

UNIVERSITY OF BIRMINGHAM  
**IMSR**  
INSTITUTE OF MIGRAINE AND SYSTEMS RESEARCH

## CSF Pressure Disorders

13th Annual Headache Cooperative of the Pacific (HCOP) Winter Conference being held on January 24-25

Alex Sinclair  
Professor of Neurology  
University of Birmingham  
[a.s.sinclair@bham.ac.uk](mailto:a.s.sinclair@bham.ac.uk)  
@IMSRBirmingham

No conflicts of interest

---

---

---

---

---

---

---

---

1

UNIVERSITY OF BIRMINGHAM  
**IMSR**  
INSTITUTE OF MIGRAINE AND SYSTEMS RESEARCH

## Conflicts of interest

- Speaker fees and Honoraria for participation in Advisor Boards for Novartis and Allergan
- Headache Clinical fellow funding for 1 year from Allergan and Novartis
- Director and share holder of Invex Therapeutics, a University of Birmingham spin-out company.

---

---

---

---

---

---

---

---

2

UNIVERSITY OF BIRMINGHAM  
**IMSR**  
INSTITUTE OF MIGRAINE AND SYSTEMS RESEARCH

## ARS

To answer the pre-test questions:

Log into [www.slido.com](http://www.slido.com)

Enter Event #2510

---

---

---

---



---

---

---

---

3

**Pre-Test Question #1**

**Is a lumbar puncture opening pressure > 25 cm CSF alone always consistent with a diagnosis of Idiopathic Intracranial Hypertension (IIH)?**

A. Yes  
B. No, papilloedema must be confirmed and a secondary cause excluded  
C. Yes, once a secondary cause is excluded  
D. I don't know

4

---

---

---



---

---

---

---

---

**Pre-Test Question #2**

**Is CSF shunting a useful therapy for headache in IIH?**

A. Yes  
B. Not in the majority  
C. Only lumboperitoneal shunting is helpful  
D. I don't know

5

---

---

---



---

---

---

---

---

**Pre-Test Question #3**

**What is the proposed mechanism of action of Glucagon like peptide 1 (GLP-1) receptor agonists to treat IIH?**

A. By suppressing appetite  
B. By directly reducing cerebrospinal fluid secretion at the choroid plexus  
C. Both thought suppressing appetite and by directly reducing cerebrospinal fluid secretion at the choroid plexus  
D. I don't know

6

---

---

---

---

---

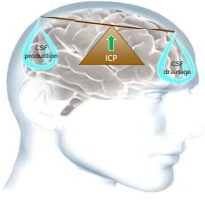
---

---

---

UNIVERSITY OF BIRMINGHAM IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SYSTEMS RESEARCH

### CSF Pressure Disorders



High pressure

- IH
- IH WOP

Low pressure

- Spontaneous CSF leaks
- Iatrogenic

---

---

---

---

---

---

---

---

---




---

7

UNIVERSITY OF BIRMINGHAM IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SYSTEMS RESEARCH

### Idiopathic Intracranial Hypertension (IIH)

- Raised intracranial pressure & papilloedema
- Population
  - 90% are **obese women** of childbearing age
- Symptoms
  - Headaches
  - Visual loss
  - Up to 25% of patients have permanent severe visual loss
- Reality:
  - Chronic condition characterised by significantly long term disabling headaches

Normal optic disc    Papilloedema    Papilloedema Optical coherence tomography

---

---

---

---

---

---

---

---

---

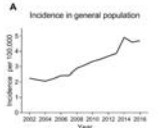
---

8

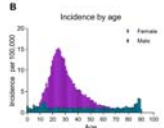
UNIVERSITY OF BIRMINGHAM IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SYSTEMS RESEARCH

### UK Hospital data

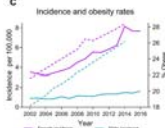
**A** Incidence in general population




**B** Incidence by age



**C** Incidence and obesity rates



**D** Management



Included:  
23,182 new IIH cases

Now: 5 per 100,000

**Rapidly rising incidence**

Mollan & Sinclair 2018 Eye

---

---

---

---

---

---

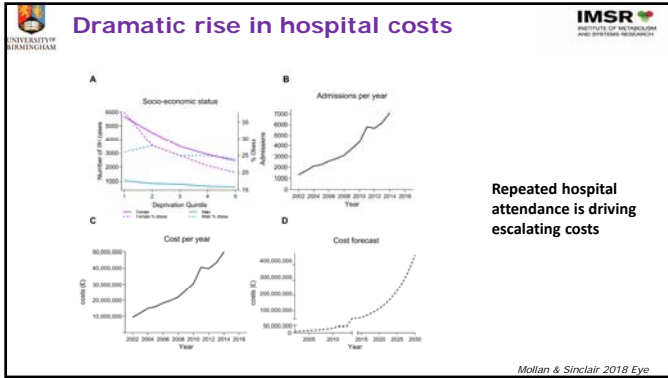
---

---

---

---

9



10

---

---

---

---

---

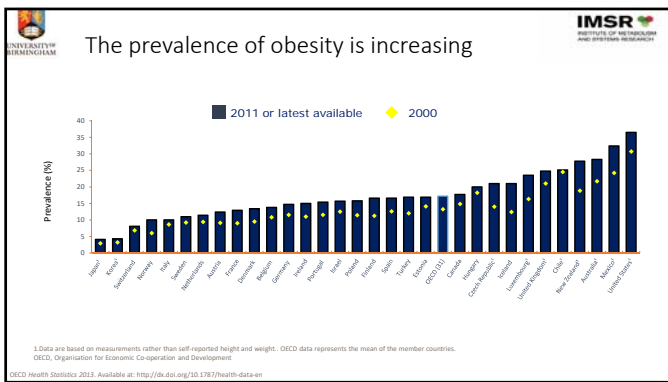
---

---

---

---

---



11

---

---

---

---

---

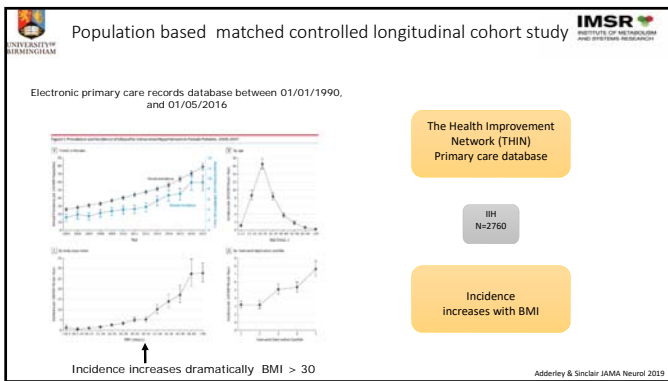
---

---

---

---

---



12

---

---

---

---

---

---

---

---

---

---



UNIVERSITY OF BIRMINGHAM IMSR  
INSTITUTE OF NEUROLOGY  
AND SENIORS RESEARCH

### Clinical practice varies widely internationally

---

I had a frank discussion that weight loss is the only sustainable treatment for her IIH. Her BMI is 38.7 and she is now undergoing investigations for obstructive sleep apnoea. I explained that OSA is often a complication of obesity and if untreated is a risk factor for hypertension and Type II diabetes.

Having reviewed her notes. In the last 2 1/2 years she has had 38 ophthalmology clinic reviews (mainly emergency clinic and visual field reviews), 4 neurosurgery OPD and 12 neurology OPD reviews. In 2018 alone she has had 6 emergency neurosurgery ward reviews. From November 2016 to date she has presented to the emergency room 19 times with concerns of shunt blockage. She has had 19 daycase or emergency admissions under neurosurgery or neurology. Since her presentation in February 2016, she has had 36 CT head scans, 22 xrays and 2 CT abdo/pelvis. She has had approximately 20 shunt procedures (shunt insertions/ revisions and ICP monitors) and over 30 lumbar punctures. This demonstrates that the current focus on her shunt has not yielded sustained clinical improvement, increased her radiation exposure and several general anaesthetics.

Pippa is understandably upset as she feels that she is not clinically progressed. I emphasised that from the outset when she was reviewed by Prof Smith, she was counselled that the only sustainable treatment would be weight loss. Indeed she acknowledges that in December 2016 her weight had reduced to 71kg and she had a good quality of life, was active in the gym and her mood was better overall. This is supported by the new IIH guidelines (Molan *et al. J Neurol Neurosurg Psychiatry* 2018;0:1-13. doi:10.1136/npp-2017-317440).

16

---

---

---

---

---

---

---

---

---

---

JNNP 2018 - IIH Guideline  
 J Headache and Pain 2018-  
 EHF IIH Guideline

Infographic in Practical  
 Neurology Aug 2018

17

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM IMSR  
INSTITUTE OF NEUROLOGY  
AND SENIORS RESEARCH

### 5 Key messages

18

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SYSTEMS RESEARCH

## Messages 1

Diagnostic error

Weight loss

medication

Headaches

IIHWOP

19

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SYSTEMS RESEARCH

## Diagnostic error in IIH

- 40% of patients labelled with IIH referred to a neuro-ophthalmology clinic don't have IIH!
- Error is due to inaccurate identification of papilloedema
  - 79% had a un-necessary LP
  - 96% received acetazolamide unnecessarily
  - 3% has shunt surgery

Papilloedema Confirmed?

Imaging

LP

Fleury et AL. Neurology 2016

20

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SYSTEMS RESEARCH

## Papilloedema

- Common presenting sign
- Once "labelled" with papilloedema it is often not questioned
  - Usually straightforward to recognise
  - Can be difficult

Papilledema

Pseudopapilloedema

Pseudopapilloedema

Papilledema

Are you sure its papilloedema?

21

---

---

---

---

---

---


---

---

UNIVERSITY OF BIRMINGHAM

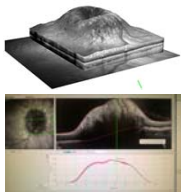
Scanning papilloedema

IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SENSORY RESEARCH



Optical Coherence Tomography (OCT)

OCT quantify and track papilloedema



22

---

---

---

---

---

---

---

---

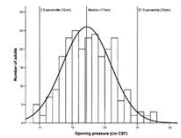
UNIVERSITY OF BIRMINGHAM

Caution in over interpreting LP OP

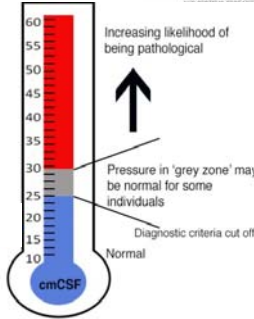
IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SENSORY RESEARCH

**Recommendations for IIH:**

- ICP  $\geq 25$  cmCSF
  - Caution – snap shot reading
  - ICP varies diurnally



*Distribution of CSF opening pressures among 442 adult neurology outpatients.*



Whitley W. Neurology 2006;67(8):1690-1

23

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM


IIH Pressure: Physiological study

IMSR  
INSTITUTE OF NEUROSCIENCE  
AND SENSORY RESEARCH

Patients with Active IIH and on remission

Defined:

- 24 hour ICP monitor
- Lying / standing
- Supine / prone / LP position
- Diurnal ICP rhythm



*Mitchell & Sinclair et al. 2020 in prep*

24

---

---

---

---

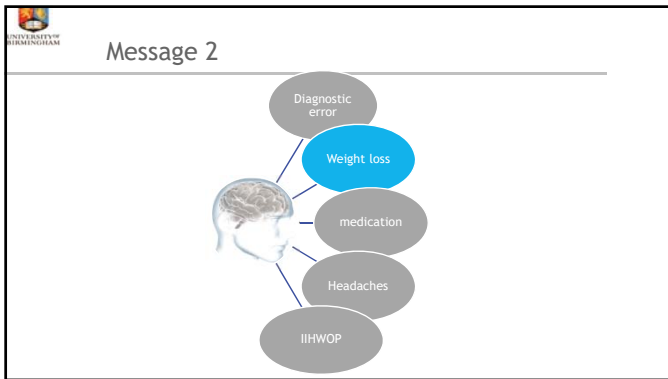
---

---

---

---





25

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

## Obesity

**Obesity:**

- > 90% of patients are obese women

Evidence for efficacy of weight loss in IIH was previously lacking

- Newborg 1974, 9 patients on a rice diet
- Kuppersmith, 1998, retrospective case note study of 58 patients
- Johnson, 1998, retrospective case note study of 15 patients

IIH Association

26

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

## Weight loss is therapeutic in IIH

**Prospective cross over study**

- Weight reduction 15%
- Significant reduction in ICP
- Significant reduction in headache
- Significant improvement in vision

LogMAR acuity Contrast sensitivity

Humphrey Visual field 24-2 (mead deviation)

Sinclair et al. 2010 - BMJ 341-c2701

27

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

**Ongoing:  
IIH Weight Trial**


IIHWA

- Long-term weight loss is difficult to achieve and maintain
  - Typically as little as 2-4 kg at 2 years irrespective of the dietary regime followed
  - Orlistat, (reduce weight by 2.89kg) - these drugs do not achieve sufficient weight loss to significantly modify IIH
- Multicentre RCT n=60
- Results forecast for Sept 2020

**IIH Weight study**

RCT

Community weight loss  
Vs  
Bariatric surgery



NIHR  
National Institute for Health Research

28

---

---

---

---

---

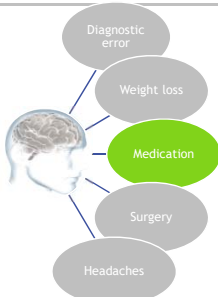
---

---

---

UNIVERSITY OF BIRMINGHAM

**Message 3**



29

---

---

---

---

---

---

---


---

UNIVERSITY OF BIRMINGHAM

**Medical treatment for IIH**

IMSR  
INSTITUTE OF NEUROLOGY AND SENIORS RESEARCH

- Cochrane review IIH updated August 2015
- Two included RCTs included: showed modest benefits for acetazolamide for some outcomes
- Insufficient evidence to recommend or reject the efficacy of acetazolamide for treating IIH.

 **Cochrane Library**  
Cochrane Database of Systematic Reviews

Piper et al. Cochrane Database Syst Rev 2015 Aug 7:8

30

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

## Medical therapy for IIH

IMSR  
INSTITUTE OF HEAD NEUROLOGY  
AND STRIKEIN RESEARCH

IIH  
CONSENSUS

- Acetazolamide
  - Poorly tolerated 48% discontinued - Ball et al J Neurol 2011;258:874-881
  - IIH Treatment Trial 2014 (n=167)
    - High doses: >40% were on 4g dose - JAMA. 2014;311(16):1641-1651

Measure	Mean (95% CI)	p
Perimetric mean deviation	0.71dB (0 to 1.43dB)	0.05
Weight loss	-4.0kg (-6.23to -1.8kg)	<0.001
Lumbar puncture pressure	-45.0mmHg (-95.2 to 5.2)	0.08
Visual acuity	0.01 (-1.45 to 1.46)	0.99
Papilloedema grade	-0.91 (-1.27 to -0.54)	<0.001
QoL (SF-36)	3.02 (0.34 to 5.70)	0.03
Headache impact test -6	-0.45 (-3.50 to 2.60)	0.77

No. of patients  
Acetazolamide  
Placebo

31

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

## Very limited evidence for drugs used in IIH

IMSR  
INSTITUTE OF HEAD NEUROLOGY  
AND STRIKEIN RESEARCH

### In-vivo evaluation of drugs used in IIH

Subcutaneous

Drug	Human equivalent clinical single dose	% Change ICP
Topiramate	50mg	-32% (p<0.0001)
Acetazolamide	1g	-15% (p<0.08)
Amiloride	5mg	-10% (p<0.52)
Dextroretide	350ug	-1% (p=0.99)
Furosemide	40mg	-1% (p=0.99)

Drug dose was determined using the FDA equation to convert drugs doses from rodents to humans

Subcutaneous

- Topiramate significantly lowers ICP
- Other drugs do not reduce ICP acutely in rodents

**Novel Therapeutic targets needed**

Scotton et al. Cephalalgia 2018

32

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

## Very Limited drug therapy for IIH

Future.....new targets

33

---

---

---

---

---

---

---

---

---

---





**ICP rises during prolonged space flight**

Collaboration with Dr. J.D. Polk  
 Chief Health and Medical Officer, NASA  
 Space flight raised ICP  
 Planning a trial in space  
 Intervention with GLP1RA exenatide

37

---

---

---

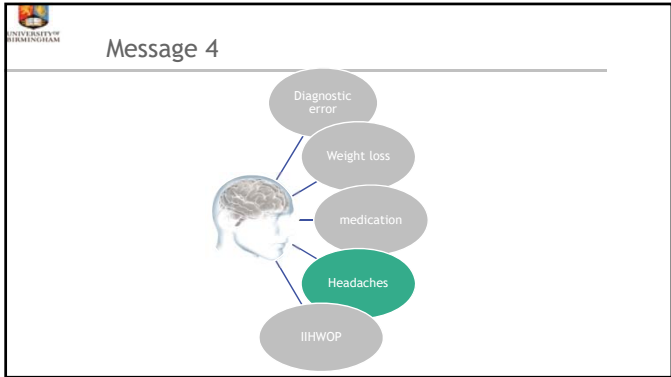
---

---

---

---

---



38

---

---

---

---

---

---

---

---

**Headache is the overwhelming disabler**

**Patient Involvement:**  
 An electronic survey specifically for this grant by patient charity IHH UK (Nov 2019)  
 Q: "How does your headache make you feel?"  
 > 500 IHH patients responded in 7 days

**Overwhelming patient perspective:**

- Patients feel abandoned
- Headache is long term and relentless
- Devastating implication on family life and ability to work

39

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

Headache impacts on Quality of Life

IMSR  
INSTITUTE OF INVESTIGATIVE NEUROSCIENCE  
AND SENSORY MOTOR RESEARCH

- QOL in IIH patients is significantly reduced
- Headache disability correlates with reduced QOL
- IIH affects QOL even in patients with mild visual impairment

Mulla & Sinclair. J Headache Pain 2015. 16: 521

Digne et al. Neurology 2015. 16: 2449-56

40

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

Headache in the IIH Treatment trial

IMSR  
INSTITUTE OF INVESTIGATIVE NEUROSCIENCE  
AND SENSORY MOTOR RESEARCH

- 84% had headache at baseline
  - 68% frontal
- Mean number of headache days per month = 12
- 37% has medication overuse
- Headache severity and disability **did not** correlate with LP pressure

NORDIC

Headache phenotype was most commonly "migrainous"

BUT:  
No "typical" IIH headache phenotype identified

Friedman D et al. Headache 2017;57:1195-1205

41

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

Headache in IIH

IMSR  
INSTITUTE OF INVESTIGATIVE NEUROSCIENCE  
AND SENSORY MOTOR RESEARCH

- Many do not have the classical features of raised ICP
  - Progressive, daily, diffuse, non-pulsatile headache with aggravation by coughing

Exacerbated by	IIH (n=44)	Controls (n=34)	occur	IIH	Controls
Bending	50%	44%	Blurred vision	66%	53%
Cough / strain	70%	35%	Pulsatile tinnitus	64%	26%
Morning	20%	29%	Obscuration's	64%	35%
Physical activity	64%	74%			

Symptoms are not pathognomonic of IIH

Controls from a headache clinic with normal ICP and no papilloedema

Yri and Jensen. Cephalalgia. 2014

42

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

## Headache relief after lumbar puncture and CSF removal

- Headaches improvement with LP
  - IIH 72%
  - Non-IIH headaches **23% also improve after LP !!**

Hanne M. Yli, and Rigmor H. Jensen Cephalalgia 2014;35:553-562

43

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

IMSR  
INSTITUTE OF HEADACHE AND SENSORY RESEARCH

## Mixed headache phenotypes in IIH

Evaluate headache phenotype

- Elevated ICP
- Migraine
- Medication overuse
- CSF shunt in situ
  - ? Low pressure
  - ? High pressure
  - ? Normal

44

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

IMSR  
INSTITUTE OF HEADACHE AND SENSORY RESEARCH

## Consensus approach - Managing Headache in Chronic IIH

Vision not at imminent risk

Phenotype headache

Evidence of on going raised pressure?

Any evidence of medication overuse?

Aim to avoid LP

- Multiple Therapeutic LP's problematic
- Exact pressure typically does not change conservative management

± Acetazolamide – no evidence that effective for headache (IIHTT 2014 JAMA)

Address medication overuse

- Simple analgesics >15d/month
- Opiates/triptans >10d/month

Withdrawal

IIH Consensus

45

---

---

---

---

---

---

---

---

Consensus approach - Managing Headache in Chronic IIH

IMSR  
INSTITUTE OF NEUROLOGY  
AND SYSTEMS RESEARCH

UNIVERSITY OF BIRMINGHAM

Vision not at imminent risk

Phenotype headache

Evidence of on going raised pressure?

+ Any evidence of medication overuse?

+ Any evidence of migraine

Aim to avoid LP

- Multiple Therapeutic LP's problematic
- Exact pressure typically does not change conservative management

± Acetazolamide  
— no evidence that effective for headache (IIHTT 2014 JAMA)

**Treat migraine headache**

Acute migraine attack	Migraine prevention
✓ Triptan	Options
✓ NSAID/paracetamol	✓ 3 month trial
✓ Anti-emetic	✓ Titrates up slowly
✗ No opiates	✓ Reach a therapeutic dose
Maximum 10 times per month	Options
	Topiramate
	Carbamazepine
	Botulinum toxin (as per NICE)
	✓ Propranolol
	✗ Propranolol
	✗ Sumatriptan
	Caution: ↑ weight, ↓ mood

IMSR  
INSTITUTE OF NEUROLOGY  
AND SYSTEMS RESEARCH

46

---

---

---

---

---

---

---

---

---

---

Should CSF diversion surgery be used in IIH patients with headache alone?

IMSR  
INSTITUTE OF NEUROLOGY  
AND SYSTEMS RESEARCH

UNIVERSITY OF BIRMINGHAM

- Where papilloedema has resolved, typically the ICP will be normalising and conservative treatment strategies should be employed.
- CSF shunting to exclusively treat headache has poor efficacy.
  - 68% will continue to have headaches at 6 months and 79% by 2 years
- CSF diversion is generally not recommended as a treatment for headache alone in IIH.

Sinclair et al Cephalalgia 2011 Dec;31(16):1627-33

IMSR  
INSTITUTE OF NEUROLOGY  
AND SYSTEMS RESEARCH

47

---

---

---

---

---

---

---

---

---

---

Message 5

IMSR  
INSTITUTE OF NEUROLOGY  
AND SYSTEMS RESEARCH

UNIVERSITY OF BIRMINGHAM

Diagnostic error

Weight loss

medication

Headaches

IIHWOP

48

---

---

---

---

---

---

---

---

---

---



UNIVERSITY OF BIRMINGHAM

IMSR  
INSTITUTE OF NEUROSCIENCE AND SYSTEMS RESEARCH

## Could it be IHHWOP?

- IHH **With Out** Papilloedema

Diagnostic criteria for adult IHH* (Friedman 2013 Neurology)	
A.	Papilloedema
B.	Normal neurological examination except for cranial nerve abnormalities
C.	Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass or structural lesion and no abnormal meningeal enhancement or venous sinus thrombosis on MRI and magnetic resonance venography; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used.
D.	Normal cerebrospinal fluid (CSF) composition
E.	Elevated lumbar puncture opening pressure ( $\geq 25\text{cmH}_2\text{O}$ ) in a properly performed lumbar puncture

\* BUT.....these criteria may well be too stringent and lead to the under identification of cases.

- Fulfil the criteria B-E above +
- Unilateral or bilateral sixth nerve palsy
- Or 3 neuro-imaging findings suggestive of raised ICP
  - Empty sella, flattening of the posterior aspect of the globe, distention of the periploic subarachnoid space & a tortuous optic nerve and transverse sinus stenosis
  - Venous stenosis

Friedman DJ, Liu GT, Diener KB. Neurology 2012; 81(12): 1159-65

49

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

IMSR  
INSTITUTE OF NEUROSCIENCE AND SYSTEMS RESEARCH

## Idiopathic Intracranial Hypertension Without Papilloedema (IHHWOP) in Chronic Refractory Headache

```

graph TD
    A[45 patients enrolled] --> B[40 patients]
    A --> C[5 patients excluded  
(protocol violations)]
    B --> D[Ophthalmologic evaluation and OCT]
    D --> E[No papilloedema  
40/40 (100%)]
    E --> F[PL]
    F --> G[OP < 200 mmHg IOP  
31/40 (77.4%)]
    F --> H[200-OP < 250 mmHg IOP  
7/40 (17.5%)]
    F --> I[OP > 250 mmHg IOP  
2/40 (5%)]
    G --> J[MRV (3 of 4 Neuroimaging findings)  
1/7 (2.5%)]
    H --> K[MRV (3 of 4 Neuroimaging findings)  
1/2 (2.5%)]
  
```

Favoni et al Front Neurol 2018; 9: 503.

50

---

---

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

IMSR  
INSTITUTE OF NEUROSCIENCE AND SYSTEMS RESEARCH

## IHHWOP – Vision

- No papilloedema
- Don't develop papilloedema
- Do not lose vision
- Functional visual loss can occur
- Visual phenomenon from migraine aura may occur

Clover leaf appearance of functional visual field

51

---

---

---

---

---

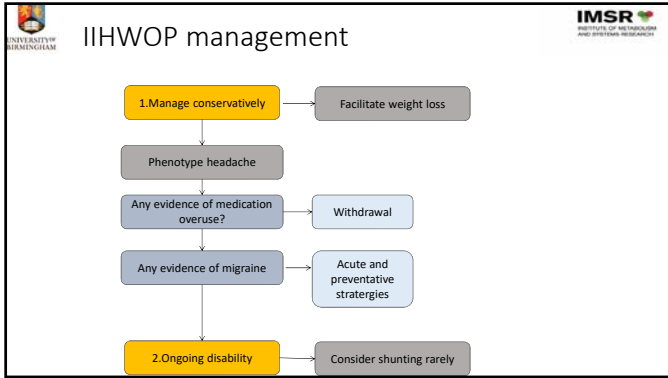
---

---

---

---

---



52

---

---

---

---

---

---

---

---

IIH International Guideline --  
JNNP 2018. Mollan and Sinclair et al  
Infographic in Practical Neurology  
Aug 2018

53

---

---

---

---

---

---

---

---

Is IIH a metabolic condition?

- Weight loss is therapeutic
- Truncal adiposity correlates with ICP
  - Loss of truncal adiposity is disease modifying
- Cardiovascular disease x 2 fold risk
- Unique androgen excess profile in IIH

Can novel therapies target metabolic pathways?

- Gut neuropeptides - GIP-1R agonists to lower ICP & reduce obesity

54

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

### 5 Key messages - summary

IIH Guideline

QR Code

- Diagnostic error: Is it papilloedema?
- Weight loss: Disease modifying
- Medication: Acetazolamide maybe used
- Headaches: Quality of life ↓
- IIHWOP: Consider in refractory CM

55

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

### ARS

To answer the post-test questions:

Log into [www.slido.com](http://www.slido.com)

Enter Event #2510

56

---

---

---

---

---

---

---

---

UNIVERSITY OF BIRMINGHAM

### Post-Test Question # 1

Is a lumbar puncture opening pressure > 25 cm CSF alone always consistent with a diagnosis of Idiopathic Intracranial Hypertension (IIH)?

- A. Yes
- B. No, papilloedema must be confirmed and a secondary cause excluded
- C. Yes, once a secondary cause is excluded
- D. I don't know

57

---

---

---

---

---

---

---

---



**Post-Test Question #2**

**Is CSF shunting a useful therapy for headache in IIH?**

- A. Yes
- B. Not in the majority
- C. Only lumboperitoneal shunting is helpful
- D. I don't know

---

---

---

---

---

---

---

---

58



**Post-Test Question #3**

**What is the proposed mechanism of action of Glucagon like peptide 1 (GLP-1) receptor agonists to treat IIH?**

- A. By suppressing appetite
- B. By directly reducing cerebrospinal fluid secretion at the choroid plexus
- C. Both thought suppressing appetite and by directly reducing cerebrospinal fluid secretion at the choroid plexus
- D. I don't know

---

---

---

---

---

---

---

---

59