頭痛通訊第三期

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【本期內容】

偏頭痛患者的預防性治療在整體治療當中，仍有許多部分亟待加強，本期通訊主要談論醫師在偏頭痛預防性治療時所需考量的準則，感謝西園醫院李詩應醫師所提供偏頭痛的機轉與治療相關新知，希望帶給大家更多的思考空間。
此外，頭痛學組和疼痛醫學會在台中所舉辦「由頭痛 ABC 到最新發展」研討會已圓滿落幕，在此感謝所有與會者的熱心參與。此次研討會講義內容也包含在通訊中，提供給各位醫師作參考。頭痛學組成立至今已半年，感謝半年來大家對頭痛學組的支持和鼓勵，未來相關教育課程仍會持續，也希望大家能繼續支持學組活動並給予指教。祝福各位新的一年事事順心如意！

偏頭痛的預防性治療

西園醫院　李詩應醫師

前言

美國神經醫學會雜誌 Neurology(綠)2003 年十月出刊的附刊—偏頭痛的進展(Advances in Migraine)，對偏頭痛的機轉與治療作了詳盡的更新。其中包括了對偏頭痛這個疾病，本質上的改變—承認它為慢性疾病，並且大聲疾呼要儘早施行急性中斷性與預防性療法，以免中樞與周邊疼痛系統的活化以及轉成慢性難治性

偏頭痛。

偏頭痛患者的預防性治療，在偏頭痛的整體治療當中，仍是目前亟待加強的部分。以美國資料為例，預估可以由偏頭痛預防性治療受惠的患者，約整體的四分之一到三分之一，而實際受到偏頭痛預防性治療的比例只有整體偏頭痛患者中的 3-5%。換算成人口數來看的話，更顯驚人。根據估計，美國約有 2800 萬偏頭痛人口，比台灣地區總人口還多，其中約 700-930 萬可由預防性治療受惠，但是實際上只有約 100 萬的人受到此治療。

雖然在美國的研究報告顯示，亞裔美國人的偏頭痛罹患率比高加索美國人要少，但是若以同等比率套到台灣人口，以感受其問題之必要性，則台灣地區推估約有 210 萬偏頭痛患者，其中約 52.5-70 萬可由預防性治療受惠，但是實際上只有約 6-10 萬的人受到此治療。以神經內科專科醫師人數約 600 名計，則平均每位神內專科醫師應有 100-160 名偏頭痛患者施行預防性治療。若要推廣至可以受惠的患者，均能接受預防性治療，則會成長 7-8 倍，到達平均每位神內專醫師要為 700-1280 名偏頭痛患者，施行預防性治療。當然並非每位需要偏頭痛預防治療的患者，經年累月需要持續就醫，而是在其生命中的某一時期特別需要。

可以由此推知，目前的醫療系統要負荷此種需要是絕對不夠的。在頭痛通訊創刊號中，對神經科醫師的問卷調查顯示，許多醫師認為他們的偏頭痛患者，需要預防性治療，但是實際給予的比率卻較少，而且大部分病人的配合度不高。事實上，要做到以下所列的各方面考量才能大大增加患者配合度與成功率，如此所花費的門診時間將是非常可觀，甚至到了行不通的程度。

偏頭痛預防性治療的考量準則

Goals of migraine prevention

- Reduce attack frequency, severity and disability
- Increased responsiveness of acute attacks to abortive therapy
- Improved quality of life
- Avoid acute headache medication escalation
- Educate & enable patients to manage their disease to enhance personal control of their migraine
- Reduce headache-related distress & psychological symptoms

EBM: AAN guideline

- Recurring migraines, significantly interfere with daily routines, despite acute treatment
- Frequent headaches
- Contraindication to or failure or overuse of acute therapies
- Adverse events with acute therapies
- The cost of both acute and preventive therapies

- Presence of uncommon migraine

Be familiar with preventive medication

- Beta-adrenergic blocking agents: propranolol, timolol, metaprolol, nadolol
- TCA: amitriptyline, nortriptyline, doxepin, imipramine, SSRIs
- CCB:verepramil, flunarizine, ditilazem
- 5-HT_2 antagonists: methysergide, cyprohepatdine, & pizotifen
- NSAID: naproxen etc
- AEP: valproate, gabapentin
- Miscellaneous: clonidine, papaverine, riboflavin, magnesium

Effect assessment difficult due to:

- Spontaneous improvement
- Unpredictable cycles of worsening in some
- High placebo effect

Agents interfered with effective prevention

- Concomitant use of analgesics (particularly combination of analgesics)
- Excessive 5-$HT_{1B/1D}$ agonist
- Oral contraceptives
- Vasodilator: NTG, nifedipine

Reasons for failure: Incorrect diagnosis, failure to recognize comorbidity, inadequate dosage of medications, inadequate time period, unrealistic expectations,

Practical considerations:

- Start small, go slow
- Give an adequate trial with optimum dose for at least 3 months
- Withdraw the medications gradually
- Drug holiday following with slow taper
- Discontinuing with continued relief
- Dose reduction
- Combinations may be needed in many

Steps before prevention therapy:

- Recognition of comorbidity such as depression, panic attacks, anxiety, and bipolar illness
- Analgesic/5-HT_{1D} agonist rebound must be recognized and detoxified
- Recognition of co-existing disease for best choice of preventive medication

Non-pharmacologic approaches include dietary adjustments, reducing triggers, physical exercise, relaxation technique

Preventive therapies for migraine:

Group 1. **Med.-high efficacy, good evidence & mild-mod side effect**

Amitriptyline, divalproex sodium, propranolol/timolol

Group 2. **Lower efficacy, or limit strength of evidence & mild-mod side effect**

β-blockers: atenolol/metoprolol/nadolol, calcium channel blocker (CCB): nimodipine/verapamil, NSAID: aspirin/ketoprofen/mefanamic acid/naproxen, fluoxetine, gabapentin, Others: feverfew/magnesium/vitamin B_2

Group 3. **Clinically efficacious, no scientific evidence**

Most antidepressants, cyproheptadine, ditilazem, ibuprofen, topiramate, phenelzine (side effect concerns)

Group 4. **Med.-high efficacy, good evidence, but with side effect concerns**

Methysergide

Group 5. **Evidence indicating no efficacy over placebo**

Carbamazepine, clomipramine, clonazepam, clonidine, indomethacin, nicardipine/nifedipine, pindolol

Principles of care that will enhance success:

- Medication use:
  - Initiate therapy with highest level efficacy
  - Lowest effective dose of drug, increase slowly
  - Give each drug adequate trial (2-3 mth)
  - Avoid interfering medications
  - Use of long-acting formulation
- Evaluation:
  - Monitor through headache diary
  - Re-evaluate therapy
  - If after 3-6 months headaches are well controlled, consider tapering or discontinuing treatment
- Take coexisting conditions into account:
  - Some comorbid and coexisting conditions are more common in persons with migraine: stroke, MI, Raynaud's phenomenon, epilepsy, affective & anxiety disorders.
  - These conditions present both opportunities & limitations
- Pregnant women: teratogenic effects considered
- Non-pharmacologic treatment
  - Behavior treatment: relaxation training, biofeedback therapy, cognitive-behavior training (EBM: grade A & B)
  - Physical treatment: acupuncture, cervical manipulation, mobilization therapy (no EBM yet)

Mechanisms:

- 5-HT_2 antagonism
- Regulation of voltage-gated ion channels

- Modulation of central & peripheral neurotransmitters
- Enhancement of GABAergic inhibition
- Alternation of neuronal oxidative metabolism

Many migraine preventive agents affect voltage-gated ion channels through membrane stablizing effects, as: Flunarizin, Verapamil, Valproate, Propranolol

Future:

- Specific antagonist act on P/Q type calcium channel (chromosome 19) may improve migraine prevention
- Contraversial prevention treatment- Botulinum toxin A
- ACE inhibitors & angiotension II receptor blockers for migraine prevention

Topiramate:mechanism

- Block voltage-sensitive sodium & L-type calcium channels
- Enhance GABA neurotransmission ($GABA_A$ receptor)
- Reduce glutamate neurotransmission (non-NMDA receptor)
- Weak carbonic anhydrase inhibitor by receptor modulation & channel phosphorylation

Topiramate:conclusion

- Effective for migraine prophylaxis
- The 100mg dose have best efficacy/tolerability ratio
- reduced weight about 3.8% after 6 weeks

Contraversial prevention treatment- Botulixium A

- More than half of patients with frequent attacks of migraine also suffer from tention type of headache(TTH)
- Improving or eliminating TTH: reduces or eliminating stress as trigger and reduce intake of acute medication
- Elimination of muscle triggers, CNS is protected from excessive sensory overflow

Copharmacy & comorbidity must be considered: (for detail see ref. 2)

- Comorbidity and therapeutic opportunities
- Comorbidity and therapeutic limitations
- Therapeutic limitations due to side effects
- Rational copharmacy
- Comorbidity and therapeutic opportunities
- Comorbidity and therapeutic limitations
- Therapeutic limitations due to side effects
- Combining abortive & preventive therapy

Possible Mechanism of action of preventive therapies

- Amitriptyline/Na channel blockade/ adenosine-mediated inhibition or aminergic-mediated modulation of decending nociceptive facilitation
- Gabapentin/modulation of intracellular calcium influx binding to $\alpha_2\delta$ subunit of calcium channels
- Magnesium/blockade of NMDA receptors
- Propranolol/ aminergic-mediated modulation of decending nociceptive facilitation
- Topiramate/potentiation of GABA inhibition/ antagonism of non-NMDA glutamate excitatory receptors
- Valproate/GABA-mediated inhibition of cell excitation
- Verapamil/blockade of intracellular calcium entry & cell depolarization

But no one really knows why current prophylatic medication works

結論與建議

就像作球鞋的企業家發現非洲大陸許多土著不穿鞋子時，他或者興奮得晚上睡不著，或者絕望得晚上睡不著，神經科醫師對於如此多，待開發的偏頭痛預防性治療患者，亦可能有此兩種心情。如果是前者，則要依上述準則好好規劃。套句古話：「勿恃敵之不來，應恃吾有以待之。」的態度以進行。雖然沒人真正了解偏頭痛預防治療的機轉，但它的有效性，確是不可忽視，而日新月異增添的機轉正足以讓我們治療的心安理得，對旁人解說時來的理直氣壯。

如果要真正做好偏頭痛的預防治療，最好是能成立頭痛特別門診，其次則是建立各自醫療機構的定型化處理準則，並進而佐以團體衛教的形式，全方位的照顧，才能收事倍功半之效。

主要參考資料

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3. The evolving management of migraine. Ashkenazi A. & Silberstein S.D. Curr Opin Neurol 2003;16:341-5.
4. Advances in Migraine. 2003;61(No. 8, Suppl 4)

頭痛 ABC 到最新發展研討會講義

偏頭痛之診斷

王博仁　新樓醫院神經科

自 1988 年，國際頭痛學會訂出頭痛之診斷標準之後，大家終於有了一個一致的標準來診斷頭痛，也使得頭痛的研究蓬勃發展。今年九月，第二版的診斷標準終於在大家的殷殷期盼下出來了。改版之診斷標準，大體上沿襲第一版之架構，採階梯式分類，共有十四群（group），底下有頭痛類別（type），次類（subtype）及亞型（subform），可根據需要診斷至適用之層級。

偏頭痛共分為六個次類，各有其診斷基準。值得一提的地方是 migraine with aura（1.2）之頭痛須區分出 migraine 與 non-migraine。預兆的時間定義有所改變。若有動作無力則歸入偏癱性偏頭痛。慢性偏頭痛是新的亞型（1.5.1 chronic migraine），當偏頭痛之頻率大於每月 15 天維持三個月以上，可考慮放上此診斷。但須排除藥物過量所致之頭痛（8.2 Medication-overuse headache），且須觀察兩個月。在不確定或證據不足時，則暫放在 1.6 probable migraine 之診斷中。在孩童周期性症候群（childhood periodic syndrome）多出 1.3.1 cyclical vomiting 與 1.3.2 Abdominal migraine。而眼肌痲痺偏頭痛（ophthalmoplegic migraine）已被移出，不再屬於偏頭痛之範疇。

儘管診斷基準已詳備，但是要熟悉並不是一件易事。偏頭痛之診斷就很有機會被低估。於是就有人想出一些方法來解決這個問題，以試圖提高偏頭痛之診斷率。無預兆偏頭痛是最常見的一種偏頭痛，偏頭痛之特徵，如單側、中等度以上、脈動般痛、頭痛隨一般體力性活動而加劇，噁心、嘔吐、怕光、怕吵則為診斷此類偏頭痛之最主要依據，而國外所提之簡易診斷方法乃是根據這些特徵去訂出來，並且有不錯的敏感度及特異性。雖然偏頭痛特徵出現之頻率，台灣之情況與國外不盡然一致，但卻仍然不失為重要之參考。

Botulinum Toxin Type A Injection in the Treatment of Upper Back Myofascial Pain

孫維仁　台大醫院麻醉科

Introduction: There is increasing evidence showing botulinum toxin type A (BTX)

could reduce pain other than those caused by muscular spasticity. The present study was undertaken to evaluate the efficacy and safety of BTX in the treatment of chronic myofascial pain.

Mehtods: Twenty five adult patients with chronic myofascial pain of the upper back who completed a three week screening phase during which bupivacaine injection of the trigger points demonstrated effective but temporary relief of pain were enrolled into this open labeled, prospective study. Each subject received BTX injection into the selected active trigger points with 25 U/site in the muscle of the upper back and assessment of pain by Visual Analog Scale (VAS), global satisfaction rating and physical examinations were done at baseline, 2, 4, 8, and 12 weeks after treatment.

Results: Thirteen males and 12 female with age ranging from 37 to 76 years (mean 49.5 10.5 yr) completed the study. The injection site distribution were 33 % in the right side, 53% in the left side and 14 % in both sides. A total of 83.3 39.5 U (range 50-200 U) was injected. The mean values of the VAS score of the localized pain at baseline, 2^{nd}, 4^{th}, 8^{th}, and 12^{th} week were 7.3 1.9, 2.9 2.8, 1.9 2.5, 2.1 3.1, and 2.2 3.3 respectively with statistically significant difference between the baseline and all the post treatment time points ($p<0.05$). The pain relief lasted through the 12 week observation period . Patient s global satisfaction score also showed a significant difference ($p<0.05$) at the 2^{nd} through the 12^{th} week when compared with baseline. Sixty eight percent of the patients rated their pain improvement as 50% or more while the physician rated 75% of the patients with such an improvement. Except for transient weakness sensation at the first postinjection week, there was no adverse reaction with the BTX injection in all the patients.

Conclusion: This preliminary study showed that botulinum toxin when injected into the trigger point of the muscle can provide prolonged relief of myofascial pain without adverse effect. Large scale controlled study with longer follow up observation to further determine the role of BTX treatment for myofascial pain will be warranted.

Summary: This study evaluated the use of botulinum toxin Type A in the relief of upper back myofascial pain with 12 week follow up .

Pathophysiology of migraine

羅榮昇 林口長庚醫院神經內科二科

1.**Genetic factors**: rare form familial hemiplegia migraine (AD) linked to chromosome 19 due to missense mutations in the α 1 subunit of P/Q type voltage-gated Ca channel (55%) (Ophoff et al. 1996)

2.**Excitatory amino acids**: glutamate and aspartate increased in plasma between migraine attacks (Ferrari et al. 1990)

3.**Neurophysiological changes**: the amplitude difference between the primary positive and negative waves of VEP is increased in migrainous subjects (Gawel et al. 1983)

4.**The hypothalamo-pituitary axis and dopaminergic transmission**: fenfluramine releases 5-HT, caused a significantly higher prolactin level in migraineurs than in controls, suggesting supersensitivity of hypothalamic 5-HT receptors (Glover et al. 1996)

5. **Opioids and the endogenous pain control system:** pain control mechanisms must be partially defective in migraine patients because headaches induced by eating ice-cream are more common in migraine patients than in controls (Drummond and Lance 1984)

6.**Vascular reactivity:** cerebral vasodilator response to CO_2 is greater in migraine patients than in controls and the reaction of extracranial arteries to exercises and stress is greater on the side of their usual migraine headaches (Drummond and Lance 1981; Drummond 1982)

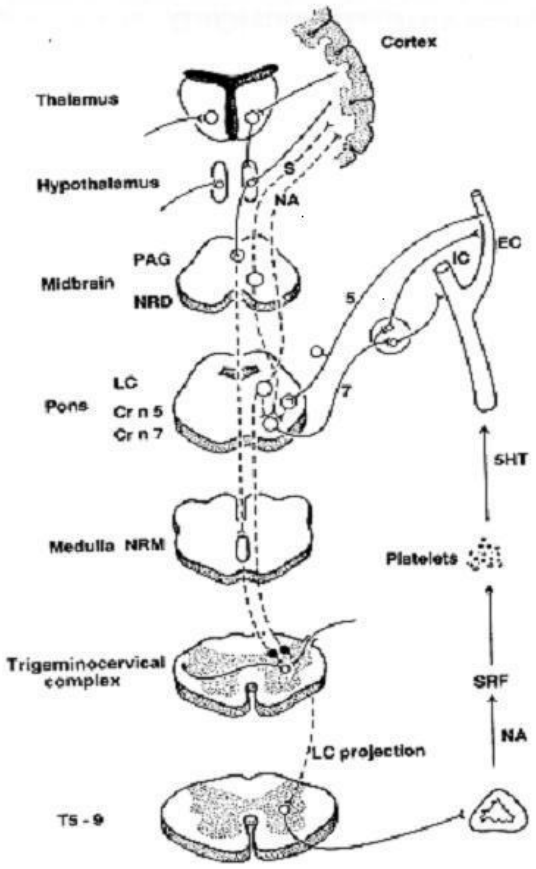

Figure 8.11 The neurovascular hypothesis for migraine. (From Lance *et al.*, 1989, by permission of the editors of *Migraine: A Spectrum of Ideas*)

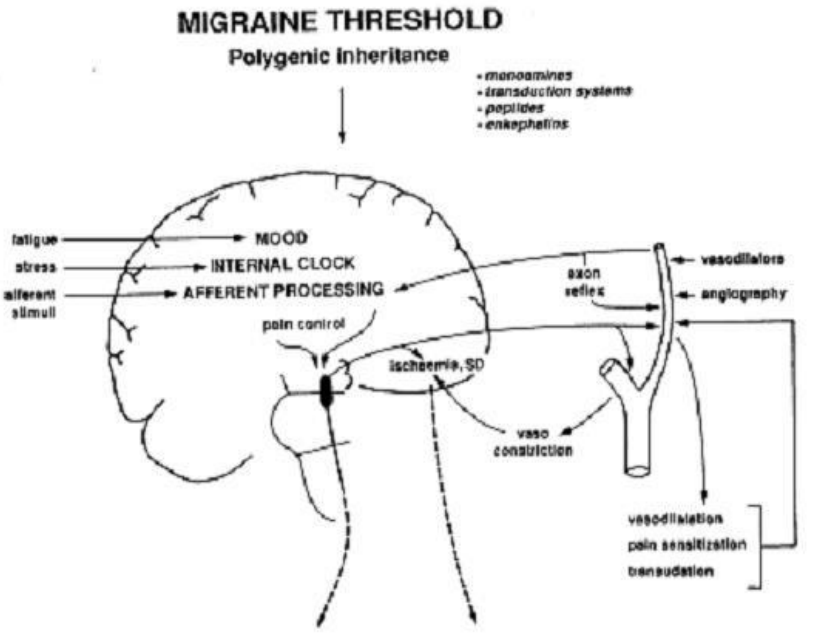

Figure 8.12 A schema for the neurovascular basis of migraine. (From Lance *et al.*, 1989, by permission of the editors of *Migraine: A Spectrum of Ideas*)

The diagnosis of chronic daily headache

王署君　台北榮總神經內科

The controversial issue on the disease entity of chronic daily headache (CDH) has been debated for almost 20 years. The new edition of the International classification of headache disorders, 2nd edition (ICHD-II)) published in September 2003 at Rome, Italy first adopted the diagnostic criteria of four common subtypes of chronic daily headache (>=15 days/month, > 3 months): Chronic migraine (coded as 1.5.1), chronic tension-type headache (2.3), hemicrania continua (4.7) and new daily persistent headache (4.8). The former two subtypes occupy the majority of patients with chronic daily headache in the field and headache clinics. The subtypes of chronic daily headache are sub-classified after exclusion of possible medication overuse headache (8.2), i.e. withdrawal of offending painkillers, ergots or narcotics for at least 2 months. In this lecture, the diagnostic criteria for each chronic daily headache subtype will be illustrated.　Furthermore, epidemiology and some experience of management of this disabling headache will also be mentioned briefly.

Medication Overuse Headache

傅中玲　台北榮總神經內科

The currently released *the International Classification of Headache Disorders, 2nd edition* (ICHD-II) has introduced medication overuse headache (MOH) as a new diagnosis although it has been known for a long time. MOH replaces previously used terms such as rebound headache, drug-induced headache, and medication-misuse headache. According to ICHD-II, the MOH is defined as headache present on more than 15 days per month, intake of the drug is at least 10 days a month on a regular basis for at least 3 months. More specific details apply for the specific drug, particularly for ergotamine, triptans, analgesic, opioids, or combinations. The headache has developed or is markedly worsened during overuse, and resolves or reverts to its previous patterns within two months after discontinuations of the drug.

Several population-based studies show that about 1% of the general population is suffering from headache caused by medication overuse. Chronic headache, which is headache for at least 15 days per month, was more than seven times more likely

among those with analgesic overuse than those without. Analgesic overuse was highest among respondents with chronic migraine, intermediate for patients with chronic non-migraine headache, and lowest for respondents with chronic neck and chronic low-back pain.

This kind of headache can be caused by the intake of a combination of analgesics, opioids, ergot alkaloids and triptans. The delay between first intake and these attacks is shortest for triptans (1-2 years), longer for ergots (3-5 years) and longest for analgesics (5-10 years). The success rate of withdrawal therapy within a time window of 1-6 months is 72.4%. Success is defined as no headache at all or an improvement of more than 50% in terms of headache days. A 5-year follow-up study found a relapse rate of 40%.

Abrupt drug withdrawal is the treatment of choice for MOH. Clinical experience indicates that medical and behavioural headache treatment fails, as long as the patient continues to take symptomatic drugs daily. The typical withdrawal symptoms last for 2-10 days (average 3.5 days) and include withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness. Treatment recommendations for the acute phase of drug withdrawal vary considerably and include fluid replacement, analgesics, tranquillizers, neuroleptics, amitriptyline, valproate, intravenous DHE, oxygen, steroid and electrical stimulation.

近期活動

高雄 2004 頭痛研討會

時間：93 年 3 月 28 日(星期日)上午　　地點：高雄金典酒店

Time	Topic	Speaker
8:30-9:00	報到	
座長：盧玉強主任（高雄榮總）		
9:00-9:35	Serotonin and headache	羅榮昇(林口長庚)
9:35-9:45	Discussion	
9:45-10:10	Menstrual migraine	王署君（台北榮總）
10:10-10:15	Discussion	
10:15-10:40	Diagnosis of migraine	王博仁（台南新樓）
10:40-10:45	Discussion	
10:45-11:00	Coffee Break	

座長：劉嘉為主任（高雄長庚）		
11:00-11:25	The treatment of myofascial pain syndrome	張英明（台北仁愛）
11:25-11:30	Discussion	
11:30-11:55	Idiopathic intracranial hypertension	傅中玲（台北榮總）
11:55-12:00	Discussion	
12:00-12:25	The acute treatment of migraine: update	盧相如（高醫）
12:25-12:30	Discussion	
12:30-2:00	Lunch	

本通訊以電子郵件方式寄發，有興趣繼續獲得本通訊者敬請告知電子郵件信箱，若有相關研討會，我們將會通知您；若您不希望繼續收到本通訊，也敬請回覆Email告知。本園地公開，竭誠歡迎所有相關醫學著述、病例討論、文獻推介、研討會講座等資訊投稿。

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