death) while non-TGA patients had a 7.7% rate. Also, there was no significant difference between the groups for those who developed epilepsy.[17] In 1992, during a study with 51 patients followed for 17.4 months, one patient developed TIA and minor stroke; there were no epilepsy cases.[51]

In 1995, a study compared 64 TGA cases, 64 TIA patients, and 108 healthy controls for 45.6 months. During the follow up, 3 patients died with TGA and 6 with TIA. There was no significant difference in mortality for the TIA and TGA group relative to vascular and non-vascular causes. In the TIA group, during follow-up, 5 TIA cases, 5 fatal or nonfatal strokes, and 3 nonfatal myocardial infarctions occurred; there were no vascular events in the TGA patients. A significant difference in the occurrence of major vascular events was shown in the TIA group.[49]

In 2005, it was found that TGA has a lower risk of stroke, MI, or death than TIA.[12] In 2014, a study comparing 4 groups of patients, 4299 with TGA, 170400 with migraine, 71087 with seizure, and 115105 with TIA, found that the cumulative risk for ischemic stroke at 5 years was 2.44% for TGA, 0.86% for migraine, 2.9% for seizure, and 12.23% for TIA. After multivariate analysis, the risk of stroke was found to be highest in patients with TIA, higher in patients with seizure, and similar to those with migraine compared to TGA.[78]

Another study, published in 2017, compared 221 patients with TGA with 221 healthy controls during an average of 12 years. It found that the risk of seizures, cerebrovascular events (TIA or stroke), and death did not increase after a TGA event.[30]

TGA and Aviation

Aeromedical certification experience

In 2012, data involving 31 subjects with a diagnosis of TGA from 1990 to 2010 contained in the United Kingdom Civil Aviation Authorities (UK CAA) archives was published. Two were first-time applicants who did not obtain initial aeromedical certification and were excluded; the remaining 29 subjects included one woman. Nineteen were private pilots, eight were professional pilots, one was a flight engineer, and one was an air traffic controller. The mean age of the group was 59 years old, with a mean follow-up period of 3.4 years. The average duration of the event was 2.8 hours. More than half of the group had notable precipitants, such as exercise, stress, or cold exposure. Less common, but also noted precipitants, were migraine headaches in six airmen and hypertension in ten airmen. Of the 29 individuals, 13 were able to regain aeromedical certification, and the others did not

reapply. The morbidity findings of this study were similar to those reported in the general population.[28]

In 2015, the FAA reviewed cases in their medical database between January 2007 and July 2014. Eight male pilots met the criteria for TGA. Two held first-class medical certificates, three held second-class medical certificates, and three held third-class medical certificates. Similar to the UK experience, no TGA events occurred during flight. The mean age was 52.1 years (range 24 to 65) and the mean duration of the events was 9.3 hours. Notable precipitating events included recent flying, driving, vigorous exercise, and chronic stress. No significant comorbidities were found. Studies performed included brain MRI or CT in 75% and EEGs in 88%—all were negative. Of the eight airmen, five were initially certificated, two were initially denied aeromedical certification but later certificated, and one did not reapply. The overall FAA experience with airmen who met strict TGA diagnosis criteria has been favorable, with a low risk for recurrence and no neurologic or other medical sequelae.[97]

In 2016, the FAA AMCD Neurology Panel reviewed 18 possible cases of TGA. Eight met the criteria for TGA and were issued a medical certificate after thorough evaluation, seven were denied, and three were deferred for further evaluation because they did not meet the TGA diagnostic criteria. Some of these included a possible TIA or some other alteration of consciousness without satisfactory medical explanation, and one had incomplete information. One of the airmen who was denied had an ambiguous diagnosis of a seizure, hence, the disposition was to wait for two years. Another one had a possible migraine vs. an unexplained alteration of neurologic function.[98]

Current FAA aeromedical certification policy on TGA states that "the initial airman medical certification or agency air traffic control specialist (ATCS) clearance shall be approved by the FAA and include a review by an agency neurology consultant." The waiting period for consideration must be at least six months after a single episode of TGA and meet all diagnostic criteria of TGA without recurrence. The waiting period could be extended 12 to 24 months if the neurology consultant concludes that the TGA criteria were not present for the event. Airmen and FAA ATCS must provide copies of applicable medical treatment records and follow-up. In addition, tests to be provided include neuroimaging (brain MRI or CT if an MRI is contraindicated), a sleep-deprived EEG (awake, asleep and with provocation—hyperventilation or photic), and other test as indicated. If the episode occurred in the previous two years, additional information must be provided to include a current assessment by board-certified neurologist at least six months after the episode and an office-based cognitive assessment (e.g., Mini Mental State Examination). The applicant should provide copies of the original neuroimaging studies. Once initially issued, airmen and FAA ATCS must provide annual follow up neurology reports for a period of time determined on a case-by-case basis.[19, 103]

According to International Civil Aviation Organization (ICAO) regulations, TGA is a disqualifying condition due to the risk of sudden impairment. In the absence of precipitants, the waiting period for TGA certification should be one year or more of symptom-free observation. "Restriction to multi-crew operations and non-safety-sensitive air traffic control duties can provide an additional measure of risk mitigation."[99]

The civil aviation authorities of Canada, the UK, and Australia, have established a symptom-free observation period after a single TGA episode of one year.[100-102]

Challenges of aeromedical certification in TGA

It has been evidenced that TGA is a benign entity when the diagnosis is certain, with low recurrence, and with minimum cognitive alteration. In the long-term follow-up period, patients with TGA do not show an increase in the occurrence of major cardiovascular events (TIA, stroke, and MI) or an increase in mortality compared to groups of healthy controls. Their mortality and vascular events are also lower compared to TIA patients and similar with the general population. Despite these findings, the challenges for aeromedical certification are multiple.

One of the challenges is that TGA behaves as a benign entity whose diagnosis is solely clinical. In the presence of a "probable TGA" diagnosis that does not meet all the diagnostic criteria, aeromedical decision is further complicated requiring more extensive evaluation to rule out other diagnoses and the possibility of longer waiting periods to obtain a medical certificate of up to two years.

Recurrence is a second challenge. TGA has a low recurrence rate, but unfortunately, there are no fool-proof predictors of recurrences. Despite an association with certain triggering events such as strenuous activity, stress, exposure to environmental extremes, etc., avoidance of these activities does not guarantee there will be no recurrences. After a recurrence, the prognosis becomes less benign because of the increased risk of TEA[17] and other cognitive impairments.[95,96] There is little data on the associated morbidities with recurrence, further studies are required.

In relation to cardiovascular and long-term stroke risk for airmen, research has shown that TGA patients have the same cardiovascular and stroke risk as the general population, and an apparent lower risk than patients with TIA. [12,17,20,30,32,49,50,78].

A large number of patients presenting with TGA have a diagnosis of migraine. This has been the only risk factor with significant association identified in the majority of the studies regarding TGA.[6,26,30,49,51] Migraine management should be approached according to the protocols already established in FAA regulations.[19, 103]

Lastly, cognitive deficits in aviation personnel are troubling because cognitive alteration can alter pilots' performance, decision-making capacity, and situational awareness. However, the most common cognitive deficit in TGA is the amnesia of the event per se. It may persist as a minimal cognitive deficit, without evidence of any other significant cognitive

deficit.[30,91,94] This minimal deficit should be thoroughly assessed; though, it does not necessarily present an absolute disqualifier for aeromedical certification.

CONCLUSION

This literature review has answered the questions posed, including the long-term prognosis of TGA, the long-term outcome for an airman experiencing this condition more than once, and the long-term limitations or neurological conditions associated with TGA. TGA can present as an alarming entity and, should it occur in flight, the impairment could have disastrous consequences. It generally presents a benign course when all the diagnostic criteria are met and long-term outcomes are usually favorable. However, there are no predictors of recurrence and should it happen, the prognosis becomes less favorable.

Based on available aeromedical data and disease information, the FAA recommended waiting time of six months before being considered for recertification and return to the flight duties appears to be acceptable for the majority of cases, though disposition of this condition must continue to be considered on a case-by- case basis.

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