Imaging in Primary Headache Disorders and the Symptomatology of Secondary Headaches

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Director Headache Program
Learning objectives

1. To learn imaging guidelines in patients with headache disorders.
2. To review the latest updates of neuroimaging findings during migraine aura, during headaches and non-ictal imaging.
3. To know the neuroimaging findings in Cluster and trigeminal autonomic disorders
Headache classification

**Primary**
- Migraine
- Cluster
- Tension

**Secondary to:**
- an underlying etiology, which if treated will stop the headache

Use the International Headache Society (IHS) classification system in diagnosis of CDH
Understand the pathophysiology of CDH
Discuss recent advances in diagnosis and treatment of CDH
Secondary Headache

99.82%

0.18%

Percent of Patients

Primary  Secondary

PATHOGENESIS: MIGRAINE

- Vasculogenic Theory
- Neurovascular Theory
INTRACRANIAL VASOCONSTRICTION AND VASODILATATION KEY TO AURA AND MIGRAINE; Wolff et al

ALL CURRENT ACUTE THERAPIES TARGET THIS APPROACH
MIGRAINE PATHOGENESIS: NEUROVASCULAR

• Neuronal hyperexcitability, especially occipital cortex

• Therefore brain susceptible to migraine attacks
Pathogenesis: aura

- An electrical event in the brain
- Cortical spreading depression (CSD)
- Rate of 2-4 mm/min
Migraine aura Imaging

Loss of stimulus evoked activation within occipital cortex on blood oxygen dependent (BOLD) imaging during exercise induced migraine visual aura
During headache an increase (11%) in regional CBF measured in medial brain stem predominantly contralateral to headache as well as in cingulate, auditory, and visual association cortices.

- PWI: no indication of change in hemodynamic parameters.
- Sumatriptan tx: decreased headache, returned regional CBF to normal in cortical areas but did not reduce the brainstem CBFc change.
CNS Activation During Migraine

Dysfunction of brain stem pain and vascular control centers

Pain Perception*
- Anterior cingulate cortex

"Migraine Generator"*
- Raphe nuclei
- Locus coeruleus
- Periaqueductal gray

*Areas of red indicate cerebral blood flow increases (P < 0.001).
(Weiller et al. 1995)
Migraine without aura - functional imaging

Dorsal pontine activation ipsilateral to headache on PET during spontaneous migraine headache
PET scan in experimentally induced pain
Nonictal imaging: CAMERA STUDY

Increased incidence of white matter lesions (WMLs) - increased T2 signal
- Nonspecific finding - could be ischemia, demyelination, connective tissue disease and many other etiologies
- Clinical significance of WMLs unknown
Nonictal imaging:

Cerebellar “infarction”- like lesion in a patient from the CAMERA Study
- Focal hypoperfusion could be explained by infarct- like lesions and reduction of CBF during migraine which ranged from 7- 53%
In addition, increase in infarct like changes in supratentorial region
Hemiplegic migraine-anatomical changes during attack

Figure. Cerebral MRI study on day 1 after symptom onset. (A) Normal T2-weighted image. (B) Quantitative analysis of gadolinium-diethylene-triaminepentaacetic acid (Gd-DTPA)-enhanced MRI. Gray scale-coded percentage enhancement values for the T1-weighted image after Gd-DTPA injection compared with the image before Gd-DTPA are demonstrated. Note the significant enhancement of the left hemispheric cortex band (white arrows), where the edema evolved later on. Cortical enhancement was most prominent in the tempororo-occipital lobes. Particularly note the enhancement in the perisylvian cortex where language skills are represented, which showed a delayed recovery. (C) Postcontrast T1-weighted coronal image shows dural enhancement restricted to the left hemisphere (white arrow, day 3). (D to F) Cerebral MRI studies on day 9. (D) Pronounced cortical edema on T2-weighted image. (E) Left hemispheric hyperintensity was detected on a diffusion-weighted imaging (DWI) slice (b 1,000 s/mm²) within the cortex (F), whereas the apparent diffusion coefficient map was unremarkable, suggesting vasogenic rather than cytotoxic edema (T2 shine through phenomena of DWI). (G) Follow-up MRI 17 months later: Regular signal intensities are seen on the T2-weighted image. There is no evidence of cortical atrophy consistent with vasogenic rather than cytotoxic edema.
2007 Harold G. Wolff Award Winner

Brainstem Dysfunction in Chronic Migraine as Evidenced by Neurophysiological and Positron Emission Tomography Studies*

Sheena K. Aurora, MD; Patricia M. Barrodale, RN; Reda L. Tipton; Ani Khodavirdi, PhD
Hypotheses: Normal inhibitory capacity of the cortex is reduced ??
Cortical excitability is raised ??

Limitations: compare it to episodic headaches
Lack of controls

Aurora SK et al Headache 2007;47:996-1003
Table 1: Mean T2 values (ms ± s.d.) of two measurements, intraclass correlation coefficient (ICC) and 95% confidence interval (CI) per structure.

<table>
<thead>
<tr>
<th>Structure</th>
<th>T2 M1 †</th>
<th>T2 M2 †</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICC  95% CI ‡</td>
</tr>
<tr>
<td>Putamen</td>
<td>74.1 ± 2.7</td>
<td>74.3 ± 2.7</td>
<td>0.98</td>
</tr>
<tr>
<td>Posterior putamen</td>
<td>71.2 ± 2.9</td>
<td>71.0 ± 3.1</td>
<td>0.86</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>82.5 ± 2.9</td>
<td>81.9 ± 3.3</td>
<td>0.81</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>71.6 ± 3.8</td>
<td>70.8 ± 3.5</td>
<td>0.85</td>
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<tr>
<td>SN pars reticularis</td>
<td>70.8 ± 5.8</td>
<td>70.0 ± 5.0</td>
<td>0.63</td>
</tr>
<tr>
<td>SN pars compacta</td>
<td>81.4 ± 4.3</td>
<td>81.5 ± 4.5</td>
<td>0.80</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>75.8 ± 4.3</td>
<td>75.8 ± 5.1</td>
<td>0.92</td>
</tr>
</tbody>
</table>

SN, substantia nigra.
†M1, 1st measurement; M2, 2nd measurement.
‡All P-values were < 0.001.
<table>
<thead>
<tr>
<th>Structure</th>
<th>All participants</th>
<th>Age &lt; 50 years</th>
<th>Age ≥ 50 years</th>
<th>P-value</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls (n = 75)</td>
<td>Migraine (n = 138)</td>
<td>Controls (n = 43)</td>
<td>Migraine (n = 69)</td>
<td>Controls (n = 32)</td>
<td>Migraine (n = 69)</td>
</tr>
<tr>
<td></td>
<td>(Crude)</td>
<td>(Adjusted)</td>
<td>(Crude)</td>
<td>(Adjusted)</td>
<td>(Crude)</td>
<td>(Adjusted)</td>
</tr>
<tr>
<td>Putamen</td>
<td>74.4 ± 2.2</td>
<td>74.1 ± 2.7</td>
<td>74.8 ± 1.8</td>
<td>74.0 ± 2.3</td>
<td>73.8 ± 2.5</td>
<td>74.3 ± 3.1</td>
</tr>
<tr>
<td>Posterior putamen</td>
<td>72.2 ± 3.2</td>
<td>71.5 ± 3.6</td>
<td>72.4 ± 2.8</td>
<td>71.0 ± 2.8</td>
<td>72.0 ± 3.8</td>
<td>71.9 ± 4.2</td>
</tr>
<tr>
<td>Head of caudate</td>
<td>82.4 ± 2.8</td>
<td>82.4 ± 2.5</td>
<td>83.2 ± 2.4</td>
<td>82.7 ± 2.5</td>
<td>81.5 ± 3.0</td>
<td>82.1 ± 2.6</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>73.0 ± 4.1</td>
<td>72.3 ± 4.3</td>
<td>73.7 ± 4.1</td>
<td>71.9 ± 4.0</td>
<td>72.0 ± 3.9</td>
<td>72.7 ± 4.5</td>
</tr>
<tr>
<td>SN pars reticularis</td>
<td>74.8 ± 10.5</td>
<td>74.4 ± 10.6</td>
<td>74.8 ± 10.2</td>
<td>74.4 ± 11.1</td>
<td>74.6 ± 11.1</td>
<td>74.3 ± 10.3</td>
</tr>
<tr>
<td>SN pars compacta</td>
<td>81.9 ± 4.1</td>
<td>81.3 ± 4.2</td>
<td>81.6 ± 4.6</td>
<td>81.4 ± 4.0</td>
<td>82.4 ± 3.3</td>
<td>81.8 ± 4.4</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>81.4 ± 12.3</td>
<td>79.3 ± 10.5</td>
<td>81.1 ± 11.1</td>
<td>77.1 ± 8.0</td>
<td>81.7 ± 13.8</td>
<td>81.6 ± 12.2</td>
</tr>
</tbody>
</table>

*Data are estimated mean ± S.E. T2 values (ms). Crude P-values are from two-tailed unpaired t-tests. Adjusted P-values are from linear regression analysis controlling for age.

SN, substantia nigra.
Table 4: Age-controlled mean T2 values (ms ± S.E.) of migraineurs with longer vs. shorter duration of migraine history (n = 138)*

<table>
<thead>
<tr>
<th>Structure</th>
<th>Age &lt; 50 years</th>
<th>Age ≥ 50 years</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 23 years</td>
<td>≥ 23 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 35)</td>
<td>(n = 34)</td>
<td>Crude</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Putamen</td>
<td>74.9 ± 1.9</td>
<td>73.1 ± 2.4</td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>Posterior putamen</td>
<td>71.8 ± 2.7</td>
<td>70.2 ± 2.8</td>
<td>0.02</td>
<td>0.1</td>
</tr>
<tr>
<td>Head of caudate</td>
<td>83.5 ± 2.0</td>
<td>82.0 ± 2.8</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>72.4 ± 3.6</td>
<td>71.5 ± 4.5</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>SN pars reticularis</td>
<td>75.8 ± 12.0</td>
<td>73.1 ± 10.0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>SN pars compacta</td>
<td>81.9 ± 4.0</td>
<td>80.9 ± 4.0</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>79.7 ± 9.6</td>
<td>74.5 ± 5.0</td>
<td>0.006</td>
<td>0.001</td>
</tr>
</tbody>
</table>

|                         | < 23 years     | ≥ 23 years     |         |         |
|                         | (n = 33)       | (n = 36)       | Crude   | Adjusted|
| Putamen                 | 74.5 ± 3.0     | 74.0 ± 3.2     | 0.5     | 0.5     |
| Posterior putamen       | 72.7 ± 4.4     | 71.2 ± 3.9     | 0.2     | 0.12    |
| Head of caudate         | 81.9 ± 2.9     | 82.2 ± 2.3     | 0.7     | 0.7     |
| Globus pallidus         | 72.9 ± 4.5     | 72.5 ± 4.6     | 0.7     | 0.7     |
| SN pars reticularis     | 75.4 ± 10.7    | 73.4 ± 10.0    | 0.4     | 0.4     |
| SN pars compacta        | 81.3 ± 4.9     | 81.2 ± 4.0     | 0.9     | 0.9     |
| Red nucleus             | 82.2 ± 11.1    | 81.0 ± 13.3    | 0.7     | 0.6     |

*Data are estimated mean ± S.E. T2 values (ms). Crude P-values are from two-tailed unpaired t-tests. Adjusted P-values are from linear regression analysis controlling for age.

SN, substantia nigra.
Trigeminal Autonomic Cephalalgias

- Cluster
- Paroxysmal hemicrania
- Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT)
- Hemicrania Continua
“Imagine, your eye is pushed out of its socket and your right eyelid is beginning to swell shut. You start squinting and your eye is tearing. You are convinced there was blood pouring out. A red-hot knife is crushed into your head, excruciating horrible, horrible pain. Your only saving grace is to pace from room to room, crying, flinging yourself to the floor, until eventually the pain drains from you.”
Cluster: Epidemiology

- Incidence 1 in 1000
- Males 80-90% (4:1). Onset 20-40 years heavy smokers and drinkers
- Unique Circadian rhythmicity. January and July peak seasons
- Usually attacks are during the first REM period, (60-90 mins after falling asleep)
- Synonyms: “Suicide headache”, Horton’s Neuralgia,
- Average time for correct diagnosis is 6.6 years
PATHOGENESIS

- Vascular Theory: Inflammation of the walls of cavernous sinus

- Neurovascular Theory: Central impulse generator
Orbital Phlebography

- Superior ophthalmic vein narrowed
- Raised intraocular pressure with pain
- Localized narrowing of the Internal carotid artery during acute attack followed by dilation
Hypothalamus: Generator in cluster

- Proinflammatory markers released: Calcitonin gene related peptide (CGRP), Vasoactive intestinal polypeptide (VIP), Histamine
- All being vasodilators, cause neurogenic inflammation of vasculature.
- Vascular events are a marker of brain activation and not the driver
Figure 3. Statistical parametric maps demonstrating activations seen in acute attacks of cluster headache and mapped in color on T1-weighted MR scans of the brain.
Figure 4. A statistical parametric map (A) demonstrates activations seen in acute attacks of cluster headache triggered by nitroglycerin and mapped in color on T1-weighted MR scans of the brain.
CLUSTER HEADACHE

Functional imaging shows activation of specific brain areas during pain.
Cluster patients: H2O PET during NTG-induced attacks, shows inferior hypothalamic gray matter activation ipsilateral to the headache side. Also, increased rCBF in contralateral ventroposterior thalamus, anterior cingulate cortex, and in insulae bilaterally.

May et al., Lancet 1998
PET SCAN: VOXEL-BASED MORPHOMETRY OF 25 CLUSTER PTS

May, Lancet, 2005:843-55
Cluster headaches

Voxel-based morphometry (VBM) structural imaging shows hypothalamus of CH patients

Hypothalamic metabolism in cluster by H-MRS
Hypothalamic metabolism in cluster

- NAA/Cr ratio is reduced
- Permanent feature of Cluster
- Expression of neuronal dysfunction
- Mechanism of this dysfunction yet unknown
PET study in 10 cluster patients with hypothalamic stimulator?

1. Local blockade of hypothalamic trigger
2. Direct antinociceptive effect by activation of PAG/medulla
3. Modulation of neuronal pain-processing pathways
   - Activation of ipsi hypoth, thal, ss cortex, precuneus, ant cingulate cortex, V n
   - Deactivation of contra insula,
   - ss cortex
Paroxysmal hemicrania

- Severe, unilateral, supraorbital and/or temporal pain lasting 1-30 mins untreated
- Frequency of attacks: 3 or more/day
- Attacks prevented completely by Indomethacin
- More common in females
Contralateral hypothalamus dysfunction PET Study

Statistical parametric maps (DPM) showing increased regional cerebral blood flow in the posterior hypothalamus during PH headache vs. indomethacin-mediated pain free state

Matharu, Am Neurology 2006
Paroxysmal hemicrania: H2O PET

Activation of hypothalamic gray matter during attacks
- contralateral posterior hypothalamus, ventral midbrain, temporal cortex, postcentral gyrus, precuneus and cerebellum and ipsilateral lentiform nucleus, anterior and posterior cingulate cortices, bilateral insulae, bilateral frontal corticies

Indomethacin administration turned off persistent activation observed during acute attack - off indomethacin

SUNCT

- Sudden Unilateral Neuralgiform HA with Conjunctival redness and Tearing
- Very short episodes of periorbital stabbing headache accompanied by autonomic symptoms from activation of the trigemino-parasympathetic reflex
- Attacks typically occur 3-200 attacks per day
- Highly refractory to prophylactic medication
- Rarest of all: <100 documented cases only
May et al. activation during the same scanning session in the ipsilateral inferior posterior hypothalamic gray matter during the attacks, compared with pain-free state.

SUNCT
fMRI-study

Cluster headache
PET-study

May A, Ann Neurol 1999;46:791-794
Hemicrania continua

- Strictly unilateral, continuous headache +
- At least one of autonomic symptom
- Responsive to indomethacin
- Significant activation of contralateral posterior hypothalamus and ipsilateral dorsal rostral pons
- Activation of ipsilateral ventrolateral midbrain - extended over red nucleus and substantia nigra and bilateral pontomedullary junction

PET study Matharu et al., Headache 2004
Summary: Migraine Neuroimaging

- AURA-BLOOD FLOW IMAGING: Xenon, SPECT, perfusion-weighted fMRI: Decreased occipital blood flow
- BOLD imaging: decreased occipital lobe activation
- Headache imaging: increased blood flow in rostral pons PET during HA
- Routine imaging:
  - MRI - increased T2 intensity in cerebral white matter
  - MRI - cerebellar infarcts in watershed distribution
- DWI: no change in apparent diffusion coefficient maps
During attacks:

- H2O PET shows inferior hypothalamic gray matter activation ipsilateral to the headache side.
- Activation in areas known to be involved in pain processing such as cingulate insula, prefrontal cortex and contralateral thalamus, midbrain, and basal ganglia.

DURING INTERICTAL PHASE:

- Hypothalamic Hypo metabolism:
- Volumetric gray matter changes
  - Increased volume of the area that is active during headache attack (slightly inferior and posterior to hypothalamus)
  - Gray matter reduction in differing locations
  - Reduction in angular and precentral gyri contralateral to pain
Summary: Cluster Neuroimaging

- Interictal headache patients - decreased metabolism in the prefrontal cortex
- Hypothalamus alterations - increased connectivity with the insula and temporal lobe - via ROI
- Hypothalamus is the center for activation for other Trigeminal Autonomic Cephalalgias.