

THE PROGNOSIS OF MEDICAL COMA

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The assessment of patients in coma is a medical emergency. The cause should be identified and, where possible, corrected and the brain provided with appropriate protection to reduce further damage. It then becomes important to identify those patients for whom the prognosis is hopeless and in whom the institution or persistence of resuscitative measures is inappropriate, serving only to prolong the anguish of relatives and carers. It is frequently the neurologist to whom the physicians turn, to establish the prognosis of the individual in coma. It is therefore important that the neurologist in training develops a system whereby he or she can reasonably and accurately determine those factors which help in identifying prognosis and thereby provide reasonable advice to colleagues, paramedical staff, and the relatives and friends of the patient.

DEFINING PROGNOSIS

The advent of cardiopulmonary resuscitation during the 1960s, together with the advances in intensive care medicine, created the need for techniques to identify prognosis early in the course of coma. The fear that large numbers of patients resuscitated after drug overdose, trauma or anoxic injury might survive in a chronic vegetative state or that costly support would be wasted on patients who were insentient has resulted in more than 70 papers during the past 40 years attempting to develop clinical scales, electrophysiological techniques, imaging systems, and laboratory assays that predict the likely outcome in the individual patient.¹⁻⁴ Regrettably, most of the reports on prognostic signs in coma include small numbers of patients, are retrospective or define outcome so poorly that adequate statistical validation is impossible. Few reports provide details of confidence limits for the specificity of individual tests, and the initial studies were almost invariably retrospective and identified length of coma or the lack of motor responses as indicative of a poor prognosis.

Factors that might be considered of potential prognostic benefit are clinical, electrophysiological, biochemical, and imaging and all four parameters have been investigated and compared.

Clinical features

The prospective papers by Jorgensen⁵ were a landmark in the methodology of identifying clinical signs in patients after cardiac arrest and defined several prognostic factors with remarkable precision: the recovery of the pupillary light reflex within 12 minutes was found to be compatible with neurological survival whereas the absence of the pupillary light reflex after 28 minutes indicated that neurological recovery was unlikely. These papers also provided some information on the predictive value of the EEG which was monitored during the course of the studies; most notably that 37/125 patients with no detectable cortical activity immediately after cardiopulmonary resuscitation regained consciousness. The limitation of these investigations was that not all patients were comatose and the outcome categories other than survival or death were not defined.

A cohort of 500 patients recruited in the USA and the UK and reported by Levy and colleagues⁶ were monitored prospectively, and the level of coma and outcome categories were clearly defined. There were sufficient patients in each of the individual diagnostic groups to produce meaningful results, and the large size of the study meant that both specificity and sensitivity of the tests could be examined and confidence intervals provided. Patients were included if they had been in coma, defined as a Glasgow coma score of 2:4:2 (eye opening: motor: verbal) or less, for more than six hours and the cause of coma was known. Traumatic coma was excluded. Outcome was defined at time intervals of up to one year on a five point scale: death, vegetation, severe disability, moderate disability or good recovery. The overall outcome was poor, with only 10% of the 500 patients making a good recovery and 63% dying without recovering from coma or recovering only to the level of vegetation.

These studies identified four important clinical features that help to determine prognosis: aetiology, depth of coma, duration of coma, and clinical signs.

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Aetiology

The outcome of coma is related to the cause independent of the physical signs, depth of coma or length of coma. This is most important and shown most dramatically in coma caused by drug overdose. All such patients should be regarded as potentially salvageable and with a good prognosis provided that they can be supported and complications are avoided during the period of coma. Patients with drug overdose coma frequently appear deeply comatose with depressed brain stem reflexes because of the effects of the drugs upon the brain stem, yet may show disproportionately high levels of motor activity. In general, metabolic causes of coma have a better prognosis than anoxic-ischaemic causes. Cerebrovascular disease (subarachnoid haemorrhage or stroke) carries the worst prognosis of all (table 1). It can be seen that the likelihood of a good recovery in all patients is only 10%. It is less than 5% in those who have suffered subarachnoid haemorrhage or stroke, about 10% in those with hypoxic-ischaemic injury, but as high as 25% in those metabolic or infective causes of coma. It is also evident that a hypoxic-ischaemic injury is the one most likely to result in the development of a vegetative state; for 20% of such patients this was the highest level they ever achieved.

Depth of coma

The level of coma as measured on the Glasgow coma scale is predictive of outcome. Even after six hours of coma it is apparent that patients with higher levels in the hierarchical scale have a better outcome (table 2). Within six hours of coma onset those patients who show eye opening have almost a one in five chance of achieving a good recovery whereas those who do not have a one in 10 chance. Those who show no motor response have a 3% chance of making a good recovery whereas those who show flexion have a better than 15% chance. Those who make no noise have only an 8% chance of making a good recovery, while those who groan have a 30% chance of so doing.

Duration of coma

The longer a patient remains in a coma the poorer his or her chance of recovery and the greater the chance that he or she will enter a vegetative state (table 3). By the third day the

Table 1 Aetiology as a prognostic factor

	Outcome (%)				
	D	PVS	SD	MD	GR
Hypoxia-ischaemia	58	20	11	3	8
Cerebrovascular	74	7	12	4	3
Metabolic	47	6	15	7	25
Total	61	12	12	5	10

D, death; PVS, persistent vegetative state; SD, severe disability; MD, moderate disability; GR, good recovery.

Table 2 Level of coma as a prognostic factor: the level of coma as measured with elements from the Glasgow coma scale (GCS)

	GCS	Outcome (%)				
		D	PVS	SD	MD	GR
Eye opening	1	64	12	12	4	8
	2	49	15	12	6	18
Motor function	1	78	10	6	3	3
	2	66	13	12	4	5
	3	48	23	10	4	15
	4	47	9	20	7	17
Verbal response	1	66	10	12	4	8
	2	40	9	10	11	30

See table 1 for key.

Table 3 Length of coma as a prognostic factor

	Outcome (%)				
	D	PVS	SD	MD	GR
Admission	61	12	12	5	10
Day 1	65	15	8	2	10
Day 3	61	25	6	1	6
Day 7	42	42	10	3	3
Day 14	25	67	8	0	2

See table 1 for key.

Table 4 Brain stem responses and prognosis (24 hours)

	Outcome (%)				
	D	PVS	SD	MD	GR
Absent oculocephalic	92	3	2	2	1
Absent oculovestibular	96	1	1	1*	1*
Absent corneal	97	3	0	0	0
Absent pupil	93	4	2	0	1

*Opiate drugs in renal failure.

See table 1 for key.

chance of making a moderate or good recovery is reduced to only 7%, and by the 14th day is as low as 2%. By the end of the first week almost half of those patients who have not recovered consciousness are in a vegetative state.

Clinical signs

The most important clinical signs identifying those patients with a poor outcome are the brain stem reflexes, and the simple tests of corneal reflexes and pupillary responses, as identified by Jorgensen,⁵ remain important (table 4). For example, none of the 90 patients who had absent corneal reflexes at 24 hours survived.

There were 210 patients with anoxic ischaemic injury, 52 of whom had no pupillary reflexes at 24 hours and all died (table 5). By the third day 70 of these patients were left with a motor response poorer than withdrawal and all died. By the seventh day there were 26 patients who had absent spontaneous eye movements and all of those died. The 95% confidence intervals for each individual criterion are given in the table, and even though this was a large study its positive predictive value of a single sign is limited.⁷ There are some clinical signs which predict a good outcome: the development of nystagmus on oculovestibular testing or the vocalisation of any recognisable word within 48 hours indicates a 50% likelihood of a good recovery and the presence of motor localising within the first 24 hours indicates a 20% chance of a good recovery.

No single clinical sign is significant as an indicator of poor prognosis in individual patients, but a combination of clinical signs may potentially improve the accuracy of prognosis; this has been analysed by Levy and colleagues.⁶ Although helping

Table 5 Clinical signs and prognosis

Time	Sign	Cohort	Patients with signs	Number with moderate or good recovery	95% confidence interval
24 hours	Absent corneal response	500	90	0	0 to 3%
24 hours	Absent pupillary response	210	52	0	0 to 7%
3 days	Motor poorer than withdrawal	210	70	0	0 to 5%
7 days	Absent roving eye movements	210	16	0	0 to 13%

Table 6 Combinations of signs and prognosis at admission

Sign	Cohort	Best outcome at one year (%)		
		Death/ vegetative	Severe disability	Moderate disability, good recovery
Two of the following absent: corneal reflex pupillary reflex oculovestibular reflex	120	97	2	1
Better than above but no motor response	83	80	8	12
Better than above but motor poorer than withdrawal	135	69	14	17
Better than above but no vocalisation	106	58	19	23
Better than above plus vocalisation	56	46	13	41

to predict a good prognosis in those patients who had or regained some clinical signs early in the course of the disease, it cannot eliminate the small possibility that some patients lacking important responses early in the course of coma might ultimately make a good recovery (table 6).

Subsequent studies including clinical and laboratory features (motor response, pupillary light response, spontaneous eye movements, and blood glucose) to manufacture an “awakening” score⁸ provide a false positive rate of almost 16% and are therefore less accurate than individual clinical features alone.

Electrophysiology

The possibility of neurophysiological investigations, including electroencephalogram (EEG) and evoked potentials, providing more definitive indicators for prognosis have been increasingly studied during the past 20 years. Five grades of EEG abnormality in coma are internationally accepted: alpha rhythm, dominant theta, diffuse dominant delta, burst suppression, and isoelectric.⁹ At 48 hours these grades provide prediction with an accuracy of about 88% and to date it seems that the evaluation of compressed spectral arrays with a “brain monitor” is unlikely to improve upon that provided by clinical assessment or standard EEG.

Evoked potential studies are believed by some to provide greater accuracy than that possible with clinical methods. In particular, the bilateral absence of N20 SSEP after coma of 72 hours is considered to be the most reasonable and useful variable for predicting poor outcome in anoxic-ischaemic coma,¹⁰ though from the figures quoted by the authors the specificity and sensitivity are not better than the absence of pupillary response at 72 hours or the absence of motor response. Brain stem evoked response and somatosensory evoked potentials have been studied as possible aids to recognising brain stem death¹¹ and in predicting outcome.¹²

Authors who describe the value of these electrophysiological processes rarely seem to take into account the technical problem of performing such measures in the circumstances of a busy intensive care unit where there are considerable potential sources of electrical interference.

Biochemistry

Biochemical studies, either of cerebral metabolic rate for oxygen or of the concentration of chemicals in cerebrospinal fluid believed to be indicative of tissue damage, such as brain type creatine kinase and neurone specific enolase, have been correlated with outcome. With sensitivity only of the order of

74%, though the specificity is claimed to be as high as 100%,¹³ problems are likely to occur in conditions such as bronchogenic neoplasm and other situations in which the enzymes may be falsely raised.

Imaging

Imaging techniques, including computed tomography, magnetic resonance imaging, and single photon emission computed tomography, together with methods of measuring blood flow are of proven use in determining the diagnosis of coma and in identifying brain stem death; however, their value in prediction is no better than clinical signs. Even the use of cerebral metabolic rate for oxygen appears only to allow correct prediction of outcome in approximately 82% of patients,¹⁴ though magnetic resonance spectroscopy may provide further and better information in the future.

Problems in prognosis

There are recognised difficulties in interpreting the outcome of studies of coma prognosis^{10 15}: the lack of prospective studies, failure to state confidence intervals, and the inevitable confounding factor that many patients included in the studies will die of non-neurological disease. There are two other problems which are impossible to eliminate and cause difficulty in evaluation; the self fulfilling nature of poor prognoses and the problem of the persistent vegetative state. The fact that a poor prognosis given by a researcher to an individual patient may be self fulfilling seems unavoidable. Even if the researcher involved in collecting the data prospectively is not actively involved in the care of the patient there will be a tendency for the future care of that patient to reflect the impressions and opinions of those responsible for management. Ideally prognostic studies should only be performed on patients who will all receive maximal life support for as long as possible, but this is inconsistent with the humane and sensitive management of patients and their relatives. The problem relating to the persistent vegetative state arises because in some studies no distinction has been made between a persistent vegetative state and death, and in others the vegetative state is combined with severe disability as a “non-acceptable outcome”.

The persistent vegetative state

The prolonged survival of patients in coma usually indicates the development of a vegetative state and the avoidance of the persistent vegetative state is frequently given as an important reason for the use of predictors in coma. The original fear that large numbers of vegetative patients might be subjected to prolonged life support has not been borne out in practice during the past 30 years. In most studies it is evident that the majority of patients who will die do so early in the course of coma. In the study reported by Levy and colleagues, 60 patients who entered a vegetative state remained; there were 25 in this state at the end of one month, six at the end of three months, four after six months, and one at a year.⁷ These figures are similar to reports from other studies and raise the important question of the use of criteria with limited positive predictive value.

The evidence from the Multi-Society task force^{16 17} and advice from the working group of the Royal Colleges¹⁸ helps define the time at which consideration can be given to the withdrawal of artificial hydration and nutrition in such patients and provide direction for the way in which this shall be achieved. The most important differentiation of the patient in a persistent vegetative state is from those who show “minimal responsiveness” or such severe disability that they

cannot respond easily, and the physician therefore has difficulty in identifying sentience. Differentiation of these conditions requires sufficient time for observation and assessment of responses and involves nursing staff, carers, and relatives as well as physicians. When patients are shown to have some level of cognition or sentience it is obligatory that their care is maintained, unless an advance directive was formally made by the patient before the onset of coma.

There is continuing debate about the potential for recovery of patients in the vegetative state. In patients who have suffered non-traumatic injury such as anoxia or ischaemia, the prognosis is poor. The Multi-Society task force^{16, 17} considered 159 patients in a vegetative state one month after non-traumatic injury; by three months 11% had recovered consciousness, 89% remained vegetative or had died; by six months only two more patients had recovered consciousness, and one year after the injury 15% of the patients had recovered consciousness, 32% were in a vegetative state, and 53% had died. Of those 15% of patients who regained consciousness, only one patient made a good recovery. The task force recommended further epidemiological studies to improve information about incidence, prevalence, and natural history of the vegetative state; they also recommended more careful clinical studies and future positron emission tomography studies to examine regional cerebral blood flow and glucose metabolism in response to visual, auditory, and somatosensory stimulation.

The working party of the Royal Colleges¹⁸ recognised the difficulty in diagnosing a permanent vegetative state and suggested that the diagnosis could be made when irreversibility was established with a “high degree of clinical certainty”, but recognised that “it is a diagnosis which is not absolute but based on probabilities”. The working party suggested that a diagnosis may be reasonably made when a patient has been in a continuing vegetative state following non-traumatic brain damage for more than six months. They recommended that once the diagnosis of a *permanent* vegetative state is established, based on an identification of the cause of the syndrome, a clinical evaluation of the patient, and the duration of time from the insult, then recovery cannot be achieved and further treatment is futile. They suggested that the clinical team of doctors and nurses, augmented when necessary by colleagues, should formally review the clinical evidence. When the decision of “hopelessness” was made it should be communicated

sensitively to the relatives who would then be given time to consider the implications, including the possibility of withdrawing artificial means of administering food and fluid. The working party pointed out that at present the courts require, as a matter of practice, that the decision to withdraw nutrition and hydration resulting in the inevitable death of the patient should be referred to the court before any action is taken.

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