1st Annual Neurology Clinical Updates

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Carolinas HealthCare System Neurosciences Institute

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Harris Conference Center
1st Annual Neurology Clinical Updates

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The First Seizure: Evaluation and Management

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First Seizure: Overview

• Is it a seizure? The Nonepileptic “Seizure”
  – Syncope
  – Psychogenic
  – Other Paroxysmal Disorders
• Is it epilepsy? Predicting Recurrence
  – History
  – EEG
  – MRI
• Treat a first seizure? Risk v Benefit
  – Risk of Untreated Seizures
  – Risk and Benefit of Treatment

Is it a Seizure?
Common Causes of Transient Loss of Consciousness

• Syncope
  – Transient global cerebral hypoperfusion
  – 51% of Emergency Dept presentations
  – Prevalence of syncope ~ 15% for adolescent and older
• TIA
  – At least 80% (those in ICA distribution) do not cause LOC
  – Vertebrobasilar insufficiency can cause LOC (and death)
• Seizure
  – Transient abnormal synchronous neuronal discharges in the brain (cortical)
  – 8% of ED presentations
  – Prevalence of epilepsy ~ 0.75%
• Psychogenic Seizures
  – Transient alteration of behavior without organic basis
  – 14% of patients with “refractory epilepsy” admitted for epilepsy monitoring
Is it a Seizure?
Uncommon Causes of Transient Loss of Consciousness

- Sleep disorders (relatively common)
  - Parasomnias
  - Narcolepsy
- Migraine (relatively uncommon)
  - Basilar migraine
- Transient rise of ICP (very rare)
  - 3rd ventricular cyst, craniocervical pathology

Is it a Seizure?
Clinical Presentation – Syncope v. Seizure

<table>
<thead>
<tr>
<th></th>
<th>Syncope</th>
<th>Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provocation</td>
<td>Standing, heat, pain, micturation, cough</td>
<td>Sleep deprived, drugs, withdrawal, fever</td>
</tr>
<tr>
<td>Ictal Behavior</td>
<td>Faced, may see brief myoclonus</td>
<td>“Blank stare”, automatisms, tonic-clonic jerking, tongue-biting, incontinent</td>
</tr>
<tr>
<td>Duration</td>
<td>10-30 seconds</td>
<td>1-2 minutes</td>
</tr>
<tr>
<td>Postictal AMS</td>
<td>Minimal (few seconds)</td>
<td>Usually several minutes</td>
</tr>
</tbody>
</table>

Is it a Seizure?
Clinical Presentation – Psychogenic v Epileptic

<table>
<thead>
<tr>
<th></th>
<th>Psychogenic</th>
<th>Epileptic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Other 2 minutes or longer (variable)</td>
<td>Usually less than 2 minutes (stereotyped)</td>
</tr>
<tr>
<td>Onset</td>
<td>Often gradual, somewhat responsive for several minutes</td>
<td>Usually unresponsive in less than 30 seconds</td>
</tr>
<tr>
<td>Ictal Behavior</td>
<td>Eyes closed</td>
<td>“Blank stare”</td>
</tr>
<tr>
<td></td>
<td>Violent asynchronous thrashing (“fish out of water”); side-to-side head in, opisthotonus, Waxes and waxes (as a function of audience), variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tears very common</td>
<td>Automatons, tonic-clonic jerking</td>
</tr>
<tr>
<td>Injury</td>
<td>Rugs burns, some incontinence, but serious injury is very rare</td>
<td>Tongue-biting, broken bones, lacerations requiring sutures</td>
</tr>
<tr>
<td>Ictal Recall</td>
<td>Common, even if convulsing</td>
<td>Almost never after generalized convulsion</td>
</tr>
</tbody>
</table>
Is it Epilepsy?
Predicting Recurrence - Provocations

- **Acute CNS Injury**: Infection, Trauma, Inflammation
- **Drugs**: Toxicity and Withdrawal
  - Drugs of Abuse: Cocaine (not marijuana), EtOH
  - Medicines (Wellbutrin)
- **Fever**
- **Hypoglycemia** (I suppose, if insulin-induced and glucose < 30)
- Sleep deprivation (…in your dreams)
- Emotional stress (…you and me too)

Is it Epilepsy?
Predicting Recurrence – Seizure Type

- Partial Onset versus Generalized Onset:
  A Witness History is Key

- Secondarily Generalized Convulsions
  - Was there an aura? An aura is a simple partial seizure and indicates a focal onset.
  - Was there with a blank stare before the convolution started? This would suggest a complex partial seizure.
  - Was there head version at the start of the convolution? This suggests generalization from the contralateral hemisphere, i.e. focal onset.

Is it Epilepsy?
Predicting Recurrence: Provocation and Seizure Onset

- GTC, generalized onset + Provocation = 25%
- GTC, generalized onset - Provocation = 50%
- Focal onset (+/- GTC) – Provocation = 75%
Is it Epilepsy?
Predicting Recurrence - History

- **Remote Febrile Seizures**
  - There is a small increase risk associated with a history of febrile convulsions
  - Simple febrile convulsions (5% risk of developing epilepsy)
  - Complicated febrile convulsions (variable, up to 50%)

- **Family History**
  - The most common inherited syndromes:
    - Juvenile Myoclonic Epilepsy (JME) – the most common
    - Childhood Absence and Juvenile Absence
    - Benign Rolandic Epilepsy
  - Even in patients JME, a family history is often negative (50%)

Is it Epilepsy?
Predicting Recurrence – The Evaluation

- A potential etiology favors recurrence
- After the history and exam are obtained, there are three primary tools in evaluating a first seizure:
  - Labs
  - EEG
  - Neuroimaging (MRI/CT)
- Predictive value after the first unprovoked seizure:
  EEG > MRI/CT > LABS

Is it Epilepsy?
Predicting Recurrence - EEG

- EEGs are abnormal in 51% after 1st seizure
- This abnormality is epileptiform in 29%
  - The yield is increased if the EEG is obtained in the first 24 hrs after a seizure
  - An EEG with sleep or following sleep-deprivation may increase the yield
- Epileptiform discharges are associated with recurrence
  - Seizures recur in 49.5% of patients with epileptiform discharges, compared to 27.4% of patients with normal EEGs
  - Partial onset w/o provocation w/ focal epileptiform >95%
Is it Epilepsy?
Predicting Recurrence - MRI

• Neuroimaging reveals a relevant finding in about 10% after 1st seizure
• CT is adequate in an ER setting
• MRI is more sensitive than CT and preferred in non-emergent setting

Is it Epilepsy?
Predicting Recurrence - Labs

• Glucose, sodium
  – Practice Guidelines from the American College of Emergency Physicians recommends obtaining blood glucose and serum sodium routinely after a 1st seizure
  – American Academy of Neurology/American Epilepsy Society guidelines do not
• Toxicology screen
  – 3% of 1st seizures presenting to ER may reflect drug toxicity or abuse. However, the history usually suggests the provocation.
  – Routine toxicology screening is not required by AAN/AES for unprovoked 1st seizures in patients who recover to their baseline mental status
• CSF
  – 8% of selected cases yield positive results
  – Without other signs of CNS infection, though, there is no evidence favoring CSF studies in patients with unprovoked 1st seizures who recover to their mental status baseline

Treat the First Seizure?

• Treating the first seizure will reduce the risk of immediate recurrence in the next year
• Treating the first seizure will not afect the long-term likelihood of achieving remission
• So, everyone will treat after a 2nd seizure — what is the rationale for anticonvulsant prophylaxis after the 1st seizure?
Treat the First Seizure?

• Your decision will be based on
  – Likelihood of recurrence
  – Consequences of the next seizure
  – Risk of treatment

Treat the First Seizure?

• To review recurrence data
  – Provoked generalized convulsion ~ 25%
  – Unprovoked generalized convulsion ~ 50%
  – Unprovoked partial-onset seizure ~ 75%
  – With relevant etiologic findings
    • Focal neuroimaging, focal neurologic exam >90%
    • Focal epileptiform discharges on EEG >95%
  – In the absence of etiologic data, the certainty of recurrence will rarely support treatment of the first seizure

Treat the First Seizure?

• Risks of a second seizure
  – Mortality associated with recurrent major convulsions, small but not negligible (increased by 2-fold over healthy subjects)
  – Does not affect long-term likelihood of remission
  – Assess in context of patient’s occupation, daily activities, other health issues, etc.
Treat the First Seizure?

- Risks of Anticonvulsant Therapy
  - Life-threatening side-effects
    - Frequency is very low except in specific situations (e.g. Felbamate ~ 1/5000 deaths)
  - Teratogenicity
    - Typically in monotherapy ~3%
  - Adverse effects (non-life threatening)
    - Neurotoxicity
    - General medical

First Seizure: In Summary

- History
  - Consider non-epileptic etiologies (medical and psychogenic)
  - Look for provocations
  - Get a good (witness) description of the seizure
  - Decide if focal v generalized

First Seizure: In Summary

- Evaluation
  - Labs – obtain if clinical context warrants
    - CBC/CMP (usually)
    - toxicology screen (often)
    - CSF (rarely)
  - Neuroimaging
    - CT emergently
    - MRI electively
  - EEG
    - Preferably in the 1st 24 hours
First Seizure:
In Summary

- Treating 1st Seizure (anticonvulsant prophylaxis)
  - Rarely indicated without data suggesting etiology
    (e.g. neuroimaging, EEG)
  - With known etiology, may consider treating after the
    1st unprovoked seizure.
  - Decide on a case-by-case basis based on
    - The likelihood of seizure recurrence
    - The consequences of the next seizure (for that patient)
    - The risks of the proposed anticonvulsant

Treat the First Seizure?
Essential References

  unprovoked first seizure in adults (an evidence-based review):
  Report of the Quality Standards Subcommittee of the American
- Hirtz D, et al. Practice parameter: evaluating a first nonfebrile
- Berg AT, Shinnar S. The risk of seizure recurrence following a first
  unprovoked seizure: a quantitative review. Neurology 41:965-972,
- Fisher RS, et al. Epileptic seizures and epilepsy: Definitions
  proposed by the International League Against Epilepsy (ILAE) and
  the International Bureau for Epilepsy (IBE). Epilepsia 46:470-472,
  2005.
- Ettore Beghi (ed). The Management of a First Seizure – Still a Major
Goals of this Presentation

- Report on more recent landmark research in stroke care
- Review stroke in the young including gaps in knowledge of caring for the young stroke patient
- all in 30 minutes or less!

Landmark Research in Stroke

- Carotid Stenosis
- Intracranial Arterial Stenosis
- Patent Foramen Ovale and Paradoxical Emboli
- Expanded IV TPA Window
- Acute Intracranial Arterial Occlusion
- Antithrombotic Agents for Atrial Fibrillation
- Aspirin and Plavix Combination Therapy for Stroke Prevention
Carotid Stenosis

August 1991 NASCET: North American Symptomatic Carotid Endarterectomy Trial

“CE is highly beneficial to patients with recent TIA (hemispheric, retinal) or non-disabling strokes and ipsilateral high-grade stenosis (70-99%) of the internal carotid artery.”
Carotid Stenosis

July 2010 CREST: Carotid Revascularization Endarterectomy vs. Stenting Trial

“Among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, MI, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization did not differ significantly in the group undergoing carotid-artery stenting and the group undergoing carotid endarterectomy.”

Carotid Stenosis

CREST did show a higher risk of stroke in the peri-procedural period (from randomization to 30 days after procedure) with stenting, and a higher risk of MI with endarterectomy.

Intracranial Arterial Stenosis
Intracranial Arterial Stenosis

September 2011 SAMMPRIS: Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis

“In patients with intracranial arterial stenosis, aggressive medical management was superior to percutaneous transluminal angioplasty and stenting (PTAS), both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected.”

Patent Foramen Ovale

2009 Last report on the risk of stroke with PFO by the Quality Standards Subcommittee of the American Academy of Neurology:

“PFO alone is not associated with increased risk of subsequent stroke or death among medically treated patients with cryptogenic stroke.”

“However, both PFO and ASA possibly increase the risk of subsequent stroke (but not death) in medically treated patients younger than 55 years.”
Patent Foramen Ovale

- PFO can be a conduit for paradoxical emboli to the brain
- But PFO is commonly found in normal populations
- What makes some people vulnerable to stroke from PFO?
- The challenge is to identify the subset of cryptogenic stroke patients who are likely to have experienced paradoxical embolization from PFO
- So what might increase the chance of a PFO contributing to stroke?

Risk factors for PFO-related stroke:

- PFO size
- Associated ASA, eustachian valve anatomy
- Hemodynamic parameters
- Presence of venous thrombus (MRI of leg, pelvis, abdomen)
- Hypercoagulable genetic variables

PFO Occluder
The case for PFO closure to prevent stroke vs. medical management remains unclear, with trials that have been inconclusive or either weaken or strengthen the argument for closure.
PFO Literature

March 2012 CLOSURE 1: Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

“In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA.”

PFO Literature

March 2013 PC Trial: Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

“Closure of a patent foramen ovale for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy.”

PFO Literature

March 2013 Respect Trial: Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

“In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks.”
PFO Literature

"It is better to have useless knowledge than to know nothing."
— Seneca

IV TPA for Acute Ischemic Stroke

IV t-PA

December 1995: Tissue Plasminogen Activator for Acute Ischemic Stroke

"Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months.”
IV t-PA

September 2008: Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

“As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage.”

Acute Intracranial Arterial Occlusion

e.g. Basilar Arterial Occlusion

Acute Intracranial Arterial Occlusion

e.g. Carotid Terminus: T-lesion
Acute Intracranial Arterial Occlusion

Embolectomy – MERCI Retriever

MERCI Retriever
Intra-Arterial Stroke Rescue

March 2013 MR RESCUE: Mechanical Retrieval and Recanalization of Stroke Clot Using Embolectomy

“A favorable penumbral pattern on neuroimaging did not identify patients who would differentially benefit from endovascular therapy for acute ischemic stroke, nor was embolectomy shown to be superior to standard care.”

Intra-Arterial Stroke Rescue

March 2013 IMS III Study Group: Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

“The trial showed similar safety outcomes and no significant difference in functional independence with endovascular therapy after intravenous t-PA, as compared with intravenous t-PA alone.”
Intra-Arterial Stroke Rescue

March 2013 Synthesis Expansion Trial: Endovascular Treatment for Acute Ischemic Stroke

“In patients with acute stroke endovascular therapy is not superior to standard treatment with intravenous t-PA.”

Atrial Fibrillation and Stroke

Atrial Fib

Atrial Fibrillation and Stroke
Atrial Fibrillation and Stroke

September 2011: Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

“In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.”

Atrial Fibrillation and Stroke

September 2009: Dabigatran versus Warfarin in Patients with Atrial Fibrillation

“In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.”

Stroke Prevention with Antiplatelet Therapy

• ASA guidelines recommend stroke patients be on antiplatelet therapy of some kind (e.g. aspirin, Plavix, or Aggrenox)
• But what about adding a second medication when stroke or TIA recurs?
Aspirin plus Plavix to Prevent Stroke

July 2004: Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial.

"Adding aspirin to clopidogrel in high-risk patients with recent ischemic stroke or transient ischemic attack is associated with a non-significant difference in reducing major vascular events. However, the risk of life-threatening or major bleeding is increased by the addition of aspirin."

Aspirin Plus Plavix to Prevent Stroke

August 2012: Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

"Among patients with recent lacunar strokes, the addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke and did significantly increase the risk of bleeding and death."

Aspirin Plus Plavix to Prevent Stroke

July 2013 CHANCE Trial: Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

"Among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage."
POINT Trial

POINT: Platelet-Oriented Inhibition in New TIA (and minor ischemic stroke)

POINT is a randomized, double-blind, multicenter clinical trial to determine whether clopidogrel 75mg/day (after a loading dose of 600mg) is effective in improving survival free from major ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death) at 90 days when initiated within 12 hours time last known free of new ischemic symptoms of TIA or minor ischemic stroke in subjects receiving aspirin 50-325mg/day.

Stroke in the Young

For stroke:
• "young" is under 40
• "children" are under 18
Stroke in the Young

Trends in Stroke Hospitalizations and Risk Factors in Children and Young Adults: 1995-2008
Annals of Neurology 2011 70;5:713-721

- CDC report on stroke admissions
- 3 age groups: 5-14, 15-34, 35-44
- Rate of stroke from 1995-1996 to 2007-2008

For age groups 15-34 and 35-44 the increase in stroke hospitalization rate from 1995 to 2008 was 30 to 37% higher!

Largest stroke increase in men:
- Men 35 to 44 strokes up by 50%
- Men 15 to 34 strokes up by 46%
- Boys 5 to 14 strokes up by 51%

For women:
- Women 35 to 44 strokes up by 29%
- Women 15 to 34 strokes up by 23%
- Girls 5 to 14 strokes up by 3%
Stroke in the Young

- Overall increase mostly ischemic strokes
- Significant increases were seen in traditional risk factors

10% of all strokes occur in the young – twice as high as long thought

Stroke in the Young

In adults:
- 80 to 85% of strokes are ischemic
- 15 to 20% of strokes are hemorrhagic

In children:
- 55% of strokes are ischemic
- 45% of strokes are hemorrhagic

Stroke in the Young

Stroke in children often from rare but identifiable disorders:
- Cardiac embolism
- Non-atherosclerotic vasculopathies
- Prothrombotic states
- Cerebral vasculitis
- Ruptured vascular malformations
- Bleeding diathesis
- Sympathomimetic drug abuse
- Intracranial tumoral bleeding
Stroke in the Young

• IV t-PA is indicated only in adults
• Used with some regularity in children as young as 15 years ("big kid = little adult")
• Absence of guidelines has led to wide ranges of dosing as well as timing of administration
• Absence of indication in children and any guidelines has also led to nihilism in pediatric stroke rescue

Thrombolysis in Pediatric Stroke (TIPS) Trial:

 Five-year multi-center international safety and dose-finding study of intravenous (IV) t-PA in children with acute ischemic stroke (AIS) to determine the maximal safe dose of intravenous Tissue Plasminogen Activator (IV-t-PA) among three doses (0.75, 0.9, 1.0 mg/kg) for children age 2-17 years within 4.5 hours from onset of acute AIS

Stroke in the Young

• Primary Outcome: symptomatic intracranial hemorrhage
• Secondary Outcome: 3 month outcome and pharmacokinetics of t-PA
• Estimated enrollment 36 patients from 2012 to 2016
Stroke in the Young

Sponsor:
- Seattle Children's Hospital

Collaborators:
- The Hospital for Sick Children
- Medical College of Wisconsin
- University of Texas at Austin
- Alberta Children's Hospital
- McMaster University

Key Summary Points

Stroke in the Young
- IV t-PA evidence-based guidelines are on the way
- Strokes are often from rare but identifiable disorders
- Stroke percentages nearly equal parts ischemic and hemorrhagic
- Ischemic strokes have been on the rise, especially in males
- Significant increases in traditional risk factors seen

Key Summary Points

Stroke in Adults - prevention
- POINT trial testing aspirin plus Plavix for short-term stroke recurrence prevention
- Aspirin plus Plavix does not reduce long-term stroke recurrence risk, but does increase bleed risk
- Current stroke guidelines support antiplatelet therapy with one agent (e.g. aspirin, Plavix, or Aggrenox)
- Dabigatran and rivaroxaban are alternatives to warfarin for stroke prevention in atrial fibrillation
Key Summary Points

Stroke in Adults – stroke rescue
- Endovascular therapy is not superior to IV t-PA (SYNTHESIS Trial)
- Endovascular therapy after IV t-PA similar to IV t-PA alone (IMS III Trial)
- Embolectomy not superior to IV t-PA (MR RESCUE Trial)
- IV t-PA window is 4.5 hours (with some exclusions)

Key Summary Points

Stroke in Adults – prevention
- PFO closure for secondary stroke prevention not found to be better than medical therapy alone
- In intracranial arterial stenosis medical therapy superior to angioplasty and stenting
- Carotid endarterectomy and carotid stenting offer equivalent efficacy

Management of the Stroke Patient: Young and Old

Thank You.
Headache
Anita Wu, MD
1st Annual Neurology Clinical Updates Symposium

• Migraine. Cumulative lifetime prevalence women 43%, men 18%. Girls 4% and boys 5% but after puberty percentages change.

• Tension Headache. Lifetime prevalence 46%
• Cluster. 0.1 frequency.

• About 1% of ER visits and physician visits are for headache.

• Over 90% of primary headaches are migraine and tension headache

More people suffer from Migraine than from Diabetes or Asthma

[Graph showing prevalence of Migraine, Diabetes, Asthma, and Epilepsy]
In 2004, the percentage of adults who experienced a severe headache or migraine during the preceding 3 months decreased with age, from 16% among persons aged 25–44 years to 9% among persons aged 65–74 years. In every age group, the proportion of women who experienced a severe headache or migraine was greater than that of men.


WHERE DO MIGRAINE SUFFERERS SEEK MEDICAL CARE?

Of the migraine sufferers who consult a doctor, about two-thirds consult primary care physicians, which includes general practitioners, family practitioners, internists, and pediatricians; 16% consult neurologists or headache specialists.

Lipton RB, Stewart WD, Norton DL. Medical consultation for migraine results from the American Migraine Study II. Headache, 1998;38(7):475-84.

Migraine Mechanism

As currently understood, the trigeminal nucleus starts off the process. Due to a variety of factors, the trigeminal nucleus becomes overactive. This leads to activation of the trigeminal nerve (which is responsible for sensation of the face, scalp, and some blood vessels). Among other things, the activation of the trigeminal nerve stimulates blood vessels in the brain causing them to enlarge (dilate). When the blood vessels enlarge, they begin to release substances into the brain that irritate it (CGRP, substance P, neurokinin A), leading to local inflammation. The inflammation then stimulates nerve endings around the blood vessel. These nerves then feedback to the TNC, further activating it.

Migraine vs. Tension Headache

**Migraine**
- >5 attacks lasting 4-72 hours
- 2 or more of the following:
  - unilateral, pulsating, moderate to severe intensity, aggravation by routine physical activity
  - Nausea or vomiting and/or photophobia/phonophobia
  - Not attributable to another disorder

**Tension**
- >10 attacks lasting 30 minutes to 7 days
- 2 or more of the following:
  - mild to moderate intensity, bilateral, not pulsating, not aggravated by routine physical activity
  - Neither nausea or vomiting; either phono or photophobia
  - Not attributable to another disorder
Exacerbating Factors

- Skipping meals
- Stress
- Medication withdrawal
- Caffeine withdrawal

Preventive Management

Level 1: Propranolol, Timolol, Divalproax Sodium, Amitriptyline

Level 2: Atenolol, Metoprolol, Nimodipine, Verapamil, Gabapentin

Level 3: Topiramate, Sertraline, Venlafaxine,

Others: Celecoxib, Cyproheptadine, Clonidine, Guanfacine, Lisinopril,

Preventive Management

Supplements

- Magnesium 400mg daily (up to twice daily)
- Riboflavin 400mg
- Coenzyme Q10 100mg three times daily
- Butterbur (but toxic)
- Feverfew (extract studied not available in the US)
- Acupuncture
- Capsaicin (cluster)

- Exercise 40 minutes 3 times a week
- Caffeine limitation
Abortive Management

- Triptans
- Tylenol-NSAIDs: Aspirin, Ibuprofen, Ketorolac, Naproxen, Diclofenac, Etodolac, Ketoprofen
- Antiemetics: Metoclopramide, Prochlorperazine, Promethazine, Ondansetron
- Oral steroids

IV

Ketorolac 30 to 60 IM
Magnesium 1000mg IV
Valproate 300 to 500mg IV
Chlorpromazine, Prochlorperazine, Metoclopramide
Dihydroergotamine

Figure 1: Effects of the Various Triptans on Patients with Migraine. The mean difference in percent change from baseline for each 2-hour interval is shown. The error bars represent the 95% confidence interval for the mean. The reference treatment is sumatriptan 100 mg IV.
OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine

**ABSTRACT**

**Objective:** To assess the effects of treatment with onabotulinumtoxinA (Botox, Allergan, Inc., Irvine, CA) on health-related quality of life (HRQoL) and headache impact in subjects with chronic migraine (CM).

**Methods:** The Phase III, Double-Blind, Randomized, Crossover, Placebo-Controlled, Multicenter Study (PREDICT1; NCT01546322) included 128 patients with CM who received 155.5 units onabotulinumtoxinA or placebo at 0, 4, and 12 weeks. The primary endpoint was change in mean Migraine-Specific Quality of Life (MSEQ) over 12 weeks. Study sites were in the United States and Canada. Data were analyzed based on modified intention-to-treat and per protocol. A post hoc analysis was performed in the onabotulinumtoxinA group to assess the impact on MSEQ and 6-minute walking distance (6MWD) for each injection.

**Results:** A total of 128 patients were enrolled in the study. Changes in MSEQ and 6MWD were compared between the onabotulinumtoxinA and placebo groups. The changes in MSEQ and 6MWD were significant in the onabotulinumtoxinA group compared with placebo. Treatment with onabotulinumtoxinA significantly reduced pain, disability, and fatigue, and improved physical function, vitality, and role limitations in the onabotulinumtoxinA group compared with placebo. Treatment with onabotulinumtoxinA significantly reduced pain, disability, and fatigue, and improved physical function, vitality, and role limitations in the onabotulinumtoxinA group compared with placebo. Treatment with onabotulinumtoxinA significantly reduced pain, disability, and fatigue, and improved physical function, vitality, and role limitations in the onabotulinumtoxinA group compared with placebo. Treatment with onabotulinumtoxinA significantly reduced pain, disability, and fatigue, and improved physical function, vitality, and role limitations in the onabotulinumtoxinA group compared with placebo.
Efficacy and tolerability of MK-0974 (telcapegan), a new oral antagonist of calcitonin gene-related peptide receptor, compared with sumatriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial

Summary

MK-0974 is a potent and selective calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is a neuropeptide involved in the pathogenesis of migraine. We aimed to compare the efficacy and tolerability of MK-0974 with sumatriptan for the acute treatment of migraine.

Methods

A randomised, double-blind, placebo-controlled, parallel-group, multicentre trial that recruited patients with migraine.CGRP antagonist MK-0974 was given as a single oral dose of 5, 10, or 20 mg twice daily, and sumatriptan was given as an oral dose of 25 or 50 mg. The primary outcome was the reduction in pain intensity from baseline to 2 hours after treatment.

Findings

1,026 patients were randomly assigned to receive MK-0974 (5 mg, 10 mg, or 20 mg) or sumatriptan (25 mg or 50 mg). The median time to pain-free status was 4.0 hours in the MK-0974 group and 2.0 hours in the sumatriptan group. The median reduction in pain intensity from baseline to 2 hours after treatment was 4.4 in the MK-0974 group and 5.0 in the sumatriptan group. The median time to next headache was 0.8 hours in the MK-0974 group and 0.8 hours in the sumatriptan group.

Interpretation

MK-0974 is effective and well tolerated as an acute treatment for migraine with efficacy comparable to that of sumatriptan 25 mg, but with different adverse effects.

Funding

Research Christine Luft.

Casein kinase i5 mutations in familial migraine and advanced sleep phase

Bennet NC, Beise S, Beise JR, Zvili A, Hallows WC, Szuver S, Lee H, Jones C, Duf Fr, Charles AG, Tsuchiya L

Department of Neurology, University of California, Los Angeles, CA, 90095, USA.

Abstract

Migraine is a common disabling disorder with a significant genetic component, characterized by severe headache and often accompanied by nausea, vomiting, and light sensitivity. We identified two families, each with a distinct missense mutation in the gene encoding casein kinase i5 (CK5), in which the mutation cosegregated with both the presence of migraine and advanced sleep phase. The resulting alterations (T444A and H62P) occur in the conserved catalytic domain of CK5, where they cause a reduced enzymatic activity. Mice engineered to carry the CK5 knock-out allele were more sensitive to pain after treatment with the migraine trigger norepinephrine. CK5-444A mice also exhibited a reduced threshold for cortical spreading depression (believed to be the physiological analog of migraine aura) and greater arteriolar dilation during cortical spreading depression. Anthocorty from CK5-444A mice showed increased spontaneous and evoked calcium signaling. These genetic, cellular, physiological, and behavioral analyses suggest that decreases in CK5 activity can contribute to the pathogenesis of migraine.

WHY IS MIGRAINE MISSED FOR TENSION-TYPE HEADACHE?

- Neck pain is very common (80%)
- Pressure is a common migraine trigger
- Migraine headache is often neural (10%)

The pain process is a product of three factors, such as: activities at the sensory portions of pain-producing structural elements, centralised with reduced function of the contralateral pain-resistant function. To avoid pain, the pain process must be reversed, which is often not possible. Nerve endings are often split, the tissue is then no longer able to fire, and the pain process is reversed. Therefore, tension headaches may be more frequent in migraineurs.
Tension Headache Treatment

- NSAIDS Ibuprofen 200mg to 800mg
- Naproxen sodium 375mg to 500mg

Tension Headaches

- Episodes last 30 minutes to 7 days
- Lifetime prevalence 46%
- Difficult to distinguish from migraine

Why is Migraine Frequently Mistaken for Sinus Headache?

- Pain is often localized over the sinuses
- Migraine is usually triggered by weather changes
- Treating episodic migraines common among both groups
- Sinus medication may help migraine
SUNCT/SUNA

- Short lasting neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic symptoms
- Unilateral orbital supraorbital or temporal pain may be in any part of head.
- 3 temporal profiles: 1. single stabs short-lived 2. groups of stabs 3. longer attacks comprised of many stabs between which the pain does not return to baseline.
- Features favoring SUNCT/SUNA vs. trigeminal neuralgia include prominent distribution of pain in the ophthalmic, ability of cutaneous stimuli to bring on attacks, and lack of refractory period to these triggers
- Vs. paroxysmal hemicrania indomethacin not reliably effective
- Lamotrigine is the most effective treatment 2/3 responsive. Topiramate and gabapentin may also work.

Cluster

- 0.1% population
- 3 male: 1 female (may be 6 men: 1 woman)
- Core features: circadian periodicity in terms of active and inactive periods over time and the lateralization of the pain
- Episodes of 1 or 2 attacks of relatively short duration 15 to 180 minutes with unilateral pain which occur daily for 8-10 weeks yearly. Asymptomatic between attacks

Cluster

- Retroorbital or temporal intense pain. Often ipsilateral autonomic symptoms
- Treatment abortive 100% oxygen high flow 12 to 15L/min for 15-20 minutes
- Sumatriptan injectable or sumatriptan nasal spray 20mg or zolmitriptan 5mg.
- Preventive 1st line. Verapamil. Also tried: lithium, topiramate, gabapentin
Deep brain stimulation for medically intractable cluster headache

Ger A. Silny1, Sephr Sato2, Philip A. Stagg2

1Department of Neurology, University of Washington, Seattle, WA
2Department of Neurology, Stanford University Medical Center, Stanford, CA

ABSTRACT

Cluster headache is the most severe primary headache disorder known. Ten to 20% of patients are medically intractable, spiking an unmet need for alternative therapies. Here, we show successful stimulation of clusters in a patient with a history of medically intractable cluster headache using a bilateral, subthalamic, deep brain stimulation (DBS) system. This patient was treated with bilateral DBS using electrodes placed stereotactically in the subthalamic region. The patient reported a 70% reduction in cluster frequency and an 80% reduction in cluster intensity. This study demonstrates the potential of DBS for the treatment of medically intractable cluster headache.

Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment: Pathway CH-1: A randomized, sham-controlled study

Joan Schonwasser1, Rigo H. Aguirre2, Jennifer H. Jensen1, Michael L. Day3, John J. Laine2, Charles Goul1, Amy M. Goodman3, Anthony Capanna1 and Arne May1

Abstract

Background: The parasympathetic component of the trigeminal parasympathetic system, innervated through the sphenopalatine ganglion (SPG), has potential to relieve pain and inflammatory states in the head and neck. We tested an SPG stimulation device that delivers a constant current and variable frequency to relieve pain.

Methods: We performed a randomized, sham-controlled, parallel-group study in 2012 to 2017. Adults with established cluster headache (CH) were randomized to undergo active (n = 10) or sham (n = 10) SPG stimulation. The study consisted of 3 treatment periods: active, sham, and washout. The primary outcome was pain relief at 20% in at least 5 of 7 days within a treatment period.

Results: Of 28 patients, 24 completed the randomized experimental period. Pain relief was achieved in 6 of 7 days in 5 of 10 active-arm patients, but not in any sham-arm patients (P < 0.001). Median percent pain reduction during active treatment was 57.5 (IQR 15.5–66.9) in active-arm patients and 0 (IQR 0–5) in sham-arm patients (P = 0.001). Both active and sham treatments were well tolerated.

Conclusions: SPG stimulation is safe and effective for the treatment of acute CH. Further studies are needed to evaluate the long-term efficacy and safety of SPG stimulation as a treatment for CH.
Trigeminal Neuralgia

- Female 3: 2 male
- Typically unilateral, 4% bilateral
- Characterized by brief paroxysms, similar to a spasm or an electric shock in one or more trigeminal divisions. Often a dull longlasting pain between attacks
- Mandibular or maxillary most frequently involved
- Pain may be provoked by specific trigger points or by stimuli such as washing, shaving, talking, or brushing the teeth.
- In the elderly, the cause is usually vascular compression of the trigeminal nerve due to abnormal arterial loops near the trigeminal nerve root entry zone.
- Other causes: tumors, malignancy, demyelination, multiple sclerosis, etc.
- Baclofen least side effects; carbamazepine.
- Microvascular decompression. Janetta procedure

Thunderclap Headache


Thunderclap headache: symptom of unruptured cerebral aneurysm.
Day JV, Rabin H.

Abstract:
Many patients with a ruptured berry aneurysm report an intense sentinel headache of sudden onset in the weeks before rupture. Such headaches have been attributed to a leak of blood, which implies that partial rupture has occurred. A case is reported of a patient who had severe headaches which seemed to be caused by an unruptured cerebral aneurysm, accompanied by diffuse cerebral vasospasm. Headache episodes with the thunderclap profile may require angiography for diagnosis even if the cerebrospinal fluid is bloodless.
**Sudden-Onset Headache**

**Primary**
- Vascular headache
- Tension-type headache
- Migraine
- Carotid headaches
- Cephalgia

**Secondary**
- Cerebral aneurysm
- Subarachnoid hemorrhage
- Intracranial hypertension
- Brain tumors
- Pelphane's headache
- CNS infections

**Diagnostic criteria for idiopathic sudden-onset headache**

1. Very severe pain intensity
2. Intermittent or dysrhythmic onset of pain >30 minutes
3. Appropriate investigations exclude the presence of an underlying cause. These include abdominal ultrasonography, cerebral doppler, venous sinus study, brain magnetic resonance imaging, intracranial hypertension, and acute hypertension crisis.

**Comment**

Sudden-onset headaches may occur spontaneously or may be precipitated by the Valsalva maneuver, sexual and the menstrual cycle, or exercise. Headaches associated with intracranial aneurysm may occur infrequently, over subsequent months to years. Investigations are usually necessary to rule out secondary causes. In a 3-5 percent of patients, headache may be caused by nasociliary segment cranial monosynapsis, which resolves within weeks to months.

![Image of diagnostic criteria for idiopathic sudden-onset headache]

**CSF Xanthochromia After SAH**

**Spectrophotometry**

<table>
<thead>
<tr>
<th>Time Post-SAH</th>
<th>Xanthochromia</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>40</td>
</tr>
<tr>
<td>1 week</td>
<td>100</td>
</tr>
<tr>
<td>2 weeks</td>
<td>100</td>
</tr>
<tr>
<td>3 weeks</td>
<td>50</td>
</tr>
<tr>
<td>4 weeks</td>
<td>40</td>
</tr>
</tbody>
</table>

**Reference**

1. Headache: a vector guidance of 0-4 and the 17 years or younger class headache practices should be performed. Medical management is not to be used by a primary healthcare provider. AE (asymptomatic) is defined as a headache that does not interfere with daily activities. Medication is given if the headache is severe and poses a risk to the patient's life.

**Note:** Xanthochromia is the yellow discoloration of the CSF that occurs after subarachnoid hemorrhage (SAH). Xanthochromia can be detected by examining the filtered CSF for the presence of bilirubin. It is seen in about 30 to 40% of SAH cases. Xanthochromia is detected in patients with SAH occurring 1-2 days after the hemorrhage, and it is detectable for about 5-10 days after the hemorrhage.
Systematic review of reversible cerebral vasoconstriction syndrome

Ahmna Sattar1, Georges Manousakis1,2, and Matthew J Jensen1,3

1 Department of Neurology, University of Wisconsin Hospital and Clinics, 600 Highland Avenue, Madison, WI 53705-2811, USA
2 Washington University School of Medicine, 660 S Euclid Avenue, St Louis, MO 63110, USA

Abstract

Reversible cerebral vasoconstriction syndrome (RCVS) is a cerebrovascular disorder associated with multifocal arterial constriction and dilation. RCVS is associated with nontraumatic subarachnoid hemorrhage, pregnancy and exposure to certain drugs. The primary clinical manifestation is repeated sudden-onset and severe (“thunderclap”) headaches over 1–3 weeks, often accompanied by nausea, vomiting, photophobia, confusion and blurred vision. The primary diagnostic dilemma is distinguishing RCVS from primary CNS angiitis. Diagnosis requires demonstration of the characteristic “string of beads” on cerebral angiography with resolution within 1–3 months, although many patients will initially have neutral vascular imaging. Many treatments have been reported to ameliorate the headaches of RCVS, but it is unclear whether they prevent hemorrhage or ischemic complications.

![Image](image.png)

Figure 1: Cerebral vasoconstrictions (a) and their resolution (b) on magnetic resonance angiography in patients with reversible cerebral vasoconstriction syndrome.

Table 1. Potential etiologies and associated conditions of reversible cerebral vasoconstriction syndrome

<table>
<thead>
<tr>
<th>Primary diagnostic hypothesis</th>
<th>Potential etiologies and associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy and the postpartum period</td>
<td>Migraine associated with sexual activity</td>
</tr>
<tr>
<td>Exposure to vascular substances</td>
<td>Recreational substances, trauma, eosinophilic, phosphorus, magnesium, leukocyte</td>
</tr>
<tr>
<td>Glioblastoma mimicking tumors</td>
<td>Peutz-Jeghers syndrome, stromal tumors, gliomas</td>
</tr>
<tr>
<td>Extra or intracranial arterial dissections or aneurysms</td>
<td>Cerebral dissection, unruptured intracranial aneurysm</td>
</tr>
<tr>
<td>Intracranial disorders or surgeries</td>
<td>Traumatic arterial injury, arteriovenous malformation, vasculitis</td>
</tr>
<tr>
<td>Others</td>
<td>Aneurysmal subarachnoid hemorrhage, vasospasm</td>
</tr>
</tbody>
</table>

Table 2. Diagnostic criteria for reversible cerebral vasoconstriction syndrome

1. New or recurrent severe headache typically lasting 1–3 weeks.
2. Cerebral angiography demonstrating multifocal arterial constriction and dilation.
3. Symptoms resolve within 1–3 months.

Table 3. Therapeutic options for reversible cerebral vasoconstriction syndrome

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Prednisone, methylprednisolone</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Warfarin, heparin</td>
</tr>
<tr>
<td>Other medications</td>
<td>Dopamine, serotonin, calcium</td>
</tr>
</tbody>
</table>

Reference

Paroxysmal Hemicrania
- 2-30 minutes usually occur several times daily
- Involves ophthalmic division
- Always unilateral although may shift sides
- 2/3 with photo or phonophobia, 80% restless or agitated.
- Do not occur at night (vs cluster)
- 10% have mechanical trigger. C2, C4, C5, bending and rotating head, greater occipital nerve
- Indomethacin responsiveness characteristic. COX II inhibitors also helpful
- Greater occipital nerve injection with lidocaine and methylprednisolone

Hemicrania Continua
- Continuous unilateral headache varies in intensity without complete resolution
- IHS criteria limits definition to responsiveness to indomethacin
- May have lacrimation, conjunctival injection, nasal symptoms, miosis, ptosis
- Can try COXII
Quick Review

• Migraine and Tensions headaches are common
• Triptans and NSAIDs work through different mechanisms and the combination of these is often helpful where one alone is inadequate for abortive use
• Headaches that reach their maximum quickly (within 30 seconds) and are severe in quality may be thunderclap headaches and warrant further investigation with imaging
Update on Alzheimer's Disease and Dementia
Arvind Vasudevan, MD

Objectives
- Brief Overview of Alzheimer Dementia
- Diagnostic principles to distinguish between Dementia and Delirium
- Clinical Screening tools in the Evaluation of Cognitive Impairment
- Appropriate workup in the setting of a patient with a new Cognitive Impairment
- Treatment options for a patient with a Cognitive Impairment

Alzheimer’s Dementia
- Most common form of Dementia
- Estimated to “affect” more than 4 million Americans.
- 2.4-3.1 million will care for people with AD.
- Cost of caring for individual estimated more than $47,000 per year.
Pathology
Two Primary Cardinal Lesions
- Neurofibrillary Tangle
- Senile Plaque

Clinical Manifestations
- Memory Impairment
- Language
- Visuospatial Skills
- Insight

Delirium vs Dementia
- Difficulty in maintaining attention
- Develops over hours to days
- Psychomotor behavioral and emotional disturbances
- Usual metabolic/medical disturbance
- Attention is usually spared
- Develops over months to years.
- Behavioral and emotional fluctuations are not as present on an hourly/daily basis.
- Sundowning
Delirium Screening Tools

Confusion Assessment Method (CAM)
1. Acute Change from Baseline?
2. Inattention and Focus?
3. Disorganized thinking?
4. Altered Level of Consciousness?
1+2 AND either 3 or 4.

Number Sequence
7 Digit Number Sequence

Cognitive Screening Tools

- Mini-Mental Status Examination (<24 suggests dementia)
- Montreal Cognitive Assessment (Superior)
- Clinical Dementia Rating (Time-Consuming)
- Neuropsychological Testing

Cognitive Workup

- B12 Deficiency (B12)
- Hypothyroidism (TSH)
- No clear data to support/refute ordering routine lab studies.
- Screening for Syphilis is NOT recommended without high clinical suspicion.
- Genetic testing is NOT recommended.
- Screening for Depression should ALWAYS be done.
- AAN recommends structural neuroimaging with either noncontrast head CT or MRI (controversial)

Picture Courtesy of Dr. David Cox and the CDC (Wikipedia)
Red Flags Prompting Further Workup

- Age <60
- Focal Neurological Signs
- Duration of symptoms <2 years

These recommendations have a low sensitivity but should probably still prompt further workup.

Possible Further Workup
- Lumbar Puncture
- EEG

Treatment of Cognitive Disorders

- Acetylcholinesterase Inhibitors
- NMDA receptor antagonist
- Other treatments (?)
- Other Management

Acetylcholinesterase Inhibitors

- Seems to have symptomatic benefit in mild to moderate dementia (MMSE 10-26)
- Studies show may have benefit in PD with Dementia, Lewy Body, Vascular Dementia, and Mixed Dementia pictures as well.
- Worsening of symptoms if therapy stopped should promote reintroduction of agent.
- Stopping therapy can be considered, however, if no benefit after eight weeks at maximum dosage.
- Can be used with memantine and other therapies.
NMDA Receptor Antagonist (Memantine)

- Seems to have better effect in moderate to advanced dementia (MMSE <17)
- Should routinely be combined with an acetylcholinesterase inhibitor but can be monotherapy.
- Should be continued despite deterioration as it may be disease modifying unless it is easier for the severely demented patient to be without.
- Has a role in the treatment of vascular dementia.

Other Agents

- Vitamin E (Possible, but probably not worth it)
- Estrogen (No evidence of benefit and may cause harm)
- Gingko (Safe, but no benefit)
- Vitamin B (No benefit)
- Omega 3 Fatty Acids (No benefit)
- Nutrition (?Tube Feeding—Does not seem to have prolonged clinical benefit)
- Cognitive Rehab/Exercise/Occupational Therapy (No Harm and may have some benefit)

Neuropsychiatric Manifestations

- Rule out Delirium
- Nonpharmacologic over Pharmacologic
- Low Dose Antipsychotic (Family MUST be aware of increased mortality of these agents and weigh this to quality of life)
- Remember Lewy Body and Antipsychotics can cause severe side-effects.
- SSRIs may be beneficial for agitation secondary to depression and should be considered
- Benzodiazepines should not be used unless absolutely necessary.
Quick Review

- Alzheimer's Dementia is the most common dementia with memory issues being the primary symptom, but also manifesting with language, visuospatial skills, and a lack of insight into the process.
- Distinguishing between dementia and delirium is critical, preferably with standardized tools.
- Using the same standardized clinical cognitive tool aids helps with validity and reliability of the patient’s progression of disease.
- B12, TSH, and an imaging scan of the head is recommended by the AAN with “red flags” prompting further evaluation.
- Acetylcholinesterase inhibitors and memantine can be initiated for mild to severe dementias of various etiologies to aid with cognitive symptoms. They do not seem to improve outcome.
- Exercise, occupational therapy, and cognitive rehab may be of benefit.
- Behavioral changes should be managed with informed consent from the family and with nonpharmacological methods over pharmacological methods. Benzodiazepines should not be used unless absolutely necessary.

References


Questions?
Objectives

- Review phenomenology of abnormal movements
- Differentiate PD and ET
- Highlight some movement disorders emergencies
- Discuss the approach to abnormal movements in the outpatient arena
- Review certain “pearls”
Hyperkinetic MD

- Dystonia
- Chorea
- Ballism
- Myoclonus

Dystonia

- Syndrome dominated by involuntary, sustained and patterned muscle contraction resulting in twisting and repetitive movements or abnormal postures
- Often has directional quality
- Sensory trick
Chorea

- Irregular, involuntary, brief movements that seemingly flow from one body part to another (Latin: dance)
- Treat with dopamine blockers or benzos only if interferes with ADL
- Avoid anticholinergics which may worsen the movements
- L-dopa dyskinesia, tardive movements, Huntington’s Disease

Ballism

- Large amplitude flinging or flailing, violent
- Ddx: structural lesion, hyperglycemia, meds (PTN, DA)
- Classically STN lesion, but think about anywhere in BG
- Tx: neuroleptics, benzos, dopamine depletors, surgery (thalamotomy)

Myoclonus

- Brief, rapid involuntary muscle jerk caused by sudden neuronal discharge
- Asterixes—negative myoclonus
- Non-epileptic vs. Epileptic
- Look for treatable causes: Wilson’s, infectious, any metabolic disturbance, L-dopa, TCA, withdrawal from benzos/barbs, heavy metal poisoning
Tremor

- Involuntary, rhythmic, oscillating movement due to contraction of antagonistic muscles
- Physiologic or pathologic
- Classification:
  - Rest
  - Action: kinetic, postural, intention

Tremor Classification

- Rest tremor: limb fully supported
  - PD: 3-5 Hz
- Action tremor: posture or movement
  - Essential Tremor
  - Cerebellar/intention tremor
  - Rubral/Midbrain tremor: violent

Postural tremor: arms outstretched
- ET: 5-7 Hz
- Physiologic: 10-12 Hz
- Enhanced physiologic:
  - drug-induced
  - endocrine/metabolic (TSH, glucose, pheo, adrenal)
- Special types:
  - orthostatic tremor 16-20 Hz
Tremorgenic Drugs

- Caffeine, cocaine, amphetamines, lithium, beta agonists, theophylline, VPA, PTN, TCA, SSRI, DA blocking agents, steroids, amiodarone, cyclosporine, FK-506, reserpine

- Withdrawal from: EtOH, beta blockers, opiates, BZD

Parkinson's Disease (PD) • First described by James Parkinson in 1817
• Approximately 1 million patients in the United States
• Mean age at onset: 55 to 60
• 85% of patients are over 65

PD

MEDICATIONS

Drugs

Toxins

CNS

PSP

MSA

CBD

LBD

Cardinal Features of PD

- Rest tremor
- Bradykinesia
- Cogwheel rigidity
- Postural instability
Essential Tremor

• a.k.a. “familial” and “benign” tremor
• most common movement disorder?
• prevalence 300-1700/100,000 population
• annoying in some, disabling in others—focus on writing and ADLs

Essential Tremor

• usually responsive to ETOH
• propranolol (Inderal®) and primidone (Mysoline®) are usually effective
• does not shorten lifespan
• cause is unknown
• familial forms have been localized to chromosomes 2 and 3 (AD)

Handwriting Samples in ET

Before Treatment  After Treatment
Alcohol?

- 50-70% of patients respond to alcohol
- benefits typically last for 1-2 hours
- some studies have shown ↑ risk for alcoholism; 60% of patients met alcoholism criteria in one study

**ET vs. PD Tremor**

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>ET</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor location</td>
<td>Hands, head, voice</td>
<td>Hands, legs, mouth</td>
</tr>
<tr>
<td>Associated signs</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Duration</td>
<td>Many years</td>
<td>Short</td>
</tr>
<tr>
<td>Family History</td>
<td>60-75%</td>
<td>15-20%</td>
</tr>
<tr>
<td>Alcohol response</td>
<td>+++</td>
<td>*</td>
</tr>
<tr>
<td>Tremor type</td>
<td>Postural, kinetic</td>
<td>Resting &gt; Postural</td>
</tr>
<tr>
<td>Response to levodopa</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Response to propranolol</td>
<td>+++</td>
<td>*</td>
</tr>
</tbody>
</table>

**Deep Brain Stimulation**
Movement Disorders Emergencies

- Neuroleptic Malignant Syndrome
- Parkinsonism-Hyperpyrexia Syndrome
- Serotonin Syndrome

Neuroleptic Malignant Syndrome

- All classes of drugs that induce blockade of dopamine (D-2) receptors have been implicated (anti-psychotics, anti-emetics)
- Clinical syndrome: **FRED**
  - Fever, rigidity, encephalopathy, dysautonomia
- Positive lab findings: increased CPK, leukocytosis, metabolic acidosis, elevated serum catecholamines, slowing on EEG

NMS treatment

- Stop offending agent
- Early or mild rigidity, low grade fever: lorazepam IV/IM q6h
- Mild to moderate rigidity and temp elevation: dopamine agonists (bromocriptine, amantadine PO/NG)
- Moderate to severe hyperthermia, full blown hypermetabolic state: dantrolene IV
Parkinsonism-Hyperpyrexia Syndrome

- PHS looks just like NMS and can also be fatal
- First described in a PD patient after sudden cessation of dopaminergic therapy during incarceration
- Avoid “drug holidays”
- Wean meds slowly, even if DBS in place
- Treat by reinstituting dopaminergic therapy and follow same algorithm for NMS

Serotonin Syndrome

- Iatrogenic disorder related to drugs that augment serotonin transmission
- Most commonly results from co-administration of SSRI and MAOI
- Seen in patients treated for depression, bipolar d/o, OCD, eating d/o, PD, migraine
- Looks a lot like NMS but evolves and improves much faster, much more myoclonus and hyperreflexia

Serotonin Syndrome

- **Cognitive/Behavioral**
  - Confusion
  - Agitation
  - Hyperactivity
  - Restlessness
  - Insomnia

- **Autonomic**
  - Fever/hyperthermia
  - Tachycardia
  - Tachypnea
  - Dyspnea
  - Hyper/hypotension
  - Diarrhea
  - Flushing

- **Neuromuscular**
  - Myoclonus
  - Hypertonia
  - Tremor
  - Shivering
  - Hyperreflexia
  - Incoordination
  - Mydriasis
  - Akathisia
  - Ataxia

Serotonin Syndrome treatment

• Prompt recognition
• Stop serotoninergic agents
• ICU monitoring
  – External cooling
  – Benzodiazepines, neuromuscular blockade
  – Non-selective serotonin receptor blockers: cyproheptadine, chlorpromazine, methysergide

Considerations in the Ambulatory setting

• Think about drug-induced movement disorders:
  – Dopamine receptor blocking anti-psychotics and anti-emetics
    • Haldol, Thorazine, Geodon, Abilify, Zyvox, Risperdal
      – Only “safe” ones are Seroquel and Clozaril
    • Phenergan, Compazine, Reglan
      – anti-depressants, AED’s, thyroid agents, steroids, chemotherapy, lithium
  • Check for metabolic derangements: thyroid status, infectious, toxicity, glucose, UDS
  • Family history, secondary gain
  • If age < 50, check serum ceruloplasmin for Wilson’s Disease

Quick Review: Iyer’s Pearls

• Phenomenology: what is the movement disorder?
  – Hyperkinetic or hypokinetic
• Look exhaustively at medications
  – Are any current meds known to cause the movement disorder?
  – Any past exposure to meds or drugs known to cause abnormal movements?
  – Have any new meds been started?
  – Have any meds been recently stopped?
• Any metabolic derangements?
  – Thyroid, glucose, liver/kidney function, infections, ammonia
• When in doubt, call or email me or Danielle Englert, MD
Diagnosis and Management of the Dizzy Patient
Christopher Connelly
September 14th, 2013
Neurology Symposium

Objectives
1. Discuss diagnostic paradigm for dizziness
2. Discuss diagnosis and treatment of positional vertigo

Traditional Approach
• Vertigo – illusion of movement
• Presyncope – impeding fainting
• Disequilibrium – unsteadiness on feet with walking
• Nonspecific dizziness – other balance related sensation

Drachman DA
Neurology 1972; 22(4) 323-334
Traditional Approach

- Vertigo: vestibular causes
- Presyncope: blood pressure/cardiovascular causes
- Disequilibrium: neurologic causes
- Non Specific dizziness: metabolic/psychiatric causes

Drachman DA. Neurology 1972; 22(4) 323-334

Pitfalls

- Patients vague and inconsistent in history
- Different patients with same condition experience different types of dizziness

Timing - and - Triggers Approach

- Acute, spontaneous, prolonged vestibular symptoms
  - Vestibular neuritis
  - Posterior fossa stroke
- Episodic Positional Vestibular Symptoms
  - BPPV (Benign Paroxysmal Positional Vertigo)
  - Central Mimics
- Episodic, spontaneous vestibular symptoms
  - Vestibular migraine
  - Meniere disease
  - TIA (Transient Ischemic Attack)
- Chronic unsteadiness
  - Cerebellar degeneration
  - Bilateral vestibular failure
  - Spinal cord compression
  - Peripheral neuropathy

Continuum Volume 18 Number 15 p 1018
Episodic positional vestibular symptoms

Ex: Benign Paroxysmal Positional Vertigo (BPPV)

Epidemiology BPPV
- Most common causes of episodic vertigo in adults (lifetime prevalence of 2.4%)
- Associated with head trauma
- Associated with labyrinthitis

Pathophysiology BPPV
- Vestibular system consists
  - 3 semicircular canals
  - Saccule
  - Utricle
Mechanism BPPV

- Dense calcium carbonate crystals from utricle dislodge and fall into the semicircular canal
- Posterior canal is most commonly effected
Diagnosis: History

- Brief episodes of spinning vertigo lasting 10-30 seconds
- Occur turning in bed
- Getting up
- Bending or tilting in the head
- Can be chronic with 30-50% recurrence rate

Dix-Hallpike Maneuver

Watch for upbeat, torsional nystagmus

BPPV nystagmus during Dix-Hallpike Maneuver

- http://youtu.be/rtS2muVf8BM
Treatment- Posterior Canal

- Epley/ Modified Epley Maneuver
- Semont Maneuver
- Canal plugging dizziness for several weeks
Effectiveness

- Semont ~ 58%
- Modified Epley ~ 95%

Diagnosis of Lateral Canal BPPV

Treatment of Lateral Canal BPPV
Quick Review

• A new paradigm for diagnosing dizziness

• Diagnosis and treatment options for the most common cause of positional vertigo (BPPV)
Peripheral Neuropathy

- Peripheral neuropathy is a group of conditions that alter the function of the motor, sensory, or autonomic components (or a combination of these) of a peripheral nerve.

- It is estimated that the prevalence of peripheral polyneuropathy in the family medicine setting is 8 percent in persons 55 years and older.
- The prevalence in the general population may be as high as 2.4 percent.

Peripheral Nerves

- Cranial nerves (except optic nerve)
- Spinal nerve roots
- Dorsal root ganglion
- Nerve trunks and their branches
- Peripheral Autonomic nerves
### Symptoms of Neuropathy

- **Sensory**
  - Numbness
  - Tingling
  - Burning
  - Pins and Needles
- **Weakness**
  - Atrophy
  - Cramps
  - Fasciculation
- **Autonomic symptoms**
  - Orthostatic hypotension
  - Sweating changes
  - Erectile dysfunction
  - Bowel and Bladder problems
  - Erythromelalgia

### Clinical Evaluation Of Neuropathy

- **History**
  - Symptoms
    - Sensory
      - Numbness
      - Parasthesias/dysesthesia
      - Imbalance
    - Motor
      - Weakness
      - Cramps
      - Fasciculation
    - Autonomic
      - Time Course
        - Acute
        - Subacute
        - Chronic
        - Relapsing
      - Exacerbating Factors
- **Examination**
  - Sensory
    - Small fiber – pin prick
    - Large fiber
      - Vibration
      - Proprioception
  - Motor
    - Strength
    - Tone
    - Atrophy
    - Fasciculation / Myokymia
  - Reflexes
  - Gait
    - Romberg
    - Orthostatic Vital Signs
    - Skin Changes

### Clinical Evaluation Of Neuropathy

- **Evaluate localization**
- **Pattern**
  - Distal
  - Proximal
  - Multifocal
  - Symmetric
  - Asymmetric
Peripheral Neuropathy

- **Mononeuropathies**
  - A single peripheral nerve
    - Ex. Median nerve – carpal tunnel
- **Mononeuropathy Multiplex**
  - Several isolated nerves
- **Polyneuropathy**
  - Multiple simultaneous peripheral nerves; usually bilaterally symmetric, usually beginning distally and moving proximally
  - Prevalence is greater than 3%
Peripheral Neuropathy

- **Causes**
  - Toxic / Metabolic
  - Medication
  - Hereditary
  - Autoimmune
  - Trauma
  - Ischemic
  - Idiopathic

Causes Of Peripheral Neuropathy

- Diabetes mellitus / Impaired Glucose Tolerance
- Excessive Alcohol
- Hereditary
- Trauma
- Hypothyroidism
- Vitamin B12 deficiency
- Folate deficiency
- Thiamine deficiency
- Copper Deficiency
- Vitamin B6 toxicity
- Uremia
- Celiac disease
- Acquired immunodeficiency syndrome
- Sjogren's
- Critical illness polyneuropathy
- Vitamin E deficiency
- Paraproteinemia
- Rheumatoid arthritis
- Polyanieritis nodosa (vasculitis)
- Systemic lupus erythematosus
- Paraneoplastic
- Antibody Mediated
- Churg-Strauss vasculitis
- Cryoglobulinemia
- Amyloidosis

Causes Of Peripheral Neuropathy

- Syphilis
- Porphyria
- Lyme disease
- Sarcoidosis
- Acrylamide
- Carbon disulfide
- Dichlorophenoxyacetic acid
- Ethylene oxide
- Hexacarbons
- Carbon monoxide
- Organophosphorus esters
- Glue sniffing
- Gouty neuropathy
- Carcinomatous axonal sensorimotor polyneuropathy
- Lymphomatous axonal sensorimotor polyneuropathy
- Whipple's disease
- Hypophosphatemia
- Lead
- Chronic arsenic intoxication
- Mercury
- Gold
- Thallium
- Radiation
Medications Associated With Neuropathy

- Axonal
  - Vincristine
  - Paclitaxel
  - Nitrous oxide
  - Colchicine
  - Isoniazid
  - Hydralazine
  - Metronidazole
  - Pyridoxine
  - Didanosine
  - Lithium
  - Alfa Interferon
  - Dapsone
  - Phenyltoin
  - Disulfiram
  - Chloroquine
  - Ethambutol

- Demyelinating
  - Amiodarone
  - Chloroquine
  - Suramin
  - Gold

- Neuronopathy
  - Thalidomide
  - Captopril
  - Pyridoxine

Neuropathy Evaluation

- EMG / NCS – Electromyography / Nerve Conduction Study
  - Generally both parts of the test are performed and the combined data is used for analysis
  - The study needs to be tailored to the clinical question to be answered
  - The study is highly dependent on the expertise of the physician performing the study
  - Unlike imaging, it is difficult if not impossible to interpret another physicians study because the data is dependent on the person performing the test
  - Neuromuscular Fellowship training
    - Board Certification

Electromyography
Neuropathy Evaluation

- Laboratory Evaluation
  - Often done in tiers of tests
    - Initial evaluation
      - CBC
      - Chemistry
      - Glucose tolerance test
      - B12 / methylmalonic acid
      - RBC Folate
      - Thyroid function tests
      - APR
      - ESR
      - Immunofixation electrophoresis – blood and urine
    - Further evaluation based on history, exam, EMG, above results
Neuropathy Evaluation

Skin Biopsy for Small Fiber Neuropathy Evaluation

- intraepidermal nerve fiber (IENF) density

Neuropathy Evaluation

- Quantification of Sweat Gland Nerve Fiber Density (SGNFD)
  - For neuropathies with autonomic involvement

Neuropathy Evaluation

- Nerve Biopsy
- Lumbar Puncture
- Quantitative Sensory Testing
- Autonomic testing
Diabetic Neuropathy

CLASSIFICATION OF DIABETIC NEUROPATHIES

Symmetric
1. Distal, primarily sensory polyneuropathy
   a. Mainly large fibers affected
   b. Mixed
   c. Mainly small fibers affected
2. Autonomic neuropathy
3. Chronically evolving proximal motor neuropathy

Asymmetric
1. Acute or subacute proximal motor neuropathy
2. Cranial mononeuropathy
3. Truncal neuropathy
4. Entrapment neuropathy in the limbs

Guillain-Barre Syndrome

• Rapidly evolving areflexic motor paralysis with or without sensory disturbance
• Usually an ascending paralysis
• Develops over hours to days – nadir by 4 weeks
• Frequently associated with tingling dysesthesias of extremities
• Usually legs more affected than arms
• 50% develop bifacial weakness
• May get bulbar weakness; difficulty handling secretions, swallowing; maintaining airway
• 30% require ventilatory assistance at some point during illness

Guillain-Barre Syndrome

• Often report a diarrheal or respiratory infection within 2 weeks prior to onset
• Can get serious autonomic dysfunction
  – Hypo- and hypertension, arrhythmia, bladder retention

• There are several variants
  – Miller-Fisher syndrome, AMAN, AMSAN, Sensory GBS, Autonomic GBS

• Evaluation
  – EMG/NCS
  – LP
  – Can evaluate for Anti-GM1 antibody, GalNAc-GD1a ganglioside
  – Can evaluate serology for Campylobacter jejuni
Guillain-Barre Syndrome

- Treatment
  - IV Ig
  - Plasma Exchange
  - NO Steroid
  - Pain Control
  - Cardiac / hemodynamic monitoring
  - Respiratory monitoring and support
  - Monitoring for infectious complications
  - Monitoring for psychiatric issues
  - Nutrition
  - DVT prophylaxis
  - Avoiding skin breakdown
  - PT/OT/ST

Chronic Inflammatory Demyelinating Neuropathy (CIDP)

- a chronically progressive or relapsing symmetric sensorimotor disorder with cytoalbuminologic dissociation and interstitial and perivascular endoneurial infiltration by lymphocytes and macrophages.
- starts insidiously and evolves slowly, in either a slowly progressive or a relapsing manner, with partial or complete recovery between recurrences
- periods of worsening and improvement usually last weeks or months

CIDP

- Initial limb weakness, both proximal and distal
- Sensory symptoms (eg, tingling and numbness of hands and feet)
- Motor symptoms (usually predominant)
- In about 16% of patients, a relatively acute or subacute onset of symptoms
- Motor deficits (eg, symmetric weakness of both proximal and distal muscles in upper and lower extremities)
- Diminished or absent deep tendon reflexes
- Sensory deficits (typically in stocking-glove distribution)
- Gait difficulty
CIDP

- Lumbar puncture shows elevated protein and normal cell count in 80%
- May have an associated paraproteinemia
  - Most common is IgM

CIDP

- Treatment - based on the proposed pathogenesis of CIDP as an immune-mediated condition.
  - Intravenous immunoglobulin (IVIg)
  - Plasma exchange (PE)
  - Prednisone
  - Azathioprine, methotrexate, mycophenolate, cyclosporine, and cyclophosphamide.
Quick Review

- Peripheral Neuropathy is a common problem.
- There are a variety of presentations of neuropathy.
- There are many causes of neuropathy.
- Evaluating neuropathy involves a detailed history and examination, and quality EMG/NCS
  - Based on these, appropriate laboratory evaluation and potential LP and nerve biopsy can be pursued if indicated.
- Diagnosing the neuropathy helps exclude other conditions in the differential for a patient’s symptoms/signs.
- Diagnosing the neuropathy may lead to specific treatment of the neuropathy itself and/or lead to a diagnosis of conditions that require treatment to prevent further morbidity.
Update on Insomnia Management
Rajdeep Singh MD, MS

Outline

• Overview of Insomnia
  – Definition
  – Classification

• Management of Primary Chronic Insomnia
  – CBTI
  – Pharmacologic
  – Combined

• AASM Algorithm

• Future directions and Summary

Case

60 year old female with sleep problems for at least last 5 years. Her night time schedule includes going to bed at around 10PM but reads in bed with low light till 11-11:30PM. She tries to fall asleep after that but “cannot get mind to shut off” and estimates that she falls asleep close to 12:30 or 1AM. She sleep several hours before she wakes up to use the restroom and then has trouble falling asleep. She typically wakes up at 4AM and may watch TV or do household work before trying to sleep again at 5-5:30AM. She blames “hot flashes” for her arousal and states she developed blood clots in the past with HRT. On most days she gets up at 7AM but few days continues to lie in bed till 8-9AM. She estimates she sleeps about 5 hours every night. During daytime she has fatigue and might fall asleep on the sofa watching TV around 7-8PM. She describes various ongoing social stressors that she thinks is contributing to her problem.
Question

• Is this Primary Insomnia or secondary to medical condition?

• What treatment(s) would you consider for this patient?
  – HRT
  – Benzodiazepine
  – Benzodiazepine Receptor Agonist (BZRA)
  – Antidepressant
  – Sleep Hygiene
  – Cognitive Behavior Therapy for insomnia (CBTI)

Insomnia

• Most common sleep disorder

• Definition:
  – Repeated difficulty with sleep initiation, maintenance, duration or quality that occurs despite adequate time and opportunity for sleep and results in daytime impairment (1)

• Key Features:
  – Persistent sleep difficulty
  – Adequate time and opportunity for sleep
  – Associated daytime impairment

Epidemiology

• Prevalence of chronic Insomnia – 10-15% (2)

• Comorbid Insomnia more common ~ 90%
  – Replaces secondary insomnia attribution
  – Co-occurring with other medical, psychiatric or sleep disorders
  – May continue even after treatment of primary condition
  – Promotes independent treatment of insomnia

• Primary Insomnia
  – 10% Insomnia
  – Independent from other disorders
Insomnia Risk Factors

- Age (older individuals)
- Gender (F>M)
- Divorce/Separation/widowhood
- Psychiatric illness
- Cigarette smoking
- Alcohol consumption
- Certain medical conditions and prescription drugs

Etiology

- Hyperarousal
  - Increased autonomic activity in sleep (HR, Temp, metabolic rate, NE secretion)
  - Increased beta/gamma bands and decreased delta on EEG activity
  - Increased brain glucose metabolism
  - NO increase in daytime sleep

Classification

- Temporal
  - Sleep-onset
  - Sleep maintenance
  - Terminal (early morning awakening)
  - Non-restorative sleep
- Etiology
  - Primary
  - Comorbid
- Duration
  - Acute (less than 1 month)
  - Chronic (more than 1-3 months)
- Severity (social/occupational functioning)
  - Mild
  - Moderate
  - Severe
Insomnia Management

- Cognitive-Behavioral Therapy for Insomnia (CBTI)
  - Stimulus Control
  - Sleep Restriction
  - Paradoxical Intention
  - Sleep-hygiene
  - Cognitive Therapy
- Pharmacologic Therapies
  - Hypnotics
  - Antidepressants
  - Anticonvulsants
  - Others
- CBTI + Medications

Behavioral Sleep Model

**Webb's 1988 Model**

- Homeostatic Mechanisms
- Circadian Rhythm
- Facilitators-Inhibitors

Sleep
Disruptors of homeostatic sleep drive

• Daytime napping
• Age
• Boredom/inactive lifestyle

Circadian Rhythm Disruption

Lack of Daytime Routine
Compensatory “sleep in”

Common Sleep Inhibitors

• Stimulating Activities before bed
• Disrupting stimulus value of the bed for sleep
  • Solving day puzzles
  • Eating/Watching TV in bed
Cognitive Behavior Therapy model for Insomnia

- Cognitive Factors
  - Sleep Effort
  - Unhelpful Thoughts & beliefs
- Sleep Hygiene
- Homeostatic Dysregulation
  - Excessive TIB
  - Napping
- Circadian Disruption
  - Irregular Sleep Schedule
- Stimulus Control
- Inhibitory Factors
  - Poor Sleep hygiene
  - Conditioned Arousal
- Sleep Restriction
- Primary Insomnia
- Relaxation Therapy

Insufficient evidence for effectiveness

- Sleep hygiene education alone
- Imagery training alone
- Cognitive therapy alone

Morgenthaler et al., Sleep 2006;29:1415-1419

PHARMACOLOGIC MANAGEMENT
Pharmacologic Therapies

- Insomnia Medications
  - Hypnotics
    - Benzodiazepines (BZD)
    - Non-BZD benzodiazepine receptor agonists (NBBRA)
  - Sedating anti-depressants
  - Others:
    - Melatonin and melatonin agonists
    - Anticonvulsants
    - Anti-Psychotics
    - Sedating anti-histamines
    - Botanical Compounds

Benzodiazepines

- MOA – GABA enhancers – mainly GABA<sub>\alpha</sub> receptors.
  - Open chloride channels and hyperpolarization
  - Receptors subtype (BZ1, omega-1; BZ2, omega2)
    - BZ1 receptor subunit: hypnotic & amnestic effects
    - BZ2/3 receptor subunit: memory, cognitive, muscle relaxation, anti-seizure & anti-anxiety properties
  - Bind non-selectively
  - Chosen mainly based on duration of action
    - for sleep onset and sleep maintenance insomnia

Benzodiazepines

- Drugs
  - Triazolam (Halcion): half-life 2-5 hours
  - Estazolam (ProSom): Half life 8 hours
  - Temazepam (Restoril)
  - Flurazepam (Dalmane): Half life 24 hours
  - Quazepam (Doral)

- Clonazepam is not approved for insomnia
Non-BZD Benzodiazepine Receptor Agonists (NBBRA)

- GABA-benzodiazepine-1 receptor subunit (BZ1) – but
  at different site from the BZD
- Flumazenil will antagonize the sedative effects
- Less likely to decrease Delta sleep.
- ? Less Likely to exacerbate OSA
- Drugs
  - Eszopiclone (Lunesta)
  - Zolpidem (Ambien)
    - CR
    - Intermezzo
  - Zaleplon (Sonata)

Sedating Anti-depressants

- Used in patients with primary insomnia without mood disorder
  - Off-label use except for doxepin
- Therapeutic efficacy and safety as hypnotics incompletely understood
- Most commonly used Antidepressants
  - Doxepin
  - Other tricyclics
  - Trazodone
  - Mirtazapine
Doxepin

- Old tricyclic anti-depressant
- Recently approved in low doses for **sleep maintenance and terminal insomnia**
- No significant side effects when compared with placebo in elderly up to 6mg
- Sleep architecture was preserved
- Half life
  - 6-8 hours
  - Food delays absorption

Doxepin

- Mechanism
  - Selective H1 receptor antagonist at low dose
  - Histamine activity greatest during latter part of night and early morning
  - Does not interfere with morning wakefulness systems (e.g. orexin)
- Dose
  - 3-6 mg
  - Can be given as Brand Silenor 3mg and 6mg tab
  - Generic in the form of capsule or oral solution 10mg/ml (measure with a pediatric dropper)

Other Sedating Medications

- Melatonin
  - Particularly helpful in delayed sleep phase circadian rhythm
  - Variability among preparations (OTC – No FDA oversight)
- Ramelteon
  - Higher standards of preparation and purity
- Anti-psychotics
  - Used in comorbid psychiatric illness for insomnia
  - Efficacy and safety for insomnia use is either limited or absent
- Anticonvulsants
  - Pregabalin and Gabapentin particularly useful in patients with pain syndrome
Other Sedating Medications

- Anti-Histamines (e.g. diphenhydramine)
  - Residual sedation common & strong anticholinergic properties, worsen RLS/PLMS
  - Tolerance develops quickly
  - Minimal efficacy data
- Botanical Compounds
  - Kava (Piper methysticum)
    - Might act at GABA
    - Hepatotoxicity concern
  - Valerian
    - Inconclusive evidence (300-400mg)
    - May interact with GABA, adenosine, and barbiturate receptors

Pharmacotherapy

- BzRA
  - Improved? Yes
  - Ongoing F/u No
- Alternate BzRA
  - Improved? Yes
  - Low Dose AD
  - Improved? No

Combination AD+BzRA


COMBINATION THERAPY
CBTI with medications
Morin et al., JAMA, 2009
N = 160 Adults – Primary Insomnia
Mean age = 50.3 yrs (range = 30-72 yrs.)

CBT – 6 weeks
N = 80

CBT+MED – 6 weeks
N = 80

CBT+ 6 months
No Tx 6 months
CBT only 6 months
CBT + MED* 6 months

6 Month follow-up after extended treatment phase
* Patients in CBT+MED received 10 mg zolpidem tablets per month during extended treatment.

CBTI alone or with medications?
• CBTI alone and CBTI+Zolpidem had similar acute response rate, but combined therapy produced a higher remission rate.
• Best Long term outcome with Zolpidem+CBTI followed by CBTI alone

FUTURE DIRECTIONS AND SUMMARY
Future Directions

- Drugs Targeting Orexin Receptors
  - Orexin (hypocretin) system is a critical regulator of sleep/wake states
  - Loss of Orexin neurons implicated in narcolepsy
  - Suvorexant – pending FDA approval
    - Non-selective Orexin Receptor Antagonists
    - Two phase III efficacy trials had promising results
    - Less rebound insomnia
    - Less addictive
    - Next day residual effects were not observed
    - Mirrors natural sleep architecture – selective subtype antagonists may impact REM sleep

Mieda M, Sakurai T. CNS drugs 2013; 27: 83-90

Summary

- Complex array of sleep-disruptive practices ➔ insomnia
- CBT Well established therapy for insomnia
- Best long term option: Combined therapy ➔ behavioral therapy alone

Questions?

Thank You
References


Medication Options

- From 1993-2006, 5 medications total approved for MS
  - Betaseron, 1993
  - Avonex and Copaxone, 1996
  - Rebif, 2002
  - Tysabri, 2006

- 2010 forward
  - 2010, Gilenya
  - 2012, Aubagio
  - 2013, TevDEDRA
    - 2013, Lemtrada expected (September)
  - Ocrelizumab (anti-CD20 similar to rituximab), perhaps 2015

Current Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>FDA approved</th>
<th>ASP price/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaseron</td>
<td>MS (relapsing remitting MS)</td>
<td>30 mg</td>
<td>1993</td>
<td>$1,096.00</td>
</tr>
<tr>
<td>Avonex</td>
<td>MS (relapsing remitting MS)</td>
<td>30 mg</td>
<td>1996</td>
<td>$1,096.00</td>
</tr>
<tr>
<td>Copaxone</td>
<td>MS (relapsing remitting MS)</td>
<td>20 mg</td>
<td>1996</td>
<td>$1,096.00</td>
</tr>
<tr>
<td>Rebif</td>
<td>MS (relapsing remitting MS)</td>
<td>30 mg</td>
<td>2002</td>
<td>$1,096.00</td>
</tr>
<tr>
<td>Tysabri</td>
<td>MS (primary progressive MS)</td>
<td>10 µg</td>
<td>2006</td>
<td>$2,000.00</td>
</tr>
<tr>
<td>Gilenya</td>
<td>Secondary progressive MS</td>
<td>30 µg</td>
<td>2010</td>
<td>$4,754.00</td>
</tr>
<tr>
<td>Aubagio</td>
<td>Secondary progressive MS</td>
<td>30 µg</td>
<td>2012</td>
<td>$4,754.00</td>
</tr>
<tr>
<td>TevDEDRA</td>
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<td>30 µg</td>
<td>2013</td>
<td>$4,754.00</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Secondary progressive MS</td>
<td>30 µg</td>
<td>2013</td>
<td>$4,754.00</td>
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<tr>
<td>Lemtrada</td>
<td>Secondary progressive MS</td>
<td>30 µg</td>
<td>2013</td>
<td>$4,754.00</td>
</tr>
</tbody>
</table>

(Original: 2012: 47:392–399.)
Medications in Development

<table>
<thead>
<tr>
<th>Name</th>
<th>Formulation</th>
<th>Dosage and Administration</th>
<th>Possible side effects</th>
<th>Absence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilenya</td>
<td>Fingolimod</td>
<td>Oral, 2 mg twice daily</td>
<td>Fatigue, nausea</td>
<td></td>
</tr>
<tr>
<td>Aubagio</td>
<td>Teriflunomide</td>
<td>Oral, 5 mg tablets daily</td>
<td>Hair loss, nausea</td>
<td></td>
</tr>
<tr>
<td>Tecfidera</td>
<td>Dimethyl Fumarate</td>
<td>Oral, 1.2 g tablets</td>
<td>Stomatitis, nausea</td>
<td></td>
</tr>
<tr>
<td>Lemtrada</td>
<td>Alemtuzumab</td>
<td>Infusion, 10 mg/kg 10 mg/kg 10 mg/kg</td>
<td>Mucosal irritation, hair loss</td>
<td>September 2013</td>
</tr>
</tbody>
</table>

Mechanism of Action of MS Therapies

Newest Medications

- Gilenya (Fingolimod)
- Aubagio (Teriflunomide)
- Tecfidera (Dimethyl Fumarate)

- Lemtrada (Alemtuzumab) expected September 2013
Fingolimod: Gilenya

- First oral medication for MS
- Approved September, 2010
- Taken once daily and well-tolerated
- Approved for relapsing forms of MS
- More than 70,000 patients worldwide

Fingolimod Mechanism of Action


FREEDOMS - Primary Endpoint: Annualized Relapse Rate

Gilenya: Safety Concerns

- Heart rate drops during first dose
  - First dose observation of 6 hours with BP and HR monitoring

- Increased infection risk
  - Potentially VZV, herpes, PML (?)
  - “Very” low lymphocytes

- Macular Edema
  - Requires ophtho exam before starting and after 4 months

- Requires monitoring the liver
  - LFTs and CBC q 2 months for 6 months, then q 6 months

Teriflunomide: Aubagio™

- Approved September, 2012

- Active metabolite of leflunomide (Arava) used since 1998
  - Leflunomide treats rheumatoid arthritis

- Once daily medication

- Approved for relapsing forms of MS
Teriflunomide: Mechanism of Action

- Resting lymphocytes
  - Basal demand for pyrimidine nucleotides
    - Alternative "salvage" pathway
    - Immune surveillance and protective immune responses
- Stimulated myelin-specific lymphocytes
  - Increased demand for pyrimidine nucleotides

CNS benefits

Teriflunomide: Efficacy

A. Adjusted annualized relapse rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients (n)</th>
<th>Number of Relapses</th>
<th>Annualized Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>360</td>
<td>1.94</td>
<td>0.055</td>
</tr>
<tr>
<td>Teriflunomide, 7 mg (n=360)</td>
<td></td>
<td>0.87</td>
<td>0.024</td>
</tr>
<tr>
<td>Teriflunomide, 14 mg (n=360)</td>
<td></td>
<td>0.37</td>
<td>0.010</td>
</tr>
</tbody>
</table>

TEMSEO: MRI Outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Placebo</th>
<th>Teriflunomide, 7 mg</th>
<th>Teriflunomide, 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in T1 Hypointense Lesion Volume</td>
<td>3.5%</td>
<td>67%</td>
<td>31%</td>
</tr>
<tr>
<td>Relative Risk Reduction</td>
<td>67%</td>
<td>p&lt;0.001</td>
<td>31%</td>
</tr>
<tr>
<td>Change in Number of Gd-Enhancing Lesions</td>
<td>1.4</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Relative Risk Reduction</td>
<td>80%</td>
<td>p&lt;0.001</td>
<td>29%</td>
</tr>
<tr>
<td>Change in Number of Active Lesions</td>
<td>3.5</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>Relative Risk Reduction</td>
<td>60%</td>
<td>p&lt;0.001</td>
<td>0.05</td>
</tr>
</tbody>
</table>

aTotal volume of all abnormal brain tissue, calculated as the sum of the total volume of T2 lesion component and T1-hypointense lesion component; bEnhanced lesions plus unenhanced new and substantially enlarged T2-hyperintense lesions; cPercent relative reduction (percent change for treatment relative to placebo) of the change from baseline (based on transformed data) at Week 108. Dashed lines = reference line at 0% change for treatment relative to placebo.
Teriflunomide: Safety Concerns

- Pregnancy Category X
- Liver monitoring required monthly for 6 months
- Risk of infection
- Hair thinning
- Cases of TB reactivation in the trials

Tecfidera: Dimethyl Fumarate

- Approved March, 2013
- Twice daily medication
- Approved for relapsing forms of MS
- Similar to Fumaderm, medication approved in Europe for psoriasis
Tecfidera: DEFINE trial

53% reduction in ARR


Tecfidera: Safety and Tolerability

- Safety concerns
  - Decreased WBC, possible infection risk?
  - Transient eosinophilia
  - Considerable decreased WBC in 6% of patients

- Tolerability
  - 35% patients with flushing
  - 30% or more with nausea, diarrhea, vomiting, abdominal pain
Quick Review

- Gilenya: monitor LFTs, CBC, first dose, macular edema
  - Interaction with other QT prolonging medications
  - Drastically decreased absolute lymphocyte count
  - Infection risk
- Aubagio: monitor LFTs, CBC, TB test before starting
  - Pregnancy Category X
  - Concern about LFTs and need for frequent monitoring
  - Hair thinning and increased infection risk
- Tecfidera: monitor CBC
  - Tolerability issues – abdominal pain, nausea, vomiting, diarrhea
  - Significant lymphocyte count drop in 6% of patients

General Recommendations

- No need to switch a medication that’s working
- Patients prefer oral medications but more safety concerns
- Monitor treatment efficacy with MRIs

Progress and Hope

- New medications available and on the horizon
- If medication not effective, consider changing
- More choices for patients means we can tailor treatment for each individual
- Progressive disease
  - Still frustrating and without good options
  - Ongoing trials