Children after Traumatic Brain Injury (with answers)

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Hormone deficiencies after TBI

- Risk for pituitary deficiencies
  - Not correlated with severity of injury
  - May be increased after intracranial hemorrhage or skull fracture
- Hypopituitarism may impair recovery after TBI
- Identification & therapy of endocrine deficiencies can improve course of rehabilitation & enhance QoL
- Assessment of GH, ACTH, & TSH requires serial testing
- Need close liaison between endocrine, rehabilitation, & neurosurgical services
Hormone deficiencies after TBI

- Variable time of onset of endocrinopathy—most within first year
- Little association among severity of TBI, symptoms, and hormone problems
- May be transient, evolving, or permanent
  - Acute deficiency (3 month) is likely to resolve
  - Total hypopituitarism is likely permanent
- Signs & symptoms of hormone deficiency are often unrecognized
- IGF-1 levels poor predictor of GHD
- GHD is most common deficiency followed by pubertal alterations
- TBI survivors should be evaluated at 6m, 12m, & yearly after injury
  - Follow height every 6 months

Reimunde 2011, High 2010
Glasgow Coma Scale

- Generally, brain injury is classified as
  - Severe, GCS <8; Moderate, GCS 9-12; Minor, GCS ≥13

- Eye Opening Response
  - Spontaneous--4 points
  - To verbal stimuli--3 points
  - To pain only--2 points
  - No response--1 point

- Verbal Response
  - Oriented--5 points
  - Confused, but answers questions--4 points
  - Inappropriate words--3 points
  - Incomprehensible speech--2 points
  - No response--1 point

- Motor Response
  - Obey commands to move--6 points
  - Purposeful movement to pain--5 points
  - Withdraws to pain--4 points
  - Flexion to pain (decorticate)--3 points
  - Extension to pain (decerebrate)--2 points
  - No response--1 point
# Evolving state after injury

## INJURY
**(Focal, Diffuse, Rotational, Penetrating, and Shearing)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Systemic Impact</th>
<th>Local Impact</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary injury</strong></td>
<td></td>
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</table>
| seconds to minutes | **Vascular Compromise / Hemorrhage**  
- critical nutrient compromise  
- iron release  
**Diffuse Axonal Injury (DAI)**  
- axonal stretching and tearing (acute)  
- synapse loss  
**Cellular Injury**  
- depolarization  
- calcium influx  
- glutamate release  
- oxidative stress (ROS)  
- mitochondrial dysfunction  |  |
| **Secondary injury** |  |  |
| hours to days | **Ischemia**  
- direct vascular injury leads to decreased cerebral blood flow  
**Swelling / Edema**  
- decreased cerebral blood flow via vascular compression  
**Inflammation**  
- contributes to edema  
- induces apoptosis (chronic)  
**Cellular Dysfunction**  
- neuronal cell loss (acute)  
- axonal degeneration  |  |
| weeks to months | **Neuroplasticity**  
- remodeling  
- inversely related to age  
- directly related to mental and physical health  
**Neuroplasticity**  
- remodeling  
- inversely related to age  
- directly related to mental and physical health  
**Neurological / Behavioral Compromise**  
- neurocognitive dysfunction  
**Cell Death / Apoptosis**  
- induced apoptosis  
- axonal degeneration  
- hormonal dysfunction  |  |
| months to years |  |  |

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**Figure 1**
Hypophyseal portal vessels supply pituitary with small perforating vessels, susceptible to shearing

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Clinical Characteristics of TBI survivors

<table>
<thead>
<tr>
<th>Age (mean)</th>
<th>Gender</th>
<th>Cause of Injury</th>
<th>GCS</th>
<th>CNS Imaging</th>
<th>Skull Fracture</th>
<th>Length of ICU stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>9yrs 10mos</td>
<td>M 12</td>
<td>MVA 4 Fall 4 MVA-Ped 3 Sports 1</td>
<td>≤8 (66%) 9-13 (33%)</td>
<td>FBI (42%) DBI (50%) CE (25%) ICP/-otomy (25%)</td>
<td>25%</td>
<td>8 days</td>
</tr>
<tr>
<td>12yrs 4mos</td>
<td>F 8</td>
<td>MVA 5 Fall 2 MV-Ped 1</td>
<td>≤8 (100%) 9-13 (0%)</td>
<td>FBI (38%) DBI (63%) CE (13%) ICP/-otomy (13%)</td>
<td>38%</td>
<td>12 days</td>
</tr>
</tbody>
</table>

MVA = Motor Vehicle Accident; FBI = Focal Brain Injury; DBI = Diffuse Brain Injury; CE = Cerebral Edema
Kaulfers 2010
Endocrinopathies after accidental TBI

Kaulfers 2010

The diagram shows the percentage of patients with various endocrine disorders after accidental TBI. The x-axis represents different endocrine disorders: ADH, Thyroid, Puberty, Prolactin, Growth, Adrenal, and Total. The y-axis represents the percentage of patients.

- **Baseline** (blue bars)
- **3 months** (red bars)
- **6 months** (green bars)
- **12 months** (purple bars)

The total percentage of patients with endocrine disorders ranges from 0 to 80%.
Case 1--Hemorrhage

- Julia, age 13y, is riding her bicycle down a hill when a car door opens in front of her stopping her bike. She tumbles over the car door, landing on pavement.
- She is unconscious after the collision.
- When the ambulance arrives, she is awake but confused, then becomes unarousable in transport.
- She is intubated, hyperventilated, and admitted to the ICU.
- Imaging shows subarachnoid hemorrhage.

---What is her Glasgow Coma Scale (GCS) at hospital arrival?

<3, 4-8, >8-12, >13
Case 1--Hemorrhage

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  <3, 4-8, >8-12, >13
Case 1

- What hormones will be elevated in the first few days?

- What hormones will be low in the first few days to weeks?

- What endocrine-related monitoring should be done in the ICU?
Case 1

- What hormones will be elevated in the first few days?
  (cortisol, prolactin)

- What hormones will be low in the first few days to weeks?
  (GH, estrogen, TSH)

- What endocrine-related monitoring should be done in the ICU?
  (Is/Os)
Case 1—1 week

- One week after her IBI, she has her first menses.

- What is likely to be the cause of this timing?

- What is likely to happen to her periods during the coming year?
One week after her IBI, she has her first menses.

What is likely to be the cause of this timing? (estrogen withdrawal in critical injury)

What is likely to happen to her periods during the coming year? (no periods for 6 months, then return to normal)
Case 1—3 months

- What hormone assessment is needed by 3 months?

- When should she undergo further endocrine screening?

- What are her chances of persistent endocrine deficiency?
Case 1—3 months

- What hormone assessment is needed by 3 months? (cortisol, thyroid, growth hormone, puberty)
- When should she undergo further endocrine screening? (6m, 1y, including measurements of height)
- What are her chances of persistent endocrine deficiency? (>25%)
At one year after injury, she has normal monthly menses.

Routine screening shows an elevated prolactin, and low Free T4 without TSH elevation.

AM to PM TSH ratio is <1.3.

She is identified to have central hypothyroidism and is started on thyroid hormone therapy.
Case 2--Concussion

- Derrick, age 6y, is playing on monkeybars at the playground a block from home with friends.
- He walks home stating that his head hurts.
  - He does not remember what happened.
  - He has bruising of the right side of his head and forehead and right shoulder.
- His headache gets worse and he is taken to the ED.
- Imaging of the head and neck is normal and he is sent home with head checks overnight.

- --What is his GCS in the ED?
  - ≤3, 4-8, >8-12, >13
Case 2--Concussion

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- Imaging of the head and neck is normal and he is sent home with head checks overnight.

- What is his GCS in the ED?
  - ≤3, 4-8, >8-12, >13
Case 2—first month

- For the next two weeks, he has difficulty focusing on his work at school and newly requires naps. He has repeated headaches but with gradual improvement.
- By 4 weeks after the concussion he is back to normal.

- --What endocrine monitoring should he have?
- --Why should he have any monitoring?
- --What are his chances of persistent endocrine deficiency?

--What different endocrine risk does he have from Julia’s case?
Case 2—first month

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- By 4 weeks after the concussion he is back to normal.

- --What endocrine monitoring should he have?
  (careful follow up of height, growth rate, timing of puberty)
- --Why should he have any monitoring?
  (endocrine disruption is not entirely correlated with severity)
- --What are his chances of persistent endocrine deficiency?
  (5-10%)
- --What different endocrine risk does he have from Julia’s case?
  (precocious puberty)
Case 2—1 year

- At age 7y, he has an excellent growth rate
- However, parents report that he has been moody and has been having body odor and acne
- Physical examination shows Tanner 2 pubic hair, mid-pubertal phallus, and 12 mL testes
- Bone maturation (BA) is consistent with 9 years at 7y of age
- GnRH agonist (GnRHa) therapy is started with decreased symptoms
- BA stops advancing
Case 2—3 years

- On GnRHa therapy, growth velocity slows and nearly stops.
- At age 9y, testing shows growth hormone deficiency (GHD).
- He is started on GH therapy.
Case 3--Skull fracture

Jamal, age 10y, is an unrestrained passenger in back seat in an auto accident, and is thrown through the windshield.

He is unconscious and transported to the hospital.

Imaging shows areas of shearing in the brain, and parietal skull and cervical fractures.

In the first 24 hours in the ICU, he does not urinate and his sodium drops to 122.

--What is his GCS at hospital arrival?
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Case 3—1\textsuperscript{st} week

- What is the reason for his low sodium?
- What is his urine output likely to be in the next few days?
- Is this a permanent deficiency?
- What hormone assessment is needed by 3 months?
Case 3—1\textsuperscript{st} week

- What is the reason for his low sodium? (SIADH)
- What is his urine output likely to be in the next few days? (polys/ DI)
- Is this a permanent deficiency? (unknown, requires follow up)
- What hormone assessment is needed by 3 months? (cortisol, thyroid, growth hormone, puberty)
Case 3—3 months

- His DI resolves by 2 months after injury.
- He is found to have low cortisol response to ACTH.
- He is started on replacement hydrocortisone (10 mg/m2/day, divided into 2 or 3 doses).

--When he requires surgery, what hormone treatment is needed?
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- When he requires surgery, what hormone treatment is needed?
  
  (stress dosing of hydrocortisone)
Case 3—follow up

- When should he undergo further endocrine screening?
- What are his chances of persistent endocrine deficiency?
Case 3—follow up

- When should he undergo further endocrine screening? (6m, 1y, including measurements of height)
- What are his chances of persistent endocrine deficiency? (>25%)
At 1y after injury, his growth rate is slow.
Thyroid and growth hormone screening are normal.
Subsequent growth rate is normal.

He is tapered off hydrocortisone at one year to allow re-evaluation.
Cortisol response to low dose ACTH stimulation test continues to be low.
He resumes hydrocortisone replacement, along with stress dosing.
Case 4--Inflicted

Erin, age 6 months, is fussy and not eating, so mother brings her to the ED.

- On exam, her fontanel is firm and full, and she cries when her left leg is touched.
- She has retinal hemorrhage.
- Skeletal survey shows several healing fractures of varying age.
- CNS imaging show bilateral subdural hematomas.
- Findings are consistent with repeated inflicted injury.
- She is admitted to the hospital.

--What would be her GCS at arrival in the ED (if someone thought of doing it)?
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Case 4—1st week

- What endocrine tests should be done on admission?
- What endocrine monitoring should be done?
- What are her chances of persistent endocrine deficiency?
Case 4—1st week

- What endocrine tests should be done on admission? (electrolytes, cortisol, TSH, free T4, prolactin, Is + Os)
- What endocrine monitoring should be done? (hormone levels & growth at 3m, 6m, 1y, etc)
- What are her chances of persistent endocrine deficiency? (25%)
Case 4--2 years

- Prolactin was elevated at initial and subsequent checks
- At 2y of age, slow growth rate is identified
- GH stimulation testing shows growth hormone deficiency.
- Growth hormone therapy is started.
At age 5y, she is noted to have faster growth rate
On physical exam, she has breast buds and no pubic hair.
Her BA shows maturation to age 6.5y at age 5y.
She is started on GnRHa with resolution of her signs of puberty
Case 5—Hemorrhage and fracture

- Kalisha, age 5y, is walking along sidewalk, balancing on the curb.
- A car passes too closely and mirror hits her in the head.
- Observers see her thrown 10 feet and the car drives off.
- She is unresponsive at the scene and is transported to ICU seizing.
- Imaging shows intracranial bleeding and skull fracture.
- She is taken to the OR to remove part of the skull for decompression
  - Skull piece saved + placed back later

- What is her Glasgow Coma Scale (GCS) at ICU arrival?
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Case 5—first 6 months

- In the ICU, she is treated with steroids to reduce CNS edema
- She has diabetes insipidus but it resolves by one month after injury
- TSH is 9 mU/L with a low free thyroxine, but these return to normal by 6 months after injury.

--Why does she have TSH elevation
Case 5—first 6 months

- In the ICU, she is treated with steroids to reduce CNS edema
- She has diabetes insipidus but it resolves by one month after injury
- TSH is 9 mU/L with a low free thyroxine, but these return to normal by 6 months after injury.
- --Why does she have TSH elevation
  (non-thyroidal illness)
Case 5—1 to 7 years after TBI

- Growth rate is slow in the 1st year, but GH and thyroid levels remain normal.
- Neurologically, she has persistent deficits and personality change.
- Breast buds start at age 10y, and puberty progresses at a normal tempo.
- How do you explain her normal endocrine function after such a severe injury?
Case 5—1 to 7 years after TBI

- Growth rate is slow in the 1\textsuperscript{st} year, but GH and thyroid levels remain normal
- Neurologically, she has persistent deficits and personality change.
- Breast buds start at age 10y, and puberty progresses at a normal tempo.

--How do you explain her normal endocrine function after such a severe injury?  
(persistent endocrine deficiency is not correlated with TBI severity)
Case 6--Complicated concussion

- Mike, age 14y, remains prone on the football field after a play, but gets up after a few minutes and is able to walk off the field.
- Wisely, his coach does not let him re-enter the game.

- Later, Mike reveals that he has had several episodes of confusion after collisions during prior games.
- He has continuing headache and is seen by his sports medicine physician the next day. Imaging is negative.

- What would be his GCS at arrival in the ED (if someone thought of doing it)?
  - <3, 4-8, >8-12, >13
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Case 6—1\textsuperscript{st} month

- He has limited energy and is bothered by lights.
- He is unable to tolerate attending school and is put on complete rest (no electronics).
- After one month, his symptoms are not improved.
- Repeat imaging remains negative.
Case 6—3 months

- By 3 months, he is better able to focus and headaches are improved
- However, he is not back to normal
  - He has poor energy and reduced stamina
  - He is unable to train with the team
  - He feels cold all the time and has constipation
- At 3 months after injury, full physical examination reveals reduction in testes size to 8ml. He has not required shaving since the injury.

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- How do you explain his loss of pubertal development?

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- Is this a permanent deficiency?

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- What hormone assessment is needed by 3 months?
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- --How do you explain his loss of pubertal development?
  (reduction of pubertal hormones after TBI)
- --Is this a permanent deficiency?
  (unknown, requires follow up)
- --What hormone assessment is needed by 3 months?
  (cortisol, thyroid, growth hormone, puberty)
Case 6—6 months

- His thyroid levels at 3m are abnormal (low TSH + low-nl FT4)
  - AM to PM TSH ratio <1.3
- Thyroid hormone therapy started with improved stamina, cold tolerance, and bowel pattern.
- By 6m after injury, puberty progresses rapidly, + he is done growing taller.

- When should he undergo further endocrine screening?
- What are his chances of persistent endocrine deficiency?
Case 6—6 months

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- Thyroid hormone therapy started with improved stamina, cold tolerance, and bowel pattern.
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- When should he undergo further endocrine screening?
  (6m, 1y, including measurements of height)
- What are his chances of persistent endocrine deficiency?
  (25%)
Recommended screening after TBI

- Accurate height and weight, observe pattern on growth chart
- Screening (8am lab)
  - Cortisol, prolactin
  - FT4, TSH (TSH at 8am plus 10am or later, for ratio)
  - IGF-I and IGFBP3
  - I’s/ O’s, urine & serum osmolality
  - (LH, FSH, T or E2-- if pubertal age or in puberty too young)
- Repeat screening at one year after injury
- Referral to endocrine if child has
  - Slow growth rate for age
  - 8am cortisol < 13
  - Polyuria, polydipsia
  - FT4 < 1.0 or TSH of 4 or higher
  - IGF-I and/ or IGFBP3 are below lower limits for age
Summary

- One cannot always predict occurrence of endocrinopathies from severity of injury.
- Regular monitoring of growth rate, and timing of onset and rate of puberty can be best markers for endocrine changes.