Referring Information

- 9 year old girl with a several year history of episodic headaches
- Previous normal MRI of the brain, diagnosed as migraine

History of Present Illness

- Episodic headaches since age 3
- Increased frequency to about 2 times per month
- Pain 8-9 out of 10 on the pain scale, entire forehead, throbbing
- No aura, some photophobia and nausea, but no focal neurologic symptoms
- Headaches often wake her from sleep, and last up to 12 hours
- Treatment with ibuprofen with some benefit
Past Medical History/Family History

- Born at term, no hospitalizations or surgeries
- Seen by Dermatology for chronic urticarial rash since infancy
- Recently diagnosed with mild sensorineural hearing loss
- Developmentally intact
- Strong family history of migraine

Physical Examination

- Normal vital signs
- Head circumference 95% for age, ht and wt 50%
- Mild frontal bossing, no other dysmorphisms
- General exam notable for urticaria, no meningismus
- Normal neurologic exam including fundi and visual fields - no papilledema

Q1: Which statement about Pediatric Migraine is FALSE?

A- Mean age of onset is 7-9 years old
B- Pain is often bilateral frontal in location
C- Photophobia and nausea are required criteria for diagnosis
D- Headache duration is typically longer than that in adults

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**Pediatric Migraine**
- Mean age of onset: 7.9 y boys, 11 girls
- Age 3-7: 3%, Adolescent: 10-25%
- Prepubertal: boys= girls; later girls>boys
- Commonly bifrontal rather than unilateral
- Photophobia can be inferred by behavior
- Often shorter, average one hour
- Vomiting less common
- Only 30% have aura
- Variants of migraine in young children: cyclic vomiting and abdominal migraine, episodic torticollis, benign paroxysmal vertigo

**Q2: How often is elevated intracranial pressure associated with papilledema in children?**

A- the majority of the time
B- as little as 20% of the time
C- it depends on the child’s age

![Graph showing percentages for A, B, and C]

**Papilledema in Children**
- Study of children with chronic elevated intracranial pressure from craniosynostosis
- only 1/3 had papilledema
- Papilledema was 98% specific for elevated ICP, but sensitivity varied by age
  - Sensitivity was 100% for those over 8 years
  - Sensitivity was only 22% for those under 8 years

**Papilledema in Children, cont.**
- 37 pediatric patients with acute increased intracranial pressure from trauma or intracranial hemorrhage
- no papilledema was noted in any patient
- Patients were followed for 7 days
- ICPs ranged from 30 to 60 mm Hg
- Papilledema is uncommon in acute elevated ICP
Case # 1 MRI

- MRI of the brain was repeated with MRA and MRV
  - mild Chiari I malformation, cerebellar tonsils just at the level of the foramen magnum
  - no parenchymal injury or malformation
  - MR angiogram normal
  - MR venogram showed smoothly narrowed sigmoid sinuses, ?? elevated intracranial pressure

Q3- Which of the following statements about Chiari I malformations in children is TRUE?

A- Children with documented Chiari I malformation are usually asymptomatic
B- Magnitude of tonsillar ectopia is not correlated with symptom severity
C- Syringomyelia is common

Chiari information in Children

- In a review of 50 pediatric patients with documented Chiari I malformation, 57% were asymptomatic
- Magnitude of tonsillar ectopia correlated with symptom severity score
- 14% of patients were found to have syringomyelia
- Of course, there is no data on the patients with Chiari I malformation who never had an MRI
Case #1 Diagnostic Testing- LP

- First lumbar puncture was performed when the patient was asymptomatic:
  - Opening pressure 30 cm water
  - 0 rbc, 93 wbc (77% neutrophils)
  - protein of 43 (normal 15-35)
  - glucose of 77
- LP was repeated during a headache:
  - OP of 43 cm water
  - 0 rbc, 930 wbc, protein 127 and glucose 46
  - IgG index elevated at 0.7, negative Oligoclonal bands
  - The patient's headache was relieved with drainage of fluid to a closing pressure of 20

Infectious disease testing

- Bacterial and fungal cultures of CSF were negative
- CSF Cryptococcal antigen was negative
- CSF Herpes PCR was negative
- RPR was nonreactive
- Serum Lyme titers were negative
- PPD was negative
- Chest X-ray was normal

Other Diagnostic Testing

- Serum C-reactive protein was elevated at 25 (normal <6) and ESR was 40
- ANA was positive at 1:320 dilution
- Anticardiolipin antibody testing was negative
- Rheumatoid factor was negative
- A mutation in the CIAS1 gene was identified = Muckle-Wells Syndrome

Muckle Wells Syndrome

- 3 related inherited inflammatory periodic disorders
  - NOMID= Neonatal Onset Multisystem Inflammatory Disease
  - FCAS= Familial Cold Autoinflammatory Syndrome
  - MWS= Muckle-Wells Syndrome
- CIAS1 gene mutation in each of these syndromes
- CIAS1 encodes the protein Cryopyrin
- Pyrin superfamily of proteins- with a 6 alpha-helix “death domain”, regulates proinflammatory signalling, leads to elevated serum IL-1 beta
• Periodic clinical symptoms, significant variability
• Triad of fevers, urticarial skin rash, arthritis
• Severe- neonatal inflammation; Mild- skin changes present in childhood and adulthood
• Other organs systems: conjunctivitis, autoimmune hepatitis, renal amyloidosis
• Neurologic: aseptic meningitis, hydrocephalus, TIA/Stroke, SNHL, cerebral atrophy, developmental delays
• Treatment- Anakinra- an injectable, recombinant IL-1 receptor antagonist

Case #1 Treatment
• Patient initially started on Diamox and Prednisone without obvious clinical benefit
• Started long-term treatment with Anakinra- has been headache-free since, off of diamox and prednisone; rash resolved
• Failed one attempt at post-treatment spinal tap, not repeated at parents’ request

Cryopyrin-associated periodic syndromes- Conclusions
• Inherited disorders with autoimmune symptoms
• Can present in childhood or adulthood
• Variable symptom severity and manifestation
• Can present first to the neurologist with headaches, hearing loss, developmental delays
• A rare disorder, but treatable

Case # 2
Consulting Information

- 16 year old girl with episodic “psychosis”

History of Present Illness

- Stereotyped episodes monthly since age 14, increasing in frequency
- Starts with a “nervous feeling” in her stomach, then she “loses grip of reality”
- Then an urge to yell out or do irrational things
- A complex auditory and visual hallucination- girl in room, talking in denigrating manner, hands touching her
- Often then will curl up in a ball or “flop on the floor” but no eye deviation, no T-C movements
- The episodes usually last 10 minutes, can last all day, mild post-event fatigue

Past Medical History/Family History

- In between episodes the patient attends school and is doing well- no cognitive or social changes noted
- Reports occasional marijuana use, but no other drugs or alcohol
- She has been on Risperidone for 6 months with no benefit and perhaps some worsening

- Born at term, developmentally intact
- Diagnosed with hypothyroidism at age 13, on supplementation with normal TSH levels
- No family history of seizures or psychiatric disease
- Some family history of autoimmune disease
Physical Examination

- Vital signs and growth parameters within normal limits
- No dysmorphisms, general exam unremarkable—no rash, no joint abnormalities, no thyroid mass
- MMSE full score, flat affect, lucid
- Cranial nerve exam normal
- Episodic mild tremulousness with posture or intention
- Otherwise normal motor, sensory and reflex examination

Q1 Which of the following is NOT a known medical cause of complex hallucinations?

A- Drugs of abuse
B- Seizure
C- Classic Migraine
D- Stroke
E- Vision loss
F- Metabolic disease

Medical Causes of Hallucination

- Migraine*
- Drugs of Abuse*
- Seizures*
- Sleep Disorders*
- Stroke*
- Vision Loss
- Metabolic Disorders
- Inflammatory disease
- Neurodegenerative disease

Migraine

- Common and classic migraine are NOT associated with complex visual hallucinations
- Complex visual hallucinations reported in familial hemiplegic migraine and migraine coma
- Seen in late stages of the attack, not aura
- Associated with ataxia
- May be different mechanism than typical migraine
Drugs of Abuse

- Acute intoxication with stimulants and hallucinogens
- Delirium tremens- alcohol withdrawal, benzo and barb withdrawal
- Lancet 2007 review of the literature shows an increased risk of psychosis in individuals who had ever used cannabis
  - Dose response effect
  - Independent of acute intoxication or confounding variables
  - Evidence for other affective variables such as depression or anxiety less strong

Seizures

- Temporal lobe epilepsy > occipital
- Pediatric Epilepsy- Panayiotopoulos type of Benign Occipital Epilepsy
  - Brief, infrequent spells characterized by visual phenomenon similar to migraine aura
  - More complex, more colors and shapes
  - Altered mental status, eye deviation
  - Followed by a migraine headache

Sleep Disorders

- Hypnagogic hallucinations- on falling asleep, associated with Narcolepsy
- Kleine-Levin Syndrome
  - Episodic, self-limited disorder
  - Primarily affects adolescent males
  - Hypersomnia, increased appetite, increase sexuality, psychiatric symptoms:
    - Irritability, depression, euphoria, disorientation, hallucinations
  - Etiology unknown, felt to be hypothalamic dysfunction

Stroke

- Peduncular hallucinosis-
  - From subcortical and brainstem pathology
  - Often posterior circulation TIA and stroke
  - Vivid, recurring, naturalistic themes- often scenic, complex details
  - Mostly visual, but also auditory and tactile
  - Associated with behavioral disturbances, abnormal sleep-wake cycle, abnormal eye movements, dysarthria, and ataxia
Medical causes of Hallucination

- Migraine*
- Drugs of Abuse*
- Seizures*
- Sleep Disorders*
- Stroke*
- Vision Loss - Charles Bonnett syndrome
- Metabolic Disorders - Porphyria, Wilson’s
- Inflammatory disease - Autoimmune
- Neurodegenerative disease - Dementia with Lewy bodies, Rapidly progressive dementias

Q2: Which neurotransmitter is thought to play a role in complex visual hallucinations?

A- Dopamine
B- 5HT-2
C- GABA
D- Glutamate

56% 21% 11% 12%

Neuroanatomy and Physiology of Complex Visual Hallucinations

- Serotonin and Acetylcholine
- Corticothalamic circuit
  - Retina and visual pathways
  - Dorsal lateral geniculate nucleus - with inputs from the brainstem/Reticular activating system
  - Visual Association Cortex

Case #2 Diagnostic testing

- An electroencephalogram was performed while the patient was actively hallucinating - no abnormalities noted
- An MRI of the brain was performed - no abnormalities noted
Lab tests
- Normal results:
  - Urine pregnancy
  - electrolytes, liver enzymes
  - ammonia, lactate, copper, ceruloplasmin, porphyria
  - drugs of abuse screen, heavy metal testing
  - ANA, RF, ESR
  - Athena Neuroephalitis Paraneoplastic profile
  - Lumbar puncture
- Abnormal results:
  - Thyroglobulin antibody elevated: 2494 IU/ml (normal <20)
  - Thyroperoxidase antibody elevated: 6.59 (normal <0.80)

Hashimoto Encephalopathy
- Also known as SREAT- Steroid responsive encephalopathy associated with autoimmune thyroiditis
- Autoimmune encephalopathy associated with Hashimoto’s thyroiditis

HE- clinical presentation
- Female more than male
- Typically 3rd to 5th decade
- Fluctuating symptoms
- Primarily recognized as cognitive impairment and behavioral change
- tremor, myoclonus, transient aphasia, sleep abnormalities, seizures, and gait difficulties
- Rapidly progressive dementia
- other neuropsychiatric symptoms

HE- Pathophysiology
- Unknown-not related to thyroid function
- Felt to be an autoimmune disorder, presenting in people with another autoimmune disorder
- Testing often normal- or can show signs of nonspecific inflammation in CSF
- MRI and EEG can have nonspecific abnormalities
- No thyroid antibodies found in CSF
Q3: The most important feature for diagnosis of HE or SREAT is:
A. Fluctuating course
B. Steroid responsiveness
C. Elevated thyroglobulin and thyroperoxidase antibodies

• Can be a progressive disorder leading to coma and death
• By definition it is a steroid-responsive disease - BUT relapse or recurrence of symptoms in about 1/3 of patients requiring other treatment
• Titer of antibodies does not correlate with disease severity, only PRESENCE of antibodies required - Note up to 20% of young adult women have detectable thyroid antibodies with no symptoms

Case #2 Treatment
• Treated with high dose IV solumedrol, with an oral taper over 3 months
• No further hallucinations or spells over 2 years
• Neuroleptics discontinued, returned to school part-time
• Remains anxious - a repeat trial of high dose prednisone did not help
• Continues regular marijuana use, has been reluctant to try other immunomodulation

Hashimoto Encephalopathy - Conclusions
• A diagnosis of exclusion
• A controversial entity
• An encephalopathy, which appears to have an autoimmune basis
• A potentially treatable disorder with disabling neurologic and psychiatric presentations