Endocrinopathies after Traumatic Brain Injury

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6th Annual Northern Kentucky TBI Conference
March 23, 2012
www.bridgesnky.org

- Supported by
  - Pfizer, Inc
    - Investigator-Initiated Research grant
  - General Clinical Research Center, NIH
    - #M01 RR08084
  - Nat'l Center for Research Resources, NIH
    - USPHS Grant #UL1 RR026314

Traumatic Brain Injury (TBI) in children

- TBI is leading cause of death & disability in children.
- Incidence
  - Infants (inflicted injury) 25/ 100,000
  - Children 180/ 100,000
  - Peak age 15-24y, 250/ 100,000
- About 6 million Americans have lifelong disability after TBI

Causes of TBI vary with age

- Infants-- inflicted injuries
- Toddlers—falls
- School-aged children--pedestrian or sports-related injuries
- Adolescents--motor vehicle crashes

Costs of TBI

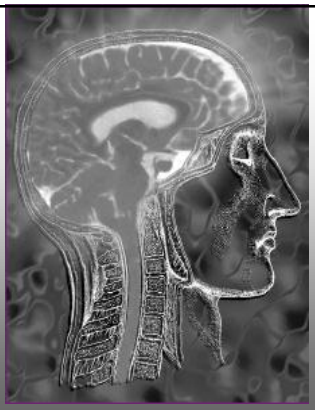
- Cost for care of one person can be $2 million
- In 1995 in USA
  - costs & lost productivity from TBI= $56 billion
- Consequences:
  - Neurologic
  - Cognitive
  - Behavior deficits
  - Social
  - Economic
  - Endocrine

However

- Endocrine outcomes of TBI are under-recognized
  - Not mentioned in
    - 1998 NIH Consensus Conference Statement
    - most TBI websites (ninds, niccyd, cdc)

Outline

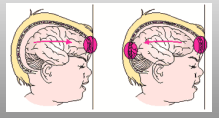
- Mechanisms of injury
- Endocrine deficiencies
- Endocrine studies after TBI
- CCHMC study
- Consensus conference
- Conclusions

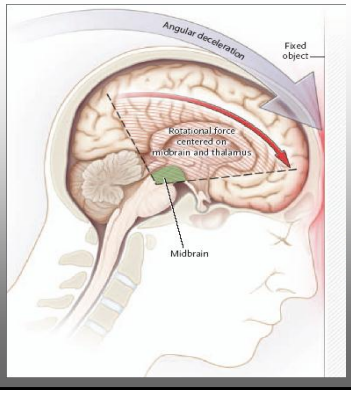


Types of CNS injury

- **Open Head Injury**
  - Penetration of the skull--focal
- **Closed Head Injury**
  - Focal & diffuse damage to axons
- **Deceleration Injuries**
  - Different parts of brain move at different speeds.
    - diffuse axonal shearing, contusion, brain swelling.
    - axons stretched until torn.
- **Hypoxia**
  - irreversible brain injury from anoxia (no oxygen)
- **Stroke**
  - cerebral vascular accident, cell death in area deprived of blood
  - bleeding in or over brain (hemorrhage or hematoma)

Coup and Contra-coup



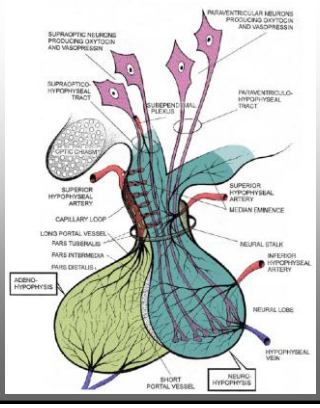


Mechanism of injury

Ropper AH,
N Engl J Med 2007

Mechanical injury to hypothalamus & pituitary in TBI

- Anatomic mechanisms responsible for injury
  - direct damage to pituitary stalk
  - disruption of vascular supply
  - indirect effects on function due to poor perfusion from cerebral edema or shock
  - pituitary antibodies after injury



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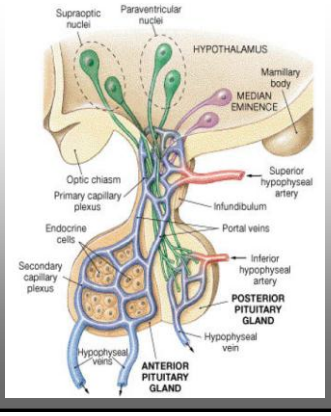

JA Jane

Location of injury

- If hypothalamus
  - low anterior pituitary hormones
  - normal response to releasing hormones.
- If lower pituitary stalk or anterior lobe
  - low anterior pituitary hormones
  - no response to releasing hormones
  - High prolactin
  - SIADH or DI
- Most severe injuries
  - damage both hypothalmus & pituitary
  - mixed endocrine picture.

Yuan 1991

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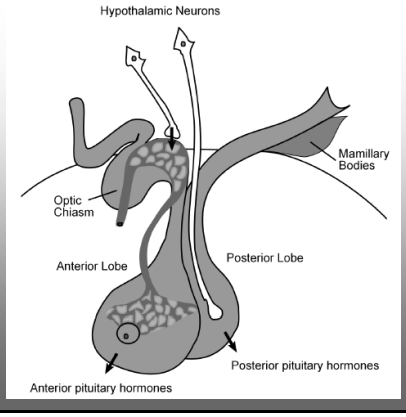

Leung 2005

Common symptoms of Hypopituitarism

- Not specific for any one deficiency
  - Weakness, fatigue, decreased exercise tolerance--low ACTH, GH, LH, FSH, TSH
  - Weight loss—ACTH, DI
  - Increased body fat--GH, LH, FSH, TSH
  - Decreased muscle mass--GH, LH, FSH
  - Low libido, erectile dysfunction--LH, FSH
  - Ischemic heart disease--GH
  - Shortened life span--GH

Each deficiency gives multiple symptoms

	GH	TSH	ACTH	Gn	DI
• Poor growth	X	X			X
• Fatigue	X	X	X	X	
• Weight change	X	X	X		
• Drinking increase					X
• Precocious Puberty (child)				X	
• Loss of libido (adult)				X	

Review of post-TBI endocrine studies

- Types of published studies
  - Cases
  - Cross-sectional
    - All cases regardless of time since TBI
  - Prospective
    - Cases evaluated at baseline, then at intervals after TBI (such as 0, 3, 6, 12 mo after TBI)

Outline

- Mechanisms of injury
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  - Adult
  - Pediatric
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Cross-sectional studies in adults

	N	GH	ACTH	TSH	hi PRL	DI	LH, FSH
• 1988 Clark	53	100%	92%	88%	70%	26%	95%
• 2000 Bevenga	367	23	58	90	45	31	100
• 2001 Lieberman	70	15	7	22			
• 2004 Agha	102	11	13	1	12		12
• 2004 Bondanelli	50	28		10	8		14
• 2005 Leal-Cerro	113	6	6	6		2	17
• 2006 Herrmann	76	3	8	3	3		17
• 2006 Kelly	44	18					
• 2007 Bushnik	64	66	60	19			14
• 2008 Tanrivierdi	29	21	6				
• 2009 Pavlovik	61	33	4.9	4.9			4.9
• 2010 Berg	246	5	4	12			9

Cross-sectional studies in adults

Overall N= 1275	Range %	Median %
• GHD	3 – 100	25
• Hypogonad	9 - 100	20
• TSHD	3 – 90	15
• High PRL	3 - 70	15
• DI	2 - 31	10
• ACTH-D	4 – 92	10

Meta-analysis

- Differences in incidence of deficiencies related to
  - Patient selection
    - All ICU admits vs referred, vs all with GHD
  - BMI
    - High BMI lowers GH peak
  - Definitions of deficiency
  - Testing methodology
  - Duration since TBI
    - Transient deficiencies in 1st y, chronic by 1y

Kokshoorn 2010

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  - Pediatric
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Acute state after TBI

- 12 days after injury
  - 18% low GH to glucagon
  - 16% low cortisol to glucagon
  - 80% low gonadotropins
  - 52% high prolactin
  - 26% diabetes insipidus
  - 14% SIADH
  - 2% TSH deficiency

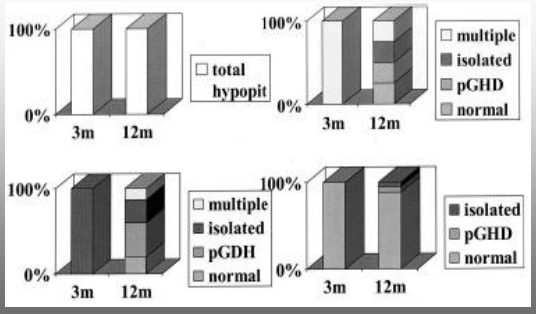
Agha 2004

Predictors of hypopituitarism

- 78 adults studied 3 & 12m after TBI
  - Diffuse axonal injury
  - Basal skull fracture
  - Older age

Schneider 2007

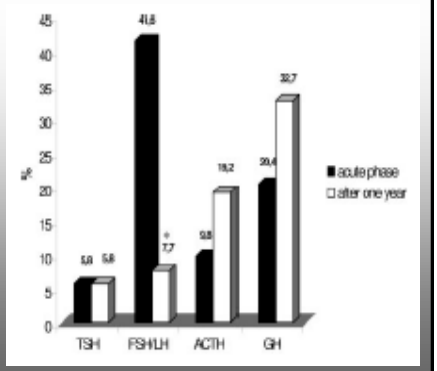
Change in pituitary function at 12 *vs* 3m after TBI



Aimaretti 2004

Prospective study, adult

Tanriverdi 2006



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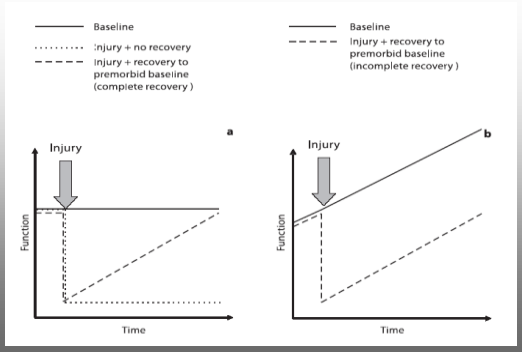
Models of injury & recovery



Giza 2006

Case studies—Children after TBI

- 400 children (m/yr after head injury)
  - poor growth
  - Precocious puberty
  - Diabetes insipidus
  - failure to progress through puberty
- not known whether young brain/ hypothalamus is more or less sensitive to injury than the older brain

Cross-sectional studies in children

	N	GH	ACTH	TSH	DI	LH,FSH
• 2006 Acerini (KIGS data)	141	100%	17%	17%		36%
• 2006 Einaudi	22	5	5			5
• 2007 Niederland	26	42	34	12		
• 2008 Poomthavorn	54	7	11	6	4	2

Cross-sectional studies in children

Overall N= 243	Range	Median
	%	%
• GHD	5 – 100	25
• Hypogonad	36	?
• Prec pub	2 - 5	?
• TSHD	6 - 17	12
• High PRL	-	?
• DI	4	?
• ACTH-D	5 – 34	20

Prospective study in older adolescents/ young adults

- 3 & 12 mo after TBI
- 9 girls, 14 boys, age 16-25y
- At 3m, hypopituitarism in 35%
  - Total 9%, multiple 4%, isolated deficits 22%
  - Diabetes insipidus (DI) in 9%
  - mild hyperprolactinemia in 4%.
- At 12m, hypopituitarism in 30%
  - Total 9%, multiple 4%, isolated deficits 17%
  - DI in 4%
  - mild hyperprolactinemia in 4%

Aimaretti 2005

Prospective trial--children

- 30 acute, 26 at 6m, 20 at 12m
- At 12m
  - 3 with cerebral salt wasting
  - 1 DI
  - 1 with low cortisol
  - 1 with GHD

Einaudi 2006

Growth monitoring

- Prospective serial growth data was only obtained in only 22 of 129 children after TBI (requiring ICU care)
- Specialist & general pediatric followup after TBI should include growth measurements

Moon 2010

Outline

- Mechanisms of injury
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  - Accidental TBI
  - Non-accidental TBI
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CCHMC prospective trial in children (support by Pfizer & GCRC)

- Authors & current location:
  - AMD Kaulfers (Alabama), PF Backeljauw, K Reifschneider (Virginia), S Blum, L Michaud, M Weiss (New York), SR Rose
  - Several prior fellows made major contributions
  - Submitted for publication
- Objectives were to determine in children
  - incidence of endocrine abnormalities after TBI timing of endocrinopathies after TBI
  - best screen for central endocrinopathies after TBI

Methods

- Prospective observation
- N=31, mean age 11.6y (2-18y), 13 girls
- GCS ≤12
  - 12 had skull fracture (7 basilar)
  - 24 had intracranial hemorrhage
- Causes of injury
  - 15 motor vehicle crash
  - 7 fell
  - 7 hit by a car (4 riding a bike, 3 pedestrians)
  - 2 football injury
- recruited prior to hospital discharge after TBI
  - Consent, baseline medical history, physical exam, & laboratory testing

Glasgow Coma Scale

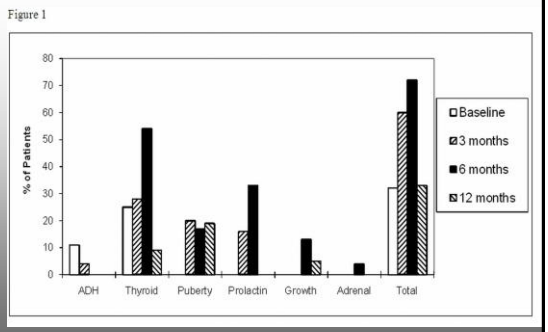
- 15 = normal
- 13 or 14+ mild head injury
- 9 - <13 moderate
- 3 - 8 severe
- ≤ 3 vegetative

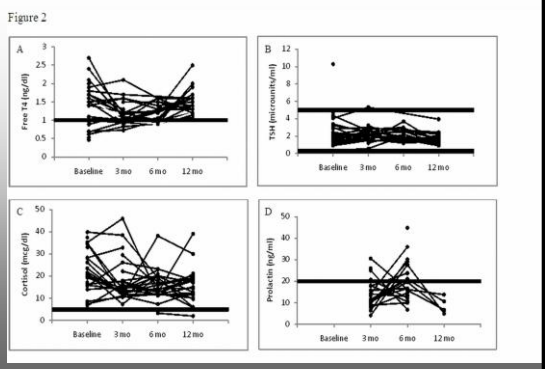
Protocol Flow sheet

Test/Procedure	At Injury	2-3	6-8m	12m
Consent	X	X		
History & Physical	X	X	X	X
Serum/urine Osm.	X	X	X	
AM Cortisol	X	X	X	X
Free T4 and TSH	X	X	X	X
IGF-I, IGFBP3	X	X	X	X
Prolactin		X	X	repeat
TSH surge			X	repeat
6 h GH secretion			X	stim tests
1 mcg ACTH test			X	repeat

Endocrinopathies after TBI

Endocrine abnl	Baseline (%)	2-3m (%)	6m (%)	12m (%)
Low thyroid	25	28	54	10
DI	7	4	--	--
Low GH	--	--	12	5
Puberty	--	20	17	19
Prolactin	--	12	33	--
Low ACTH	--	--	4	--
Any abnl	32	56	67	20





TBI severity did not predict endocrinopathy

	GCS	Skull Fracture	Intracranial Hemorrhage
Endocrinopathy at 12mo	6.7	43%	100%
Normal at 12mo	4.9	50%	92%

Conclusion from our study

- Similar to adults, many children have endocrine abnormalities persisting >6m after TBI
- Some abnormalities resolve by 1y after TBI
- Children <10yo may develop precocious puberty after TBI

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Children after inflicted injury in infancy

- No prior publications
- Cross sectional study of children with inflicted TBI
- IRB approved, informed consent obtained
- Inclusion criteria
  - inflicted TBI requiring hospitalization
  - injury at <3y of age
  - ≥1y since injury
  - currently ≥2 to 9y of age
- 14 patients studied to date, ongoing

Methods

- Evaluation in overnight hospitalization
  - Height & weight
    - Height by stadiometer or length by infantometer
  - Morning cortisol & peak cortisol to low-dose cosyntropin
  - TSH nadir to peak rise at night (TSH surge) & free T4
  - 6h, every 20min GH sampling 10pm to 4am
    - hourly if <15kg
  - IGF-I, IGFBP3
  - Prolactin
  - Fasting serum & urine osmolality
  - LH, FSH, & estradiol or testosterone
    - If signs of puberty
- Patients grouped by prolactin level

Clinical Characteristics

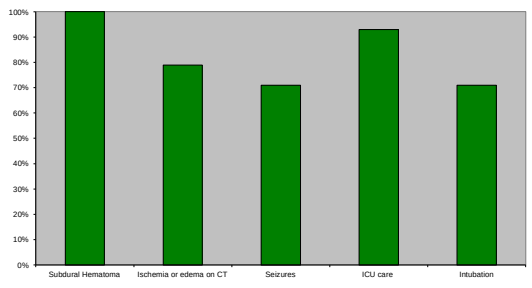
(according to Prolactin level)

Prolactin Group Mean ±SD (ng/mL)	**Gender**	**Average Age at Injury** Mean ±SD (months)	**Time Elapsed at Study** Mean ±SD (months)	**# Endocrine Abnormalities** Mean ±SD
High (n = 8) 25.7 ± 12.3	6 M 2 F	10.6 ± 11.5	36 ± 21.6	2.6 ± 0.7
Normal (n = 6) 10.8 ± 6.7	5 M 1 F	3.2 ± 3.4	36 ± 8.4	0.8 ± 0.8

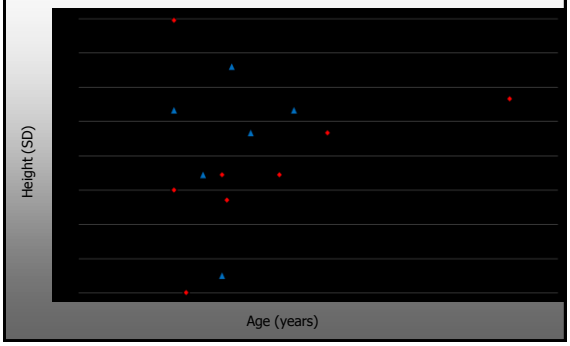
Injury characteristics

- all patients had subdural hematoma
- most required ICU care
- 12 of 14 had ischemia or edema on CT

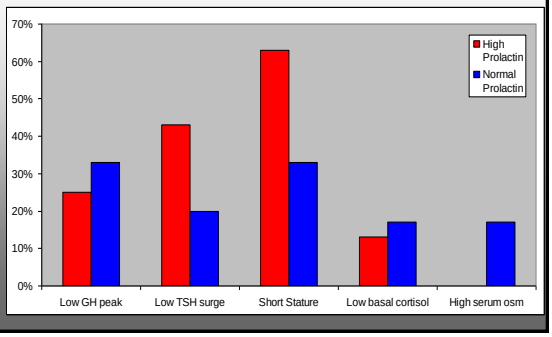
Acute injuries after iTBI (n = 14)



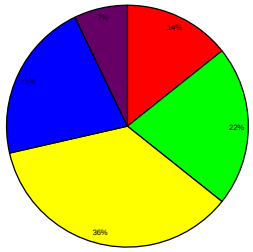
Height vs Age, High vs Normal Prolactin Groups



Pituitary Abnormalities according to Prolactin Group



Number of Pituitary Abnormalities



Results

- 86% (12 of 14)
  - at least 1 endocrine abnormality
- 64%
  - 2 or more abnormalities
- Elevated prolactin
  - most common, followed by short stature, abnormal thyroid function, & low GH peak
- High prolactin levels
  - associated with increased frequency of abnormal pituitary function
- Patients who required endocrine treatment are being followed clinically

Summary

- After inflicted TBI, many children have abnormal pituitary function
- If prolactin is elevated
  - need more complete hypothalamic-pituitary evaluation

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Consensus conference

- Better coordination needed among specialists
  - trauma surgeons, neurosurgeons, rehabilitation MDs, internists & endocrinologists
- Need to be aware of
  - risks for TBI–induced endocrinopathies
  - need for endocrine testing/ therapies

Ghigo 2005

Consensus conference

- Screening (8am lab) should include
  - cortisol
  - FT4, TSH
  - IGF-I
  - LH, FSH, T or E2
  - Prolactin
  - I's/ O's, serum sodium, urine & serum osmolality

Ghigo 2005

Recommendations

- After TBI in children
  - monitor length or height at least every 6 months
- Full pituitary function
  - evaluate at one year after injury
- Patients with elevated prolactin are likely to have other deficiencies

Conclusions

- Hypopituitarism may impair recovery after TBI
- Identification & therapy of deficiencies can improve chances of rehabilitation & enhance QoL
- Assessment of GH, ACTH, & TSH requires serial testing (re-eval at 1y)
- Need close liaison between endocrine, rehabilitation, & neurosurgical services