Neuroendocrine dysfunction in fatigue and sleep disorders after acute brain injury

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The neuroendocrine dysfunction post AHI relates to the consequences of damage to the hypothalamus, pituitary stalk and pituitary gland.

- Pituitary protected in sella
- Hypothalamus partially protected by surrounding soft tissue
- Pituitary stalk particularly vulnerable
- Haemorrhage, necrosis, disruption of stalk
Incidence

- Autopsy results
- 40-63% some kind of damage
  - Anterior pit infarction 9-38% (oedema or disruption of portal blood supply)
  - Post pit haemorrhage 12-35%
  - Traumatic lesion of stalk 5-30%
- Recovered patients
  - 4% in retrospective studies (under diagnosis++)
  - 30-50% in prospective studies
Prognosis

- Most patients with severe closed head injury do not survive (severe cerebral oedema)
- Intractable hypernatraemia (cerebral salt retention) associated with higher incidence of extreme cerebral injury and brain death
- Neuroendocrine diagnosis and prognosis unpredictable
- From days post injury to years post injury
Diagnosis

- Index of suspicion increased if set back during recovery
- Active investigations in immediate post-injury period
- Regular monitoring for years after injury
- Investigating unexplained but recurring or persistent vague symptoms eg sleep disorders, tiredness, memory problems
Endocrine complications

- Immediate
  - SIADH
  - Anterior hypopituitarism
  - Cerebral salt wasting
- Later
  - Hypogonadism
  - Hypothyroidism
  - Adrenal insufficiency
  - Hyperprolactinaemia
  - DI
  - GH deficiency
Reasons for underdiagnosis

- Non specific symptoms and signs, presentation any time from time of injury to years later
- Subtle
- Initial tests may be normal
- DI only obvious complaint
Reasons for underdiagnosis

- In acute phase of brain injury index of suspicion high
- With time incidence less
- After 1 year rare – index of suspicion low
Associations

- **DI** –
  - usually severe ABI, basilar scull fractures, cranial nerves, craniofacial trauma, arrest

- **Ant pit** –
  - moderate injury, brain swelling, hypoxia – endocrinopathy often much later

- **SIADH** –
  - hypothalamic injury (mild to severe)

- **Cerebral salt wasting** –
  - rare, subtle, misdiagnosed for SIADH

- **Cerebral salt retention** –
  - any time from time of injury to yrs later, misdiagnosed
Symptoms

- Vague (except DI)
- Often just
  - tiredness,
  - depression,
  - Insomnia
  - Not ‘right’
  - Libido
- Baseline tests may be normal
- Initial tests may be normal
Patient 1

- Roofer, male 55yrs
- Referred because of ‘unstable’ serum electrolytes
- Serum Na 120-150 no apparent reason
- Knows when things not right
- Wife theatre sister
Patient 1

- OPD-
- well, smoker, drinker (4 cans/day reg, much more at week ends)
- Attacks when insomnia, nightmares, irritable, slow, memory problems,
- inconsistent polyuria and polydypsia ?beer

- PH
- Only fall from roof 6/12 ago- closed head injury
- Complete recovery and back to work after 6/12
- Still roofer
Patient 1

- O/E NAD

- Bloods
  - LFT, Cortisol, TFTs, FBC normal
  - Low Vit D –
  - RFT
    - Sodium 120-150, rest ‘normalish’ over 12/12
Patient 1

- First detailed 24 hr fluid and electrolyte profile consistent with SIADH
- But why attacks of polyuria?
- Do serial fluid and electrolyte profiles at weekly intervals particularly when polyuria
Patient 1

- Results
- 1 typical SIADH
  - 24 hr urine output 1L, serum Na 123, urine Na 50, overhydrated
- 2 typical renal salt wasting state
  - Output 3 L, serum Na 130, urine Na 300, dehydrated
- 3 typical SIADH
- 4 ?
  - Output 1L, serum sodium 150, urine sodium 200, dehydrated
- 5 typical SIADH
Patient 1

- Diagnosis
- SIADH and cerebral salt wasting

- Treatment
  - Doxycycline and slow NaCL,
  - Intake according to output
  - Wife keeping close eye
  - Frequent fluid and electrolyte tests
  - Well but only if closely supervised
  - Still working
  - Died 3 years later unrelated problem
Patient 2

- Male 45yrs
- Referred for ? Hypothyroidism but with normal TFTs
- Other routine tests also normal
Patient 2

- Came with wife who did most of the talking
- Engineer from Slovakia
- Increasingly slow, monotonous, ?depressed
- No libido
- Just work, eat, sleep, constant headache
- No life, no interrelation with wife and children
- Children 10 and 12 yrs old
Patient 2

- O/E clinical features suggestive of deep hypothyroidism (face, skin, reflexes)
- Slow++, monotonous++, ‘not with it’
- Tired+++
- ‘Sniffly’ nose
Patient 2

- PH
- Sinusitis, indigestion
- Medication none

Routine tests Na 130, TSH 1.2, FT4 12

Further questioning
Severe head injury while still in Slovakia 15 years before
Tennis ball
Basal fracture, CSF rhinorrhoea
Recovery 3/12, follow up 12/12
Well until ?7 years ago when progressively slower
Patient 2

- Investigations
- Full pituitary function tests
  - TRH test-secondary hypothyroidism
  - Short synacthen test and ACTH pituitary hypoadrenalism (insulin stress test ?too dangerous)
  - GHRH response normal!
  - Fluid and electrolyte profile normal
  - MRI atrophic anterior pituitary
Patient 2

- Replacement with thyroxine and hydrocortisone
- 3/12
- Smiling
- Wife happy ++
- ‘My husband and the children’s father is back’
- Sadness about complete unawareness of the children’s life over previous 5 years
- Recent MRI for sinusitis
- Destruction of frontal sinuses, hydrocoele,
  - Utmost care – future head injuries or ENT procedures
Patient 3

- 44 yrs male
- Referred for unexpected and unexplained high serum Na (170) – routine test
- OPD
- Well, groomed, young looking, working on surveyors exams, articulate
- But also often unduly tired, cannot sleep, attacks of polyuria and polydypsia
Patient 3

- Past results
- Unremarkable except
- Occasionally Na > 145
- Serum creatinine normal to high
- ??
Patient 3

- PH
- Nil except!!!
- Drug addict and alcoholic until age of 21 when
- Thought he could fly (from 2\textsuperscript{nd} floor balcony)

- Severe open head injury,
- titanium plate, part of frontal lobe gone
- 6 month coma, 2 year recovery thereafter
- Living at home since and slowly got back to normal but still does not feel not quite right
Patient 3

- Pituitary endocrine investigations
  - including TRH, insulin stress test, GNRH all normal
- Fluid and electrolyte profiles (variable)
  - DI
  - and/or
  - Cerebral salt retention
- Advice
  - Keep fluid intake exactly as output and never go dry
Patient 3

- No further problems,
- Sleeping well
- Passed exams
- OPD when not ‘quite right’
DI

- Impaired ADH secretion by hypothalamus/posterior pituitary
- Dehydration
- Signs and symptoms due to polydypsia and nocturia, dehydration
  - Disturbed sleep
  - Tiredness
  - Headaches
SIADH

- Inappropriate ADH production secretion
- Hyponatraemia and fluid overload, cerebral oedema (but also total body salt loss)
- Symptoms and signs
  - Headache, confusion, memory, tiredness
Cerebral salt wasting

- Impaired renal salt retention due to
- Uric acid renal handling
- Impaired brain natriuretic peptide secretion (BNP) in hypothalamus

- Signs and symptoms due to hyponatraemia, polyuria, dehydration
Cerebral salt retention

- Often due to very severe head injury
- (usual feature in brain death)
- ?inappropriate natriuretic peptide secretion
- Often precipitated by dehydration

- No symptoms or
  Headaches, nightmares, insomnia, not quite right