Persistent Vegetative State & Minimally Conscious State:

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Relevance & Importance

- Definition of terms PVS & MCS in the severely disabled
- Limitations of the definitions
- Recent research in cognitive awareness in PVS
- Therapies to stimulate cognitive awareness
- Possibility of emergence from PVS
- Providing for optimal medical care in the LCP will maximize life expectancy
Terry Schiavo
Brain Death

• Brain damage vs. brain death
• Mechanical ventilation, life support
• Organ transplantation
• 1959, Mollaret and Goulon, *coma depasse* (irreversible coma): no cortical or brain stem functions, no respirations and flat EEG
• 1968, ad hoc committee, Harvard Medical School, similar definition
Brain Death

• 1971, Mohandas and Chou: damage to brain stem is a critical component
• 1976, Conference of Medical Royal Colleges, UK, complete and irreversible loss of brain stem function
• 1981, President’s Commission guidelines: use of confirmatory tests to reduce duration of observation; 24 hour wait for anoxic damage
Brain Death

• 1995, American Academy of Neurology, practice parameters

• The Diagnosis of Brain Death, Wijdicks, New England Journal of Medicine, 344: 1215-1221, 2001
Brain Death

- Precise clinical examination
- Establishment of the cause of the coma
- Ascertainment of irreversibility
- Resolving any misleading clinical neurologic signs
- Recognition of possible confounding factors
- Confirmatory laboratory tests
Coma and absence of motor response
Pain response, corneal reflex, pupillary response, caloric testing, gag/cough reflex
Apnea Testing: temp 36.5, BP 90 mm Hg, + fluid balance 6 hours, O2 ventilation to reach 200 mm Hg, 8-10 min observe and rise in PCO2 of 20 mm Hg
Interval between 2 evaluations / Need for confirmatory tests

- Term to 2 m old: 48 hrs—2 tests
- 2 m to 1 year old: 24 hrs—1 test
- 1 to 18 years: 12 hrs—optional
- Over 18 years: optional—optional
Confirmatory Tests

- Cerebral angiography
- Transcranial Doppler ultrasonography
- Electroencephalogram
- Cerebral Scintigraphy (technetium)
Persistent Vegetative State

Persistent Vegetative State

- 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
Persistent Vegetative State

- Intermittent wakefulness manifested by the presence of sleep-wake cycles
- Sufficiently preserved hypothalamic and brain stem autonomic functions to permit survival with medical and nursing care
- Bowel and bladder incontinence
- Variably preserved cranial nerve and spinal reflexes (pupillary, oculocephalic, corneal, gag, spinal withdrawal)
Persistent Vegetative State

• PVS can be diagnosed 1 month after acute brain injury
• PVS can be judged to be permanent 12 months after traumatic brain injury in children and adults
• PVS can be judged to be permanent for nontraumatic brain injury in children and adults after 3 months
Persistent Vegetative State: Degenerative / Metabolic

- Degenerative and metabolic disorders of the brain: as the disease progresses, impairment of consciousness takes place.
- Intercurrent illnesses and medication effects can produce temporary PVS.
- If the vegetative state persists for several months, then can be considered PVS.
Persistent Vegetative State: Infants

- Severe developmental malformations of the nervous system
- PVS can be diagnosed at birth only in infants with anencephaly
- Other severe malformations: must wait for 3 to 6 months before diagnosing PVS
Table 54.15: Glasgow outcome scale classification for recovery of consciousness and function in adults in a persistent vegetative state (PVS) beyond 1 month

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3 Months (%)</th>
<th>6 Months (%)</th>
<th>12 Months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traumatic Brain Injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>15</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>PVS</td>
<td>52</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Conscious</td>
<td>33</td>
<td>46</td>
<td>52</td>
</tr>
<tr>
<td>Severe disability</td>
<td>—</td>
<td>—</td>
<td>28</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>—</td>
<td>—</td>
<td>17</td>
</tr>
<tr>
<td>Good recovery</td>
<td>—</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td><strong>Nontraumatic Brain Injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>24</td>
<td>40</td>
<td>53</td>
</tr>
<tr>
<td>PVS</td>
<td>65</td>
<td>45</td>
<td>32</td>
</tr>
<tr>
<td>Conscious</td>
<td>11</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Severe disability</td>
<td>—</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>—</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Good recovery</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>

1994 Multi-Society Task Force on PVS
Persistent Vegetative State: Emergence

- 13 out of 30 emerged from PVS
- Time from injury to improvement: 4 to 60 months
Persistent Vegetative State
Pediatric / Young Adult
Long-Term Care

• Years of 24-7 attending physician care
• Peds / Young Adult: 3,813
• Adult: 1,320
• Total: 5,133
• Many referred cases diagnosed PVS
• No actual cases of PVS
Persistent Vegetative State

• “The PVS means an irreversible state, a definition, as with all clinical diagnoses in medicine, based on probabilities, not absolutes.”

• “A PVS patient becomes permanently vegetative when the diagnosis of irreversibility can be established with a high degree of clinical certainty, ie, when the chance of regaining consciousness is exceedingly rare.”
PVS: Donald Herbert

- Buffalo, NY firefighter
- Dec. 1995, trapped under a collapsed roof during a fire
- Anoxia for several minutes
- PVS, Dr. Ahmed, PMR
PVS: Donald Herbert
April 30, 2005, started talking, responding
PVS: Donald Herbert
April 30, 2005, started talking

- 3 months after starting a combination of a stimulant, a SSRI and a dopamine agonist
- Unknown which medicines were used
- No neurology involvement for many years
- Multifactorial injury: anoxia, carbon monoxide, traumatic brain injury
- 1996 was communicative, responsive, 1997 lapsed into an unresponsive state
- 2005 improvement lasted only 14 hours
Minimally Conscious State

- American Academy of Neurology recommends this report as an educational tool
- Endorsed by the AAPMR, AANS, ACRM, BIA and CNS
Minimally Conscious State

• Severe alteration in consciousness, but do not meet criteria for PVS
• Behavioral evidence of consciousness but remain unable to reproduce this behavior consistently
• Partial preservation of conscious awareness
• Prevalence estimate, adult and pediatric: 112,000 to 280,000 in US
Minimally Conscious State Diagnostic Criteria

• For MCS, limited but clearly discernible evidence of self or environmental awareness must be demonstrated on a reproducible or sustained basis, by one or more of the 4 behaviors:
  1. Following simple commands
  2. Gestural or verbal yes / no responses (regardless of accuracy)
Minimally Conscious State
Diagnostic Criteria

3 Intelligible verbalization
4 Purposeful behavior, including movements or affective behaviors that occur in contingent relation to relevant environmental stimuli, and are not due to reflex activity, such as:
   appropriate smiling or crying
   vocalizations or gestures in response to language
Minimally Conscious State
Diagnostic Criteria

4 Purposeful behavior (continued):
  reaching for objects, relation between object and direction of reach
  touching or holding objects that accommodates the size and shape of the object
  pursuit eye movement or sustained fixation in response to moving or salient stimuli
Emergence from the Minimally Conscious State: 1

FUNCTIONAL INTERACTIVE COMMUNICATION

• Accurate yes / no answers to 6 of 6 basic questions on two consecutive evaluations
• Examples: Are you sitting down?, Am I pointing to the ceiling?
• Speech, writing, yes / no signals, augmentative communication devices
FUNCTIONAL USE OF TWO DIFF OBJECTS

Demonstrates behavioral evidence of object discrimination

• Appropriate use of 2 different objects on 2 consecutive occasions

• Examples: bringing a comb to the head, putting a pencil to a sheet of paper
Emergence from the Minimally Conscious State: 3

QUESTIONS / CONCERNS

• Severe physical impairment

• Severe cerebral palsy

• Even MCS diagnostic criteria are of uncertain applicability
Signs of consciousness
Minimally Conscious State
fMRI scans, verbal and tactile

- Columbia, Cornell, Georgetown Univ.
- 2 patients with MCS, 7 more since then
- Patient A, MCS 18 m, left temporal spontaneous intracerebral hemorrhage
- Patient B, MCS 24 m, TBI and SDH
fMRI scans controls, passive listening: forward-yellow, reverse-blue, overlap-red
Composite fMRI scans controls passive listening:
forward-yellow, reverse-blue, overlap-red
Minimally Conscious State
fMRI scan patient A
Minimally Conscious State
fMRI scan patient B
Minimally Conscious State
fMRI scans patient A and B
Minimally Conscious State
fMRI; tactile stimulation; Pt A, Pt B, Control
 Persistent Vegetative State

- Auditory brain stem response: P300
- Fabien Perrin PhD, et al., Lyon, France, Archives of Neurology, 63:562-569, 2006
- Own first name / mixed with 7 equiprobable names
- PVS: 3 / 5
- MCS: 6 / 6
Persistent Vegetative State / Minimally Conscious State

- Many other techniques: PET, SPECT, EEG, Event Related Potentials (ERP’s)
- Kotchoubey, et al., Tubingen, Germany, Clinical Neurophysiology, 2005, 2441-53
- 98 patients, 50 PVS, 38 MCS
- Complex verbal tasks for late ERP’s
<table>
<thead>
<tr>
<th>Brain response</th>
<th>Groups</th>
<th>PVS slow EEG N=12</th>
<th>PVS ok EEG N=38</th>
<th>MCS N=38</th>
<th>Cons. Recovering N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CG1</td>
<td>EG1</td>
<td>EG2</td>
<td>CG2</td>
</tr>
<tr>
<td>N1-(P2)</td>
<td>33*(36*)</td>
<td>89***(92***</td>
<td>95***(97***</td>
<td>100***</td>
<td></td>
</tr>
<tr>
<td>MMN</td>
<td>8(9)</td>
<td>65***(63***</td>
<td>34***(38***</td>
<td>100***</td>
<td></td>
</tr>
<tr>
<td>P3 (sine tones)</td>
<td>0</td>
<td>15(14)</td>
<td>8(4)</td>
<td>60***</td>
<td></td>
</tr>
<tr>
<td>P3 (complex tones)</td>
<td>0</td>
<td>22*(19)</td>
<td>31***(30***</td>
<td>56***</td>
<td></td>
</tr>
<tr>
<td>P3 (vowels)</td>
<td>0</td>
<td>19(16)</td>
<td>22*(20)</td>
<td>56***</td>
<td></td>
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<tr>
<td>at least one P3 response</td>
<td>0</td>
<td>32***(30**)</td>
<td>36***(35**)</td>
<td>80***</td>
<td></td>
</tr>
<tr>
<td>P600 (semantic oddball)</td>
<td>0</td>
<td>23**(22*)</td>
<td>13(11)</td>
<td>44***</td>
<td></td>
</tr>
<tr>
<td>N400</td>
<td>0</td>
<td>14(16)</td>
<td>20*(18)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>(word-pairs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N400</td>
<td>0</td>
<td>23*(22*)</td>
<td>18(16)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>(sentences)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one semantic response</td>
<td>0</td>
<td>22**(24**)</td>
<td>25**(24**)</td>
<td>60***</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate component frequencies when patients with less typical etiology (fat emboli, encephalitis) were excluded. Asterisks show how significantly the corresponding numbers differ from those expected by chance: *P<0.05; **P<0.01; ***P<0.001.
Persistent Vegetative State

- July 2005, 23 year old female, MVA, TBI
- 5 months later in a vegetative state
- “There was milk and sugar in the coffee” vs. acoustically matched noise sequences
- “The creak came from a beam in the ceiling” ambiguous words, more response
Speech minus acoustically-matched noise

Patient

X = -60

Y = -30

Controls

L ← → R
Persistent Vegetative State

- Imagine playing a game of tennis
- Imagine walking through all of the rooms in your house
PVS & MCS: Medications

- Levodopa
- 4 with PVS, 1 with MCS
- Parkinsonian symptoms
- MRI changes in the dopaminergic pathway
- What percentage PVS & MCS is levodopa effective?
PVS & MCS: Medications

- Zolpidem (Ambien)
- 3 with PVS for more than 3 years
- 10 mg in AM, effect peaked 20-60 min., lasted up to 4 hours
- Cases with marked functional improvement
- Continued response for 3 to 6 years
- ? How many cases Zolpidem was tried
PVS & MCS: Medications

- Zolpidem (Ambien) effects:
  - Meaningful conversation
  - Telephone conversation
  - Able to feed self and swallow
  - Count to five
  - Understand humor, laugh and make jokes
  - Knows names of Rugby players
  - Theory: omega-1 GABA receptor-based re-activation of dormant neural tissue
MCS: Terry Wallis
MCS: Terry Wallis

• 19 years old, 1984, truck roll-over, TBI and PVS for several months
• In nursing home MCS—no improvement
• 19 years after accident, 38 years old, 2003, first word: “Mom”
• Recognized daughter
• Remembered use of cell phones
• Progressively more awareness and motor movement
MCS: Terry Wallis


• Possible axonal regrowth in late recovery from the minimally conscious state

• MRI Diffusion Tensor Imaging—track flow of water along axons—axonal regrowth

• FDG PET Scans—radioactively labeled glucose uptake by neurons—neuronal activity
Diffusion Tensor Imaging before and after 18 months
Minimally Conscious State: Serious Questions

• Misuse and / or misdiagnosis of MCS (Robert Wendland case--to the CA Supreme Court)
• Can consciousness be quantified?
• How much consciousness do you need to be human?
• Other measures of consciousness:
  • IQ (MCS—low IQ) and other distinctions
  • MCS is not a useful diagnosis
Persistent Vegetative State / Minimally Conscious State

- Life expectancy / survival rates
- Most important factors:
  - Degree of disability
  - Ongoing and intercurrent medical / neurologic illnesses
- Access to optimal acute and ongoing medical / nursing care
PVS & MCS: Implications

- Recent research: majority PVS patients, all MCS patients have cognitive awareness
- Clinical improvement can occur, spontaneously or with medicines
- Reactivation of dormant neuronal systems; axonal regrowth—neuronal interconnections
- Areas of awareness:
  - Auditory, especially familiar words, sounds
  - Somatosensory, visual
- Appropriate therapies may hasten recovery
PVS: Previous Studies


• Meta-analysis of 24 individual published cases: multimodal sensory stimulation was of benefit


• Meta-analysis of reports 1996-2002. Only 3 reports with total of 68 cases. Techniques extremely varied, comparative analysis could not be done.

• **Summary:** No good studies, but new information
PVS & MCS: Implications

- Speech & music therapy: familiar words, expressions, voices, stories, music, etc.
- Somatosensory stimulation: standard PT & OT, massage, other forms
- (Vestibular—ABR data)
- With evidence of posterior cortical activity, visual stimulation programming: TV shows, especially familiar programs, photographs
- Providing for optimal medical care will maximize life expectancy
Thank you

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