員生醫院・神經內科
蔡宗儒

FROM EPISODIC TO CHRONIC MIGRAINE

INTRODUCTION

Migraine

- Migraine is a common neurologic disorder that has a wide variety of subtypes, many comorbidities, and a variable prognosis.

Prevalence

- 美國
  - 女性：18%
  - 男性：6.5%
- 台灣十五歲以上的成人
  - **女性：14.4%**
  - 男性：4.5%
  - 慢性每日頭痛：3.2%

Acta Neurol Taiwan 2008;17:132-148

Definition

- Recurrent headache disorder manifesting in attacks lasting 4–72 hours.
- Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic Criteria – 1.1 Migraine without Aura

- A. At least 5 attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
  - 1. Unilateral location
  - 2. Pulsating quality
  - 3. Moderate or severe pain intensity
  - 4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- D. During headache at least one of the following:
  - 1. Nausea and/or vomiting
  - 2. Photophobia and phonophobia
- E. Not attributed to another disorder

The International Classification Of Headache Disorders-2nd Edition
Cephalalgia, Volume 24 Supplement 1, 2004

Diagnostic Criteria – 1.5.1 Chronic Migraine (CM)

- Description:
  - Migraine headache ≧ 15 days/month, > 3 months
  - Absence of medication overuse
- Diagnostic criteria:
  - A. Headache fulfilling criteria C and D for 1.1 Migraine without aura on ≥15 days/month for >3 months
  - B. Not attributed to another disorder

The International Classification Of Headache Disorders-2nd Edition
Cephalalgia, Volume 24 Supplement 1, 2004

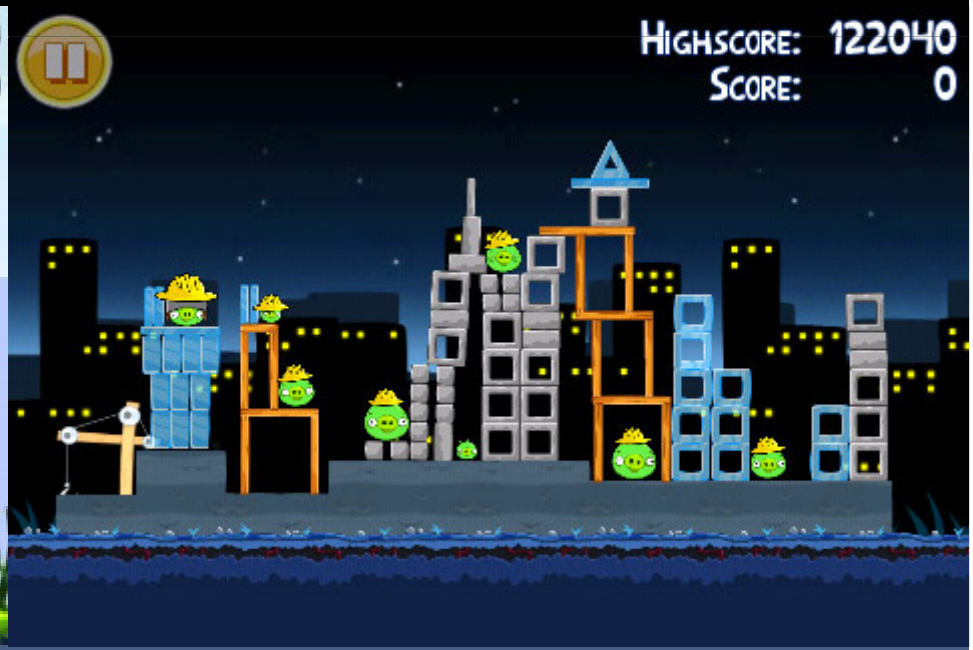
Table 1 MIDAS in CM and EM: lost days per 3 months[9]

	CM	EM
Missed work or school, d	2.4	0.54
≥50% Reduced productivity at work or school, d	10.4	1.7
Incomplete household work or chores, d	21.4	3.5
≥50% Reduced productivity in household work or chores, d	18.7	2.6
Missed time with family, social, or leisure activities, d	10.5	1.7
Total	63.4	10.0

MIDAS = migraine disability assessment scale; CM = chronic migraine; EM = episodic migraine; d = days.

Neurology 2009;72 (Suppl 1):S3–S7


HIGHSCORE: 29090
SCORE: 0


HIGHSCORE: 122040
SCORE: 0

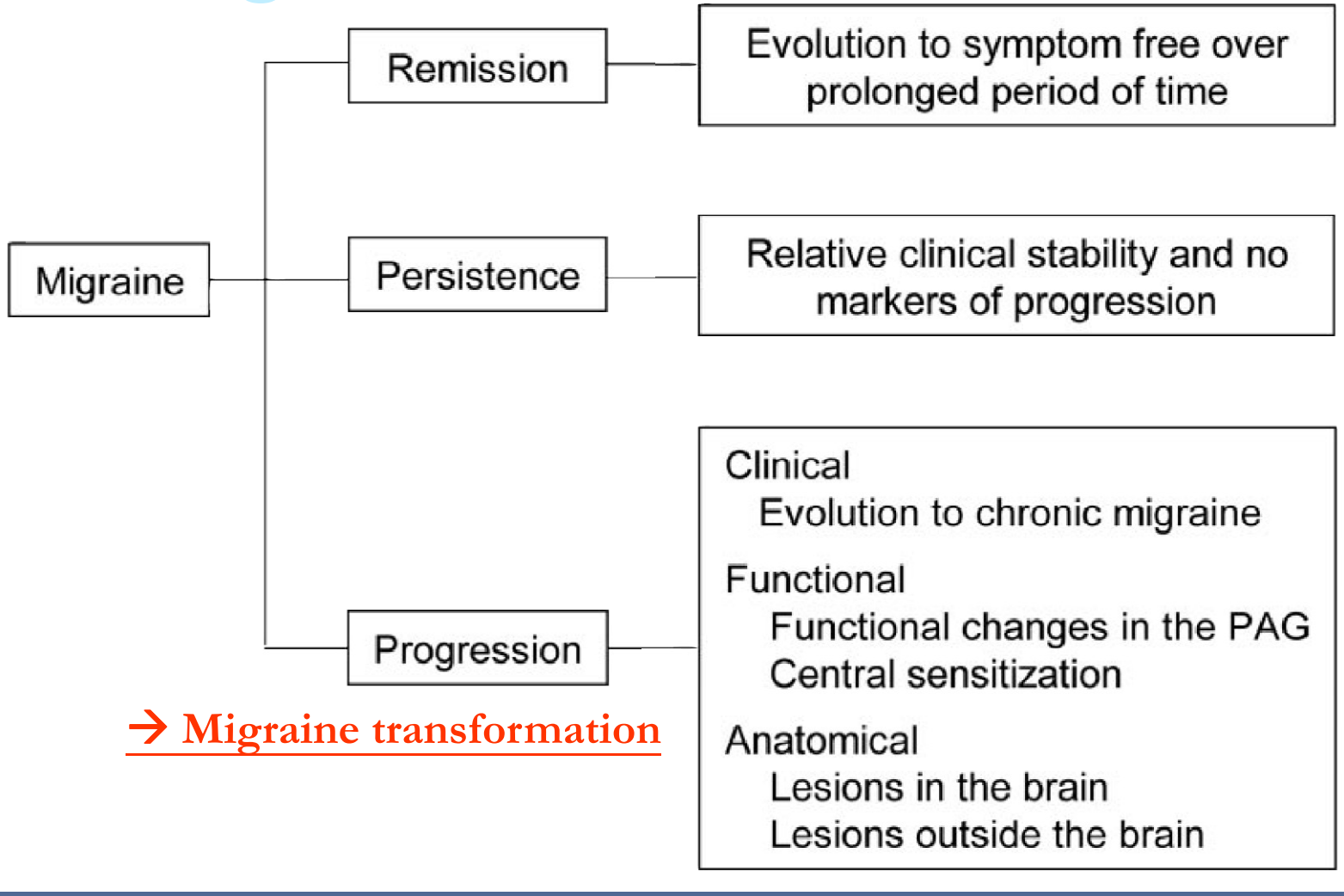
CLINICAL COURSE IN MIGRAINE

Clinical Course in Migraine

- The conceptual framework for understanding migraine has evolved over the past decade.
- More recent evidence supports the concept that migraine is a chronic disorder with episodic attacks.
- Between headaches, patients with migraine have an enduring predisposition to attacks including abnormalities in brain excitability and impaired health-related quality of life.

Neurology 2008;71:848–855

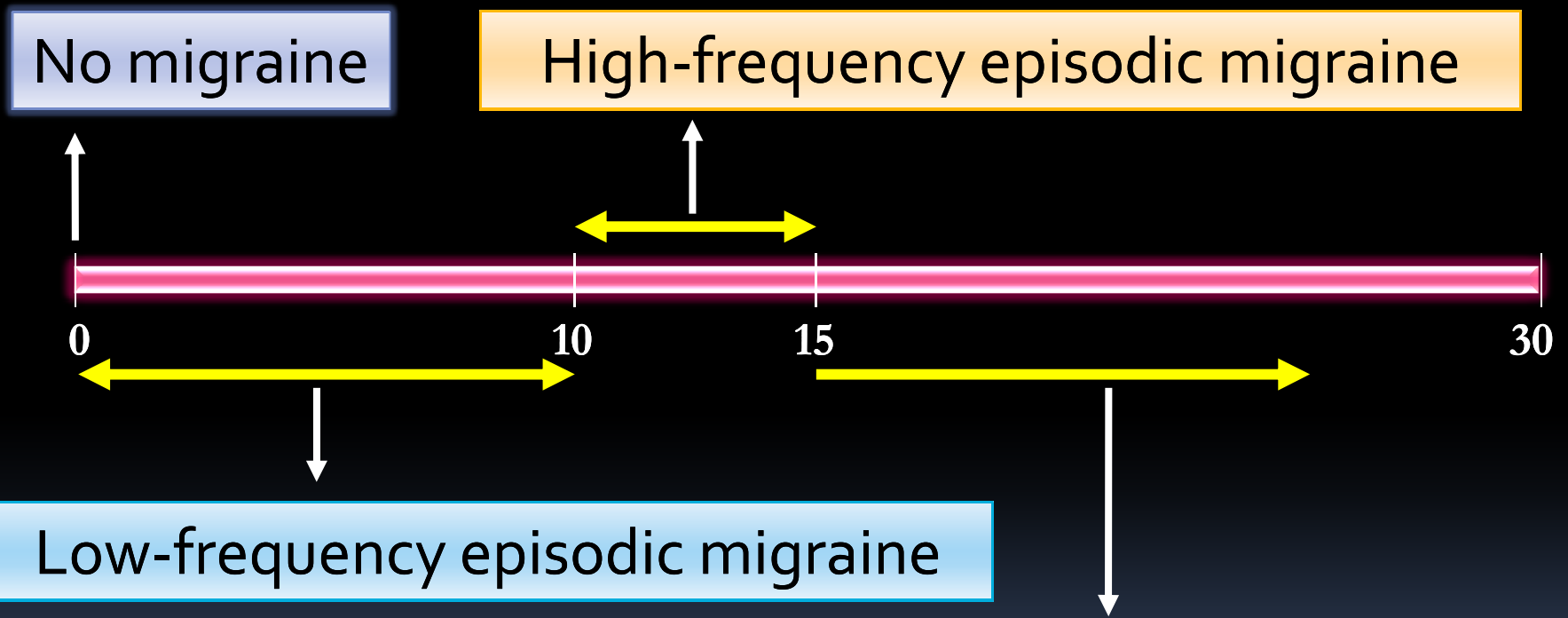
Pathway in the Natural History of Migraine



→ Migraine transformation

Neurology 2008;71:848–855

Four Distinct States of Migraine



Neurology 2009;72 (Suppl 1):S3–S7


BUMBLEBEE
TRANSFORMATION
OF MIGRAINE

Transformation of Migraine

- Daily or near-daily headaches with migrainous features and/or attacks have been described in the literature with multiple names and different classifications (eg, transformed migraine, chronic migraine).

Chronic daily headache (CDH) =
Chronic migraine =
Transformed migraine ?

Chronic Daily Headache

- CDH: high frequency of headaches (15 days/month)

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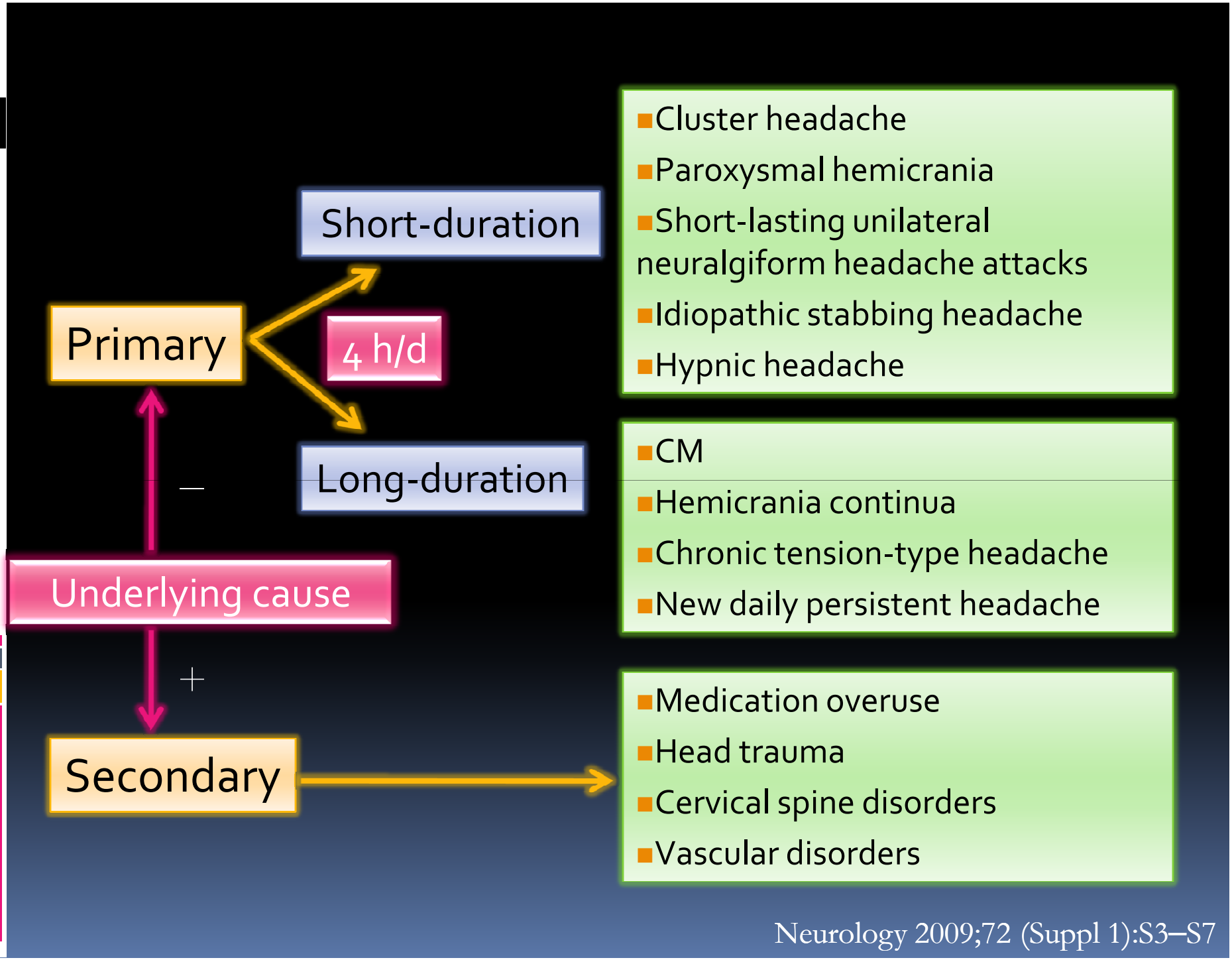

Short-duration
Primary
4 h/d
Long-duration
Underlying cause
Secondary
Cluster headache
Paroxysmal hemicrania
Short-lasting unilateral neuralgiform headache attacks
Idiopathic stabbing headache
Hypnic headache
CM
Hemicrania continua
Chronic tension-type headache
New daily persistent headache
Medication overuse
Head trauma
Cervical spine disorders
Vascular disorders
Neurology 2009;72 (Suppl 1):S3–S7

Chronic Daily Headache

- Long-duration CDH is a prevalent problem, with 3% to 5% of the worldwide population experiencing daily or near-daily headaches.
- Most patients with long-duration primary CDH have CM.

Neurology 2009;72 (Suppl 1):S3–S7

Transformation of Migraine

- Clinical transformation: increases in attack frequency over time leading to CM, occurs in about 3% of episodic migraine sufferers.
- Physiologic transformation: physiologic changes in the CNS manifested through alterations in nociceptive thresholds (allodynia) and in pain pathways.
- Anatomic transformation: definitive brain lesions including stroke and deep white matter lesions emerge

"Clinical course in migraine", Neurology 2008;71:848–855

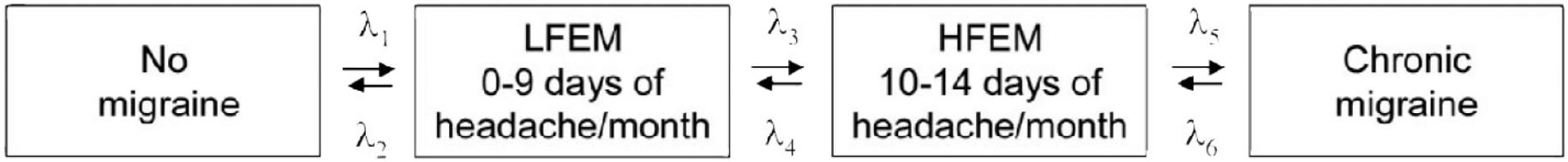
Transformation of Migraine

- Although the data for anatomic changes are for patients with episodic migraine with aura only, we consider it a form of migraine as transformation because the prevalence of brain lesions seems to increases with attack frequency.

"Clinical course in migraine", Neurology 2008;71:848–855

Conceptual Framework for Transitions in Migraine

- Although it is not well established if migraine may not progress abruptly, clinical evidence suggests that most frequently attacks increase in frequency over a period of time.
- All transition rates can be modeled as a function of demographic, environmental, and genetic risk factors.



λ are described in the text. LFEM = low-frequency episodic migraine; HFEM = high-frequency episodic migraine.

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Diagnostic Criteria of Transformed Migraine

- Patients with migraine headaches that progress in severity and frequency have been described since the early 1980s.
- Mathew first proposed the term transformed migraine to describe patients with migraines that increase in frequency until they transform into a daily or near-daily occurrence.
- In 1988, the HIS published diagnostic criteria entitled The International Classification of Headache Disorders (ICHD-1).

Headache 2009;49:1206-1213

Transformed Migraine
Silberstein and Lipton Criteria, 1996

- Daily or near-daily headache with migraine that begins with episodic migraines and as the headaches grow more frequent over months to years the associated symptoms become less severe and less frequent
- A. Daily of almost daily (>15 days/month) head pain for >1 month
- B. Average headache duration of >4 hours day (if untreated)
- C. At least **1** of the following:
  - 1. History of episodic migraine meeting any IHS criteria 1.1 to 1.6
  - 2. History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months
  - 3. Headache at some time meets IHS criteria for migraine 1.1 to 1.6 other than duration
- D. Does not meet criteria for new daily persistent headache or hemicrania continua
- E. At least 1 of the following:
  - 1. There is no suggestion of one of the disorders listed in groups 5-11
  - 2. Such a disorder is suggested, but it is ruled out by appropriate investigations

Headache 2009;49:1206-1213

Chronic Migraine (original) ICHD-2, 2004

- Migraine headache occurring on 15 or more days/month in the absence of medication overuse
  - A. Headache fulfilling criteria C and D for migraine without aura on ≧15 days/month for >3 months
  - B. Not attributed to another disorder
- When medication overuse is present → antecedent migraine subtype + probable chronic migraine + probable medication overuse headache.

Headache 2009;49:1206-1213

Chronic Migraine (revised) ICHD-2 (revised), 2006

- Frequently occurring headache (>15 days per month) with at least 8 days of migraine or probable migraine per month in the absence of medication overuse
- A. Headache (tension-type and/or migraine) on >15 days per month for >3 months
- B. Occurring in a patient who has had >5 attacks fulfilling criterion 1.1 migraine without aura
- C. **On >8 days** per month for >3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura
  - 1. Has at least 2 of a-d: (a) unilateral location; (b) pulsating quality; (c) moderate or severe pain intensity; (d) aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs); and at least 1 of a or b: (a) nausea and/or vomiting; (b) photophobia and phonophobia
  - 2. Treated and relieved by triptan or ergot before expecting development of C1 above
- D. No medication overuse and not attributed to another causative disorder.

Headache 2009;49:1206-1213

Chronic Migraine (revised) ICHD-2 (revised), 2006

- The ICHD-2 did not include the name or criteria for transformed migraine.
- The explanation for the name change was that transformed migraine implied the evolution of headache over time.
- Not all patients evolved, and many did not remember their transformation.

Headache 2009;49:1206-1213

Classification Overlap

- In field testing of ICHD-2R in clinic patients without medication overuse, Bigal et al demonstrated
  - 92.4% agreement with Silberstein and Lipton's 1996 transformed migraine criteria

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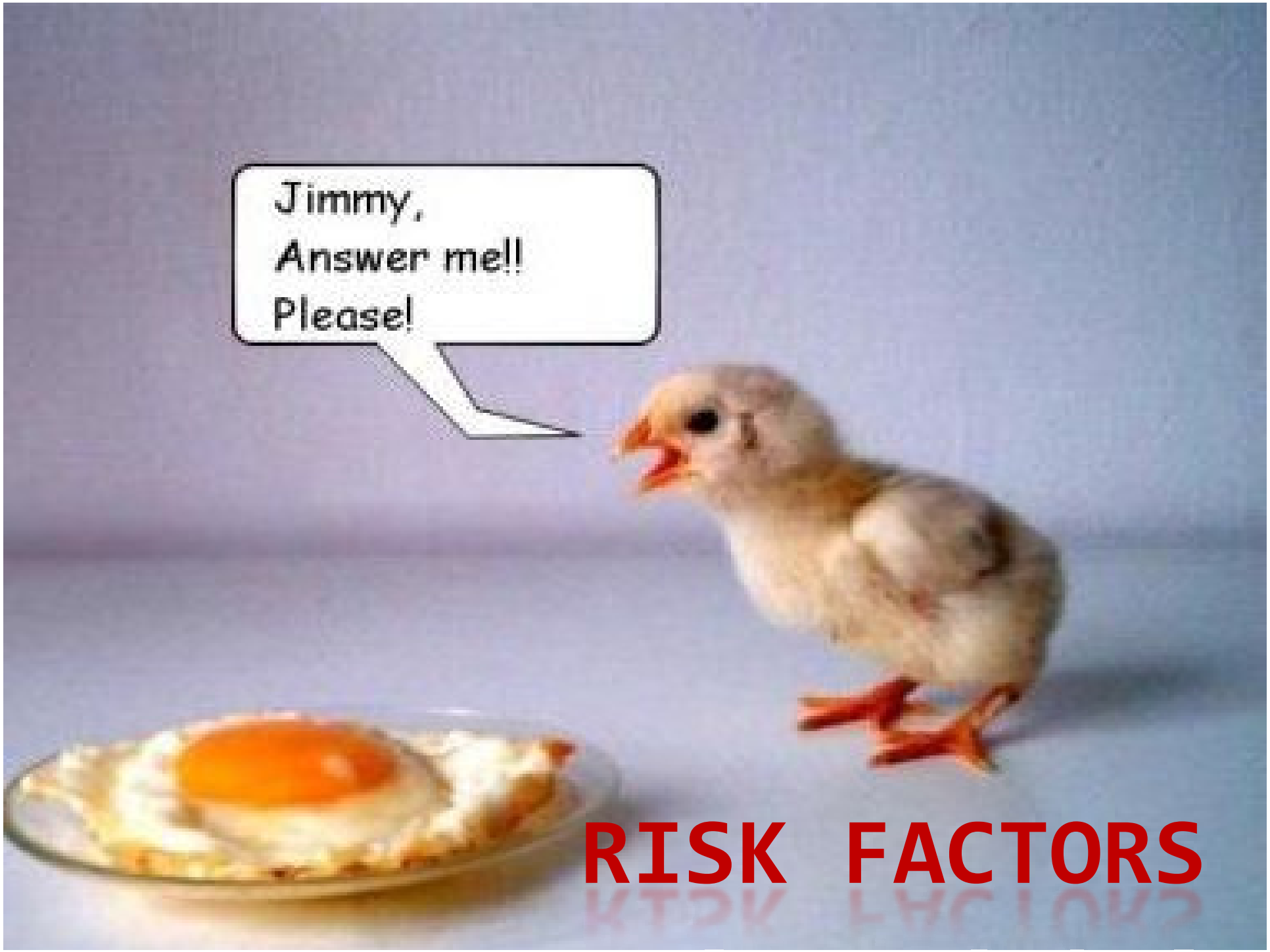
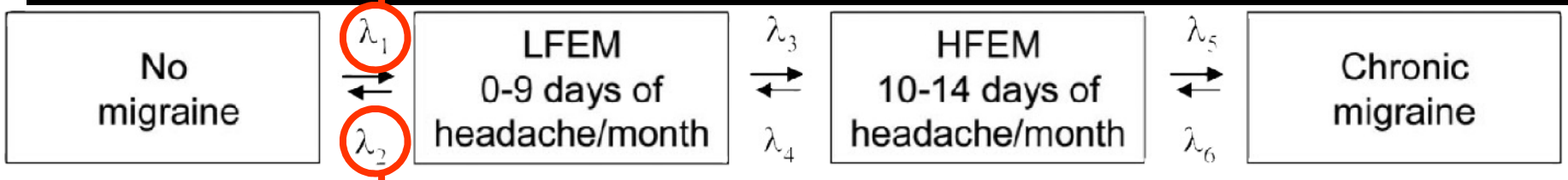
Transformation of Migraine

- IHCC still has not developed globally accepted criteria that are easy to apply in the clinic, epidemiologic studies, and clinical trials.

Headache 2009;49:1206-1213


Jimmy,
Answer me!!
Please!
RISK FACTORS

Genetic predisposition
Environmental risk factor



Older age
Male gender
Postmenopasual state

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Risk Factors for Migraine Progression

Not readily modifiable	Modifiable	Putative, currently being investigated
Age	Attack frequency	Allodynia
Low education/ socioeconomic status	Obesity	Proinflammatory states
	Medication overuse	Prothrombotic states
	Stressful life events	
Head injury	Caffeine overuse	Specific genes
	Snoring	
	Other pain syndromes	

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Attack Frequency

- One of the most important risk factors for progression was frequency of headache attacks at baseline.
- The risk increased in a nonlinear manner with baseline headache frequency; elevated risk for developing CM occurred in subjects who experienced three or more headaches per month.
- The risk of HFEM also increased with attack frequency at baseline.

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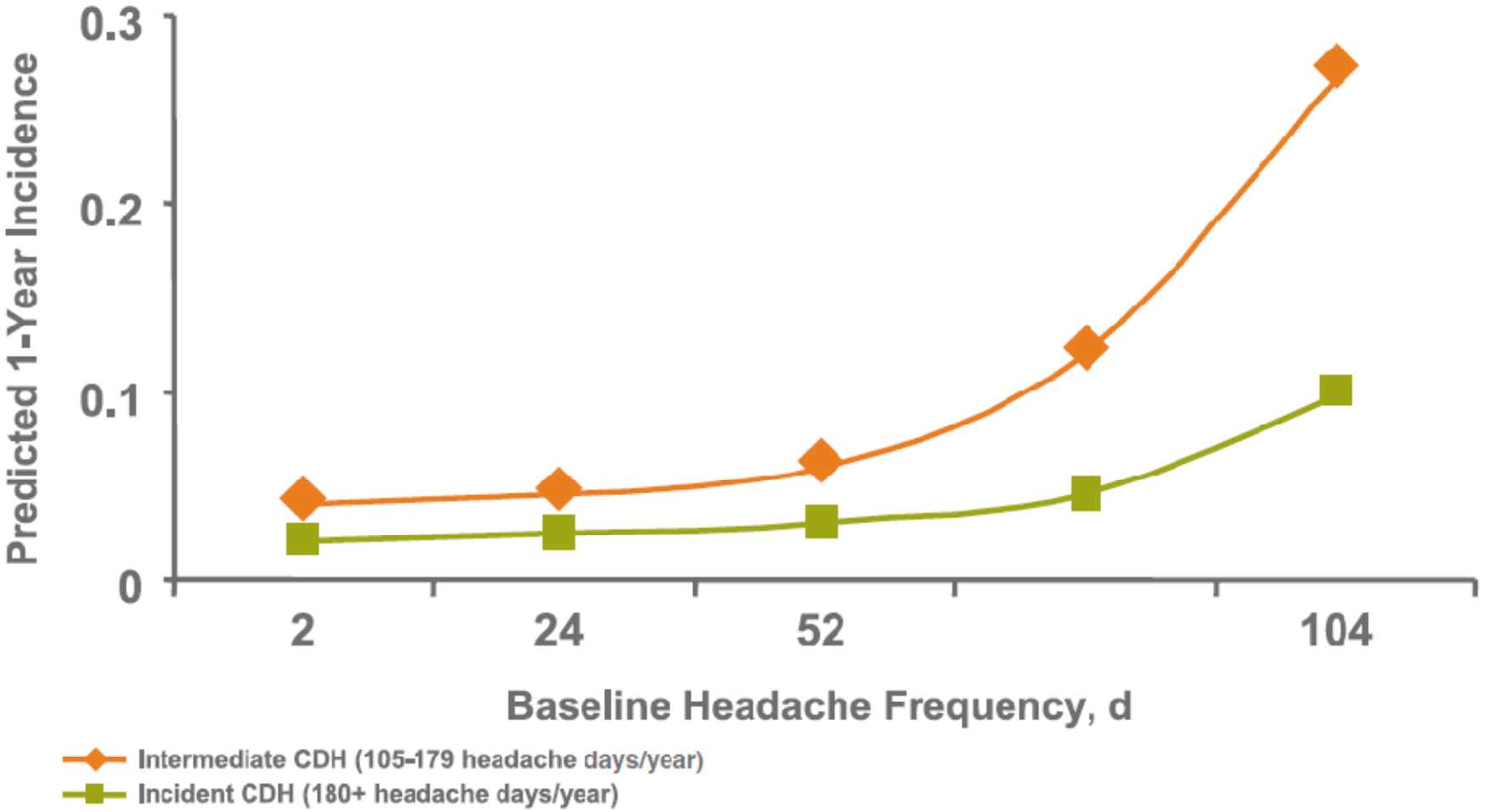
Figure 1 Headache frequency predicts progression to CDH



Estimates were calculated using multinomial logistic regression ($p < 0.005$). CDH = chronic daily headache. Adapted with permission.[4]

Neurology 2009;72 (Suppl 1):S8–S13

Attack Frequency

- Why? → repetitive episodes of pain may lead to central sensitization and generation of free radicals and anatomic changes to the brain and brainstem.
- 但這是因？還是果？

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Obesity

- More recently, obesity was shown to be an exacerbating factor for migraine, and not for headaches overall.
- BMI was associated with the frequency of headache attacks in migraineurs:
  - Normal weight: 4.4% of migraine sufferers had 10–14 headache days per month
  - Overweight: 5.8%
  - Obese: 13.6%
  - Severely obese: 20.7%
- CM
  - Normal weight: 0.9%
  - Severely obese: 2.5%

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Relationship Between Obesity and Migraine Progression

Comments	Main findings
Case-control followed by a longitudinal design.Only longitudinal study currently published.Sample size = 1,932.	In the longitudinal arm, the odds of CDH were 5 times higher in obese and 3 times higher in overweight, relative to normal weight.
Cross-sectional, assessing the influence of obesity on migraine frequency. Sample size = 30,215.	Relative to the normal weight group, the odds of having very frequent headache attacks were 2.9 in the obese and 5.7 in the severely obese.
Cross-sectional, assessing the relationship between obesity and CDH. Sample size = 30,215.	Chronic daily headache and obesity are associated. Obesity is a stronger risk factor for chronic migraine than for chronic tension-type headache.
Cross-sectional, assessing the relationship between obesity and several episodic headaches. Sample size = 30,703.This study has a longitudinal phase, ongoing.	Obesity was strongly associated with the frequency and severity of the attacks experienced by migraineurs, intermediately associated with probable migraine, and not associated with episodic tension-type headache.

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Acute Medication Overuse

- The importance of acute medication overuse as a risk factor for progression is still a matter of debate.
- While most patients with CM seen in specialty care overuse acute mediations, just one-third in the population do so.
- Acute medication overuse does not seem to cause de novo headache in patients without preexisting migraine.
- 因或果？

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Acute Medication Overuse

- When nonsteroidal anti-inflammatory drugs (NSAIDs) were used daily for rheumatic pain, they did not cause CDH in subjects without preexisting primary headache disorders.
- In contrast, analgesics were a strong risk factor for CDH in individuals with preexisting migraine.
- In another study, patients with a previous history of migraine who used daily opiates for treatment of bowel problems developed CDH, whereas the patients without preexisting migraine did not.

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Acute Medication Overuse

- American Migraine Prevalence and Prevention study
  - One year latter, 2.7% evolved to CM in 2006.
  - Relative to acetaminophen, the increased risk of developing CM
    - Compounds containing butalbital → 2 倍 (OR=2.09, 95% CI=1.38–3.17)
    - Opioid → 2倍 (OR=2.01, 95% CI=1.43–2.83)
    - Triptans → X (OR=1.25, 95% CI=0.89–1.75)
    - Anti-inflammatory medications → X (OR=0.85; 95% CI=0.63–1.17)

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Caffeine Overuse

- The role of caffeine in the development of CDH has been studied extensively due to wide exposure to dietary and medication caffeine.
- Caffeine is the only substance shown to cause withdrawal headache.
- A case-control study reported association between daily consumption of more than 100 mg of caffeine and CDH.

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Snoring and Sleep Apnea

- Snoring was associated with any form of headache.
- The mechanisms of relationship between obstructive sleep apnea and migraine progression are not fully understood, but may involve intracranial and arterial pressure fluctuations during snore in an indiindividual susceptible to pain progression, hypoxia, hypercapnia, sleep fragmentation and disruptions and increased muscle activation during awakenings.

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Psychiatric Comorbidity and Stressful Life Events

- In a cross-sectional study, relative to chronic tension-type headache, patients with CM were more likely to have depressive (70% vs 59%, p=0.062) and anxiety symptoms (43% vs 25%, p=0.005).
- More recently, CM was found to be more common in women with major depressive disorder (OR= 31.8).
- Recent history of stressful life events, such as divorce or separation, moving, work changes, or problems with children, is an independent risk factor for CDH.

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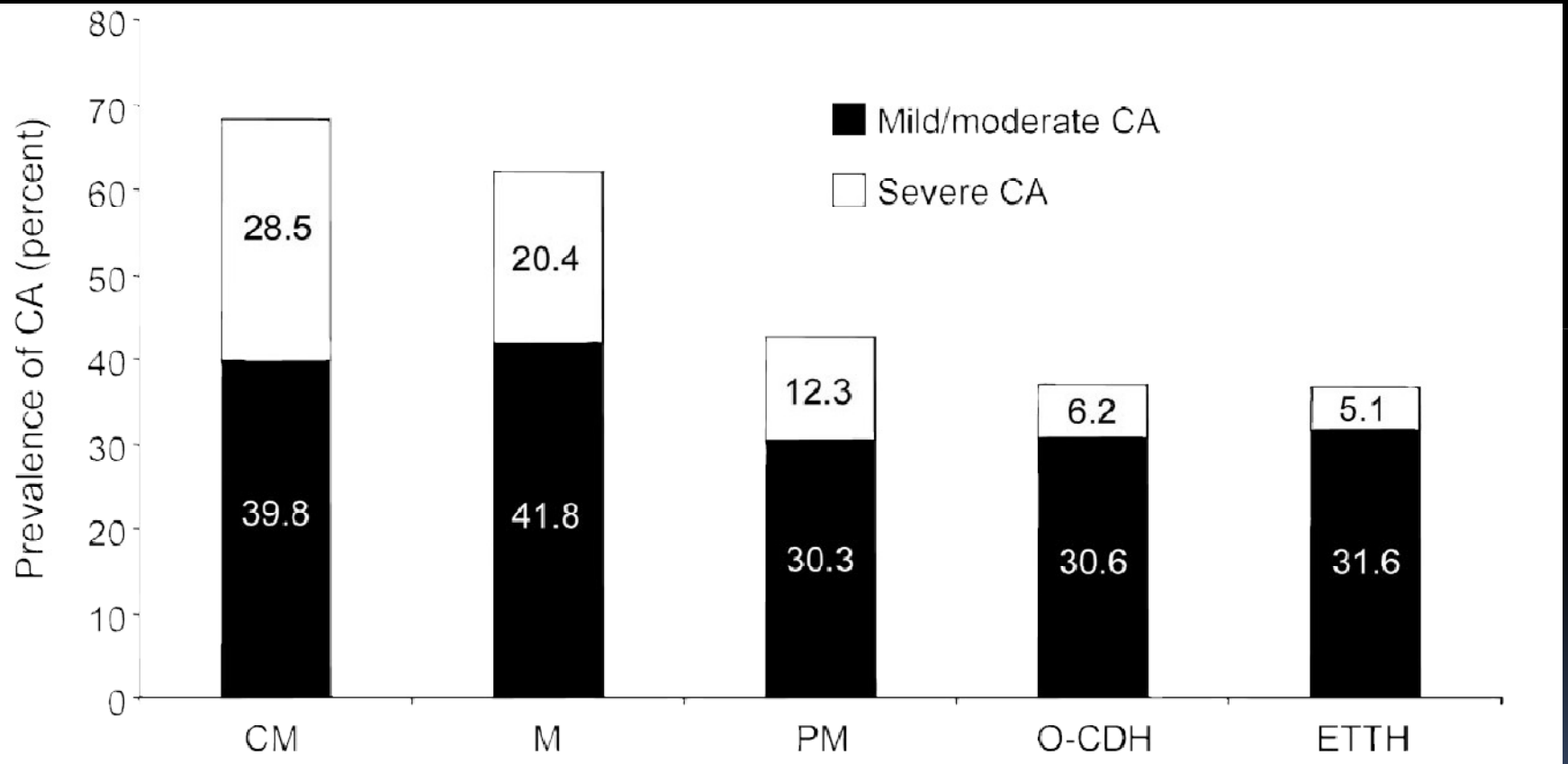
PHYSIOLOGIC ,AND ANATOMIC
TRANSFORMATION

Physiologic Transformation of Migraine

- Approximately 60% of patients experience cutaneous allodynia during migraine episodes, especially in the periorbital region of the painful side.
- A significantly higher frequency of allodynia was reported during headache episodes by patients with CM (66%) or migraine with aura (65%) vs migraine without aura (41%)

Physiologic Transformation of Migraine



CA = cutaneous allodynia; CM = chronic migraine; M = migraine; PM = probable migraine; O-CDH = other chronic daily headaches; ETTH = episodic tension-type headache.

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Physiologic Transformation of Migraine

- Physiologic transformation: sensitization of the second order sensory neurons whose cell bodies are in the trigeminal nucleus caudalis, and to the cutaneous allodynia (CA) which arises as a consequence.

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Physiologic Transformation of Migraine

- The trigeminal nucleus caudalis is a structure that has reciprocal anatomic connections with the periaqueductal gray (PAG) area.
- Repetitive activation of trigeminovascular neurons seems to lead to repetitive activation of modulatory pain pathways involving the PAG.
- In turn, this may lead to impairment of neuronal function through the liberation of free radicals, in the PAG (involved with migraine modulation) or eventually in areas involved with migraine generation.

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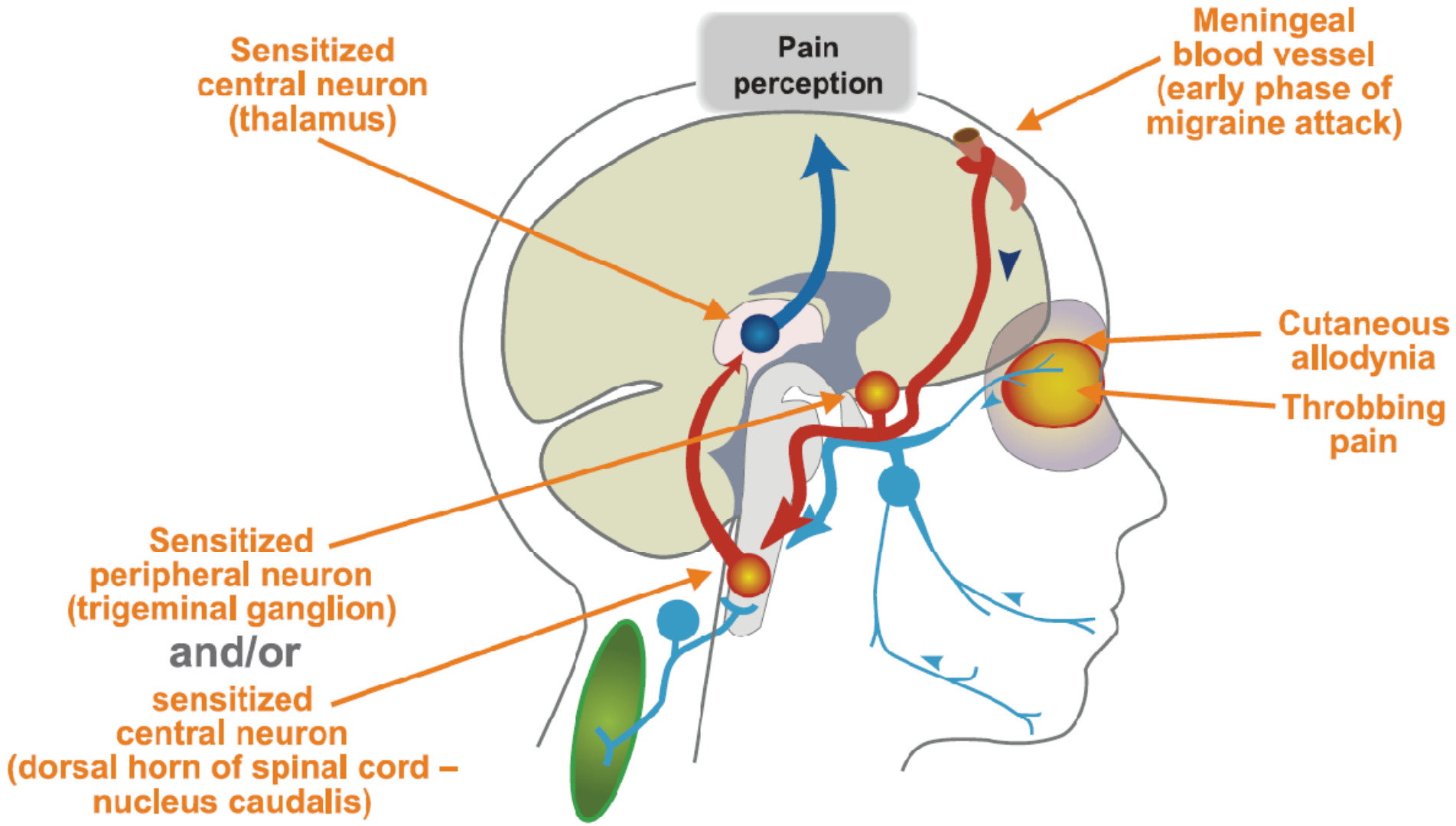
Figure 4 Central sensitization: sensitization of second-order neurons in the trigeminal nucleus caudalis mediates cutaneous allodynia. Adapted with permission[14]



Risk Factors for Cutaneous Allodynia

- Nonmodifiable risk factors
  - Male gender
  - African American race
  - Low educational level
- Potentially modifiable risk factors
  - High attack frequency
  - High pain intensity
  - High levels of headache related disability
  - Obesity
  - Depression

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Anatomic Progression of Migraine

- Limited cross-sectional data, show that the number of deep white matter lesions and the number of strokes is associated with migraine aura and with attack frequency.

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Anatomic Progression – Deep Brain Lesion

- White matter hyperintensities (WMHs) have been considered to be more common in migraineurs.
- WMHs were more common in migraineurs than controls (OR=3.9, 95% CI 2.2–6.7) and the risk was independent of age and vascular risk factors.
- Male subjects with migraine with aura, and women with migraine with or without aura were at a higher risk ofvdeep white matter lesions.
- WMH increased with attack frequency, possibly demonstrating progression of the disease.
- Dose-response effect: the number of lesions increased with migraine attacks frequency.

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Anatomic Progression – Deep Brain Lesion

- Migraineurs with infratentorial ischemia were more likely to have supratentorial white matter lesions as well and hemodynamic changes may give rise to both deep white matter lesions and posterior fossa strokes.
- A cohort study that followed nearly 28,000 women for an average of more than 10 years, migraine with aura increased the risk of nonfatal ischemic stroke by twofold.
- The association remained significant after adjusting for many cardiovascular risk factors and did not occur in the most common type of migraine, migraine without aura.

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Risk Factors for Anatomic Progression

- Brain lesion → migraine with aura
- Brain lesion ↑ → attack ↑
- Mechanisms of aura → mechanisms of anatomic change

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Cortical Spreading Depression (CSD)

- CSD is a self-propagating wave of neuronal and glial depolarization that marches across the cortical mantle.
- CSD alters the permeability of the blood-brain barrier and activates matrix metalloproteinases (MMPs).
- MMP-9 is activated within 15 to 30 minutes of CSD onset.
- Levels of MMP-9 are elevated in individuals with migraine, and this has been suggested to increase vascular permeability in the CNS as a consequence of migraine attacks.
- CSD cascade includes the formation and release of oxygen free radicals, nitric oxide, and proteases.
- While the diminution in cerebral blood flow during CSD does not generally fall below the ischemic threshold at the macroscopic level, emerging evidence suggests that small regions of focal ischemia occur and that on occasion frank ischemia may occur.
- These changes in perfusion may help explain why migraine with aura is a risk factor for stroke and deep brain lesions.

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Shared Biologic Risk Factors

- Migraine with aura was associated with a significantly increased risk for hyperlipidemia, hypertension, and elevated Framingham scores.
- Furthermore, a polymorphism in the methyltetrahydrofolate reductase gene (C677T) is associated with moderately elevated levels of homocysteine which, in turn, is associated with risk of stroke.
- The same polymorphism is overexpressed in migraine with but not migraine without aura.

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Clinical Implications

- Herein we have argued that clinical progression (increasing attack frequency) is associated with physiologic progression in the form of allodynia and perhaps anatomic progression in the form of brain lesions.
- The temporal and causal sequence linking increasing attack frequency, allodynia, and brain lesions remains to be determined.

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MANAGEMENT

Management – Recognize Risk Factors

- Recognizing risk factors for CDH is an important step toward identifying methods to manage CDH more effectively and determining preventive strategies.
- Sleep disorders may result from or may cause headache. Chronic headache and depression may cause disturbed sleep, and sleep deprivation or excessive sleep may cause migraine attacks.

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- We suggest that clinicians consider risk factor modification as part of migraine management, aspiring to not just relieve current pain and disability, but to avoid migraine progression.
- Reducing attack frequency
- Avoiding medication overuse
- Preventive drugs
- Behavioral therapies
- Weight loss

Clinical Intervention on Selected Risk Factors for Migraine Progression

Risk Factors	Intervention
Attack frequency	Effective preventive treatment
Obesity	Weight loss
Medication overuse	Detoxification
Caffeine overuse	Reduction in caffeine consumption
Stressful life events	Stress management
Snoring (sleep apnea)	Weight loss, CPAP
Other pain syndromes	Treatment of chronic pain
Allodynia	Effective early acute treatment Preventive treatment

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Clinical Intervention on Selected Risk Factors for Migraine Progression

- For anatomic progression, most patients with migraine have migraine without aura and, therefore, are not at increased risk of cardiovascular disease.
- Theoretical interventions include targeting CSD.
- Clinicians should also have heightened vigilance for modifiable cardiovascular risk factors (e.g., hypertension).
- Future studies should investigate the possibility that screening for homocysteine and administering folate for those in need as well as antiplatelet therapy might reduce the risk of cardiovascular disease in patients with migraine with aura.

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THANKS FOR YOUR ATTENTION


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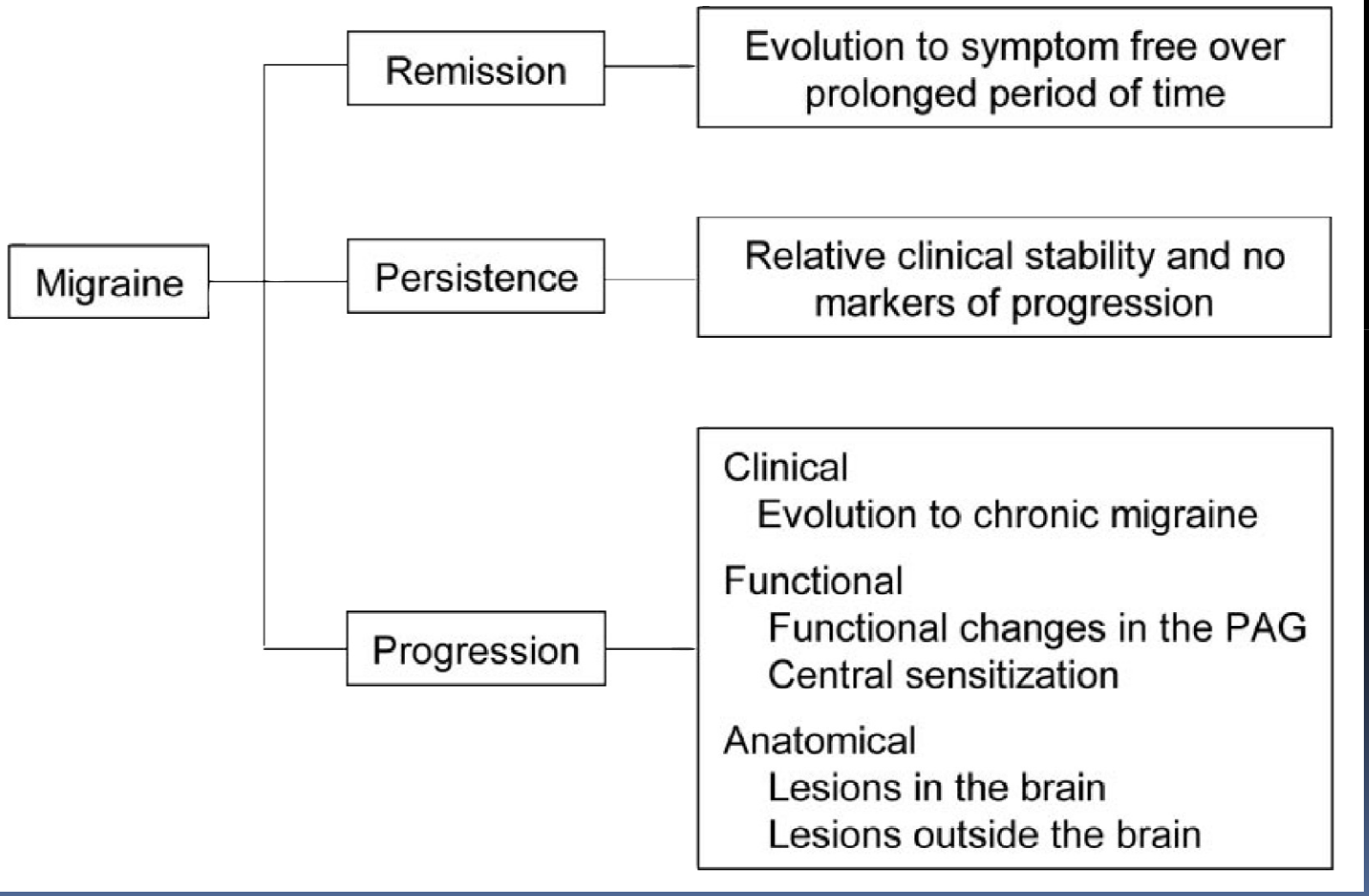
Migraine
Remission
Evolution to symptom free over prolonged period of time
Persistence
Relative clinical stability and no markers of progression
Progression
Clinical
Evolution to chronic migraine
Functional
Functional changes in the PAG
Central sensitization
Anatomical
Lesions in the brain
Lesions outside the brain