Prolonged disorder of consciousness in children, an update
Trastornos prolongados de conciencia en pediatría, una mirada actual

Marta Hernández, Génesis Calderón, Paulina C. Tejada, Nasser Duk

Received: May 18, 2020; Approved: August 10, 2020

Abstract

The children who remain in a prolonged disorder of consciousness (PDoC) present a complex clinical, ethical, and legal challenge to health professionals and other caregivers. PDoC is defined as any disorder of consciousness that has continued for at least 4 weeks following sudden-onset brain injury. The PDoC includes the vegetative state/unresponsive wakefulness syndrome (EV/ UWS), and the minimally conscious state (MCS). Patients with PDoC lack of mental capacity to make decisions regarding their care and treatment, so these decisions have to be made for them based on their best benefits. These benefits may vary from patient to patient, between physicians, family, and the general public, creating conflict within their respective efforts to do what they believe is right for the patient. The diagnosis is based on clinical evaluations. These evaluations have an estimated misdiagnosis rate up to 45%, therefore they should be complemented with standardized...
Introduction

Pediatric patients with prolonged disorders of consciousness (PDoC) are a challenge to pediatric teams, families, and caregivers. The PDoC are any disorder of consciousness that continues for at least 4 weeks after an acute brain injury, leading to a coma. The PDoC include the vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS)\(^1\). The PDoC represent an imbalance between the components of consciousness\(^2\), which can be measured quantitatively (wakefulness level) and qualitatively (self- and environment awareness) (See Figure 1). Despite the specific guidelines and criteria for PDoC, there is a diagnostic error rate up to 30-45%\(^3,4\), which interferes with treatment decisions, resource allocation for rehabilitation, and medical-legal assistance\(^5\). Health professionals may have difficulties in measuring very narrow ranges of behavior, with variable response latency and poorly defined intentional gestures. In addition, there are patient-specific difficulties, such as fluctuating fatigue over the day, undiagnosed sensory and motor disorders, and medical complications (infections, hydrocephalus, among others), that influence their responses\(^6\).

The objective of this review is to deepen in the different clinical diagnostic criteria of the PDoC, including the most used assessment scale, to analyze the evidence on the available paraclinical tests; and to describe the evolution and prognosis of the VS and MCS in pediatric patients, in order to allow a comprehensive and updated management of these patients by the medical team and highlighting this specific population.

PDoC etiology in pediatrics

The most common causes of PDoC in adults and children are acute traumatic brain injury or non-traumatic one (hypoxia-ischemia, CNS infection, stroke)\(^7\). Less frequent causes are the progression of neurodegenerative, metabolic diseases, or severe CNS malformations\(^8,9\).

There are few epidemiological studies on PDoC in geographically defined populations. A systematic review showed an adult prevalence between 0.2 and 1.5 per 100,000 for VS/UWS and MCS\(^10\), about one-third had traumatic etiology and two-thirds a non-traumatic one. In 1994, Ashwal described a VS prevalence of 6-80 per million children under 15 years of age\(^11\) and, according to a US census, in 2000, he estimated a prevalence of MCS between 44 and 110 per 100,000 children under 18 years of age\(^7\). There are no updated prevalence studies in children. Considering advances in intensive care, CPR education, emergency medicine, and long-term clinical management, these prevalences may be higher today.

Differential diagnosis of PDoC-related conditions

Different disorders of consciousness can be confusing at the time of PDoC diagnosis (see Table 1)\(^12\). Coma is a state of persistent and deep pathological unconsciousness, lasting more than 1 hour up to 4 weeks, with closed eyes, secondary to bihemispheric dysfunction or the ascending reticular activating system in the brainstem\(^13\). In contrast, in the locked-in syndrome, the patient is awake and conscious but has an extremely limited range of motor responses (generally vertical eye movement or blinking)\(^14\). In akinetic mutism, the patient loses her/his speech with bradykinesia or akinesia, maintaining wakefulness and self-awareness. Finally, brain death is an irreversible coma with permanent absence of all brain functions, including loss of brainstem reflexes and cranial nerve functions\(^15\).

Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS)

The VS/UWS is a clinical state of total self- and environment unawareness, along with sleep-wake cycles, and complete or partial preservation of hypothalamic and brainstem autonomic functions. It also includes a range of unintentional movements, spontaneous, or in response to stimuli (visual, auditory, tactile, or noxious), and brainstem reflex responses\(^16\).

Using adult criteria, the pediatric population can
be diagnosed with VS/UWS, however, sometimes it is difficult, especially in patients under 2-3 months, due to inconsistencies in sleep-wake cycles and social and voluntary responses\(^8,9\).

In 1972, Jennet proposed the denomination of VS in patients recovered from a post-traumatic coma, who maintained a “physical life free of social and intellectual activity, primitive reflexes to stimuli, and relative preservation of autonomic control”\(^14\). Due to the ambiguity of the term “vegetative” (preservation of autonomic control) interpreted as “vegetable”, suggesting that the patient was no longer human but vegetable\(^17\), the European Task Force on Disorders of Consciousness (2009) rename it as “unresponsive wakefulness syndrome” (UWS). However, this name has not been accepted worldwide, but it was agreed to join them as VS/UWS\(^17,18\).

Although VS was described in 1972, the US Multi-Society Task Force published the diagnostic criteria of VS/UWS in 1994\(^19\). Among them were the absence of self- and environment awareness, inability to interact with others, responses to non-reproducible stimuli, involuntary and unintentional, absence of expressive and comprehensive speech, bladder and bowel incontinence, preservation of sleep-wake cycles, and partial or total preservation of autonomic functions and some spinal reflexes. In addition to the diagnostic criteria, the VS/UWS was subcategorized into persistent VS/UWS when it lasted more than 1 month and permanent VS/UWS, after 3 and 12 months for non-traumatic and traumatic injury, respectively\(^20\).

Initially, for permanent VS/UWS, “enough medical and nursing care to maintain the patient’s dignity” was recommended. Indications for the administration of oxygen, antibiotics, artificial nutrition, or hydration were considered extraordinary measures and were decided by caregivers and physicians, and they had no indication to resuscitate\(^21\). Later in 2013, the Royal College of Physicians defined 6 months and 12 months period for classifying a permanent VS/UWS of non-traumatic and traumatic cause, respectively\(^22\).

The extensive amount of literature describing functional progress up to 5 and 7 years after acute injury\(^23,24\) allowed the American Academy of Neurology, the US Multi-Society Task Force, and the Royal College of Physicians\(^1,25\) to redefine permanent VS/UWS as chronic VS/UWS, which promoted changes in treatments and resources for the patient\(^2\). However, if a patient in chronic VS/UWS remains more than 6 months without any change, she/he could be diagnosed as permanent VS and should be evaluated by a PDoC expert\(^1\).

Neuropathological patterns in VS/UWS vary according to traumatic and non-traumatic etiology. On the one hand, in traumatic injury, diffuse axonal injury in the corpus callosum, cerebellum, and brainstem predominates, sometimes associated with focal bleeding of the corpus callosum or focal dorsolateral bleeding of the brainstem\(^26-28\). On the other hand, in non-traumatic injury (hypoxic-ischemic) predominate extensive multifocal or diffuse cortical laminar necrosis with hippocampal involvement and sometimes infarction areas or neuronal loss in deep gray matter nuclei, hypothalamus, or brainstem\(^29\).

The prognosis of VS/UWS depends on the age at the time of the acute injury, the time spent in the same sta-
Table 1. Clinical and neurophysiological characteristics of the different pathological states of consciousness

<table>
<thead>
<tr>
<th>Disorder of consciousness</th>
<th>Akinetic disorders</th>
<th>Prolonged disorders of consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coma</td>
<td>VS/UWS</td>
</tr>
<tr>
<td>Duration</td>
<td>&gt; 1 month</td>
<td>&gt; 1 month</td>
</tr>
<tr>
<td>Awareness</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial</td>
</tr>
<tr>
<td>Sleep-wake cycle</td>
<td>Absent</td>
<td>Partial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Response to noxious stimuli</td>
<td>Atypical</td>
<td>Atypical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Purposeful movement</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some inconsistent</td>
</tr>
<tr>
<td>Respiratory function</td>
<td>Absent</td>
<td>Preserved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preserved</td>
</tr>
<tr>
<td>EEG activity</td>
<td>Slow wave</td>
<td>Slow wave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Cerebral metabolism</td>
<td>Severely reduced</td>
<td>Severely reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate reduction</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Recovery, PCD or death Within weeks</td>
<td>Variable; if permanent continued VS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variable; if permanent continued MCS or death</td>
</tr>
</tbody>
</table>

Note. Modified from Houston et al. VS: Vegetative state. UWS: Unresponsive wakefulness syndrome. MCS: Minimally conscious state. eMCS: Emergent minimally conscious state.

te, and its etiology. Regarding age, pediatric patients have higher rates of recovery of consciousness and survival than adults (21% vs 9%) except for children under 1 year of age, whose mortality is higher. The time spent in VS/UWS is negatively correlated with the possibility of regaining consciousness and independence. Traumatic causes have a better prognosis of regaining independence (24% vs 4%) and consciousness (52% vs 13%) than the non-traumatic ones. The median survival in non-traumatic etiology is 3 years and 8.6 years in the traumatic one. The long-term outcomes are more devastating in the pediatric population, considering the lost developmental potential. Only 11% of the patients recover without disability, and many require long-term care.

Minimally Conscious State (MCS)

In 1995 at the American Congress of Rehabilitation Medicine, the concept of the “minimally responsive state” was first described by observing patients diagnosed as VS/UWS who had some cognitively mediated, minimal, but definite responses and, unless there was a careful and guided evaluation, these responses were not considered. The MCS appeared subtly and sometimes intermittently, alternating with periods of prolonged non-response. Between 1997 and 2002, Giacino et al. finally re-named this “minimally responsive state” as “minimally conscious state” and proposed diagnostic criteria.

The diagnostic criteria of MCS included reproducible and sustained evidence of one or more of the following four behaviors: follow simple commands, gestural or verbal yes/no responses regardless of accuracy, intelligible speech, and movements or affective behaviors occurring in contingent relation to relevant environmental stimuli rather than by reflex activity. Likewise, the criteria for recovering from MCS were defined and then named the emergence from the minimally conscious state (eMCS).

The eMCS criteria required a consistent demonstration of one or both of the following functions: the use of interactive functional communication and functional use of two different objects. For functional communication, the answer must be right in 6/6 basic situational orientation questions in two consecutive assessments (are you sitting? am I pointing upwards?). For functional use of objects, it should be appropriate for at least two different objects, such as carrying a comb to the head or a pencil to a sheet of paper.

Between 2009 and 2012, studies by Bruno et al. proposed a division of the MCS into subcategories ‘minus’ and ‘plus’ depending on the complexity level of the observed behavioral response. Patients with minus (-) MCS show only simple responses such as non-re-
**Table 2. Clinical assessment of prolonged disorders of consciousness**

<table>
<thead>
<tr>
<th>What should we know before starting?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The terminology of PDOC</td>
</tr>
<tr>
<td>• The signs of VS/oVS/UWS, MCS, EMCS</td>
</tr>
<tr>
<td>• Reproducible responses to command; visual pursuit, automatic motor response (e.g., scratching, grabbing objects), adapted emotional behavior, localization to noxious stimulation, intelligible verbalization, object recognition and localization, nonfunctional communication, resistance to eye-opening</td>
</tr>
<tr>
<td>• Reflex behaviors: auditory startle, blinking to threat, flexion withdrawal/stereotyped to pain, yawning, oral reflexes</td>
</tr>
<tr>
<td>• Debated behavior: visual fixation, localization to sound</td>
</tr>
</tbody>
</table>

**Paraclinical tests to evaluate patients with impaired consciousness**

Brain imaging and electrophysiology techniques have provided valuable information and important approaches to research in this group of patients. Their high cost, equipment, and specialized personnel for interpretation is a challenge, although, in the future, some techniques may even be used at the patient's home. There are no validated studies in children or adults, so they must be analyzed along with the medical records.

**Positron emission tomography (PET)**

It measures the cellular metabolic activity and the brain’s functional integrity using radioactive substances such as fluorine-deoxyglucose (FDG) which helped to confirm that in the VS/UWS there is a decrease...
between 40-50% of the normal values at rest\textsuperscript{43}. In a study of 120 patients, the FDG-PET correctly classified the PDoCs in 85% of the cases and predicted the result in 74% of the patients in the sub-acute (weeks) or chronic (months) phase of the VS/UWS or MCS\textsuperscript{44,45}. So far, there are no FDG-PET studies in children with PDoC.

**Functional magnetic resonance imaging (MRI)**

It can be performed at rest (patients without behavioral response) or in task-based modality (cortical activation) in patients with MCS. It allows visualizing the location of activity and functional interaction between brain regions by evaluating areas of sensory, motor, cognitive, and affective processes in normal and pathological brains\textsuperscript{6,46}.

**Blood-oxygenation-level-dependent imaging (BOLD)**

It registers the hemodynamic brain changes associated with neuronal activation\textsuperscript{46}. Regarding its diagnostic power in populations with PDoC, it is not yet clear when it can work as a predictor of good individual prognosis\textsuperscript{47}. In addition, there are no studies in children.

**Electroencephalography (EEG) and polysomnography (PSG)**

The EEG at rest helps the diagnosis and prognosis of consciousness disorders considering that the reorganization of the subsequent rhythms and presence of sleep patterns are associated with a favorable prognosis\textsuperscript{48}. A first work of PSG carried out in a group of children and adolescents with PDoC by Avantaggiato et al.\textsuperscript{49}, reaffirms the relevance of sleep spindles as prognostic markers of consciousness improvements from VS/UWS to MCS (whose base pattern is similar to a healthy patient), and adds that the higher the complexity level in the PSG signal, the better the functional outcome.

**Cognitive Evoked Potentials (P300)**

They are event-related potentials (N100, MMN, P300, and N400) of late latency. The P300 is the most widely used and its neurophysiological detection requires attention and perception, therefore, it is used as an indicator of conscious perception\textsuperscript{49}. A study of 10 children with VS/UWS and MCS compared with 10 healthy children, found a P300 wave adequate in 7 of them (6 MCS/exit-MCS and 1 VS/UWS), thus it was considered a good prognostic marker\textsuperscript{51,52}.

**Interventions for consciousness rehabilitation in PDoC**

There are few established therapies for children with PDoC, and studies have been limited by age, lack of long-term follow-up, and ethical limitations on a developing brain. These therapies may be either non-pharmacological or pharmacological.

---

**Table 3. Coma Scale Recovery-Revised**

<table>
<thead>
<tr>
<th></th>
<th>Auditory Function Scale</th>
<th>Visual Function Scale</th>
<th>Motor Function Scale</th>
<th>Oromotor Verbal Function Scale</th>
<th>Communication Scale</th>
<th>Arousal Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 Consistent Movement to Commando*</td>
<td>5 Object Recognition*</td>
<td>6 Functional Object Use**</td>
<td>3 Intelligible Verbalization*</td>
<td>2 Functional: Accurate**</td>
<td>3 Attention*</td>
</tr>
<tr>
<td></td>
<td>3 Reproducible Movement to comand*</td>
<td>4 Object localization: Reaching*</td>
<td>5 Automatic Motor Response*</td>
<td>2 Vocalization7oral movement</td>
<td>1 Non-Functional: Intentional*</td>
<td>2 Eye opening w/o Stimulation</td>
</tr>
<tr>
<td></td>
<td>2 Localization to Sound</td>
<td>3 Visual Pursuit*</td>
<td>4 Object Manipulation*</td>
<td>1 Oral reflexive Movement</td>
<td>0 None</td>
<td>1 Eye Opening with Stimulation</td>
</tr>
<tr>
<td></td>
<td>1 Auditory Startle</td>
<td>2 Fixation*</td>
<td>2 Flexion Withdrawal</td>
<td>0 None</td>
<td>0 None</td>
<td>0 Unarousable</td>
</tr>
<tr>
<td></td>
<td>0 None</td>
<td>1 Visual Startle</td>
<td>1 Abnormal Posturing</td>
<td>0 None/Flaccid</td>
<td>0 None/Flaccid</td>
<td>0 Unarousable</td>
</tr>
</tbody>
</table>

\textsuperscript{**}Emergence from minimally conscious state. \textsuperscript{*}Minimally conscious state. Fuente: Arch Phys Med Rehabil. 2014;95(12): 2335-4139.
Non-pharmacological therapies

Multidisciplinary rehabilitation programs (MRP) should start upon discharge from the ICU and before 6 months after acute brain injury. The protocols consist of daily multidisciplinary interventions, such as sensory stimulation, occupational therapy, speech and motor therapy, alternated with rest, personal care, and family visits. A study of two cohorts of children who were admitted with VS/UWS and participated in MRP showed that 38-39% of the patients regained full consciousness, 27-41% progressed to MCS, 14-33% remained in VS/UWS, and 6% of them died. 80% of the children admitted with MCS regained consciousness compared with 38% of those admitted with VS/UWS. MRP reported no side effects \cite{12, 53}.

Pharmacological therapies

There has been less use of drugs in the pediatric population with PDoC than in adults and the most used are dopamine agonists (DA), which enhance dopamine pathways. These DA stimulate functions of behavior, mood, speech, motor control, hypothalamic functions, and wakefulness. Within this group, amantadine has level I evidence on wakefulness improvement in children and adolescents with PDoC \cite{54}. Donepezil (acetylcholinesterase inhibitor that enhances the function of acetylcholine in cognitive functions), did not show conclusive results \cite{55}. Apomorphine, levodopa, and baclofen have shown some beneficial effects in a few children \cite{56}. Stimulants such as methylphenidate have been used in acute traumatic brain injury \cite{57}, however, there are no reports on its use in PDoC.

New neuromodulation therapies

Non-invasive brain stimulation (NIBS) techniques such as transcranial direct-current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are accepted in PDoC rehabilitation. tDCS can induce neuroplasticity and modulate cortical function through a weak direct current applied to the scalp, and TMS is a safe, non-invasive, and painless technique that has also demonstrated neuromodulatory effect when administered repeatedly. Both can act as an exciter or an inhibitor of brain activity in specific regions \cite{58} but only stimulate superficially, losing effect in deep gray nuclei.

Other neuromodulation therapies, such as the electrical vagus and median nerve stimulation, also modulate functional brain activity \cite{59}.

Despite its wide use, flaws in study designs, sample size, and lack of a control group have limited the research’s power. In addition, some researchers have expressed concern that the potential overstimulation in non-responders patients (specifically median nerve stimulation) could lead to a reduction in the perception of some stimuli \cite{58}.

Invasive stimulation electrically stimulates deep structures through electrode implantation. Examples are deep brain stimulation with electrodes in the thalamus, and spinal cord stimulation with electrodes in the epidural space between C2 and C4. Surgical risks have limited their use \cite{60}.

Other proposed therapies such as hyperbaric oxygen, pharmacological nutrients, stem cell therapy, and petroleum products have insufficient evidence to support or refute their use and have many associated risks \cite{25}.

Prognosis of regaining consciousness and survival

The term “recovery” is best avoided since it evokes a “return to the pre-injury state”. Patients who have a PDoC for more than one or two months will have permanent and important physical and cognitive deficiencies in most cases \cite{5}. The improvement in consciousness or even in the functional state does not necessarily mean an improvement in the quality of life, because for many patients, to be more aware of their limitations, can mean a worse perception of their situation.

The possibility of regaining consciousness depends on the etiology (traumatic vs. non-traumatic), type (VE vs. MCS), time of PDoC evolution after the coma, the structural pattern of the injury (axonal vs. cortical damage), age, and medical stability \cite{22}. According to the etiology, traumatic injury (with axonal damage) has a better prognosis than the non-traumatic one (diffuse cortical damage).

Some patients evolve from a coma to VS/UWS, and from a coma to MCS, with more probabilities of recovering some degree of independence in the last one. Out of 106 children in VS of traumatic cause, 24% regained wakefulness at 3 months. One year after, 29% remained in VS, 9% died, and 62% had regained consciousness \cite{37}.

A study of 145 cases aged between 0 and 25 years, evaluated at admission and discharge, showed that almost 2/3 regained full consciousness, and the factors that predicted this result were the type of PDoC at admission, etiology, and time between the injury event and admission \cite{61}.

Regarding the age at the time of the acute injury, the younger the age, the better the rate of independence at the year of evolution, with 21% to 9% of patients recovered and 0% in those younger than 20, 20-30, and
Conclusions

Recovery in consciousness of patients with PDoC is a clinical challenge, especially in the chronic stages. Early support with rehabilitation techniques, pharmacological, and neuromodulation therapies have made PDoC visible, although there is still a long way to go. The high rates of diagnostic errors have intensified efforts to develop technical methods to prevent them, but their sensitivity and specificity are limited due to the lack of a gold standard, which means more questions than answers.

The most outstanding changes in PDoC are the separation of the VS/UWS from the MCS (1994-2002), the division of the MCS according to behavioral skills into minus and plus (2002-2012), and the renaming of the permanent VS as chronic VS (1994-2018).

The lack of information regarding prevalence, evolution, and treatments in the pediatric population is noteworthy. The few studies that present data on the evolution of PDoC in children are from 1990. There is a need for updated research with an improved evidence base, to which health personnel can consult and select the optimal measures for the patient.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

References


Disorder of Consciousness - M. Hernández-Chávez et al


