CHAPTER 4

Aerospace Neurology

Joseph I. Sirven, John Daniel Hastings, and Scott J. Wood

In the practice of medicine, the neurologist is called upon to answer the following questions (1):

1. Does the patient have neurologic disease?
2. If so, what is the localization of the lesion or lesions?
3. What is the pathophysiology of the process?
4. What is the preliminary differential diagnosis?

Utilizing the tools of the neurologic and medical history, the neurologic examination, ancillary studies, and one's education, training, and experience, the neurologist arrives at a diagnosis. The aerospace medicine physician (evaluator) has the additional challenge of relating the neurologic condition to aviation safety and achieving an appropriate aeromedical disposition. Whether it is the aviation medical examiner (AME), flight surgeon, or Federal Aviation Administration (FAA) regulator, the aerospace medicine physician shoulders the responsibility of a determination that may decide one's career in aviation or spaceflight. Considering the individual, and yet preserving aerospace safety, is a never-ending challenge for the aerospace medicine physician. The evaluator has the dual responsibility of applying the standards and also considering exceptions to the standards in allowing waivers from standards, while assuring aerospace safety.

An important consideration in making an aeromedical disposition is the nature of the operation or the mission, as a condition might not be compromising in all aerospace operations. The evaluator must consider the condition in relation to space operations, potentially of long duration, military versus civilian operations, single versus multicrew operations, and the nature of the mission. Demands within private, commercial, and airline transport operations must be considered. For example, a history of migraine with certain characteristics might potentially compromise military operations where immediate worldwide deployment is possible, but the condition might be considered an acceptable risk for multicrew or private pilot operations.

PRINCIPLES OF AEROSPACE NEUROLOGY

When a neurologic condition exists, the evaluator should consider the following:

1. Is the condition static? If so, what is the degree of functional incapacitation?
2. Is the condition progressive? If so, is the course predictable or unpredictable?
3. Can the condition be monitored successfully?
4. Can the condition result in sudden incapacitation?
5. Can the condition result in subtle incapacitation?

A pitfall in aeromedical disposition of aviators with neurologic disorders is making a major decision based on limited information. In neurologic diagnosis, the history is most often the richest source of information. The neurologic examination is often normal. Ancillary studies including laboratory studies, neuroimaging procedures, and studies such as cardiac electrophysiologic studies may also be normal. Often, the history is the sole means of diagnosis. One need only consider the migraineur—a person with migraine headaches—the person with seizures with a normal electroencephalogram (EEG), the person with a transient ischemic attack (TIA) and no vascular bruit, or the victim of transient global amnesia (TGA) to grasp the importance of history.

The aerospace medicine physician is somewhat disadvantaged because evaluation is often based on medical records and history taken by others. Most often, the evaluator has no opportunity to interact with the individual or obtain one's own history. Yet efforts to obtain additional information when the history is inadequate often bear the most fruit. Observations of emergency services personnel, description of an event by a spouse or other observer, or comments from fellow aircrew may hold the key to diagnosis and appropriate aeromedical disposition. Diligent pursuit of a complete history is the evaluator's best guide to aeromedical disposition.

Another important consideration in neurologic diagnosis is the role of psychological factors. Symptoms that reflect true neurologic illnesses are often intertwined with complaints that have an emotional basis, and teasing out the respective contributions is important for the evaluator. Moreover, psychological influences often play an important role in a number of common disorders encountered by the neurologist. The influence of emotions in migraine, syncope, and chronic daily headache exemplifies this relationship.

This chapter generally does not address individuals in whom neurologic disease is absent. Rather, it addresses those who suffer from a neurologic condition, which may or may not compromise aviation safety, resulting in temporary or permanent disqualification or operational limitations. An exception is the area of spaceflight, where the aeromedical physician has the task of determining when the adaptive recovery of healthy individuals is sufficient to perform operational tasks.

Episodic versus Fixed Deficit Neurologic Disorders

Episodic neurologic disorders, including migraine, cluster headache, TGA, syncope, epilepsy, the single seizure, and vertigo, are of aeromedical significance because of the potential for sudden incapacitation. Some merit permanent disqualification, whereas others may be accommodated with treatment or operational limitations. Vertigo will be dealt with in Chapter 5. Although "central" vertigo may occur in association with brainstem disease (e.g., multiple sclerosis [MS] or ischemic vascular disease), most cases of paroxysmal vertigo represent peripheral vestibulopathies.

Ancillary Neurologic Studies

In neurologic diagnosis, a frequently occurring and vexing problem is the proper interpretation of ancillary studies. This is of utmost importance in aeromedical disposition because an inadequate or inaccurate history coupled with a misinterpreted laboratory study can erroneously hamper or end an aerospace career. Interpretations that commonly confound neurologic diagnosis include those of head-up tilt studies (HUT), electroencephalography (EEG), and magnetic resonance imaging (MRI) studies.

Head-Up Tilt Studies

As mentioned in the section "Syncope" in this chapter, HUT studies may aid the evaluation of unexplained syncope. Kapoor reported approximately 50% of patients with unexplained syncope have a positive response to passive tilt-table testing (2). In that study, two thirds of positive responses occurred with pharmacologic activation (isoproterenol) as opposed to passive tilt. However, a significant proportion of asymptomatic individuals may have a positive response. Kapoor and Brant reported a false-positive rate of 20% without pharmacologic evaluation and 31% with isoproterenol activation (3). Reproducibility is another issue. In a study involving 109 subjects undergoing HUT on two consecutive days, Brooks et al. reported a high degree of variability in responses to HUT, with frequent lack of reproducibility of vasodepressor responses on the second day (4). Reproducible vasodepressor responses occurred in only 11 of 36 subjects (31%).

The aeromedical evaluator must be cautious in coupling a false-positive tilt table response with a nonsyncopal neurologic event, such as seizure. Such errors are common.

Electroencephalogram (EEG)

In the general population, there is a 10% to 15% incidence of minor nonspecific EEG abnormalities, and 2% to 3% of the population demonstrates moderate abnormalities (5). These changes may also occur in the presence of disease, and careful clinical judgment is necessary in determining their significance, if any. For example, a nonspecific EEG abnormality appearing in an individual with syncope accompanied by twitching and incontinence may lead to an erroneous diagnosis of epilepsy with its far-reaching implications.

The aeromedical evaluator must keep in mind that individuals without seizures may demonstrate epileptiform abnormalities on EEG, whereas individuals with epilepsy may have persistently normal EEGs ("spikes without fits and fits without spikes"). Engel notes that 2% of the population demonstrates specific epileptiform abnormalities on EEG (6). This may lead to an inappropriate diagnosis of epilepsy.

It is well known that a significant proportion of individuals with epilepsy have a normal EEG (7–9). Studies in the literature report that 50% to 60% of routine EEGs (30-minute routine recordings without sleep deprivation), obtained after a seizure in patients later clearly diagnosed as having epilepsy, demonstrate epileptiform abnormalities (10). Activation techniques, including hyperventilation, photic stimulation, sleep recording, and sleep-deprived recording, may increase the diagnostic yield. Interictal EEG abnormalities may be intermittent, and a 30-minute recording is a small sample of a 24-hour day. Serial EEG recordings may also increase yield, but little additional yield is obtained after four recordings (10). Recently, there has been an emphasis on longer recordings performed using ambulatory EEG systems that allow 24 to 72 hour recordings at home. It is important for the EEG interpreter to state that a normal EEG does not exclude the possibility of epilepsy, as well as mentioning sampling effect (10). In difficult cases, sustained video-EEG recording (days or more) can be accomplished in an epilepsy monitoring unit or alternatively at home with the use of ambulatory EEGs.

Lastly, there are known benign EEG patterns with epileptiform morphology that might be interpreted by less-experienced clinicians as being significant. Examples include 14 and 6 Hz positive spikes, small sharp spikes, 6 Hz spike and wave, and wicket spikes (10). These patterns can be seen in normal individuals.

Magnetic Resonance Imaging

A frequent finding in cerebral MRI is the presence of T2-hyperintense lesions, commonly referred to as *unidentified*

bright objects (UBOs), or *nonspecific white matter hyperintensities* (WMHs). The reporting of these lesions may lead to diagnostic uncertainty for the AME or flight surgeon and have far-reaching implications for the aviator or astronaut if interpreted incorrectly. A fully trained and experienced neuroradiologist might report "normal" findings, whereas other interpreters might report concern for small vessel cerebrovascular disease (multi-infarct state) or demyelinating disease (MS).

In one study, UBOs were present in 5.3% of healthy individuals aged 16 to 65, but were less common in younger individuals (11). In another study, pathologic features of T2-silent WMHs in patients without neurologic signs or symptoms represented myelin pallor associated with vessels showing hypertensive and arteriosclerotic changes (12). Others feel the lesions represent dilated normally occurring perivascular (Virchow-Robin) spaces. UBOs occur with greater frequency in individuals with migraine (13) (see also Chapter 17).

The neurologic literature reflects considerable debate regarding the nature and significance of UBOs. The debate is also reflected in practice, as evidenced by variable interpretations among general radiologists, neuroradiologists, neurologists, and neurosurgeons. The aeromedical evaluator with less frequent exposure to MRI is further disadvantaged. One can only advise that the ability to distinguish between nonspecific WMHs (UBOs, WMHs) and disease-specific white matter lesions is an important consideration for the clinician. As in other ancillary studies, the test must be interpreted in the context of the patient and the clinical setting. This is especially germane given the rapidly changing Tesla (T) strength of clinical MRIs from 3T MRI and now 7T studies becoming more commonplace with T strength being directly proportional to higher anatomopathologic detail. The increase in MRI detail with higher Tesla strength MRIs has led to more lesions being observed than ever before, yet without a clear consensus as to what findings are clinically relevant.

SPECIFIC NEUROLOGIC CONDITIONS

Syncope

The importance of history in neurologic diagnosis is clearly apparent when dealing with disorders of consciousness. Differentiating syncope from seizure is a never-ending challenge for the aeromedical physician. An erroneous diagnosis has profound implications for the aviator. Up to one third of persons suffering syncope with convulsive accompaniments are incorrectly given a diagnosis of epilepsy (7).

The essence of syncope is loss of consciousness and postural tone due to global cerebral hypoperfusion followed by spontaneous recovery. In near syncope (presyncope), the process is incomplete (perhaps by a compensatory action such as sitting down), with partial preservation of consciousness.

Syncope is common, with a reported occurrence of 3+% in the Framingham Study (14). Approximately 75% of these individuals reported a single occurrence with a mean follow-up of 26 years. In a study of 3,000 healthy United States Air Force (USAF) personnel averaging 29 years of age, 2.7% reported syncope (5).

Syncope occurs due to impaired homeostasis, the normal state of appropriate balance and regulation of cardiac output, circulating blood volume, and peripheral resistance provided by peripheral arterial smooth muscle tone. When standing, 70% of circulating blood volume lies at or below the heart level. Gravity, when standing, pools 500 to 800 mL of blood in dependent vascular spaces in the abdomen and lower extremities, with concomitant reduction in central venous pressure by 3 to 5 mm Hg and stroke volume by 50%. Resultant diminished baroreceptor stimulation leads to compensatory mechanisms including enhanced sympathetic and inhibited parasympathetic activity. Heart rate increases 10 to 25 bpm and sympathetic efferents to arterioles command an increase in peripheral resistance. Mean arterial blood pressure is preserved, assuring maintenance of homeostasis. Sudden pain, fear, and a host of other precipitants can momentarily defeat the delicate balance of homeostatic mechanisms, and syncope occurs.

The term *vasovagal syncope*, coined by Lewis in 1932, refers to the dual mechanism of loss of peripheral vasoconstriction (collapse of peripheral resistance) and cardio inhibition (vagus-induced bradycardia) (15). Terms appearing in contemporary literature including neurally mediated, neuroregulatory, and neurocardiogenic syncope are synonymous. Lewis recognized that loss of peripheral resistance was the predominant mechanism in most instances of syncope. The term *vasodepressor syncope* denotes hypotension without significant bradycardia, whereas *cardioinhibitory syncope* refers to vagally induced bradycardia as the predominant mechanism. This is a clinically important distinction.

The cardioinhibitory reflex can be powerful. Ventricular standstill and fibrillation have been reported with psychological stimuli. In contrast to vasodepressor syncope, cardiac syncope is sudden in onset. With asystole, presyncope occurs within several seconds and loss of consciousness within 6 to 8 seconds when upright. Injury and sudden death are attendant risks in malignant forms of cardioinhibitory syncope.

When evaluating syncope, the evaluator must ask first "Is it syncope or something else?" The following historical points aid accurate diagnosis:

1. **Postural setting:** Syncope characteristically occurs when arising to an upright position, less often while seated, and rarely in recumbency. Seizures do not respect posture.
2. **Length of prodrome:** In vasodepressor (noncardiac) syncope, there is usually a lengthy prodrome of 2 to 5 minutes. Feelings of uneasiness, warmth, anxiety, and queasiness are common during the prodrome, along with a desire for cool air and ventilation. In contrast, seizure auras, if present, are usually brief.
3. **Antecedent symptoms:** Visual complaints including pale, yellow, white, bleached, darkened, or constricted vision ("tunnel vision") denote retinal ischemia, indicating an extracerebral mechanism for the event. Respiratory antecedents might include yawning or deep breathing. Gastrointestinal (GI) symptoms include an empty, hollow, or

unsettled sensation in the epigastrium. Anxiety, dry mouth, and clamminess in the forehead and hands are common. Giddiness and lightheadedness may occur as the systolic blood pressure approaches 70 mm Hg, but, unlike true vertigo, there is no element of rotation of the environment or the body.

4. **Syncopal episode:** Syncope is a brief event, lasting 10 to 15 seconds, with little or no confusion. It is a hypotonic rather than rigid event ("syncopal slump") with pallor (white—loss of color, rather than blue). Respirations are shallow and often imperceptible. Return of consciousness is rapid, as is alertness. The embarrassed victim may rise quickly only to repeat the episode. This feature is diagnostic of vasovagal syncope.
5. **Convulsive accompaniments and urinary incontinence:** In experimental syncope, the EEG background frequency slows, lowers in amplitude, and eventually becomes flat, devoid of activity, as syncope ensues. In 10% to 15% of fainters, brief myoclonic jerks of the face and hands, tonic posturing, or other brief seizure-like activity occurs. This phenomenon constitutes the *convulsive accompaniment* that may occur in syncope. This is *not* a seizure, which is characterized by excessive neuronal discharges rather than absence of cortical activity. This convulsive accompaniment rather reflects a state of functional decerebration. In addition, approximately 10% of fainters experience urinary incontinence, which, if coupled with convulsive accompaniments, may lead to an erroneous diagnosis of seizure or epilepsy in one third of cases.
6. **The syncopal setting:** The situation or the circumstances in which the event occurs is of utmost importance. Worry, emotional upset, medication, alcohol, physical exertion, dehydration, medical procedure, or other precipitants may be present.

The evaluator, having determined that syncope has indeed occurred, must attempt to determine the cause or mechanism if possible. Table 4-1 (16) lists potential causes of syncope.

Fortunately 50% or more of syncope is benign and does not signify underlying disease. A careful history and physical examination may indicate the cause of syncope in 25% to 35% of fainters and in 75% of persons in whom a cause is found (7). Basic laboratory tests (complete blood count, chemistry panel) and 12-lead electrocardiogram (ECG) may provide an answer in 5% to 10% of patients. Further studies should be guided by the history and physical findings, and may direct one toward cardiac studies such as echocardiogram, Holter monitor, ambulatory event recording, or ultimately electrophysiologic studies such as autonomic reflex screens. Brain MRI and EEG studies are usually not helpful.

When initial studies do not provide an explanation, HUT table testing may be helpful in the evaluation of syncope. HUT may be positive in 50% of cases of syncope of unknown cause, supporting a vasovagal mechanism for the event. However, HUT without pharmacologic activation has a false-positive

TABLE 4-1

Etiology of Syncope

Reflex-mediated vasomotor instability
Vasovagal (neurocardiogenic, neurally mediated, neuroregulatory) syncope: the common faint
Situational syncope (related to a particular circumstance)
Cough (tussive) syncope
Sneeze
Swallow
Defecation
Postmicturition syncope
Weight lifting
Exercise induced
Trumpet player
Mess trick
Valsalva
Medical procedure: physical examination (eye-oculovagal, ear, etc.), venipuncture, genitourinary or gastrointestinal instrumentation, etc.
Hot tub or shower
Orthostatic/dysautonomic
Primary autonomic dysfunction (autonomic neuropathy, CNS disorders)
Secondary autonomic dysfunction
Medications, alcohol
Prolonged illness, prolonged bedrest
Hypovolemia (blood loss, dehydration)
Impaired cardiac output
Obstructive disease: aortic stenosis, idiopathic hypertrophic subaortic stenosis, pulmonary stenosis
Pump failure: myocardial infarction, coronary artery disease, cardiomyopathy
Impaired cardiac rhythm
Bradycardias
Tachycardias
Mixed rhythm disturbances: sick sinus (brady/tachy) syndrome
Psychiatric disease
Miscellaneous
Carotid sinus syncope
Glossopharyngeal neuralgia
Anemia
Unknown

CNS, central nervous system.
Adapted from Benditt DG, Lurie KG, Adler SW, et al. Pathophysiology of vasovagal syncope and Kapoor WN. Importance of neurocardiogenic causes in the etiology of syncope. In: Blann JJ, Benditt D, Sutton S, eds. *Neurally Mediated Syncope: Pathophysiology, Investigations and Treatment. The Bakken Research Center Series*. Vol 10. Futura; 1996; with permission.

rate of approximately 10%, rising to 27% or more with pharmacologic activation (commonly nitroglycerine) (17). False-positive studies have led to an incorrect diagnosis of syncope in individuals with clinical seizures. Other caveats involving HUT include nonstandard tilt angles, variable tilt duration, and lack of reproducibility in some studies. HUT is not recommended in the routine evaluation of syncope.

Aeromedical disposition in syncope can be favorable in most instances in which a benign mechanism, that is not likely to recur in flight, can be demonstrated. Satisfactory exclusion of serious causes of syncope can be accomplished with appropriate testing, and a period of symptom-free observation might provide further assurance.

Seizures and Epilepsy

Seizure disorder, convulsive disorder, and epilepsy are synonymous terms. A seizure is an abnormal, paroxysmal excessive discharge of cerebral neurons. Epilepsy is a chronic condition characterized by a tendency for recurrent (two or more), unprovoked seizures. The cumulative incidence of epilepsy is between 1.3% and 3.1% by age 80, with high incidence peaks in those younger than 20 and older than 60 (14). Epilepsy is idiopathic in two thirds of patients.

Not all seizures represent epilepsy. All persons have a constitutional or genetically determined threshold for seizures, which if exceeded, leads to a clinical event. This threshold may fluctuate with time of day, hormonal influences, sleep deprivation, and other factors. *Acute symptomatic* seizures may occur with electrolyte disturbances (e.g., severe hypoglycemia or hyponatremia), infectious processes (e.g., pneumococcal meningitis with high-dose penicillin), and cardiac arrest with prolonged asystole and ensuing cerebral ischemia and hypercapnia.

Individuals with low-seizure threshold may experience seizures when exposed to medications (tricyclic antidepressants, bupropion, theophylline, tramadol, and other medications). Additionally, some individuals with established epilepsy may achieve permanent remission (e.g., benign childhood epilepsy with centrotemporal spikes).

For aeromedical purposes, a simple classification for seizures is adequate; it is presented in Table 4-2 (18). Seizures are generalized from the onset in approximately half the cases and of partial onset in the remainder. Whereas generalized seizures are accompanied by simultaneous appearance of abnormal discharges throughout the cerebral cortex at onset, as the name implies, focal seizures (previously known as partial seizures) arise in a discrete area of the cerebral cortex. This is significant in that a focal seizure implies a focal lesion, which must be identified (scar, tumor, abscess, cavernous angioma, others).

In some focal seizures, consciousness is preserved. Localized convulsive twitching of one hand might be caused from a lesion in the contralateral cerebral cortex. The individual remains alert, can carry on activity, and ordinarily suffers no aftereffects with cessation of the seizure.

TABLE 4-2

Basic Classification of Seizures

1. Seizures that are generalized from the onset (e.g., absence, generalized tonic-clonic seizures)
2. Focal seizures with preservation of consciousness (e.g., focal motor seizure)
3. Focal seizures with alteration of consciousness (e.g., frontal lobe seizure, temporal lobe seizure, automatism)
4. Focal seizures with secondary generalization (focal onset, progressing to generalized tonic-clonic seizure)

Adapted from Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017;58(4):531-542.

In focal seizures with loss of awareness, consciousness is impaired or even lost. Focal seizures with loss of awareness are commonly preceded by an aura of myriad descriptions. *Déjà vu* experiences, an unpleasant smell (olfactory aura) or taste (gustatory aura), a forced thought, vivid visual memory, or feeling of detachment from one's self, may precede the seizure. The victim may engage in stereotyped movements such as repetitive lip-smacking, chewing movements, or hand or body movements such as fumbling with an object or rubbing a table. Awareness of surroundings is either compromised or lost, and one may or may not lose consciousness.

Any focal seizure may spread to adjacent areas of cortex and eventually to deep-seated midline structures that project to all areas of the cerebral cortex, culminating in a generalized tonic-clonic (grand mal) seizure. For example, a focal seizure beginning in one hand as described earlier may spread to the forearm, upper arm, face, and leg (Jacksonian march described by Hughlings Jackson), followed by collapse and a grand mal seizure. This is a partial seizure with secondary generalization.

A generalized tonic-clonic seizure is announced by a tonic phase lasting 10 to 20 seconds, with brief flexion, then muscular rigidity with arms raised, abducted, partially flexed at the elbows, and externally rotated. Leg involvement is minor. Eyes remain open with upward deviation of the globes. Extension of the back and neck then follows, perhaps accompanied by an "epileptic cry" resulting from forced expiration through partially closed vocal cords. Arms and legs are extended, with apnea and cyanosis. The clonic phase then begins, which is in reality a rhythmic relaxation of tonic contractions. Clonic jerks become coarser and decline in frequency as relaxation phases lengthen. Tongue biting and urinary incontinence are common.

Generalized tonic-clonic seizures are characteristically followed by a postictal state, which often includes a deep, snoring sleep. Return of consciousness follows with a confused and often combative arousal phase, which gradually clears. Nausea, vomiting, and headaches are common. Violent muscular contractions leave the trunk and extremity muscles sore and

tender, and shoulder dislocations or vertebral compression fractures may occur. The victim wants to sleep, and upon returning to wakefulness is amnesic for the event.

Absence seizures represent another variety of generalized epilepsy. Frequently appearing in childhood, these seizures are characterized by brief lapse of awareness that may or may not be accompanied by myoclonic jerks and alterations of muscle tone. Brief loss of awareness, with repetitive eye flutter for 2 to 3 seconds, would be a representative example. The individual immediately resumes normal activity, and, if the spell is brief, may remain unaware of its occurrence.

As with syncope, a careful history is of utmost importance in the evaluation of one or more seizures. Description by an observer might be the most important ingredient in accurate diagnosis. Records from paramedics and ambulance personnel, and detailed emergency room records including physician evaluations and nursing notes, may provide important details in accurately defining the clinical event. Personal history, family history, medication, and social history including alcohol and substance misuse are clearly important.

Seizure evaluation, particularly in adults, must include brain MRI with and without gadolinium and a sleep-deprived wake and sleep EEG. Computed tomography (CT), even with contrast, is insufficient because lesions such as mesial temporal sclerosis, hamartoma, or cavernous malformation might be overlooked. Wake-only EEG recordings are not sufficient because activation of a potentially epileptiform discharge might occur only during sleep recording. Photic stimulation and hyperventilation is employed to elicit reflex-induced seizures (photic epilepsy) in susceptible individuals. It is important to note that up to 40% of individuals with epilepsy have normal EEGs throughout their lives (10), again emphasizing the importance of history.

Clearly, a detailed evaluation is needed in the aeromedical disposition of persons with seizures or a question of seizures. A history of febrile seizures does not imply chronic seizure potential. Some persons with seizures achieve complete remission in adulthood, such as benign Rolandic epilepsy with centrotemporal spikes. Individuals with acute symptomatic seizures—that is seizures caused by an acute symptomatic cause such as electrolyte derangements or infections—do not harbor chronic seizure potential. A thorough neurologic evaluation, at times coupled with a defined period of seizure-free and medication-free observation, may allow medical certification.

The Single Seizure

A single unprovoked seizure does not constitute epilepsy unless it is followed by a second unprovoked event. An individual suffering a first-ever seizure should undergo a comprehensive general medical and neurologic evaluation.

Degree of recurrence risk following a single unprovoked seizure can be related to risk factors. A history of febrile seizures or seizure occurrence in a first-degree relative elevates the risk, as does a history of remote neurologic insult or previous acute symptomatic seizure. An abnormal neurologic examination or abnormal imaging study is associated with increased risk of recurrence. EEG abnormalities are also important. Specifically, epileptiform abnormalities are associated with a 60+% risk of recurrence, nonspecific slowing with a 30% to 40% risk, and with a normal EEG 10% to 25% risk (19–21).

Absent risk factors, recurrence risk is in the 26% to 33% range over 5 years (19). Most epileptologists elect not to treat individuals with a first-ever seizure and no risk factors because the majority would be treated unnecessarily. This is important for the aviator because a 5-year period of seizure-free and medication-free observation might allow consideration for aeromedical recertification depending upon the cause of the seizure.

Initial treatment with anticonvulsants delays the process. A second seizure during that period satisfies the criteria for epilepsy (two or more unprovoked seizures), and recurrence risk following a second seizure escalates to 73%.

Transient Global Amnesia

TGA is a fascinating condition whose prime characteristic is severe anterograde and extensive retrograde amnesia. Initially described in 1954, TGA is a global amnesic state that resolves within 24 hours (21). Personal identity, level of consciousness, awareness, and ability to perform complex acts are well preserved, distinguishing TGA from confusional states. Strict diagnostic criteria include presence of a capable witness, clear anterograde amnesia, alert wakefulness, normal content of consciousness beyond memory, absence of focal symptoms and a normal neurologic examination, and resolution within 24 hours.

Although TGA has been reported from age 5 to 92 years, 90% of cases occur in the 50 to 80 range. Most attacks are 4 to 6 hours in duration, with retrograde amnesia ranging from hours to months and sometimes years, which upon recovery shrinks to a permanent retrograde gap of 1 hour.

Precipitating circumstances reported in TGA include cold-water immersion, sexual intercourse, painful experiences, and medical procedures such as angiography on rare occasions. Association with physical exertion is present in 18%, emotional stress in 14% to 44%, and with migraine in 25% to 33% of cases.

At the onset of TGA, there is disorientation for time and place, but preservation of personal identity. Repetitive asking of questions is a near universal feature. Preserved ability to perform complex acts such as operating an aircraft or performing detailed carpenter work is a constant feature of TGA. Migraine-like headaches are associated with TGA in approximately 50% of patients.

Unilateral or bilateral medial temporal hypoperfusion has been demonstrated during TGA with MRI techniques, and experimentally, a slowly spreading cortical depression across the cerebral cortex has been shown. Interestingly, a similar mechanism of cortical spreading depression has been postulated in the aura of migraine.

Most individuals with TGA suffer a single episode, although recurrence rates of 3% annually over 5 years have been reported. Aeromedical disposition often depends on specific

precipitating factors and often a period of symptom-free observation.

A monograph by Hodges (22) and Arena (23) provides a comprehensive review and discussion of TGA.

Migraine

Migraine is common, with a prevalence of 17% in women and 6% in men. Common features of migraine include unilaterality (exclusively or predominantly one-sided), throbbing nature, nausea, vomiting, photophobia, phonophobia, and prostration. The migraine sufferer commonly prefers a dark, quiet room and relief may follow sleep. The headache may last hours to days and is commonly followed by a drained feeling and remnants of pain with head movement. Although migraine may be spontaneous, there are many precipitants including sleep deprivation, hunger, sun exposure, fatigue, menses or oral contraceptives, certain foods, alcohol, and emotional stress. Migraineurs tend to have family history that is positive in 60% of cases. Migraine can appear at any age but commonly in adolescence, sometimes entering remission and appearing years later.

In common migraine, the headache begins without an antecedent aura. In classic migraine, an aura precedes the headache by 15 to 30 minutes. Visual auras are common with myriad descriptions including scintillating or sparkling lights, visual field defects such as hemianopia, colored or kaleidoscopic whorls or patterns, or patterns such as zigzag lightning ("fortification spectra") or herringbone patterns. An important diagnostic feature is the "positive" nature of the visual aura, meaning the presence rather than the absence of light (ischemia characteristically is a "negative" visual phenomenon with absence of light). Nonvisual auras also occur, with symptoms such as marching face and hand numbness, or expressive speech difficulty.

A third variety of migraine is "migraine equivalent" (migraine variant, acephalgic migraine), in which a migraine aura occurs without developing a headache. Visual migraine equivalents are not uncommon beyond age 40 (24), sometimes being mistaken for TIA due to cerebrovascular disease.

Rare forms of migraine include "complicated migraine," such as hemiplegic migraine accompanied by stroke, ophthalmoplegic migraine with oculomotor nerve palsy, and basilar migraine with ataxia and confusion.

Migraine may or may not be of aeromedical significance depending on its characteristics in a specific individual, and operational considerations (e.g., potential global military deployment vs. private pilot operations). To guide aeromedical disposition, the evaluator should consider a host of factors, including the following:

1. **Prodrome:** Some migraine sufferers will experience a prodrome of hours to a day or more, characterized by a sense of uneasiness, anxiety, apprehension, or general feeling of ill being. Recognition of the prodrome may allow the aviator to avoid flying.
2. **Precipitating factors:** Many migraineurs will report specific precipitating factors, which, if avoided, may reduce migraine risk or preclude migraine altogether. These include emotional stress, multitask overload, sleep deprivation, fasting, certain food and certain alcohols, menses, and other precipitants.
3. **Migraine aura:** Is the aura minor, or is there significant functional impairment? For example, slight perioral and unilateral fingertip paresthesias may be inconsequential, as would a sliver of shimmery light in the far periphery of the visual field. Alternatively, a complete homonymous hemianopia or prominent aphasia would significantly compromise the individual.
4. **Rapidity of onset:** Some migraines develop rapidly, with vomiting and prostration occurring within 15 to 30 minutes of onset. Others develop slowly, perhaps beginning as an annoying discomfort over one eye, but not developing into a severe headache for hours. Onset during flight would allow corrective measures in this circumstance.
5. **Frequency:** Migraine-free intervals can vary widely from days to years or even decades. An individual experiencing several migraines per month would cause concern; a frequency of two per year would be far less worrisome.
6. **Acute treatment measures:** Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen may be effective if taken early. These would be acceptable in an aviation environment. Triptans may be acceptable with timing limitations in relation to flight—typically no flying for 24 hours after a dose. Anticonvulsants, narcotic analgesics, and barbiturate-containing analgesics would be prohibited with flying duties (25).
7. **Preventive treatment:** Medications employed in migraine prophylaxis include β-blockers, calcium channel blockers, anticonvulsants, and antidepressants including tricyclic and selective serotonin reuptake inhibiting agents. β-Blockers and calcium channel blockers may be acceptable in aviation, whereas the others are prohibited due to potential central nervous system (CNS) effects. There are several new preventive options for chronic migraine whose aeromedical risk has not been well studied. These include new calcitonin gene-related peptide (CGRP) monoclonal antibodies, botulinum toxin injections, and neuromodulation devices.

Considering the prevalence of migraine, the diagnosis need not be disqualifying in most individuals. Individual consideration with attention to the features enumerated earlier may allow favorable aeromedical disposition depending on the aviation environment.

Cluster Headache

True cluster headache has very distinct clinical characteristics. The term *cluster* refers to a series of headaches lasting from weeks to months separated by symptom-free intervals of many months to several years or more. Each headache is identical for that individual. Clinical characteristics may include abrupt onset with intense pain peaking within a minute or two, unilateral location in or behind one eye, unilateral

nasal stuffiness, drainage, eye redness, tearing, and perhaps a Horner syndrome on the side of the headache (ptosis and pupillary constriction). Excruciating pain persists for 30 to 45 minutes followed by rapid resolution of symptoms. Headaches may occur precisely at the same time each day. After one or more headaches daily for a period, the cluster ends, affording welcome relief.

Cluster headache is treated with narcotic analgesics and other analgesics, lithium carbonate, and at times oxygen (a potent vasoconstrictor). Severe pain and analgesic requirements during a cluster are disqualifying, but long periods of remission usually allow consideration for certification once the cluster ends.

Other Headache

Although not included in the episodic disorders, the most commonly occurring headache is chronic daily headache, formerly referred to as *tension headache*. This is a frequent (daily or nearly so) headache; often dull to moderate, nagging but not incapacitating, with resistance to treatment. It may be a component of a somatoform disorder, and in one study, 46% of individuals with a primary complaint of chronic headache suffered from endogenous depression (26). The underlying condition and therapeutic agents utilized (narcotic- or barbiturate-containing analgesics, antidepressants, tranquilizers) ordinarily preclude aeromedical certification unless underlying issues are resolved. It is also important to note that sleep deprivation often results in persistent headaches, which is an aeromedical risk.

CEREBROVASCULAR DISEASE

Stroke is a major health concern and was the fifth leading cause of U.S. deaths in 2017 (27). Stroke risk doubles with each decade after age 55 (28). The International Civil Aviation Organization (ICAO) has long set airline pilot retirement age at 65. In 2015, Japan extended airline pilot retirement age to 67. Though age is an important factor, as many as one third of hospitalized stroke patients are under age 65 (29).

The definition of stroke includes thrombotic cerebral infarction with associated symptoms (ischemic stroke) or without symptoms (silent stroke) (30). Ischemic stroke accounts for 87% of all strokes, hemorrhagic stroke the remainder. Hemorrhagic stroke can also be symptomatic or silent (e.g., microbleeds). Subarachnoid hemorrhage and central venous thrombosis are also included in stroke definition (30).

Stroke risk factors are many with hypertension and diabetes prominent among them. Others include hyperlipidemia, overweight/obesity, metabolic syndrome, physical inactivity, coagulation disorders, and family history. Cardiac risk factors include valvular heart disease, coronary artery disease, congenital defects, cardiomyopathy, and disturbances of cardiac rhythm—especially atrial fibrillation. In approximately one third of cases, no cause is found (cryptogenic stroke) (31). Risk factors for TIA and stroke are largely shared.

Transient Ischemic Attack

Initially, TIA was defined as a temporary episode of focal neurologic deficit lasting less than 24 hours. With the advent of CT and MRI brain imaging, it became evident that up to 50% of individuals with a clinical diagnosis of TIA demonstrated completed infarcts on imaging. This led to a consensus recommendation to modify the definition of TIA to a "transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction" (32). This represented a tissue based as opposed to time-based definition. Many TIAs are brief, lasting 2 to 15 minutes. Risk of stroke after TIA has been reported as 18.6% at 10 years, and associated cardiac risk rises significantly (33).

Fleeting blindness (amaurosis fugax) is the classical manifestation of a retinal TIA, characteristically related to embolization from the carotid artery. A monocular ascending or descending shade of blindness (altitudinal visual field defect) consumes the entire visual field and usually resolves within 1 minute. A hemispheric anterior circulation (carotid system) TIA may produce unilateral weakness, sensory loss or expressive speech difficulty. Posterior circulation (vertebral-basilar system) TIAs may produce vertigo, ataxia, diplopia, and dysarthria. Bilateral or crossed symptoms implicate the posterior circulation.

Ischemic Stroke

Ischemic stroke results from arterial obstruction with tissue infarction. In contrast to TIA, CNS infarction is defined as "brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury" (30). Ischemic stroke is accompanied by symptoms referable to the appropriate vascular territory, or without symptoms in silent stroke. Both large and small arteries may be affected.

Hemorrhagic Stroke

Intracerebral hemorrhage comprises 13% of strokes. The most common etiology is hypertension with hemorrhage into basal ganglia, pons, or cerebellum. Other causes of hemorrhagic stroke include cerebral amyloid angiopathy, vascular malformations, and coagulation disorders.

Subarachnoid Hemorrhage

The occurrence of subarachnoid hemorrhage should trigger a search for intracranial aneurysm, which is responsible in 87% of cases. A specific subtype of subarachnoid hemorrhage is peri-mesencephalic (prepontine, nonaneurysmal, interpeduncular) hemorrhage that represents 5% of cases (34). Long-term outcome with this entity is good (35).

Cerebral Venous/Dural Sinus Thrombosis

Cerebral venous thrombosis (CVT) has numerous causes, both infectious and noninfections, though in 20% to 35% of cases etiology is unknown (36). CVT has been associated with pregnancy, oral contraceptive use, malignancies, and connective tissue diseases. Coagulopathies have also been implicated.

Intracranial Aneurysm

Intracranial aneurysm prevalence is approximately 3%. Aneurysmal rupture accounts for 85% of subarachnoid hemorrhages. Most aneurysms are small and asymptomatic, measuring less than 0.5 mm. Medium-sized aneurysms range from 6.5 to 25 mm and large are greater than 25 mm. Saccular (berry) aneurysms are most common, in which arterial tunica media is absent and the internal elastic lamina is compromised. Rupture of an intracranial aneurysm can be fatal in 25% to 50% of cases and 50% of survivors have permanent disability.

Stroke Subtypes

Aside from research and acute clinical applications, a stroke classification system serves the aeromedical evaluator seeking etiology, the first step in entertaining medical certification. Ischemic stroke can be divided into four major categories (37).

- Atherothrombotic
- Small vessel
- Cardioembolic
- Other

Atherothrombotic

Large artery atherothrombotic stroke (cortical ischemic stroke) refers to ischemic cerebral infarction arising from atherosclerotic disease involving major intracranial arteries or their branches, or the extracranial circulation including the great neck vessels and thoracic ascending aorta. Mechanisms include local thrombosis or embolism from atherosclerotic plaques and hemodynamic factors.

Small Vessel

Small artery (lacunar) stroke refers to MRI or CT evidence of a small, deep penetrating artery infarction less than 15 mm in diameter and clinically matching symptoms (37). Though hypertension and diabetes have commonly been associated with small vessel disease, risk factor profiles are similar for small and large artery stroke (38). Exceptions include atrial fibrillation and carotid stenosis, which are more common in large artery stroke. Commonly postulated causes of small vessel stroke include degenerative changes in penetrating arteries (lipohyalinosis) and atherosclerosis involving the artery or parent artery at its origin (39). Less commonly proposed mechanisms include embolism, vasculitis, infection, hypercoagulable states, cerebral autosomal dominant encephalopathy with subcortical infarcts (CADASIL), and cerebral amyloid angiopathy (CAA) (40). Locations of small vessel stroke include subcortical cerebral white matter, caudate nucleus, putamen, thalamus, internal capsule, and pons.

Cardioembolic

Cardioembolic sources for stroke include disorders of cardiac output (e.g., primary cardiomyopathies or other diseases resulting in a cardiac ejection fraction below 35%) and disturbances of cardiac rhythm (e.g., atrial fibrillation/flutter). Embolic sources include valvular diseases, prosthetic valve, mural thrombus, left ventricular aneurysm, and endocarditis. When patent foramen ovale is present, presence of deep venous thrombosis or pulmonary embolus raises the question of paradoxical embolus as a stroke mechanism.

Other

Included here are arterial dissection, thrombophilic disorders, coagulopathies, vasculitis reversible cerebral vasoconstriction syndrome, and Moyamoya disease. Also included are genetic/inherited/developmental disorders (CADASIL, Fabry's disease, Marfan's disease, and others).

Aeromedical Evaluation after Stroke

The aeromedical evaluator first encounters an aviator when medical certification is sought, usually after a significant period of poststroke observation. Important factors in aeromedical disposition include stroke etiology, recurrence risk, and mitigation measures.

With over 150 known causes of stroke, guidance regarding stroke subtyping and evaluation can be helpful (41). Review must include history and physical, neurologic evaluation, laboratory findings including coagulation studies when indicated, brain imaging and vascular imaging (CTA, MRA, ultrasound). Search for disturbances of cardiac function and cardiac rhythm are essential. Transthoracic echocardiogram is indicated, and transesophageal echocardiogram may be needed in search for a cardioembolic source. Though Holter monitoring has long been a feature of stroke evaluation, recent studies have shown that atrial fibrillation is undetected in short-term monitoring of individuals with cryptogenic stroke—that is a stroke for which no obvious cause is found (41). Atrial fibrillation was detected in 12% of subjects at 1 year and 30% of subjects at 3 years (42). There is increasing application of long-term monitoring in cryptogenic stroke.

Risk mitigation includes optimization of modifiable risk factors including diabetes, hypertension, hyperlipidemia, tobacco use, body weight, and physical inactivity. Correction of a stroke mechanism with carotid endarterectomy or cardiac valve replacement may allow consideration.

Aeromedical Disposition: Fitness to Fly after Stroke

Whether medical certification should be granted at all after TIA and stroke and, if so, in what circumstances is not a settled matter. Significant variations in policy exist among civil and military regulatory bodies. In some ICAO states, return to airline flying after stroke is precluded in most, if not all cases. In others, individual consideration may be given with a high bar for reconsideration. In the United States, FAA policy generally allows reconsideration following a 2-year period of observation. Aeromedical disposition rests upon stroke etiology, clinical recovery of function, mitigation of modifiable risk factors, and expected recurrence risk.

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is a frequent cause of neurologic disability in the 20 to 55 age group and is commonly encountered in aviators (43). The aeromedical evaluator is not concerned with acute management, but rather the possibility of persistent residual neurologic impairment. Essential ingredients in the evaluation of aviators with TBI include determination of the nature and severity of TBI.

Medical records will disclose the nature of TBI. Concussion is characterized by transient loss or alteration of consciousness (seconds to hours) caused by a blow to the head without evident tissue destruction. However, there may be microscopic neuronal injury, and petechial hemorrhage, axonal shearing with retraction bulbs, and edema may occur. Frank injury to brain parenchyma may occur through brain contusion, diffuse edema, laceration or penetration by a foreign object, and hemorrhage within the brain substance (intracerebral hematoma). Additionally, extraparenchymal bleeding (subdural or epidural hematoma) may cause cerebral injury through compression and herniation mechanisms by mass effect.

Severity of TBI can be assessed utilizing the Glasgow Coma Scale (Table 4-3) (44) and duration of posttraumatic amnesia (PTA) (Table 4-4) (45). A Glasgow Coma score of 13 to 15 denotes mild TBI, a score of 9 to 12 moderate TBI, and below 3 to 8 severe TBI by these criteria. When Glasgow Coma score and duration of PTA are coupled with records documenting the clinical course during the acute recovery period, the evaluator can accurately determine the severity of TBI. A Glasgow Coma score below 9 and/or PTA greater than 24 hours should heighten concern for persistent neurologic impairment. Sequelae of TBI include postconcussion syndrome, focal neurologic deficit, posttraumatic epilepsy (PTE), and neuropsychological residual.

Postconcussion Syndrome

Postconcussion syndrome (PCS) is a nonspecific constellation of symptoms that commonly follow minor or seemingly inconsequential head injury, perhaps without loss of consciousness. Multiple consequences can include physical (e.g., headache, tinnitus, nonspecific dizziness), cognitive (e.g., inattention, memory difficulty, inability to concentrate), and emotional (e.g., depression, insomnia, irritability). Neurologic examination and imaging studies are normal. In most individuals, symptoms are self-limited and resolve in the majority of cases within 3 months, although the more symptoms reported, the longer the time to recovery. Risk factors include prior concussions, female gender, age (>40 years), and prior history of affective disorder such as depression (43). While this syndrome ordinarily does not pose long-term implications for the aviator, PCS may persist for years in some individuals (46).

Focal Neurologic Deficit

Focal neurologic deficit following TBI can take many forms, including cranial nerve palsies (olfactory nerve, optic nerve, nerves to extraocular muscles, facial nerve, acousticovestibular nerve, other), expressive aphasia, hemiparesis or other focal motor deficit, and ataxia. The site is usually deduced through history and physical examination before imaging. While CT may be preferable for evaluating bony trauma and acute subarachnoid blood, MR imaging is more sensitive for detecting the small hemorrhagic foci commonly associated with vascular malformations (47). Most neurologic recovery occurs within 6 months, with further recovery occurring more slowly over a span of 2 to 3 years.

TABLE 4-4

Posttraumatic Amnesia (PTA)

Mild brain injury	0–1 hr of PTA
Moderate brain injury	1–24 hr of PTA
Severe brain injury	1–7 d of PTA
Very severe brain injury	Beyond 7 d of PTA

Adapted from Russell WR, Smith A. Post-traumatic amnesia in closed head injury. *Arch Neurol*. 1961;5(1):4-17.

TABLE 4-3

Glasgow Coma Scale

Eye Opening	*E*	*Best Verbal Response*	*V*	*Best Motor Response*	*M*
Spontaneous	4	Oriented and converses	5	Obeys commands	6
To voice command	3	Confused	4	Localizes to pain	5
To pain stimuli	2	Inappropriate words	3	Withdraws from pain	4
No response	1	Incomprehensible sounds	2	Decorticate (flexion) posturing	3
		No sounds	1	Decerebrate (extension) posturing	2
				No response	1

E + V + M = 3 to 15.
From Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974;304:81-84.

Posttraumatic Epilepsy

A major aeromedical concern following TBI is risk of seizures. Whereas penetrating injuries involving dural laceration and violation of brain parenchyma confer a 20% to 40% risk of PTE, risk in closed head injury is approximately 5% (48,49).

A history of febrile seizures, family history of seizures in a first-degree relative, cerebral contusion, and hematoma (epidural, subdural, intraparenchymal) are associated with increased risk for PTE. An impact seizure, occurring as the name implies at the time of contact, ordinarily does not portend chronic seizure potential. Delayed seizures beginning weeks or months after TBI imply gliotic scar with risk of persistent seizure potential (48,49).

Risk of PTE increases with head injury severity (49), particularly with severe TBI. In this study by Annegers et al., 1-year risk with severe TBI was 6%, compared to less than 1% with mild to moderate TBI. Cerebral cortical contusion, cerebral hematoma, early seizures, loss of consciousness or PTA beyond 1 day, and depressed skull fracture are associated with increased seizure risk. The presence of subdural hematoma confers increased risk, as well as epidural hematoma to a lesser extent. Approximately one third of individuals with PTE will have a first event within 3 months, 50% within 6 months, 75% within 1 year, and 90% within 2 years. As high as 86% of patients with one seizure after TBI will have a recurrent seizure within 2 years of the first seizure (50). While the risk of seizure is difficult to predict, the seizure rate for aircrew that met USAF waiver criteria was 24.53/100,000 person-years (51).

Neuropsychological Residual and Cognitive Deficits

Accelerative and rotational forces can injure brain tissue exposed to irregular bony surfaces within the cranial vault. The frontal poles and orbitofrontal surfaces of the frontal lobes may suffer contusion injury, and the anterior temporal lobes are similarly susceptible.

The frontal lobes have to do with personality, behavior, and executive functions, whereas the temporal lobes are more related to intellect and memory. Frontal lobe injury may lead to behavioral changes including disinhibition, irritability, and impaired anger control with explosive outbursts. Alternatively, an individual might exhibit apathy, indifference, and depression. Impaired judgment, planning, reasoning, abstraction, and initiation of activity may reflect impaired executive functions. Perseveration (inability to change mental set) and inability to employ a problem-solving strategy are common. Deep white matter injury may cause impaired attention and concentration. Temporal lobe injury may lead to significant memory impairment, which is often a major sequelae of TBI.

There is a clear relationship between the severity of the TBI and neuropsychological impairments. Impairments from mild TBI include deficits in fluency and delayed memory recall that typically resolve within 90 days (52). Nevertheless, mild TBI (mTBI) appears associated with increased risk for neuropsychiatric disorders (e.g., PTSD and depression) for at least 6 months compared with a similarly injured non-mTBI control group (51). The aeromedical evaluator should remain mindful of the possibility of neuropsychological impairment, especially in persons with moderate to severe TBI. If indicated by clinical evaluation and review of records, formal neuropsychological testing might be needed depending on extent of cortical injuries.

NEOPLASMS

Benign Neoplasms

Benign intracranial neoplasms can involve the dura, cranial nerves, or brain parenchyma. Extraparenchymal tumors include meningioma, acoustic neuroma, neurofibroma, and pituitary adenoma. Benign parenchymal tumors include ependymoma, colloid cyst of the third ventricle (in reality a cyst), and choroid plexus papilloma. Symptoms usually arise from compression of neural structures rather than invasion. Some benign lesions cannot be safely removed for fear of compromising major or vital structures, giving rise to the term *malignant by position*. These may include tumors involving the clivus, the cavernous sinus, and craniopharyngiomas adherent to the floor of the third ventricle. Residual tumor may lead to recurrence.

Benign dura-based tumors or cranial nerve tumors lend themselves to complete resection, particularly if removed when small. These include meningiomas overlying the cerebral cortex, acoustic neuroma, trigeminal neurofibroma, and pituitary adenoma. Colloid cysts, choroid plexus papillomas, and pinealomas can often be totally removed.

Malignant Neoplasms

Malignant intracranial neoplasms usually arise in brain parenchyma, are invasive, and have potential for rapid growth when of high grade. The gliomas (astrocytomas and oligodendrogliomas) are the most common malignant primary parenchymal tumors. The term *glioblastoma multiforme* refers to high-grade astrocytomas. Invasive features include finger-like projections of malignant cells that interdigitate with normal neural tissue. The surgeon can "debulk" the tumor, but cannot employ the principle of wide excision without compromising neurologic function.

Recurrence is the rule with gliomas, albeit possibly many years later when the tumor is of low grade. Surgical removal without recurrence is uncommon. There are exceptions, such as cystic astrocytoma of the cerebellum with mural nodule in children.

For aeromedical disposition, the evaluator must consider the nature (benign or malignant) and location of the tumor, the presenting signs, the nature and degree of residual deficit (motor, sensory, cognitive), potential for recurrence, and the possibility of seizures. As with resection of vascular malformations, complete tumor resection does not assure freedom from seizures, which may continue to arise from the altered neuronal bed of the lesion. Often a period of observation is employed. Despite apparent neurologic stability over a long period, even years, with low-grade gliomas, malignant parenchymal tumors

characteristically recur, ordinarily barring medical certification. However, given the rise of precision-based medicine with molecular markers that characterize response to treatment, each case must be assessed individually.

HEREDITARY DEGENERATIVE AND DEMYELINATING DISORDERS

Included here for discussion are several conditions that may be nonprogressive, intermittently active and cumulatively progressive, or follow a slowly progressive temporal profile. With appropriate monitoring, medical certification may be appropriate unless and until the condition compromises aviation safety.

Familial and Essential Tremor

Essential tremor is the most common movement disorder with a reported prevalence of up to 5.6%. Familial tremor and essential tremor are the same, the only difference being the presence or absence of a family history of tremor. Autosomal dominant inheritance is present in 60% of cases (53). Although tremor may appear early in life, the mean age of onset is 35 to 45 years. Hand tremor is present in 94%, head tremor in 33%, voice tremor in 16%, and leg tremor in 12%. Slow worsening of tremor over many years is a characteristic feature.

Tremor is usually postural (voluntarily maintaining posture against gravity, such as arms outstretched) and with intention or use (directed voluntary movement toward a target). The tremor frequency is 8 to 12 Hz. Victims often describe difficulty in writing, balancing peas on a fork or soup on a spoon, carrying an empty cup on a saucer, using a screwdriver, or bringing a glass to the mouth. Rest tremor rarely occurs. Improvement with alcohol ingestion is commonly reported.

Essential/familial tremor may have aeromedical implications (e.g., difficulty targeting and manipulating small closely spaced cockpit switches).

Fortunately, for the most individuals, tremor causes little or no impairment, progressing very slowly and often not requiring treatment. If treatment is warranted, β-blockers are often highly effective. Primidone, an older anticonvulsant, is useful in pediatric dose ranges. However, primidone is a barbiturate derivative that can cause drowsiness, barring its use in the aviation environment. Gabapentin and benzodiazepines are also precluded because of potential CNS effects.

Parkinson's Disease

Parkinson's disease is characterized by a classic triad of symptoms including tremor at rest, muscular rigidity, and slowness of movement (bradykinesia). Common clinical features include a slow-shuffling gait, freezing or gait arrest, a general attitude of flexion, impaired postural reflexes, diminished vocal volume, and paucity of facial expression (mask-like face). The examiner observes these features, and neurologic examination usually discloses cogwheel rigidity and impaired rapidly alternating movements (foot tapping, finger wiggle, pronation–supination).

An individual may seek medical attention early in the course of the illness for purposes of identifying the condition, but with no desire or need for treatment. Aeromedical certification may be allowed with appropriate monitoring mechanisms for progression. When treatment is indicated, potential side effects of medication warrant consideration.

Anticholinergics, with their attendant risk of drowsiness and cognitive changes, were the only agents available for treatment until the advent of levodopa in the late 1960s. Levodopa remains the gold standard treatment, and many individuals function well with this agent, remaining relatively free of side effects. In later years, dopamine agonists, primarily pramipexole and ropinirole, came into favor as initial treatment, adding levodopa later if necessary. These agents were initially approved for use by the FAA, but due to reports of excessive daytime sleepiness, approvals were withdrawn. Amantadine has been employed for treatment of tremor, and entacapone delays the breakdown of dopamine in individuals taking levodopa.

Some individuals with Parkinsonian symptoms exhibit evidence of a more widespread cerebral disturbance, giving rise to the term *Parkinson-plus* syndromes. Additional features may include dementia, impaired eye movements, ataxia, orthostatic hypotension, and dysautonomic manifestations. Multiple system atrophy and progressive supranuclear palsy are examples. The neurologist or movement disorder subspecialist differentiates these entities based on clinical features.

Early or mild Parkinson's disease causing little or no impairment need not preclude medical certification. Some medications, such as levodopa or amantadine, might be acceptable without significant side effects.

Multiple Sclerosis

MS is a chronic disease affecting young- and middle-aged adults with slight female preponderance. The illness is characterized by multiple lesions of the nervous system, separated by space and by time. Lesions in MS consist of plaques, localized areas of inflammation, demyelination, and glial scarring involving the white matter of brain and spinal cord. Episodes of demyelination and remyelination account for the exacerbations and remissions commonly seen in MS.

The clinical course of MS may vary among individuals. In primary progressive MS, the disease follows a slowly progressive clinical course without interruption. In the more commonly encountered relapsing and remitting variety of MS, the characteristic exacerbations and remissions occur. Each exacerbation may incompletely resolve, resulting in cumulative neurologic deficit. In secondary progressive MS, a relapsing and remitting clinical course gives way to a slowly progressive decline in neurologic function in later years.

Clinical manifestations of MS can be highly variable depending on plaque distribution in brain and spinal cord. Unilateral optic neuritis is a common presenting sign of MS. Other symptoms might include diplopia, dysarthria, ataxia, motor or sensory symptoms, and bladder or bowel dysfunction. Approximately 14% of individuals with MS have mild or inconsequential neurologic deficit, giving rise to the term *benign MS* (54).

Acute exacerbations are commonly treated with intravenous corticosteroids, specifically methylprednisolone. Immunomodulatory therapy is employed in an effort to reduce the frequency and severity of exacerbations and slow the accumulation of neurologic deficit. Therapy consists of parenteral administration of an interferon preparation or glatiramer acetate. In individuals with significant progression despite steroids and immunomodulatory therapy, chemotherapeutic agents may be employed and agents that are prescribed include cyclophosphamide, azathioprine, methotrexate, teriflunomide, dimethyl fumarate, alemtuzumab, natalizumab, ocrelizumab, fingolimod, and novantrone.

Aeromedical disposition may be favorable in some individuals with MS. Pilots with "benign MS" may present no risk to aviation safety. Some with slowly progressive MS, and others with widely separated and relatively minor exacerbations without accumulation of significant neurologic deficit might warrant consideration. Others with significant functional disability, symptoms clearly related to aviation safety (e.g., vertigo, diplopia, cognitive change), or frequent severe exacerbations will not be candidates for medical certification.

COGNITIVE DISORDERS

Aircrew neurocognitive function safe piloting requires intact cognition including memory, thinking, and reasoning. Neurocognitive functions are those associated with brain structures, areas, pathways, and processes. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) identifies six cognitive domains (complex attention, executive functions, learning and memory, language, perceptual-motor abilities, social cognition) and their subdivisions (55–57). A neurocognitive disorder, also described as neurocognitive impairment (deficiency, inefficiency) and brain dysfunction, is caused by a deficit in one or more cognitive domains due to nonpsychiatric medical conditions.

Neurocognitive impairment may result from developmental or acquired neurologic conditions. Developmental disorders include attention-deficit/hyperactivity disorder (ADHD), learning disabilities, hydrocephalus, cerebral dysgenesis, and other conditions under the umbrella term "cerebral palsy." Acquired conditions include infections (including human immunodeficiency virus [HIV]), TBI, stroke, neoplasm, demyelinating (MS), and degenerative disorders (Parkinson's disease, Alzheimer's disease, and the dementias). In addition, neurocognitive effects of alcohol and substance abuse warrant consideration, as do effects of medication including selective serotonin reuptake inhibitor (SSRI) antidepressants, and other psychoactive substances.

A pilot comes to aeromedical attention when neurocognitive dysfunction is evident or questioned. Whether prompted by diagnosis, observed difficulty with line or training performance or other means, the evaluator must determine whether neurocognitive impairment exists and may impact aviation safety. A history of ADHD or other developmental condition may require assessment. Cognitive effects of acquired conditions such as TBI, stroke, neoplasm, and neurodegenerative disorders merit consideration. Whether cognitive impairment may be responsible for unsatisfactory line or training, performance becomes an important question. Periodic assessment is necessary to monitor cognition in conditions such as Parkinson's disease, MS, and other conditions in which cognitive decline may develop.

Methods of assessing neurocognitive performance vary among ICAO member states. In some, neurocognitive assessment is not prescribed by regulation. When clinical evaluation (neurologic, cardiac, other specialty), laboratory, and imaging studies are satisfactory, medical certification is granted. The pilot returns to the airline for requalification training and satisfactory performance is accepted as validation of the pilot's ability to "do the job." This pathway does not exist in the United States, where satisfactory performance on office-based neurocognitive assessment is often a prerequisite to medical certification. Absent medical certification, flying is precluded for all classes.

An FAA review panel in 1986 recommended inclusion for brief cognitive screening by the AME at each periodic examination (58). Further research exposed the inadequacy of brief office screening instruments such as the mini-mental status examination (MMSE) in detecting early/subtle cognitive dysfunction. This led to the development of a computerized neurocognitive assessment tool with both speed and accuracy components entitled CogScreen Aeromedical Edition (56). Initially intended as a screening tool to indicate need for more comprehensive assessment, CogScreen was later incorporated into a "core battery" for potential neurocognitive impairment that along with CogScreen includes an array of traditional noncomputerized test instruments (57). Domains assessed by core battery testing include attention, memory, spatial abilities, language, psychomotor abilities, executive function, and personality.

Application of office testing of neurocognitive function in a regulatory setting is not without challenges. Ideally, a fellowship-trained PhD board-certified neuropsychologist performs neuropsychological assessment. Important, if not critical, components of the assessment include the interview, behavioral observations, record review, obtaining of collateral information, and interpretation of scores in the context of the total body of evidence (57,58). Interpretation based upon test scores alone can lead to erroneous inferences (57,58).

Since an unfavorable outcome of office-based neurocognitive testing can lead to certification denial with far-reaching effects, test validity must be assured. Test development and selection must meet rigorous scientific standards. Careful attention is needed for a normative database, a comparative group to whom the pilot will be compared (57). The ecologic validity of office-based methods (ability to predict safe performance in the real world of flying) is a matter of great importance. Test administration pitfalls include excessive length of testing, failure to address test limitations, use of inappropriate tests for the question being asked, failure to interpret test scores in context (the total body of medical evidence),

provider qualification issues, failure to address ecologic validity and drawing of unsubstantiated inferences (58,59). These concerns are especially important in a regulatory setting, in which the individual and the provider are distant from the decision-making process.

Optimal methods of assessing neurocognitive fitness to fly are a subject of ongoing debate. The goal of neurocognitive assessment is to determine whether a pilot can perform safely in the real world of flying. Arguably, the closer the method replicates assessment of abilities needed in the real world of flying, the more valid the testing. Today's advanced full-motion simulator has achieved a high degree of physical and perceptual validity, such that a new-hire airline pilot receives his or her type rating in the simulator. The first flight in the actual aircraft is a revenue flight with passengers. Along with physical and perceptual fidelity, there is now interest in cognitive fidelity aspects of simulator design and applications in which higher cortical functions receive focus (60,61). No doubt additional research will contribute to optimal methods of neurocognitive assessment of aviators.

SPACEFLIGHT ADAPTATIONS

In addition to considerations of preexisting neurologic conditions for flight certification, there are unique risks associated with spaceflight that depend on flight duration (62). Recent centrifuge studies have demonstrated that civilian space flight participants with a variety of well-controlled medical conditions can tolerate the acceleration forces associated with typical spaceflight launch and reentry profiles (63). Nevertheless, even in healthy individuals, spaceflight drives adaptive changes that are appropriate for neurologic function in a microgravity environment. These changes are maladaptive for return to earth's gravity. Therefore, the aeromedical physician has the dual tasks of assessing the individual's capacity to tolerate the neurologic stressors associated with spaceflight adaptation and recommending fitness for duty following each G-transition.

G-Transition-Induced Neurovestibular Adaptation

Space motion sickness represents one of the greatest clinical challenges impacting astronaut activities during the first few days on orbit (see also Chapter 5). The intersubject variability is striking with approximately one third experiencing mild symptoms and one third moderate to severe symptoms (64). Unfortunately, there is not a ground-based analog that has proven to be predictive of in-flight space motion sickness susceptibility. In-flight symptoms generally last for 2 days, although there has been at least one case report of protracted motion sickness throughout a spaceflight lasting more than 1 week (65). Promethazine is an effective treatment with few side effects when taken intramuscularly during spaceflight (66). The intensity and incidence of other perceptual and sensorimotor signs and symptoms generally follow this same pattern of intersubject variability. These include gaze, eye-hand coordination, and spatial orientation disturbances for which multisensory integration is a key factor (67,68).

Perceptual disturbances upon transition back to earth's gravity reflect changes in how the CNS adapted to the novel sensory cues experienced during motion on orbit. The most common symptom reported by astronauts associate an exaggerated perceived motion with head tilts during reentry and after landing (64). The incidence of postflight motion sickness is significantly higher following longer (6 month) durations, with all crewmembers experiencing at least mild symptoms. Positive signs using tandem gait with eyes open increased from around half following short-duration flights to all crewmembers following long-duration flights (67). The greatest decrements in postflight functional performance involve tasks requiring dynamic control of postural equilibrium (69). Deficits in manual dexterity, dual tasking, and motion perception may also lead to decrements in ability to operate vehicles, for example, driving (70). Since these results reflect symptoms when returning to land, the incidence and severity of neurovestibular signs and symptoms may be increased following water landings (71).

Gravitational Unloading

The removal of gravitational loading itself can have profound effects that can alter neuromotor skills that depend on accurate proprioception and reduce one's capacity to overcome the neurovestibular deficits (72). Crewmembers must learn to refine the forces needed to manipulate objects or to push off surfaces when navigating on orbit (73). Astronauts often report perceived heaviness of their body and limbs during the early postflight period (74). Gravitational unloading also results in cephalad-fluid shifts and deconditioning of the cardiovascular and musculoskeletal systems. Recent ocular findings include optic disc edema, globe flattening, choroidal folds, and hyperopic shifts in astronauts after long-duration space flight (75). While the etiology of this spaceflight-associated neuro-ocular syndrome (SANS) is still under investigation, chronic cephalad venous and cerebrospinal fluid shift that in the absence of daily unloading by the upright posture may be a primary factor (76). The long-term health consequences of SANS signs and symptoms and volumetric gray matter changes remain an open question (77).

Fitness for Duty Assessments following G-Transitions

Given the relatively short adaptation time course of neurovestibular signs and symptoms, the primary risk mitigation to date has been to limit critical crew activities during the initial days following G-transitions. For example, participation in extravehicular activity is typically constrained during the first 3 days on orbit as is driving or piloting following spaceflight (78,79). Concerns over landing and emergency egress activities for a deconditioned crewmember that cannot be delayed are compounded by other contributing factors such as the acceleration profile of the landing vehicle, dehydration, fatigue, and heat

stress. Beyond the management of motion sickness symptoms during the early recovery, standard neurologic assessments have been supplemented post flight with computerized dynamic posturography (80). For additional information, the reader is referred to Chapter 35. The diagnostic performance of these measures has been improved by requiring active head movements with eyes closed on unstable support conditions. In addition to supporting return-to-duty decisions by flight surgeons, this standardized measure has been useful feedback to instruct crewmembers on their reconditioning status when resuming activities of daily living upon return to Earth.

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