24.8 Headache 5987 Peter J. Goadsby

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ESSENTIALS Headache is among the most common of human maladies. So much so that it is generally (and often incorrectly) assumed to be under- stood, especially by doctors. The classification of headache, with formal definitions of different diagnostic entities, by the International Headache Society into (1) primary—occurring in the absence of ex- ternal causes, and (2) secondary—some of which may have sinister cause, has greatly simplified the description, understanding, and management of this often challenging symptom. It also allows those headaches with serious or life-threatening consequences to be dis- tinguished from other forms. Pathophysiology of primary headaches The key structures involved in producing pain appear to be the:
(1) large intracranial vessels and the dura mater, (2) trigeminal nerve, (3) higher centres in the thalamus and cortex, (4) modulatory centres in the diencephalon and brainstem. Two of the most common and best studied primary headaches, migraine, and cluster headache, should be regarded as being neuro- logical or brain disorders with any vessel change being secondary, ie neurovascular. Migraine might be part of the spectrum of diseases known as channelopathies or ionopathies: the three genes currently identified as being responsible for familial hemiplegic migraine alter ion fluxes. Moreover, in studies of the more common forms of mi- graine across large patient cohorts, genome-wide association studies have implicated excitatory, in particular glutamatergic, transmission to be key to the pathophysiology. Migraine Epidemiology and clinical features—migraine affects 12 to 18% of the population in any one year, and about 45% of females over their lifetime; it can be highly disabling. It presents with headache, often throbbing and generally accompanied by other features such as sen- sitivity to light, sound, or movement, and often with nausea or (less often) vomiting, but none of the features is compulsory. For example, the migraine aura—visual disturbances with flashing lights or zigzag lines moving across the fields or other neurological symptoms—is reported in only about 25% of patients. It is noteworthy that the word migraine is used to describe the diagnosis—a patient has mi- graine; as well as an individual attack—a patient is having a migraine. Although a subtle distinction this concept underpins the fact that not all attacks, in all patients, every day, need to conform to standard diagnostic criteria. Treatment—principles of management include (1) explanation— migraine is an

inherited tendency to have headache and cannot therefore be ‘cured’; (2) the condition can be modified and con- trolled by lifestyle adjustment and the use of medicines; (3) it is not life-threatening; (4) management takes time and cooperation. Most migraine sufferers will benefit from a healthy diet, regular ex- ercise, regular sleep patterns, avoiding excess caffeine and alcohol and (as far as practical) modifying or minimizing changes in stress. Preventive treatments include pizotifen, β-blockers, some tricyc- lics, some anticonvulsants, candesartan, flunarizine, noninvasive neuromodulation, calcitonin gene-related peptide (CGRP) mono- clonal antibodies and botulinum toxin type A (the latter for chronic migraine). Acute treatments include (often in combination with an antiemetic) nonspecific drugs such as aspirin, paracetamol (acet- aminophen) and nonsteroidal anti-inflammatory drugs, and specific agents such as triptans, serotonin 5-HT1B/1D receptor agonists and ergot derivatives and noninvasive neuromodulation. In the coming years newer agents for acute therapy will be, ditans (serotonin 5- HT1F receptor agonists), and gepants (calcitonin gene-related pep- tide (CGRP) receptor antagonists) that, will offer novel and added benefits to patients with migraine and the physicians who treat them. Tension-type headache Tension-type headache is common, unexplained, and completely featureless, with no nausea, no vomiting, no photophobia, no phonophobia, no osmophobia, no throbbing, and no aggravation with movement. It is referred to by patients as annoying rather than disabling. When episodic, it is generally amenable to simple anal- gesics; when chronic, amitriptyline is the only proven treatment. Trigeminal–autonomic cephalalgias Cluster headache—characterized by bouts of excruciating retro- orbital boring pain associated with ipsilateral symptoms of cra- nial parasympathetic activation (a red or watering eye, the nose running or blocking) or cranial sympathetic dysfunction (eyelid droop). Prevention is with agents including verapamil, lithium, topiramate, and melatonin, while oral corticosteroids are used as bridge therapy. Treatments for acute attacks include oxygen inhal- ation, sumatriptan by subcutaneous injection, or nasal spray and zolmitriptan by nasal spray. 24.8 Headache Peter J. Goadsby

 Other conditions—these include (1) paroxysmal hemicrania; (2) short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing or cranial autonomic activation (SUNCT/SUNA); and (3) hemicrania continua. Other primary headaches Specific conditions include (1) cough headache, (2) exercise head- ache, (3) sex headache, (4) thunderclap headache, (5) cold stimulus headache, (6) external pressure headache, (7) stabbing headache, (8) nummular headache, and (9) hypnic headache. Many of these can present with daily headache and are often misdiagnosed as tension-type headache. They can readily be identified from the his- tory, often leading to effective and specific treatments, an important element of which is reduction/elimination of analgesic overuse. New daily persistent headache—this presents with abrupt onset of headache that then persists. Possible causes include: (1) primary— migrainous type, featureless (tension-type); (2) secondary— subarachnoid haemorrhage, low cerebrospinal fluid volume headache, raised cerebrospinal fluid pressure headache, post- traumatic headache, chronic meningitis, giant cell arteritis. Effective and specific treatments are available for many of these conditions
if a precise diagnosis can be made. Secondary headache Clinical approach—the length of the history is crucial: if this is short, the patient requires prompt attention; if this is long, then time and patience are needed rather than alacrity. Associated fever, sudden onset of pain, or the presence of neurological signs need a positive diagnosis of a benign disorder or require brain imaging with com- puted tomography or magnetic resonance imaging. Causes and management—medically sinister headaches requiring urgent attention include subarachnoid haemorrhage, meningitis, giant

cell arteritis, and raised intracranial pressure. Other important causes of secondary headache include low volume (pressure) cerebrospinal fluid, post-traumatic headache, and cerviocogenic headache. Many of these disorders require persistent diagnostic skills and investigation; but when combined with knowledge of general principles, including the anatomy and physiology of the key cranial structures, the management of head- ache is generally productive and beneficial for the sufferer. General principles To manage headache can be a source of extreme frustration or undiluted pleasure—the difference simply reflects to what extent the practitioner is familiar with the subject. A formal nosology for headache disorders is to be found in the third edition of the International classification of headache disorders. Although it seems obvious, the key to successful management is establishment of a clear diagnosis. The general concept is that there are primary and secondary forms of headache, following the generic medical principle that clinical syndromes may be caused by something exogenous or secondary, or may manifest anew as the primary disease process. Such a system is outlined in Table 24.8.1. Mild secondary headache, such as that seen in association with upper respiratory tract infections, is common but only rarely worrisome. The clinical dilemma remains that, although life-threatening headache is relatively uncommon in Western society, it occurs, and its detection requires suitable vigilance by doctors. Primary headache, in contrast, often confers considerable disability over time and although not life-threatening certainly robs patients of quality of life. Some pointers to secondary headache are listed in Box 24.8.1. Primary headache disorders The primary headaches are a group of fascinating disorders in which headache and associated features are seen in the absence of any exogenous cause. The common syndromes (see Table 24.8.1) are tension-type headache, migraine, and cluster headache. Some other less well-known, indeed rarer, syndromes are mentioned because they are easily treated when diagnosed, and the most burdensome headache problems, the chronic daily headache syndromes, are explicitly covered because concepts have altered considerably in this area in recent years. Anatomy and physiology The most common disabling primary headaches, migraine, and cluster headache, have been studied extensively in re- cent times and they are now relatively well understood insofar as neurological disorders that involve the brain are concerned. In experimental animals the detailed anatomy of the connec- tions of the pain-producing intracranial extracerebral vessels and the dura mater has built on the classic human observations of Wolff, Feindel, Penfield, McNaughton, and others. It is these structures, and not the brain itself, that are primarily involved in head pain, although it is not at all clear to what extent there is nociceptive activation as such, or simply the perception of that activation.
Table 24.8.1 Common causes of headache Primary headache Secondary headache Type Prevalence (%) Type Prevalence (%) Migraine 16 Systemic infection 63 Tension-type 69 Head injury 4 Cluster headache 0.1 Subarachnoid haemorrhage <1 Idiopathic stabbing 2 Vascular disorders 1 Exertional 1 Brain tumour 0.1 After Olesen J, et al. (2005). The headaches. Lippincott, Williams & Wilkins, Philadelphia.

24.8 Headache 5989 The key structures involved are: • the large intracranial vessels and dura mater • the peripheral terminals of the trigeminal nerve that innervate these structures • the central terminals and second-order neurons of the caudal tri- geminal nucleus and dorsal horns of C1 and C2 (trigeminocervical complex) • higher-centre processing in the thalamus, ventroposteromedial, and posterior thalamus and cortex • modulatory centres in the diencephalon and brainstem, such as periaqueductal grey matter, locus coeruleus, and parts of the hypothalamus The innervation of the large intracranial vessels and dura mater by the trigeminal nerve is known as the trigeminovascular system. Cranial parasympathetic autonomic outflow from

the superior salivatory nucleus through the seventh cranial nerve and periph- erally through the sphenopalatine ganglion, provides the basis for symptoms such as lacrimation and nasal stuffiness, which are prom- inent are lateralized in cluster headache and paroxysmal hemicrania, although they may also be seen in migraine. It is clear from human functional imaging studies that vascular changes in migraine and cluster headache are driven by these neural vasodilator systems so that these headaches should be regarded as neurovascular. The con- cept of a primary vascular headache should be abandoned because it does not explain the pathogenesis of what are complex central nervous system (CNS) disorders, or necessarily predict treatment outcomes. The term 'vascular' headache has no place in modern medical practice when referring to primary headache disorders. Migraine is an episodic syndrome of headache with sensory sen- sitivity, such as to light, sound, and head movement, probably due to dysfunction of aminergic brainstem/diencephalic sensory control systems (Fig. 24.8.1). The first of the migraine genes has been identi- fied for familial hemiplegic migraine, and includes mutations in the CACNA1A gene for the CaV2.1 (α1A) subunit of the neuronal P/Q voltage-gated calcium channel, the Na+/K+ ATP pump α2-subunit gene ATP1A2, and the voltage-gated sodium channel SCN1A. These findings and the clinical features of migraine suggest that it might be part of the spectrum of diseases known as channelopathies, or now ionopathies—disorders involving dysfunction of ion channel fluxes. Moreover, recent large-scale investigations, genome-wide association studies, have identified consistently excitatory, glutamatergic path- ways, and the transient receptor potential—TRPM8 cold receptor, in migraine genomics even in the most common form of migraine without aura. Functional neuroimaging has suggested that brainstem regions in migraine (Fig. 24.8.2), and the region of the posterior hypothalamic grey matter, site of the human circadian pacemaker cells of the suprachiasmatic nucleus, in cluster headache (Fig. 24.8.3), are good candidates for specific involvement in primary headache. Secondary headache It is imperative to establish in the patient presenting with any form of head pain whether there is an important secondary headache declaring itself. The headaches of subarachnoid haemorrhage, men- ingitis, giant cell arteritis, and raised intracranial pressure are im- portant examples of medically sinister headaches requiring urgent attention. Perhaps the most crucial clinical feature to elicit is the length of the history. Patients with a short history require prompt attention and may require prompt investigation and management. Patients with a longer history generally require time and patience Box 24.8.1 Warning signs in head pain • Sudden onset of pain • Fever • Marked change in pain character or timing of attacks • Neck stiffness • Pain associated with higher-centre complaints • Pain associated with neurological disturbance, such as clumsiness or weakness • Pain associated with local tenderness, such as of the temporal artery Cervical DRG TCC NRM PAG Thalamus Hypothalamus Cortex Vg Dural-vascular structures LC
Fig. 24.8.1 Pathophysiology of migraine. Diagram of some structures involved in the transmission of trigeminovascular nociceptive input and the modulation of that input which form the basis of a model of the pathophysiology of migraine. Afferents from dural–vascular structures innervated predominantly by branches of the first (ophthalmic) division of the trigeminal nerve, with cell bodies found in the trigeminal ganglion (Vg), project to second-order neurons in the trigeminocervical complex (TCC). The TCC extends from trigeminal nucleus caudalis to the caudal portion of the dorsal horn of the C2 spinal cord. Input from cervical structures, such as joints or muscle, project through cell bodies in the upper cervical dorsal root ganglia (DRGs) to the TCC. TCC neurons project to ventrobasal thalamus (thalamus) and thence to the cortex. Sensory modulation can occur by descending influences on to the TCC that largely respect the midline (dashed line), such as those from the hypothalamus, midbrain periaqueductal grey (PAG), pontine locus coeruleus (LC), and nucleus raphe magnus (RVM). These influences are pictured as being direct but both

direct and indirect projections are recognized. In addition sensory modulation can occur from at least the LC and PAG, and hypothalamic projects to thalamus nuclei as ascending systems again largely respect the midline. From Goadsby PJ (2005). Can we develop neurally-acting drugs for the treatment of migraine? Nat Rev Drug Discovery, 4: 741–50.

section 24 Neurological disorders 5990 Fig. 24.8.2 Activations identified on positron emission tomography (PET) in migraine. In the premonitory phase hypothalamic activation is observed (a), while consistently in the headache phase there is dorsolateral pons activation in episodic migraine without aura, triggered by nitroglycerin (b), or spontaneously studied (c), and in chronic migraine (f). Moreover, there is lateralization to the right (d) and left (e) in this structure that parallels the unilateral presentation of the pain. (a) from Maniyar F, et al. (2014) Brain activations in the premonitory phase of nitroglycerin triggered migraine attacks. Brain. 2014;137:232–42; (b) from Bahra A, et al. (2001). Brainstem activation specific to migraine headache. Lancet, 357: 1016–17; (c) from Matharu MS, et al. (2004). Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain, 127: 220–30; (d, e) from Afridi S, et al. (2005). A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Brain, 128: 932–9; (f) from Afridi S, et al. (2005). A PET study in spontaneous migraine. Arch Neurol, 62: 1270–5. (b) (a) Fig. 24.8.3 Activations on PET in the posterior hypothalamic grey matter in patients with acute cluster headache (a). The activation demonstrated is lateralized to the side of the pain (May et al., 1998). When comparing the brains of patients with cluster headache with a control population,
using an automatic anatomical technique known as voxel-based morphometry which employs high-resolution T1-weighted MRI, a similar region is demonstrated (b) and has increased grey matter. (a) (May et al., 1998), (b) (May et al., 1999a).

24.8 Headache 5991 rather than alacrity. There are some important general features, including associated fever or sudden onset of pain (see Box 24.8.1); these demand attention. Patients with a history of recent-onset head- ache or neurological signs need a positive diagnosis of a benign dis- order or require brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI). Patients with a history of recur- rent headache over a period of 1 year or more, fulfilling International Classification of Headache Disorders (ICHD) criteria for migraine (Box 24.8.2), and with a normal physical examination, have posi- tive brain imaging in only about 1/1000 images. In general, it should be noted that brain tumour is a rare cause of headache, and rarely a cause of isolated long-term histories of headache. A notable ex- ception to the general rules about secondary headache is a pituitary tumour, which can frequently trigger underlying primary headache biology, and should always be considered, especially in the differen- tial diagnosis of trigeminal autonomic cephalalgias (see next). The management of secondary headache is generally self- evident: treatment of the underlying condition, such as an in- fection or mass lesion. An exception is the condition of chronic post-traumatic headache in which pain persists for long periods after head injury. This is an interesting generic problem that may be seen after CNS infection, trauma, both blunt and surgical, intra- cranial bleeds, and other precipitants. Although the syndrome is generally self-limiting up to 3–5 years after the event, treatment of the headache may be required if it is disabling (see ‘Chronic daily headache’, next). Migraine Clinical features Migraine is an episodic brain disorder that affects about 12 to 18% of the population in any one year, and about 45% of females over their lifetime; it is recognized as the most common cause of neurological disability on a worldwide basis. It has been estimated to be the most costly

neurological disorder in the European Union at more than €27 billion per year and its cost to the economy of the United States of America is a staggering US$19.6 billion per year. Migraine presents with a headache generally accompanied by features, such as sensitivity to light, sound, or movement, and often with nausea, or less often vomiting (see Box 24.8.2). None of the features is compul- sory, and indeed, given that the migraine aura, visual disturbances with flashing lights or zigzag lines moving across the fields, or other neurological symptoms, are reported in only about 25% of patients, a high index of suspicion is required to diagnose migraine. In a controlled study of patients presenting to general practitioners with a main complaint of headache over the previous 3 months, mi- graine was the diagnosis on more than 90% of occasions, so a high index of suspicion is well rewarded. A headache diary can often be helpful in making the diagnosis, although in reality the diary usually helps more in assessing disability or recording how often patients use acute attack treatments. Phenotyping remains an essentially clinical art, mixing experience and an understanding of the prob- lems likely to present—good headache histories are taken, not given. In differentiating the two main primary headache syndromes seen in clinical practice, migraine at its most simple level is headache with associated features, and tension-type headache is headache that is featureless; furthermore, most disabling headache coming to the attention of physicians is probably migrainous in biology. By features is meant throbbing pain, or sensitivity to sensory stimuli—visual, auditory, olfactory—or to head movement itself. Frequent migraine If headache with associated features describes migraine attacks, then 'headachy' describes the person who has migraines over a lifetime. It is important to realize that the word migraine can describe both the attacks using standard criteria (see Box 24.8.2) and the disorder itself, which is more than just the attack. People who have migraines (migraineurs) inherit a tendency to have headache that is amplified at various times by their interaction with their environment, the much-discussed 'triggers'. The brain of the migraineur seems more sensitive to sensory stimuli and to change; and this tendency is not- ably amplified in women during their menstrual cycle. People who have a migraine may have headache when they oversleep, when tired, when they skip meals, when they overexert, or when they relax from a stressor. They are less tolerant to change, and part of successful management is to advise them to maintain regularity in their lives in the knowledge of this fluctuating biology. It is this biology that marks migraine and in clinical practice must override the phenotype of individual headaches. Migraine can certainly occur daily, indeed chronic migraine— defined as 15 days or more of headache a month for three months on a migrainous basis, is probably the largest part of the group of headaches known collectively as chronic daily headache that pre- sents to doctors (see next). After making a diagnosis, the second step in the clinical process is to be sure that the disease burden has been captured, how much headache patients have and, more important, what patients cannot do—what is their degree of disability? One can ask the patient directly to get a flavour for this, keep a diary, or get a quick but accurate estimate using the Migraine Disability Assessment Scale (MIDAS), which is well validated and very easy to use in practice (Fig. 24.8.4). Principles of management of migraine After diagnosis the management of migraine begins with an explan- ation of some aspects of the disorder to the patient: • Migraine is an inherited tendency to have headache; this is caused by the patient's genes, therefore it cannot be cured. Box 24.8.2 Simplified diagnostic criteria for migraine Repeated attacks of headache lasting 4–72 h that have these features, normal physical examination, and no other reasonable cause for the headache: • At least two of: — Unilateral pain — Throbbing pain — Aggravation by movement — Moderate or severe intensity • At least one of: — Nausea/vomiting — Photophobia and phonophobia Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society (2004). The

international classification of headache disorders, 2nd edn. Cephalalgia, 24: 1–1604).

section 24 Neurological disorders 5992 • Migraine can be modified and controlled by lifestyle adjustment and the use of medicines. • Migraine is not life-threatening or associated with serious illness, with the exception of women who smoke and use oestrogenic oral contraceptives, but migraine can make life a misery. • Migraine management takes time and cooperation (e.g. when a headache diary has to be collected, or enquiry made about the disability). Nonpharmacological management of migraine This approach aims to help migrainous patients identify things making the problem worse and encourage them to modify these. Patients need to know that the brain sensitivity that is migraine varies, so that the effect of triggers will vary. Patient associations are often very helpful in supporting migraineurs to identify triggers. The knowledge that there is variability will remove considerable frustration on the patient's part, and will ring true to most as they have had the experience. The cru- cial lifestyle advice is to explain to the patient that migraine is a state of brain sensitivity to change. This implies that these people need to regulate their lives: healthy diet, regular exercise, regular sleep pat- terns, avoiding excess caffeine and alcohol, and, as far as practicable, modifying or minimizing changes in stress. The balanced life with fewer highs and lows will benefit most people who have migraines. Preventive treatments of migraine Patients need to understand they have an inherited, noncur- able, but manageable problem. To start a preventive they need to have sufficient disability to wish to take a medicine to reduce the effects of the disease on their life. The basis of considering preventive treatment from a medical viewpoint is a combination of acute at- tack frequency and attack tractability that confers an unacceptable degree of disability. Patients with attacks unresponsive to abortive medications are easily considered for prevention, whereas patients with simply treated attacks may be less obvious candidates. Another important consideration is disease progress. If a patient diary shows a clear trend of an increasing frequency of attacks, it is better to ini- tiate with prevention than wait for the problem to worsen. A simple rule for frequency might be that for one to two headaches a month there is usually no need to start a preventive; for three to four it may be needed but not necessarily; and for five or more per month, prevention should definitely be considered. Options available for treatment are covered in detail in Table 24.8.2 and vary somewhat by country. One problem with preventives is that they have fallen into use for migraine from other indications and often bring unwanted or intolerable side effects. The development of calcitonin gene-related peptide (CGRP) mechanism antagonists delivers specific therapy for migraine, which is well tolerated, and treatment with a clear mech- anism of action. It is not clear how current preventives work, although it seems likely that they modify the brain sensitivity that underlies mi- graine. Another key clinical point is that generally each drug should be started at a low dose and gradually increased to a reasonable max- imum if there is going to be a clinical effect. Relatively little has been done in terms of systematic study of patients with more intractable forms of migraine. Noninvasive neuromodulation approaches are proving helpful. Interestingly, functional imaging studies show that central processing of pain signals in migraine in the thalamus may be modified by therapy. This is an exciting and developing area. Acute attack therapies of migraine Acute attack treatments for migraine can be usefully divided into non-disease-specific treatments (analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs)) and disease-specific treat- ments (ergot-related compounds and triptans). It is important to be aware that most acute attack medications seem to have a propensity to aggravate headache frequency and can induce a state of refrac- tory daily or near-daily headache—medication-overuse headache. As evidence is gathered, this seems to occur in patients with mi- graine: either a previous clear history or a family or

personal his- tory of headachiness. Codeine-containing compound analgesics are particularly troublesome when available in over-the-counter pre- parations. Patients with migraine should be advised to avoid taking acute attack medicines on more than 2 days a week. A proportion of patients who stop taking regular analgesics will have substantial improvement in their headache with a reduction in frequency; how- ever, for some it will not make any difference. It is crucial to empha- size to the patient that standard preventive medications often simply do not work in the presence of regular analgesic use. Treatment strategies Given the array of options to control an acute attack of migraine, how does one start? The simplest approach to treatment has been described as ‘stepped care’. In this model all patients are treated, assuming no contraindications, with the simplest treatment, such as aspirin 900 mg or paracetamol 1000 mg with an antiemetic. Aspirin is an effective strategy, has been proven so in double-blind INSTRUCTIONS: Please answer the following questions about ALL your headaches you have had over the last 3 months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months (Please refer to the calendar below, if necessary)

1. On how many days in the last 3 months did you miss work or school because of your headaches? ..... ||| days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches (Do not include days you counted

in question 1 where you missed work or school)? ..... ||| days 3. On how many days in the last 3 months did you not do household work because of your headaches? ..... ||| days 4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches (Do not include days you counted

in question 3 where you did not do household work)? ..... ||| days 5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? ..... ||| days

A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than one day, count each day) ..... ||| days

B. On a scale of 0–10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain as bad as it can be) ..... ||| Version 3.0 © Innovative Medical Research 1997 Fig. 24.8.4 Migraine Disability Assessment Score (MIDAS) questionnaire.

24.8 Headache 5993 Table 24.8.2 Some preventive treatments in migrainea Drug Dose Selected side effects Pizotifen 0.5–2 mg daily Weight gain Drowsiness β-Blocker Propranolol 40–120 mg twice daily Reduced energy Tiredness Postural symptoms Contraindicated in asthma Metoprolol 25–100 mg twice daily Tricyclics Amitriptyline Dosulepin (dothiepin) Nortriptyline 25–75 mg at night Drowsiness Note: some patients are very sensitive and may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required Venlafaxine 75–150 mg Drowsiness, urinary retention, arrhythmias Anticonvulsants Valproate 400–600 mg twice daily Drowsiness Weight gain Tremor Hair loss Fetal abnormalities Haematological or liver abnormalities Other

mechanism Topiramate 50–200 mg/day Paraesthesiae Cognitive dysfunction Weight loss Care with a family history of glaucoma Nephrolithiasis Candesartan 4–16 mg daily Dizziness Flunarizine 5–15 mg daily Drowsiness Weight gain Depression Parkinsonism Calcitonin gene-related peptide (CGRP) mechanism blockers erenumab 70 to 140 mg monthly s/c Mild injection site reactions fremanezumab 225 mg monthly or 675 mg quarterly s/c Mild injection site reactions Neuromodulation Single pulse transcranial magnetic stimulation 2 to 8 pulses two to three times daily Transcutaneous supraorbital nerve stimulation Twenty minutes daily galcanezumab 120 to 240 mg monthly s/c Mild injection site reactions Botulinum toxin type Ad 155 units in 31 sites Neck pain Muscle weakness Single studiesb Lisinopril Neutriceuticalsc Riboflavin Coenzyme Q10 Feverfew 20 mg daily 400 mg daily 100 mg three times daily 6.25 mg three times daily Cough Gastrointestinal upset No convincing controlled evidence Verapamil Gabapentin studies shown to have been falsely reported Controlled trials to demonstrate no effect Nimodipine Clonidine SSRIs: fluoxetine a Commonly used preventives are listed with reasonable doses and common side effects. The local national formulary should be consulted for detailed information. b Compounds not widely considered mainstream but with a positive randomized control trial against placebo. c Nonpharmaceuticals with at least one positive randomized controlled trial against placebo. d Using the PREEMPT strategy (Dodick et al., 2010—see Further reading) and only proven in chronic migraine. SSRI, selective serotonin reuptake inhibitor.

section 24 Neurological disorders 5994 controlled clinical trials, and is best used in its most soluble formula- tions. The alternative is a strategy known as ‘stratified care’, by which the physician determines, or stratifies, treatment at the start, based on the likelihood of response to levels of care. An intermediate op- tion may be described as stratified care by attack. This is what many headache authorities suggest, and what patients often do when they have the option: they use simpler options for their less severe attacks, relying on more potent options when their attacks or circumstances demand them (Table 24.8.3). Nonspecific acute migraine attack treatments As simple drugs, such as aspirin and paracetamol, are cheap and can be effective, dosages should be adequate and the addition of domperidone (10 mg orally), metoclopramide (10 mg orally) or ondansetron 4 mg can be very helpful. NSAIDs can very useful when tolerated. Their success is often limited by inappropriate dosing, and adequate doses of naproxen 500–1000 mg orally or rectally, with an antiemetic, ibuprofen 400 to 800 mg orally, or tolfenamic acid 200 mg orally can be extremely effective. Specific acute migraine attack treatments When simple analgesic measures fail or more aggressive treatment is required, the specific antimigraine treatments are required (Table 24.8.4). Although ergotamine remains a useful treatment, it can no longer be considered the treatment of choice in acute migraine. There are particular situations in which ergotamine is very helpful, but its use must be carefully controlled as ergotamine overuse produces dreadful headache in addition to a host of vascular problems. The triptans, serotonin 5HT1B/1D-receptor agonists, have revolutionized the life of many patients with migraine and are clearly the most powerful option available to stop a migraine attack. They can be rationally applied by considering their pharmacological, physicochemical, and pharmaco- kinetic features, as well as the formulations that are available. Recent data suggest that combining a triptan with an NSAID can improve efficacy and reduce headache recurrence. Neuromodulation approaches to migraine Neuromodulation approaches to migraine have now emerged, with single pulse transcranial magnetic stimulation (TMS) being proven with a randomized placebo-controlled trial. It is a safe, effective strategy that works for acute treatment and may have a preventive role. Its proper place in management is yet to be de- termined, but its simplicity suggests a potentially major shift in

treatment approach because neuromodulation such occipital nerve stimulation has hitherto been aimed at medically refrac- tory patients using invasive techniques. Other techniques such as supraorbital nerve and noninvasive vagal nerve stimulation are being studied. Table 24.8.3 Oral acute migraine treatments Nonspecific treatmentsa Specific treatments Aspirin 900 mg Ergot derivatives Paracetamol [acetaminopheno] 1000 mg Ergotamine 1–2 mg NSAIDs Triptans Naproxen 500–1000 mg Sumatriptan 50 or 100 mg Ibuprofen 400–800 mg Naratriptan 2.5 mg Tolfenamic acid 200 mg Rizatriptan 10 mg Diclofenac K 50 mg Zolmitriptan 2.5 or 5 mg Eletriptan 40 or 80 mg Almotriptan 12.5 mg Frovatriptan 2.5 mg a Often used with antiemetic/prokinetics, such as domperidone 10 mg (care in patients using medicines altering the QT interval), metoclopramide 10 mg or ondansetron 4 mg. Table 24.8.4 Stratification of acute migraine treatments Clinical situation Treatment options Failed analgesics/ NSAIDS First tier Sumatriptan 50 mg or 100 mg orally Almotriptan 12.5 mg orally Rizatriptan 10 mg orally Eletriptan 40 mg orally Zolmitriptan 2.5 mg orally Slower effect/better tolerability Naratriptan 2.5 mg orally Frovatriptan 2.5 mg orally Single pulse transcranial magnetic stimulation Infrequent headache Ergotamine 1–2 mg orally Dihydroergotamine nasal spray 2 mg Dihydroergotamine 0.5 mg by inhalation Early nausea or difficulties taking tablets Zolmitriptan 2.5 mg by dissolving wafer or nasal spray Sumatriptan 20 mg nasal spray Rizatriptan 10 mg MLT wafer Sumatriptan transdermal patch Headache recurrence Ergotamine 2 mg (most effective rectally/usually with caffeine) Naratriptan 2.5 mg orally Almotriptan 12.5 mg orally Eletriptan 40 mg Dihydroergotamine 0.5 mg by inhalation Tolerating acute treatments poorly Naratriptan 2.5 mg Almotriptan 12.5 mg Single pulse transcranial magnetic stimulation Early vomiting Zolmitriptan 5 mg nasal spray Sumatriptan 25 mg rectally Sumatriptan 6 mg subcutaneously Menstrually related headache Prevention Ergotamine orally at night Oestrogen patch Treatment Triptans Dihydroergotamine nasal spray Very rapidly developing symptoms Zolmitriptan 5 mg nasal spray Sumatriptan 6 mg subcutaneously, needle or needle-free Dihydroergotamine 1 mg intramuscularly

 Tension-type headache Clinical features As its name suggests, tension-type headache (TTH) is the least understood primary headache form. TTH is diagnosed often and, although the phenotype is common, much of the disabling headache that goes under the name TTH is likely to be migrainous in terms of its biology. TTH has two forms—episodic TTH, where attacks occur on fewer than 15 days a month, and chronic TTH, where attacks, on average over time, are seen on 15 days or more a month. The latter is part of the broader clinical syndrome of chronic daily headache, but these terms are not equal. TTH has been defined by the International Headache Society for both its episodic and chronic forms, although the admixture of symptoms allowed has consistency problems. A useful clinical ap- proach is to diagnose TTH when the headache is completely fea- tureless: no nausea, no vomiting, no photophobia, no phonophobia, no osmophobia, no throbbing, and no aggravation with movement. Such an approach neatly divides migraine, which has one or more of these features and is the main differential diagnosis from TTH. Pathophysiology The pathophysiology of TTH is very poorly understood. This results from the fact that the name implies to most that it is a product of nervous tension, for which there is no clear evidence, and the defin- itions employed have undoubtedly admitted patients with migraine to the studies. Moreover, the concept that TTH in some way involves muscle contraction is incorrect because the evidence is that muscle contraction is no more likely than it is in migraine. It seems likely that TTH is due to a primary disorder of CNS pain modulation alone in contrast with migraine, which is a more generalized dis- turbance of sensory modulation. Management Adopting the clinical approach to TTH outlined here earlier results in diagnosing a headache form that is usually

less disabling, more often described by patients as irritating. Its episodic form is generally amenable to simple analgesics, paracetamol, aspirin, or NSAIDs, which can be purchased over the counter. There are clear clinical studies to dem- onstrate that triptans in TTH alone are not helpful, although, germane to the previous discussion, triptans are effective in TTH where the pa- tient also has migraine. For chronic TTH, amitriptyline is the only treatment with a clear evidence base; the other tricylic antidepressants, selective serotonin reuptake inhibitors, or benzodiazepines have not been shown in controlled trials to be effective. Similarly, there is no controlled evidence for the use of electromyography (EMG) biofeed- back, relaxation therapy, or acupuncture. Botulinum toxin has been shown reasonably clearly to be ineffective. Stress management has been shown to be an effective approach in a controlled trial. Trigeminal–autonomic cephalalgias Cluster headache Cluster headache is a rare form of primary headache with a population frequency of 0.1%. It is covered in specialist books. As a clinical anchor, it is about as common as multiple sclerosis in the United Kingdom, and must be regarded as a disorder best managed by neurologists or headache specialists. It is perhaps the most painful condition of humans; in the cohort of more than 1000 patients seen by the author not a single one has had a more painful experience, including childbirth, multiple fractures of the limbs and renal stones. It is one of a group of conditions known now as trigeminal–autonomic cephalalgias (TACs), whose clinical Table 24.8.5 Cluster headache, other trigeminal–autonomic cephalalgias (TACs), and short-lasting headaches TACsa Other short-lasting headaches Cluster headache Primary stabbing headache Paroxysmal hemicranias Trigeminal neuralgia SUNCT/SUNAb syndrome Primary cough headache Primary exercise headache Cold stimulus headache External pressure headache Nummular headache Hemicrania continua Primary sex headache Hypnic headache a Beware of pituitary tumour-related headache in the differential diagnosis of these TACs. b Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features. Box 24.8.3 Diagnostic criteria for cluster headache Diagnostic criteria A At least five attacks fulfilling B–D B Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min if untreated C Headache is accompanied by at least one of the following: (1) ipsilateral conjunctival injection and/or lacrimation (2) ipsilateral nasal congestion and/or rhinorrhoea (3) ipsilateral eyelid oedema (4) forehead and facial sweating (5) ipsilateral forehead and facial sweating (6) ipsilateral miosis and/or ptosis or (7) a sense of restlessness or agitation D Attacks have a frequency from one every other day to eight per day E Not attributed to another disorder Episodic cluster headache Description: occurs in periods lasting 7 days to 1 year separated by pain- free periods lasting 1 month or more Diagnostic criteria A All fulfilling criteria A–E of 3.1 B At least two cluster periods lasting from 7 to 365 days and separated by pain-free remissions of ≥3 month Chronic cluster headache Description: attacks occur for more than 1 year without remission or with remissions lasting less than 3 month Diagnostic criteria A All alphabetical headings of 3.1 B Attacks recur over more than 1 year without remission periods or with remission periods less than 1 month Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society (2018). The international classification of headache disorders, 3rd edn. Cephalalgia, 38:1–211).

section 24 Neurological disorders 5996 signature is lateralization of symptoms, and thus needs to be differ- entiated from other TACs and the short-lasting headaches without cranial autonomic symptoms, such as lacrimation or conjunctival injection (Table 24.8.5). The core features of cluster headache are lateralized symptoms and signs, and periodicity, be it circadian or in terms of active and inactive bouts over weeks and months (Box 24.8.3). The typical cluster headache patient is

male, with a 3:1 predominance, who has bouts of one to two attacks of relatively short duration unilateral pain every day for 8–10 weeks a year. They are generally perfectly well in between. Patients with cluster headache tend to move about during attacks, pacing, rocking, or even rubbing their head for relief. The pain is usually retro-orbital, boring, and very severe. It is asso- ciated with ipsilateral symptoms of cranial (parasympathetic) auto- nomic activation: a red or watering eye, running or blocked nose, or cranial sympathetic dysfunction—eyelid droop. Cluster headache is likely to be a disorder involving neurons in or around the central pacemaker regions of the posterior hypothalamic grey matter (see Fig. 24.8.2). Although cluster headache patients may also experi- ence nausea, photophobia, and phonophobia, the last two, particu- larly photophobia, tend to be ipsilateral to the pain only in TACs. The TACs—cluster headache, paroxysmal hemicrania, SUNCT syndrome, and hemicrania continua—present a distinct group to be differentiated particularly from short-lasting headaches that do not have prominent cranial autonomic syndromes, notably trigem- inal neuralgia, idiopathic (primary) stabbing headache, and hypnic headache. By determining the cycling pattern, length of attack, fre- quency of attack, and timing of the attacks, most patients can be usefully classified. The importance of clinical classification of this group is threefold: first, the clinical phenotype determines the likely secondary causes that must be considered and appropriate investi- gations ordered; second, the appropriate classification gives clarity to the patient with a clear diagnosis and allows the physician to draw on available literature to comment on natural history; and third, the correct diagnosis determines therapy that can be very different in these conditions, being very good if the diagnosis is correct but largely ineffective if it is not (Table 24.8.6). Managing cluster headache Cluster headache is managed using acute attack treatments and pre- ventive agents. Acute attack treatments are usually required by all cluster headache patients at some time, whereas preventives can seem almost life-saving for the patients with chronic cluster head- ache, and are often needed to shorten the active periods in patients with the episodic form of the disorder. Preventive treatments The options for preventive treatment in cluster headache depend on the bout length (Table 24.8.7). Patients with short bouts require medicines that act quickly but will not necessarily be taken for long periods, whereas those with long bouts or indeed those with chronic cluster headache require safe, effective medicines that can be taken for long periods. Verapamil is now widely considered as the first- line preventive treatment when the bout is prolonged, or in chronic cluster headache. By contrast, limited courses of oral corticosteroids or a greater occipital nerve injection can be very useful strategies when the bout is relatively short. Verapamil has been suggested as a useful option for the last decade and compares favourably with lithium or topiramate. What has clearly emerged from clinical practice is the need to use higher doses than had initially been considered and certainly higher than those used routinely in cardiological indications. Although most patients will start on doses as low as 40 to 80 mg twice daily, doses up to 960 mg daily are often re- quired. Side effects, such as gingival hyperplasia, constipation, and leg swelling, are recognized, as are cardiac dysrhythmias. Verapamil can cause heart block by slowing conduction in the atrioventricular (AV) node, monitored clinically by the PR interval on the electrocardiogram (ECG). Given that the effects on the AV node take up to 10 days to manifest, 2-week intervals are recommended between dose changes on the first exposure, with ECGs before the next escalation, and routine six-monthly ECGs after the dose has been established. Acute attack treatment Cluster headache attacks often peak rapidly and thus require a treat- ment with quick onset. Many patients with acute cluster headache Table 24.8.6 Differential diagnosis of short-lasting headaches Feature Cluster headache Paroxysmal hemicrania SUNCT/SUNAa Primary stabbing headache Trigeminal neuralgiaa Hypnic headache Gender M > F 3: 1 F = M 1.5 M to 1 F F > M F > M M = F Pain Type Boring/ throbbing Boring/throbbing

Stabbing/throbbing Stabbing Stabbing Throbbing Severity Very severe Very severe Very severe Severe Very severe Moderate Cranial location Any Any Any Any V2/V3 >V1 Generalized Duration 15–180 min 2–30 min 15–600 s <10 s <5 s 15–30 min Frequency 1–8/day 1–40/day 1/day–30/h Any Any 1–3/night Autonomic + + + – – – Alcohol + One-third – – – – Cutaneous trigger to attacks – – + – + – Indometacin – + – + – – SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms. a SUNCT/SUNA generally has no refractory period to trigger additional attacks, although this is a very common feature of trigeminal neuralgia.

24.8 Headache 5997 respond very well to treatment with oxygen inhalation. This should be given as 100% oxygen at 10 to 12 litres/min for 15–20 min. It is important to have a high flow and high oxygen content. Injectable sumatriptan 6 mg is effective, rapid in onset, and has no evidence of tachyphylaxis. Sumatriptan 20 mg and zolmitriptan 5 mg nasal sprays are effective in acute cluster headache in controlled trials, and offer a useful option. Sumatriptan is not effective when given pre-emptively as 100 mg orally three times daily, and there is no evidence that it is useful when used orally in the acute treatment of cluster headache; indeed it can be associated with medication-overuse headache prob- lems. Most recently, two sham-controlled randomised studies dem- onstrated that noninvasive vagal nerve stimulation (nVNS) is effective for the acute treatment of attacks in episodic cluster headache. Surgical treatment The surgical treatment of cluster headache has been completely revolutionized with the introduction of neurostimulation therapies. Surgical treatment of cluster headache is reserved for the most refrac- tory patients, typically with chronic cluster headache. Destructive procedures, such as sphenopalatinectomy (pterygopalatinectomy) or radiofrequency lesions of the trigeminal ganglion, have been used: the former with no clear effects, and the latter being helpful, but often at significant cost, including ocular complications or an- aesthesia dolorosa. Trigeminal rhizotomy has also been employed, with all the complications of radiofrequency lesions and the occa- sional death. Destructive procedures have no place in the modern treatment of chronic cluster headache. Driven by functional imaging work describing activations in the posterior hypothalamic region, deep brain stimulation approaches in the same region seem to be highly effective in about two-thirds of medically refractory patients, although they are hazardous, with risk of death. Occipital nerve stimulation has proved a frustrating approach to management of in- tractable chronic cluster headache with technical issues and a lack of any controlled trial evidence. Sphenopalatine (pterygopalatine) ganglion stimulation now has one randomized sham-stimulation controlled trial and represents a logical and very promising ap- proach. Noninvasive vagal nerve stimulation is being studied and its early results are also very promising. Paroxysmal hemicrania Sjaastad and Dale (1976) first reported eight cases of a frequent uni- lateral severe but short-lasting headache without remission coining the term chronic paroxysmal hemicrania. In a large series Cittadini and colleagues (2008) reported a daily frequency of attacks varying from 2 to 50 with a median of 9, and with pain persisting for a me- dian of 19 minutes. The site and associated autonomic phenomena were similar to cluster headache, and the attacks of chronic parox- ysmal hemicrania were suppressed completely by indomethacin. The essential features of paroxysmal hemicrania that we have seen from a substantial cohort of patients are: • unilateral, very severe pain • short-lasting attacks, typically 20 min in length • very frequent attacks (usually >5/day with a mean of 10) • marked autonomic features ipsilateral to the pain • robust, quick (<72 h), excellent response to indomethacin The pathophysiology of paroxysmal hemicrania is marked by acti- vations on PET (positron emission tomography) in the contralateral posterior hypothalamic region and

contralateral ventral midbrain. The posterior hypothalamic region activity is shared with cluster headache, SUNCT, and hemicrania continua, whereas the ventral midbrain activity is only seen in hemicrania continua, which re- markably is also an indometacin-sensitive primary headache. The therapy of paroxysmal hemicrania may be complicated by gastrointestinal side effects seen with indometacin, in which topiramate and noninvasive vagal nerve stimulation (nVNS) may be helpful. Secondary paroxysmal hemicrania is more likely if the pa- tient requires high doses (>200 mg/day) of indometacin and raised cerebrospinal fluid pressure should be suspected in apparent bilat- eral paroxysmal hemicrania. It is worth noting that indometacin reduces cerebrospinal fluid pressure by an unknown mechanism. Recent evidence suggests the mechanism of action of indometacin is via nitric oxide synthase. It is appropriate to image patients, with MRI if practical, when a diagnosis of paroxysmal hemicrania is being considered. SUNCT/SUNA Sjaastad and colleagues (1989) reported three male patients whose brief attacks of pain in and around one eye were associated with sudden conjunctival injection and other autonomic features of cluster headache. In a large series attacks Cohen and colleagues (2006) reported three attack phenotypes: stabs, groups of stabs, or a saw-tooth pattern. They were not abolished by indomethacin. Brain imaging has suggested that they share with cluster headache and par- oxysmal hemicrania the feature on activation studies of involvement of the posterior hypothalamic region. Of the patients recognized with this problem, males dominate slightly and the paroxysms of pain may last between 5 and 300 s, although longer, duller interictal pains are recognized. In SUNCT conjunctival injection and tearing are often obvious. If one of either conjunctival injection or tearing is absent, or nei- ther is present but another cranial autonomic symptom is seen, the term SUNA is used. The key clinical features of SUNCT/SUNA are that the attacks can be triggered with no refractory period to triggering. The latter serves as a very useful distinction between SUNCT/SUNA and trigeminal neuralgia. SUNCT/SUNA can be treated very frequently with lamotrigine, and if that is unhelpful topiramate or gabapentin. Carbamazepine often has a useful but incomplete effect. Given what has been reported, cranial MRI with pituitary and posterior fossa views is highly recommended when SUNCT/SUNA is considered as a diagnosis.
Table 24.8.7 Preventive management of cluster headache Short-term prevention (episodic cluster headache) Long-term prevention (episodic cluster headache and prolonged chronic cluster headache) Prednisolone Verapamil Daily nocturnal frovatriptan Lithium Topiramate Greater occipital nerve injection Melatonin ? Gabapentin ? Noninvasive vagal nerve stimulation Sphenopalatine ganglion stimulation ? = unproven but promising.

 Hemicrania continua Two patients were initially reported with this syndrome, a woman aged 63 years and a man of 53, who developed unilateral headache without obvious cause. Both patients were relieved completely by indometacin whereas other NSAIDs were of little or no benefit. Cittadini and colleagues (2010) reported 39 patients with strictly lat- eralized headache and cranial autonomic symptoms. When present photophobia and phonophobia were ipsilateral to pain in nearly one- half. The following are the essential features of hemicrania continua: • Unilateral pain • Pain is continuous but with exacerbations that may be severe • Complete resolution of pain with indometacin • Exacerbations may be associated with cranial autonomic features Apart from analgesic overuse as an aggravating factor, and a re- port in an HIV-infected patient, the status of secondary hemicrania continua is unclear. Cittadini and colleagues (2010) proposed a placebo-controlled Indotest with 100 or 200 mg of intramuscular indomethacin. Used in conjunction with PET, it has been shown that there is activation of the contralateral posterior hypothalamic region and ipsilateral dorsal rostral pons in association with the headache of hemicrania continua, as well as activation of the ipsi- lateral ventrolateral

midbrain. The alternative is a trial of oral indo- methacin, initially 25 mg three times daily, then 50 mg three times daily, and 75 mg three times daily. One should allow up to 2 weeks for any dose to have a useful effect. After the headache is controlled the dose can usually be reduced yet control maintained. Acute treat- ment with sumatriptan has been employed and reported to be of no benefit. Cyclooxygenase II (COX-II) antagonists seem effective, al- though undesirable now, and topiramate is helpful in some patients, as is and noninvasive vagal nerve stimulation (nVNS) and greater occipital nerve injection. Other primary headaches Primary cough headache Sharp pain in the head on coughing, sneezing, straining, laughing, or stooping has long been regarded as a symptom of organic intra- cranial disease, commonly associated with obstruction of the cerebrospinal fluid pathways. The presence of an Arnold–Chiari malformation or any lesion causing obstruction of cerebrospinal fluid pathways or displacing cerebral structures must be excluded before cough headache is assumed to be benign. Cerebral aneurysm, carotid stenosis, and vertebrabasilar disease may also present with cough or exercise headache as the initial symptom. The term 'be- nign Valsalva's manoeuvre-related headache' covers the headaches provoked by coughing, straining, or stooping but 'cough headache' is more succinct and so widely used that it is unlikely to be displaced. The following are the essential clinical features of primary cough headache: • Bilateral headache of sudden onset, lasting seconds to 2 h • Brought on by cough, strain, or other Valsalva manoeuvre • May be prevented by avoiding coughing • Diagnosed only after structural lesions, such as posterior fossa tumour, have been excluded by neuroimaging Indomethacin is the medical treatment of choice in cough head- ache. Raskin followed up an observation of Sir Charles Symonds reporting that some patients with cough headache are relieved by lumbar puncture. This is a simple option when compared with pro- longed use of indomethacin. The mechanism of this response re- mains unclear. Primary exercise headache The relationship of this form of headache to cough headache is un- clear and certainly much is shared. Indeed the relationship to mi- graine also requires delineation. The following are the clinical features: • Pain specifically brought on by strenuous physical exercise • Lasting less than 48 hours • Prevented by avoiding excessive exertion, particularly in hot weather or at high altitude. The acute onset of headache with straining and breath-holding, as in weightlifter's headache, may be explained by acute venous dis- tension. The development of headache after sustained exertion, particularly on a hot day, is more difficult to understand. Anginal pain may be referred to the head, probably by central connections of vagal afferents, and may present as exercise headache, so-called cardiac cephalgia. The link to exercise is the important clinical clue. Phaeochromocytoma may occasionally be responsible for exercise headache. Intracranial lesions or stenosis of the carotid arteries may have to be excluded as discussed for benign cough headache. Headache may be precipitated by any form of exercise. The most obvious form of treatment is to take exercise gradually and pro- gressively whenever possible. Indomethacin at daily doses varying from 25 to 150 mg is generally very effective in exercise head- ache. Indomethacin 50 mg, ergotamine tartrate 1–2 mg orally, or dihydroergotamine by nasal spray, 30 to 45 min before exercise are useful preventive measures. Primary sex headache Sex headache may be precipitated by masturbation or coitus and usually starts as a dull bilateral ache while sexual excitement in- creases, suddenly becoming intense at orgasm. The term 'orgasmic cephalgia' is not accurate because not all sex headache requires orgasm. Two types of primary sex headache are recognized in practice: a dull ache in the head and neck that intensifies as sexual excitement increases, and a sudden severe ('explosive') headache occurring at orgasm, although this distinction has no known physiological basis. Low cerebrospinal fluid volume headache may also be precipitated by sexual activity and is considered as a form of new daily persistent headache (see next). The following are the essential clinical features of a sex

headache: • Precipitation by sexual excitement • Bilateral at onset • Severe headache may be present from one minute to 24 h • Prevented or eased by ceasing sexual activity before orgasm Headaches developing at the time of orgasm are not always benign, and consideration of a diagnosis of subarachnoid headache is es- sential. Sex headache affects men more often than women and may occur at any time during the years of sexual activity. It may develop

24.8 Headache 5999 on several occasions in succession, and then not trouble the patient again, despite no obvious change in sexual technique. In patients who stop sexual activity when the headache is first noticed it may subside within a period of 5 min to 2 h, and it is recognized that more frequent orgasm can aggravate established sex headache. About one-half of the patients with sex headache have a history of exercise headache, but there is no excess of cough headache in patients with sex headache. In about 50% of patients, sex headache will settle in 6 months. Migraine is reported in about 25% of patients with sex headache. Primary sex headaches are usually irregular and infrequent in oc- currence, so management can often be limited to reassurance and advice about ceasing sexual activity if a milder, warning headache develops. When the condition recurs regularly or frequently, it can be prevented by the administration of propranolol; the dosage required varies from 40 mg to 200 mg daily. An alternative is the calcium channel blocking agent diltiazem 60 mg three times daily, which this author finds particularly useful in such patients. Frovatriptan 2.5 mg or indomethacin (25–50 mg) taken about 30–60 min before sexual activity can also be helpful. Primary thunderclap headache Sudden-onset severe headache may occur in the absence of sexual activity; the differential diagnosis includes the sentinel bleed of an intracranial aneurysm, cervicocephalic arterial dissection, re- versible cerebral vasoconstriction syndrome, and cerebral venous thrombosis. Headaches of explosive onset may also be caused by the ingestion of sympathomimetic drugs or tyramine-containing foods in a patient who is taking monoamine oxidase inhibitors, and can also be a symptom of a phaeochromocytoma. Whether thun- derclap headache can be the presentation of an unruptured cere- bral aneurysm is debated. Day and Raskin (1986) reported on a woman with three episodes of sudden-onset, very severe headache who was found to have an unruptured aneurysm of the internal ca- rotid artery, with adjacent areas of segmental vasospasm. In the ab- sence of a CT scan or cerebrospinal fluid evidence of subarachnoid haemorrhage, studies indicate that such patients do very well, and there indeed seems to be a form of benign or primary thunderclap headache. Wijdicks et al. (1988) followed up 71 patients whose CT scans and cerebrospinal fluid findings were negative for an average of 3.3 years: 12 patients had further such headaches and 31 (44%) later had regular episodes of migraine or tension-type headache. Factors identified as precipitating the headache were sexual intercourse in 3 cases, coughing in 4, and exertion in 12, while the remainder had no obvious cause. A history of hypertension was found in 11 and of previous headache in 22. Markus (1991) compared the presenta- tion of 37 patients with subarachnoid haemorrhage and 189 with a similar thunderclap headache and normal cerebrospinal fluid exam- ination, and could not discern any characteristic to distinguish the two conditions. Investigation of any sudden-onset severe headache, be it in the context of sexual excitement or isolated thunderclap headache, should be driven by the clinical context. The first presentation should be vigorously investigated with CT and cerebrospinal fluid examination, and where possible MRI/MR venography/MR angiog- raphy. Bearing in mind the entity of reversible cerebral vasoconstric- tion syndrome, which may be seen in apparent primary thunderclap headache without there being an intracranial aneurysm, caution in interpretation of the findings is crucial. Cold stimulus headache It has become recognized that cold stimuli applied either externally or by ingestion can provoke

headache. For external cold stimulus headache the pain is generalized, de- velops during exposure to lowered temperature, and resolves with the removal of the stimulus. For headache associated with ingestion or inhalation of a cold stimulus there is typically a short-lasting frontal or temporal pain as the cooling substance passes over the palate or posterior pharyn- geal wall, sometimes called ice cream headache. Typically, the pain resolves in 10 min after cessation of the stimulus. The phenomenon has previously been termed ‘ice cream headache’ and is often seen in migraineurs. External pressure headache Headache can arise from compression or traction on pericranial structures as may be seen, for example, with swimmer’s goggles or long hair in a ponytail. It is bought on by the pressure, distributes around the pressure or traction, and is relieved within an hour of relief of the compression or traction. Primary stabbing headache Short-lived jabs of pain, defined by the International classification of headache disorders as primary stabbing headache, are well docu- mented in association with most types of primary headache. The following are the essential clinical features: • Pain confined to the head, although rarely is it facial • Stabbing pain lasting from 1 to 10 seconds and occurring as a single stab or a series of stabs • Recurring at irregular intervals (hours to days). These pains have been called ice-pick pains or jabs and jolts. They generally respond to indometacin 25–50 mg two to three times daily. The symptoms tend to wax and wane and after a period of control on indometacin it is appropriate to withdraw treatment and observe the outcome. Most patients will not want treatment when the nature of the problem is explained and they are reassured that the attacks are not sinister in any way. Nummular headache The pain occurs in a small circumscribed area of the head without any underlying lesion. The area of pain is generally round or ellip- tical and of fixed size and shape, typically 1–6 cm in diameter. The pain can be continuous or may come and go. There is no clear patho- physiology, and sensory change including tenderness, dysaesthesia, or allodynia are often reported. The treatments are typically tricylics or anticonvulsants as are used in migraine. Hypnic headache This syndrome was first described by Raskin in patients aged from 67 to 84 who had headache of a moderately severe nature which typically came on a few hours after going to sleep. A large series in imaging has suggested structural changes in the posterior hypo- thalamic region with loss of grey matter volume. These headaches last from 15 to 30 min, are typically generalized, although may be

section 24 Neurological disorders 6000 unilateral, and can be throbbing. Patients may report falling back to sleep only to be awoken by a further attack a few hours later, with up to three repetitions of this pattern over the night. In Dodick’s series of 19 patients, 16 (84%) were female and the mean age at onset was 61 ± 9 years. Headaches were bilateral in two-thirds and unilateral in one-third, and in 80% of cases mild or moderate. Three patients reported similar headaches when falling asleep during the day. None had photophobia or phonophobia and nausea is unusual. Patients with this form of headache generally respond to a bed- time dose of lithium carbonate (200–600 mg); in those who do not tolerate this, verapamil at bedtime may be alternative strategies. Remarkably one to two cups of coffee or caffeine 60 mg orally at bed- time can be very helpful. This is a simple approach that is effective in about one-third of patients, and should be tried in each patient first. An important secondary cause of hypnic headache is hypertension, which should be carefully pursued and appropriately investigated as treatment of the blood pressure will arrest the headache problem. Chronic daily headache Each of the aforementioned primary headache forms can occur very frequently. When a patient experiences headache on 15 days or more a month one can apply the broad diagnosis of chronic daily headache. Chronic daily headache is not one thing but a collection of very different problems with different management

strategies. Crucially not all daily headache is simply TTH (Table 24.8.8). This is a very common clinical misconception in headache, confusing the clinical phenotype with the headache biotype. Population-based estimates of daily headache are remarkable, demonstrating that about 5% of Western populations have daily or almost daily head- ache. Daily headache may again be primary or secondary, and it seems clinically useful to consider the possibilities in this way when making management decisions (Table 24.8.8). It should be said that population-based studies bear out clinical practice in that a large group of refractory daily headache patients overuse various over-the-counter preparations. Chronic migraine Although it is widely accepted that some of the primary head- aches, tension-type headache, cluster headache, and paroxysmal hemicrania, have chronic varieties, this question seems to have be- come unnecessarily troublesome for migraine. The concept behind chronic migraine is that some patients who inherit a migrainous biology end up with daily headache. The typical patient will have daily dull, nonspecific head pain, punctuated by more severe attacks that would often, in isolation, fulfil standard criteria for migraine. In headache specialty clinics this group is dominant, with about 90% of patients in referral headache clinics having chronic migraine, usu- ally with medication overuse. It could be suggested that they have a biologically more difficult problem and this is the basis for their overrepresentation in referral centres, although it is equally possible that they are simply more disabled. If one applies the concepts outlined for TTH (see earlier) then the diagnosis of chronic TTH (CTTH) is made when the patient has 15 days or more a month of entirely featureless generalized dull or pressure-like pain. When any of the attacks on some days have migrainous features—nausea, photophobia, phonophobia, throbbing, or aggravation with movement—then chronic migraine is more likely to be the diagnosis. Formally the current International Classification of Headache Disorders seeks eight such days a month. Clearly both chronic migraine and CTTH exist. Moreover, some pa- tients must simply have coexisting CTTH and episodic migraine; however, it is simply impossible on clinical or other grounds to de- termine whom they are in biological terms. The approach outlined here may overdiagnose chronic migraine, taking that to be a bio- logical entity, and underdiagnose the coexistence of CTTH and epi- sodic migraine. The converse would be true—if one diagnoses them all as CTTH and episodic migraine then chronic migraine is missed. In clinical practice the concept of chronic migraine is particularly helpful. Given that the lifestyle advice is identical for both TTH and migraine, and that the range of therapeutic options for preventive treatment in migraine is so much greater, the clinician loses abso- lutely nothing diagnosing chronic migraine, and the patient has much to gain. For research there are other imperatives. Management The management of daily headache can be very rewarding. Most pa- tients overusing analgesics respond very sensibly when the problem is explained. The keys to managing daily headache are: • Exclude treatable causes (see Table 24.8.8) • Obtain a clear analgesic history • Make a diagnosis of the primary headache type involved Medication overuse Medication overuse is defined as consuming an acute attack therapy on 10 days or more per month, except for paracetamol [acetamino- phen] where 15 days is allowed under current guidance. It is es- sential that analgesic overuse be reduced and eliminated if one is to see the underlying headache phenotype and start to manage the

Table 24.8.8 Classification of chronic daily headache Primary Secondary

> 4 h daily <4 h daily Chronic migrainea Chronic cluster headacheb Post-traumatic Head injury Iatrogenic Postinfectious Chronic tension-type headachea Chronic paroxysmal hemicrania Inflammatory, such as giant cell arteritis Sarcoidosis

> Behçet’s syndrome Hemicrania continuaa SUNCT Chronic CNS infection New daily persistent headachea Hypnic headache Substance abuse headache CNS, central nervous system; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing. a May be complicated by analgesic overuse. In the case of substance abuse headache, the headache is completely resolved after the substance abuse is controlled (Headache Classification Committee of the International Headache Society, 202013—see ‘Further reading’). Clinical experience suggests that many patients continue to have headache even after cessation of analgesic use. The residual headache probably represents the underlying headache biology. b Chronic cluster headache patients may have more than 4 h/day of headache.
> The inclusion of the syndrome here is to emphasize that, by and large, the attacks themselves are less than 4 h duration.

24.8 Headache 6001 problem. Patients can reduce their use by, as an example, 10% every week or two, depending on their circumstances, or if they wish, and there is no contraindication, by immediate cessation of use. Either approach can be facilitated by first keeping a careful diary over a month or two to be sure of the size of the problem. A small dose of an NSAID, such as naproxen 500 mg twice daily if toler- ated, will take the edge off the pain as analgesic use is reduced, as does a greater occipital nerve injection with local anaesthetic and depo-corticosteroid. It is a useful aside that NSAID overuse does not seem to be a common issue in daily headache when patients are dosed once or twice daily, whereas with more frequent dosing problems may develop. When the patient has reduced analgesic use substantially a preventive should be introduced. It must be empha- sized that preventive therapies often do not work in the presence of analgesic overuse. Thus, some patients must reduce the anal- gesics or the entire attempt to use the preventive is largely wasted, although this helpful rule must have some limitations that require study. The most common cause of intractability to treatment is the use of a preventive when analgesics continue to be used regularly. For some patients this is very difficult, and often one must be blunt that some degree of pain is inevitable in the first instance if the problem is to be controlled. Some patients with medication overuse will require admission for detoxification. Broadly this consists of two groups—those who fail outpatient withdrawal or those who have a significant complicating medical indication, such as brittle diabetes mellitus, or complicating medicines, such as opioids or barbiturates, where withdrawal may be problematic as an outpatient. When such patients are admitted acute medications are withdrawn completely on the first day, unless there is some contraindication. Antiemetics, such as domperidone orally or as a suppository, ondansetron, or aprepitant; and fluids are administered as required, as well as clonidine for opioid withdrawal symptoms. For acute intolerable pain during the waking hours as- pirin (1 g intravenously) is useful and at night chlorpromazine by injection, after ensuring adequate hydration. To settle the headache optimally a course of intravenous dihydroergotamine can be used over 5 days. As time goes by, one feels that dihydroergotamine is indispensable in this setting. Often 5HT3 receptor antagonists, such as ondansetron and granisetron, or even sometimes the substance P/neurokin 1 receptor antagonist aprepitant will be required with dihydroergotamine because it is essential to ensure that the patient does not have significant nausea. Preventive treatments The tricylic antidepressants (TCAs), amitriptyline, dosulepin (dothiepin), and nortriptyline, at doses up to 1

mg/kg are very useful in patients with chronic migraine. TCAs are started in low dose (10–25 mg) daily and best given 12 h before the patient wishes to wake up to avoid excess morning sleepiness. The other very useful medications for these patients are the anticonvulsants, such as val- proate, topiramate, and gabapentin, and AII receptor antagonist candesartan. For valproate, doses up to 1500 mg daily are used, starting at 200 mg twice daily and increasing to 400 or 600 mg twice daily as tolerated over 2- to 4-week intervals. The blood count and liver enzymes should be checked at baseline and the various side effects explained to patients, especially the fetal abnormalities to women. For topiramate one can start at 25 mg nightly and in- crease by 25 mg every 10–14 days to aim for 50 mg twice daily. For gabapentin the dose is 1800–3600 mg daily; it is very well tolerated, although probably less effective from a population viewpoint. For candesartan one can start at 4 mg nightly after checking electro- lytes and renal function and increase to 16 mg nightly as tolerated. For some patients flunarizine can be very effective, as can phenel- zine, although the latter is little used currently. Botulinum toxin type A (onabotulinum toxin) has been shown in a randomized controlled trial to be useful in chronic migraine. One might con- sider its use, for example, in chronic migraine perhaps after three preventive classes have failed. There is now open label experience with single pulse transcranial magnetic stimulation, which is ex- tremely well tolerated. New daily persistent headache New daily persistent headache (NDPH) is a clinically useful con- cept with a range of important possible causes because some are very treatable (Table 24.8.9). The new International Classification of Headache Disorders sees a widening of the primary NDPH category to include what is listed in Table 24.8.9 as primary (i.e. it may have migrainous features). It seems clinically useful to re- member the secondary headaches that may commence in this fashion lest such patients go undiagnosed and thus untreated. The patient with NDPH presents with a history of headache on most if not all days, starting from one day to the next. The onset of headache is abrupt, often from one moment to the next, but at least in less than a few days with three suggested as an upper limit. The typical history is for the patient to recall the exact day and circum- stances, so from one moment to the next a headache develops that never leaves them. This presentation triggers certain key questions about the onset and behaviour of the pain. The pressing issues arise from considering the secondary headache possibilities. Although subarachnoid haemorrhage is listed for some logical consistency, as the headache may certainly come on from one moment to the next, it is not likely to produce diagnostic confusion in this group of patients. Suffice it to say that subarachnoid haemorrhage is so im- portant that it must always be considered if only to be excluded, ei- ther by history or by appropriate investigation.
Primary NDPH Initial descriptions of primary NDPH recognized that it occurs in both males and females. Migrainous features were common, with unilateral headache in about one-third and throbbing pain in about one-third. Nausea was reported in about one-half of the patients, as were photophobia and phonophobia. Many of these patients have a previous history of migraine, but not more than one might Table 24.8.9 Differential diagnosis of new daily persistent headache (NDPH) Primary Secondary Migrainous type Subarachnoid haemorrhage Featureless (tension-type) Low CSF volume headache Raised CSF pressure headache Post-traumatic headachea Chronic meningitis CSF, cerebrospinal fluid. a Includes postinfective forms.

 expect given the population prevalence of migraine. It is remark- able that the initial report noted that 86% of patients were headache free at 24 months. It is general experience among those interested in headache management that primary featureless NDPH is per- haps the most intractable and least therapeutically rewarding form of headache. In general one can classify the dominant phenotype— migraine or TTH—and treat with preventives

according to that subclassification. Secondary NDPH The secondary causes of the syndrome of NDPH are worthy of con- sideration, because they have distinctive clinical pictures that can guide investigation (Box 24.8.4). Low cerebrospinal fluid volume headache The syndrome of headache as a result of persistent low cerebro- spinal fluid volume is an important diagnosis not to miss. The more immediately obvious version of this problem is encountered com- monly after lumbar puncture. In that situation the headache usually settles rapidly with bed rest. In the chronic situation the patient typ- ically presents with a history of headache from one day to the next. The pain is generally not present on waking, worsens during the day, and is relieved by lying down. Recumbency usually improves the headache in minutes, and it takes only minutes to an hour for the pain to return when the patient is again upright. The patient may give a history of an index event: lumbar puncture or epidural injection, or a vigorous Valsalva manoeuvre, such as with lifting, straining, coughing, clearing the Eustachian tubes in an aeroplane, or multiple orgasms. Patients may volunteer, or a history may be obtained, that soft drinks with caffeine provide temporary respite. Spontaneous leaks are recognized, and the clinician should not be put off the diagnosis if the headache history is typical when there is no obvious index event. As time passes from the index event the postural nature may be less obvious; certainly cases with an index event several years before the eventual diagnosis are recognized. The term ‘low volume’ rather than ‘low pressure’ is used, because there is no clear evidence at which point the pressure can be called low. Although low pressures, such as 0 to 5 are often identified, a pressure of 16 cmCSF has been recorded with a documented leak. One should be aware of the possibility of the development of sub- dural collections in patients with low cerebrospinal fluid volume headaches, which makes imaging before any invasive studies all the more important. The investigation of choice is MRI with gadolinium (Fig. 24.8.5), which produces a striking pattern of diffuse pachymeningeal en- hancement, although in about 10% of cases a leak can be docu- mented without enhancement. The finding of diffuse meningeal enhancement is so typical that in the clinical context immediate treatment is appropriate. It is also common to see Chiari malforma- tions on MRI with some degree of descent of the cerebellar tonsils. This is important because surgery in such settings simply worsens the headache problem. It seems appropriate that any patient being considered for such surgery for a headache indication should first be reviewed by a neurologist. If the diagnosis is clear clinically treatment is bed rest in the first instance. False-positive transient improvement in persistent low cerebrospinal fluid volume headache with chiropractic and other similar therapies is recognized where the treatment necessi- tates the patient lying down for a prolonged period for the therapy. Intravenous caffeine (500 mg in 500 ml saline administered over 2 h) is a standard and often very efficacious treatment. The ECG should be checked for any arrhythmia before administration. A reason- able practice is to carry out at least two infusions separated by four Box 24.8.4 Other secondary headaches • Giant cell arteritis • Cervicogenic headache • Reader’s paratrigeminal neuralgia • Tolosa–Hunt syndrome • Headache as a presentation of cervical dystonia • Headache in temporomandibular dysfunction • Cardiac cephalalgia • Headache with endocrine disturbance, particularly pituitary tumour • Neck–tongue syndrome • Red-ear syndrome Fig. 24.8.5 MRI scan showing diffuse meningeal enhancement after gadolinium administration in a patient with low cerebrospinal fluid volume (pressure) headache.

 weeks after obtaining the suggestive clinical history and MRI with enhancement. As intravenous caffeine is safe, and can be curative, by an unknown mechanism, it spares many patients the need for further tests. If that is unsuccessful, an abdominal binder may be helpful. Investigation for leaks is evolving. Lumbar puncture alone seems counterintuitive, while

indium-111-labelled DPTA (diethyl aminetriaminepentaacetic acid) cerebrospinal fluid studies have a high false negative rate in practice, although they can demon- strate the site, early emptying of tracer into the bladder, or lack of progression of tracer over the cerebral convexities. Most centres would now do spinal T2-weighted MRI, and then consider either CT myelogram, or more recently some radiologists are using intra- thecal gadolinium with MRI. If a leak is identified, an autologous blood patch is usually curative. In more intractable situations where as leak is not identified theophylline is a useful alternative that offers outpatient management, although its onset of action is rather slow. Raised cerebrospinal fluid pressure headache As is the case for low cerebrospinal fluid pressure states, raised cere- brospinal fluid pressure as a cause of headache is well recognized by neurologists. Brain imaging can often reveal the cause, such as raised pressure due to a space-occupying lesion. The particular setting in which patients enter the spectrum of NDPH are those with idio- pathic intracranial hypertension who present with headache without visual problems, particularly with normal fundi. It is recognized that intractable chronic migraine can be triggered by persistently raised intracranial pressure. These patients typically give a history of gener- alized headache that is present on waking, and gets better as the day goes on. It is generally worse with recumbency. Visual obscurations are frequently reported. Fundal changes on raised intracranial pres- sure would make the diagnosis relatively straightforward, but it is in those without such changes that the history must drive the investi- gation. Patients often report a curious whooshing sensation in the occipital region. Brain imaging is mandatory if raised pressure is suspected, and it is most simple in the long run to obtain an MRI scan, and include MR venography (MRV). The cerebrospinal fluid pressure should be measured by lumbar puncture, taking care to do so when the pa- tient is symptomatic, so that both the pressure and response to re- moval of cerebrospinal fluid can be determined. A raised pressure and improvement in headache with removal of cerebrospinal fluid are diagnostic of the problem. The fields should be formally docu- mented even in the absence of overt ophthalmic involvement. Initial treatment can be with acetazolamide (250–500 mg twice daily). The patient may respond in weeks with improvement in headache. If this is not effective topiramate has many actions that may be useful in this setting: carbonic anhydrase inhibition, weight loss, and neur- onal membrane stabilization probably through actions on phos- phorylation pathways. A small number of severely disabled patients who do not respond to medical treatment will come to intracranial pressure monitoring and even shunting. In patients who are over- weight, some would advocate bariatric surgery at this point. This is an evolving area. Post-traumatic headache The issue of post-traumatic headache is vexed. The Headache Classification Committee accepts the existence of such a syn- drome. Much of the scientific discussion becomes marred by the often-quoted medicolegal morass concerning delayed effects of head injury. Recent military experience suggests that even mild trauma can produce headache and through this sad path the condition is be- coming more widely investigated. The term is used here to indicate trauma in a very broad way. NDPH may be seen after a blow to the head but more commonly after an infective episode, typically viral, or even malarial meningitis. A recent series identified that one-third of all patients with NDPH reported the headache starting after an influenza-like illness. The patient may note a period in which they had a significant infection: fever, neck stiffness, photophobia, and marked malaise. The headache starts during that period and never stops. Investigation reveals no current cause for the headache. It has been suggested that some patients with this syndrome have a per- sistent Epstein–Barr virus infection, but this syndrome is anything but clearly delineated. A complicating factor will often be that the patient had a lumbar puncture during that illness, so a persistent low cerebrospinal fluid volume headache needs to be considered first. Post-traumatic headache may be seen after carotid artery

dissection, subarachnoid haemorrhage, and following intracranial surgery for a benign mass. The underlying theme seems to be that a traumatic event involving the dura mater can trigger a headache process that lasts for many years after that event. The treatment of this form of NDPH is substantially empir- ical. TCAs, notably amitriptyline, and anticonvulsants, valproate, topiramate, and gabapentin, have been used with good effects. The monoamine oxidase A inhibitor phenelzine may also be useful in carefully selected patients. On the positive side, the headache seems to run a limited course of 3–5 years in most patients, so will eventu- ally settle. It can certainly be very disabling in that period. Other important forms of secondary headache See Box 24.8.4. Giant cell arteritis This is an important cause of headache because delay in steroid treatment may result in blindness due to retinal artery ischaemia. It is also known as temporal arteritis or cranial arteritis. Patients are usually older with focal tenderness of the scalp, which may be pro- voked markedly by resting the head on the pillow. Jaw claudication provoked by chewing is a characteristic, but relatively uncommon, feature. Constitutional symptoms are common, particularly weight loss, malaise, or polymyalgia rheumatica. An elevated erythrocyte sedimentation rate (ESR) is a strong pointer to the diagnosis. The temporal artery may be tenderly inflamed, swollen, or pulseless. On suspicion of this diagnosis, corticosteroid treatment should be started pending the result of temporal artery biopsy. Treatment is very often long term and requires careful monitoring for reactiva- tion and the side effects of corticosteroids. Cervicogenic headache It is a time-honoured concept that the neck is responsible for many headaches. Unfortunately, as with much of history, the good story is often ruined by the facts. Although there is little doubt that there is a rich overlap between the innervation of intracranial pain-producing structures by the ophthalmic division of the trigeminal nerve, and the posterior fossa and high cervical innervation by branches

section 24 Neurological disorders 6004 especially of the C2 dorsal root, causality is another issue. The Headache Classification Committee recognizes that head pain can arise from the neck and labels this ‘cervicogenic headache’. The term has been used by others to define a syndrome that is so poorly de- scribed as to be useless in practice. Most patients with neck discom- fort and headache referred to specialty practice have migraine. They will have neck stiffness or discomfort as a premonitory symptom that can clearly persist in all stages of the attack. They may respond to local therapies, such as greater occipital nerve injection; how- ever, this implies no more than triggering, and is to be expected. The pursuit of neck pathology and the treatment of patients with migraine by manipulative or physical means have no support in the controlled literature, and are rarely of long-lasting value. FURTHER READING Afridi S, et al. (2005). A PET study in spontaneous migraine. Arch Neurol, 62, 1270–5. Afridi S, et al. (2005). A PET study exploring the laterality of brain- stem activation in migraine using glyceryl trinitrate. Brain, 128, 932–9. Afridi SK, et al. (2006). Greater occipital nerve injection in primary headache syndromes—prolonged effects from a single injection. Pain, 122, 126–9. Akerman S, et al. (2011). Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci, 12, 570–84. Andlin-Sobocki P, et al. (2005). Cost of disorders of the brain in Europe. Eur J Neurol, 12, 1–27. Andreou AP, Shields KG, Goadsby PJ (2010). GABA and valproate modulate trigeminovascular nociceptive transmission in the thal- amus. Neurobiology of Disease, 37, 314–23. Antonaci F, Fredriksen T, Sjaastad O (2001). Cervicogenic head- ache: clinical presentation, diagnostic criteria, and differential diag- nosis. Current Pain Headache Rep, 5, 387–92. Antonaci F, et al. (1998). Chronic paroxysmal hemicrania and hemicrania continua. Parenteral indomethacin: the ‘Indotest’. Headache, 38, 122–8. Bahra A, et al. (2001). Brainstem activation specific to migraine head- ache. Lancet, 357, 1016–17. Bartsch T, Goadsby PJ (2005). Anatomy and physiology of pain re- ferral in

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