Prognosis for recovery from prolonged post-traumatic unawareness: logistic analysis

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Abstract

This study reviews the course and outcome of 130 patients who remained in a state of prolonged unawareness 30 days after severe cranio-cerebral trauma. Prognostic indicators and outcome were fitted by a logistic model. The significant prognostic factors observable in the first week after trauma were found to be ventilatory status, motor reactivity and significant extraneural trauma. The significant prognostic factors after the first month of unawareness were early ventilatory status, early motor reactivity, late epilepsy and hydrocephalus. The estimated probability of recovery of awareness (that is, consciousness) ranged from 0.94 in patients with early decorticate posturing in the absence of both extraneural trauma and ventilatory disturbance to 0.06 in patients with flaccidity, extraneural trauma and ventilatory disturbance in the first week after injury.

Prolonged unawareness following brain trauma is an increasingly common problem. It develops in one to 12% of all patients suffering from coma ≥ 24 hours after trauma.¹⁻¹⁰ This condition is often referred to as prolonged coma or as persistent vegetative state, but neither of the latter two terms is accurate, in view of the fact that these patients open their eyes and show body movements. The condition is characterised clinically by a state of wakefulness without awareness, together with primitive postural activity, reflexes of cortical liberation and pathological motor response.¹¹⁻¹² The most common pathological or imaging finding is disintegration of periventricular white matter, mainly in the frontal and parietal lobes.¹³⁻¹⁵ About 54% of patients showing persistent unawareness a month after trauma recover consciousness;¹²⁻¹⁶⁻¹⁷ the remainder continue in a state of unawareness until their death, which may be postponed for as long as ten years.¹⁻⁵⁻⁷⁻¹⁸⁻²³ These patients pose difficult social and ethical problems, and it is likely that accurate early prognostication may help solve some of these problems.

A few studies have attempted to derive a prognoses from the early findings, but isolated data such as age, duration and/or depth of coma, pupillary reactivity, ocular movements and others have shown little prognostic value.³⁻⁶⁻⁸⁻²²⁻²⁴⁻²⁸

In a previous study we evaluated the prog-

nostic value of a number of other single clinical features observed early (in the first week after trauma) and late (after the first month).¹⁷ We present the results of integrating the various clinical features, after proper treatment of the records with incomplete data, into a logistic model for predicting the outcome.

Patients and methods

A total of 148 patients who remained unaware 30 days or more following trauma were admitted to our unit during the years 1974-83. In 134 of these the follow up data were sufficiently complete to permit inclusion in this study. They included 108 males and 26 females. The variables studied included demographic data, circumstances of accident, type of brain injury, neurological and extraneurological lesions, surgical interventions, vital signs, initial Glasgow coma scale, intracranial pressure, central endocrine disorders, early and late epilepsy, motor reactivity, hydrocephalus, and shunts. The mean duration of hospital stay was 15.4 months, with a range of 3-52 months. Mean age was 27 years. 92 patients (69%) were victims of road accidents. 72 (54%) regained consciousness, all of them within the first year.

The motor reactivity of the patients was classified as decerebrate posturing, decorticate posturing or flaccidity. Four of the patients failed to fit any of these categories and showed apparently normal limb withdrawal or localisation upon stimulation. None of these four patients regained consciousness. Since no valid statistical conclusions could be drawn from this small subset of the population with "normal" motor reactivity, and since they could not be plausibly combined with any of the other three categories, we limit our statistical analysis to the 130 patients with decerebration, decortication or flaccidity.

Statistical methods

Table 1 shows that more than half of the cases had incomplete information on at least one parameter, despite the considerable effort devoted to recording and collecting the data. A two-stage procedure therefore was developed for the analysis of the data. In the first stage, estimates were derived to substitute the missing values of the relevant parameters. For each such patient, the estimates are completed using the values of other parameters of the patient for which there is complete information. The computation is based on appropriate log-linear models. In the second stage logistic models

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Table 1 Combinations and frequencies of missing data

Combination	
Hydrocephalus alone	21
Motor reactivity alone	20
Ventilatory disturbance alone	4
Sweating (all combinations)	76
Fever (all combinations)	58
Motor reactivity and:	
Extraneural trauma	1
Epilepsy	1
Abnormal ADH secretion	1
Hydrocephalus	5
Ventilatory disturbance	3
Plus hydrocephalus	2
Ventilatory disturbance and:	
Hydrocephalus	1
Epilepsy, hydrocephalus, and ADH	2

were fitted to the now-complete contingency table.

1) Treatment of missing data

The estimates for missing values were derived from the available parameters and from their correlations with the parameter for which there is no information in a particular patient. The procedure is valid only if the missing data on a given parameter are missing at random (that is, the fact that the data are incomplete is unrelated to the prognosis). This condition was not met in two of the parameters: fever and sweating. Data were missing in these categories for more patients who recovered than for those who did not. Since they were not missing at random, the values of these parameters could not be estimated in the cases with incomplete information. The two parameters were omitted from further analysis.

To avoid biased estimation in cases with a considerable amount of incomplete information, the estimation procedure was applied only to the patients who had missing data on no more than two parameters. Four of the patients who had missing data on three of the prognostic factors (see table 1) were dropped from the study. Among the remaining 126 subjects, 45 had missing data on one parameter and 12 lacked data on two.

The estimation of the missing values was performed as a two-step procedure. First, estimators were derived from the 69 records in which information was complete. For each parameter, we assessed which single prognostic factor (among the remaining five parameters) is the best predictor for that parameter. Similarly, we assessed which two factors were the

Table 3 Frequencies and percentage of recovery of awareness versus each predictor parameter

	Recovery	No recovery
Extraneural trauma		
Absent	35.2 (65%)	19.0 (35%)
Present	36.8 (49%)	38.0 (51%)
ADH dysfunction		
Absent	67.0 (59%)	46.9 (41%)
Present	5.0 (33%)	10.1 (67%)
Ventilatory disturbance		
Absent	34.1 (72%)	13.1 (28%)
Present	37.9 (49%)	39.3 (51%)
Hydrocephalus		
Absent	50.8 (79%)	13.1 (21%)
Present	21.2 (32%)	44.1 (68%)
Epilepsy		
Absent	55.7 (68%)	26.6 (32%)
Only early	4.1 (51%)	4.0 (49%)
Late	12.2 (31%)	26.5 (69%)
Motor reactivity		
Decortication	15.4 (71%)	6.3 (29%)
Decerebration	53.2 (58%)	37.7 (42%)
Flaccidity	3.4 (21%)	13.1 (79%)

Numbers are not integers due to the process of estimating missing data. Percentages are in brackets.

best pair for predicting the value of that parameter. For each such parameter, the decision was based on the five log-linear models with one predictor variable and on the ten log-linear models with two predictors. The "best" single predictor and the "best" pair were those which yielded the lowest p-values in the respective models. Single predictors were used to derive estimates for missing parameters whenever a patient's record had missing data on two parameters, and one of them was in the best predictor pair for the other parameter; pairs of predictors were used to derive estimates for all other missing parameters. The resulting predictors for the configurations of incomplete information are given in table 2. As an example, the one patient with missing information on antidiuretic hormone dysfunction and on pathological motor reactivity, the values of both parameters were estimated on the basis of a single predictor, namely his hydrocephalus status. On the other hand, for the 20 patients with missing data for pathological motor reactivity alone, the missing data were estimated by the predictor pair of antidiuretic hormone status and hydrocephalus status. The best predictor pair does not always include the best single predictor. When two parameters with I and J levels respectively were missing, we approximated the probabilities for the $I \times J$ combinations of levels as if the two parameters were independent. Other methods for estimat-

Table 2 Best predictors of missing data

Missing single variable	Best predictor pair
Hydrocephalus	ADH + Motor reactivity
Motor reactivity	ADH + hydrocephalus
Ventilatory disturbance	Hydrocephalus + Motor reactivity
Extraneural trauma	Hydrocephalus + ventilation
Epilepsy	Hydrocephalus + trauma
Two variables missing	Best predictor(s)
1 ADH status	Hydrocephalus
Motor reactivity	Hydrocephalus
2 Hydrocephalus	Epilepsy
Motor reactivity	ADH status
3 Hydrocephalus	Motor reactivity + ADH status
Ventilatory disturbance	Extraneural trauma
4 Motor reactivity	Hydrocephalus + ADH status
Ventilatory disturbance	Extraneural trauma

Table 4 Estimated probabilities of recovery of awareness for combinations of the significant early predictor variables

Ventilatory disturbance	Motor reactivity	Extraneural trauma	
		Absent	Present
Absent	Decortication	0.94	0.85
	Decerebration	0.90	0.75
	Flaccidity	0.30	0.13
Present	Decortication	0.86	0.68
	Decerebration	0.72	0.53
	Flaccidity	0.14	0.06

ing missing data in contingency tables are more fully described elsewhere.²⁹

The application of this estimation procedure resulted in a complete but somewhat unusual contingency table, in which some of the values are not integers.

Model fitting

Table 3 presents the relationship between prognosis and each of the six predictor variables, after corrections for missing data. It shows that the estimated probability of recovery from the state of prolonged unawareness was 65% in the absence of associated extraneural trauma, as contrasted with a 49% in its presence. Similarly, disturbed antidiuretic hormone secretion decreased the estimated probability of recovery from 59–33%, hydrocephalus reduced it from 79–32%, and disturbances of ventilation reduced it from 72–49%. The marginal probability of recovery was 68% in the absence of epilepsy, 51% in those who showed only early seizures and only 32% among those with later seizures. The probability of recovery was 71% among those who showed postures of decortication, 58% among those with decerebration, and 21% among those with flaccidity.

Logistic models were fitted to these data using the BMDPLR computer program,³⁰ with outcome as the response variable and the six parameters as categorical predictors. Logistic models were fitted separately for two sets of predictors. The early predictor set includes only the variables observed during the first week after onset of coma. The late set includes the late hydrocephalus status and the possible late appearance of epilepsy in addition to the five early variables. The stepwise model fitting ended whenever the contribution of an additional parameter did not achieve a significance level of 0.1.

Results

Eight of the parameters studied were shown to be very significantly associated with prognosis for recovery of awareness. Associated extraneural trauma, pathological motor reactivity, disturbed secretion of antidiuretic hormone (ADH) (either inappropriate antidiuretic hormone secretion or diabetes insipidus), fever of central origin, and sweating in the first week after trauma were all associated with the prognosis. Hydrocephalus at one to three months after trauma was also a significant prognostic finding. Epilepsy was also significantly associated with the outcome, although its correlation with the prognosis varied depending on whether it was noted in the first week after trauma or later.

Table 4 presents the results of model fitting to the early set of five predictor parameters. Three parameters made significant contributions to prognosis: respiratory disturbance, pathological motor reactivity and associated extraneural injury. The estimated probability of recovery is given for each combination of levels of these three early predictor variables. Given the information contained in these predictor variables, the additional contribution of early antidiuretic hormone status and early epilepsy did not add significantly to the prediction of outcome.

Table 5 presents the results of logistic regression fitting to the more complete later set of six predictor variables, including three possible levels of epilepsy status (no epilepsy, early onset without persistence, late epilepsy).

The predictor variables contributing significantly to prognosis were hydrocephalus, epilepsy, respiratory disturbance, and pathological motor reactivity, in that order. The addition of antidiuretic hormone status and associated extraneural trauma did not add significantly to prognostic accuracy.

Discussion

Three observations may be made about the relative prognostic value of the various late and early parameters:

- 1) The single parameter with the highest correlation with outcome is the presence or absence of hydrocephalus, recorded only after the first month.
- 2) The presence or absence of epilepsy in the first week did not contribute significantly to the prognosis. However, when the additional level

Table 5 Estimated probabilities of recovery of awareness for combinations of all significant predictor variables

Hydrocephalus	Ventilatory disturbance	Motor reactivity	Epilepsy		
			None	Early	Late
Absent	Absent	Decortication	0.93	0.86	0.78
		Decerebration	0.86	0.74	0.62
		Flaccidity	0.59	0.39	0.27
Absent	Present	Decortication	0.89	0.78	0.67
		Decerebration	0.77	0.61	0.47
		Flaccidity	0.44	0.26	0.17
Present	Absent	Decortication	0.75	0.58	0.44
		Decerebration	0.57	0.38	0.26
		Flaccidity	0.24	0.13	0.08
Present	Present	Decortication	0.63	0.44	0.31
		Decerebration	0.43	0.26	0.16
		Flaccidity	0.15	0.07	0.04

of late epilepsy was added to this variable, it showed a high correlation to outcome. Thus, later epilepsy is correlated with outcome, while early epilepsy is not.

3) The presence or absence of associated extraneural trauma made a significant contribution to prognosis when only the five early predictor variables were considered. When the later parameters of presence or absence of hydrocephalus and of later epilepsy were considered, the factor of associated trauma added nothing significant to prediction of outcome. It may be that this factor is in fact a predictor or even a pathogenic factor in the causation of late hydrocephalus and/or later epilepsy.

There are no combinations of factors which predict recovery, but there are a few combinations which predict non-recovery. Patients without ventilatory disturbance and without major extraneural trauma who show decorticate posturing in the first week after injury have a 94% probability of recovering their awareness, and such patients with early decerebrate posturing have a 90% probability of doing so. In the presence of extraneural trauma, patients without ventilatory disturbance but with decorticate posturing have an 85% chance of recovering full consciousness. In the presence of extraneural trauma and ventilatory disturbance, the finding of flaccid muscle tone is associated with less than a 6% probability of regaining full consciousness. Other combinations of parameters give intermediate probabilities for recovery.

The above estimated probabilities relate to clinical observations during the first week after injury, in patients without awareness 30 days after trauma. A more finely grained prognostic table may be arrived at if the later variables are used as well, as itemised in table 2. Thus decorticate posturing in the absence of epilepsy and hydrocephalus entails a 93% likelihood of recovery. The probability of recovery drops to 44% for the same posturing in the presence of hydrocephalus and late epilepsy, and to 31% if in addition to these two factors the patient suffers from ventilatory disturbance. The prognosis arrived at on the basis of the late variables is based on a follow up period of several months. Since the purpose of prognosis is both to inform the families of the likely outcome and to make possible the assigning of priorities to candidates for scarce resources for intensive care in rehabilitation facilities, the prognostic table based on the early variables may be expected to be more useful.

Our prognostic model applies to a somewhat different group of patients than for the Glasgow Coma Scale (GSC) and its variants. The GSC is a prognostic indicator for outcome in cases of acute traumatic coma, and it applies to patients in the first week after trauma. By contrast, the prognostic matrix we present applies to patients who have emerged from acute coma, have entered a state of prolonged unawareness, and have remained in this state 30 days after injury, and it predicts recovery of awareness rather than survival.

It should also be emphasised that our prognostic probabilities are based only on the patient population which was used to develop them. The overall prognostic value of this model can only be determined by additional validation studies in other groups of patients with the syndrome of prolonged post-traumatic unawareness.

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