Neuropathology of the Persistent Vegetative State. A Review

HANNAH C. KINNEY, M.D. AND MARTIN A. SAMUELS, M.D.

Key Words: Anoxic encephalopathy; Arousal; Attention; Brainstem; Cognition; Consciousness.

INTRODUCTION

There is no more devastating or morally challenging condition in modern medicine than the persistent vegetative state (PVS). In the United States today, 10,000 to 25,000 adults and 4,000 to 10,000 children are in the PVS (1). The term "vegetative state" is used to describe the condition of patients with severe brain damage in whom vegetative functions (sleep–wake cycles, autonomic control, and ventilation) persist, but awareness (including all cognitive function and emotion) is abolished (1–4). The vegetative state may be a transient stage in the recovery from severe acute or chronic brain damage, the end-stage in the progression of neurodegenerative disease, or a permanent state reflecting the failure to recover from brain damage caused by a nonprogressive process (e.g. after cardiac arrest). The foremost feature of the PVS is a cyclic, albeit irregular, pattern of sleeping and waking unaccompanied by "any behaviorally detectable expression of self-awareness, specific recognition of external stimuli, or consistent evidence of attention or inattention or learned responses" (1). During wakeful periods, patients in the vegetative state move their extremities, but not in any meaningful way (1–4). They lack purposeful or voluntary responses to visual, auditory, tactile, or noxious stimuli. Patients may grunt, moan, or scream, even smile or shed tears, but they totally lack language comprehension or expression (1–4). Indeed, patients in the PVS have survived for as long as 37 years (5) without any demonstrable awareness of their environment, their families, or (presumably) themselves. At the most fundamental levels, the PVS raises critical questions about the nature of human consciousness.

Recently, the medical aspects of the PVS, including standards of care, were extensively reviewed by the Multi-Society Task Force on PVS (1). The purpose of the present article is to review the neuropathology of the PVS, with emphasis upon the insight the topography of lesions provides into the neuroanatomic basis of human consciousness. In analyzing the neuropathology of the PVS, it is therefore first useful to consider the neuroanatomy of human consciousness.

Neuroanatomic Basis of Human Consciousness

Background: For centuries, philosophers have wrestled with the concept of consciousness. Only recently have neuropathologists, neurologists, neurosurgeons, psychiatrists, and neuroscientists entered the fray, arguing that consciousness resides in the brain, that it is the brain's essential function, and that it depends on complex but potentially decipherable, well-defined neural networks. This medical interest in consciousness occurred in part because of the PVS itself and the technical advances that allow support of such patients at different stages in their illness (e.g. mechanical ventilation, antibiotics). The PVS, as well as the comatose state, requires that medical personnel have at least a working definition of consciousness, one capable of relating clinical phenomenology with anatomic and physiologic pathology, and of practical value in diagnosis and decision-making. There have been several recent attempts to construct a detailed brain-based theory of consciousness, including by Edelman (6), Mesulam (7), Dennett (8), and Crick (9). Efforts to understand the molecular biology of cognition have also been initiated (10, 11). In the following discussion, human consciousness is considered primarily in anatomic terms for the purposes of histopathologic analysis of the brains of patients dying in the PVS (Fig. 1).

For clinical purposes, consciousness has two components: arousal and awareness (1, 3, 12). Arousal is that group of behavioral changes that occur when a person awakens from sleep or makes the transition to a state of readiness. Of the array of changes that occur upon awaking, the most conspicuous is that of opening the eyes. Although one can be asleep with the eyes open, or awake with the eyes closed, an individual with his/her eyes open is probably awake. Put simply, an individual with eyes that will open may be said to be awake, and therefore at least partially conscious. Awareness refers to the collective thoughts and feelings of the individual and denotes the knowledge of one's own existence, sensations, and cognition in the external and internal worlds. The vegetative state refers to a state of wakefulness without demonstrable awareness, and thus raises basic questions about the nature of brain pathology which can lead to a
Fig. 1. A simplified diagram of essential brain structures postulated to be involved in human awareness and arousal. Awareness is considered dependent upon interactions between the cerebral cortex and thalamus. Arousal is postulated to be mediated by thalamic and extrathalamic ascending systems. See text for complete explanation. Abbreviations: ACh, acetylcholine; NE, norepinephrine; 5HT, serotonin; HA, histamine; Glu, glutamate; Post., posterior; nTS, nucleus tractus solitarii; nPB, nucleus parabrachialis.

Dissociation of awareness from arousal. This dissociation suggests that the two components of consciousness, awareness and arousal, are mediated by separate and distinct anatomic, neurochemical, and/or physiological systems, and that arousal alone does not ensure awareness (3). Given the uniqueness of the human mind/brain, neuropathologic studies of patients with PVS are crucial for helping to define the anatomic regions essential for human awareness and arousal.

Awareness: Almost all inputs to the cerebral cortex from the external world reach the cerebral cortex by passing through thalamic nuclei which receive, in turn, reciprocal projections from the cortical areas to which they project (13; Fig. 1). All sensory stimuli (except smell) are projected via specific thalamic nuclei to sensory cortex, with visual and somatosensory stimuli projected as point-to-point receptive fields. Cortical neurons responsive to the same stimulus appear to be arranged in vertical columns which are contiguous to columns of neurons which respond to a different stimulus (13–15). Although other functional arrangements may become apparent, it now appears that the entire cerebral cortex, including the association cortices, represents a complex of vertical columns and that adjacent columns are linked by local circuit neurons into information-processing modules defined by specific afferent and efferent connections with modular units in other cortical and subcortical regions (14–20). Current research indicates that the cortical modules...
are linked together into distributed neuronal networks and that the brain operates by parallel processing in which several cortical regions are connected in parallel circuits with each other and key subcortical regions (20–24). The components of a particular cognitive function are distributed among interconnected regions, each region involved in a different aspect of the cognitive ability (7, 23, 24). Consequently, lesions in one anatomic region of a network may impair its functional component of the cognitive ability, or of the entire cognitive ability mediated by the network as a whole (7, 23, 24).

Historically, the prefrontal and parietotemporal association areas of the cerebral cortex have been considered the neuroanatomic loci of cognitive function, an idea supported by the observation that these areas increase in relative size across phylogeny and reach their greatest size in humans. Patients with isolated prefrontal lesions lose insight, judgment, and planning abilities (7, 25). The parietotemporal association cortex integrates somatosensory, visual, and auditory sensory information for perception and language, and is essential for perceptual motor tasks dependent upon polymodal sensory integration (7). The prefrontal cortex was once considered unique among cortical areas as the common end-point for diverse sensory (extero- and intersecptive) information, and thus the foremost structure for synthesizing the external and internal worlds (23, 26). Cortical connections were viewed as organized in a step-wise hierarchical sequence proceeding from relatively raw sensory input at the primary sensory cortices through successive stages of elaboration in secondary sensory cortices, and were ultimately conveyed to the frontal association areas where both sensory and limbic data were integrated in preparation for the individual to respond to sensory stimuli by an appropriate (motor) response (23, 27). According to this hierarchical model of cortical organization, information flow was mainly unidirectional, i.e. from sensory through associational to motor cortices. Yet, no single place in the prefrontal cortex has been found upon which the output of sensory centers converge, thus weakening the “prefrontocentric” view of higher cortical function (23). In contrast, there is mounting anatomic and physiologic evidence that places subdivisions of the prefrontal cortex within parallel systems of distributed neural networks and emphasizes their cooperative, rather than preeminent, role in cognitive functions (23). Blood flow studies in normal human subjects also support a distributed processing model: the act of thinking increases blood flow in multiple cortical fields simultaneously and the constellation of cortical areas activated differs with different types of thinking or internal operations (23, 28, 29).

The thalamus plays a key role in cerebral cortical processing, not only with certain nuclei relaying sensory information from the external world, but also with other nuclei positioned as critical components of distributed neuronal networks. In the vertical columnar organization of the cerebral cortex, certain thalamic nuclei are preferentially and reciprocally connected with association cortices: dorsomedial nucleus with prefrontal association and limbic/paralimbic regions; anterior nuclei with cingulate (paralimbic) cortex; and lateral posterior nucleus and pulvinar with parietotemporal association and paralimbic areas (7, 13). The idea that an individual thalamic nucleus is a critical component of a distributed neural network that subserves a particular cognitive ability is supported by clinical observations that lesions in a thalamic nucleus which is heavily interconnected with an association cortex result in functional impairments similar to damage in the cortical region itself (7, 30–35). The function of the thalamo-cortico-thalamic circuitry in the association cortices is not known but likely involves modulation or integration by thalamic neurons in information processing. The question of integration across cortical networks is of fundamental interest: how is the knowledge of the color or form of an object, for example, integrated with knowledge of its position in space, knowledge that would appear to involve cross-talk between two functional systems. Based upon anatomic data, it has been suggested that integration may occur by a thalamic nucleus (e.g. pulvinar in visual processing) that receives innervation from all of the multiple components of a network (23, 36).

Arousal: Waking is characterized by behavioral activation and EEG desynchronization; it is followed in a cyclic pattern by non-rapid eye movement (NREM) sleep which is associated with EEG sleep spindles and slow waves. The alteration between waking and NREM sleep is postulated to involve the depression of the cortical activating (excitatory) systems of waking by inhibitory systems of NREM sleep that are influenced by multiple central and peripheral chemical factors. During waking, the EEG pattern reflects desynchronous neuronal activity; neuronal excitability is increased, consistent with cognition and attention. During drowsiness and NREM, EEG sleep spindles and slow waves appear, reflecting rhythmic oscillations secondary to thalamocortical synchrony. Historically, arousal has been considered dependent upon the activation of cerebral cortex by relay of inputs from brainstem reticular formation via diffuse and widespread projections from the intralaminar and midline nuclei of the thalamus (“reticular activating system”) (13, 37; Fig. 1). In addition, the thalamic reticular nucleus has been regarded as the “pacemaker” which globally modulates thalamic activity during different levels of arousal from brainstem inputs (13, 38). Cholinergic (ACh) neurons in the mesopontine reticular formation (particularly the pedunculopontine nucleus) compose the major excitatory reticulothalamic pathway to the nonspecific thalamocortical system: they influence this system by direct excitation of thalamocortical neurons, as well as by disinhibition of...
the thalamic reticular nucleus (Fig. 1). The reticular nucleus also receives a substantial cholinergic projection from ACh neurons in the basal forebrain (Ch4). The induction of NREM sleep is thought to involve depression of the ascending activating systems through separate and inhibitory neuronal populations (39). The ACh neurons in the rostral pons and midbrain (Ch5 and Ch6) are leading candidates for the regions controlling rapid eye movement (REM) sleep and its events (39).

Recently, the essential role of the thalamus in arousal has been challenged, in part by the recognition that there are neurotransmitter systems originating in the brainstem, basal forebrain, and hypothalamus which project monosynaptically to the cerebral cortex and activate it directly without relay through the thalamus (37, 39–43; Fig. 1). These ascending systems include cholinergic projections from the basal forebrain (Ch4) and mesopontine reticular formation, serotonergic projections from the brainstem raphe nuclei, noradrenergic projections from the brainstem locus coeruleus, and histaminergic projections from the posterior hypothalamus (39–43; Fig. 1). Moreover, near-total destruction of the thalamus in animals does not prevent cortical activation (44), and the EEG desynchronization characteristic of arousal disappears in rats given blockers of serotonergic and cholinergic transmission, even though thalamocortical transmission is preserved (43). Based upon such experimental studies, it is now considered likely that behavioral arousal reflects the activity of the several ascending arousal systems that stimulate the neocortex and thalamus in parallel; thalamocortical transmission may not be sufficient or even necessary to produce cortical activation. Suppression of the cortical slow waves of NREM sleep likely results from the synergistic actions of the cholinergic, serotonergic, noradrenergic, and histaminergic neurons, although the precise roles of these transmitter systems in waking relative to one another are controversial. The ascending transmitter systems most likely underlie different components of arousal, and EEG cortical desynchronization may be controlled by different transmitters than those underlying the behavioral or motor components characteristic of states.

The Limbic System, Awareness, and Arousal: Awareness depends upon memory which "connects past categorized values related to adaptive internal states with current categorizations based on exteroceptive signals" (6). Memory is linked with the limbic system, composed of limbic and paralimbic areas with major hypothalamic interconnections; these areas include the septal nuclei, amygdala, hippocampus, orbitofrontal cortex, insula, temporal pole, entorhinal cortex, medial temporal cortex, and nucleus basalis of Meynert (7; Fig. 1). The limbic system is also concerned with the homeostasis of the internal milieu: various chemical and other receptors monitor the internal milieu and ultimately project information about it to the hypothalamus, the key structure for autonomic and endocrine control (Fig. 1). In considering arousal, the nucleus basalis of Meynert is an important relay critical for the maintenance of tonic cortical activation (40–42; Fig. 1). It receives inputs from the pontomesencephalic reticular neurons, as well as serotonergic, noradrenergic, and cholinergic neurons, and it projects widely to the cerebral cortex and amygdala (Fig. 1). The common feature of nearly all of the projections to the nucleus basalis is that they originate in limbic–paralimbic areas (45). This organization suggests that the nucleus basalis is a cholinergic relay for transmitting predominantly limbic and paralimbic information to the cerebral cortex, and is responsible for conveying information concerning the relationships between complex environmental events and the internal milieu to many cortical areas involved in many different functions (45). In addition, motivation and emotion influence cognitive processing via the limbic system. In the monkey, for example, single unit recordings show that Ch4 neurons are especially sensitive to motivational variables and reward, and alter their activity when the animal detects an edible object, especially if hungry and the object is a favorite food (7). Thus, Ch4 also appears to act as a pivotal relay for rapidly switching the physiological state of the entire neocortex in a way which reflects the internal motivational and emotional state as encoded by limbic and paralimbic areas (45). In addition to the nucleus basalis, connections between the neocortex and limbic system occur via certain thalamic nuclei (7, 13; Fig. 1). The limbic and paralimbic thalamic nuclei include the mediodorsal nucleus, pulvinar, and anterior and midline nuclei (7, 13). The effects of lesions in these nuclei are consistent with their pattern of cortical connectivity.

Attention: One of the characteristics of patients in the PVS is a lack of attention to the world around them, so that a consideration in the PVS is the neural basis of attention, i.e. those mechanisms that regulate consciousness by selecting a part of the stimuli from the external (or internal) world to be the focus of awareness, while excluding, at least momentarily, other parts of the stimuli which may be sources of distractability (7, 24, 46). Attention is considered a composite of two functions: one regulates overall information processing capacity (arousal) and is associated with the brainstem–thalamic "reticular activating system"; and the second directs attention to a specific target in the external (or internal) world and is associated with the cerebral cortex (7, 24). There is now evidence that a distributed neuronal network mediates attention in the external world and involves three cortical regions which are reciprocally and monosynaptically connected: the posterior parietal cortex, concerned with the sensory aspects of attention and likely containing a sensory template of the external world; the frontal cortex (frontal eye fields and adjacent associative cortex),
<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases (N)</th>
<th>Cerebral cortex</th>
<th>Cerebral white matter</th>
<th>Hippocampus</th>
<th>Basal ganglia</th>
<th>Thalamus</th>
<th>Cerebellum</th>
<th>Brainstem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brierley et al, 1971 (51)</td>
<td>2</td>
<td>+ +</td>
<td>Severe, generalized necrosis</td>
<td>Generalized demyelination; gliosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Severe NLG ant. nuclei, dorsomedial n. pulvinar</td>
</tr>
<tr>
<td>Doughtery et al, 1981 (52)</td>
<td>10</td>
<td>+ +</td>
<td>Substantial injury to cerebral hemispheres: laminar necrosis, multifocal infarction, or both</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NLG</td>
<td>NLG</td>
</tr>
<tr>
<td>Ingvar et al, 1978 (53)</td>
<td>8</td>
<td>+ +</td>
<td>Almost total destruction and disappearance of telencephalic neurons; severe gliosis</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>French, 1952 (Case 4) (57)</td>
<td>1</td>
<td></td>
<td>Particularly free of microscopic change</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Caudate</td>
<td>+</td>
</tr>
<tr>
<td>Reilkin et al, 1990 (56)</td>
<td>3</td>
<td>+</td>
<td>Some diffuse damage, mild relative to degree of thalamic scarring</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Minimal ischemic change</td>
<td>+</td>
</tr>
<tr>
<td>Kinney et al, 1994 (55)</td>
<td>1</td>
<td>+</td>
<td>Focal bilateral infarcts parieto-occipital borderzone and calcarine cortex</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>CA4 gliosis</td>
<td>+</td>
</tr>
<tr>
<td>Ginsberg et al 1976(60)</td>
<td>3</td>
<td>+/-</td>
<td>Focal necrosis</td>
<td>+ +</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jellinger, 1977 (50)</td>
<td>80</td>
<td>+</td>
<td>2nd Ischemic damage</td>
<td>+</td>
<td>Mechanical damage</td>
<td>+</td>
<td>Hemorrhage and necrosis; focal infarctions</td>
<td>+</td>
</tr>
</tbody>
</table>

**Hypoxic-ischemic injury: Predominantly cerebral cortical damage**

**Hypoxic-ischemic injury: Predominantly thalamic damage**

**Hypoxic-ischemic injury: Predominantly cerebral white matter damage**

**Traumatic injury**
<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases (N)</th>
<th>Cerebral cortex</th>
<th>Cerebral white matter</th>
<th>Hippocampus</th>
<th>Basal ganglia</th>
<th>Thalamus</th>
<th>Cerebellum</th>
<th>Brainstem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters and Rodhamud, 1977</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2&lt;sup&gt;+&lt;/sup&gt; Ischemic change</td>
<td>Generalized demyelination, corpus callosal lesions</td>
<td>Mechanical damage</td>
<td>Focal necrosis</td>
<td>Focal or widespread necrosis</td>
<td>NLG</td>
<td>2&lt;sup&gt;+&lt;/sup&gt; Lesions: periaqueductal lesions; necrosis of mesencephalic tegmentum</td>
</tr>
<tr>
<td>Adams et al, 1982</td>
<td>45</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diffuse axonal injury, corpus callosal lesions</td>
<td>+</td>
<td>-</td>
<td>+ Focal hemorrgages</td>
<td>NLG</td>
<td>2&lt;sup&gt;+&lt;/sup&gt; &quot;degeneration of cerebral white matter&quot;</td>
<td></td>
</tr>
<tr>
<td>Strich, 1956</td>
<td>5</td>
<td>+/-</td>
<td>Healed contusions; small cortical infarcts; focal hemorrhages; in general, &quot;looks remarkably normal&quot;</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Legend: N, number of cases; +, damage present; ++, proportionately severe damage present; -, no damage described; NLG, neuronal loss and gliosis; VL, ventrolateral nuclei; VA, ventro-anterior nuclei; ant., anterior; sup., superior.

**Table 1** (Continued)

**Neuropathology of the PVS**

**Etiology:** The causes of the PVS in adults and children are multiple, but fall into three broad categories: 1) acute traumatic injuries, 2) degenerative diseases, and 3) developmental malformations. The most common acute causes of the PVS at all ages are head trauma and cerebral contusion. Many degenerative and metabolic nervous system disorders in adults and children can result from lesions sustained during birth or in the neonatal period. Examples include cerebral palsy, Huntington's disease, and Creutzfeldt-Jakob disease. In children, they include congenital anomalies, such as spina bifida, Arnold-Chiari malformation, and hydrocephalus.

**Neuropathology of the PVS:**

- The PVS is characterized by the presence of widespread cortical and subcortical lesions, including demyelination, gliosis, and neuronal loss. These lesions can affect the entire brain, including the thalamus, basal ganglia, and cerebellum. The thalamus is particularly vulnerable to injury, as it is a major relay station for sensory and motor information. The basal ganglia, which play a role in movement control, are also commonly affected. The cerebellum, which is involved in motor coordination and control, is also frequently involved. The lesions are often bilateral and symmetrical, affecting both hemispheres.

- The PVS is commonly associated with other neurological disorders, such as multiple sclerosis, cerebral palsy, and congenital anomalies. The lesions can be diffuse, affecting large areas of the brain, or focal, affecting specific regions.

- The clinical symptoms of the PVS are varied and can include weakness, ataxia, and impaired motor function. The severity of the symptoms can range from mild to severe, and can be acute or chronic. The symptoms can be caused by the direct damage to the brain, or by the secondary effects of the lesions, such as decreased metabolism and oxygenation.
orhagic foci in the corpus callosum; and 3) hemorrhagic foci in the dorsolateral quadrant(s) of the rostral brainstem adjacent to the superior cerebellar peduncle (48, 49). Axonal swellings cannot be identified by conventional techniques until about 12–15 hours after injury (48). Thus, a definitive diagnosis of DAI cannot be made in patients who survive only a short time; focal hemorrhage in the corpus callosum and dorsolateral rostral brainstem, however, suggest the diagnosis. Secondary brainstem damage may be superimposed upon DAI, thereby making primary brainstem lesions difficult to recognize; nevertheless, the brainstem can be traumatized directly by mechanical forces at the moment of injury (48, 49).

Widespread damage to axons in DAI is postulated to result from acceleration from head movement in the instant after injury, leading to pressure gradients within the skull and brain, as well as shear, tensile, and compressive strains (48, 49). The features of DAI are similar to lesions produced by experimental angular acceleration of the head in subhuman primates (49). The head injuries in DAI are typically uncomplicated, that is, without skull fractures, intracranial hematoma, brain lacerations, or evidence of increased intracranial pressure (48, 49). In long-term survivors, the most striking finding is a diffuse and severe degeneration of the white matter throughout the cerebral hemispheres that is readily detectable, particularly with the Marchi method. Over time, there is reduced volume and increased firmness of the white matter, corpus callosal thinning, and compensatory ventricular enlargement; there is a marked loss of axons associated with abundant lipid-laden macrophages and gliosis. In patients with axonal injury complicated by acute circulatory or respiratory failure, diffuse laminar necrosis may also be present. Indeed, the neuropathology of the PVS following closed head injury may be dominated by secondary lesions due to posttraumatic circulatory disorders and increased intracranial pressure (50; Table 1).

Hypoxic–Ischemic Encephalopathy and the PVS: Hypoxic–ischemic encephalopathy can result from cardiopulmonary arrest, prolonged hypotension, near-drowning, suffocation, strangulation and, in neonates, perinatal asphyxia. In adults who survive in the PVS, acute, global hypoxia and ischemia may result in laminar necrosis in the cerebral cortex which is diffuse or multifocal and extensive (51–53; Table 1). Superimposed upon diffuse cortical lesions may be ischemic damage to arterial border zones, e.g. the parasagittal parieto-occipital cortex. Moreover, cerebral cortical necrosis is typically accompanied by neuronal loss and/or small areas of infarction in the basal ganglia, thalamus, and cerebellum; the hippocampus is invariably involved. There is, however, relative sparing of the hypothalamus, brainstem, basal forebrain, and amygdala. This pattern of damage reflects, to a large extent, the known selective vulnerability of brain regions to hypoxia–ischemia in the adult brain: the most vulnerable regions are the cerebral cortex, hippocampus, and cerebellar cortex; intermediate region, the thalamus; and least vulnerable regions, the brainstem and hypothalamus (48). The basis for selective vulnerability is complex and not completely understood but includes such factors as variable oxygen requirements of specific neuronal populations and differential densities of glutamate receptors, an important component of hypoxia-induced, excitotoxic injury. Of importance in considering the PVS in pediatrics, the patterns of vulnerability to hypoxia–ischemia change with age: in premature and term infants, for example, the thalamus and brainstem are two grey matter regions especially susceptible to hypoxia–ischemia, with relative cerebral cortical resistance (54).

In contrast to cerebral cortical damage, a second pattern of hypoxic–ischemic injury in the PVS is selective necrosis of the thalamus (55–57; Table 1). In this pattern of damage, the cerebral cortex is not completely spared, but rather, the cortical lesions are limited and focal, and the thalamus is disproportionately involved. The brainstem, hypothalamus, and basal forebrain are also preserved. While this pattern of damage appears to be less common than bilateral and widespread cortical damage, its clinical consequences are equally severe. A possible mechanism for selective thalamic damage, other than an intrinsic metabolic vulnerability, relates to cerebral edema complicating hypoxia–ischemia, and partial or immediately reversed transtentorial herniation (58). With herniation, the posterior cerebral artery and its branches, including those supplying the thalamus (thalamogeniculate arteries) are compressed. In certain cases of selective thalamic damage, the occurrence of transtentorial herniation is further supported by associated parahippocampal scars consistent with temporal lobe compression and by infarcts in the calcarine cortex, also in the posterior cerebral artery distribution (55). Of note, necrosis of the thalamus secondary to compression of the penetrating arteries can be seen following blunt head trauma as well (59).

A third pattern of hypoxic–ischemic injury underlying the PVS is a leukencephalopathy (60; Table 1). In this pattern, there are extensive symmetrical necrotic lesions in the central white matter of the cerebral hemispheres, with minimal or no damage to grey matter structures (60; Table 1). These cases share a clinical history of a prolonged period of hypoxemia, hypotension, and elevated venous pressure (60).

Secondary Lesions in the PVS: Given that patients survive relatively long periods in the PVS, it is not surprising that they can develop secondary nervous system abnormalities. Such patients are in a debilitative state and suffer the secondary effects of medication, infection, superimposed medical or surgical illnesses, seizure activity, or decreased nutritional intake. The degeneration of the posterior column of the spinal cord and peripheral nerve

abnormalities, for example, have been attributed to nutritional inadequacies (61). Peripheral nerve lesions have also resulted from compression injury (61). Neuronal loss may occur secondary to retrograde direct and/or transsynaptic degeneration; for example, thalamic neuronal loss and gliosis has been considered secondary to widespread cerebral cortical damage (62), and severe neuronal loss and gliosis in the inferior olive secondary to widespread cerebellar cortical damage and loss of Purkinje cells. In addition, neuronal atrophy and loss in the cerebral cortex is postulated to result from long-standing cortical deactivation and decreased use of oxygen and glucose, which have been shown by physiologic neuroimaging studies to accompany the PVS (63, 64).

The Pediatric Population and the PVS: The PVS is seen in patients from birth, the classic example being newborns with anencephaly. The diagnosis of the vegetative state is difficult in infants less than 3 months of age, as newborns and young infants have a limited ability to show higher cognitive functions before that age (1). The concept of the vegetative state cannot be applied to preterm infants because of the developmental immaturity, including the lack of recognizable sleep-wake cycles (1). Other considerations in the pediatric population relate to developmental patterns of brain injury that differ from adults. Hypoxic–ischemic encephalopathy, for example, may underlie the PVS in newborns and infants, but because the brainstem is especially vulnerable to hypoxia–ischemia in early life, ventilator-dependence, not the PVS, may result. In addition, the developing brain has considerable potential for reorganization of structure and function following injury (62).

Topography of PVS Lesions and Human Consciousness

The question arises: what does the topography of lesions in the PVS tell us about the regions in the human brain that are critical for awareness and arousal? The most telling cases are those in which the lesions are secondary to hypoxia–ischemia or trauma, for, in these instances, the lesions may be isolated and regional. In contrast, degenerative and metabolic disorders tend to be diffuse and involve multiple regions. In Table 1, neuropathologic reports are highlighted in which the lesion description is sufficiently detailed to be useful in considering critical brain structure involvement in the PVS.

In effect, the PVS represents a “locked-out syndrome” in which the cerebral cortex is disconnected from the external world, and all awareness of the external world is lost. This state results from widespread and bilateral damage to: 1) the cerebral cortex itself; 2) the thalamus; or 3) all intra- and subcortical connections via axonal injury and/or demyelination of the cerebral hemispheric white matter (Fig. 2; Table 1). In patients in the PVS with widespread cortical damage, the involvement of the association cortices, in conjunction with the primary and secondary sensory cortices, is considered the critical neuroanatomic substrate. The role of the thalamus in the PVS relates to the highly interdependent relationship between this structure and the cerebral cortex (see above). The damage to the thalamus is not simply to the sensory relay nuclei, such that incoming sensory information from the external world is abolished. Rather, neuropathologic studies indicate that the most severe damage typically is in the associative and limbic nuclei (55, 56). It is therefore likely that the global impairment in patients in the PVS with disproportionately severe thalamic damage results from damage to these nuclei which are critical components of distributed neuronal networks underlying various cognitive and affective functions, including attention in the external world. Given that the thalamus is, in a sense, a compact version of the cerebral cortex con-

Fig. 2. The loss of awareness in the PVS appears to result from widespread and bilateral damage (shown in black) in the: A. cerebral cortex; B. intra- and subcortical connections in the cerebral hemispheric white matter; or C. thalamus.
fined to a small locus and vascular distribution, it is not surprising that bilateral damage to it could result in the global deficits of the PVS.

In considering the neuroanatomic substrate of the PVS, it is clear that lesions are rarely, if ever, restricted to a single locus (Table 1). Indeed, the multiplicity of lesions, including the secondary changes and retrograde direct and/or transsynaptic degeneration at different levels of the neuroaxis, helps explain the many manifestations of sensory, pyramidal, extrapyramidal, and cerebellar abnormalities seen clinically in the PVS (1, 4). Focal infarcts or Wallerian degeneration in the pyramidal, striatal, and cerebellar systems, for example, likely contribute to decerebrate posture and flexion contractures (55). Moreover, the neuroanatomic substrate of the PVS varies from patient to patient, in part because the interval between brain injury and death affects the nature and severity of pathologic changes (1). In hypoxic–ischemic injury, other factors contribute to the variability, e.g. the underlying degree of atherosclerotic cerebrovascular disease. Multifocal lesions suggest the possibility of a fourth pattern of brain injury underlying the PVS, i.e. a combination of focal cortical and subcortical lesions that in some way exert a cumulative effect. Contributing to this pattern, focal damage in the cerebral cortex may alter function in undamaged regions, given the extensive interconnections between cortical regions in distributed neuronal networks. Yet, current information about the lateralization of brain function indicates that the cerebral cortex and thalamus are the strategic structures for awareness. Isolated lesions in the hippocampus, amygdala, basal ganglia, and cerebellum do not result in the global deficits of the PVS, although these structures are all known to be involved in cognitive processing (7, 65, 66). The effects of isolated lesions in the human basal forebrain are, to our knowledge, unknown.

A hallmark of the PVS is that the brainstem is preserved relative to rostral structures, allowing for the maintenance of vegetative functions. For autonomic and ventilatory control, the key neuronal populations are in the lower brainstem and include the vagal nuclei and ventrostral reticular subdivisions of the medulla. For maintenance of the sleep–wake cycle, the source neurons of the cholinergic, serotonergic, and noradrenergic ascending systems, as well as the rostral pontine and mesencephalic reticular formation, are important. The preservation of the brainstem also accounts for the presence of cranial nerve reflexes in the PVS, such as the pupillary, oculocephalic, corneal, vestibulo-ocular, and gag reflexes. The sparing of the hypothalamus is also relevant to the maintenance of vegetative functions. There is no autopsy study of patients in the PVS with severe damage confined to the hypothalamus (1).

Primary lesions confined to the brainstem cause unconsciousness, but result in coma and are fatal in a relatively short time (1, 67). In severe anoxic encephalopathy, for example, "brain death" results from brainstem pan-necrosis associated with forebrain damage. Secondary brainstem lesions due to transtentorial herniation following blunt head trauma have been postulated to result in a PVS (50, 59), but others have questioned this possibility, arguing that the relevant lesion is the associated DAI in the cerebral hemispheres (2, 48). Presumably a primary or secondary lesion in the reticular formation of the rostral pons and midbrain would destroy source neurons and fiber pathways of the ascending (thalamic and extrathalamic) arousal systems which are critical for the generation of arousal. The resultant clinical picture thus would lack arousal, indicative of coma ("eyes shut unconsciousness"), not the PVS ("eyes open unconsciousness"). The case of a patient with a brainstem hemorrhage and coma for 3 years with a selective lesion in the rostral pontine and mesencephalic reticular formation supports this idea (63). French (57), on the other hand, reported three patients with coma who developed periods of eye opening without awareness and who survived 6–9 months in whom the lesions were restricted primarily to the rostral pontine or mesencephalic reticular formation. The role of the rostral brainstem reticular formation in the PVS requires clarification.

The question arises in the PVS: is the cerebral cortex and/or thalamus necessary for arousal? In those cases in which the thalamus is disproportionately involved relative to the cerebral cortex, the extrathalamic ascending arousal systems, via brainstem projections to the cerebral cortex directly or through the basal forebrain and posterior hypothalamus, likely play a critical role, such that widespread damage to the thalamus does not abolish arousal. These cases support the hypothesis from animal data that extrathalamic pathways mediate arousal in parallel to thalamic pathways, and the thalamus may not be essential for arousal. In those cases with widespread cerebral cortical damage, the preservation of arousal has traditionally been related to a functionally intact brainstem and thalamus, with the analogy to anencephaly in which these structures are intact but the cerebral cortex is congenitally absent. The answer to the necessity of the cerebral cortex for arousal may lie with experimental data in which complete removal of the cerebral cortex or transection at the rostral midbrain level results in animals with alternating waking and sleep patterns, and with complex behaviors when awake (68–70). Experimental lesion studies suggest that there are likely arousal systems located both in the brainstem and forebrain (68, 70), and that the brainstem alone is sufficient for arousal.

The question arises whether patients in the PVS have "inner" thoughts and mental images based upon an internal world (independent of sensory input) and of which they are aware. This question will never be resolved, as patients in the PVS do not communicate and the answer

---

depends upon communication. Nevertheless, it is most probable that the patients' inner thoughts are abolished, given the organization of the cerebral cortex into vertical modules with reciprocal subcortical (thalamic) connections: while there may be a distributed network for awareness of the internal, as well as external, world, it likely involves the same basic thalamo-cortico-thalamic circuitry, such that widespread cortical or thalamic damage alters it as well.

Conclusions

In conclusion, patients in the PVS are "locked-out" from the external world due to widespread and bilateral damage to the cerebral cortex, its intra- and subcortical connections (cerebral hemispheric white matter), or the thalamus. In evaluating the brain of a patient dying in the PVS, the neuropathologist should be alert to the underlying etiology and distribution of the primary and secondary lesions. Also of considerable interest are those cases in which isolated and regional lesions provide insight into the critical neuroanatomic substrate of the PVS. In such cases, reference to involved cortical areas according to Brodmann's classification will be useful for correlating clinical and anatomic data; extensive (serial) sectioning will be needed to define precisely involved regions; and computer-based, three-dimensional reconstructions will be helpful in mapping and graphically displaying involved regions relative to non-involved regions (55). More information is needed about the topography of the PVS in infants and children, and if and how it differs from that of adults, addressing questions about developmental changes in the structure–function and plasticity of consciousness (62). More information is also needed about the role of primary and secondary brainstem lesions in producing awareness deficits. To date, neuropathologic studies of the PVS support the idea that separate anatomic pathways mediate arousal and awareness, and that brain diseases can differentially affect each component of consciousness. It is through rigorous clinicopathologic correlations of the PVS that valuable clues about the key brain structures related to human consciousness will be forthcoming.

REFERENCES

31. Isseroff A, Rosvold HE, Galkin TW, Goldman-Rakic PS. Spatial memory impairments following damage to the mediodorsal nucleus of the thalamus in Rhesus monkeys. Brain Res 1982;232:97–113


