Uncommon but important Headache disorder
TCA and other primary headaches

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Why important?

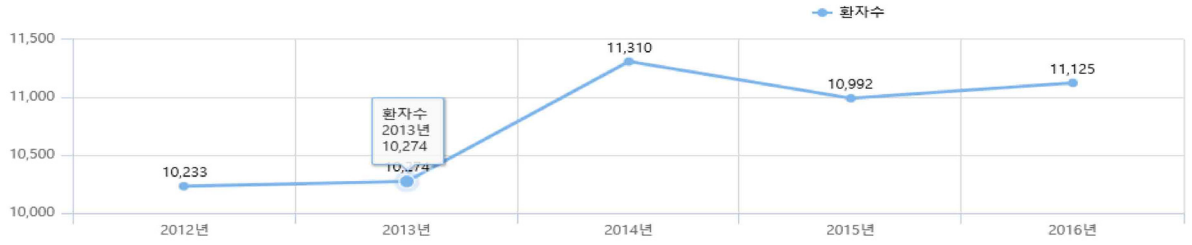
- High risk of secondary headache: about 10%?
- Disease specific medication is required

How rare are CH?

- Korean ICHD-3 beta registry study: 1.3%
- Population-based study: about 0.1%

life-time prevalence 124/10만명

1 year prevalence 53/10만명



Trigeminal Autonomic Cephalalgia

3.1 Cluster headache

3.1.1. episodic cluster headache

3.1.2. **chronic** cluster headache (< 1 month of remission period for 1year)

3.2 Paroxysmal hemicrania

3.3 Short-lasting unilateral neuralgiform headache attacks

3.3.1 SUNCT (Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)

3.3.2 SUNA (Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms)

3.4 Hemicrania continua

3.5 Probable trigeminal autonomic cephalalgia

Structure of diagnostic criteria

A. 총 횟수/*일측*
B. 위치/*기간*
C. 동반증상
D. 빈도/*약물반응*
E. 감별

Italic- HC criteria

1. at least one of the following symptoms or signs, ipsilateral to the headache
a) conjunctival injection and/or lacrimation
b) nasal congestion and/or rhinorrhea
c) eyelid edema
d) forehead and facial sweating
e) forehead and facial flushing
f) sensation of fullness in the ear
g) miosis and/or ptosis
2. a sense of restlessness or agitation

Higher frequency, shorter duration

	Hemicrania continua	cluster headache	Paroxysmal hemicrania	SUNCT/SUNA
여성:남성	2:1	1: 3-7	1:1	1:2
지속시간	지속	**15**-180분	**2**-30분	**1초**-10분
빈도	≥3개월	0.5-8/일	≥5/일 (~40)	≥1/일 (~200)
주기성	-	일주기성/연주기성	-	일주기성
급성기치료	?	산소, triptans	?	?
예방치료	인도메타신	Verapamil, Lithium, steroid	인도메타신	Lamotrigine, Gabapentin, Pregabalin
최소 총횟수	-	5회	20회	20회

Pathophysiology of CH

- Trigeminovascular activation: ↑ CGRP, PACAP-38 (↓ interictal, ↑bout)
- Hypothalamic (posterior) dysfunction: ↓melatonin, ↓ testosterone ?
- Autonomic dysfunction (parasympathetic activation, sympathetic deficits..): ↑ VIP
- Inflammation or immunological activation: ↑ interleukin-2

Posterior hypothalamus activation in CH

Peter J Goadsby

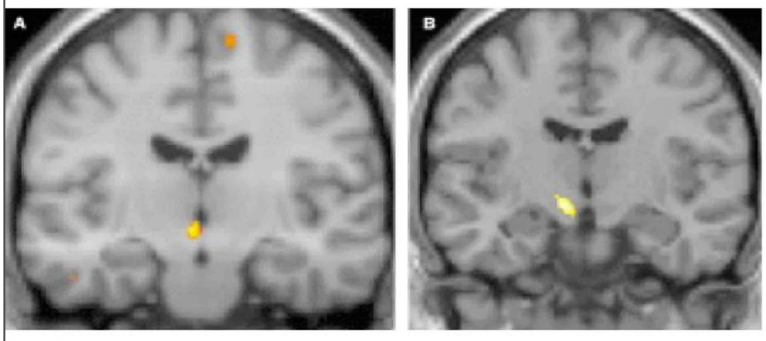
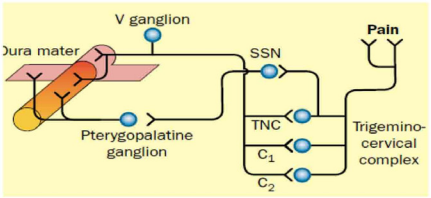


Figure 2. Activation on PET in the posterior hypothalamic grey matter in patients with acute cluster headache (A). The activation shown is only on the side of the pain.[32] When the brains of patients with cluster headache are compared with those of a control population by VBM, which uses high-resolution T1-weighted magnetic resonance imaging, a similar region is highlighted (B) and has increased grey matter.[92]



Lancet Neurology 2002; **1:** 251–57

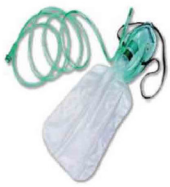
Evidence based Treatment for CH

Acute therapy	A	B	C
AAN, AHS	**100% oxygen** Suma 6mg sc Zolmi 5mg nasal	**Zolmi 5,10mg oral** Suma 20mg nasal Sphenopalatine stimulation (CCH)	Lidocain intranasal Octretide **Predinisone**
EFNS, German	Same Suma 20mg nasal	Same Lidocain intranasal Octretide	-

Prevention	A	B	C
AAN, AHS	**Suboccipital sterioid injection**	Civamide	Verapamil **Lithium** **Melatonin** Warfarin (CCH)
EFNS, German	**Verapamil** **Steroid**	Lithium Methysergide Ergotamine tartrate	**Valproic acid** Melatonin **Baclofen**

산소치료 (A)

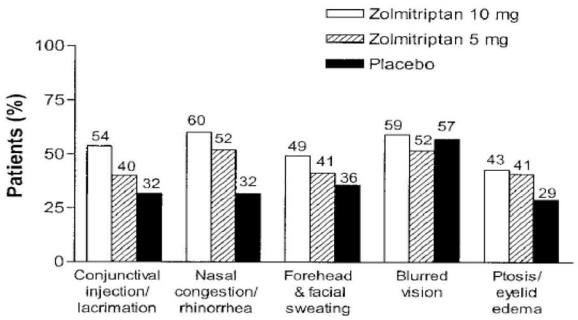
- Oxygen 6L/min for 15 minutes : pain relief 56% vs 7% (Arch Neurol 1985)
- Oxygen 12L/min for 15 min: Pain free at 15 min: 78% vs 20%

JAMA. 2009;302:2451

Zolmitriptan 5, 10mg (B)

- Response rate at 30m in ECH: 10mg 46.8%, 5mg 39.8%, placebo 28.9%
- Escape medication: 22.8% 21.7% vs 44.6%
- Mild or no pain at 30m: 59.5% 56.5% vs 42.2%



NEUROLOGY 2000;54:1832–1839

Preventive medications for CH

1. Must start early in the active phase
2. Must continue for at least 2 weeks after disappearance of attacks
3. Must be suspended gradually
4. If the attacks reappear, dosages must be increased to therapeutic levels
5. Must be re-started at the onset of a subsequent active period
6. Choice depends on age, lifestyle of the patient (avoid alcohol), expected duration of the CH period, reported SE, Contraindications, comorbid diseases
7. Polytherapy is indicated only in patients resistant to monotherapy or do not tolerate recommended dosages

J Headache Pain (2012) 13 (Suppl 2):S31–S70

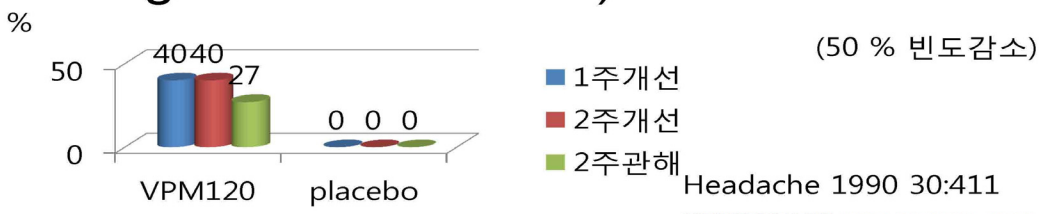
Suboccipital steroid injections (A)

- 2.5 ml mixture of Betamethasone (long acting dipropionate 12.46mg + rapid acting disodium phosphate 5.26mg + xylocaine 2%) 1 shot: pain free 85% at 1주, 61.5% at 4주
- Cortivazol (Altim, half life>60 hr) 3.75mg/1.5ml vs placebo 3 times, each 48-72hr apart: 95% vs 55% (A reduction to ≤ 2 attacks per day) Early a-7 day remission

Pain 118 (2005) 92–96
Lancet Neurol 2011; 10: 891–897

Verapamil (C)

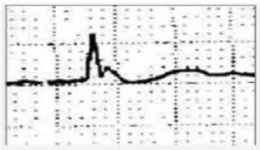
- Modulatory action on opiate system?
- 1 study for CCH comparison to Lithium
- VPM 120mg tid vs placebo for 14 days for ECH compared to initial run-in periods: effective in 2nd week (attack/d 0.6 vs 1.65, analgesics/d 0.5 vs 1.2)



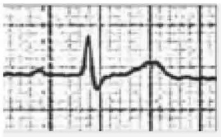
(50 % 빈도감소)
Headache 1990 30:411
NEUROLOGY 2000;54:1382–1385

Verapamil for CH (C)

- VPM 120mg tid vs placebo for 14 days for ECH compared to initial run-in periods: effective in 2nd week
- Constipation, lethargy, gingiva hyperplasia, ankle swelling, bradycardia, stomach cramp
- Highest prescribed dose 240-960mg



B. Junctional rhythm on 720 mg



. *Neurology*® 2007;69:668-675

. Verapamil 240 mg/day, first degree

Melatonin (C)

- low nocturnal melatonin & metabolites
- Small RCT (n=20), Melatonin 10mg to placebo for 2 weeks after 1 run-in week, compared to run-in period (freq/d 3.3->1.5 vs 2.4->2.5 analgesics/d 2.5->1.2 vs 2.1 vs 2.3), Response rate 50% vs 0%, No predictor for response
- Cross over study after 1mon to placebo with VPM (CCH 6 ECH 3), melatonin CR 2mg: no efficacy, but 3 wish to continued melatonin

Headache. 2002;42:787-792

Cephalalgia 1996;16:494

Lithium (C)

- Affecting serotonergic system
- 800mg to placebo in ECH: cessation within 1주 15.3% vs 14.2% improvement 62% vs 43%
- 900mg to VPM in CCH: improvement 37% in Lithium vs. 50% in VPM

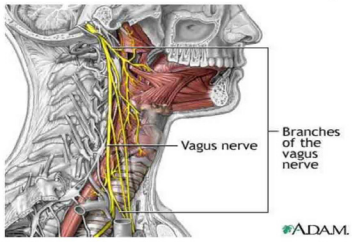
Prednisone (U or A or II)

- Pd 10-80mg/day: reduction in 72%, remission in 58% within 3-10 days
- Better results for dosage ≥ 40mg/d
- Attack recurrence < 20mg/d
- As a transition with other preventive medication
- 250mg methylpd bolus with 100ml saline for 3 days, than 90mg daily, tapered for 4 wks

Headache 1978;18;219

FDA approved nVNS as an abortive treatment for eCH 18 Apr 17

- Parasympathetic, analgesic and vascular effect
- gammaCore based on ACT1 (n=133, 34.2% vs 10.6%) and ACT2 trials (n=495, 47.5% vs 6.2%) in eCH.
- Available in Austria, Canada, Germany, Italy, Switzerland, UK, (and USA soon)



Treatments for CH are….

- ✓ For acute therapy, oxygen, sumatriptan, zolmitriptan
- ✓ For preventive therapy, suboccipital steroid injection, verapamil 360 mg (at least 240mg), steroid 50-100mg for 10-17 days, with considering about GI protection, laxatives
- ✓ Goal: improvement during cluster period rather than remission
- ✓ Personal variation, collecting the personal history of medication response.

SUNA (Short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms)

- Very short attacks
- Sometimes resolve without intervention
- Tx of choice: lamotrigine
- Possible NSAIDs or Indomethacin response

Probable Trigeminal Autonomic Cephalalgia: one criteria missing

3.5 Probable trigeminal autonomic cephalalgia

3.5.1. Probable cluster headache

3.5.2 Probable paroxysmal hemicrania

3.5.3. Probable short-lasting unilateral neuralgiform headache attacks

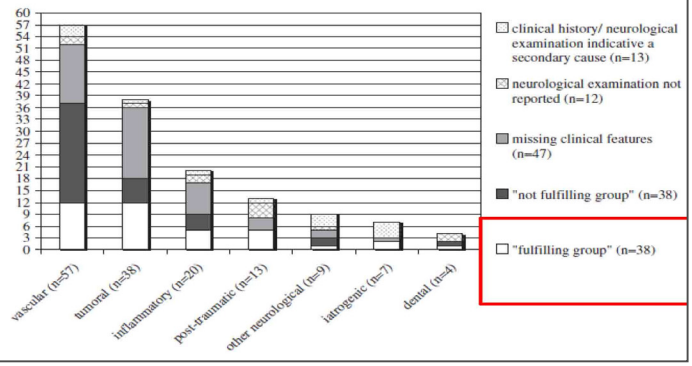
3.5.4 Probable hemicrania continua

A. 총 횟수/일측성: less than 5 or 20 attacks
B. 위치: bilateral / 기간: 3개월 미만
C. 동반증상: none
D. 빈도/약물반응 : no trial or response

Not two missing criteria

Secondary CH or Cluster-like headache

- AVM, aneurysm, carotid VA dissection, sinusitis, glaucoma, pituitary tumor, meningioma, zoster, multiple sclerosis, cerebral venous thrombosis
- Rule of exclusion



Cephalalgia 2010;30:399

Other primary headache disorders

Physical exertion

- 4.1 Primary cough headache 원발기침두통
- 4.2 Primary exercise headache 원발운동두통
- 4.3 Primary headache associated with sexual activity 성행위와 연관된 원발두통
- 4.4 Primary thunderclap headache 원발벼락두통

Direct physical stimuli

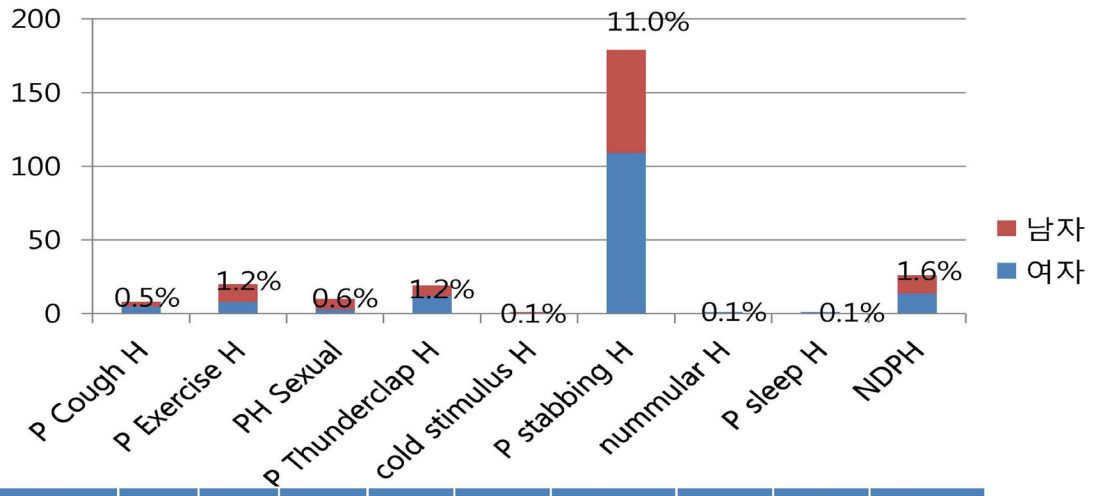
- 4.5 Cold-stimulus headache 저온자극두통
- 4.6 External pressure headache 외압력두통

scalp

- 4.7 Primary stabbing headache 원발찌름두통
- 4.8 Nummular headache 원형두통

- 4.9 Hypnic headache 수면두통
- 4.10 New daily persistent headache 신생매일지속두통

How uncommon are OPH?



Probable Dx %	50	30	30	-	0	1.7	100	100	73.1

Unpublished data from ICHD 3b registry study

Physical activity related PH

	Primary cough H	Primary exercise H	PH ass with sexual activity	Primary thunderclap H
유발요인/양상	기침, 힘주기, 발살바	격렬한 운동	성행위 흥분/오르가즘	심한 통증
경과	갑자기		증가/갑자기	1분내 최고
지속시간	1초-2시간	<48시간	1분-24시간	5분 이상
치료제	Indomethacin Acetazolamide Propranolol	Propranolol Indomethacin	Propranolol Indomethacin	Nimodipine propranolol
최소 횟수	2회 (1회:개연)	2회(1회:개연)	2회(1회:개연)	1회(개연 없음)

Among Thunderclap headache

Variable	Total	PTH (n=25)	PCH (n=23)	PEH (n=15)	PSH (n=9)
Age (years±SD)	45.1±12.6	47.1±13.2	48.9±11.9	36.6±11.9*	43.7±6.9
(range)	15-70	20-68	27-70	15-51	31-52
Male sex (%)	37.5	28.0	34.8	46.7	55.6
Severity (VAS**±SD)	8.5±1.3	8.6±1.1	8.5±1.7	8.2±1.0	8.6±1.4
Duration (minute)	40.7	47.8	45.3	25.2	35.9
Pulsatility (%)	29.9	22.7	21.7	35.7	62.5
Unilateral HA (%)	15.3	16.0	8.7	26.7	11.1
Nausea/Vomiting (n)	43.1	48.0	52.2	26.7	33.3
Recurrence (n)	68.1	48.0	73.9	73.3	100*
Attack (n)	3.2	1.7	2.8	3.4	9.3*

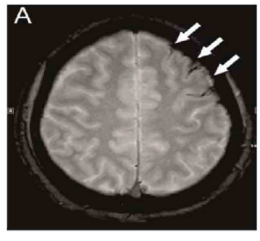
- Provoking factors: defecation> intercourse

Valsalva maneuver (n=47)	Defecation	13 (16.0)	Exertion (n=23)	Running/Bicycling	3/1 (3.7/1.2)
	Cough/vomiting	5/5 (6.2/6.2)		Soccer/Tennis	1/1 (1.2/1.2)
	Head bending	5 (6.2)		Water skies	1 (1.2)
	Shout	6 (7.4)		Swimming/Diving	7/1 (8.6/1.2)
	Crying/Laughing	3/1 (3.7/1.2)		Climbing the stairs	2 (2.5)
	Lifting	4 (4.9)		Others	6 (7.4)
	Hold of breathing	3 (3.7)	Intercourse (n=11)	Preorgasmic/Orgasmic	3/5 (3.7/6.2)
	Cold exposure	2 (2.5)		Unspecified	3 (3.7)

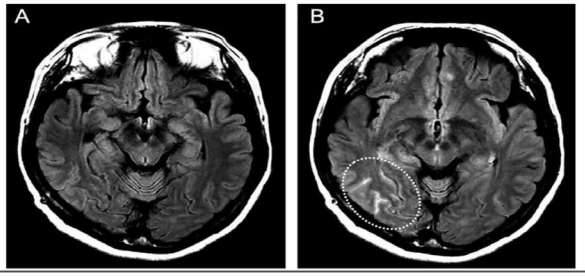
Korean Journal of Headache 12(2):85-90, 2011

RCVS

- 20-50 years of age, female predominance
- Recurrent thunderclap headache, with sometimes triggerring factors
- Cortical SAH, ICH, Cerebral infarction, BBB breakdown on enhanced FLAIR images
- Clinically resolve within 1 m, radiologically within 12 weeks



ANN NEUROL 2017;81:454–466



Diagnostic criteria of Reversible Cerebral Vasoconstriction Syndrome

A. Any **new** headache fulfilling criterion C

B. Reversible cerebral vasoconstriction syndrome (RCVS) has been diagnosed (if not meet, probably…)

C. Evidence of causation demonstrated by at least one of the following:

1. headache, with or without focal deficits and/or seizures, has led to angiography (with 'strings and beads' appearance) and diagnosis of RCVS (if not meet, probably…)

2. headache has either or both of the following characteristics:

a) recurrent during < 1 month, and with thunderclap onset

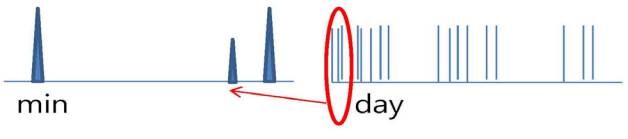
b) triggered by sexual activity, exertion, Valsalva maneuver, emotion, bathing and/or showering

3. no new significant headache occurs >1 month after onset

D. Not better accounted for by another ICHD-3 diagnosis, and aneurysmal subarachnoid haemorrhage has been excluded by appropriate investigations

Primary stabbing headache

- Short-lasting, single or series of stabs, irregular
- No associated symptoms except scalp tenderness
- Relatively low risk of secondary headache, but caution for secondary stabbing headaches such as sine herpete zoster, prodromal symptom of facial palsy, dissection, etc
- Intractable to simple analgesics-> consider combination or short-term prevention
- Indomethacin, COX-2 inhibitors, gabapentin, nifedipine, melatonin



New daily persistent headache

- remember the day of the headache started
- Presence of headache when wake up
- Some preceding events
- Rule of exclusion (SIH, IICP, medical conditions, etc)
- More than 3 months
- No drug of choice

Take home messages

- Severe, recurrent, unilateral headache-> ask about autonomic symptoms and agitation-> classification based on duration/frequency
- New recurring headache -> ask about triggering factors, mode
- Try to make a diagnosis, even if it's probable
- Two tracks from the first visit (diagnosis and treatment)