Neuropsychological and behavioral function 23 years after mild traumatic brain injury
A comparison of outcome after pediatric and adult brain injuries

Erik Hessen, PhD
Department of Neurology
Akershus University Hospital
Oslo, Norway
Presentation based on three papers:


Introduction-mild traumatic brain injury (mTBI)

• Annual incidence of mTBI ranges from 100 to 550 per 100,000 (Duus et al., 1991; Evans, 1992; Thornhill et al., 2000 and Andersson et al., 2001).

• Estimates suggest 250 pediatric mTBI per 100,000 annually in the US (Kraus, 1995).

• 80-90% of all TBI classified as mild
Introduction - outcome after mTBI

• Acute cognitive problems common: processing speed, concentration, attention and memory. Usually recovery in 3 months (Dikmen et al., 1986; Levin et al., 1987 & Rutherford et al., 1978).

• Some patients experience cognitive and neurological symptoms long after mTBI (Dikmen et al., 1986; Nestvold et al., 1988 and Hartlage et al., 2001).

• Typical postconcussive complaints: headache, fatigue, dizziness, depression, anxiety, irritability, concentration and memory.

• Incidence of postconcussive syndrome varies across studies from 7-8% (Binder et al., 1997) to about 15% (Alexander, 1995).

• Etiology uncertain: both organic and psychological causes suggested (Miller, 1996; Hayes & Dixon, 1994; Bryant & Harvey, 1999; Lishman, 1988).
Acute brain disturbance in mTBI

- fMRI after one month show different patterns of regional brain activation in response to working memory loads compared with controls (McAllister et al., 1999).

- Positron emission tomography (PET) after one month show abnormalities specific to the injury (Bergsneider et al., 2000).

- PET abnormalities (cortical and global) not present in chronic postconcussional syndrome in which frontotemporal hypometabolism is seen (Ruff et al., 1994).

- This pattern not unique to brain injury - more common with depression (Dolan et al., 1994).
Neuropsychological outcome after adult mTBI

Several meta-analytic reviews published:

- **Binder et al. (1997)**: 8 studies at least 3 months post injury. Inclusion based on head trauma, not symptoms. Only measures of attention had an effect size greater than zero.

- **Zakzanis et al. (1999)**: 12 studies, both clinic-based and unselected samples included. Time since injury not specified. Effect sizes reported for all 7 cognitive domains included, largest effect for abstraction/flexibility.

- **Belanger et al. (2005)**: 39 unselected or prospective samples. Assessment of nine cognitive domains. No impairment by 3 months.
Long term neuropsychological outcome after adult mTBI

• Only few studies:

• Vanderploeg et al. (2005) examined outcomes of self reported mTBI 8 years postinjury in a non-referred sample of 254 male veterans:

• No group differences between this group or any of two control groups on a neuropsychological test battery.

• However, subtle attention problems compared with control groups: (i) lower rate of continuation to completion on Paced Auditory Serial Addition Test (PASAT) and (ii) excessive proactive interference on California Verbal Learning Test.

• Conclusion: mTBI can have adverse long-term neuropsychological outcomes on subtle aspects of complex attention and working memory.
Neuropsychological outcome after pediatric mTBI

No adverse effects on academic-psychosocial outcome or definite neuropsychological impairments.

However, increasing variability in neuropsychological outcome with increasing severity of mild TBI.

Differential outcome in pediatric TBI – depending on age at injury

- Academic achievement in children (5-15 years) from baseline to 5 years after mild to severe TBI (Ewing-Cobbs et al., 2004):
  1. Persistent deficit on all scores with severe TBI compared to mild/moderate TBI.
  2. Increased improvement in arithmetic and reading for children injured at older age - deceleration in growth for the younger children with both mild/moderate and severe TBI.

- Early traumatic brain injury vs. injuries later in childhood (Anderson et al. 2005):
  3. Age did not predict outcome with mild/moderate TBI - except poorer outcome for infants (between 0-2.11 years) with moderate TBI than older children with similar injuries.
Very long-term outcome after mild pediatric TBI:

- Only one previous study report on very long-term outcome (23 years) following mainly mTBI in children (Klonoff et al., 1993)

- Klonoff et al.:
- TBI determined by: Coma, neurological status, skull fracture, EEG, post-traumatic seizures and a composite measure.

- Outcome measures: Physical complaints, subjective intellectual function and psychological/psychiatric problems

- Results:
- A composite measure of neurological variables best predictor of long-term outcome
- IQ in the post–acute phase reliable predictor of long-term outcome
- Subjective sequelae within the outcome categories specified as due to the head injury reported by 31% of the sample
Why variable outcome in mTBI? Definition – a key problem

American Congress of Rehabilitation Medicine (1991). Includes a wide range of trauma variables and severity:

1. Any period of LOC of <30 minutes and Glasgow Coma Scale score (GCS) of 13-15 after this period of LOC

2. Any loss of memory for events immediately before or after the accident, with PTA of <24 hours

3. Any alteration in mental state at the time of the accident (e.g. feeling dazed, disoriented, or confused)

4. Focal neurological deficit(s) that may or may not be transient
Glasgow Coma Scale (GCS) definition of mild TBI

- Generally accepted definition is Glasgow Coma Scale (GCS) score of 13-15. **A definition without sufficient precision:**

- Heterogenity in pathophysiology is evident in patients with GCS 13-15:

- Studies show development of traumatic intracranial haematoma in 15-20% of patients with perfect GCS (Miller et al. 1990)

- One study reports intracranial abnormalities evidenced by pathological CT in 31% of patients with GCS 13-15 (Tellier et al. 1999)
Complicated and uncomplicated mTBI - a useful distinction
(Williams et al. 1990)

• **Brief description:**

• **Uncomplicated mild TBI:**
  1. GCS 13-15
  2. *Brief disruption of consciousness and/or brief PTA*
  3. *No evidence of intracranial brain pathology*
  4. Often excellent recovery

• **Complicated mild TBI:**
  1. GCS 13-15
  2. *Brief loss of consciousness and/or PTA<24 hours*
  3. *Abnormal neuroimaging, objective signs of brain pathology*
  4. Complicates understanding of recovery from mild TBI
Purpose of the present study

Investigate neuropsychological and behavioral function in patients 23 years after sustaining mainly mTBI. Questions asked:

1. Will the group show neuropsychological and behavioral function in the normal range?

2. Can diagnostic head injury variables predict differences in neuropsychological and behavioral function?

3. Can neuropsychological and behavioral function be explained by other variables like pre- and post traumatic illness?

4. Are children sustaining mild injuries more vulnerable to long-term neuropsychological problems than adults sustaining similar brain injuries?
Methods

- All patients referred to Akershus Central Hospital for a 12-month period (1974/75) due to injuries to the head, face or neck included in a prospective study (Nestvold and Lundar, 1988)

- **Standardized data-collection at admission:** About the accident, transport to hospital, clinical condition: Emphasis on coma and PTA.

- **Within first 24 hours:** neurological examination, information from patient/relatives about education, work, family, social relations, previous hospitalization, accidents and illness.

- Information from the National Insurance about previous sick leave and previous diagnosis.

- **Additional information:** intracranial hematomas, x-ray of the skull, face and cervical columna, standard EEG within the first 24 hours and length of hospitalization.

- 92% of the patients suffered mTBI with PTA < 24 hours.
Methods

• Patients still living in Oslo and Akershus (n=170) invited to a follow up study 23 years post injury. 70% (119 patients) accepted the invitation.

• Patients did not receive payment or any benefits for taking part in the study other than undergoing a neurological and a neuropsychological examination.

• None of the patients were compensation-seekers related to their TBI.

• Data also collected about possible confounding factors like pre- and post injury somatic health and mental health. In addition data were collected about highest level of education and current work status.
Neuropsychological assessment

- **Wechsler Adult Intelligence Scale (WAIS):**
  Information, Similarities, Digit Span, Picture Arrangement, Block Design and Digit Symbol

- **Wechsler Memory Scale-Revised (WMS-R):**
  Digit Span forward and backward, Visual Memory Span forward and backward, Logical Memory I and II and Visual Reproduction I and II

- **Halstead-Reitan Test Battery (HRB):**
  Category Test, Trail Making Test, Seashore Rhythm Test, Finger Tapping Test, Grooved Pegboard Test and Dynamometer Test

- **Scoring:**
  Test results converted to T-scores, a normally distributed scale with a mean score of 50 and standard deviation (SD) of 10.

- **Deficit Index:** Tests with a T-score 39 or below (impaired range) was given a score of 1 and tests with a T-score above 39 was given a score of 0 - resulting in a deficit index score ranging from 0 to 24 for each patient
Behavioral assessment

- **MMPI-2**: Behavioral function evaluated with The Norwegian Edition of The Minnesota Multiphasic Personality Inventory–2 (MMPI-2)

- **Norms**: Norwegian normative data

- **Scoring**: Test results converted to T-scores, a normally distributed scale with a mean score of 50 and standard deviation (SD) of 10

- **Postconcussional symptoms**: In addition to the 10 standard clinical scales, the other MMPI-2 scales chosen with emphasis on typical postconcussional symptoms like depression, anxiety and somatic complaints (Content scales and Harris-Lingoes subscales)
Testing and scoring procedures

- Testing conducted by an experienced specialist in clinical neuropsychology (EH).

- Information about head injury severity not revealed until after completion of examination and scoring.

- Two experienced specialists in clinical neuropsychology blinded to patient characteristics, checked the protocols independently to ensure correctness in scoring procedures.
### Demographic Variables

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>All patients (n=119)</th>
<th>Above 15 years at injury (n=74)</th>
<th>15 or below at injury (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at testing M (SD)</td>
<td>45.2 (14.6)</td>
<td>53.2 (13.0)</td>
<td>32.2 (3.4)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>47 (39%)</td>
<td>26 (35%)</td>
<td>21 (47%)</td>
</tr>
<tr>
<td>Education (yrs) M(SD)</td>
<td>12.1 (3.3)</td>
<td>11.3 (3.3)</td>
<td>13.3 (3.0)</td>
</tr>
<tr>
<td>Age at injury M (SD)</td>
<td>21.9 (14.4)</td>
<td>29.8 (12.8)</td>
<td>8.9 (3.4)</td>
</tr>
<tr>
<td>Disability benefit n (%)</td>
<td>5 (4%)</td>
<td>3 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Head injury variables</td>
<td>All patients (n=119)</td>
<td>Above 15 years at injury (n=74)</td>
<td>15 or below at injury (n=45)</td>
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<tr>
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<tr>
<td>PTA &gt; ½ hour n (%)</td>
<td>40 (34%)</td>
<td>25 (34%)</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>PTA &gt; 24 hours n (%)</td>
<td>9 (8%)</td>
<td>6 (8%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Skull fracture n (%)</td>
<td>10 (8%)</td>
<td>5 (7%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>2 or more path. neurol. signs first 24 hours n (%)</td>
<td>27 (23%)</td>
<td>15 (20%)</td>
<td>12 (27%)</td>
</tr>
<tr>
<td>EEG pathology first 24 hrs n (%)</td>
<td>60 (50%)</td>
<td>36 (49%)</td>
<td>24 (53%)</td>
</tr>
<tr>
<td>PTA &gt; ½ hour and EEG path. n (%)</td>
<td>27 (23%)</td>
<td>17 (23%)</td>
<td>10 (22%)</td>
</tr>
<tr>
<td>Headache first 24 hours n (%)</td>
<td>50 (42%)</td>
<td>27 (37%)</td>
<td>23 (51%)</td>
</tr>
</tbody>
</table>
### Pre- and post traumatic risk factors

<table>
<thead>
<tr>
<th>Pre-traumatic risk factors</th>
<th>All patients (n=119)</th>
<th>Above 15 years at injury (n=74)</th>
<th>15 or below at injury (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concussion n (%)</td>
<td>14 (12%)</td>
<td>9 (12%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Psychological or somatic illness n (%)</td>
<td>39 (33%)</td>
<td>30 (41%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Period with sick leave within 2 years before injury n (%)</td>
<td>27 (23%)</td>
<td>16 (22%)</td>
<td>11 (24%)</td>
</tr>
</tbody>
</table>

### Post-traumatic risk factors

| Concussion n (%)                                              | 6 (5%)               | 2 (3%)                          | 4 (9%)                      |
| No psychological or somatic illness n (%)                     | 67 (56%)             | 35 (47%)                        | 32 (71%)                    |
Overall results - neuropsychology

- Total study population, adult group and pediatric group:
- Mean group scores on all 24 subtests in the normal range
- Borderline results on the Category test (abstraction/concept formation) in all three groups: (Total: T=41.0, Adult: T=40.8, Pediatric: T=41.5)
- Number of subtests in impaired range (T ≤ 39) similar in all groups: (Total: 4.3, Adult: 4.4, Pediatric: 4.1)
Figure 1. Mean scores. Adult and pediatric group.
Overall results – MMPI-2 (Pediatric group)

- All mean T-scores in the normal range

- Only 2 of the scores deviate more than 5 points above normative mean: T=50:
  1. Mean score on the Hs-scale (Hypochondriasis-vague physical symptoms) $T= 56.8$ (SD: 12.1)
  2. Mean score on the D3 from Harris-Lingoes subscales (Physical Malfunctioning) $T=56.9$ (SD: 13.2)
MMPI-2
Clinical Scales - Pediatric group

All study patients
N=41
Influence of pre- and post injury risk factors on current neuropsychological and behavioral function

- Pre- and post injury risk factors:
  No significant relations were found between risk factors and current neuropsychological or behavioral function for the total sample or for the pediatric or the adult group
Influence of head injury variables on current neuropsychological and behavioral function

Neuropsychological function:

- Significant relations found only in the pediatric group for the variables (1) PTA $> 30$ min. and (2) a combination of PTA $> 30$ min. and path. EEG within 24 hours after TBI.
- Measures of attention, memory and the composite Deficit index score most sensitive to increased TBI severity

Behavioral function – pediatric group:

- (1) Skull fracture and (2) a combination of PTA $> 30$ min. and pathological EEG within 24 hours: significantly elevated MMPI-2 subscales.
- Elevated subscales: somatic complaints, fatigue, health worry and negative experience of work capability – typical postconcussive symptoms.
# Wechsler Memory Scale-R (WMS-R)

<table>
<thead>
<tr>
<th>Test</th>
<th>15 years and below Mean(SD) N=45</th>
<th>Amnesia &gt;30 min. N=15 Df: 43 n.s.</th>
<th>Amnesia &gt;30 min/path. EEG. N=10 n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Span: Forward</td>
<td>44.7(14.6)</td>
<td>47.3(14.5) 39.5(14.0)</td>
<td>46.7(13.9) 37.8(15.8)</td>
</tr>
<tr>
<td>Digit Span: Backward</td>
<td>48.5(14.3)</td>
<td>51.9(10.7) 41.7(18.3)*</td>
<td>51.1(10.8) 39.6(21.2)*</td>
</tr>
<tr>
<td>Visual Memory Span: Forward</td>
<td>51.8 (11.3)</td>
<td>54.3(8.3) 46.7(14.7)*</td>
<td>53.2(8.3) 46.7(18.1)n.s.</td>
</tr>
<tr>
<td>Visual Memory Span: Backward</td>
<td>52.5 (11.4)</td>
<td>54.8(9.3) 48.0(8.1)*</td>
<td>53.9(10.3) 47.6(9.6)n.s.</td>
</tr>
<tr>
<td>Logical Memory I</td>
<td>52.6 (10.6)</td>
<td>54.8 (9.3) 48.2(11.8)*</td>
<td>54.3(9.4) 46.6(12.6)*</td>
</tr>
<tr>
<td>Logical Memory II</td>
<td>52.8 (9.8)</td>
<td>54.8(9.2) 48.9(10.0)n.s.</td>
<td>54.4(8.9) 47.2(11.1) *</td>
</tr>
<tr>
<td>Visual Reproduction I</td>
<td>51.2(10.0)</td>
<td>53.5(9.4) 46.5(9.7)*</td>
<td>53.3(9.5) 43.8(7.9)**</td>
</tr>
<tr>
<td>Visual Reproduction II</td>
<td>49.0(10.6)</td>
<td>51.4(9.9) 44.3(10.6)*</td>
<td>50.7(9.9) 43.2(11.5)*</td>
</tr>
</tbody>
</table>

* p< .05  ** p< .01
Number of subtests out of 24 in the impaired range (T-score ≤ 39)

- **Pediatric group**
  - PTA>30 min (n=15)
  - PTA<30 min (n=30)
  - PTA>30 min & path EEG (n=10)
  - PTA<30 min & normal EEG (n=35)
  - P>0.021

- **Adult group**
  - PTA>30 min (n=25)
  - PTA<30 min (n=47)
  - PTA>30 min & path EEG (n=17)
  - PTA<30 min & normal EEG (n=55)
  - P>0.002

n.s.: not significant
Figure 4. PTA – Pediatric group

T-scores

PTA 0-30' (n=30)  
PTA > 30' (n=15)
PTA/pathological EEG – Pediatric group

T-scores

- PT A 0-30' & normal EEG (n=35)
- PT A > 30' & pathological EEG (n=10)
MMPI 2
Clinical Scales – T scores

No scull fract. N=35
Scull. Fract. N=4
MMPI 2
Harris-Lingoes subscales of selected somatic and depressive complaints – T scores


PTA<30 min/norm. EEG N=32  PTA>30 min/path. EEG N=8

0.005  0.046  0.033
Discussion 1

1. Pediatric mTBI variables (PTA > 30 minutes or a combination of PTA > 30 minutes and pathological EEG within 24 hours) - predicted poorer neuropsychological outcome after 23 years. No similar findings in the adult group.

2. Pediatric mTBI variables (Skull fracture and a combination of PTA > 30 minutes and pathological EEG within 24 hours) - predicted elevated subscales on the MMPI-2 - somatic complaints, fatigue, worry about health problems, negative experience of work capability.
Discussion 2

3. No pre- or post injury risk factors could explain neuropsychological or behavioral function

4. Patients with mild TBI 23 years ago had mean neuropsychological test scores and behavioral function in the normal range, average length of education and employment rate as expected for Norwegians
Discussion 3

- **Strengths:**
- Prospective longitudinal design
- Previous studies have not been able followed a sample of pediatric and adult mTBI for such long period and attain equally good retention rates
- Previous studies have not been able to demonstrate no differences between initial and follow up samples
- No other study of very long term outcome of mTBI have administered a comprehensive face-to-face neuropsychological battery or a comprehensive and psychometrically robust personality inventory
Limitations:

• Lack of a control group, substituted by standardized tests with two different sets of available normative data (Heaton, Grant & Matthews, 1991; Wechsler Memory Scale Revised, 1987).

• These and other US norms are used in clinical practice and research in Norway - and have been shown to compare well with neurologically normal Norwegians (Lund et al., 2005, Egeland et al., 2005, Egeland et al., 2006).
Discussion 5

• Study initiated before introduction of the Glasgow Coma Scale (GCS) and head injury severity was determined by length of PTA.

• It may thus be unclear if the sample meet the current criteria for mTBI with a GCS-score of 13-15.

• However, GCS not designed to measure the milder types of injury, and is not sensitive in mild injury (Rees, 2003).

• Of note, in mild TBI clinical outcome has been found to correlate better with PTA than GCS (Dikmen & Levin, 1993; van der Naalt et al., 1999; van der Naalt et al., 1999).

• On this basis it has recently been suggested to use of PTA as a severity measure for the milder degrees of injury (Rees, 2003).
Discussion 6

• The study conducted before neuroimaging was available

• Even today neuroimaging is only employed clinically in a small proportion of TBI presentations

• Several patients would probably have shown evidence of neuropathology and comparison of neuropsychological function with neuroimaging would have been of particular interest

• However, the strength of the study is the longitudinal design, and the representative nature of the sample, not previously available in the literature.
Conclusions 1

• A good overall outcome was found 23 years after both pediatric and adult mTBI.

• Cognitive and behavioral function was in the normal range, the patients had average length of education and a lower percentage of the patients were on disability benefit than normally expected.

• Children with complicated mild head injuries had poorer neuropsychological outcome than adults with similar brain injuries and similar demographic characteristics.

• The findings suggest a greater vulnerability of the younger brain, even after a mild insult.
Conclusions 2

• The results support the notion of potentially differential impact of uncomplicated versus complicated mild traumatic brain injury.

• The findings suggest that children with complicated mTBI should be regarded at potential risk of developing chronic mild neuropsychological dysfunction.

• These children may need to be monitored during childhood and adolescence about potential problems that should be addressed for optimal development.

• Functions like attention, learning and memory may be at particular risk of subnormal development.
Future perspectives

- Possibility of persistent cognitive and postconcussive symptoms after pediatric complicated mTBI calls upon further studies

- This group never followed in a prospective, controlled and longitudinal study with current diagnostic criteria of mTBI, current neurodiagnostic technology, and cognitive/behavioural measures

- If present findings are possible to replicate, this ought to have consequences for diagnostic practice, and for treatment/rehabilitation of a large group of children:

  - First, it should provoke a reevaluation of the diagnostic practice of pediatric mTBI

  - Second, it will necessitate better monitoring of children with complicated mTBI regarding prevention/treatment of possible cognitive and behavioural problems