Modelling early recovery patterns after paediatric traumatic brain injury

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Short title
Recovery patterns after traumatic brain injury

Abbreviations
GCS Glasgow Coma Scale/Score
NLME non-linear mixed effects [models]
PTA [Duration of] post-traumatic amnesia
TBI traumatic brain injury
TFC time to follow commands (for definition see text)
RCT randomised controlled trial
WeeFIM Functional Independence Measure for children (for details see text)

Key words
Traumatic brain injury, outcome prediction, non-linear mixed effects modelling

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Abstract

Objective
To describe the range of early recovery patterns seen in children admitted for inpatient rehabilitation after traumatic brain injury and to build simple predictive models of expected recovery.

Patients
103 consecutive paediatric admissions to a neurological rehabilitation facility after closed head injury

Methods
Children’s recoveries were defined by repeated scores on the WeeFIM (a validated paediatric measure of functional independence) assembled into recovery trajectories. Non-linear mixed effects modelling was used to define “typical” recoveries and to identify useful simple predictor variables.

Results
WeeFIM recovery curves showed a characteristic sigmoidal form with an initial slow phase followed by a mid-phase of fastest improvement and a late plateau. Final WeeFIM scores ranged from 18 to 125 (median 105, interquartile range 87-117). The time taken to reach 50% final WeeFIM score ranged from 5 to 145 days (median 27, interquartile range 17-46). Both final WeeFIM and time to reach 50% final WeeFIM correlated with Time to Follow Commands (TFC), defined as the post-injury day on which a child was first observed to follow two simple commands in a 24h period

Conclusions
Simple models predicting outcome trajectory can be built incorporating early rate-of-recovery indices (such as TFC) as proxies of injury severity. Such models allow informed discussion with families of likely rates of progress, and the confidence intervals on these estimates. Models of this nature also potentially allow identification of children making better- or worse-than-expected recoveries.
Introduction

Traumatic Brain Injury (TBI) remains a major health problem in children (1). Heterogeneity is a major obstacle to improving outcomes after TBI at many levels: it complicates the design and delivery of optimal services, and it limits the ability to advise parents of what to expect in individual situations. It also greatly hinders rehabilitation research: it is hard to evaluate the effect of a novel intervention when the expected recovery without intervention cannot be predicted with any confidence (2, 3). This study is an example of Disease Progress Modelling (3) – using NLME or similar techniques to model change in health status over time — which has potential applicability to a wide range of paediatric conditions.

Although outcomes after paediatric TBI have been extensively reported this has typically been a “snapshot” approach: detailing the complex picture of combined behavioural (4, 5), social (6), psychiatric (7-9) and cognitive (10, 11) morbidity at one or two time points post injury. Whilst of great value this data is of limited relevance to a family wanting to know what can reasonably be expected in the way of change in the first weeks and months after injury, during which period the “currency” of recovery is mobility, communication and self-care. The aim of this study was to describe the early recovery courses seen in children admitted for inpatient rehabilitation TBI and to build simple predictive models of expected recovery. To do this a longitudinal approach was taken, assembling recovery trajectories from repeated application of a summary health status score, the WeeFIM.

The WeeFIM (12, 13) is a paediatric adaptation of the adult Functional Independence Measure. It summarises the need for assistance in activities of daily living on a seven-point ordinal scale (1 = complete dependence; 7 = complete independence) over 18 items in six domains (self-care, sphincter control, transfers, locomotion, communication and social cognition). The use of the WeeFIM as an outcome measure in early rehabilitation after TBI is well established (14, 15) (see also Discussion).

Mixed effects modelling is a statistical technique particularly suited to the analysis of longitudinal data collected repeatedly in the same individuals, such as growth curves(16). Unlike conventional “repeated measures” statistics, the dataset can be unbalanced (i.e. without observations at precisely the same time points for all individuals) and relatively sparse (few observations per individual). Its power comes from assuming a general form to the shape of an individual’s trajectory. For example if inspection of the data suggests it is warranted the assumption could be made that each individual’s measurements could be fitted with a straight line. Often however this is not realistic and a curvilinear shape may be suggested by the data. The mathematical formulae for such curvilinear shapes are technically known as non-linear equations, and Non-Linear Mixed Effects (NLME) models are an important class of mixed effect models.

Whether linear or non-linear, the term “mixed effects” refers to the estimation from the data of both population level fixed and individual random effects. The fixed effect is the recovery common to all members of the population: in effect the most likely or most typical recovery seen. Optionally this can incorporate independent covariates (i.e. in this particular context, the most likely post-head injury recovery trajectory given some information about injury severity). The random effects are the
unpredictable components of the recovery: the additional scatter of individual children’s actual data around the expected, fixed effects.

Methods

The study population comprised 103 consecutive admissions with moderate or severe TBI (defined as first available GCS < 12 or presence of relevant intracranial imaging abnormalities) to the Commission on Accreditation of Rehabilitation Facilities (CARF)-accredited pediatric inpatient rehabilitation programme at the Kennedy Krieger Institute, Johns Hopkins School of Medicine, Baltimore MD between 1998 and 2008. The large majority were referred from the two regional Level I pediatric trauma centers: Johns Hopkins Hospital in Baltimore, MD, and Children's National Medical Center in Washington, DC. The remainder come from regional hospitals, with a minority from regional, national and international hospitals.

Children with inflicted, open or penetrating injuries, prior neurological morbidity or previous episodes of traumatic brain injury were excluded. A prior diagnosis of attention deficit hyperactivity disorder did not exclude a child from the study. The Johns Hopkins School of Medicine Institutional Review Board approved the study.

The dependent variable for the study was the unweighted sum of the sub-domain scores of the WeeFIM, giving a single score with a possible range from 18 to 126. In this retrospective sample, application of the WeeFIM increased systematically during the study period and thus more recently-admitted children have greater numbers of observations. WeeFIM ratings were obtained by children’s primary therapists during the first three days of admission, and as often as every 1-2 weeks throughout the hospitalization.

The maximum possible WeeFIM score is age-dependent, and a score of 126 is typically achieved at a developmental age of approximately seven years (an illustration of the WeeFIM score that parents may find meaningful as a yardstick in the early stages of recovery). Although the use of WeeFIM developmental quotients has been described to “normalise” scores in very young children the large majority of the children in this study were over seven and absolute scores are used throughout (but see also Discussion).

Additional routinely collected data included: post-injury day of admission to the rehabilitation facility (DayAdmitted), duration of post-traumatic amnesia (PTA) measured using the Children’s Orientation and Amnesia Test (17), Glasgow Coma Score (GCS), the WeeFIM score on admission to rehabilitation (FirstWeeFIM), the length of stay in rehabilitation (LOS), age at injury (AgeAtInjury) and time to follow commands (TFC). TFC data was more reliably available than information on duration of PTA, which could be missing because a child was too young to assess, was still in PTA at discharge or had exited PTA prior to admission to rehabilitation without adequate documentation by the acute facility. TFC and duration of PTA were highly correlated and so TFC was used in preference in analyses.

TFC was defined the post-injury day on which a child was first noted by staff to follow two simple one-step commands (e.g. “squeeze my hand”) within a 24h period. If this had been achieved prior to admission TFC was estimated by retrospective chart review. It should be noted that DayAdmitted, FirstWeeFIM and TFC are all
reflections of early progress and hence indirectly of injury severity: a less severely injured, rapidly recovering child will tend to be admitted to rehabilitation early after injury, to have an already-higher WeeFIM on admission due to a degree of spontaneous recovery, and to have a shorter TFC.

WeeFIM recovery trajectories were modelled using the nlme library (18) of the R statistical environment (19), running under Mac OS X. A logistic function (described in more detail in Figure 1) was chosen as a flexible curve shape capable of fitting the range of outcomes seen. Potential covariates were identified graphically from plots against random effect residuals. Preferred models were identified using the Akaike and Bayesian Information Criteria (AIC and BIC) (16).

Results

The clinical characteristics of the 131 children are shown in Table 1. As with most TBI series there is a male predominance. The median TFC was 9 days post injury. WeeFIM observations were made up to 1122 days post injury, with a median of four observations per child (range 2-28 observations). Of the 103 children, 21 had data at just two time-points and 14 at only three time-points.

The individual recovery curves (Figure 2) confirmed a wide range of recovery patterns from rapid good recovery (top row of Figure 2) to minimal recovery (bottom row). Although final outcomes after TBI vary widely, inspection of the curves suggested it was reasonable to assume a common sigmoidal form to all trajectories with initial slow, faster mid-, and late plateau phases.

A simple NLME model fitted a sigmoidal curve (Figure 1) to each recovery, summarising each recovery in terms of three parameters: the ultimate WeeFIM reached (the asymptotic value, Figure 1); T50, the time taken to reach 50% of this ultimate WeeFIM; and a scale parameter that reflects the maximum steepness of the recovery curve. See the legend to Figure 1 for further information. Ultimate WeeFIM scores ranged from 18 to 125 (median 105, interquartile range 87-117). The time children took to make 50% of their observed recovery (see comment in legend to Figure 1) ranged from 5 to 145 days (median 27, interquartile range 17-46).

This simplest possible NLME model (not actually shown) estimates as the fixed (population) effect a single “average” or “most typical” recovery amongst all those observed. Individual children’s estimated ultimate WeeFIMs, T50s and scales will be scattered around this most typical value for each of these parameters, and the residuals (individual child’s parameter value minus population value) can be examined visually as a means of identifying potential predictor variables.

Figure 3 shows residuals for ultimate WeeFIM (asymptote), T50 and scale for each child plotted against DayFirstAdmitted, AgeAtInjury, TFC and FirstWeeFIM. Recalling that small values for DayFirstAdmitted and high FirstWeeFIM scores imply a faster recovery, several plausible relationships are noted. Ultimate WeeFIM (asymptote) is negatively correlated with DayFirstAdmitted (Figure 3 panel A1) and positively correlated with FirstWeeFIM (panel A4). This implies that children who are making faster early progress also make better ultimate recoveries (the residuals of their asymptotes relative to the most typical value is positive, i.e. their Ultimate WeeFIMs are larger). Likewise TFC is negatively correlated with asymptote (panel
A3). Again recalling that small values of T50 represent faster recovery, the correlations noted in panel B are as expected. There were no clear correlations between AgeAtInjury and either asymptote or T50 (panels A2, B2) (see Discussion). GCS data performed poorly as an explanatory variable (data not shown).

Although the correlations of Figure 3 are weak, they can be incorporated into the fixed effects of the model to improve prediction. Instead of a single “best overall fit” fixed effect for the entire sample, the fixed effect becomes “the most typical recovery given some information about injury severity”. For example, a best fit straight line through the points of Figure 3 panel A3 would have a slope of approximately – 0.6, suggesting the fixed effect estimate for ultimate WeeFIM (asymptote) for any child should be reduced by (very approximately) 0.6 WeeFIM unit for every additional day’s delay in TFC. Similarly the fixed effect estimate for T50 could be adjusted in light of FirstWeeFIM data (Figure 3 panel B4). Since however FirstWeeFIM and DayFirstAdmitted are potentially confounded by factors such as delays in arranging admission TFC was chosen as a single relatively robust covariate. More elaborate models were rejected on AIC/BIC criteria (see Methods). The estimates of the fixed effect parameters of the logistic function for each child are:

Ultimate WeeFIM (asymptote) = 111.98 – 0.59 * TFC

T50 = 10 + 2.11 * TFC

Scale = 8.84

The solid lines in each panel in Figure 2 show the predicted recovery curve for each child (adjusting Ultimate WeeFIM and T50 for each child’s TFC) alongside a dashed line representing that child’s individual curve fit (i.e., fully flexible fitting of a sigmoidal curve to that child’s recovery data, also incorporates that child’s random effects). The extent to which the solid and dashed lines diverge represents the variability not explained by this simple model. Individuals’ ultimate WeeFIMs differed from the fixed effect predicted value with a standard deviation of 20 WeeFIM units, giving a 95% confidence interval of ±39 WeeFIM units.

Discussion

A number of approaches to the analysis of longitudinal recovery data after TBI have been reported. To date there has been an emphasis on cognitive domains of outcome, typically measured on two or three occasions at intervals of up to a year (20, 21). Linear modelling techniques have predominated (22, 23) although some use of NLME techniques has been reported (24). Novel aspects of this paper include the application to the early rehabilitation phase and to functional independence outcome measures, attention to the form of the recovery trajectory, and the attempt to predict outcomes (and define the confidence intervals on these predictions) rather than simply seeking associations with outcome. As in any model-building process, there is a trade-off between simplicity and accuracy. We have prioritized simplicity and Figure 2 demonstrates clear limitations to the predictability of outcome. In some cases (e.g., children 8, 24) the sparseness of the outcome data has clearly affected the ability to estimate curve parameters: fuller delineation of individual recoveries through more frequent WeeFIM measurement will improve this. The approach allows identification of outliers: children who have made significantly ($p<0.05$) poorer outcomes (e.g., case
than might have been anticipated. Review of these cases may be a useful clinical audit tool. Child 83 did in fact start following commands (as defined) at 21 days but then had a number of additional complications and became less responsive. Four years later he remained in a minimally conscious state, intermittently following commands.

The finding of correlations between high admission WeeFIM scores and early admission to rehabilitation with good late outcome is consistent with previous reports in children (15) and adults (25). The use of early rate-of-progress indices (such as TFC or duration of post-traumatic amnesia, PTA) as proxies of injury severity has a pragmatic appeal, although accurate assessment of duration of PTA is time-consuming and requires training in appropriate instruments (17). TFC offers a simple alternative. Our data suggest that estimates of an individual child’s ultimate WeeFIM score should be reduced by about 0.6 units for every day that a child fails to re-establish basic command following, although in counselling parents the confidence interval of ± 39 WeeFIM units on this prediction should be emphasised. The use of early progress indicators to predict late progress is somewhat tautologous, and will be particularly problematic in a research setting where therapy or drug interventions that are hoped to change rate of progress are being evaluated. In such settings alternative intrinsic indicators of injury severity will be required such as radiological data (26, 27).

The impact of age at injury on outcome after TBI has been the subject of much debate (28). These data do not provide any evidence for strong age-at-injury effects. There is certainly little evidence of an effect on rate of recovery (Figure 3 panels B2, C2). Interpretation of panel A2 (age at injury versus ultimate extent of recovery) is complicated by the use of absolute WeeFIM scores in this study. The maximum WeeFIM score of 126 reflects a developmental age of approximately seven years and thus maximum possible scores are age-dependent below this threshold age. This probably underlies the apparent weak positive correlation between age at injury and asymptote in the youngest children in this plot.

Our data confirms a clinical impression that children often show a phasic recovery curve with an initial slow phase, a rapid change period, and a late plateau (but see below). Another intuition supported by these data is that late recoveries tend to be ultimately poor recoveries: TFC correlates negatively with asymptote (Figure 3 panel A3). Interestingly, less can be assumed about the maximum rate of recovery (proportional to 1/scale): Figure 3 panel C shows no strong relationships between scale and indices of injury severity.

The WeeFIM predominantly reflects the changes in physical impairment and function relevant in early rehabilitation, but is relatively insensitive to late cognitive morbidity (29-31). It is important to bear in mind therefore that the late plateau seen in these recovery curves is to an extent the result of ceiling effects of the outcome instrument chosen. Although WeeFIM data were used in these analyses, the methods illustrated are generic and could be adapted to any uni-dimensional summary outcome measure.

**Funding**

None
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None

What is already known on this topic

• Outcomes after TBI vary widely, are poorly predictable and comprise morbidity in multiple domains

What this study adds

• Slow recoveries tend to be poor recoveries
• Simple measures of early recovery can be used to estimate medium term recovery patterns
Legends to tables and figures

**Table 1**

Characteristics of study population. Ranges are shown as median (range; interquartile range)

**Figure 1**

The logistic function used to describe individual recovery trajectories in terms of three parameters: asymptote representing final recovery at late time post injury (i.e., ultimate WeeFIM score); T50, the time taken to reach 50% of this ultimate WeeFIM score (from a baseline of zero); and scale, a parameter which is approximately the time taken to improve from 50% to 75% of the ultimate WeeFIM score. Small values of Scale imply steep recovery (the maximum steepness occurs at time T50).

Note that this function has a baseline value of y=0 at time = minus infinity, not time = zero. Since T50 is the time to reach 50% asymptote from zero, for very rapidly recovering children T50 underestimates the time for a child to make 50% of the actual observed recovery from his/her initial (already high) WeeFIM scores but this can be calculated from the curve parameters. To allow use of a function with baseline value of zero with the WeeFIM scale whose minimum value is 18, WeeFIM scores were adjusted by subtracting 18 for analysis (but converted back to the conventional 18-126 scale for reporting)

**Figure 2**

The results of fitting a simple NLME model to the data. Each plot represents an individual child, identified by a case number. Open circles represent WeeFIM observations, adjusted to a scale of 0 to 108 (see legend to Figure 1). Data are shown for the first 365 days post injury for clarity (case 83 had observations in the second year post injury).

The dashed lines in each plot represents an individual “curve fit”. The solid line in each plot represent the fixed or “expected” recovery of each child given information about individual children’s TFC (see Results).

**Figure 3**

Plots of residuals of random effects against potential independent predictor variables. Points represent the residuals (individuals’ best fit values for each parameter minus the population “average”) for asymptote (ultimate WeeFIM, panel A), T50 (panel B) and scale (panel C). In each panel the residuals are plotted against DayFirstAdmitted (top left in each panel), AgeAtInjury (top right), TFC (bottom left) and FirstWeeFIM (bottom right).
## Tables

**Table 1**

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<table>
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<tr>
<td>Age at injury (years)</td>
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<td>Male:Female</td>
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<td>Admission Glasgow Coma Scale</td>
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<tr>
<td>Admission date (days post injury)</td>
<td>13 (4-46; 8-26)</td>
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<td>Time to follow commands, TFC (days post injury)</td>
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<tr>
<td>Total WeeFIM score on admission (possible range 18-126)</td>
<td>32 (18-119; 18-48)</td>
</tr>
<tr>
<td>Assessment times (days post injury)</td>
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</tr>
<tr>
<td>Number of observations per child</td>
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</tr>
<tr>
<td>Average interval between observations for each child(days)</td>
<td>28 (3-218; 15-63)</td>
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</tbody>
</table>
References


Description and prediction of early recovery patterns after paediatric traumatic brain injury

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Short title

Recovery patterns after traumatic brain injury

Abbreviations

GCS—Glasgow Coma Scale/Score
NLME non-linear mixed effects [models]
PTA—[Duration of] post-traumatic amnesia
TBI—traumatic brain injury
TFC—time to follow commands (for definition see text)
RCT—randomised controlled trial

Key words

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Financial disclosure

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Abstract

Objective
To describe the early recovery courses seen in children admitted for inpatient rehabilitation after traumatic brain injury and to build simple predictive models of expected recovery.

Patients
103 consecutive paediatric admissions to a neurological rehabilitation facility after closed head injury

Methods
Children’s recoveries were defined by repeated WeeFIM measurements assembled into recovery trajectories. Non-linear mixed effects modelling was used to define “typical” recoveries and to identify useful simple predictor variables.

Results
WeeFIM recovery curves showed a characteristic form with an initial slow phase followed by a rapid improvement phase and a late plateau. Final WeeFIM scores ranged from 18 to 125 (median 105, interquartile range 87-117). The time taken to reach 50% final WeeFIM score ranged from 5 to 145 days (median 27, interquartile range 17-46). Both final WeeFIM and time to reach 50% final WeeFIM were predicted by the Time to Follow Commands (TFC), defined as the post-injury day on which child was first observed to follow two simple commands in a 24h period

Conclusions
Simple models predicting outcome trajectory can be built incorporating early rate-of-recovery indices (such as TFC) as proxies of injury severity. Such models allow informed discussion with families of likely rates of progress, and the confidence intervals on these estimates. Simple models of this nature also potentially allow identification of children making better-or worse-than-expected recoveries.
Introduction

Traumatic Brain Injury (TBI) remains a major health problem in children (1). Heterogeneity is a major obstacle to improving outcomes after TBI at many levels: it complicates the design and delivery of optimal services, and it limits the ability to advise parents of what to expect in individual situations. It also greatly hinders rehabilitation research: it is hard to evaluate the effect of a novel intervention when the expected recovery without intervention cannot be predicted with any confidence (2, 3).

Although outcomes after paediatric TBI have been extensively reported, the typical approach has emphasized detailed snapshot descriptions at one or two time points post injury (often twelve months) across multiple domains (4, 5) detailing the complex picture of combined behavioural (6, 7), social (8), psychiatric (9-11) and cognitive (12, 13) morbidity. Whilst of great value this data is of limited relevance to a family wanting to know what can reasonably be expected in the way of change in the first weeks and months after injury, during which period the “currency” of recovery is mobility, communication and self-care. In this study we used relatively simple, repeated assessments to define multiple points that allowed the delineation of recovery trajectories of children in the post-acute rehabilitation phase (i.e. the first year or two post injury) with the aim of informing these issues.

The WeeFIM (14, 15) is a paediatric adaptation of the adult Functional Independence Measure. It summarises the need for assistance on a seven-point ordinal scale (1 = complete dependence; 7 = complete independence) over 18 items in six domains (self-care, sphincter control, transfers, locomotion, communication and social cognition). The use of the WeeFIM as an outcome measure in early rehabilitation after TBI is well established (16, 17) (see also Discussion). A maximum WeeFIM score of 126 is typically achieved at a developmental age of approximately seven years (an “illustration” of the WeeFIM score that parents find meaningful as a yardstick in the early stages of recovery).

Non-linear mixed effects (NLME) modelling techniques can be used to analyse growth data (18). “Non-linear” refers to the ability to accommodate curvilinear (e.g. sigmoidal) shapes of change over time. “Mixed effects” refers to the estimation of both fixed population level and individual random effects. In this context, the fixed effect is the expected (loosely, the “average”) recovery obtained by estimating the most likely, or most typical recovery. Optionally this can incorporate independent covariates (i.e. the most likely trajectory given some information about injury severity). The random effects comprise the additional scatter of actual individual children’s data about the fixed effect.

Methods

Opportunistically-collected WeeFIM data were available for 103 consecutive admissions to the TBI inpatient rehabilitation programme at the Kennedy Krieger Institute, Johns Hopkins School of Medicine, Baltimore MD. Children with inflicted, open or penetrating injuries, prior neurological morbidity or previous episodes of traumatic brain injury were excluded. A prior diagnosis of attention deficit...
hyperactivity disorder (ADHD) did not exclude a child from the study. The Johns Hopkins School of Medicine Institutional Review Board approved the study.

The dependent variable for the study was the unweighted sum of the sub domain scores of the WeeFIM, giving a single score with a possible range from 18 to 126. Additional routinely collected data included: post injury day of admission to the rehabilitation facility (DayAdmitted), duration of post-traumatic amnesia (PTA) measured using the Children’s Orientation and Amnesia Test (19), Glasgow Coma Score (GCS), the WeeFIM score on admission to rehabilitation (FirstWeeFIM), the length of stay in rehabilitation (LOS), age at injury (AgeAtInjury) and time to follow commands (TFC). TFC was defined the post injury day on which a child was first noted to follow two simple commands within a 24h period. DayAdmitted, FirstWeeFIM and TFC are all reflections of early progress and hence indirectly of injury severity: a less severely injured, rapidly recovering child will tend to be admitted to rehabilitation early after injury, to have an already higher WeeFIM on admission due to partial spontaneous recovery, and to have a shorter TFC.

Data were modelled using the nlme library (20) of the R statistical environment (21), running under Mac OS X. A logistic function was chosen as a flexible curve form capable of fitting the range of outcome trajectories seen. See Figure 1 for a description of the parameters of the logistic function. Potential covariates were identified graphically from plots against random effect residuals. Preferred models were identified using the Akaike and Bayesian Information Criteria (AIC and BIC) (18).

Results

Clinical characteristics of the study sample are shown in Table 1. As with most TBI series there is a male predominance. The median TFC was 9 days post injury. WeeFIM observations were made up to 1122 days post injury, with a median of four observations per child. Of the 103 children, 21 had data at just two time points and 14 at only three time points. However it was possible to fit an NLME model, and extract estimates of asymptote, T50 and scale (see Figure 1) for each child. Final WeeFIM scores (i.e. asymptotes) ranged from of 18 to 125 (median 105, interquartile range 87–117). The individual recovery curves (Figure 2) confirmed a wide range of recovery patterns from rapid good recovery (top row of Figure 2) to minimal recovery (bottom row). Although final outcomes after TBI vary widely, the modelling took advantage of the commonality in the general form of the recovery trajectory (initial slow, faster mid, and late plateau phases). The time children took to make 50% of their observed recovery (see comment in legend to Figure 1) ranged from 5 to 145 days (median 27, interquartile range 17–46).

TFC data was more reliably available than information on duration of PTA, which could be missing because a child was too young to assess, was still in PTA at discharge or had exited PTA prior to admission without documentation by the acute facility. TFC and duration of PTA were highly correlated and so TFC was used in preference.

The simplest possible NLME model estimates as the fixed effect the single “most typical” recovery amongst all those observed. The random effect residuals (i.e. the differences between individual children’s estimated asymptotes, T50s, and scales and
those of this most typical recovery) can be examined visually as a means of identifying potential predictor variables. Figure 3 shows these residuals for each child plotted against DayFirstAdmitted, AgeAtInjury, TFC and FirstWeeFIM. Recalling that small DayFirstAdmitted and high FirstWeeFIM scores reflect greater early recovery, several plausible relationships are noted. Asymptote is negatively correlated with DayFirstAdmitted (Figure 3 panel A1) and positively correlated with FirstWeeFIM (panel A4) implying that children who make faster initial progress also make better ultimate recoveries. Likewise TFC is negatively correlated with asymptote (panel A3). Again recalling that small values of T50 represent faster recovery, the correlations noted in panel B are as expected. There were no clear correlations between AgeAtInjury and either asymptote or T50 (panels A2, B2) (see Discussion). GCS data performed poorly as an explanatory variable (data not shown).

Although the correlations of Figure 3 are weak, they can be incorporated into the fixed effects of the model to improve prediction. “Most typical” recovery becomes “most typical given some information about injury severity”. For example, a best fit straight line through the points of Figure 3 panel A3 would have a slope of approximately –1, suggesting the fixed effect estimate for Asymptote for any child should be reduced by approximately one WeeFIM unit for every additional day’s delay in TFC. Similarly for example the fixed effect estimate for T50 could be adjusted in light of FirstWeeFIM data (Figure 3 panel B1). Since however both FirstWeeFIM and DayFirstAdmitted are potentially confounded by severity-independent factors (such as delays in arranging admission) TFC was chosen as a single relatively robust covariate. More elaborate models were rejected on AIC/BIC criteria (see Methods). The estimates of the fixed effect parameters of the logistic function for each child are:

Asymptote = 111.98 – 0.59 * TFC

T50 = 10 + 2.11 * TFC

Scale = 8.84

The solid lines in each panel in Figure 2 show the fixed effect, i.e. the predicted recovery curve given that child’s TFC, alongside a dashed line representing that child’s individual curve fit (i.e. incorporating that child’s random effects). The extent to which the solid and dashed lines diverge represent the variability not explained by this simple model. Individuals’ final WeeFIMs differed from the fixed effect predicted value with a standard deviation of 20 WeeFIM units.

Discussion

A number of approaches to the analysis of longitudinal recovery data after TBI have been reported. To date there has been an emphasis on cognitive domains of outcome, typically measured on two or three occasions at intervals of up to a year (22, 23). Linear modelling techniques have predominated (24, 25) although some use of NLME techniques has been reported (26). Novel aspects of this paper include the application to the early rehabilitation phase, attention to the form of the recovery trajectory, and the attempt to predict outcomes (and define the confidence intervals on these predictions) rather than simply seeking associations with outcome. As in any model-building process, there is a trade-off between simplicity and accuracy. We
have prioritized simplicity and Figure 2 demonstrates clear limitations to the predictability of outcome. In some cases (e.g., children 8, 24) the sparseness of the outcome data has clearly affected the ability to estimate curve parameters; fuller delineation of individual recoveries through more frequent WeeFIM measurement will improve this. The approach allows identification of outliers: children who have made significantly (p<0.05) poorer outcomes (e.g., case 83) than might have been anticipated. Review of these cases may be a useful clinical audit tool. Child 83 did in fact start following commands (as defined) at 21 days but then had a number of additional complications and became less responsive. Four years later he remained in a minimally conscious state, intermittently following commands.

The finding of correlations between high admission WeeFIM scores and early admission to rehabilitation with good late outcome is consistent with previous reports in children (17) and adults (27). The use of early rate-of-progression indices (such as TFC or duration of post-traumatic amnesia, PTA) as proxies of injury severity has a pragmatic appeal, although accurate assessment of duration of PTA is time-consuming and requires training in appropriate instruments (19). TFC offers a pragmatic alternative. However, the use of early progress indicators to predict late progress is somewhat tautological, and will be particularly problematic in a research setting where therapy or drug interventions that are hoped to change rate of progress are being evaluated. In such settings, alternative intrinsic indicators of injury severity will be required (e.g., radiological data (28, 29)).

The impact of age at injury on outcome after TBI has been the subject of much debate (30). These data do not provide any evidence for strong age-at-injury effects. There is certainly little evidence of an effect on rate of recovery (Figure 3 panel B2, C2). Interpretation of panel A2 (age at injury versus ultimate extent of recovery) is complicated by the use of absolute WeeFIM scores in this study. The maximum WeeFIM score of 126 reflects a developmental age of approximately seven years and thus maximum possible scores are age-dependent below this threshold age. This probably underlies the apparent weak positive correlation between age at injury and asymptote in the youngest children in this plot.

Figure 2 confirms a clinical impression that children often show a phasic recovery curve with an initial slow phase, a rapid change period, and a late plateau (but see below). Another intuition supported by these data is that late recoveries tend to be ultimately poor recoveries: TFC correlates negatively with asymptote (Figure 3 panel A3). Interestingly, less can be assumed about the maximum rate of recovery (proportional to 1/scale): Figure 3 panel C shows no strong relationships between scale and indices of injury severity.

The WeeFIM predominantly reflects the changes in physical impairment and function relevant in early rehabilitation, but is relatively insensitive to late cognitive morbidity (31-33). It is important to bear in mind therefore that the late plateau seen in these recovery curves is to an extent the result of ceiling effects of the outcome instrument chosen. Although WeeFIM data were used in these analyses, the methods illustrated are generic and could be adapted to any uni-dimensional summary outcome measure.

**Funding**

None
Acknowledgements

None

What is already known on this topic

• Outcomes after TBI vary widely, are poorly predictable and comprise morbidity in multiple domains

What this study adds

• Data on typical rates and extents of recovery as described by WeeFIM scores.

• Simple measures of early recovery can be used to estimate medium term recovery patterns.

• Slow recoveries tend to be poor recoveries.
Legends to tables and figures

**Table 1**

Characteristics of study population. Ranges are shown as median (range; interquartile range).

**Figure 1**

The logistic function used to describe individual recovery trajectories in terms of three parameters: an asymptote representing final recovery at late time post injury; T50, the time taken to reach 50% asymptote (from a baseline of zero); and scale, a parameter which is approximately the time taken to improve from 50% to 75% asymptote. Small values of Scale imply steep recovery (the maximum steepness occurs at time T50).

Note that this function has a baseline value of y = 0 at time = -∞, not time = 0. Since T50 is the time to reach 50% asymptote from baseline, for very rapidly recovering children T50 underestimates the time for a child to make 50% of his/her observed recovery from his/her initial (already high) WeeFIM scores but this can be calculated from the curve parameters.

Before modelling, WeeFIM data were adjusted to a scale of 0 to 108 by subtracting 18 from all observations. This allowed the assumption of a zero baseline at time = -∞ for all children, removing the need to estimate baseline as an additional parameter in the NLME model (WeeFIM scores are reconverted to the conventional 18-126 scale before being reported in Results).

**Figure 2**

The results of fitting a simple NLME model to the data. Each plot represents an individual child, identified by a case number. Open circles represent WeeFIM observations, adjusted to a scale of 0 to 108 (see legend to Figure 1). Data are shown for the first 365 days post injury for clarity (case 83 had observations in the second year post injury).

Dashed lines in each plot represent individual “curve fits”. Solid lines in each plot represent the fixed or “expected” recovery of each child given information about individual children’s TFC (see Results).

**Figure 3**

Plots of residuals of random effects against potential independent predictor variables. Open circles represent individuals’ values of asymptote (panel A), T50 (panel B) and scale (panel C) plotted against DayFirstAdmitted (top left in each panel), AgeAtInjury (top right), TFC (bottom left) and FirstWeeFIM (bottom right).
Tables

Table 1

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at injury (years)</td>
<td>10.5 (1.8–18.4; 6.7–13)</td>
</tr>
<tr>
<td>Male:Female</td>
<td>70:34</td>
</tr>
<tr>
<td>Admission Glasgow Coma Scale</td>
<td>5 (3–15; 3–7)</td>
</tr>
<tr>
<td>Admission date (days post injury)</td>
<td>13 (4–46; 8–26)</td>
</tr>
<tr>
<td>Time to follow commands, TFC (days post injury)</td>
<td>9 (0–126; 2–21)</td>
</tr>
<tr>
<td>Total WeeFIM score on admission (possible range 18–126)</td>
<td>32 (18–119; 18–48)</td>
</tr>
<tr>
<td>Assessment times (days post injury)</td>
<td>54 (4–112; 23–114)</td>
</tr>
<tr>
<td>Number of observations per child</td>
<td>4 (2–28; 3–5)</td>
</tr>
<tr>
<td>Average interval between observations for each child (days)</td>
<td>28 (3–218; 15–63)</td>
</tr>
</tbody>
</table>
Figures

Table 1

Characteristics of study population. Ranges are shown as median (range; interquartile range)

Figure 1

The logistic function used to describe individual recovery trajectories in terms of three parameters: an asymptote representing ultimate recovery; T50, the time taken to reach 50% of this value (from zero); and scale, a parameter which reflects the steepness of the central section of the curve (approximately the time taken to improve from 50% to 75% asymptote). Small values of Scale imply steep recovery (the maximum steepness occurs at time T50).

Note that this function reaches y=0 at time = -∞, not time = 0. Rapidly recovering children with WeeFIM scores already greater than zero at early times are accommodated by using a negative value of T50 (shifting the curve far to the left). Under these circumstances T50 underestimates the time for a child to make 50% of his observed recovery from his early (already high) WeeFIM scores but this can be calculated from the curve parameters.

Figure 2

The results of fitting a simple NLME model to the data. Each plot represents an individual child, identified by a case number. Open circles represent WeeFIM observations, adjusted to a scale of 0 to 108 (see Methods). Data are shown for the first 365 days post injury for clarity (case 83 had observations in the second year post injury). In each plot the solid line represents the fixed effect: in each plot they are
adjusted in light of individual children’s TFC and FirstWeeFIM (see Results). Dashed lines incorporate each child’s random effects and represent individual curve fits.

Figure 3

Plots of residuals of random effects extracted from model against potential independent predictor variables. Open circles represent residuals (individuals’ values minus fixed effect estimate) for asymptote (panel A), T50 (panel B) and scale (panel C) plotted against DayFirstAdmitted (top left in each panel), AgeAtInjury (top right), TFC (bottom left) and FirstWeeFIM (bottom right). For definitions of these variables see Methods.
References


Figure 1

Asymptote

Total WeeFIM

Time

\[ \text{Total WeeFIM} = \frac{\text{asymptote}}{1 + e^{-\frac{\text{scale}}{T50}}} \]