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Editorial

Defining prognosis in medical coma

The advent of cardiopulmonary resuscitation during the 1960s together with advances in intensive care medicine focussed interest on the development of clinical and laboratory methods 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 resulted in many attempts to develop clinical scales, electrophyiological techniques and laboratory tests that would predict the likely outcome in individual patients.[1] It is disappointing that most of the reports of prognostic signs in coma are on such small numbers of patients, retrospective or poorly defined so that adequate statistical validation is impossible. Few reports provide details of confidence limits. The specificity of such tests, that is the avoidance of false positive error in predicting a poor outcome in a patient who recovers, has been widely recognised to be more important than their sensitivity, or risk of a false negative error. However, few reports in the literature document these important figures for their own findings.[2] The original clinical studies, which were retrospective, proposed the length of coma or lack of motor response to pain as indicators of a poor prognosis but the inaccuracies were high and the criteria consequently of little use.[3–5]

Clinical signs

The papers by Jorgensen were a land-mark in the methodology of identifying clinical signs in patients after cardiac arrest and indicated some prognostic factors with remarkable precision: the recovery of the pupillary light reflex within 12 minutes is compatible with neurological survival whereas the absence of a pupillary light reflex after 28 minutes indicates that neurological recovery is unlikely.[6] These papers also provided some information of predictive value relating to the EEG which was monitored throughout the course of the studies; most notably the fact that 37 of 125 patients with no detectable cortical activity immediately after resuscitation regained consciousness. The limitation of these painstaking investigations was that not all patients were comatose and the outcome categories were not clearly defined. The advantage of this study was that it was the first prospective study of clinical signs in recovery from anoxic brain injury.

The international studies of a cohort of 500 patients reported by Levy *et al*[7] were prospective and clearly defined the level of coma and outcome categories. They contained sufficient patients in each of the individual 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. Only patients who had been in coma, defined as a Glasgow Coma Score of 2:4:2 or less (table 1) for more than six hours and in whom the diagnosis of the cause of coma was known and non-traumatic or drug induced were included. Outcome was defined at time intervals up to one year on a five point scale: death, vegetation, severe disability, moderate disability or good recovery. The overall outcome was poor; only 12% of the 500 patients making a good recovery and 73% dying without recovering from coma or recovering only to the level of vegetation.

These studies showed that outcome is related to the cause of the coma independent of the physical signs, depth of coma or length of coma. Metabolic causes of coma have, in general, a better prognosis than anoxic causes and cerebrovascular disease carries the worse prognosis of all. The level of coma as measured on the Glasgow Coma Scale is predictive of outcome, patients with higher levels having better outcomes, and the duration of the coma also correlates with outcome. None of these features are sufficiently specific or selective to help in establishing the prognosis in an individual patient. Some clinical signs are significantly associated with a poor prognosis: in the total cohort of 500 patients corneal reflexes were absent 24 hours after the onset of coma in 90 patients and this sign was incompatible with survival (table 2). In a more uniform group who had suffered anoxic injury there were 210 patients: 52 of these had no pupillary reflex at 24 hours, all of whom died. By the third day 70 were left with a motor resposne poorer than withdrawal and all died. By the seventh day the absence of roving eye movements was seen in 16 patients all of whom died. The confidence intervals for all of these individual criteria were 0·95 and yet, statistically, even with such a large prospective study it remains possible that up to 5% of individual patients with such clearly defined abnormal signs could actually make a good or moderate recovery.[2]

The possibility of using combinations of different clinical signs to improve accuracy of prognosis was analysed by Levy *et al*[7] but although this improved the accuracy of

Table 1 The Glasgow coma scale

Eyes	Open	Spontaneously	4
		To verbal command	3
		To pain	2
	No response		1
Best motor response	To verbal command	Obeys	6
	To painful stimulus	Localises pain	5
		Withdrawal	4
		Flexion	3
		Extension	2
		No response	1
Best verbal response		Orientated	5
		Disorientated	4
		Inappropriate words	3
		Incomprehensible sounds	2
		No response	1

Table 2 Clinical signs and prognosis

Time	Sign	Cohort	Patients with the Sign	False Positive Survivors	95% Confidence Interval
24 hours	Absent corneal response	500	90	0	0–5%
24 hours	Absent pupillary response	210	52	0	0–5%
3 days	Motor poorer than withdrawal	210	70	0	0–5%
7 days	Absent roving eye movements	210	16	0	0–5%

Summarised from Levy *et al.*[27]

prediction of good prognosis in those patients who had or regained some clinical signs early in the course of the disease it could not eliminate the small possibility that some patients lacking important responses early in the course of coma might ultimately make a good recovery (table 3). More recent studies from Longstreth[8] utilising a combination of clinical and laboratory features (motor response, pupillary light response, spontaneous eye movements and blood glucose) to manufacture an "awakening" score have a false positive rate in the poor outcome category of 16 out of 98 patients (16%). This study was based on patients surviving out of hospital cardiac arrest and the timing of the assessments with relation to the resuscitation is varaible and difficult to evaluate. A large retrospective study performed by Mullie *et al*[9] using the Glasgow Coma Score alone to predict outcome made a false positive prediction of one in 54 patients (2%). In both of these studies the confidence intervals would suggest that the possibility of error would lie between five and 20% making these indicants unacceptable for purposes of deciding to withdraw therapy in the course of coma.

Electrophysiology

The possibility of neurophysiological, imaging or chemical investigations providing more definitive indicants for prognosis has 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. At 48 hours these grades provide prediction with an accuracy of about 88%.[10] The evaluation of compressed spectral arrays (CSA) of EEG is still being undertaken though it seems that the accuracy is unlikely to improve upon that provided by clinical assessment. CSA is a useful method for monitoring patients in coma and variation in pattern of response may indicate a potential for neurological recovery.

Evoked potential studies have also failed to demonstrate greater accuracy than that possible with clinical methods. In general brainstem evoked responses (BSER) are of use in identifying brain death[11] and somatosensory evoked potentials (SSEP) are of greater value in the prediction of outcome.[12] It is suggested that the bilateral loss of cortical SSEP is of value in the early prediction of a poor outcome from coma but currently available results involve small numbers of patients and are not uniform. There is also the technical problem of difficulties arising in the peripheral nerves and roots which might cause false positive errors. It is unlikely that these methods will achieve better accuracy than clinical evaluation.

Imaging

Imaging techniques including computer tomography, magnetic resonance imaging and single photon emission spectroscopy, together with other methods measuring blood flow are extremely useful in determining the diagnosis of coma and in identifying brain death but their value in prediction is not better than clinical signs. Even the use of cerebral metabolic rate for oxygen ($CMRO_2$) appears only to allow correct prediction in approximately 82% of patients.[13] Although invasive studies are still being reported, particularly in paediatric coma, there is no evidence that their accuracy is an improvement over clinical signs. Most of the statistics relating to clinical signs have been derived from adult populations and may not necessarily be applied in a paediatric population.

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 neuron specific enolase, have been correlated with outcome. The sensitivity obtained is only of the order of 74% though the specificity is said to be as high as 100%.[14] Problems will be likely to occur in conditions such as bronchogenic neoplasm and neuroblastomas where the enzyme levels may be falsely elevated.

Interpretation of prognostic studies

The problems in interpreting studies of coma prognosis have been recently reviewed[15] and relate to the retrospective nature of many studies, the lack of confidence limits and the fact that many patients included in the studies die of non-neurological disease. Two other problems which are impossible to eliminate and cause difficulty in evaluation relate to the self-fulfilling nature of poor prognoses and the problem of the persistent vegetative state. That a poor prognosis given to an individual patient may be self-fulfilling is 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. Experimentally prognostic studies should be performed on patients who will all be given maximal life support for as long as possible but this will be impracticable in the humane and sensitive management of patients. The problem relating to persistent vegetative state arises because in some studies no

Table 3 Combinations of signs and prognosis at admission

Sign	Cohort	Best Outcome 1 Year (%)		
		Death Vegetative	Moderate Severe Disability	Disability Good Recovery
2 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

distinction is made between a persistent vegetative state and death and in others the vegetative state is combined with severe disability as a non-acceptable outcome.

Chronic vegetative state

The avoidance of the persistent vegetative state is frequently given as one of the main reasons for the use of predictors in coma though the fear of large numbers of vegetative patients being subjected to prolonged life support has not been borne out 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 and in the study reported by Levy less than 25 of the 500 patients were vegetative at the end of one month, six at the end of three months, four at the end of six months and only one at a year. These figures are similar to other studies which have been reported and raise the important question of the use of criteria, which at best might have a 5% false positive error rate, to attempt to prevent the prolongation of insentient life which will occur in less than 1% of patients. In general, even when the cost of care is taken into account, it is hard to justify the withdrawal of therapy for patients in medical coma simply on the basis of prognostic information available at present. In this respect it seems unlikely that the guidelines produced by the American Medical Association[16] which suggest that when "a patient's coma is beyond doubt irreversible and there are adequate safeguards to confirm the accuracy of the diagnosis . . . it is not unethical to discontinue means of life prolonging medical treatment" will ever be achieved for the individual patient. Indeed a recent analysis of early prognosis in anoxic coma[15] calculated that "To achieve 99% probability that a false positive risk associated with a particular predictor of chronic vegetative state among survivors is no more than one in a 1000, a study would have to be large enough to contain a sub-set of at least 4603 patients who met that criterion, survived at least three months and remained in a chronic vegetative state". Such statistics would only be achieved by massive studies involving tens of thousands of patients and are impracticable.

One other area which needs more study is the life expectancy of patients in long term vegetative state. Although few patients enter this category it has been suggested that 10% of such patients may regain awareness during a five year period of follow up, 25% may survive for more than five years, and up to 4% of patients for more than ten years.[17 18] These results are not truly applicable to the adult population in non-traumatic coma since they include large numbers of head injured patients and children with developmental disorders, many of whom were only assessed after more than one year in a vegetative state. There are isolated reports of patients in a persistent vegetative state who have begun to show some evidence of cognition and there would be considerable benefit in the collection of data about a large cohort of patients alive in a vegetatative state after three months of an ictus who were then followed over the ensuing years. The importance of such life table figures for medico-legal asessment of the need for provision of care and establishing life expectancy is self evident.

Conclusion

It is apparent that clinical signs, paticularly those of brainstem responses, motor and verbal responses are the most useful and best validated of predictors. They form the "gold standard" of assessment in terms of coma outcome and future assessments of newer techniques should be compared with clinical predictors and be made prospectively. However, even the clinical predictors which are most accurate are not sufficient to avoid a 5% risk of positive error without being proven on massive numbers of patients and therefore, although the test results are of great value in providing information to colleagues and the relatives of patients, they should not be used to make decisions to withhold therapy. In the future they might be of benefit in identifying those patients in whom it would be reasonable to assess the potential of neuroresuscitative drugs and therapies but, at present, they cannot be regarded as criteria for withholding life support.

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