A practical guide to treating persistent headaches following concussion

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Disclosures

- **NIH/NHLBI K23 (PI)**: A link between sleep-wake disturbances and enlarged perivascular spaces in youth with traumatic brain injury
- **NIH/NHLBI R21 (PI)**: The perivascular space: A structural link between inadequate sleep, glymphatic dysfunction, and neurocognitive outcomes in adolescents
- **DoD CDMRP (PI)**: TBI Exosomal Activity in Military Personnel: Perivascular Space and Role of Indicators of Sleep Metrics TEAM-PRISM
- **NIH/NINDS R01 (co-I)**: Defining the Role of Post-TBI Sleep Disruption in the Development of CTE and Alzheimer's Disease-Related Neuropathology
- **NIH/NINDS R01**: Development of Serum, Imaging, and Clinical Biomarker Driven Models to Direct Clinical Management after Pediatric Cardiac Arrest
- **Collins Trust (PI)**: Enlarged perivascular spaces as a marker of glymphatic dysfunction in youth with chronic post-concussive syndrome
- **Friends of Doernbecher (PI)**: Linking glymphatic pathway impairment and post-concussive headaches in youth with traumatic brain injury

PTH: WHEN and HOW to treat them?

- What treatment models should we employ, both evidence-based and novel, in acute and persistent PTH?
- What role does early treatment play in preventing persistent PTH?
- How does PTH interact with other symptoms of persistent post-concussive syndrome?

Acute PTH treatment models

- If approximately 80% of patients recover spontaneously by 4 weeks, why prescribe medications?
  - After 24-48 hours, early sub-threshold activity, both physical and cognitive, is beneficial.
  - Early treatment of headaches can facilitate early return to activity, decrease avoidant behavior, and lower the likelihood of pain catastrophizing.

Intravenous migraine therapy in children with posttraumatic headache in the ED☆,☆☆,★

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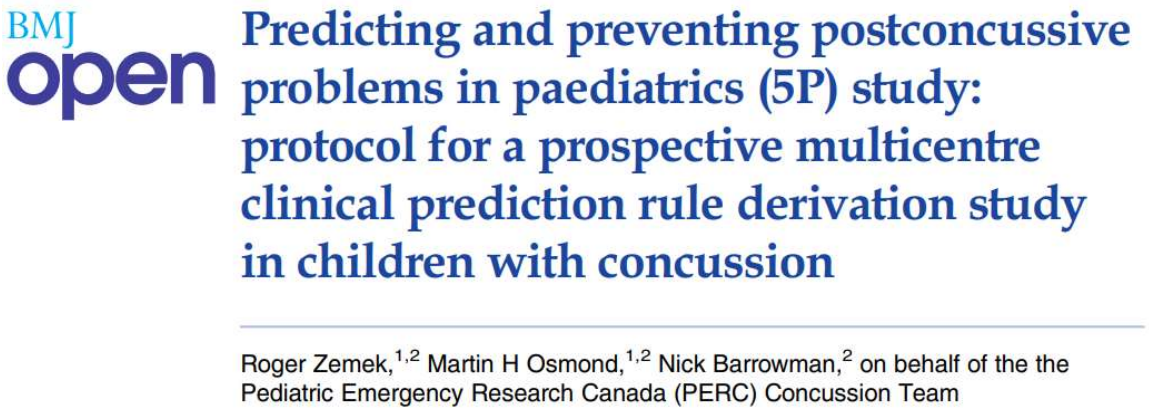
- ED-based, retrospective study of children 8-21 years old (n=254) seen at t tertiary pediatric ED with mTBI (within 14 days of ED presentation) and PTH.
- IV medications administered: ketorolac, prochlorperazine, metoclopramide, chlorpromazine, ondansetron.
- Primary outcome: treatment success (greater than 50% reduction in pain during the ED visit).
- 83% of patients had treatment success, with 52% experiencing complete resolution.

Who should be considered for early treatment of PTH



- Established to design a clinical risk prediction score for PPCS in children, though not PTH specifically.
- Significant risk factors:
  - Adolescent or female
  - Prior concussion with >1 week recovery
  - History of migraines
  - Acute symptoms of headache, fatigue, phonophobia
  - Answering questions slowly in the ED

Who should be considered for early treatment of PTH

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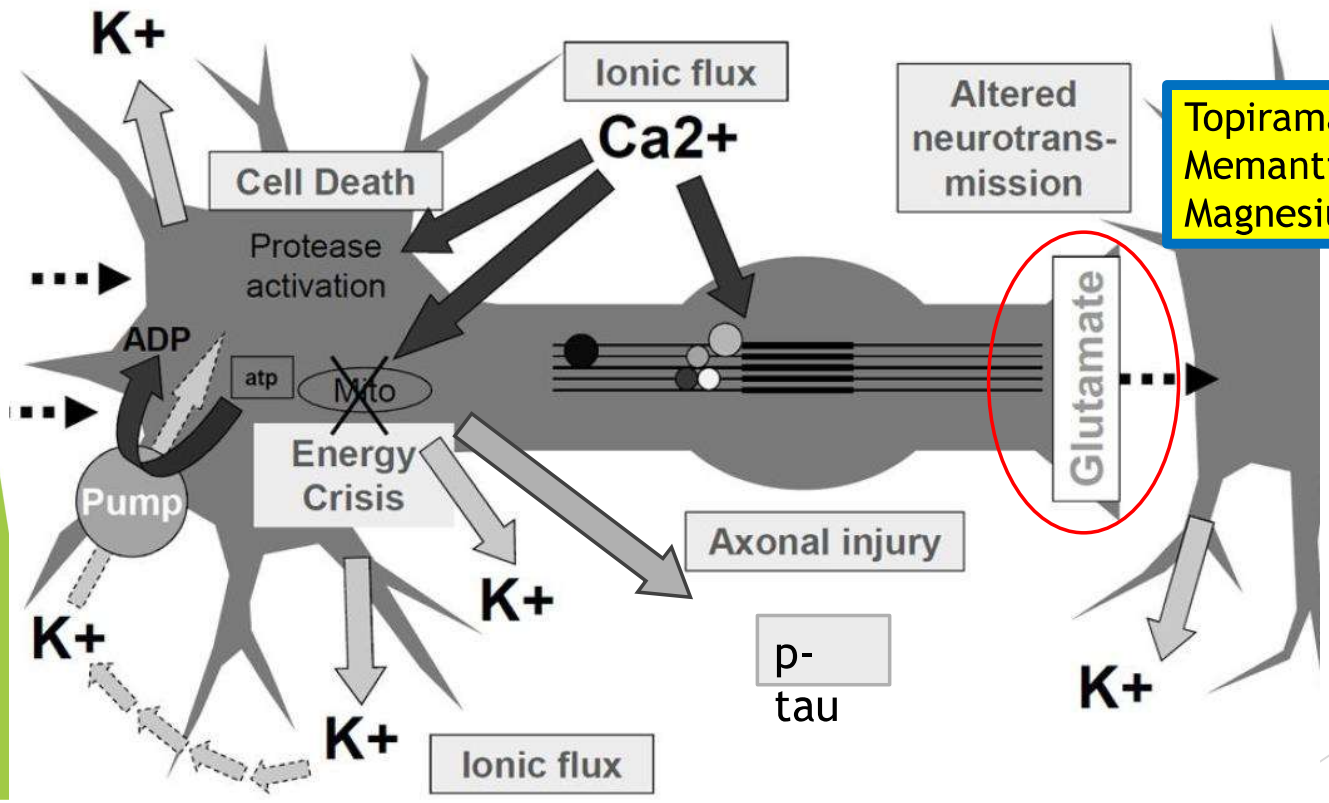
Original Investigation | Neurology

Evaluation of Posttraumatic Headache Phenotype and Recovery Time After Youth Concussion

Joshua Kamins, MD; Rachel Richards, MS; Bradley J. Barney, PhD; Christopher Locandro, MS; Christina F. Pacchia, PhD; Andrew C. Charles, MD; Lawrence J. Cook, PhD; Gerard Gioia, PhD; Christopher C. Giza, MD; Heidi K. Blume, MD, MPH

- Cohort study of 281 patients with PTH
- Ages 5 to 18 years
- Main outcome: time to recovery and headache at 3 months post-injury
- At initial visit: 46.5% migraine phenotype, 20% non-migraine phenotype, 34% no PTH
- Subjects with migraine phenotype took longer to recover
- Association between female sex and migraine phenotype

What drugs to use in acute PTH treatment? Physiology-guided therapy



Topiramate
Memantine
Magnesium

NEUROINFLAMMATION
CGRP
PACAP
Substance P

Giza et al., 2014

Acute PTH treatment models: targeting neuroinflammation

Original Article

CGRP-dependent and independent mechanisms of acute and persistent post-traumatic headache following mild traumatic brain injury in mice

- Administration of an anti-CGRP monoclonal antibody at 2 h and 7 days after mTBI blocked injury-induced allodynia.
- Administration of the antibody on day 10, after the resolution of allodynia, did not prevent bright light stress-induced cutaneous allodynia.
- Conclusions: Acute expression of CGRP drives the development of central sensitization, increasing vulnerability to headaches
- CGRP elevation can be targeted by
  - Triptans ($$)
  - Gepants: small-molecule CGRP antagonizes ($$$$)
  - CGRP monoclonal antibodies ($$$)
  - NSAIDs or corticosteroids ($)

Persistent PTH treatment models

- The neurometabolic cascade triggered by concussion resolves within 4 weeks.
- Persistent PTH occurs in a significant number of individuals after mTBI.
- Unknown/unclear mechanism:
  - CGRP may play a role
  - Glutamate and cortical spreading depression may also play a role
  - LIFESTYLE CAHNGES
    - Worsened sleep
    - Decreased physical activity
    - Increased anxiety and depressive symptoms
  - Central sensitization (daily pain with allodynia and photosensitivity), with superimposed migraine-like headaches

Persistent PTH treatment models

- Reluctance to initiate headache-specific treatment (Pearson et al.)
  - Many providers wait 8 to 12 weeks after injury to initiate therapy.
  - Popular treatments:
    - Vitamins/supplements
    - Amitriptyline
    - Topiramate
  - Melatonin is not effective in the treatment of PTH

Persistent PTH treatment models

Gabapentin and Tricyclics in the Treatment of Post-Concussive Headache, a Retrospective Cohort Study

Daniel M. Cushman, MD ; Lauren Borowski, MD; Colby Hansen, MD; John Hendrick, MD; Troy Bushman, MD; Masaru Teramoto, MPH, PhD

- Retrospective analysis of 277 patients with PTH
  - Gabapentin and tricyclic antidepressants
  - Both treated and untreated patients recovered over time
  - Headaches decreased in the visit following initiation of gabapentin but no further decrease after
  - TCA group continued to improve

Persistent PTH treatment models

Botulinum Toxin Type A for the Treatment of Post-traumatic Headache: A Randomized, Placebo-Controlled, Cross-over Study

Milena D. Zirovich, MD[,†]; Sanjog S. Pangarkar, MD[*,†]; Christina Manh, MD[*]; Lucia Chen, MS[‡]; Sitaram Vangala, MS[‡]; David A. Elashoff, PhD[‡,§,¶]; Ifeoma Stella Izuchukwu, MD, MPH[†,‖]*

- Study design: Placebo-controlled cross-over
- Population: 40 subjects, median age 34 years old, 95% male
- Primary outcome: number of headaches per week
- Results: The number of headaches/week decreased by 2.24 (43.3%) with Botox ($p<0.001$), and increased with placebo.

PTH treatment: special considerations

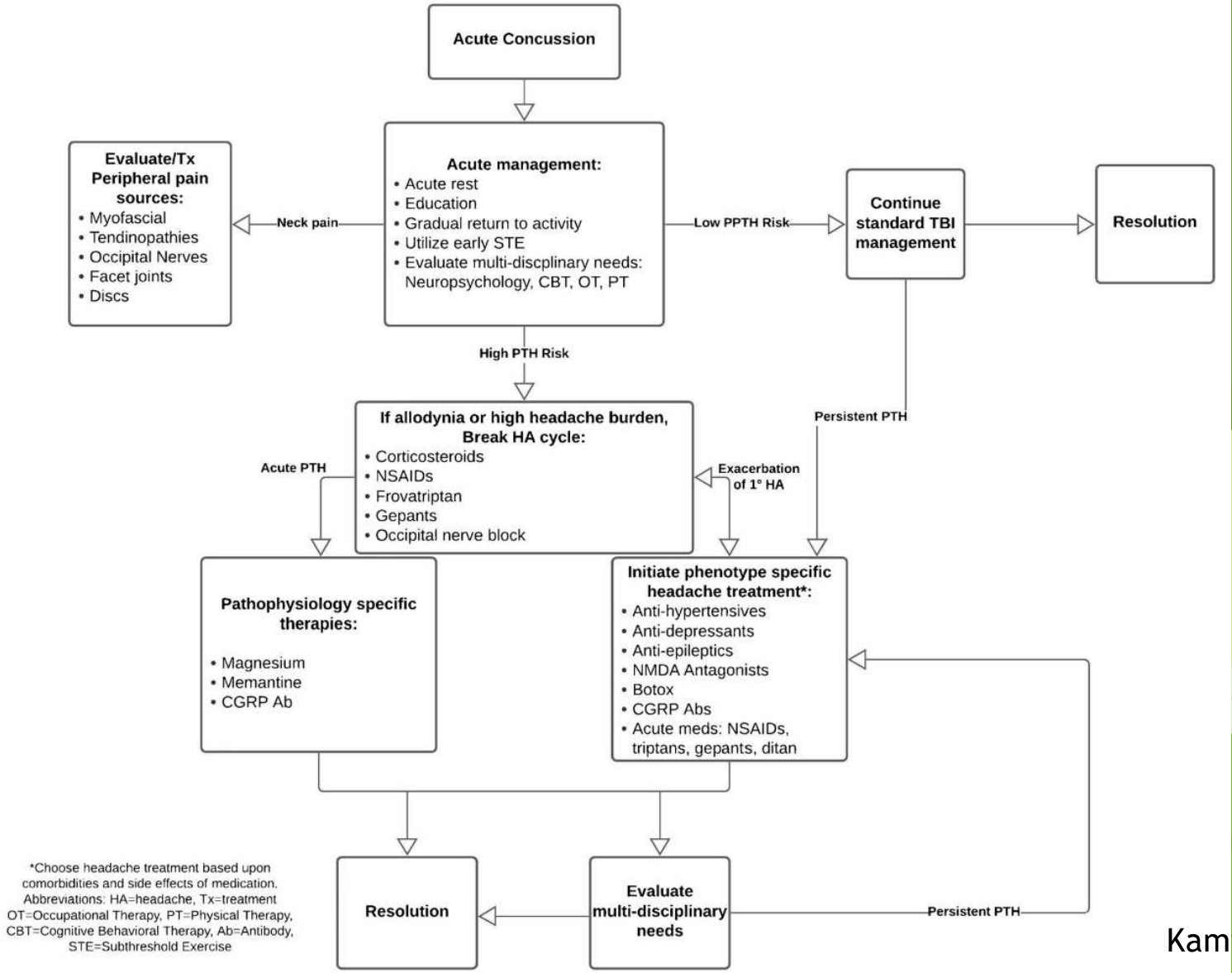
- Sports-related concussions
  - Avoid medications that limit heart rate, cardiac output, and exercise tolerance: beta-blockers, calcium-channel blockers
  - Be aware of banned substances: beta-blockers during competition
- Be aware of medications that may trigger cognitive symptoms:
  - Topiramate, amitriptyline (cholinergic effects), sedating medications (gabapentin)
- Take autonomic dysfunction into account while prescribing medications:
  - TCAs can cause orthostatic tachycardia, beta-blockers and exacerbate postural hypotension
- Take anxiety and mood disorders into consideration:
  - Duloxetine can be a dual treatment for anxiety and headaches
  - Flunarizine and Topiramate can exacerbate depression
  - Titrate stimulating drugs (e.g., SNRIs or memantine) slowly in those suffering from anxiety
- Always consider secondary headaches due to other etiologies
  - Intracranial hypotension
  - CSF leak

PTH versus cephalalgia

- TBI exerts a force on the cervical spine
- Attention should be paid to peripheral pain sources: cervical facet joints, ligaments, muscles, tendons, spinal/peripheral nerves
- The upper cervical nerve roots (C1-3) and rostral cervical spinal cord may play a role in the generation of headaches.
- Consider occipital nerve blocks +/- steroid injections
- Consider physical therapy

PTH treatment: multidisciplinary approach

- “One sure way to fail in treatment of PTH is to provide medication without additional support.” (Kamins et al., 2021)
- PTH is often part of the larger persistent post-concussion symptom picture.
- Neuropsychology:
  - Cognition
  - Emotional state
  - Psychotherapy
  - Coping strategies
  - Anxiety/depression/PTSD treatment
- Nutrition, exercise, sleep
- Occupational and physical therapy



Kamins, et al., 2021