DISORDERS OF CONSCIOUSNESS AFTER ACQUIRED BRAIN INJURY

A REVIEW OF POSSIBILITIES WITH DEEP BRAIN STIMULATION METHOD

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VEGETATIVE STATE (VS)

Some patients after anoxic or traumatic brain injury (1-3):

- Demonstrate preserved normal circadian rhythm
- Absence of self-awareness AND absent response from environment
- Remain with completely / partially preserved autonomic functions of hypothalamus and brainstem

Due to:

- Focal (bilateral) injury of thalamic and subthalamic – as well rostrocaudal regions
- Neurons of those structures: role in maintaining and regulation of sleep - wake mechanism and awareness
- Neurons in centro-thalamic region are extremely sensitive to mechanism of diffuse axonal injury and hypoxic / anoxic injury

CRITERIA / WHEN TO DECLARE VS (I)

American Academy for Neurology, 1994

- No evidence of awareness of self or environment and an inability to interact with others
- No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli
- No evidence of language comprehension or expression;
- Intermittent wakefulness manifested by the presence of sleep-wake cycles

CRITERIA / WHEN TO DECLARE VS (II)

American Academy for Neurology, 1994 (4)

- Sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care;
- Bowel and bladder incontinence
- Variably preserved cranial nerve (pupillary, oculocephalic, corneal, vestibulo-ocular, gag) and spinal reflexes.
COMMON & FREQUENT MISLEADING

→ After a period of coma the patient opens his/her eyes, at first to pain and then to less arousing stimuli. This is then followed by periods with the eyes open (5).

→ Some authorities do not like to talk in terms of ‘sleep–awake’ since this implies a higher cortical function. They prefer to use the simple terms of eye opening and closing (6-9).

→ It is very difficult, however, to persuade caring staff and relatives not to talk in terms of a sleep and awake.

COMMON & FREQUENT MISLEADING

- There may be roving eye movements and the patient’s eyes may seem to briefly follow moving objects.
- The movement is usually inconsistent and never sustained.
- The main early sign that the patient is emerging from the vegetative state is that he begins to focus on and/or tracks a moving object or person.

- Andrews et al found that 60% of patients who were misdiagnosed as being vegetative were blind or had severe visual impairments which would make focussing an impossibility.
COMMON & FREQUENT MISLEADING

- A non-volitional grasp reflex may be present. This can cause considerable concern to relatives who feel that the patient recognises them when they hold his hand.

- Chewing movements or grinding of teeth, sometimes accompanied by constant movement of the tongue. These again cause concern to relatives who may feel that the patient is indicating that he is thirsty or hungry.

- Grunting and groaning may be provoked by noxious stimuli but no speech occurs. These sounds are often interpreted by relatives as indicating an attempt to communicate. This can cause disagreement between family and clinicians when some relatives claim to be able to ‘understand’ the words spoken when others only hear sounds.

Strens LHA, Mazibrada G, Duncan JS, Greenwood J. Brain Inj 2004. 18: 213-22
PERSISTIVE / PERMANENT VS DEFINITION

The *persistent vegetative state* can be defined as a vegetative state present at 1 month after acute traumatic or nontraumatic brain injury, and present for at least 1 month in degenerative/metabolic disorders or developmental malformations.

The *permanent vegetative state* means an irreversible state, a definition, as with all clinical diagnoses in medicine, based on probabilities, not absolutes.

VS can be judged to be *permanent 12 months after traumatic injury* in adults and children. Special attention to signs of awareness should be devoted to children during the first year after traumatic injury.

PVS can be judged to be *permanent for nontraumatic injury* in adults and children after 3 months.

PROGNOSIS

- Expected life-span time of persons in VS is 2 – 5 years.
- Survival for more than 10 years is very unlikely.
- Survival for more than 15 years is anecdotal.
- Recovery of consciousness after TBI – PVS is 46% after 6 months and 52% after 12 months, most of those patients are severely disabled.
- Recovery of consciousness after nonTBI – PVS is 15% after 6 and 12 months (6).
INCIDENCE & PREVALENCE OF VS (5)

- UK: Incidence 14 / million pop. (overall, after 1 month)
- ISR: Incidence: 4.5 / million pop. (TBI, after 1 month)
- DK: Prevalence: 1.3 / million pop. (TBI, after 5 years)
- FRA: Incidence: 67 / million pop. (overall, after 1 month)
- AUT: Prevalence: 19 / million pop. (overall)
- N.IRL: Prevalence of VS + MCS: 19 / million pop. (overall)
- USA: Incidence: 46 / million pop. (overall, after 1 month)
  Prevalence: 40 – 168 / million pop. (overall)
Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome

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Abstract

Background: Some patients awaken from coma (that is, open the eyes) but remain unresponsive (that is, only showing reflex movements without response to command). This syndrome has been coined vegetative state. We here present a new name for this challenging neurological condition: unresponsive wakefulness syndrome (abbreviated UWS).

Conclusion: Since after 35 years the medical community has been unsuccessful in changing the pejorative image associated with the words vegetative state, we think it would be better to change the term itself. We here offer physicians the possibility to refer to this condition as unresponsive wakefulness syndrome or UWS. As this neutral descriptive term indicates, it refers to patients showing a number of clinical signs (hence syndrome) of unresponsiveness (that is, without response to commands) in the presence of wakefulness (that is, eye opening).
MINIMAL CONSCIOUS STATE - MCS
DEFINITION & CRITERIA

MCS is distinguished from VS by the presence of behaviors associated with conscious awareness.

In MCS, cognitively mediated behavior occurs inconsistently, but is reproducible or sustained long enough to be differentiated from reflexive behavior.

The reproducibility of such evidence is affected by the consistency and complexity of the behavioral response.

Extended assessment may be required to determine whether a simple response (e.g., a finger movement or eye blink) that is observed infrequently is occurring in response to a specific environmental event (e.g., command to move fingers or blink eyes) or on a coincidental basis (11).

Comparison of clinical features associated with coma, vegetative state and minimally conscious state

<table>
<thead>
<tr>
<th>CONSCIOUSNESS</th>
<th>WAKE/SLEEP</th>
<th>MOTOR FUNCTION</th>
<th>AUDITORY FUNCTION</th>
<th>VISUAL FUNCTION</th>
<th>COMMUNICATION</th>
<th>EMOTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMA</td>
<td>NONE</td>
<td>Reflex and postural responses only</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>VS</td>
<td>NONE</td>
<td>Postures or withdraws to noxious stimuli</td>
<td>Startle</td>
<td>Startle</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brief orienting to sound</td>
<td>Brief visual fixation</td>
<td></td>
<td>Reflexive crying or smiling</td>
</tr>
<tr>
<td>MCS</td>
<td>PARTIAL</td>
<td>Localizes noxious Stimuli</td>
<td>Localizes sound location</td>
<td>Sustained visual Fixation</td>
<td>Contingent Vocalization</td>
<td>Contingent smiling or crying</td>
</tr>
</tbody>
</table>
Future questions / directions for research...

- Incidence and prevalence of MCS
- Natural history, recovery course and outcome.
- Interrater and test–retest reliability of the diagnostic criteria for MCS.
- Validation of diagnostic criteria for MCS with respect to pathophysiologic mechanisms and outcome.
- Differences in rate of recovery and outcome between adults and children.
- Interactions among cause of the injury (e.g., trauma vs anoxia vs. dementia), length of time after onset, and recovery of consciousness.
Future questions / directions for research...

- Predictors and patterns of emergence from VS and MCS.
- Utility of existing assessment methods and scales for monitoring recovery and predicting outcome.
- Treatment efficacy.
- Efficacy and cost analysis of different care settings.
- Issues related to family beliefs and their relation to functional outcome, service use, and evaluative decisions regarding quality of life.
- Cross-cultural differences in evaluation and management practices.
Guidelines for Quality Management of Apallic Syndrome / Vegetative State

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Abstract
Introduction: Epidemiology in Europe shows constantly increasing figures for the apallic syndrome (AS)/vegetative state (VS) as a consequence of advanced rescue, emergency services, intensive care treatment after acute brain damage and high-standard activating home nursing for completely dependent end-stage cases secondary to progressive neurological disease. Management of patients in irreversible permanent AS/VS has been the subject of sustained scientific and moral-legal debate over the past decade.

Methods: A task force on guidelines for quality management of AS/VS was set up under the auspices of the Scientific Panel Neurotraumatology of the European Federation of Neurological Societies to address key issues relating to AS/VS prevalence and quality management. Collection and analysis of scientific data on class II (III) evidence from the literature and recommendations based on the best practice as resulting from the task force members’ expertise are in accordance with EFNS Guidance regulations.

Findings: The overall incidence of new AS/VS full stage cases all etiology is 0.5–2/100,000 population per year. About one third are traumatic and two thirds non traumatic cases. Increasing figures for hypoxic brain damage and progressive neurological disease have been noticed. The main conceptual criticism is based on the assessment and diagnosis of all different AS/VS stages based solely on behavioural findings without knowing the exact or uniform pathogenesis or neuropathological findings and the uncertainty of clinical assessment due to varying inclusion criteria. No special diagnostics, no specific medical management can be recommended for class II or III AS treatment and rehabilitation. This is why sine qua non diagnostics of the clinical features and appropriate treatment of AS/VS patients of “AS full, remission, defect and end stages” require further professional training and expertise for doctors and rehabilitation personnel.

Interpretation: Management of AS aims at the social reintegration of patients or has to guarantee humanistic active nursing if treatment fails. Outcome depends on the cause and duration of AS/VS as well as patient’s age. There is no single AS/VS specific laboratory investigation, no specific regimen or stimulating intervention to be recommended for improving higher cerebral functioning. Quality management requires at least 3
DEEP BRAIN STIMULATION METHOD

Current use: neurology, psychiatry, neurosurgery

Successful: extrapyramidal movement disorders, obsessive-compulsive disorders

Unconfirmed: MCS and VS


Kinamura (1996): importance of intralaminar nuclei for sustained awareness and short memory formation

V d Werf (2002): relevance of thalamo-cortical connections and thalamic centro-lateral nuclei for sustained wakefullness and awareness
IMPLANTABLE DBS SYSTEM

Routine clinical practice from 1970's
Neurosurgical procedure under 3D stereotactic guidance
Implantation of two wired electrodes with four stimulation electrodes each in the region of subthalamic nuclei
Wired electrodes are subcutaneously connected with the stimulator placed infraclavicular.
Figure 1. CM-pf complex stimulation therapy for VS. The skull X-P (upper) and axial CT scans (lower) indicate the location of the DBS electrode.
Hassler, 1969: 19 days of stimulation of R pallidum and L latero-polar thalamic nuclei in male patient 5 months after TBI

Raised wakefulness, spontaneous left limbs movement, turning to objects and subjects as well beginning of non-functional vocalisation.

Additionally: EEG changes in term of decreased delta activity L temporal, asymmetry reduction and partial restoration of alpha rhythm.

Majority of effects diminished soon after the stimulation was switched off.
**DBS – literature overview**

**Sturm, 1971**: Stimulation of polar reticular subthalamic nuclei in male patient after stroke in mesencephalic region – with subsequent condition described as “*intermediate between coma and apalic syndrome*”.

More reliable following to commands, longer awareness periods, improved oral communication, more efficient oral intake.

Patient died two months after permanent DBS system implantation.
DBS – literature overview

Tsubokawa, 1990: Eight patients in VS of at least six months duration.
Three patients after TBI, two after anoxic injury and three after spontaneous CVI (ICH and / or SAH).

System for permanent stimulation of RF and non-specific subthalamic nuclei was implanted in all patients.

Previous neurophysiological assessment: EEG, SEP, SSEP, APBS

Neuro assessment: response to painful stimuli, spontaneous eye-opening, spontaneous limb movement, eye movement, emotional response, oral intake, vocalisation, verbal response and following to commands
Tsubokawa (1990) - RESULTS:

Six months after DBS:

Two patients after CVI regained effective oral communication, following of commands, proper emotional response and oral intake.

One patient after CVI showed partial and inconsistent following of commands, full object eye-tracking and spontaneous limb movement.

In five patients (including all after TBI), there was no improvement in neurological condition or level of awareness.
DBS – literature overview

Tsubokawa (1990) - CONCLUSIONS:

It is recomended to wait up to three months to assess the effect of DBS.

Effect of DBS is not only early activation of ascendent RAS but predominantly increase of brain circulation and glucose metabolism in cortex and thalamus.

Later might induce neuroplasticity in those regions as well surrounding tissue and so a basis of improved awareness and consciousness.
DBS – literature overview

Schiff et al., 2007:
Intervention:
Implantation of permanent DBS of subthalamic pf nuclei in a patient six months after TBI

Observation:
Primary parameter: „JFK – Coma recovery scale – revised“ during double blind “on” and “off“ stimulation for period of six months. Secondary parameter: object naming, following motorical commands, oral intake.

Conclusion:
Significant correlation between „on“ period and qualitative changes in patient’s behaviour – prolonged eye opening periods, following commands, trying of functional use of objects and verbalisation.
DBS – literature overview

Yamamoto et al., 2010 (18)

Study group: 21 patients in VS (AAN criteria), four to eight months after TBI or stroke (9 stroke, 9 TBI, 3 anoxic BI)
Average age 44 yrs (range 19-72)

Control group consisted of 86 patients in VS (AAN criteria) of various aetiologies

Methods: In two patients DBS electrodes were implanted in the region of mesencephalo-RF and 19 patients in the subthalamic CM-pf nuclei of dominant haemisphere
DBS – literature overview

Yamamoto et al. (2010)

Prior to DBS implantation:
- ABsR for assessment of brainstem function
- SEP over primary somatosensory cortex to assess cortico-thalamic connections
- Pain related P250 to assess higher neural activity
- Continuous EEG

After DBS implantation:
DBS „on“ for 30 minutes every 2 – 3 hours during day.
Follow up in study group for 10 years after implantation or until death
Follow up in control group for two years.
Yamamoto et al. (2010) - RESULTS
All 86 patients in control group remained in VS.

21/21 patients in study group showed early arousal immediately after switching the system „on“ in term of:
- eye opening with dilated pupils,
- raise of heart frequency and arterial pressure,
- as well mouth opening.

8/21 patients emerged from VS, and could communicate with some speech or other responses, but needed some assistance with their everyday life in bed.
Even after long-term rehabilitation, their state of being bedridden remained unchanged in seven of these eight cases. The other case became able to live in a wheelchair.

The remaining 13 cases were unable to communicate at all and failed to emerge from the VS.
DBS – literature overview

Yamamoto et al. (2010) – RESULTS in MCS GROUP

All of the 5 cases of MCS displayed inconsistent behavioural evidence of consciousness before DBS therapy, and they became able to communicate with definite behavioural responses after the DBS.

Four cases emerged from the bedridden state, and were able to enjoy life in their own home.

The other case still remained in a bedridden state.
DISCUSSION

DBS seems to be promising in patients, that show preserved connectivity among the brainstem and cortex as well with preserved cortico-thalamic connectivity.

- Immediate response in term of eye-opening, arterial pressure elevation and heart rate dynamics is a favourable prognostic factor for long term positive effect of DBS
- All patients in Yamamoto et al „large“ study group who improved awareness had electrodes implanted in CM-pf complex
- No „spontaneous“ improvement in a control group
DBS – literature overview

DISCUSSION

DBS seems to be far from recommended for general use in patients in VS or and MCS. Even when clinical status in different patients seem to be similar, their basal brain activity is undoubtfully different.

• Prior to consideration about the DBS, assessment of cortico-thalamic and cortico–mesencephalic connectivity with neurophysiology diagnostic and neuro imaging is recommended (SSEP, ABR, EEG, PET, f-MRI)

• We are not aware of any reliable prognostic factors that could predict the outcome with DBS therapy.