

Prolonged disorder of consciousness in children, an update

Trastornos prolongados de conciencia en pediatría, una mirada actual

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What do we know about the subject matter of this study?

Prolonged disorders of consciousness (PDOC) are conditions that appear after a coma secondary to acute severe brain injury and last longer than 4 weeks. They are classified into two states, the vegetative one, also called unresponsive wakefulness syndrome, and the minimally conscious state. It is difficult to differentiate clinically between different PDOC and to exclude neurological disorders such as locked-in syndrome and akinetic mutism, resulting in a high rate of diagnostic errors, which interferes with treatment decisions, resource allocation for rehabilitation, and medical-legal assistance.

What does this study contribute to what is already known?

This article updates the diagnostic criteria for PDOC in children and the main differential diagnoses. It describes variables that influence improvements in consciousness and survival. We analyze the need for using standardized scales to measure consciousness and, if necessary, paraclinical tests to reduce the high diagnostic error. We also explore medical treatments that would optimize functional wakefulness, communication, and consciousness contents, and highlight this pediatric population.

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 interests. 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

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clinical guidelines, and often with neuroimaging and neurophysiological studies. Other aspects that difficult the evaluation are variable definitions and subcategorizations of PDOC, among different groups at the international level. The objective of this review is to present an update of the different types of PDOC, their definition, subcategorization, etiology, prognostic, comprehensive evaluation, and treatment in pediatrics, to contribute to the best clinical practice based on currently available evidence.

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 consciousness², 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 assistance⁵. 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 responses⁶.

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 re-

view showed an adult prevalence between 0.2 and 1.5 per 100,000 for VS/UWS and MCS¹⁰, 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 age¹¹ 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 age⁷. 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 brainstem¹³. 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 functions¹⁵.

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 responses¹⁶.

Using adult criteria, the pediatric population can

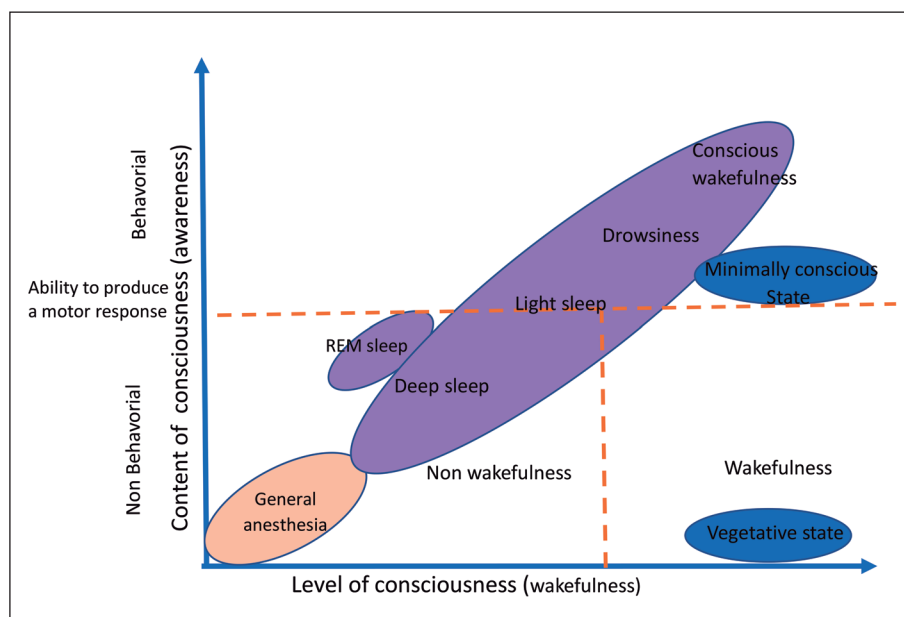


Figure 1. Oversimplified illustration of the two major components of consciousness: the level of consciousness (i.e. wakefulness or arousal) and the content of consciousness (i.e. awareness or experience). In normal physiological states (lightblue) level and content are positively correlated (with the exception of dream activity during REM-sleep). Patients in pathological or pharmacological coma (that is, general anesthesia) are unconscious because they cannot be awakened (pink). Dissociated states of consciousness (i.e. patients being seemingly awake but lacking any behavioral evidence of 'voluntary' or 'willed' behavior), such as the vegetative state or much more transient equivalents such as absence and complex partial seizures and sleepwalking (purple), offer a unique opportunity to study the neural correlates of awareness.

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 vegetable¹⁷, 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 1994¹⁹. 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, respectively²⁰.

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 resuscitate²¹. 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, respectively²².

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 patient⁵. 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 expert¹.

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 brainstem²⁶⁻²⁸. 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 brainstem²⁹.

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

	Akinetic disorders	Disorder of consciousness		Prolonged disorders of consciousness	
	Coma	VS/UWS	MCS	Locked-in syndrome	Akinetic mutism
Duration	> 1 month	> 1 month	> 1 month	> 1 month	> 1 month
Awareness	Absent	Absent	Partial	Present	Present
Sleep-wake cycle	Absent	Present	Present	Present	Present
Response to noxious stimuli	Atypical	Atypical	Present	Present (in eyes only)	Present
Purposeful movement	Absent	Absent	Some inconsistent	Vertical eye movements	Some response purposeful motor behaviour
Respiratory function	Absent	Preserved	Preserved	Preserved	Preserved
EEG activity	Slow wave	Slow wave	Insufficient data	Normal	Normal
Cerebral metabolism	Severely reduced	Severely reduced	Intermediate reduction	Mildly reduced	Mildly reduced
Prognosis	Recovery, PCD or death Within weeks	Variable; if permanent continued VS	Variable; if permanent continued MCS or death	Full recovery unlikely	Full recovery likely

Note. Modified from Houston et al.¹². VS: Vegetative state. UWS: Unresponsive wakefulness syndrome. MCS: Minimally conscious state. EMCS: Emergent minimally conscious state.

te, and its etiology. Regarding age³⁰, 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^{6,31}. 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 care³².

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 considered³³. The MCS appeared subtly and sometimes intermittently, alternating with periods of prolonged non-response. Between 1997³⁴ and 2002,

Giacino et al. finally re-named this “minimally responsive state” as “minimally conscious state” and proposed diagnostic criteria³⁵.

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 activity³⁵. Likewise, the criteria for recovering from MCS were defined and then named the emergence from the minimally conscious state (eMCS)³⁵.

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.³⁶ 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-

flective search and location movements, while plus (+) MCS show complex responses with more interactive behaviors (intelligible speech). The neuropathology of the MCS is less known than the VS. It presents damage to bilateral multifocal or diffuse cortical or subcortical structures, and sometimes thalamic and diencephalic structures are damaged to a lesser extent than VS/UWS^{26,29}.

There is little updated epidemiological data on MCS in children. Survival after age 8 is 65% for children with very reduced mobility and 81% for those with less limited mobility^{30,37}.

Clinical evaluation of consciousness in PDoC

The clinical evaluation of consciousness is based primarily on the observation of spontaneous and stimulus-evoked behaviors. Wakefulness is considered as the time of eye-opening and the stimulus needed to achieve it. The content of consciousness in these patients is evaluated through command following and observation of non-reflex movements³⁸. The etiology, list of medications in use, and the presence of treatable pathologies (hydrocephalus, metabolic diseases, infections, etc.) should be recorded. In the neurological examination, primary neural pathways (visual, auditory, somatosensory, motor, and spinal cord) should be evaluated to rule out interference in responses (see Table 2).

There are tools designed to assess consciousness³⁹ such as the Coma Recovery Scale-Revised (CRS-R) (See Table 3), which is the most used given its psychometric properties and sensitivity. The CRS-R has not been formally validated in children due to the wide ranges of age in pediatrics, from infants to adolescents⁴⁰.

If there is ambiguity or confusion for a valid clinical evaluation, despite trained personnel, standardized guidelines, and serial evaluations, paraclinical tests can be incorporated, considering benefits, risks, feasibility, and costs.

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)⁴² which helped to confirm that in the VS/UWS there is a decrease

Table 2. Clinical assessment of prolonged disorders of consciousness

¿What should we know before starting?

- The terminology of PDOC
- The signs of VS/ o VS/UWS, MCS, EMCS
- 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
- Reflex behaviors: auditory startle, blinking to threat, flexion withdrawal/stereotyped to pain, yawning, oral reflexes
- Debated behavior: visual fixation, localization to sound

What should we do before starting?

- Collect patient's past and current medical history: sensory deficits, cause of coma, time since onset, localized pain and sedative medication.
- Always consider as if the patient were conscious, even if he or she is apparently unresponsive. Explain the aim of the exam and the need for full collaboration.
- Place the patient in sitting position, all limbs must be visible
- Ensure enough light and quiet environment with a period of rest before starting
- Apply arousal protocol if needed
- Perform a few minutes of observation of spontaneous behavior

What to do during the assessment?

- Assess all modalities: audition, vision, motricity/tactile stimulation, oromotor behavior, communication, arousal
- Way to assess: assess the most reactive part of the body (from medical history, spontaneous behavior)
- Use specific tools: mirror for visual pursuit
- Ask several command-following questions based on spontaneous behaviors, use finger for blinking to threat, evaluate visual pursuit in horizontal and vertical planes. Use own name for auditory localization, oral and written commands, colorful objects, meaningful/emotional stimuli
- Give encouragement to the patient
- If signs of fatigue: break and/or arousal protocol

Other recommendations

- Repeat assessments combining morning and afternoon evaluations, minimum 5 times total for a final diagnosis
- Extended evaluation time (20-60 min) needed
- Qualified and trained assessor

Fuente: Annu Rev Neurosci. 2014;37:457-78³⁸. VSA/UWS :Vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state EMCS: Emergence from minimally conscious state.

between 40-50% of the normal values at rest⁴³. 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^{44,45}. So far, there are no FDG-PET studies in children with PDoC.

Table 3. Coma Scale Recovery-Revised

Auditory Function Scale

4	Consistent Movement to Command*
3	Reproducible Movement to comand*
2	Localization to Sound
1	Auditory Startle
0	None

Visual Functiuon Scale

5	Object Recognition*
4	Object localization: Reaching*
3	Visual Pursuit*
2	Fixation*
1	Visual Startle
0	None

Motor Function Scale

6	Functional Object Use**
5	Automatic Motor Response*
4	Object Manipulation*
3	Localization to noxious Stimulation*
2	Flexion Withdrawal
1	Abnormal Posturing
0	None/Flaccid

Oromotor Verbal Function Scale

3	Intelligible Verbalization*
2	Vocalization7oral movement
1	Oral reflexive Movement
0	None

Communication Scale

2	Functional: Accurate**
1	Non-Functional: Intentional*
0	None

Arousal Scale

3	Attention*
2	Eye opening w/o Stimulation
1	Eye Opening with Stimulation
0	Unarousable

**Emergence from minimally conscious state. *Minimally conscious state. Fuente: Arch Phys Med Rehabil. 2014;95(12): 2335-41³⁹.

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^{6,46}.

Blood-oxygenation-level-dependent imaging (BOLD)

It registers the hemodynamic brain changes associated with neuronal activation⁴². Regarding its diagnostic power in populations with PDoC, it is not yet clear when it can work as a predictor of good individual prognosis⁴⁷. 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 prognosis⁴⁸. A first work of PSG carried out in a group of children and adolescents with PDoC by Avantaggiato et al.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 perception⁵⁰. 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^{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.

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^{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 PDoC⁵⁴. Donepezil (acetylcholinesterase inhibitor that enhances the function of acetylcholine in cognitive functions), did not show conclusive results⁵⁵. Apomorphine, levodopa, and baclofen have shown some beneficial effects in a few children⁵⁶. Stimulants such as methylphenidate have been used in acute traumatic brain injury⁵⁷, 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 regions⁵⁸ 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 activity⁵⁹.

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 stimuli⁵⁸.

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 use⁶⁰.

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 risks²⁵.

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 cases⁵. 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 stability²². 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 consciousness³⁷.

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 admission⁶¹.

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

over 40 years old. Coexisting morbidity worsens the regain of consciousness (e.g., renal failure, heart failure, etc.).³⁷

In children under age 15, the 1994 Multi-Society Task Force indicates that 24% of children with VS/UWS will have regained consciousness after 3 months and 62% after 12 months, with less predictable recovery of consciousness than in adults. Similarly, long-term outcomes are more devastating in children, considering the years of healthy life lost and the developmental potential involved^{8,9}.

The prognosis for survival will depend to some extent on improvements in consciousness, age, and other comorbidities, and health conditions present. Life expectancy is more favorable in children than in adults, with 9% vs. 33% of mortality, respectively, except for the infant aged under 1 year, whose mortality is higher³⁷.

Conclusions

Recovery in consciousness of patients with PDoC is a clinical challenge, especially in the chronic stages. Early support with rehabilitation techniques, pharma-

cological, 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 resort and select the optimal measures for the patient.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study

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