



김 병 건
울지의대

Headache disorders

- Common
- Disabling
- Widespread

Headache disorders are common

Global Burden of Disease 2016 (GBD2016)

Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators*

Lancet 2017; 390: 1211–59

Top 10 prevalent disease

1. Dental caries
2. Latent tuberculosis
3. Tension-type headache
4. Hearing loss
5. Iron-deficiency anemia
6. Migraine

In GBD 2016, TTH and migraine are also included in the top 10 prevalent disease.

Headache disorders are disabling

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GBD 2016 Disease and Injury Incidence and Prevalence Collaborators*

Lancet 2017; 390: 1211–59

Findings Globally, low back pain, migraine, age-related and other hearing loss, iron-deficiency anaemia, and major depressive disorder were the five leading causes of YLDs in 2016, contributing 57.6 million (95% uncertainty interval [UI] 40.8–75.9 million [7.2%, 6.0–8.3]), 45.1 million (29.0–62.8 million [5.6%, 4.0–7.2]), 36.3 million (25.3–50.9 million [4.5%, 3.8–5.3]), 34.7 million (23.0–49.6 million [4.3%, 3.5–5.2]), and 34.1 million (23.5–46.0 million [4.2%, 3.2–5.3]) of total YLDs, respectively. Age-standardised rates of YLDs for all causes combined

Migraine has become the second largest cause of disability in 2016.

The rise of migraine over these years is not indicative of increasing prevalence. Because GBD is dependent on data from the entire world, many recent headache epidemiological studies outside the America and Western Europe were reflected on Global Burden of Disease study.

한국에서 두통의 1년 유병률

	남자	여자	
두통	51.5%	70.4%	60.9%
편두통	8.9%	26.0%	17.5%
긴장형두통	32.2%	29.3%	30.7%
만성매일두통	1.6%	2.0%	1.8%

KIM et al, Journal of clinical neurology 2012

최근의 편두통 역학조사 결과들

			Headache	migraine	TTH
Zebenigus (2016)	Ethiopia	2,385	44.9%	17.7%	20.6%
Mbewe (2015)	Zambia	1,085	61.6%	22.9%	22.8%
Herekar (2017)	Pakistan	4,223	76.6%	22.5%	44.6%
Manandhar (2015)	Nepal	2,100	84.9%	34.1%	41.5%
Kulkami (2015)	India	2,329	63.9%	25.2%	35.1%
Yu (2012)	China	5,041	23.8%	9.3%	10.8%
Ayzenberg (2012)	Russia	2,025	62.9%	20.8%	30.8%

LTB study using HARSHIP questionnaire

The prevalence of migraine in neurologists

Randolph W. Evans, MD; Richard B. Lipton, MD; and Stephen D. Silberstein, MD

Abstract—To assess the prevalence of migraine among neurologists and neurologist headache specialists, the authors performed a survey of neurologists who attended a headache review course. The 1-year and lifetime prevalences of migraine in the 220 respondents were as follows: male neurologists, 34.7%, 46.6%; male headache specialists, 59.3%, 71.9%; female neurologists, 58.1%, 62.8%; and female headache specialists, 74.1%, 81.5%. Migraine is much more prevalent among neurologists than in the general population.

NEUROLOGY 2003;61:1271-1272

Prevalence	Neurologist		Headache specialist	
	male	female	male	female
One year	34.7%	58.1%	59.3%	74.1%
Lifetime	46.6%	62.8%	71.9%	81.5%

The prevalence of migraine among neurologists is much higher than in the general population.

The prevalence among headache specialists is even higher than general neurologists.

Migraine Among Norwegian Neurologists

Karl B. Alstadhaug, MD, PhD; Antonio Hernandez, MD; Halvor Naess, MD, PhD;
Lars Jacob Stovner, MD, PhD

(*Headache* 2012;52:1369-1376)

Lifetime prevalence of self reported migraine

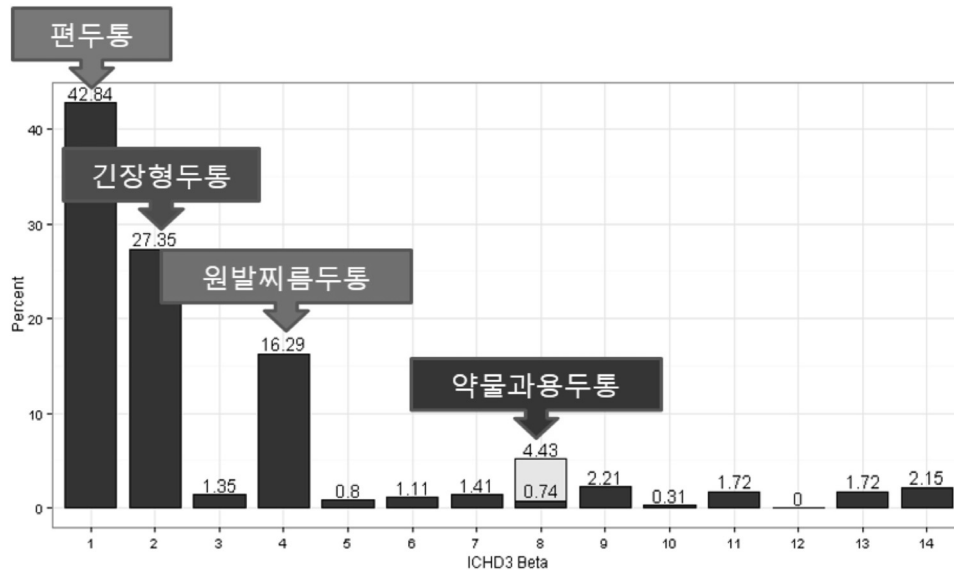
Diagnosis	n (♀/♂)	Prevalences (%)			
		Overall*	♀	♂	P**
Migraine aura	95 (36/59)	39.1	39.1	39.1	.952 (NS)
Migraine with and without aura	86 (47/39)	38.5	51.1	25.8	.020
Migraine with aura only	12 (7/5)	5.5	7.6	3.3	.370 (NS)
Visual aura without headache only	39 (6/33)	14.2	6.5	21.9	.001
Hemiplegic migraine	1 (0/1)	0.4	0	0.7	.732 (NS)
Basilar type migraine***	7 (5/2)	3.4	5.4	1.3	.170 (NS)
Retinal migraine	2 (1/1)	0.9	1.1	0.7	.931 (NS)
Migraine	125 (53/72)	52.7	57.6	47.7	.090 (NS)

Neurologists can make accurate diagnoses of themselves.
Neurologists will have fewer problems with recalling headache episodes, through professional experience.

These data suggest that the prevalence of migraine in the general population could be greater than previously studied.

Maybe the most precise estimate of the true population prevalence !

신경과 외래에서 가장 흔한 두통 질환은? (JKMS 2016)



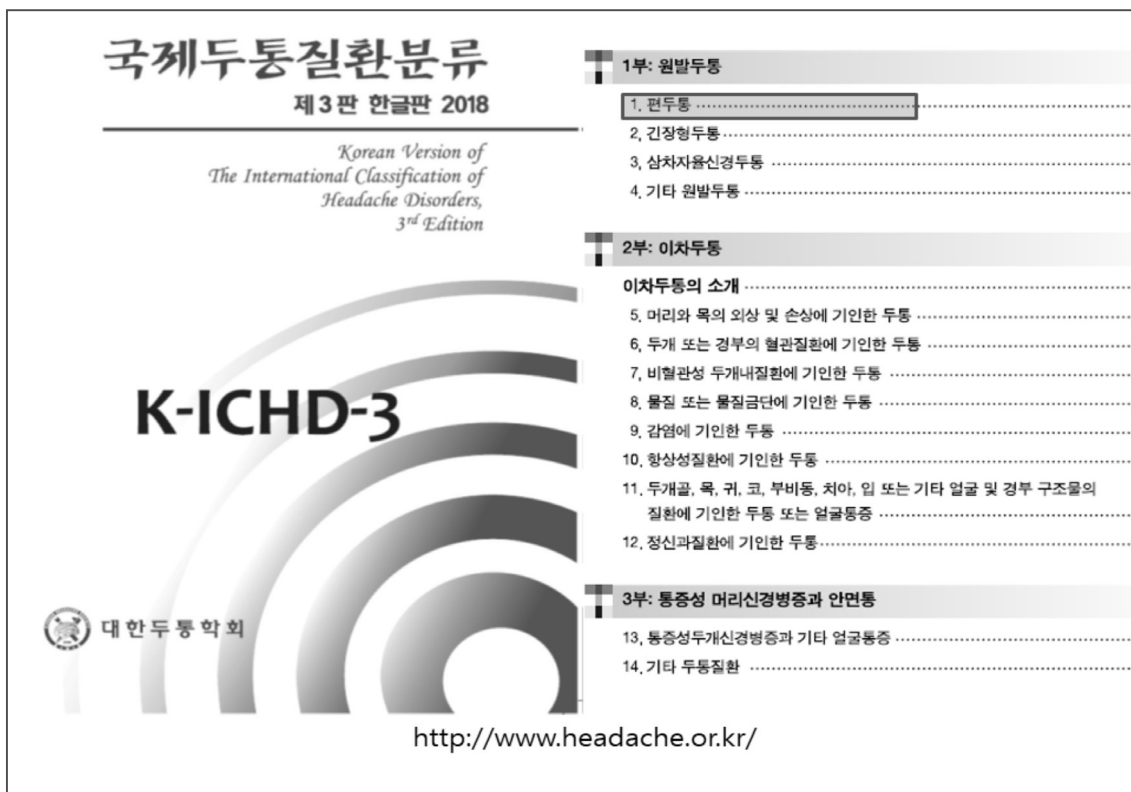
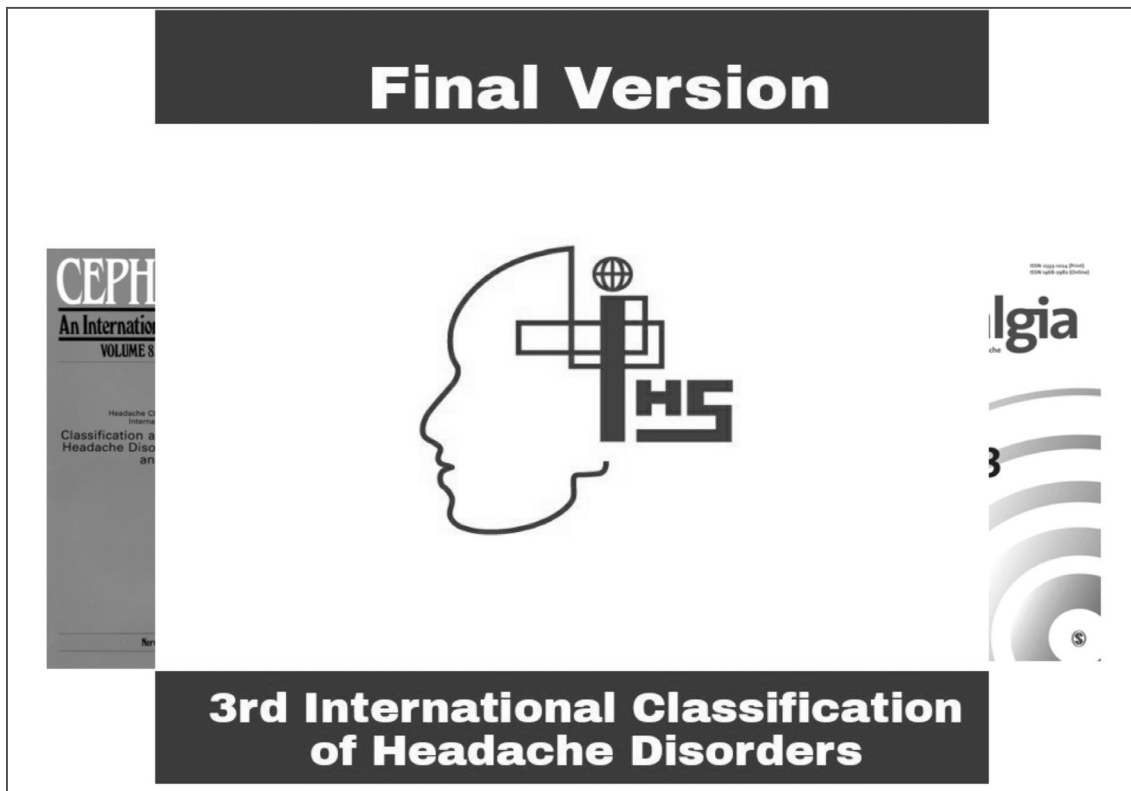
신경과외래에서 가장 흔한 두통질환 Big 3 (JKMS 2016)

- Migraine
- Tension-type headache
- Primary stabbing headache

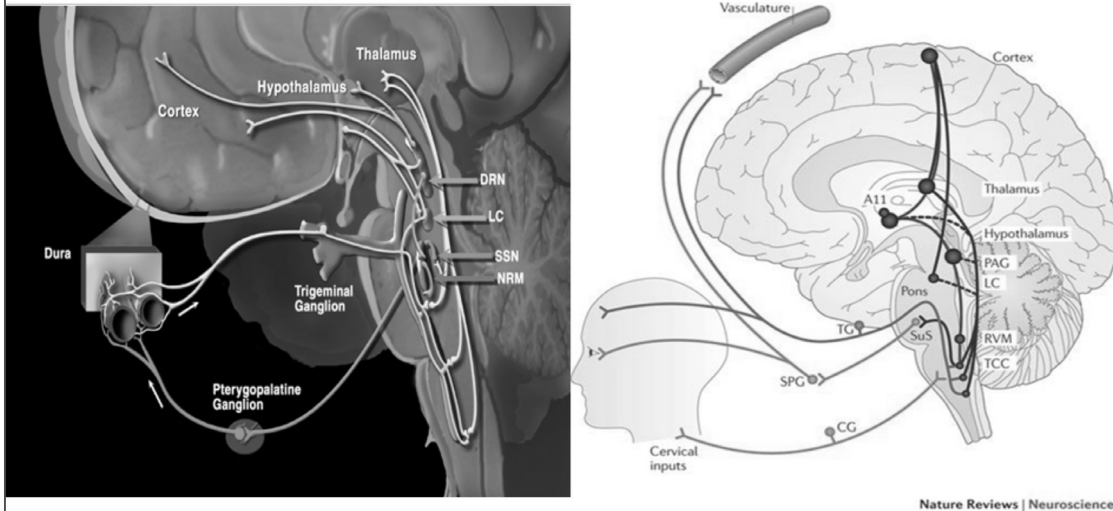
편두통

국제두통질환분류





Migraine *a systems disorder*



편두통의 분류

- 1.1 Migraine without aura
- 1.2 Migraine with aura
- 1.3 Chronic migraine
- 1.4 Complications of migraine
- 1.5 Probable migraine
- 1.6 Episodic syndrome that may be associated with migraine

Migraine & TTH

Migraine without aura

- A. At least 5 attacks
- B. Duration: 4 to 72 hours
- C. At least two of characteristics
 - Unilateral location
 - Pulsating quality
 - Moderate to severe intensity
 - Aggravated by routine work
- D. At least one of following
 - Nausea and/or vomiting
 - Photophobia & phonophobia

Tension type headache

- A. At least 10 attacks
- B. 30 min to 7 days
- C. At least two of characteristics
 - bilateral location
 - Pressing/tightening quality
 - Mild to moderate intensity
 - Not aggravated by routine work
- D. Both of following
 - No nausea or vomiting
 - No photo- and phono-phobia

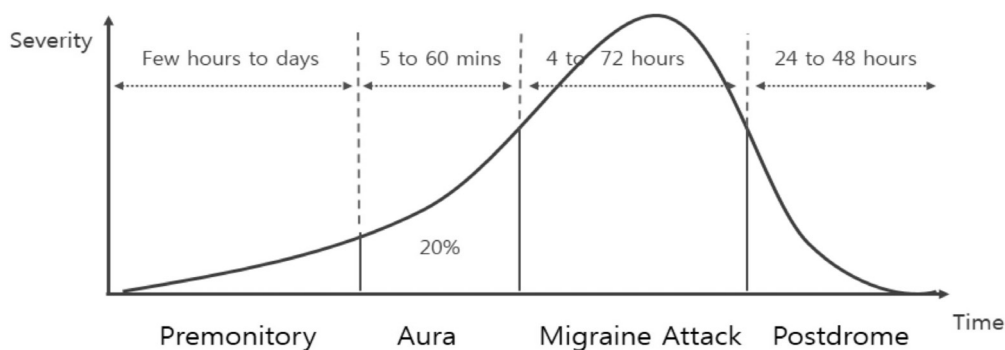


“일부 제재완화 요구” vs “말장난”...북-미, 사사건건 날선 책임공방

동아일보 PICK | 8시간 전 | 네이버뉴스 |

‘말장난(parsing words)’이라고 정면 반박했다. 지난달 28일 베트남 하노이에서의 양국 정상회담이 끝난 후 리용호 외무상은 같은 날 심야 기자회견을 열어 “북한이 요구하는 것은 전면적인 제재 해제가 아니고 일부...”

Phase of acute migraine attack



Migraine

The Attacks & the Disorder

Attacks

- **Premonitory symptoms**
- **Aura**
- **Pain**
 - unilateral
 - throbbing
 - movement worse
- **Nausea/vomiting**
- **Sensory sensitivity**
 - photophobia
 - phonophobia
 - osmophobia
 - dizziness

Disorders

- **Repeated attacks**
 - < 15 days/month: Episodic
 - 15 days/month: Chronic
- **Family history**
- **Triggers**
 - Sleep: missing/excess
 - Food: skipping meals/overeat
 - Chemical: alcohol or nitroglycerin
 - Weather
 - Sensory: light, smells
 - Hormonal
 - Stress

편두통의 유발요인은?

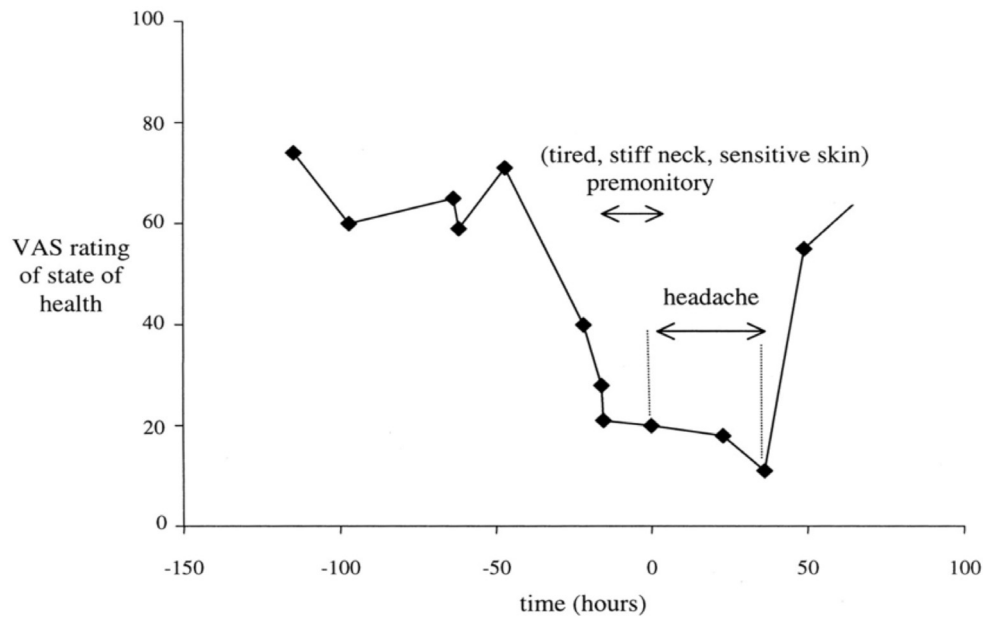
흔한 유발요인

- 스트레스
- 피로
- 수면부족, 수면과다
- 체할때, 과식, 기름진음식
- 월경, 주말
- 술
- 냄새, 소리, 빛
- 추운날씨, 저기압
- 운동

드물거나 확실치 않은 유발요인

- 조미료
- 치즈
- 핫도그
- 햄
- 커피
- 초콜릿

When does migraine start?



Premonitory Symptoms

- **Cognitive**
 - mood change, concentration difficulties
- **Sleep related**
 - fatigue, yawning
- **Homeostatic symptoms**
 - thirst, urinary frequency, food cravings and bowel habit
- **Migraine-like symptoms**
 - Pain: mild head or eye discomfort and neck stiffness
 - Photo/phono-phobia, nausea/indigestion

Yawning: Dopamine & Hypothalamus

nature
International journal of science

Letter | Published: 23 July 1971

Yawning and Penile Erection induced in Rats by Cortical Spreading Depression

Behav Brain Res, 2012 May 1;230(2):355-64. doi: 10.1016/j.bbr.2012.02.033. Epub 2012 Feb 25.

Dopamine agonist-induced penile erection and yawning: differential role of D₂-like receptor subtypes and correlation with nitric oxide production in the paraventricular nucleus of the hypothalamus of male rats.

Sanna E¹, Succu S, Melis MB, Arriola A.



Pharmacology Biochemistry and Behavior
Volume 19, Issue 6, December 1983, Pages 917-919



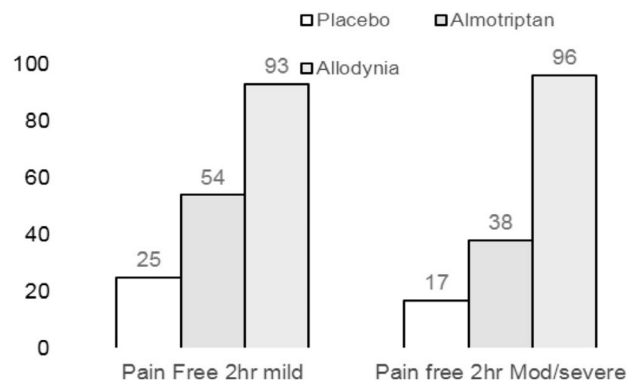
Hypophysectomy prevents yawning and penile erection but not hypomotility induced by apomorphine

“Act when Mild” Study

- Randomised Double-Blind Placebo Controlled Parallel Group
- Allodynia surrogate: cutaneous sensitivity

Outcome

- Patients treating at mild pain did better
- The presence of allodynia did not determine outcome



(Goadsby *et al.*, Cephalalgia 2008; 28383-391)

조짐(=전조, aura)



1.2. Migraine with aura

- A. At least two attacks fulfilling criteria B and C
 B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language

Typical aura

4. motor -----> Hemiplegic migraine
5. brainstem -----> Migraine with brainstem aura
6. retinal -----> Retinal migraine

- C. At least three of the following six.

1. at least one aura symptom spreads gradually over 5 minutes,
2. two or more symptoms occur in succession
3. each individual aura symptom lasts 5-60 minutes (Motor < 72h)
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes by Ha

두통기

Minimum 5 attacks

- If < 5 attacks, diagnose with “Probable migraine without aura”

Headache lasts 4*-72 hours

- This is a duration for an **untreated** headache
- This includes time spent sleeping
- Peds: Minimum is lower -> 2 hours

Headache has 2 of the following:

1. Unilateral

Peds: <15 yrs may be bilateral frontotemporal – *not* occipital!

2. Pulsating quality

3. Moderate or severe pain intensity

4. Aggravation by or causing avoidance of routine physical activity (walking, climbing)

During the headache, 1 of the following:

1. Nausea or Vomiting

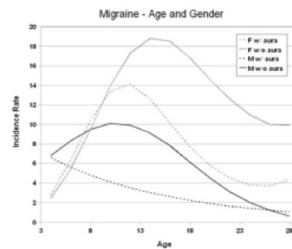
2. Photophobia AND Phonophobia (can be inferred from behavior)

Postdrome symptoms

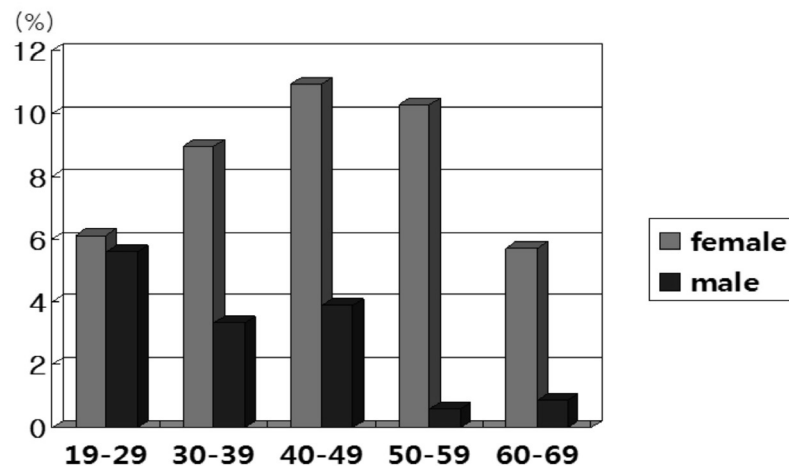
- Difficult to determine
 - Definition? (symptom onset time)
 - Sleep during the attack
- Frequency
 - 68-94%
 - More frequent in women & MWA
- Duration
 - < 6 h: 54%
 - > 24h: 7%

기타 편두통 진단에 중요한 몇 가지..

- 약물: triptan과 ergotamine에 반응
- 가족력
- 발병연령

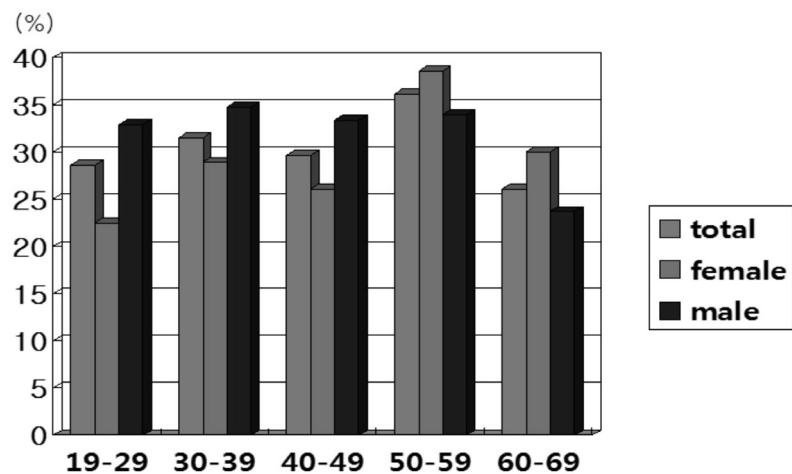


편두통의 나이와 성별에 따른 유병률



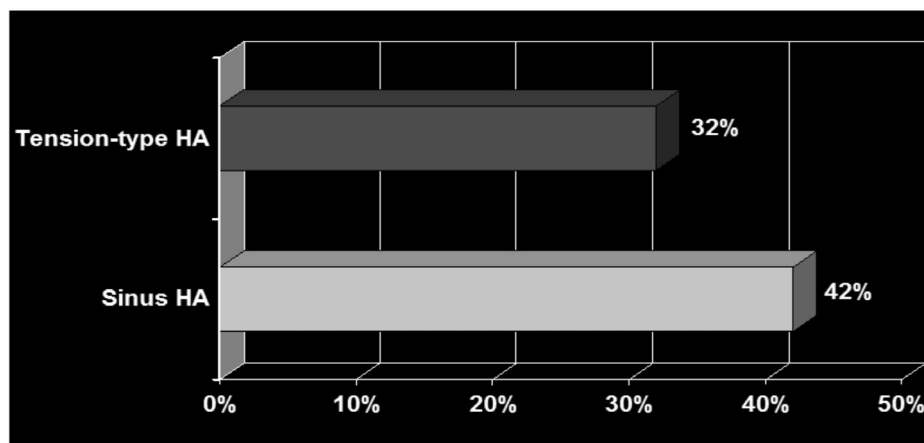
KIM et al, Journal of clinical neurology 2012

긴장형두통의 성별과 연령에 따른 유병률



KIM et al, Journal of clinical neurology 2012

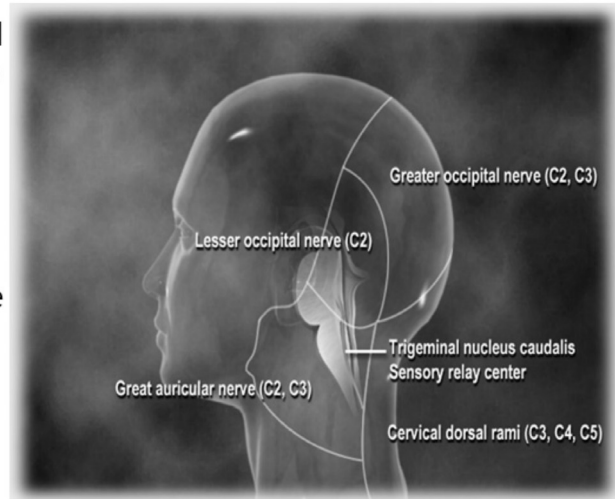
편두통은 흔히 다른 두통질환으로 오진된다



Lipton RB et al. *Headache*. 2001.

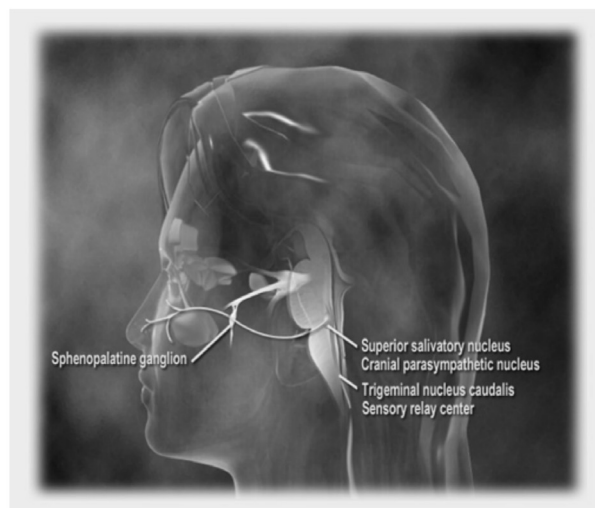
편두통이 긴장형두통으로 흔히 오진되는 이유는?

- Neck pain is very common during migraine attacks (75%)
- Migraine headache is often bilateral (40%)
- Stress is a common migraine trigger



편두통이 감기나 부비동염으로 흔히 오진되는 이유는?

- Pain is often located over the sinuses
- Migraine is frequently triggered by weather changes
- Tearing and nasal congestion common during attacks
- Sinus medication may help migraine

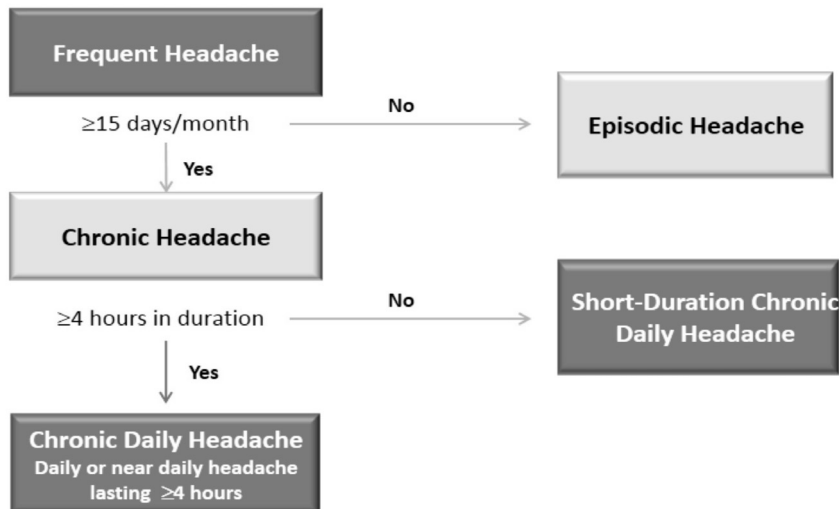


편두통을 빨리 진단하는 세가지 질문

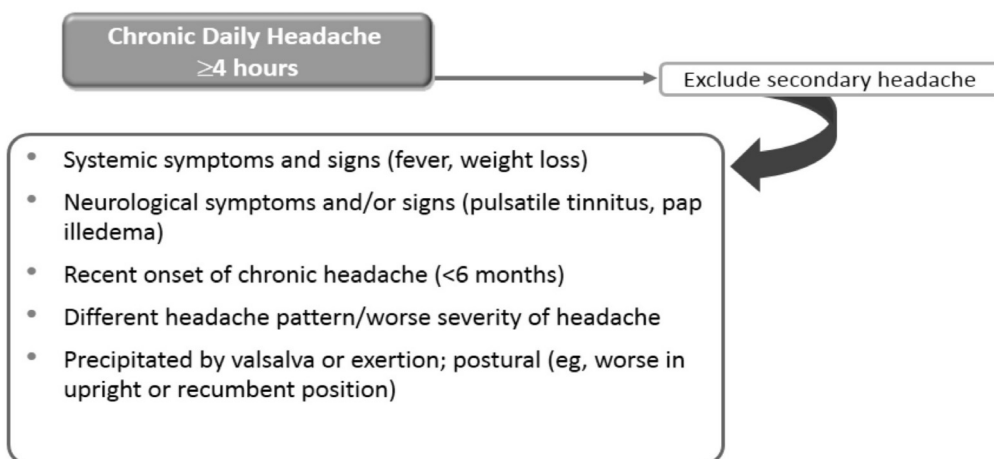
- 반복되는 심한 두통
- 머리가 아프면 울렁거리거나 체하면 머리가 아프다
- 움직이면 두통이 더 심해진다

만성편두통

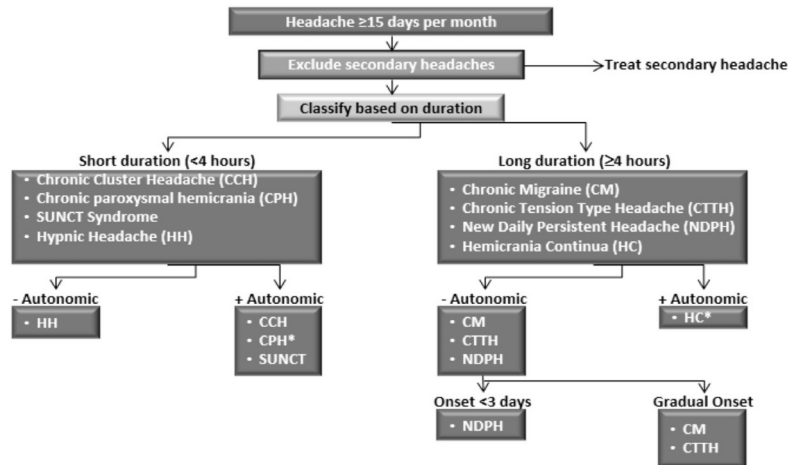
Differential Diagnosis of Frequent Headache



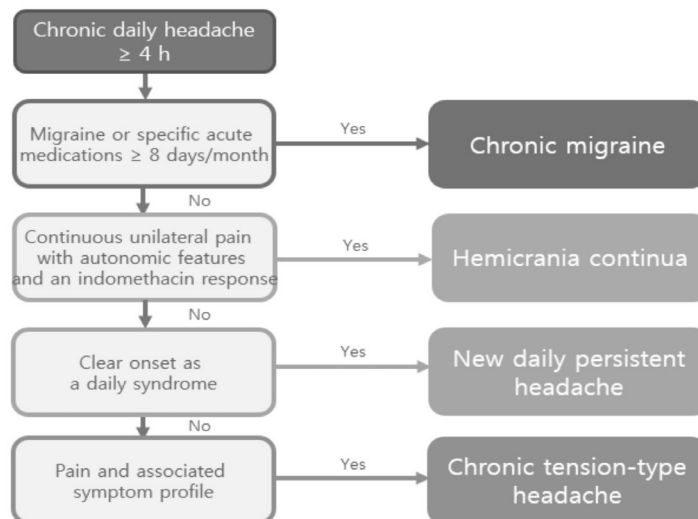
Warning Signs of Secondary Headache



Clinical Approach to Chronic Migraine Diagnosis



만성매일두통의 감별진단



Adapted from Bigal & Lipton. J Headache Pain 2007;8:263-72.

편두통의 치료

1. 유발요인의 차단과 생활습관의 교정
2. 예방치료
3. 급성기치료

예방약제는 언제 투여하나?

- 주 2회 이상 편두통발작
- 주 1회 이상 조절되지 않은 편두통발작
- 월 1회 이상 응급실 방문할때

예방치료가 필요한 환자들에서 실제 치료를 받고 있는 환자는?

Headache-related impairment	Headache frequency, days per month					
	≤1	2	3	4-5	6-10	11-14
No impairment	4.5%	0.6%	0.7%	0.6%†	0.5%*	0.4%*
Some impairment	22.6%	3.5%†	4.4%†	3.5%*	3.1%*	2.0%*
Severe impairment or bed rest required	33.0%	4.6%†	5.2%*	4.1%*	3.9%*	2.9%*

▪ Experts recommended *offering* migraine prevention (**25.7%**)

(*Neurology*, 2007)

▪ Expert recommended *considering* migraine prevention (**13.1%**)

- Although more than 38% of migraineurs need preventive therapy, only a small proportion (3-13%) were actually receiving preventive therapy for migraine

예방약제 효과의 평가방법은 ?

1. 빈도가 50% 이상 감소
2. 두통의 강도와 지속시간의 감소
3. 급성기두통약에 대한 반응

편두통 치료시 고려사항

- 동반이환질환과 병용약제를 고려
 - avoid drugs which aggravate co-morbidity
 - drug interaction
 - identify medications which cause or aggravate headache
- 부작용을 고려
 - sometimes effect of side effects are differ in elderly
- 편두통약물의 효과 근거가 제한적임
 - > limitation of treatment options available.

급성기 편두통치료의 일반적인 원칙

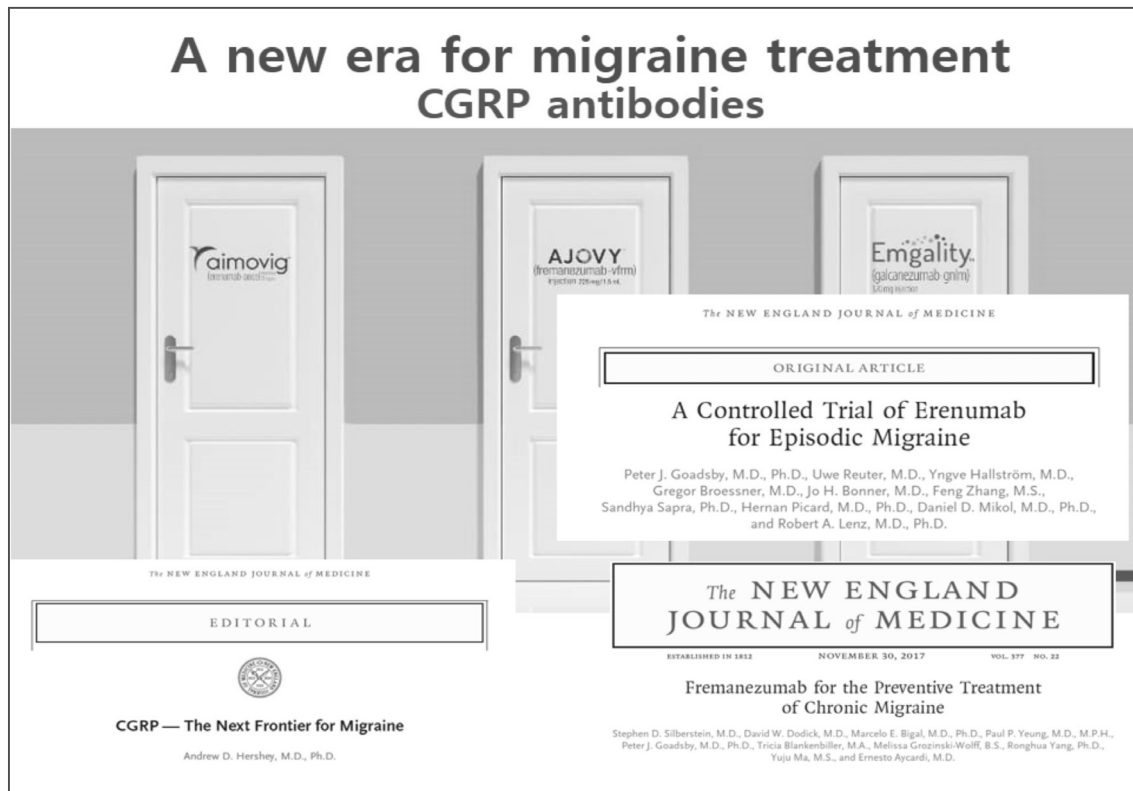
- 1. 특정약물의 치료효과를 미리 예측할 수 없다**
- 2. 조기투약**
- 3. 두통의 중증도에 맞춤**
- 4. 환자에 맞춘 투약경로**
- 5. 진통제는 주2회 이하로 제한**
- 6. 마약성진통제와 카페르고트함유제는 피해야**

급성기 치료제의 평가

- 몇 시간 안에 좋아지는가?
- 효과가 일관성이 있는가?
- 24시간 내에 재발은 없는가?
- 부작용은 없는가?

A new era for migraine treatment





US FDA approves Amgen's first ever drug that prevents migraines on 17th May 2018

aimovig
(erenumab-aooe)
injection

FDA APPROVED

MIGRAINE

This product, the process of its manufacture, or its use, may be covered by one or more U.S. Patents, including U.S. Patent No. 9,102,731 and U.S. Patent No. 9,862,771.

aimovig
(erenumab-aooe)
injection

TV5 HEALTH ALERT FDA APPROVES MIGRAINE TO FIGHT CHRONIC MIGRAINES

Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial

Vladimir Skljarevski, Manjit Matharu, Brian A Millen, , , more...

First Published May 31, 2018 | Research Article | Check for updates

Article Information ^

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Vladimir Skljarevski¹, Manjit Matharu², Brian A Millen¹, Michael H Ossipov³, Byung-Kun Kim⁴, Jyun Yan Yang¹

¹Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, USA
²National Hospital for Neurology and Neurosurgery, London, United Kingdom
³Clinical Division, Syneos Health, Raleigh, NC, USA
⁴Eulji General Hospital, Seoul, Republic of Korea

Corresponding Author: Vladimir Skljarevski, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA. Email:

A new era for migraine treatment

- CGRP antagonist (Gepants)
- 5-HT_{1F} agonist (Lasmiditan)

The Journey of the Non-Vascular Relief for Migraine: From 'Triptans' To 'Ditans'

Author(s): Alphonse S. Xavier*, Mageshwaran Lakshmanan, Vikneswaran Gunaseelan.

Journal Name: Current Clinical Pharmacology

Volume 12, Issue 1, 2017 DOI: 10.2174/1574884712666170419155048

- PACAP



Supplement Article

PACAP38: Emerging Drug Target in Migraine and Cluster Headache

Anne Luise Haulund Vollesen MD, Messoud Ashina MD, PhD, DMSc

First published: 9 May 2017 Full publication history

A new era for migraine treatment



군발두통의 특징

- 일년에 한번
- 1-2달
- 1-2회/일
- 1-2시간



남자, 자율신경계증상

군발두통의 치료

급성기

- 100% 산소
- 트립탄경구

예방

- 후두스트레로이드주사
- 경구스테로이드
- 베라파밀
- 리튬
- 멜라토닌
- 트립탄경구?
- 발프로산?

기타원발두통의 분류

Physical exertion

- 4.1 Primary cough headache
- 4.2 Primary exercise headache
- 4.3 Primary headache associated with sexual activity
- 4.4 Primary thunderclap headache

Direct physical stimuli

- 4.5 Cold-stimulus headache
- 4.6 External-pressure headache

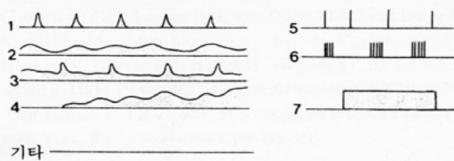
Epicranial (scalp) headaches

- 4.7 Primary stabbing headache
- 4.8 Nummular headache
- A 4.11 Epicrania fugax

Others

- 4.9 Hypnic headache
- 4.10 New daily persistent headache (NDPH)

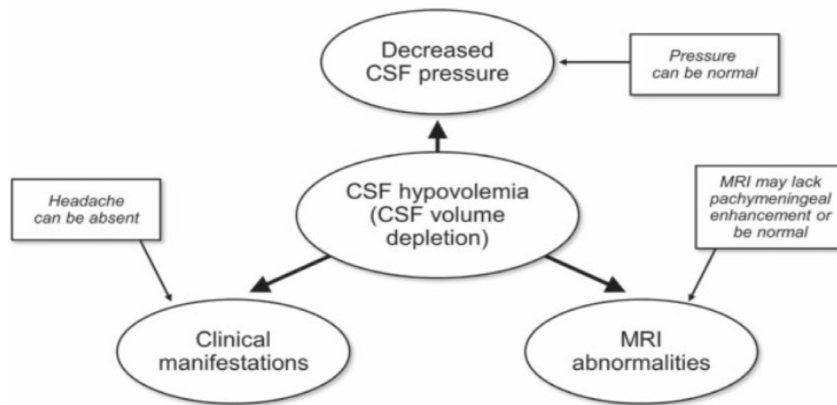
원발찌름두통 (Primary Stabbing Headache)



- 주로 후두부와 두정부에
- 수십초 - 수분 간격으로
- 꼭 찌르는 두통
- 깜짝 놀람
- 찌름사이에도 이상감각
- NSAIDs에 잘 반응
- 1년에 한번정도 재발하기도
- 감별진단: 대상포진 또는 후두신경통

Low CSF Pressure Headache

The concept of CSF hypovolemia

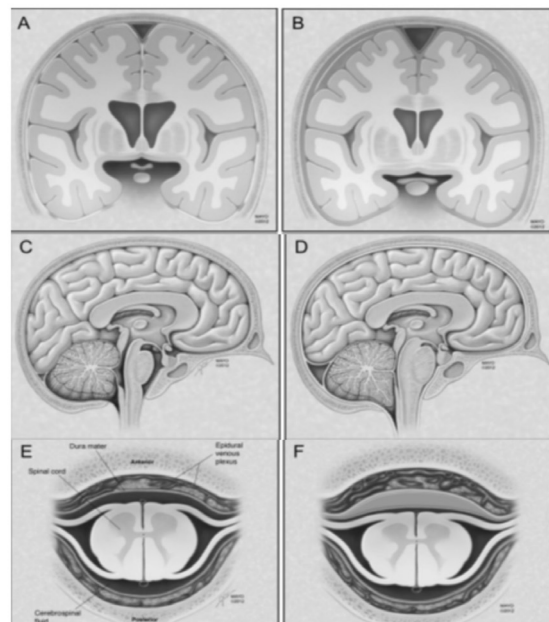
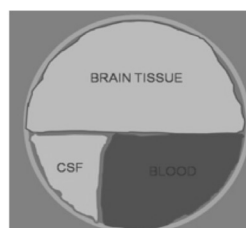
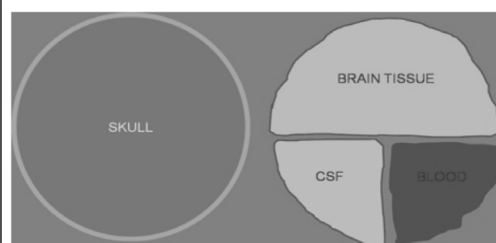


ICHD-3 Criteria

1. Low CSF pressure (<60mmH₂O) and/or evidence of CSF leakage on imaging
2. Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery

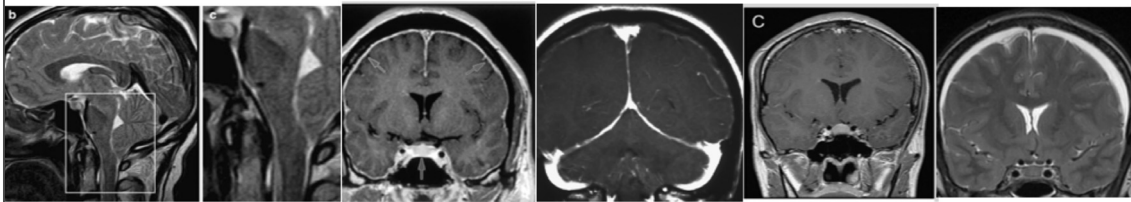
Schematic demonstration of effect of CSF volume loss on MRI

Monro-Kellie doctrine



MRI brain - SEEPS

- Sagging of the brain (75%)
- Enhancement of Pachymeninges (85%)
- Engorgement of venous structures (90%)
- Pituitary hyperemia (66%)
- Subdural fluid collections



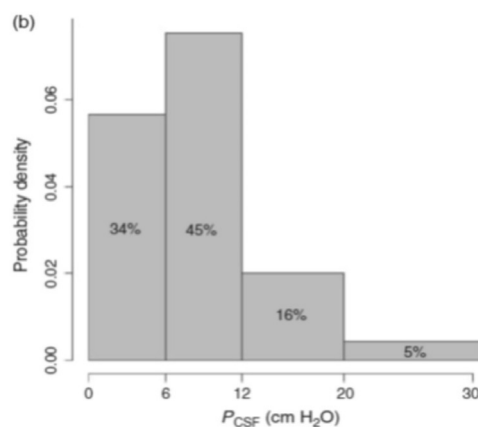
Atypical Headache Presentations

- Orthostatic headache which evolves into a non-orthostatic constant daily headache
- Second half of the day headache
- NDPH (non-orthostatic from the start)
- Thunderclap headache (and/or Valsalva-induced headache)
- Paradoxical orthostatic headache – worse on lying down
- No headache

Non-Headache Manifestation of SIH

- Nausea
- Tinnitus, distorted hearing & dizziness
- Gait unsteadiness
- Diplopia
- Facial Numbness
- Cognitive change and memory difficulties
- Stupor
- Chorea, tremor

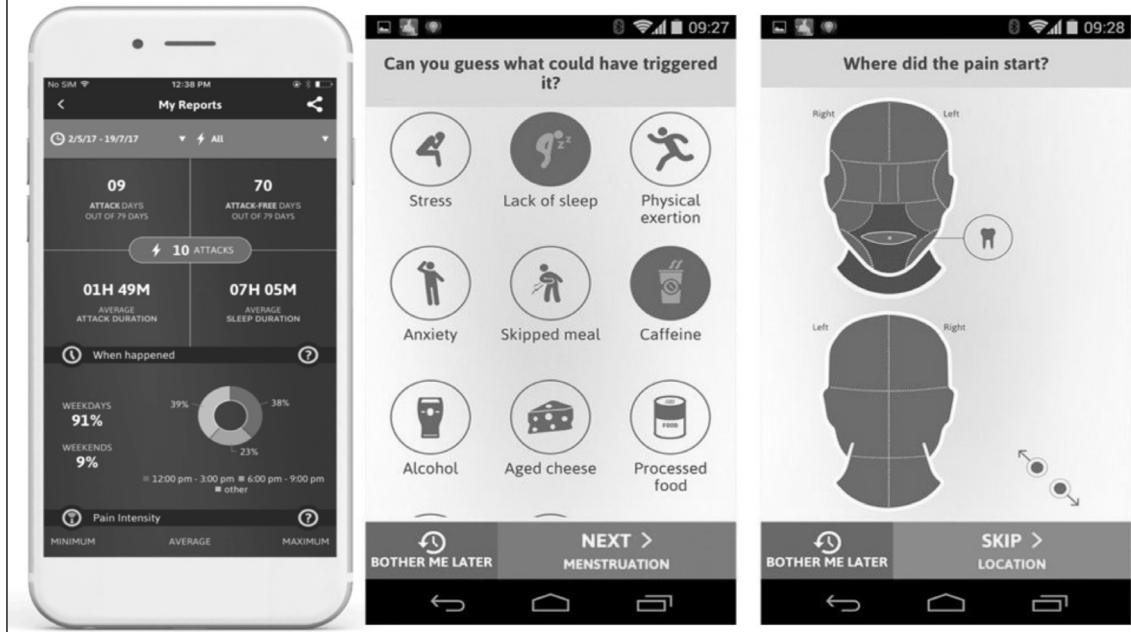
CSF pressure in 106 patients with “SIH”



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두통일기



두통이 있는 날에 두통의 정도를 다음과 같이 숫자로 표시하여 주십시오.

- 참을만하며 일하는데 거의 지장이 없는 정도 : ①
- 두통으로 근무 및 일상 생활에 지장이 많은 정도 : ②
- 두통으로 근무를 할 수 없고 누워 있어야 하는 정도 : ③

	1월	2월	3월	4월	5월	6월	7월	8월	9월	10월	11월	12월
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