Disorders of Consciousness in Children: Assessment, Treatment, and Prognosis

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KEYWORDS

• Pediatric • Child • Coma • Vegetative state • Minimally conscious state

KEY POINTS

- Many children with acquired brain injury experience disorders of consciousness.
- Assessment tools studied in adults with disorders of consciousness (DoC) may require additional consideration and/or modification for use in young children.
- In light of limited data specific to evaluation and management of children with DoC, it is reasonable to apply clinical standards that have been developed in adults with DoC to children while considering developmental differences.

INTRODUCTION

Disorders of consciousness (DoC) including coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), and minimally conscious state (MCS) have been described in children. In fact, soon after the Aspen Neurobehavioral Conference workgroup published definition and diagnostic criteria for MCS,[1] Ashwal and Cranford[2] presented a case series describing the clinical and neuroimaging data for five children diagnosed with DoC following acquired brain injury and associated with neurodevelopmental disorders. Since that time, there has been a growing body of literature focusing on diagnosis, prognosis, and treatment in pediatric DoC. In this review, the authors provide an overview of the state-of-the-art literature in each of these areas.

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DISCUSSION

Diagnosis

In adults, there are relatively recent guidelines developed for evaluation and management of DoC. The practice guideline recommendations developed by the American Academy of Neurology (AAN) and the American Congress of Rehabilitation Medicine (ACRM) provide 18 recommendations, only 3 of which focus on children.[3] According to the AAN/ACRM practice guidelines recommendations, neurobehavioral assessment is recommended to diagnose prolonged DoC (DoC lasting ≥28 days). Clinicians should use standardized neurobehavioral assessment measures that have adequate psychometric properties to diagnosis states of DoC. In addition, serial standardized neurobehavioral assessments should be used, and clinicians should attempt to increase arousal and treat confounding conditions before assessment. Further when there is ambiguity regarding evidence of awareness, multimodal assessment (eg, electroencephalography [EEG], fMRI) may be considered, and if there is evidence of consciousness on these functional and electrophysiological measures, frequent neurobehavioral reevaluation may be conducted to identify emerging signs of DoC.[3] Given the paucity of literature exploring tools and methods for diagnosing state of DoC in children with prolonged DoC, it is reasonable to apply the recommendations developed for adults.

The European Academy of Neurology (EAN) Scientific Panel on Coma and Chronic Disorders of Consciousness generated a guideline on the diagnosis of coma and other DoC focused exclusively on adults.[4] Although the guideline was not based on pediatric literature, such as the AAN/ACRM guideline, it is reasonable that these recommendations may also be applied to children. Like the AAN/ACRM guideline, the EAN guideline focused on the importance of thorough and repeated neurobehavioral assessment. Specific recommendations were provided related to stimuli used and measurement tools to include in a neurobehavioral assessment. A summary of the strong recommendations is provided below.

Strong recommendations included passively opening eyes of patients who do not display spontaneous eye opening, use of a mirror to diagnose visual pursuit, and the use of the Coma Recovery Scale Revised (CRS-R) to classify level of consciousness for patients in the subacute state (or later), including in the intensive care setting once sedation is stopped and when patients are in rehabilitation and long-term care facilities. Owing to ease of use and improved detection of signs of consciousness over the Glasgow Coma Scale, the Full Outline of Unresponsiveness score should be used in the intensive care setting. In addition, serial assessment was also recommended and the guideline states that classification of state of DoC should never be made based on an isolated assessment. The EAN guideline also included a strong recommendation for the use of EEG-based techniques to detect preserved consciousness. Overall, this guideline highlighted that patients should receive multimodal assessment and be given the highest level of consciousness identified by any of these three approaches (neurobehavioral assessment, EEG, and neuroimaging).[4]

Neurobehavioral assessment tools and qualitative assessment of behavioral features have been used to delineate state of DoC in children. There is a growing literature demonstrating the efficacy of several tools and methods that have also been used to diagnose VS/UWS and MCS, including MCS+ and MCS− in children. In children, several measures have been used to diagnosis DoC. Measures reported in the pediatric literature including the CRS-R,[5] Coma Near Coma Scale (CNCS),[6] Post-Acute Level of Consciousness Scale (PALOC-s),[7] Western Neurosensory Stimulation Profile (WNSSP).[8] Despite the use of standardized neurobehavioral assessment measures,

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reports of reliability and validity is lacking in these measures. See **Table 1** for more details about these measures.

Although the CRS-R is the gold standard tool for adults,[9] the use of the CRS-R has only been reported recently in pediatric DoC. Three studies recently came out of the Alarm Clock Clinic, described as a model hospital for children with severe brain injury, in Warsaw, Poland.[10–12] These three studies examined multimodal assessment in children ages 6 to 18 years. In all three, the CRS-R was used to delineate state of DoC based on five administrations over a 2-week period. The performance on the administration indicating the highest level of consciousness was used to determine state of DoC.

More recently, Frigerio and colleagues examined the CRS-R in children with DoC.[13] In this prospective observational study, children were assessed with both the CRS-R and the Rappaport CNCS for clinical purposes. The investigators found moderate agreement between the two scales; however, the investigators noted that the CRS-R has high motor demands and may be particularly challenging in children emerging from MCS who have significant motor impairment. These investigators recommend using multiple neurobehavioral scales to assess the full spectrum of behavior in children emerging from DoC.

The CNCS has also been described in the pediatric literature. In addition to the study described above, it was used by Pham and colleagues combined with behavioral observations to determine state of DoC.[14] More recently, the CNCS was used in combination with the Levels of Cognitive Function Assessment Scale (LOCFAS) to diagnosis state of DoC in children.[15] In that study, the investigators using both measures more accurately characterized states of DoC.

The PALOC-s[7] was recently revised.[16] The PALOC-s has been used to examine the levels of consciousness in children and young adults. When the measure was initially developed, it included eight levels of consciousness. The various levels mapped on to coma (level 1), VS (levels 2–4), MCS (levels 5–7), and consciousness (level 8). The recent revision, PALOC-sr, includes a table where these levels of consciousness are mapped onto the currently accepted DoC terminology, including MCS+, MCS−, and confusional state. The investigators recommend its use for patients from 2 years of age and older but combined with other standardized neurobehavioral assessment measures.

Diagnosing states of DoC is particularly challenging in young children given the limited range of expected developmental skills that are required for diagnosing DoC, especially language skills. Recently, a pediatric version of the CRS-R was developed (Coma Recovery Scale for Pediatrics, CRS-P).[17] The CRS-P was developed by modifying the CRS-R assessment and scoring. For example, toys were added to the stimuli, language was simplified, and some items were based on observation of spontaneous behavior rather than requiring the child to respond to commands. The measures were examined in a group of typically developing children ages 6 months to 4 years. Inter-rater reliability was strong. With modifications of stimuli, administration, and scoring, children as young as 12 months of age were able to demonstrate signs consistent with emergence from MCS (eg, functional object use). In contrast, the other marker of emergence from a Minimally Conscious State (eMCS), functional communication, was not observed in any child under 2 years of age and not observed consistently, even with the CRS-P modifications, until age 3 years.

A qualitative assessment of neurobehavioral features has also been used to categorize states of DoC in the youngest patients. In the same period that the CRS-P was being developed, another study examined behavioral features of DoC in young children with acquired brain injury who were admitted to an inpatient neurorehabilitation facility.[18] In that study, medical records were reviewed to identify behavioral features outlined in the

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Table 1
Neurobehavioral assessment tools used to assess children with disorders of consciousness

Tool	Description	Developed for Children	Developed to Assess DoC Only	Designed to Diagnose Recognized States of Doc	Estimated Administration Time (Minutes)
CALS[24]	20 items to assess cognitive recovery after brain injury in children admitted to an inpatient rehabilitation setting, two items relevant to DoC are rated based on administration of another measure, typically CNCS and/or CRS-R or informal observation	Y	N	N	30
CNCS[6]	11 items assessing responses to visual, auditory, and tactile stimulation. Items are rated based on observed responses such as eye opening, postural and motor movements, yawning, and some degree of arousability on stimulation	N	Y	N	10
CRS-P*,[17]	Modifications of the CRS-R (below) to include pediatric appropriate stimuli, administration, and scoring guidelines	Y	Y	Y	15–25
CRS-R[5]	23 items that comprise six subscales addressing auditory, visual, motor, oromotor, communication, and arousal functions. CRS-R subscales are composed of hierarchically arranged items associated with brain stem, subcortical, and cortical processes.	N	Y	Y	15–25
LOCFAS[15]	10 levels of recovery after brain injury, rated based on observation. Levels I–III described as corresponding with DoC	N	N	N	10
PALOC-sr[16]	Levels of consciousness from 1 to 8 based on observations during administration of a structured examination of the patient such as the WNSSP	Y	Y	N	NA
WNSSP[8]	32 items making up six subscales including auditory comprehension, visual comprehension, visual tracking, object manipulation, arousal/attention, and tactile/olfactory	N	Y	N	45

Abbreviations: CALS, cognitive and linguistic scale; CNCS, coma near coma scale; CRS-P, coma recovery scale for pediatrics; CRS-R, coma recovery scale, revised; LOCFAS, levels of cognitive functioning assessment scale; PALOC-sr, post-acute level of consciousness scale revised; WNSSP, western neuro sensory stimulation profile.

*not validated in patients with DoC.

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Aspen Neurobehavioral Conference workgroup.[1] Common features of MCS were contingent affective responding, visual fixation or tracking, automatic motor behavior, and contingent communicative intent. No children in MCS showed command following or intelligible verbalization. In addition, although all of the children diagnosed as emerged from MCS showed functional object use, only a subset of children considered emerged from MCS showed higher level language skills including command following, intelligible verbalizations, and functional communication.

Taken together, several standardized neurobehavioral assessment measures have been used with children to diagnose states of DoC, although assessment of reliability and validity is lacking. Especially in the youngest children, who have not yet developed necessary language skills to demonstrate signs of eMCS, clinicians need to rely more heavily on visual and motor responses. When visual and motor impairment is present, multimodal assessment may be beneficial.

Multimodal Assessment

Data regarding the use of multimodal assessment tools (ie, specialized functional imaging, electrophysiologic studies) in children with DoC after acquired brain injury (ABI) are very limited though recently beginning to grow. Wijnen and colleagues studied visual evoked potentials (VEPs) in children and young adults with DoC.[19] It is important to note that despite behavioral improvements in visual function over the course of recovery, no change in VEPs was identified in association with improved cognitive function, suggesting that VEPs are not meaningful for this purpose. Ishaque and colleagues described preserved resting-state functional MRI (rsfMRI) networks in a cohort of 11 children with a history of anoxic brain injury from drowning and associated spastic quadriplegia felt to masking true cognitive function.[20] A case report of an 11-year-old boy demonstrates potential benefit of rsfMRI for identifying both the existence of intact functional networks which may suggest better potential for recovery as well as the possibility of simultaneously identifying potentially treatable coexisting conditions, in this case concern for high likelihood of seizures despite no epileptiform activity on EEG.[21]

Evidence from two different research groups supports the potential for use of EEG for evaluating cognitive function in pediatric patients presenting in DoC and throughout the stages of cognitive recovery after ABI. Passive EEG assessment provides an advantage of no active demands on the child (other than tolerating the EEG equipment/positioning). Zieleniewska and colleagues demonstrated that features of EEG recordings from sleep (eg, power of sleep spindles, spectral entropy) differ in children with differing clinical states within DoC.[11] Duszyk and colleagues[10] and Kim and colleagues[22,23] have both reported on the use of auditory oddball paradigms and observed differential responses (based on EEG) to different tones; further, Kim and colleagues demonstrated an effect of cognitive state, across the spectrum of recovery, on magnitude of EEG responses.

Both of these research groups have also demonstrated the use of EEG-based techniques to identify “covert” command following in children with DoC and no evidence of command following on neurobehavioral evaluation. Dovgialo and colleagues studied patients treated at the aforementioned “Alarm Clock Clinic” and used personalized stimuli as the basis for EEG paradigms designed to evaluate command following and reported that 2/7 children in UWS and 3/9 children in MCS− showed command following based on EEG.[12] More recently, using an expanded battery of EEG paradigms in addition to motor imagery and spatial navigation fMRI paradigms, Kim and colleagues reported the identification of cognitive-motor dissociation in two adolescents (ages 15 and 18 years old) based on physiologic evidence; one presented clinically in MCS− and the other in VS/UWS.[22,23]

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Prognosis

According to the AAN/ACRM guideline, the natural history of pediatric DoC is not well-defined, and clinicians should counsel families of children in DoC that there are no evaluations that can improve prognosis. Although the literature is scant, there is emerging evidence that specific factors can be used to help prognosticate when children experience prolonged DoC. Factors that are emerging to be important include initial state of DoC on entrance into rehabilitation and etiology.

Several studies suggest that early signs of responsiveness are associated with subsequent emergence from MCS. Most of these studies have focused on children with TBI; however, there is some evidence in children with a range of etiologies. Pham and colleagues found that in a group of children in DoC after TBI, initial CNCS score was associated with emergence from MCS.[14] In addition, higher admission score on the responsiveness item of the Cognitive and Linguistic Scale (CALS)[24] was also associated with emergence from MCS. The CALS responsiveness item is a rating based on behavioral observation of the consistency of responsiveness throughout a 30-minute neurobehavioral assessment. More recently, when examined very long-term outcome in survivors of pediatric DoC following TBI, 68% of those who were admitted to inpatient neurorehabilitation in VS emerged from MCS, whereas all of those in MCS at admission emerged from MCS.[25] Similarly, in a cohort of the youngest children admitted to one inpatient neurorehabilitation facility after ABI, none of the patients admitted in VS emerged from MCS, whereas a third of those in MCS emerged before discharge.[26] In a mixed sample PALOC-s scores at admission and discharge to a specialized neurorehabilitation program predicted long-term disability.[27]

There is also evidence to suggest etiology of DoC is associated with outcome with better outcome noted after traumatic brain injuries relative to anoxic brain injuries. The larger studies that compared children with traumatic and anoxic brain injuries, however, are several decades old. In 1993, in a cohort of 60 children who were "unconscious" for 90 days and admitted to an inpatient rehabilitation unit, none of the 13 children with anoxic injury regained cognitive or motor skills, although three were described as socially responsive. In contrast, of the 36 children with TBI, 27 regained consciousness and displayed functional cognitive skills.[28] Kriel and colleagues compared outcomes in 127 children and adolescents who were reported to be in a "persistent vegetative state" for at least 30 days following either traumatic or hypoxic brain injury.[29] At 3-month post-injury 34% of the traumatic brain injury (TBI) group and 13% of the hypoxic group regained consciousness, and by 19-month post-injury 84% of traumatic group and 55% the hypoxic group regained consciousness. Of note, the definition of regaining consciousness is similar to what we think of as MCS today. Specifically, in that study, regaining consciousness was defined as at least one recognizable and reproducible behavior, including turning eyes and head to sound. More recently, in a study of 10 to 12 year follow-up of children and young adults admitted to inpatient rehabilitation in DoC, of the 23 surviving patients with follow-up data, 18/20 of those with TBI emerged from MCS, whereas of the three with other etiologies, one emerged, one remained in MCS, and one remained in VS. In addition, of those who died, most (7/11, 64%) had etiologies other than traumatic.[30]

Treatment

The AAN/ACRM guideline states that there are no established therapies for children with a prolonged DoC.[3] In adults, guideline recommendations for treatment include systematically facilitating prevention, early identification, and treatment of medical complications common in the first few months; treating suspected pain; and

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prescribing amantadine for patients with traumatic etiology of injury within 4 to 16 weeks post-injury.[3] Similar to considerations regarding assessment, in the absence of pediatric-specific evidence, these recommendations should be considered in the care of children with DoC.

Inpatient rehabilitation programs for children with DoC[31,32] facilitate repeated neurobehavioral assessment, caregiver education, and the systematic treatment approach to prevention and treatment highlighted by the Guideline.[3] Comprehensive treatment for children with DoC encompasses environmental modifications to optimize arousal and responsiveness, therapy-based interventions, and pharmacologic management. Emerging data suggest that other types of brain stimulation also merit additional evaluation.

Environmental modifications are used to facilitate return of normal circadian rhythm to facilitate daytime arousal and nighttime sleep to aid with optimal assessment and engagement in therapeutic activities during the day as well as to improve ease of care in the home setting.[31] Environmental recommendations often include upright positioning and use of light to stimulate daytime arousal along with a bedtime routine and good sleep hygiene to facilitate nighttime sleep.[32] Therapy sessions may need to incorporate a daytime rest/nap time; for very young children, more than one naptime may be needed.

Structured preference assessments are designed to identify stimuli which are arousing and/or calming and can be used to facilitate optimal engagement in therapeutic activities. Amari and colleagues published a caregiver interview called the Preference Assessment for Youth with Disorders of Consciousness which is an adaptation of the Reinforcer Assessment for Individuals with Severe Disabilities.[33] In this work, the investigators demonstrated the utility of a standardized evaluation methodology for identifying highly idiosyncratic stimuli that elicit often subtle behavioral signs of responsiveness and how identified preferred items are used in varying ways as part of a treatment program. Music has been identified as a particularly important stimulus for consideration in treatment of children with DoC; music is both salient and familiar to children, and there is evidence that music activates and fosters interactions between regions of the brain involved in cognition and affective processing.[34]

Therapy (eg, physical, occupational, speech) interventions for children with DoC include improving arousal and awareness and laying the foundation for additional recovery of function through rebuilding fundamental motor skills such as head control and treating and/or preventing complications such as joint contracture.[31,32] Given that well-fitted wheelchairs and other positioning devices intentionally restrict active movement, Yeh and colleagues highlighted the importance of therapy activities out of the wheelchair (eg, positioned with therapist support on a mat table or using body weight support devices).[32] Some children seem to respond best to more challenging activities, and providing support for standing and/or gait may elicit motor responses.[32]

Pharmacologic intervention in children with DoC comprises most of the literature related to treatment in this population; however, all of the pediatric-specific clinical trials are limited by small sample sizes.[35] Consistent with amantadine having the most data to support use in adults with DoC[3,36] amantadine has been the focus of much of the limited literature on pharmacologic intervention for children with DoC (and acquired brain injury more broadly). One hospital system reported on the use of neurostimulant medications in children with TBI severe enough to require admission to the intensive care unit; amantadine was the most frequently prescribed neurostimulant.[37] Only 1.4% of greater than 30,000 children in this broad group of children with TBI (eg, not DoC-specific) received amantadine, with a significant increase in prescription over

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the study years (from 2005 to 2014). Neurostimulant prescription was more common in older children and those with markers of more severe injury (injury sustained in motor vehicle collision, ICP monitoring, craniotomy/craniectomy, mechanical ventilation).[37]

Recently, McLaughlin and colleagues published retrospectively collected data on amantadine use in children with TBI across eight different inpatient rehabilitation units in the United States.[38] In this cohort, 21% of all children with TBI, and 45% of children with TBI admitted to rehabilitation in a DoC, received amantadine during the inpatient admission. The children who received amantadine were older (mean 11.6 vs 3.0 years) and had longer rehabilitation lengths of stay (mean 47 vs 31 days) than children who did not receive amantadine. Importantly, data demonstrated the use of amantadine in children as young as 1 year of age and at a wide range of weight-based dosing, including higher than that previously reported in the literature.[38] Particularly in light of a previous, small pharmacokinetic study suggesting that younger/smaller children may benefit from higher doses of amantadine,[39] the multisite data presented by McLaughlin and colleagues[38] set the stage for exploration of evaluating tolerability and efficacy of higher doses of amantadine in this population.

Levodopa/carbidopa has been described as a pharmacologic therapy for adults with DoC in case reports/case series.[40] More recently, Yeh and colleagues reported that retrospective review of clinical data from a pediatric DoC inpatient rehabilitation program yielded anecdotally higher positive response rate to levodopa/carbidopa and methylphenidate compared with other neurostimulant medications, including amantadine; however, adverse effects were also noted more frequently with these two agents compared with others.[32] Fridman and colleagues demonstrated, using PET in a small group of adults with DoC, that use of levodopa/carbidopa to restore dopamine is necessary to elicit benefit from medications that inhibit dopamine reuptake, such as amantadine and methylphenidate.[41]

The use of zolpidem has been somewhat sporadically reported in children with DoC.[32,35,42] There remain no published cases of significant behavioral recovery associated with use in a child with DoC, in contrast to the adult literature.[43] Given the safety and ease of trialing zolpidem as well as the known low rate of adult responders (suggesting that there may be pediatric responders identified as more children with DoC are exposed to zolpidem), a brief trial of zolpidem remains a reasonable option to consider for a child with DoC who is not showing rapid gains in arousal and responsiveness. Anecdotally, some caregivers of pediatric patients prefer not to proceed with a trial of zolpidem for their child due to the short window of improved function and reported habituation with ongoing administration.[44]

Noninvasive brain stimulation is emerging as an intervention for DoC with applicability for children.[42] In adults, a meta-analysis showed favorable response in adults with DoC, with increasing CRS-R scores in response to transcranial direct current stimulation (tDCS).[45] Potential benefit of tDCS has been established in other pediatric brain injury populations (ie, children with cerebral palsy).[46] Although a protocol for the study of safety and tolerability of tDCS in children with DoC has been published[47]; thus far, there is no pediatric-specific evidence for this intervention in children with DoC.

SUMMARY

As is evident from this review, much of current evaluation and care of children with DoC is based on adult practices. Although the literature surrounding assessment of children with DoC is growing, more research is needed to optimize evaluation particularly of very young children and to translate laboratory-based use of neurophysiological assessments into clinical practice. The standardization of assessment techniques will

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improve precision in prognostication for children with DoC and thus set the stage for improving homogeneity and/or subgroup evaluation in treatment trials to ultimately optimize outcome after pediatric DoC.

CLINICS CARE POINTS

- A number of neurobehavioral measures have been used to diagnose states of disorders of consciousness (DoC) in children; however, studies exploring the psychometric properties of these measures in children with DoC are limited.
- Early signs of responsiveness and traumatic (vs hypoxic) brain injury are variables associated with greater likelihood of emergence from minimally conscious state after pediatric DoC.
- Recent advancements in description of fMRI and EEG approaches to evaluating cognitive function in children with DoC may herald the beginning of development of clinical measures to complement neurobehavioral assessment in this population
- Growing data from clinical use of amantadine in children can be used to increase confidence in use with young children and at higher doses than were previously reported.

DISCLOSURE

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