Electronic annex 1b

Summary of the literature on prognosis for recovery

For patients in a vegetative state (VS) or a minimally conscious state (MCS), the likelihood of significant functional improvement diminishes over time.[1,2]

Vegetative state

The US Multi-Society Task Force[1] calculated average probabilities for recovery of consciousness and degree of functional disability at 12 months post-injury based on type of injury (traumatic vs non-traumatic) and duration of VS, utilising a sample of 434 patients with traumatic brain injury (TBI) and 169 non-traumatic brain injury (NTBI) adult patients.

The data clearly illustrated that cause of injury was a strong determinant of outcome from VS, with NTBI patients having a shorter window for recovery and considerably greater severity of disability after 1 year.

Isolated case studies exist of patients in vegetative states who emerge later on to prove the exception to the rule.[3–5] Close inspection of these cases often demonstrates that they would not have been diagnosed as VS on current criteria. For example, one case with predominantly brainstem pathology was almost certainly locked in, rather than vegetative,[5] and two others had already emerged to a minimally conscious state within 6 months of injury.[4]

More recently, Estraneo *et al* (2010) reported a systematic follow-up of 50 patients with long-lasting VS.[6] The patients were followed for up to 4 years, using serial testing with the Disability Rating Scale and the Coma Recovery Scale (CRS-R) at monthly intervals. Of the 50 patients, 21(42%) died, 17 remained in VS and 2 emerged within 12 months.

However, 10 patients (20%) progressed to an improved level of responsiveness more than 12 months after injury: 4 progressed to MCS, while 6 recovered consciousness.

- All of these remained severely to extremely severely disabled.
- Nine of the 10 had recovered responsiveness by 24 months, and the remaining 1 by 28 months.
- Six of these late recoveries had traumatic brain injury, but 3 had anoxic brain injury (emerging at 14, 16 and 22 months) and 1 had an aneurysmal haemorrhage (emerging at 15 months).

- All of those who recovered consciousness had spared pupillary light reflexes at entry, whereas 9 of the 17 survivors who did not recover consciousness had absent light reflexes.
- Neuroimaging features were diverse and did not distinguish those who emerged.

This study should be treated with some caution at the current time as it is a single-centre study, which used only one test of responsiveness. It needs replication in another setting as the results are in contrast to other published studies. Nevertheless, it was carefully conducted, with CRS-R recorded every month while patients were in hospital and bi-monthly thereafter. It emphasises the importance of serial testing to look for trends towards improved levels of responsiveness over time (see below). Unfortunately, no information is given about the results of these serial tests, or the extent to which trends were evident in the level and frequency of responses in those who subsequently recovered consciousness.

Minimally conscious state

Four published articles were found that addressed the longer-term prognosis for recovery in MCS.

Giacino and Kalmar[7] followed 104 patients diagnosed with VS (n= 55) or MCS (n=49) on admission to rehabilitation during the first 12 months after injury.

- The MCS group showed more continuous improvement and attained significantly more favorable outcomes on the Disability Rating Scale by 1 year than the VS group.
- The differences were more pronounced in patients diagnosed with MCS after traumatic brain injury.
  - 50% of patients in the MCS group with traumatic brain injury were found to have none to moderate disability at 12 months
  - whereas none of the patients in the MCS group without traumatic brain injury were classified in these outcome categories.
- Although it is not known how many patients will emerge from MCS after 12 months after injury, most patients in MCS for this length of time remain severely disabled.

Lammi *et al*[8] followed up a series of 18 patients who were in a minimally conscious state for at least 1 month post traumatic brain injury. The results highlighted heterogeneity of outcome even after a prolonged period of MCS. The range of duration of MCS was 27–615 days, with two patients still in MCS at the end of the follow-up period (at 48 and 53 months post trauma respectively).

Katz *et al*[9] followed up a consecutive series of 36 patients who were in VS or MCS on admission to a specialised, slow-to-recover brain injury programme for 1–4 years. 72% of MCS patients had emerged by the latest follow-up. Duration of MCS was a strong predictor of duration of confusional state or post traumatic amnesia after emergence from MCS, accounting for 57% of the variance.

In a retrospective cohort study, Lauate *et al*[10] compared the long-term functional outcome, improvement or deterioration, of patients considered to be in a VS or a MCS 1 year after coma onset, then yearly for up to 5 years using the five categories of the Glasgow Outcome Scale.

They followed 12 patients in VS and 39 in MCS:

- None of the patients in VS improved during the follow-up period: 1 was lost to follow-up, 9 died, and 2 remained in VS.
- Among the 39 patients in MCS, 3 were lost to follow-up.
- Five years after coma onset, the outcomes of the other 36 patients were as follows:
  - 13 severe disabilities (33.3%)
  - 9 MCS (23.1%)
  - 14 deaths (35.9%).
- Of those who emerged from MCS, 8 (61%) had emerged by 2 years, and a further 4 by 4 years. Only 1 more had emerged by the fifth year of follow-up.

Late recovery

Once again there are isolated case studies of patients emerging several years after diagnosis of MCS:

- One young woman was considered to be in a MCS 2 years after injury and became the subject of legal debate in the UK with regard to withdrawal of artificial feeding and hydration. Before injury, she made a verbal advanced directive that she would not wish to continue living if ever becoming severely disabled. Neuropsychological assessment found statistically significant evidence for sentience and expression of a wish to live and the application to Court was withdrawn. Further meaningful recovery occurred between 7 and 10 years after injury and, although remaining severely disabled, she returned to live in the community with 24-hour care.[11]
- Another patient regained fluent language after 19 years in MCS, although he still had very severe physical and cognitive disabilities.[12,13]

Predictors of recovery

Three studies have looked at factors which predict outcome in terms of recovery.

- Lauate *et al*[10] showed that VS, age >39 years, and bilateral absence of cortical components of middle-latency auditory evoked potentials, were significantly associated with deterioration.
- In an analysis of WHIM behaviours, Shiel *et al* showed that time taken to achieve certain behaviours (including eye contact, eye pointing, focusing on the person giving attention, initiating contact) tended to be associated with better cognitive recovery (verbal and performance IQ).[14]
- In a retrospective analysis (regression and data mining) of prospectively collected data for n=333 patients in VS of TBI or NTBI aetiology, the following were strongly predictive of recovery of consciousness:[15]
  - early reappearance of spontaneous motility or eye tracking
  - disappearance of doll's eye phenomenon and oral automatisms (chewing sucking etc).

A number of studies have highlighted the trajectory of recovery on serial testing (eg with the WHIM) as a potential indicator of prognosis for recovery of consciousness,[16] but as yet no studies have formally attempted to distinguish prognosis for patients in different levels of MCS, or related outcome to trajectory of recovery on serial testing.

In summary

- For both VS and MCS, the likelihood of significant functional improvement diminishes over time.
- The cause of brain injury is a strong determinant of outcome for both VS and MCS, with non-traumatic brain injury patients having a shorter window for recovery and greater long-term severity of disability.
- For patents in VS, the large majority of those who regain consciousness have done so by 12 months for traumatic brain injury and by 3 months for non-traumatic brain injury, but a smaller number of patients (12% in one study) may emerge between 12 and 24 months post injury.
- The prognosis for recovery is more heterogeneous for MCS than for VS, although age and level of awareness may have some predictive value.
- In both VS and MCS there are isolated reports of recovery even after many years, but these are a rarity, and inevitably those who recover remain severely dependent.
- There is only one case report in the literature documenting emerging from MCS after more than 5 years from injury.

Further large-scale cohort studies are required to determine whether there is a cut-off point for 'permanency' in a minimally conscious state. The evidence from this evaluation suggests that duration is an important factor; although there are well-documented cases of MCS emerging up to 4 years after injury, recovery of full awareness after being in MCS for 5 years or more is extremely rare. However, other factors are also likely to influence outcome, including the nature and severity of the injury, the level of responsiveness and the trajectory of any change. The combination of these factors is likely to have stronger predictive value than a simple time limit.

In the meantime, as any progression is likely to be gradual, the findings highlight the importance of serial testing to look for trends towards improved levels of responsiveness.

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