Pituitary Complications in Traumatic Brain Injury

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Conflict of interest

• None from pharmaceutical companies

• Granting agencies
  Career Award from FRQS
  Operating grants from CIHR and FRQS
Objectives

• Describe the **pathophysiology** of pituitary complications in traumatic brain injuries (TBI)

• Review the current literature regarding the **prevalence, predictors** and **clinical impacts** of pituitary complications in this population

• Present the objectives of the **PIT-TBI pilot study**
Where this idea is coming from?

Acquired growth hormone deficiency and hypogonadotropic hypogonadism in a subject with repeated head trauma, or Tintin goes to the neurologist

43 concussions
Delayed growth
Delayed onset of puberty
Lack of libido

Cyr A et al., CMAJ 2004;171:1433-4
Post-mortem lesions

50 %

Microhemorrhages of the hypothalamus

Anterior pituitary infarct

Compton R, *Brain* 1971;94:165-72
Daniel PM et al., *J Pathol* 1973;111:135-8
Early MRI:
Abnormal findings in 30%

Late MRI:
Decreased in pituitary size

Maiya B et al., *Intens Care Med* 2008;34:468-75
Apparent Diffusion Coefficient

ADC at 2 weeks might be associated with pituitary disorders at 6 months

Zheng P et al., *J Neurosurg* 2015;123:75-80
Auto-immunity?

- 25 patients from 1 center
- 50 % with pituitary disorder at 1 year
- No antibodies in non-TBI pts
- Anti-hypothalamus antibodies
  - In 71 % of pts with pituitary disorders (vs. 17%)
- Anti-pituitary antibodies
  - In 80 % of pts with pituitary disorders (vs. 20%)

Tanriverdi F et al., *J Neurotrauma* 2013;30:1426-33
Genotype APO E3/E3?

Protecting effect?
Odds ratio: 0.3 (95% CI 0.11-0.78)

Tanriverdi F et al., J Neurotrauma 2008;25:1071-7
What is the real prevalence of pituitary disorders following TBI?
Clinical Outcomes, Predictors, and Prevalence of Anterior Pituitary Disorders Following Traumatic Brain Injury: A Systematic Review

François Lauzier, MD, MSc¹,²,³; Alexis F. Turgeon, MD, MSc¹,²; Amélie Boutin, MSc¹; Michèle Shemilt, BSc¹; Isabelle Côté, MD¹,³; Olivier Lachance¹; Patrick M. Archambault, MD, MSc¹,²,⁴,⁵; François Lamontagne, MD, MSc⁶; Lynne Moore, PhD¹,⁷; Francis Bernard, MD⁸,⁹; Claudia Gagnon, MD³,¹⁰; Deborah Cook, MD, MSc¹¹,¹²

(Crit Care Med 2014; 42:712–721) March 2014 • Volume 42 • Number 3
Systematic search

**Inclusion criteria**
- Any study design including at least 5 TBI adults for whom at least one pituitary axis was assessed

**Exclusion criteria**
- No control group, mixed population with no distinction of patients with other acute neurological conditions

**13,559 records reviewed**
- 66 articles included for prevalence
- 27 articles included for predictors
- 14 articles for clinical outcomes

Lauzier F et al., *Crit Care Med* 2014;42:712-21
Low risk of bias if

- Description of inclusion/exclusion criteria (56% of studies)
- No voluntary sampling (24% of studies)
- Description of diagnostic criteria
- > 90% of eligible patients underwent appropriate diagnostic testing

Risk of bias evaluated for each pituitary axis and each time-frame

Lauzier F et al., *Crit Care Med* 2014;42:712-21
At least one pituitary deficit

Around 30% at one year
Growth hormone deficit

Around 15% at one year

<table>
<thead>
<tr>
<th></th>
<th>Acute phase (&lt;3 months)</th>
<th>Mid term (3-12 months)</th>
<th>Long term (&gt;12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies including &lt;10% mild TBI</td>
<td>6 (572)</td>
<td>13 (898)</td>
<td>25 (2024)</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 96.2%$</td>
<td>$I^2 = 73.9%$</td>
<td>$I^2 = 88.3%$</td>
</tr>
<tr>
<td>Studies at low risk of bias</td>
<td>5 (423)</td>
<td>6 (384)</td>
<td>17 (1390)</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 96.2%$</td>
<td>$I^2 = 0%$</td>
<td>$I^2 = 77.8%$</td>
</tr>
<tr>
<td>Studies including &lt;10% mild TBI and at low risk of bias</td>
<td>3 (287)</td>
<td>6 (384)</td>
<td>13 (1195)</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 98.0%$</td>
<td>$I^2 = 0%$</td>
<td>$I^2 = 78.8%$</td>
</tr>
<tr>
<td>All studies</td>
<td>10 (957)</td>
<td>16 (1103)</td>
<td>35 (2716)</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 93.5%$</td>
<td>$I^2 = 76.0%$</td>
<td>$I^2 = 88.4%$</td>
</tr>
</tbody>
</table>
Hypogonadism

Around 10% at one year

<table>
<thead>
<tr>
<th></th>
<th>Acute phase (&lt;3 months)</th>
<th>Mid term (3-12 months)</th>
<th>Long term (&gt;12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies including &lt;10% mild TBI</td>
<td>8 (614) ( I^2 = 97.6% )</td>
<td>13 (963) ( I^2 = 79.7% )</td>
<td>22 (1812) ( I^2 = 85.1% )</td>
</tr>
<tr>
<td>Studies at low risk of bias</td>
<td>6 (444) ( I^2 = 96.0% )</td>
<td>7 (328) ( I^2 = 84.0% )</td>
<td>15 (1013) ( I^2 = 78.1% )</td>
</tr>
<tr>
<td>Studies including &lt;10% mild TBI and at low risk of bias</td>
<td>4 (321) ( I^2 = 95.4% )</td>
<td>6 (276) ( I^2 = 81.7% )</td>
<td>11 (818) ( I^2 = 85.9% )</td>
</tr>
<tr>
<td>All studies</td>
<td>13 (1051) ( I^2 = 96.3% )</td>
<td>16 (1168) ( I^2 = 76.9% )</td>
<td>31 (2482) ( I^2 = 87.4% )</td>
</tr>
</tbody>
</table>
Adrenal failure

Around 7% at one year

<table>
<thead>
<tr>
<th></th>
<th>Acute phase (&lt;3 months)</th>
<th>Mid term (3-12 months)</th>
<th>Long term (&gt;12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies including &lt;10% mild TBI</td>
<td>25 (1985)</td>
<td>11 (738)</td>
<td>9 (847)</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 92.7%$</td>
<td>$I^2 = 87.9%$</td>
<td>$I^2 = 92.4%$</td>
</tr>
<tr>
<td>Studies at low risk of bias</td>
<td>7 (646)</td>
<td>4 (270)</td>
<td>14 (1179)</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 93.8%$</td>
<td>$I^2 = 92.2%$</td>
<td>$I^2 = 84.9%$</td>
</tr>
<tr>
<td>Studies including &lt;10% mild TBI and at low risk of bias</td>
<td>6 (646)</td>
<td>3 (218)</td>
<td>11 (575)</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 94.6%$</td>
<td>$I^2 = 94.8%$</td>
<td>$I^2 = 84.5%$</td>
</tr>
<tr>
<td>All studies</td>
<td>33 (2513)</td>
<td>14 (943)</td>
<td>13 (1211)</td>
</tr>
<tr>
<td></td>
<td>$I^2 = 90.0%$</td>
<td>$I^2 = 84.6%$</td>
<td>$I^2 = 91.2%$</td>
</tr>
</tbody>
</table>
Hypothyroidism

Around 4% at one year
Could some predictors help to inform targeted screening?
### TBI severity

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-mild TBI</th>
<th>Mild TBI</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pituitary disorders</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Aimaretti 2005</td>
<td>9</td>
<td>37</td>
<td>27.8%</td>
<td>1.15 [0.48, 2.73]</td>
</tr>
<tr>
<td>Bondanelli 2004</td>
<td>21</td>
<td>34</td>
<td>41.3%</td>
<td>1.65 [0.83, 3.27]</td>
</tr>
<tr>
<td>Kelly 2000</td>
<td>8</td>
<td>19</td>
<td>3.4%</td>
<td>3.40 [0.24, 47.76]</td>
</tr>
<tr>
<td>Klose 2007</td>
<td>14</td>
<td>60</td>
<td>11.2%</td>
<td>5.13 [1.23, 21.44]</td>
</tr>
<tr>
<td>Klose 2007b</td>
<td>5</td>
<td>24</td>
<td>3.0%</td>
<td>10.12 [0.59, 173.06]</td>
</tr>
<tr>
<td>Tanturri 2008</td>
<td>4</td>
<td>11</td>
<td>13.4%</td>
<td>2.50 [0.63, 8.45]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>185</strong></td>
<td></td>
<td></td>
<td><strong>1.91 [1.17, 3.13]</strong></td>
</tr>
</tbody>
</table>

Total events: 185

Heterogeneity: Tau² = 0.03; Chi² = 5.39, df = 5 (P = 0.37); I² = 7%

Test for overall effect: Z = 2.59 (P = 0.010)

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### Skull fracture

<table>
<thead>
<tr>
<th>Study</th>
<th>Skull fracture</th>
<th>No skull fracture</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pituitary disorders</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Bavisetty 2008</td>
<td>9</td>
<td>31</td>
<td>13.9%</td>
<td>1.89 [0.75, 4.73]</td>
</tr>
<tr>
<td>Bondanelli 2004</td>
<td>6</td>
<td>12</td>
<td>18.1%</td>
<td>0.90 [0.48, 1.71]</td>
</tr>
<tr>
<td>Kelly 2000</td>
<td>6</td>
<td>13</td>
<td>15.8%</td>
<td>0.92 [0.42, 2.03]</td>
</tr>
<tr>
<td>Krahalik 2010</td>
<td>7</td>
<td>10</td>
<td>17.7%</td>
<td>4.61 [2.38, 8.92]</td>
</tr>
<tr>
<td>Richard 2001</td>
<td>5</td>
<td>10</td>
<td>15.6%</td>
<td>2.42 [1.09, 5.37]</td>
</tr>
<tr>
<td>Wachter 2009</td>
<td>8</td>
<td>13</td>
<td>19.0%</td>
<td>1.54 [0.87, 2.75]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>89</strong></td>
<td></td>
<td></td>
<td><strong>1.73 [1.03, 2.91]</strong></td>
</tr>
</tbody>
</table>

Total events: 74

Heterogeneity: Tau² = 0.29; Chi² = 15.96, df = 5 (P = 0.007); I² = 69%

Test for overall effect: Z = 2.06 (P = 0.04)

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### Brain edema on CT

<table>
<thead>
<tr>
<th>Study</th>
<th>Brain edema on CT</th>
<th>No brain edema on CT</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pituitary disorders</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Agha 2004</td>
<td>9</td>
<td>13</td>
<td>27.2%</td>
<td>0.98 [0.66, 1.44]</td>
</tr>
<tr>
<td>Bavisetty 2008</td>
<td>13</td>
<td>41</td>
<td>19.9%</td>
<td>4.60 [1.12, 18.84]</td>
</tr>
<tr>
<td>Kelly 2000</td>
<td>8</td>
<td>15</td>
<td>11.1%</td>
<td>8.50 [0.56, 129.42]</td>
</tr>
<tr>
<td>Krahalik 2010</td>
<td>8</td>
<td>10</td>
<td>25.9%</td>
<td>5.75 [3.06, 10.79]</td>
</tr>
<tr>
<td>Wachter 2009</td>
<td>1</td>
<td>11</td>
<td>15.9%</td>
<td>0.32 [0.05, 2.19]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>39</strong></td>
<td></td>
<td></td>
<td><strong>2.24 [0.69, 7.23]</strong></td>
</tr>
</tbody>
</table>

Total events: 88

Heterogeneity: Tau² = 1.28; Chi² = 28.71, df = 4 (P < 0.000001); I² = 86%

Test for overall effect: Z = 1.35 (P = 0.18)
Do pituitary disorders really affect TBI outcomes?
### Pituitary disorders vs. No pituitary disorders

<table>
<thead>
<tr>
<th>Study</th>
<th>Death</th>
<th>Total</th>
<th>Death</th>
<th>Total</th>
<th>Weight</th>
<th>M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimopoulou 2004</td>
<td>4</td>
<td>18</td>
<td>0</td>
<td>16</td>
<td>4.0%</td>
<td>8.05 [0.47, 138.87]</td>
</tr>
<tr>
<td>Krahulik 2010</td>
<td>32</td>
<td>98</td>
<td>22</td>
<td>88</td>
<td>45.3%</td>
<td>1.31 [0.82, 2.07]</td>
</tr>
<tr>
<td>Llompart–Pou 2008</td>
<td>8</td>
<td>39</td>
<td>19</td>
<td>126</td>
<td>31.2%</td>
<td>1.36 [0.65, 2.86]</td>
</tr>
<tr>
<td>Matsuura 1985</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>30</td>
<td>19.5%</td>
<td>4.23 [1.40, 12.73]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>45</td>
<td>156</td>
<td>46</td>
<td>260</td>
<td><strong>100.0%</strong></td>
<td><strong>1.79 [0.99, 3.21]</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Tau² = 0.14; Chi² = 5.17, df = 3 (P = 0.16); I² = 42%

**Test for overall effect:** Z = 1.94 (P = 0.05)

---

### GOS score comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean GOS</th>
<th>SD</th>
<th>Total</th>
<th>Mean GOS</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bondanelli 2004</td>
<td>4.5</td>
<td>0.5</td>
<td>27</td>
<td>4.4</td>
<td>0.5</td>
<td>23</td>
<td>35.5%</td>
<td>0.10 [−0.18, 0.38]</td>
</tr>
<tr>
<td>Jeong 2010</td>
<td>2.86</td>
<td>0.75</td>
<td>17</td>
<td>3.37</td>
<td>0.75</td>
<td>48</td>
<td>32.9%</td>
<td>−0.51 [−0.92, −0.10]</td>
</tr>
<tr>
<td>Krahulik 2010</td>
<td>4</td>
<td>1</td>
<td>19</td>
<td>5</td>
<td>0.667</td>
<td>70</td>
<td>31.6%</td>
<td>−1.40 [−1.48, −0.52]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>63</strong></td>
<td></td>
<td><strong>141</strong></td>
<td><strong>114</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>−0.45 [−1.10, 0.20]</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Tau² = 0.29; Chi² = 17.12, df = 2 (P = 0.0002); I² = 88%

**Test for overall effect:** Z = 1.35 (P = 0.18)
Could hormonal replacement therapy improve outcomes?
Low doses of corticosteroids in the acute phase?

HR for pneumonia: 0.75, 95% CI 0.55-1.03

Hydrocortisone 200 mg die for 7 days, 100 mg for 2 days, 50 mg for 1 day + fludrocortisone

Asehnoune K et al., Lancet Respir Med 2014; 2: 706–16
The primary end point, the GOS score at 6 months, did not differ significantly between the progesterone group and the placebo group (Table 2). The proportional-odds model revealed no effect of progesterone treatment in either unadjusted or adjusted analyses (adjusted odds ratio, 0.96; 95% confidence interval [CI], 0.77 to 1.18).

After the second interim analysis, the trial was stopped because of futility. For the primary hypothesis comparing progesterone with placebo, favorable outcomes occurred in 51.0% of patients assigned to progesterone and in 55.5% of those assigned to placebo.
Growth hormone in the chronic phase?

Level of evidence

• 1 RCT (n=21)$^1$

Modest improvement in processing speed

$^1$High Jr. WM et coll, *J Neurotrauma* 2010;27:1565-75
Growth hormone in the chronic phase?

Level of evidence
- 1 RCT (n=21)\(^1\)
- 1 non randomized study including some patients with no GH deficit (n=50)\(^2\)

Modest improvement in quality of life

\(^1\)High Jr. WM et coll, J Neurotrauma 2010;27:1565-75
\(^2\)Moreau OK et coll, J Neurotrauma 2013;30:998-1006
Growth hormone in the chronic phase?

Level of evidence

- 1 RCT (n=21)<sup>1</sup>
- 1 non randomized study including some patients with no GH deficit (n=50)<sup>2</sup>
- Case series (n=161)<sup>3</sup>

Modest improvement in quality of life

<sup>1</sup>High Jr. WM et coll, *J Neurotrauma* 2010;27:1565-75
<sup>2</sup>Moreau OK et coll, *J Neurotrauma* 2013;30:998-1006
Growth hormone in the chronic phase?

Level of evidence
• 1 RCT (n=21)¹
• 1 non randomized study including some patients with no GH deficit (n=50)²
• Case series (n=161³, n =11⁴)

Modest improvement in intelligence quotient

¹High Jr. WM et coll, *J Neurotrauma* 2010;27:1565-75
Growth hormone in the chronic phase?

Level of evidence

- 1 RCT (n=21)\(^1\)
- 1 non randomized study including some patients with no GH deficit (n=50)\(^2\)
- Case series (n=161\(^3\), n =11\(^4\))

Ready for an RCT?
A sufficiently powered RCT to assess the effect of GH on neurological prognosis or depression risk would cost more than $3 millions

\(^1\)High Jr. WM et coll, *J Neurotrauma* 2010;27:1565-75
\(^2\)Moreau OK et coll, *J Neurotrauma* 2013;30:998-1006
\(^3\)Gardner CH et coll, *Eur J Endocrinol* 2015;172:371-81
### Why the PIT-TBI study is needed now?

Additive contribution of pituitary disorders to the debilitating symptoms experienced by TBI survivors?

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>TBI¹,²</th>
<th>Hypothyroidism³</th>
<th>Growth hormone deficit⁴,⁵</th>
<th>Hypogonadism⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>45-50 %</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Insomnia</td>
<td>25-35 %</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Memory</td>
<td>45-50 %</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Concentration</td>
<td>35-50 %</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Irritability</td>
<td>40-50 %</td>
<td></td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Depression</td>
<td>50 %</td>
<td>✓</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

¹Hellawell DJ et al., *Brain Injury* 1999;171:489-504
²Bombardier CH et al., *JAMA* 2010; 303:1938-45
³Samuels MH et al., *Curr Opin Endocrinol Diabetes Obes* 2014;21:377-83
⁵Morselli, LL et al., *Eur J Endocrinol* 2013;168:763-70
⁶Bhasin S et al., *J Clin Endocrinol Metab* 2010;95:2536-59
The PIT-TBI study: Study population

- 70 patients in 6 Level-1 Canadian ICU

Inclusion criteria
- Adults, moderate/severe blunt TBI, ICU ≤ 48 hours

Exclusion criteria
- Known hypopituitarism, pregnant or lactating women
- Brain death or not committed to aggressive care
- Significant altered life-expectancy at 12 months
- Neurological conditions influencing functional status assessment
- 12-month follow-up visit unlikely (no fixed address, unable to return to the study center)

ClinicalTrials.gov Identifier: NCT02480985
Course of the PIT-TBI study

ICU admission

Eligibility assessment

Consent

Data collection

Recruitment

Secondary insults

Hormone levels and biobank at D1, 3 and 7

Pituitary MRI D7

Early pituitary disorders

Late/persistent pituitary disorders

Hospital discharge

Prognosis (e GOS)

Functional status (FIM)

Quality of life (EQ-5D)

Depression (PHQ-9)

6 and 12 months follow-up
Assessment of pituitary function

**Pituitary axis**

- **Thyroid**
  - Static testing: TSH, FT4, T3

- **Sexual hormones**
  - Static testing: FSH/LH, estradiol or testo

- **Adrenals**
  - Dynamic testing: ACTH 1 mcg

- **Growth hormone**
  - Dynamic testing: Glucagon 1 mg
Conclusions

- TBI represents a significant socioeconomic burden
- A modest improvement of symptoms could have a significant impact
- The association between pituitary function and outcome is unclear
- **If there is no independent association:** no need for screening
- **If there is an independent association:** RCTs