Towards an understanding of sex differences in functional outcome following moderate to severe traumatic brain injury: a systematic review

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ABSTRACT

Background and aim: A clear understanding of the impact sex differences play in clinical traumatic brain injury (TBI) outcome remains elusive. Animal research suggests that females have better functional outcomes following TBI than males. Therefore, this paper aims to systematically review all studies that have examined sex differences in functional outcome measures following moderate to severe TBI in humans. It was predicted that women would exhibit better functional outcome than men.

Methods: A predefined study selection criteria was adopted to screen studies eligible for inclusion. A comprehensive and systematic search of various databases, up to the end of April 2007, was undertaken. Two independent reviewers screened studies for eligibility. Selected studies were assessed for methodological quality.

Results: 13 studies were included. Because of the heterogeneity of the functional outcome measures and lack of appropriate statistical information, a qualitative analysis was performed. More than half of the papers were considered high quality. Strong evidence was found to suggest that women do not have better functional outcome than men following moderate to severe TBI.

Conclusion: The results of this review are contrary to the suggestions from animal literature. Consideration of factors such as the woman patient's hormonal status at the time of injury and other sources of heterogeneity such as age and injury severity should be addressed in future prospective studies.

An important factor mediating the incidence of traumatic brain injury (TBI) is a patient's sex. Epidemiological reports have indicated that men are overrepresented among those patients with TBI who are less than 65 years of age while this pattern is reversed for those over the age of 65 years.[1] As scientists gain a greater understanding of the similarities and differences between healthy human brains of men and women, TBI research is increasingly taking into account the potential influence a patient's sex may play in determining their outcome.[2]

Laboratory studies of TBI have consistently found sex differences, with female animals often demonstrating a better outcome following experimental TBI.[3] Conversely, human studies have been inconclusive, potentially because of the heterogeneous nature of TBI. Also important is injury severity and that the sexes may differ in the types of injuries sustained. This could arise from sex differences in mode of injury through to differences in premorbid brain morphology. Finally, the lack of age matching between the sexes may contribute to inconsistency of results, with greater mortality and worse functional outcome demonstrated in older people following TBI.[4]

To date, there has only been one systematic review of this topic. In 2000, Farace and Alves[5] conducted a meta-analysis of gender differences on TBI outcome, finding that on average, outcome after TBI was worse in women than in men, with 17 of the 20 comparisons demonstrating a negative trend for women.

The current review adds to these earlier findings by systematically reviewing studies that examined sex differences in functional outcome measures following moderate to severe TBI in an attempt to determine whether women have better functional outcome.

METHOD

Studies which included measures of functional outcome that addressed at least three or more specific World Health Organization's International Classification of Functioning, Disability and Health[6] activity and participation domains—namely, general tasks and demands; communication; mobility; self care; domestic life; and major life areas—and used instruments with published psychometric criteria that were not solely self report, were considered in this review.

Studies were selected through searches of Medline, EMBASE, PsycINFO and CINAHL to 30 April 2007. Abstracts and titles were used to initially determine relevance to the review topic, and full text of potentially relevant articles were retrieved to assess the article for inclusion. The reference lists of retrieved articles were checked for any further relevant citations. Studies were included if they met specific methodological criteria (see table 2 in supplementary file available online). Methodological quality was assessed using a modified version of an established criteria list for prognostic studies.[7]

There was substantial heterogeneity in the eligible studies, and statistical pooling was not feasible. A strength of evidence synthesis was performed using the four levels of evidence for prognostic factors (strong, moderate, limited and inconclusive—see table 1 in the supplementary file online).[8] Relative risks ratios, odds ratios (ORs) or significant associations ($p<0.05$) were used to determine the strength of evidence. When multivariate analysis was performed in the studies, these results were used to establish levels of evidence. Otherwise, results from univariate analysis were used. Further details of the analysis are presented in the supplementary file online.

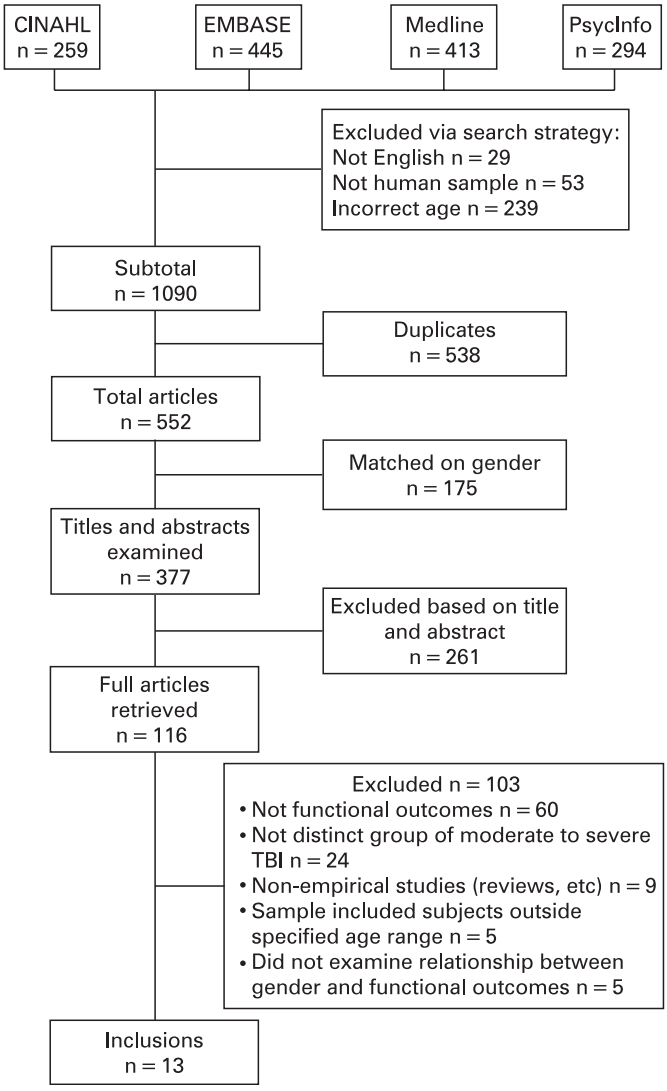

Figure 1 Flow diagram of papers accepted and rejected during the selection process. TBI, traumatic brain injury.

RESULTS

Selection of studies and methodological quality

Figure 1 depicts the flow chart for identifying the included studies.

Quality scores for each study are shown in table 1. More than half of the studies scored 5 points and thus were considered high quality. By far the greatest contribution to the methodological shortcomings of the remaining studies was failure to appropriately account for confounding variables (three out of the remaining five papers), and unequal numbers of complete follow-up between the sexes accounting for the other two studies not scoring 5 out of 5.

Study characteristics, outcome measures and results

The main characteristics of the included studies are shown in table 1. Of the 13 studies examined, only four had a primary aim to investigate sex differences in measures of functional outcome, with the remaining nine studies examining sex differences as a secondary analysis. Eight out of 13 were retrospective cohort studies. Roughly equal numbers of studies examined solely patients with severe TBI as those with a combination of moderate to severe TBI population (five vs six out of 13 studies) with the remaining two studies including mixed TBI severity. The time frame at which functional measures were assessed varied widely, ranging from a minimum of 3 months up to 24 years post injury, with the majority of papers reporting measures at 6 months (six out of 13 studies). A qualitative summary of the results is presented in the table 1.

Levels of evidence after stratification by study quality and overall direction of the evidence

Overall there was strong evidence that women do not achieve better functional outcomes following moderate to severe TBI. Two of the eight high quality studies reported that women had a worse outcome following TBI with the remaining six papers reporting no sex differences on their respective outcome measures. When considering the low quality studies, there was one positive finding indicating that women experience better outcome following TBI, and one negative finding reporting worse outcome in women. The remaining four low quality papers concluded there was no sex differences in the functional outcome measures examined.

DISCUSSION

This systematic review concludes that strong evidence is available suggesting that women do not have better functional outcome than men following moderate to severe TBI. This is contrary to the bulk of animal research indicating females experience better outcome compared with males.

However, the studies included in this systematic review do not consider a number of potentially relevant factors. Firstly, in the studies that reported a worse outcome in women (three out of 13), this pattern was observed in older females (likely to be post menopause), with no differences being noted between the sexes in the younger subgroups. Hormones such as progesterone and oestrogen may play a role in a patient's response to brain injury.[15] Briefly, it has been suggested that higher levels of progesterone relative to oestrogen reduce the complex cascade of events that accompanies TBI, known as secondary brain damage, by maintaining better immune function activity and protecting against physiological shock.[16] The studies included do not report female hormonal status at the time of injury and issues such as the use of the contraceptive pill in the younger females and hormone replacement therapy in the older females are not considered. Secondly, it should be noted that most of the functional outcome measures used in studies included in this systematic review do not detail the men to women ratio in their original development and validation cohort. Therefore, limited outcome measurement sensitivity to sex differences could explain the negative result reported in this systematic review. Furthermore, one of the most common criticisms of scales such as the Glasgow Outcome Scale and Rancho Los Amigos Levels of Cognitive Functioning Scale is their lack of sensitivity to change in general and this is also a factor to consider.

Finally, the idea that time post injury may be an important factor in determining potential sex differences in functional outcome should be highlighted. In this review, Devitt *et al*[17] reported that women between 7 and 24 years post injury experienced a better outcome, as measured by the Community Integration Questionnaire. The majority of the other studies had assessment periods that ranged from 3 to 18 months post injury. Thus it is possible that the reported female advantage following TBI is best demonstrated in longer term outcome where factors such as psychosocial influences start to come into effect.

Table 1 Summary of included studies: outcome measures and results

Study‡	Methodological quality score	Study type and participants	Outcome measures in which sex differences were reported	Subject numbers relevant to functional outcome measure			Univariate results (crude estimates and 95% CI, significant differences or associations)	Multivariate results (adjusted estimates and 95% CI)	Direction of results
				Men	Women	Total			
Baguley *et al* 2000*	5/5	Retrospective cohort Severe TBI	FAM[9]	Alive group = 243	Alive group = 70	Alive group = 313	NS between sexes (p = 0.241)	None conducted	No difference
Bayir *et al* 2004†	4/5	Prospective cohort Severe TBI	GOS[10]	51	17	68	NS between sexes (p = 0.707)	None conducted	No difference
Devitt[17]	4/5	Retrospective cohort Moderate to severe TBI	CIQ[11]	214	92	306	Males had lower CIQ scores (p<0.0001)	Significant factors that contributed greatest variation in total CIQ scores in order: sex, SF-36 physical function subscale and TMT-Part B, transportation (p<0.0001)	Males worse
Gan *et al* 2004	5/5	Retrospective cohort Mixed severity but primarily severe (60%)	GOS[10]	Young group = 129 Older group = 38	Young group = 19 Older group = 27	Young group = 148 Older group = 65	Young group: NS sex differences Older group: greater mortality (GOS = 1) in women (p ⩽ 0.0019)	None conducted	Older women worse
King *et al* 2005	5/5	Prospective cohort Severe TBI	GOS[10]	122	37	159	NS between sexes (p = 0.688)	None conducted	No difference
Kirkness *et al* 2004	5/5	Prospective cohort Moderate to severe TBI	GOS-E[12] and FSE[13]	Young group = 60 Older group = 64	Young group = 16 Older group = 17	Young group = 76 Older group = 81	None conducted	Older women had poorer outcomes (GOS-E) after controlling for initial injury severity (OR 0.107; CI 0.020 to 0.558, p ⩽ 0.008) Older women had poorer outcomes (FSE) after controlling for initial injury severity (p ⩽ 0.034)	Older women worse
Kraus *et al* 2000	4/5	Prospective cohort Moderate to severe TBI	GOS[10]	263	50	313	NS between sexes (p = 0.16)	NS sex difference after controlling for age, initial injury severity, type of head injury and presence of multiple traumas (p value not reported)	No difference
Labi *et al* 2003	5/5	Retrospective cohort Moderate to severe TBI	RLAS[14]	163	70	233	None conducted	NS sex difference after controlling for age, initial injury severity, type of head injury and presence of multiple traumas and blood alcohol levels (p value not reported)	No difference

Continued

Table 1 Continued

Study‡	Methodological quality score	Study type and participants	Outcome measures in which sex differences were reported	Subject numbers relevant to functional outcome measure			Univariate results (crude estimates and 95% CI, significant differences or associations)	Multivariate results (adjusted estimates and 95% CI)	Direction of results
				Men	Women	Total			
Ng *et al* 2006	5/5	Retrospective cohort Severe TBI	GOS[10]	348	84	432	Women had significantly poorer outcome compared with men (OR 2.09, CI 1.25 to 3.51, $p \leqslant 0.005$)	NS sex difference on GOS after controlling for age, multiple injuries, post resuscitation pupil abnormalities and GCS (OR 1.78, CI 0.96 to 3.32, $p \leqslant 0.069$)	No difference
Slewa-Younan[2]	5/5	Retrospective cohort Moderate to severe TBI	GOS[10] and FAM[9]	54	54	108	NS sex difference on GOS ($p = 0.921$) or FAM ($p = 0.871$)	None conducted	No difference
Spettell *et al* 1991	4/5	Prospective cohort Mixed severity, but primarily moderate to severe (75%)	GOS[10]	40	19	59	NS relationship between sex and GOS (p value not reported)	None conducted	No difference
Tan *et al* 2004	5/5	Retrospective cohort Moderate to severe TBI	GOS[10]	27	11	38	Women had significantly poorer outcome compared with men (OR 9.01, CI 1.60 to 50.00, $p \leqslant 0.007$)	NS sex difference on GOS after controlling for age, initial injury severity, interval to detection of deterioration, craniotomy and coagulopathy (p value not reported)	No difference
Visca *et al* 2006	4/5	Retrospective cohort Severe TBI	GOS[10] and some GOS-E[12]	Neurosurgical Centre (CTO) group = 264 Peripheral group = 118	CTO group = 85 Peripheral group = 77	CTO group = 349 Peripheral group = 195	None conducted	NS sex differences in outcome in the CTO group (p value not reported) In peripheral group age, Marshall scores, GCS and sex (men) were predictors of better outcome ($p \leqslant 0.005$)	Older women worse in general hospital

*Access to raw data was made available by authors for independent statistical analysis.
†Independent analysis (t test) performed on raw data provided in the paper.
‡For references of selected studies see the reference list in the supplementary file online.
CIQ, Community Integration Questionnaire; FAM, Functional Assessment Measure; FSE, Functional Status Examination; GOS, Glasgow Outcome Scale; GOS-E, extended GOS; RLAS, Rancho Los Amigos Levels of Cognitive Functioning Scale.

In the previous systematic review, Farace and Alves[5] reported that women had a worse outcome for 85% of the variables examined. Plausible reasons for the differing results are our different search period, inclusion criteria (particularly all TBI vs moderate to severe TBI) and which outcomes were evaluated. Without examining the methodological quality of the studies, Farace and Alves' meta-analysis quoted an average effect size of −0.15 without associated confidence intervals. This simple average did not take into account the differing sample sizes between studies and therefore was not appropriately weighted. Furthermore, 10 out of the 20 individual effect sizes came from a single study,[18] increasing the likelihood that they were correlated, a factor not addressed or adjusted for in the subsequent meta-analysis.

The current review presents strong evidence to suggest that, in contrast with the animal literature, women do not experience better functional outcomes than men following moderate to severe TBI. It is suggested that future studies should be designed with careful consideration of the complex issues surrounding human sex differences. Factors such as female hormonal status at the time of injury and other sources of heterogeneity such as age and injury severity should be addressed.

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Ataxia Rating Scale (ICARS) score was 38/100. No strength and sensory deficits were detected. Corticospinal signs were absent.

Routine blood tests showed only hyperglycaemia. Antinuclear and extractable nuclear antigen antibodies, anti-thyreoglobulin and anti-thyreoperoxidasis, anti-gliadin and anti-endomysium antibodies, thyroid hormones and inflammatory indices resulted negative. Vitamin E dosage was normal. Genetic analysis for the heritable forms of spinocerebellar ataxia (SCA 1, 2, 3, 6, 7 and 17) was normal. Cerebrospinal fluid (CSF) examination showed normal proteins and cells. However, a mild increased IgG index and few oligoclonal bands were detected. CSF and serum virology were also negative. Cytological analysis of CSF was negative. Anti-neuronal antibodies (anti-Hu, anti-Yo, anti-Ri, anti-CV2, anti-Tr, anti-amphiphysin) were absent. Increased titres of anti-GAD65-Ab (14.6 U/l; n.v., 1.5 U/l) were detected by radioimmunoassay (RIA) performed 3 months after the onset of symptoms. These titres normalised in a subsequent detection on both the serum and CSF sample, performed during hospitalisation after initiation of steroid treatment.

Total body PET and CT scan, and bone scintigraphy did not detect any malignancy. Brain and spine MRI with gadolinium excluded other inflammatory CNS disorders. Neurophysiological examination and magnetic stimulation were normal. The patient was treated with intravenous methylprednisolone (1000 mg/day for 5 consecutive days) followed by oral prednisone 25 mg/day for 2 months. On the second day of steroid treatment, a dramatic clinical improvement was observed, and the ICARS score was 29/100. One week after the beginning of treatment, the ICARS score was 22/100, slow gait was possible with a walker, and dysmetria was improved on the finger-to-nose test as well as diadochokinesis and dysarthria. After 40 days of oral prednisone (25 mg/day), the patient showed a further improvement in dysarthria, dysmetria and diadochokinesis. Writing and drawing the Archimedes spiral became normal. Interestingly, the patient showed an impressive improvement in trunk and gait ataxia in the capacity of walking without a walker and maintaining the Romberg position (ICARS score 19/100). A further clinical improvement (ICARS score 7/100) was observed 3 months later, when the patient was receiving 12.5 mg of oral prednisone therapy every other day. At this time, steroids were stopped without any change in the patient's clinical condition and at the last follow-up in December 2007.

The clinical course in relation to therapy is presented in fig 1.

Discussion

GAD-Ab are considered a marker of autoimmune diabetes, in which they can be found in patients' sera, sometimes before clinical onset. GAD-Ab have also been reported in a few cases of cerebellar ataxia,[1] even if their pathogenetic role remains unclear. In our case, we detected low levels of anti-GAD antibodies. These antibodies were absent in measurements performed after hospitalisation. Although anti-GAD antibodies were not highly positive, a diagnosis of anti-GAD cerebellar ataxia has been presumed, since it has already been shown that GAD-Ab can be undetected and can be absent or present at different times in the course of the disease.[5] This floating of antibody titres in the same patient may be related to a complex activation or suppression of auto-reactive immunity that could involve a cell-mediated immune response against GAD or other cerebellar antigens.[1] According to previous reports,[1] we believe that in our patient, the CSF inflammatory profile (mild increase in IgG index and presence of CSF oligoclonal bands) supports the hypothesis of a cerebellar specific inflammatory process, probably mediated by GAD-Ab. In fact, the persistence of CSF oligoclonal bands, even when the patient was anti-GAD-Ab-seronegative, may be a sign of an immunomediated mechanism possibly triggered by anti-GAD-Ab. From the analysis of the available literature on the treatment of anti-GAD cerebellar syndromes, we can argue that immunomodulating therapies could represent a possible treatment approach. High-dose intravenous immunoglobulins were not effective or induced only a transient improvement in few patients. Plasmapheresis does not seem to improve cerebellar dysfunction.

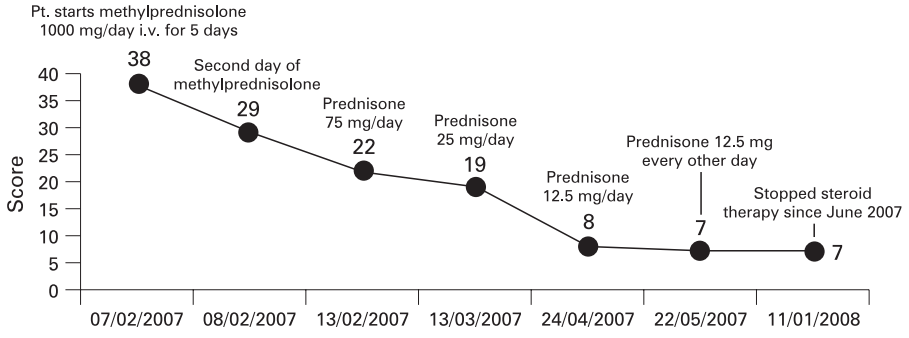

Figure 1 International Cooperative Ataxia Rating Scale score changes in response to therapy.

Indeed, two authors reported a good response to steroids in two cases with anti-GAD cerebellar ataxia.[4 5] Our case presented a sudden and consistent clinical response after lasting administration of corticosteroids, providing further evidence of the efficacy of this treatment and supporting the immunogenesis of the anti-GAD-Ab cerebellar syndrome.

R Virgilio,[1,2] S Corti,[1,2] P Agazzi,[3] D Santoro,[1,2] S Lanfranconi,[1] L Candelise,[1] N Bresolin,[1,2] G P Comi,[1,2] A Bersano[1]

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CORRECTION

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