Migraine in vascular EDS

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Prevalence of headaches in hypermobile disorders

- **“Of all the complications that may arise in hypermobility syndromes, chronic pain is arguably the most menacing and difficult to treat.” Rodney Grahame (1)**

- **Sparce literature with several limitations:**
  - Case definitions of JHS/EDS/BJH variable
  - International Classification of Headache Disorders (ICHD) diagnostic criteria generally not utilised
  - Small series, often poorly controlled

- **51 EDS patients (13 classic type, 28 EDS-HT, 1 with JHS, 7 vascular type, 2 unclassified type) showed that headache and neck pain is present in 30-40% of cases. (2)**
- **28 JHS female patients and 232 matched controls: prevalence of migraine 75% in JHS, 43% in controls (OR 3.19) (3)**
- **170 JHS female patients and 50 female hospital staff (controls): prevalence of migraine 40% in JHS, 20% in controls (4)**

(1) Grahame R. Curr Pain Headache Rep. 2009;13(6):427-33.
(2) Sacheti A, et al J Pain Symptom Manage 1997;14:88-93.
(3) Bendik EM, et al. Cephalalgia 2011;31:603-613.
(4) Hakim AJ, Grahame R. Rheumatology (Oxford). 2004;43(9):1194-5.

Causes of headache disorders in hypermobile syndromes.

- **Primary headache syndromes**
  - Migraine
  - New daily persistent headache (NDPH)
  - Tension-type headache
- **Orthostatic Headaches**
  - Spontaneous intracranial hypotension
  - Headache secondary to Postural tachycardia syndrome (PoTS)
- **Headaches due to structural disorders**
  - Carotid cavernous fistula*
  - Temporomandibular dysfunction
  - Cervicogenic headache
  - Chiari malformations
  - Craniocervical instability
  - Trigeminal neuralgia
  - Neck-tongue syndrome
  - Cervical artery dissection

Migraine

ICHD-III Diagnostic criteria: [1]

- **Episodic attacks of headache lasting 4-72 hours with the following features:**

Headache has at least two of the following characteristics:

- **Unilateral location**
- **Pulsating quality**
- **Moderate or severe pain intensity**
- **Aggravation by routine physical activity**

During headache at least one of the following:

- **Nausea and/or vomiting**
- **Photophobia and phonophobia**

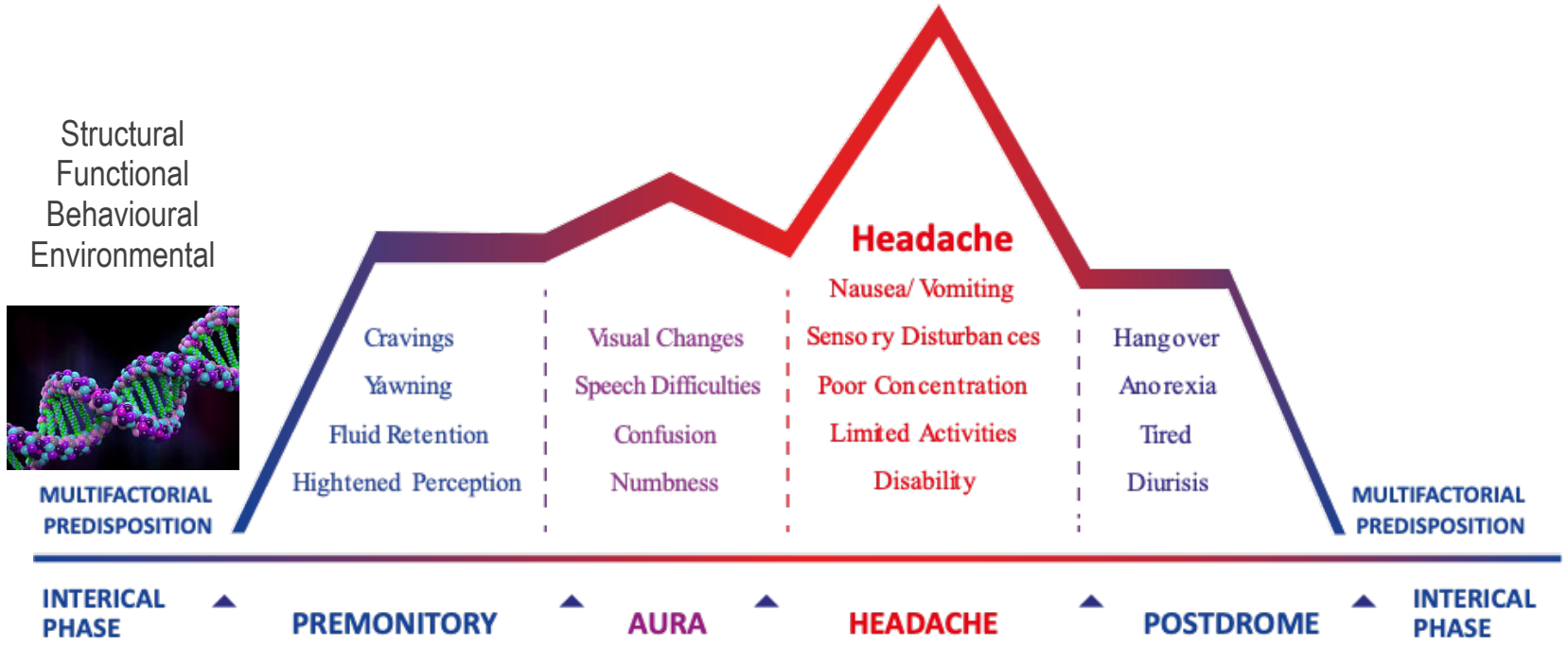
- **Further sub-classified on basis of aura and frequency of headaches**
  - Headaches ≤15 days/month: episodic migraine
  - Headaches ≥15 days/month: chronic migraine
- **Overall prevalence of migraine: 12-15%**
  - Chronic migraine: 0.9-2.2%

ICHD = International Classification of Headache Disorders

1. Headache Classification Subcommittee of The International Headache Society. The International Classification of Headache Disorders 3rd edition. Cephalalgia. 2018;38:1-211.

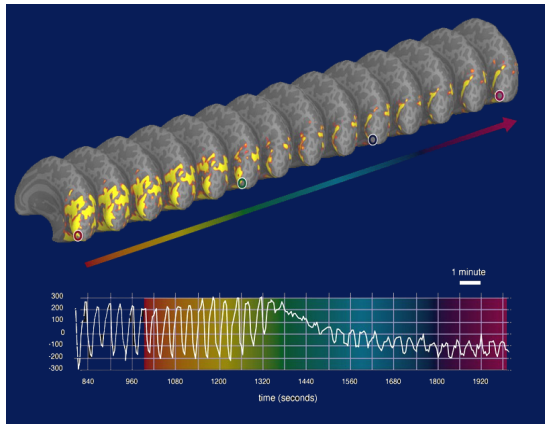
Migraine – a polyphasic brain disorder

- **A complex clinical syndrome characterised by headache with specific features and associated symptoms**



Adapted from Blau JN. Lancet 1992; 339: 1202–7

Pathophysiology of Migraine



Hadjikhani et al, *PNAS* 2001

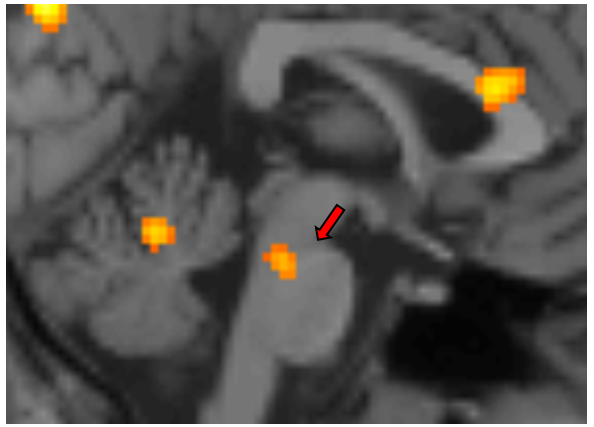
Abnormal cortical activity

Hyperexcitable brain (↑Ca++, ↑Glu, ↓Mg^{++})

⇔

Abnormal brain stem function

Excitation of brain stem, PAG, etc.



Matharu *et al*, Brain 2004

Cortical Spreading Depression

Activation/Sensitization of TGVS

Headache Pain

Vasodilation
Neurogenic
Inflammation

Central Sensitization

TGVS=trigemino-vascular system.

Adapted from Pietrobon D, Striessnig J. *Nat Rev Neurosci.* 2003;4:386-398.

Multifaceted Approach to Management of Migraine

- **Lifestyle modification and trigger management**
- **Pharmacological and Injectable treatments**
  - Acute treatment
  - Preventive treatment
- **Neuromodulation**
  - Non-invasive neuromodulation
  - Invasive neuromodulation

Abortive Treatments in Migraine

Non-specific Treatments

- **Paracetamol 1g**
- **NSAIDs (high-dose & soluble)***
  - Aspirin 600-900mgs
  - Ibuprofen 600-800mgs
  - Naproxen 500-1000mgs
  - Tolfenamic acid 200mgs
- **+/- Anti-emetics:**
  - Domperidone 10mgs
  - Metoclopramide 10mgs
  - Ondansetron 4mg
  - Prochlorperazine 5mg

Caution: medication overuse headache

Specific Treatments

- **Ergot derivatives**
  - Ergotamine 1-2mg tablets/suppository
  - Dihydroergotamine
- **Triptans (5-$HT_{1B/D}$)**
  - Sumatriptan
  - Rizatriptan
  - Zolmitriptan
  - Almotriptan
  - Eletriptan
  - Naratriptan
  - Frovatriptan
- **Ditans (5-HT_{1F} receptor agonists)**
  - Lasmiditan
- **Gepants (CGRP receptor antagonists)**
  - Rimagepant
  - Ubrogepant
- **Neuromodulation**
  - Supraorbital nerve stimulation
  - Remote Electrical Neuromodulation (REN)
  - Transcranial magnetic stimulation

Preventive Treatments in Migraine

- **Antidepressants**
  - TCAs: Amitriptyline
  - SNRIs: Venlafaxine, Duloxetine
- **Beta-blockers***
  - Propranolol.
- **Serotonin antagonists**
  - Pizotifen
- **Anticonvulsants**
  - Topiramate, Valproate
- **Ca Channel blockers**
  - Flunarizine
- **Angiotensin-based***
  - Candesartan, Lisinopril
- **Neutriceuticals (metabolic)**
  - Magnesium, Riboflavin, CoEnzyme Q10
- **Injectable treatments**
  - Botulinum toxin type A (chronic migraine)
- **CGRP receptor antagonists**
  - Atogepant
- **CGRP monoclonal antibodies**
  - Erenumab
  - Fremanuzemab
  - Galcanezumab
  - Eptinezumab
- **Neuromodulation**
  - Supraorbital nerve stimulation
  - Transcranial magnetic stimulation
  - Occipital nerve stimulation

Migraine in hypermobile syndromes

- Comparison of headache in JHS and controls (1)

Headache characteristic	JHS (n=28)	Controls (n=232)	P value
Migraine	**75%**	**43%**	**<0.01**
Migraine without aura	90%	91%	
Migraine with aura	43%	24%	
Mean headache frequency days/ month (SD)	**10.5 (9.5)**	**5.6 (7.9)**	**0.01**
Mean MIDAS score	**36.6 (30.3)**	**9.3 (16.2)**	**<0.01**
Medication use n(%)			
Preventive treatments	**71%**	**44%**	**<0.01**
Abortive treatments	**82%**	**82%**	**0.97**

- **Migraine presentation in hypermobile syndromes is more florid, frequent (1.7 fold) and disabling compared (3 fold) to non-hypermobile patients.**
- **Medication overuse headache likely to be a contributor in patients suffering from recurrent/chronic musculoskeletal pain**
- **Management of migraine in vEDS:**
  - Acute treatments: use NSAIDs with caution in vEDS, medication overuse headache can be challenging to address
  - Preventive treatments: avoid antihypertensives (Betablockers/Candesartan)

(1) Bendik EM, et al. Cephalalgia 2011;31:603-613.

Comorbid disorders impacting on Headache disorders.

- **Anxiety disorders**
  - Anxiety in 32% of JHS patients as compared to 12% within a control population.[1]

- **Sleep disorders**
  - Periodic limb movements are found in 67% of adults with EDS compared to 8% in controls [2]
  - Sleep disturbances including sleep apnoea, restless leg syndrome, and snoring frequently co-occur in patients with migraine and other headache disorders

- **Mast cell activation syndrome (MCAS)**
  - 24-66% of EDS patients have MCAS/histamine sensitivity [3,4]
  - Histamine is potent trigger for headaches

- **Medication overuse headache [5]**
  - Develops through chronic overuse of acute medication taken to treat headache or other pain

1) Hakim AJ, Grahame R. Rheumatology (Oxford). 2004;43(9):1194-5.
2) Verbraecken J et al. Clin Genet. 2001;60(5):360-5.
3) Song B, et al. Proc (Bayl Univ Med Cent). 2020;34(1):49-53.
4) Cheung I, Vadas P.J Allergy Clinical Immunol. 2015;135(2)
5) Headache Classification Subcommittee of The International Headache Society. The International Classification of Headache Disorders 3rd edition. Cephalalgia. 2018;38:1-211

Why are primary headache disorders over-represented in hypermobile syndromes?

- **Abnormal vascular endothelial function**
  - Showering of the cerebral vasculature with atheroemboli, which might trigger attacks of aura in these patients. (1)

- **Dysautonomia**
  - Khurana and Eisenburg found that 23 of 24 patients (96%) with POTS had a diagnosis of migraine or probable migraine. (2)
  - Kanjwal et al. demonstrated that migraine occurred in 73% of patients with both JHS and POTS as compared to 23% of those with POTS but without JHS ($P<0.001$). (3)

- **Pro-inflammatory cytokines**
  - Pain might be due to chronic central nervous system inflammation, cytokine production and persistent glial activation that arise in response to precipitating events (4)

- **Centrally mediated pain neuromatrix dysregulation**
  - Altered modulation of pain in JHS patients with fibromyalgia may lower the threshold for primary headache syndromes and other pain syndromes.

(1) Martin VT, Neilson D. Headache. 2014;54(8):1403-11.
(2) Khurana RK et al. Cephalalgia. 2011;31(4):409-15.
(3) Kanjwal K et al. Indian Pacing Electrophysiol J. 2010;10(4):173-8.
(4) Rozen T, Swidan SZ. Headache. 2007;47(7):1050-5.

Headache in EDS

- Headaches are common in hypermobile disorders
- There is large differential diagnosis for headaches in hypermobile disorders.
- Individual hypermobile patients often have multiple causes for headaches.
- Clinicians looking after these patients need to carefully assess for the various potential causes of headaches and implement appropriate management strategies.
- A multidisciplinary approach is ideally required as the multisystem involvement often impacts on headaches
- More research needs to be done regarding the interrelationships between hypermobile disorder and headache/neck pain as this may represent a subgroup of patients with a different pathogenesis and treatment.