The definition of the clinical picture known as persistent vegetative state was given by Jennett and Plum in 1972 when they described patients after severe brain damage who had progressed from a state of coma to a state of wakefulness without detectable awareness. However, since the term persistent vegetative state includes within it a prognostic component (persistent) and a diagnostic component (vegetative state), it was decided at a meeting in London in March 1995 – in the presence of Prof. Jennett – to omit the word “persistent” and to retain “vegetative state.” This point is important because it prevents the possibility during the decision-making process of using the prognostic measure in the ongoing treatment of these patients [1]. It should be mentioned that other authors suggested alternative terms – namely, prolonged coma or post-comatose unawareness [2].

Characteristics of the clinical picture

In patients in a vegetative state it is not possible to discern or produce an intentional behavioral reaction to a visual, auditory or tactile stimulus. There are also no signs of the patient understanding or producing language. These patients may experience sleepwake cycles and the autonomic functions of the brain stem are partially or fully preserved. They do not have sphincter control, but there is at least a partial preservation of spinal reflexes. They often open their eyes but are unable to follow moving objects. In fact they are in a state characterized by the inability to consciously experience either the environment or their inner world.

They may exhibit spontaneous movements of their facial muscles and limbs, e.g., chewing movements, grinding of their teeth or grimacing but, as stated, these movements are considered to be not intentional and without purpose. The diagnosis of VS is not acceptable if the patient is able to exhibit, even to the smallest degree, tracking with the eyes, continuous focusing of the gaze, or intentional movement. This state is known in the literature as the minimal conscious state. For the experienced clinician these diagnostic criteria are not intended to be a significant obstacle when examining a patient after a severe head injury – a state characterized by fluctuations in the level of arousal and awareness. The clinician should be especially meticulous in order to avoid confusing the clinical picture of the vegetative state with other clinical pictures. This applies particularly to the locked-in syndrome in which the patients are totally aware of themselves and their surroundings but are unable to react or express themselves due to their loss of motor ability. Some of them have occasional eye movements.

There is a clear dichotomy in the rate of improvement of the state of consciousness of patients in a vegetative state as a result of a severe head injury, as compared to those in a vegetative state due to a non-traumatic cause, such as hypoxic-ischemic brain damage, encephalopathy, stroke, hypoglycemia, intracranial infection, tumor or hemorrhage. Nevertheless, an improvement in the level of consciousness occurs in about 33% of patients one year after the trauma, although 20% will remain with severe disabilities. The outcome of patients in VS due to a non-traumatic cause is significantly worse, with an improvement in the level of consciousness in only 7% [1,3].

Diagnostic procedures in VS

The need to clarify the exact diagnostic criteria of the vegetative state became clear after several authors found that patients had been misdiagnosed [4]. Childs et al. [5] found that 18 patients (37%) in a cohort of 49 bore the diagnosis of VS despite the fact that they were in a conscious state. Andrews and co-authors [6] identified 17 (43%) of 40 patients diagnosed as being in a vegetative state to be incorrectly diagnosed. Of these, seven had had the diagnosis of VS for more than a year and three patients for more than 4 years. Most of them were able to express their preferences regarding matters concerning their quality of life and some were even able to communicate in a sophisticated manner.

Some patients can recover from a vegetative state to a higher level of consciousness, known as the minimal conscious state. This state is characterized by the ability to express certain types of behaviors which, although inconsistent, indicate awareness and
Vegetative State

a minimal level of consciousness that are totally absent in the vegetative state [7].

Clinical repeated observations by the multidisciplinary team still constitute the most important diagnostic tool for this syndrome and can prevent the above-mentioned mistakes. Other conventional supplementary tests include electroencephalography, which generally manifests a diffuse slowing with polymorphic activity delta or theta waves showing no responses to external stimuli, except perhaps to painful stimulation. In some patients monotonous activity of very low voltage is noted; in others a persistent alpha rhythm is observed. In about 10%, the EEG seems apparently normal, but the alpha block is absent when the eyes are opened. As the patient emerges from the vegetative state the alpha rhythm can be restored together with the reappearance of the reaction to external stimuli.

It is much more prudent to describe this syndrome as a “vegetative state” and not as a “persistent vegetative state,” thereby avoiding the entanglement of a premature prognostic bet.

Somatosensory evoked potentials are an important tool for evaluating the prognosis, but here too it is less important for the diagnosis itself. Lew et al. [4,8] found a close connection between the prognoses of severely head-injured patients and the results of this test. The significance of a lack of cortical response to stimuli of both median nerves is the worst prognostic sign. These patients will definitely remain in a vegetative state for 6 months or will even die within 6 months. These researchers found that the existence of cognitive event-related potentials is a sensitive and exact prognostic measure to indicate a positive prognosis. Preliminary evidence of the use of positron emission tomography for evaluating the prognosis is promising but this test is not yet routinely accessible in daily practice and there is insufficient substantiated research regarding this technique.

The neurophysiology of brain damage
Focal brain injuries occur after contusion or disruption of the continuity of brain tissue, including hematomas and hemorrhages in the extramural, subarachnoid, subdural and intraparenchymal spaces. Contusion usually occurs at the apex of gyri and consists of numerous small puntiform hemorrhages with a tendency to spread towards the adjacent white matter. The areas where contusions most frequently occur are the frontal poles, orbital frontal lobes, temporal poles, the lateral and inferior surfaces of the temporal lobes, and the cortex above the Sylvian fissures. Following contusion and widespread bleeding in the adjacent cortex, the neurons become necrotic secondary to the ischemia. Injury causes inflammatory and cytotoxic phenomena that may occur at a later stage.

Stroke is another kind of injury. It may be divided into hemorrhagic or occlusive. Hemorrhagic stroke is an ischemic event to the neural tissue following interruption of the blood supply, and the distribution of the damage depends on the vessel that is bleeding. The occlusive stroke, on the other hand, is caused by a blockage of the blood supply to a specific area of the brain. The injury causes inflammatory and cytotoxic phenomena that may occur at a later stage. These inflammatory and cytotoxic phenomena are often secondary to ischemia, which is considered to be the most significant factor associated with secondary damage to the brain. In addition, in the areas adjacent to the injury, where the brain tissue did not suffer a critical ischemia, an additional phenomenon may occur and cause damage and death of brain tissue, especially because of the glutamate neurotoxicity. A high extracellular concentration of glutamate causes an influx of Ca²⁺, which in turn can cause an additional secretion of glutamate, in a sort of positive feedback.

Edema is related to the secondary brain damage and in extreme cases causes death due to increased intracranial pressure, which may cause herniation. Edema is in fact the endpoint of a number of pathologic processes that occur following the injury. There are two initial types of edema: vasogenic and cytotoxic. Vasogenic edema occurs at the endothelial level in which it is supposed to prevent the transfer of macromolecules from the blood vessels into the interstitium. Mild and moderate injuries can cause a strong and sudden hypertensive reaction that can damage the integrity of the blood-brain barrier. Another contributing factor to the formation of the vasogenic edema is the secretion of arachidonic acid, which is responsible for mild vasomotor changes with an additional increase in permeability to small and large molecules from the blood vessels. The cytotoxic edema does not necessarily involve the blood-brain barrier. One of the reasons for the cytotoxic edema that is characteristic of hypoxic episodes in which the neurons become swollen within minutes is the failure of the ATP-dependent Na⁺ and K⁺ pump. This causes sodium to accumulate in the neuron, followed by the influx of water due to the osmotic gradient, which causes neuron edema. Another cause of cytotoxic edema is the rise in the level of amino acid neurotransmitters, such as glutamate, aspartate and glycine. A high concentration of extracellular glutamate causes the neuron membrane channels to open, causing an influx of Na⁺, depolarization and the secondary influx of Cl⁻ and water that cause pathologic excitotoxic swelling. This pathology and the late degeneration are dependent on the influx of Ca²⁺, which is also caused by the glutamate, and lead to irreversible neuronal damage. Another cause for the cytotoxic edema is deformation of the neuronal membrane following a trauma. This, in turn, leads to a massive outflow of K⁺ into the extracellular space with astrocytic edema. Indeed, in severe head injuries the edema is seen in the grey matter, the white matter and in the astrocytes because of the combination of all the mechanisms mentioned above.
As to the physical forces applied during acceleration/deceleration, it is clear that these shearing forces cause shearing only rarely. On the other hand, these forces are responsible for the secondary cytotoxic cascade, which actually causes the “shearing” hours and days after the traumatic event. Focal damage occurs at the superficial levels of the brain and, from there, damage spreads into the deeper layers. The focal damage is actually a primary trauma to neurons and the adjacent vasculature, with secondary damage that occurs due to ischemia and cytotoxic cascade. The microscopic findings are characterized by the misalignment of the microtubuli and microfilaments with aggregation and swelling of the mitochondria. These findings actually indicate the disruption of the cell skeleton, the transportation system and the cellular respiration chain. With regard to diffuse axonal injury, it is important to understand that it is a process and not an event. The neurons in the central nervous system are very stretchable. The axons can be stretched up to 65% of their length before being sheared. The tearing does not actually occur at the time of the traumatic event but hours and days later [9].

Acceleration/deceleration is only rarely responsible for direct axonal shearing, which is the result of a later cytotoxic cascade.

Neuropharmacologic treatment
The main goal of neuropharmacologic treatment is to improve arousal and attention, as well as memory at a later stage. Damage to the brain stem and frontal lobes causes a disruption in the neurotransmitter system. Among the most common medications that improve arousal and attention are dopaminergic drugs (bromocriptin, levodopa/carbidopa, amantadine), classic stimulants (methylphenidate, dextroamphetamine, pemoline), antidepressants (desipramide, protriptylin) and the new-generation drugs of serotonin specific reuptake inhibitors (fluoxetine). The drugs that we most commonly use in our unit are levodopa/carbidopa, amantadine, amitriptyline tricyclic antidepressant and methylphenidate. Levodopa/carbidopa turns into active dopamine in a decarboxylation process. Amantadine causes presynaptic stimulation and the release of dopamine in the dopaminergic structures, and it is possible that it acts as a direct dopamine agonist. It is postulated that brain damage causes a reduction in the turnover of dopamine in the brain as a result of damage to the midbrain. Amantadine affects the synthesis, accumulation, release and reuptake of catecholamines in the central nervous system; it induces the release of dopamine from the neurons and is responsible for the delay in reuptake of dopamine by the neurons. There is evidence that it also has significant antagonistic properties for the NMDA receptors, which constitute the basis of the cytotoxic process and for this reason already imparts neuroprotective qualities at an early stage of brain damage [11]. In their prospective study, Krimchansky and collaborators [12] found that all eight patients in a post-traumatic vegetative state treated with levodopa/carbidopa showed an improvement of consciousness after an average of 13 days treatment, and seven of them became conscious to different degrees after an average of 31 days treatment. Since psychostimulants are aimed to improve arousal attention and memory [13], we use them mostly in the minimal conscious state.

Complications of the VS
Patients in the vegetative state, especially those in the subacute phase, suffer from a wide variety of complications, including cachexia, pressure sores, pyrexia of central origin, dysphagia, and others, which I will briefly consider [14].

Urinary
Patients should be examined to determine the capacity, pressure and tone of the detrusor with the aim of preventing misdiagnosis of the neurogenic bladder, which can damage the urinary system. Krimchansky et al. [15] performed urodynamic testing on 17 patients in a vegetative state and found that all of them had a hypertonic bladder of the upper motor neuron type (spastic) even though none of the patients showed a vesicoureteral dyssynergia. Urolithiasis is very rare (2%), although urinary tract infections are quite common (38%).

Gastrointestinal
Gastrointestinal problems are common and are observed in about 50% of patients. Hemorrhages of the digestive system are common, both in the acute stage and in the months and even years following brain damage. Mostly the hemorrhages are microscopic, and endoscopic examination reveals gastritis, esophagitis or stomach ulcers. The mechanism is not clear. Gastrooesophageal reflux is also frequent and is followed by bronchial aspiration, especially in patients who are not mobile and mostly in a supine position. Constipation due to immobility, or diarrhea due to a hyperosmotic feeding is common. Isolation of the clostidium difficile toxin is also frequently seen in this group of patients.

Motor impairments
The pathology of brain damage leads to disturbances in movement and tone such as spasticity, rigidity, paresis, plegia and motor reactivity, which manifests in uncontrolled movements such as chewing, sucking, scratching and stretching.

Epilepsy
Epilepsy is a common phenomenon in patients with VS and was found to have a frequency of 50%. The attacks can occur soon after the brain damage (between seconds to a month post-injury) or as late epilepsy from the first week onwards.

Hydrocephalus
Hydrocephalus is the most common complication in VS patients, mainly in post-traumatic cases. The reported incidence ranges
between 0.7 and 62%. It may be due to the atrophy of the white and gray matter (ex vacuo hydrocephalus), to a disruption in the flow of cerebrospinal fluid due to adhesions of the meninges (obstructive hydrocephalus), or to problems of absorption of the cerebrospinal fluid (normopressure hydrocephalus).

Respiratory
Normal breathing rhythms may be observed in the vegetative patient, but they also show signs of periodic respiratory rhythms and central hyperventilation. The latter is the worst prognostic factor. A certain amount of hypoxia with PO$_2$ 60–80 in the arterial blood with hypercarbia is the rule. Tracheobronchial infection is also a complication that is unavoidable, especially in patients who have been intubated or have a tracheostomy. Tracheal granulation is common and may also cause stenosis and failure of the decannulation process, thereby affecting the whole rehabilitation process. Tracheomalacia and tracheoesophageal fistula are also frequently observed. Occasionally one encounters a rare but fatal complication, such as erosion of the innominate artery.

Keren and co-workers found that longer periods of unconsciousness and mechanical ventilation significantly correlate with respiratory complications ($P < 0.0001$ and $P < 0.001$, respectively). However, the presence of tracheotomies, per se, did not affect vocational rehabilitation. Parenchymal lung infection is the most common complication (37%), while a lung abscess is rare. Fat emboli due to skeletal fractures and thrombotic emboli from the limbs are not uncommon [16,17].

The etiology of brain injury may be variable (traumatic, stroke anoxic, etc.), however the vasogenic and cytotoxic processes that accompany the process are the same.

Cardiovascular system
The most common manifestation is the hyperdynamic cardiovascular reactivity to head injury, which is mainly expressed by systemic hypertension with systolic values of 160 mmHg and higher. Changes in heart rate are mostly tachycardia, although bradycardia may also occur and generally has a worse prognosis. While there may be various types of disturbances in heart rate, they are mainly ventricular premature beats, which are often accompanied by non-specific changes in the ST segments. The hypothalamus and the nucleus of the solitary tract are involved in this hyperdynamic cardiovascular reaction [16].

Keren et al. found a variability in heart rate in patients in the subacute stage after severe head injury, as compared to a control group. This variability is observed in different parameters such as heart rate and the R-R interval. The heart rate gradually becomes balanced within the first 3 months of hospitalization following trauma, which hints at a gradual recovery of the autonomic nervous system [18].

Periarticular new bone formation
The formation of new bone affects primarily, but not only, the large joints. It is caused by metaplasia of the periarticular connective tissues into bone tissue. This phenomenon is common and its occurrence ranges from 11 to 76% in different studies. Much has been written about this pathology, which gravely affects the functional prognosis and the rehabilitation process. Most of the studies tried unsuccessfully to deduce the etiology from the epidemiologic data. The research by Kubota and associates [19] demonstrated that in ectopic bone formation, the bone morphogenetic protein family members, which are essential signaling molecules during limb development, cooperate with the fibroblast growth factor family members in the process of the new bone formation.

Life expectancy of patients in VS
The multi-society task force that discussed the vegetative state determined that the life expectancy of patients in VS ranges from 2 to 5 years. However, more recent data show that the life expectancy is longer due to the global advancement in medical technology together with the accumulation of knowledge regarding the treatment of these patients.

Strauss and team [20] studied the life expectancy of patients in VS and the risk factors for mortality. Their work is based on an investigation of the data of 1021 VS patients in California in the years that preceded the publication of the paper. From the analysis of the data it became apparent that the mortality in the adult VS population declines by about 8% each year from the onset of the clinical condition. This linear relationship is found to be accurate in the first few years of VS. The need for a gastrostomy tube increases the risk of death, especially in children and older patients. It was found that the mortality rate in patients fed with a feeding tube is double that of patients who are fed orally. Dependence on respiratory support is also a factor that increases the risk of death. Most patients with respiratory support are also fed with a gastrostomy tube and in this group of VS patients the mortality rate increases to 66%. The life expectancy in VS patients according to the research by Strauss et al. is 10.1 extra years in a 15 year old patient who had already been in a vegetative state for a year and 12.2 years for a 15 year old who had been in a VS for 4 years [1,20].

Summary
Nowadays more and more patients survive severe brain injury, whether due to traumatic or other causes, owing to the technological advances in medicine. Added to this is a better understanding of pathophysiologic processes, the quality and availability of emergency medicine, and increased medical knowledge in the field. More patients are regaining consciousness than previously. Recovery of functional ability ranges from those still requiring significant nursing care to those able to function independently in activities of daily living. These changes in the
levels of consciousness and function can also occur after very long periods of vegetative state [21]. In our personal experience in the hospital, in 2004, 81% of patients in a post-traumatic vegetative state recovered some level of consciousness.

References


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A library is thought in cold storage

Herbert Samuel (1870-1963), British-Jewish statesman and philosopher. During World War I he began to take part in Zionist activities and in 1920 was appointed the first High Commissioner in Palestine. He was knighted in 1920 and in 1937 was made a Viscount. He led the Liberal Party in the House of Lords from 1944 to 1955. Samuel’s interest in the development of the Jewish National Home never dimmed. He was a constant supporter of the Hebrew University and a member of its Board of Governors.

Capsule

Telephone counseling reduces mortality in patients on polypharmacy

Periodic telephone counseling by a pharmacist improves compliance and reduces mortality in non-compliant patients receiving polypharmacy. Wu and colleagues randomized 442 non-compliant patients receiving five or more drugs for chronic disease to telephone counseling or to the control group. After adjustment for confounders, telephone counseling was associated with a 41% reduction in the risk of death after 2 years. Also, the use of healthcare resources was reduced in the counseling group. Continuous support is needed to change behavior and reinforce positive health behaviors.

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