13.9 Headaches

13.9.1 General considerations: primary and secondary headaches

Acute headaches account for approximately 8% of visits to the emergency department. Common headaches occur generally, but when a patient presents with a new-onset (something else) severe headache, it should be managed as an urgent matter. Delayed diagnosis and management may have catastrophic consequences. Some of the headaches discussed in this section occur rarely, but should be considered to prevent morbidity and mortality.

The patient may present with either an old or a new problem. However, the new headache may be the first of recurring headaches, or the headache may be different from the known recurring headaches. The pain may have been present at different times, or the frequency has changed; they are familiar with the pain, or it has changed character, or it has become associated with other symptoms.

If a patient presents with a headache, the attending doctor must always assess the patient as if they present for help for the first time. This includes a complete history (when, what happened, suddenly/gradually, associated symptoms, other diseases [including HIV], history of head or neck injury, dental or jaw problems, medication, medication overuse, family history, etc.) as well as a general clinical examination (all the vital signs, pregnancy test, targeted ENT and neurological examination, assessment of visual acuity, including fundoscopy). Never miss the signs of *increased ICP*, namely headache, vomiting *without* nausea, diplopia (due to ocular paresis), decreased vision (due to papilloedema), deteriorating consciousness, and back pain. The aim of the history and clinical examination is to *exclude secondary causes* and thereafter to manage the more common acute headaches, namely the *primary headaches*.

Headaches can be *primary or secondary* (Table II and Table III). *Primary headaches* are much more prevalent, and although the pathophysiology may be known and have a predictable character, the causes may remain obscure, and these may have a high morbidity, but low mortality. The causes of *secondary headaches* are known, it may be from intra- or extracranial origin, have a character that is determined by the cause, may be treatable, and have, depending on the cause, a high morbidity and mortality (Table III). Treatable causes include mass lesions (hydrocephalus, tumours, cysts, abscesses, subdural and extradural haematomas), and vascular lesions (stroke, aneurysms, subarachnoid haemorrhage [SAH], vascular malformations and cerebral venous sinus thrombosis).

The doctor must never get use to a patient's headache. The first task of the caregiver is to decide whether further investigations are justified to exclude secondary causes (red flags). The SNNOOP10 is a screening tool, depicted in Table III.

Table II: Primary and secondary headaches

Primary headaches	1. Migraine 2. Tension-type headache (TTH) 3. Cluster headache (CH) and other trigeminal autonomic cephalalgias 4. Other primary headaches
Secondary headaches	1. Headache attributed to head and/or neck trauma 2. Headache attributed to cranial or cervical vascular disorder 3. Headache attributed to nonvascular intracranial disorder 4. Headache attributed to a substance or its withdrawal 5. Headache attributed to infection 6. Headache attributed to disorder of homoeostasis 7. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures 8. Headache attributed to psychiatric disorder
Cranial neuralgias, central and primary facial pain, and other headaches	1. Cranial neuralgias and central causes of facial pain 2. Other headaches, cranial neuralgia, central or primary facial pain

Table III: Secondary headache: SNNOOP10 list of red flags

Sign or symptom	Related secondary headaches
Systemic symptoms including fever	Headache due to infection or nonvascular intracranial disorders, carcinoid, pheochromocytoma
Neoplasm in history	Neoplasms of the brain, metastases
Neurologic deficit or dysfunction (including consciousness)	Attributed to vascular, nonvascular intracranial disorders, brain abscess/ other infections
Onset sudden or abrupt	Subarachnoid haemorrhage, other attributed to cranial or cervical vascular disorders
Older age (> 50 years)	Giant cell arteritis, other due to cranial or cervical vascular disorders Neoplasms, other nonvascular intracranial disorders
Pattern change, recent onset	Neoplasms, headaches due to vascular, nonvascular intracranial disorders
Positional headache	Intracranial hypertension/hypotension
Precipitated: sneezing, coughing, exercise	Posterior fossa malformations, Chiari malformation
Papilloedema	Neoplasms/nonvascular intracranial disorders, intracranial hypertension
Progressive, atypical presentations	Neoplasms, nonvascular intracranial disorders
Pregnancy, puerperium	Headaches due to cranial/cervical vascular disorders, postdural puncture headache, hypertension-related disorders (e.g. preeclampsia), cerebral sinus thrombosis, hypothyroidism, anaemia, diabetes
Painful **eye** with autonomic features	Pathology in posterior fossa, pituitary region, or cavernous sinus Tolosa-Hunt syndrome, ophthalmic causes
Posttraumatic onset	Acute, chronic posttraumatic headache Subdural haematoma, other headache due to vascular disorders
Pathology of immune system	Opportunistic infections, HIV
Pain killer overuse, new drug at onset	Medication overuse, drug incompatibility

Shortened SNOOP

- **S**ystemic symptoms (fever, weight loss, HIV, systemic cancer)
- **N**eurologic symptoms or signs (confusion, impaired alertness or consciousness)
- **O**nset (sudden, abrupt, split-second)
- **O**lder (new onset, progressive, especially middle-age > 50 years [giant cell arteritis])
- **P**revious headache history (first headache, different [frequency, severity, features])

In order to identify the cause and decide on the most appropriate management, the doctor must appreciate the clinical features of the different disorders that present with acute headaches. Remember that nonneurological disorders can present with acute headache.

13.9.2 Types of presentation of acute headaches

New-onset headache with fever: exclude meningitis

The most common cause of acute headache associated with fever is *systemic illness headache*. The headache is usually self-limiting and improves when the systemic infection resolves, but may be complicated by a nonspecific persistent headache. The most common causes of acute headache with fever are acute paranasal sinusitis and viral infections, such as influenza.

The most important cause to exclude is that of acute bacterial meningitis. The most common causes of bacterial meningitis are meningococcal, pneumococcal and tuberculous infections. If the history and clinical examination points to meningitis, a lumbar puncture should be performed to exclude aseptic meningitis (which occurs more commonly) and to direct antibacterial therapy. IV ceftriaxone must be started immediately. If there is no history of HIV, convulsions, the patient is fully conscious, and there is no lateralisation (abscess), further imaging is unnecessary, but should be left to the discretion of a specialist.

Headache accompanied by focal neurological symptoms: migraine

These headaches are accompanied by sensory, motor and vision complaints. The most common cause of this triad is migraine with an aura. However, if this is the first time the patient presents with these complaints, imaging is indicated to exclude vascular (stroke, haemorrhage) and mass lesions.

Migraine is the most common cause of headache in patients visiting the emergency department. It occurs in approximately 16% of the population; an aura precedes the headache in a third of patients. It is more prevalent among women. Migraine may occur either without a preceding aura or with a preceding aura, but rarely present with *an aura only* (silent migraine).

Migraine is a neurovascular disorder that is characterised by a usually unilateral frontotemporal pulsating (throbbing) headache and several hypersensitivity-related symptoms (aura), such

as photophobia, phonophobia and olfactophobia. It is often accompanied by autonomic symptoms (lacrimation, nausea, vomiting), sensory symptoms (paresthesiae, scotomata and other visual disturbances), motor symptoms (focal weakness or paralysis), cognitive symptoms (amnesia), or fluctuation in consciousness. It is often associated with a trigger, including emotional stress, sleep disturbances, hormonal changes, fasting, noise, light, etc. It seems as though migraines are the result of a brain state of altered sensitivity (hyperexcitability), which can activate the trigeminovascular system in genetically susceptible people.

The aura is caused by cortical spreading depression (CSD). CSD occurs in genetically predisposed individuals. It is a physiological response to irritant stimuli in the cerebral cortex. In these patients, the cortex is hyperexcitable, which is caused by a disturbed excitatory/inhibitory imbalance. This response of the cortex in response to irritant stimuli occurs before the onset of the headache.

In CSD, the stimulus induces a slowly spreading (2–8 mm/minute) wave of depolarisation across the cortex, followed by slow repolarisation. The depolarised cortical tissue becomes isoelectric and does not function properly. The evolving nature of the aura is indicative of CSD. The areas affected determines the characteristics of the aura. *Serotonin* (increased levels) *and dopamine* (hypersensitivity due to chronic dopamine deficiency) may be involved in CSD.

The aura reaches a peak within approximately 5–20 minutes and persists for about 30 minutes, followed by complete resolution. In about 4% of patients, the neurological deficit may last for more than a day.

Central and peripheral sensitisation occurs when there is a reduction in the excitatory thresholds of peripheral and central trigeminal neurons (spinal trigeminal nucleus and cervical spinal neurons 1–3). Peripheral sensitisation results in hypersensitivity of trigeminal afferents in the face, scalp and neck. This results in a pain response to a normally nonpainful stimulus, including vascular pulsations in arteries supplying the scalp, face or arms. Note: it is not dilatations or extracranial arteries that cause pain, but hypersensitivity of afferents that cause the pain with a throbbing character.

Central sensitisation also involves activation of the trigeminovascular system, which causes *intracranial (pial)* arterial *vasodilatation* causing traction on blood vessel walls. These arteries are accompanied by trigeminal afferents and when stimulated (sensitised), nociceptive signals are transmitted via the trigeminal nerve. The intracranial vasodilatation is responsible for the headache. Extracranial arteries do not dilate.

During CSD, neurons, glia and vascular cells release ADP, H^+, and K^+, while perivascular nerves (trigeminal afferents) release NO and calcitonin gene-related polypeptide (CGRP). These substances trigger a *neurogenic inflammatory response* involving the release of inflammatory cytokines, prostanoids and histamine. These substances trigger neurogenic inflammation-

causing intracranial vasodilatation. They also diffuse to the surface of the cortex where they stimulate pial nociceptors in trigeminal afferents and cause vasodilation. The patient becomes more sensitive to the slight increase in ICP caused by the vasodilation, resulting in the throbbing quality of migraines.

Migraine without aura is diagnosed if the patient experiences:

A. At least five attacks fulfilling criteria B through D

B. Headache lasting 4–72 hours (untreated or unsuccessfully treated)

C. At least two of the following pain characteristics: unilateral location, pulsating, moderate or severe, or aggravating routine physical activity

D. At least one of the following during the headache: nausea and/or vomiting or photophobia and phonophobia

Cranial autonomic symptoms may also be present, including nasal congestion, ptosis, eye lid oedema, tearing, conjunctival injection and miosis. *Cutaneous* allodynia may also occur during attacks.

Migraine with aura is diagnosed if a patient experiences:

A. The diagnostic criteria for migraine without aura

B. At least two attacks fulfilling criteria C

C. At least three of the following during a headache:
    1. One or more symptoms indicating focal, cerebral, cortical and/or brainstem dysfunction; a sensory aura may consist of unilateral paresthesiae and sensory aphasia, while a motor aura consists of focal weakness or paralysis; visual auras may present as shimmering lights or zigzagging lines of different colours and/or brainstem dysfunction (fainting, unconsciousness, disorientation, tinnitus, loss of balance, dizziness, vertigo, diplopia, dysarthria) or retinal symptoms; an aura may also present as transient amnesia.
    2. At least one of the aura symptoms develops gradually over more than 4 minutes, or two or more symptoms in succession.
    3. No aura symptom lasts more than 60 minutes.
    4. The aura is followed by a headache, with a free interval of less than 60 minutes.
    5. The aura is unilaterally spreading over more than 5 minutes, lasts less than 60 minutes and are followed by a headache within 60 minutes; the headache may begin before or during the aura.

Management of acute migraine

The patient who seeks help for a headache is either a known migraineur, or a patient with a 'new' headache. Regarding the latter, the priority is to exclude secondary causes and to treat the headache while a diagnosis is being made. The migraineur knows that the headache is a migraine, and visits the healthcare facility due to failure of home medication.

Management of acute migraine attempts to address the neurologic and vascular processes by targeting receptors involved in neural, vascular and inflammatory responses.

General principles

1. By the time a patient arrives at the healthcare facility, they may be dehydrated due to an inability to eat or from vomiting. These patients should receive an IV infusion of Ringer's lactate of approximately 10 ml/kg.
2. The infusion also facilitates the administration of other drugs, especially for inpatients who vomit.
3. The time between the start of the attack and the treatment should be kept as short as possible. All treatment modalities, especially the triptans, are more effective if administered early in the episode. Early treatment is recommended for migraine without aura. Regarding migraine with aura, it is suggested that a triptan should be taken at the onset of the headache. However, taking an oral triptan during the aura appears to be effective and safe.
4. Patients react differently to treatment; analgesics (paracetamol and NSAIDs) may suffice in some, while a particular triptan is required in others (genetic factors). Moreover, the severity, duration of the headache, and vomiting determine the modalities, dosages and drug formulations used.
5. Drug combinations are useful. Drug combinations are often more effective than the components alone. These include a triptan + NSAID + a dopamine antagonist (antiemetic).
6. The choice of drug formulation is determined by the characteristics of the attack: severity, duration and vomiting. If an attack builds up rapidly to a severe headache, especially if accompanied by vomiting, an SC or IN triptan should be used first. When the attack is less severe, oral and nasal preparations can be used. Oral formulations that facilitate faster absorption may be used, including oral dispersible tablets or wafers and effervescent tablets.
7. A measure of the efficacy of treatment modalities is the pain-free period after administration. These endpoints are usually the 2-hour and the 24-hour pain-free rate (sustained effect of mild or no pain).
    - Headache syndromes, including migraine, is often complicated by *medication-overuse-induced headache.* This is a headache that is exacerbated by the frequent use of over-

the-counter (OTC) analgesic combinations. These usually contain paracetamol, NSAIDs, a sedative (usually an antihistamine), as well as codeine. Opiates should not be used as these are less effective than the other drugs used for the management of migraine headaches, are habit-forming, and lead to medication overuse headache (MOH).

8. In patients in whom vasoconstrictors (the triptans) are contraindicated, treatment is limited to paracetamol, an antiemetic (sedating antihistamine), and an NSAID. Owing to its better CV and antiplatelet effect, naproxen sodium is the first-choice NSAID. An opioid may be added in exceptional cases.

Drugs used for a migraine attack

Antidopaminergic antiemetics

Metoclopramide and domperidone are not only antiemetics, but are also prokinetics, which promote the absorption of oral drugs, including the triptans. The dose of *metoclopramide* is 10 mg p.o. or IVI up to 6-hourly. *Domperidone* 10 mg is given p.o. 8-hourly. Domperidone has several drug interactions, is affected by liver and kidney function, and prolongs the QT interval (see the SAMF).

Prochlorperazine can be added for refractory vomiting. The dose is 20 mg p.o. followed by 5–10 mg 6-hourly, if necessary. If nausea prevents oral administration, prochlorperazine 12.5 mg can be administered IMI or 25 mg per rectum.

Droperidol is an effect antiemetic. The dose is 20 µg/kg. This drug can prolong the QT interval.

All antidopaminergic drugs, especially prochlorperazine and droperidol, have extrapyramidal adverse effects. It can be treated with centrally acting anticholinergic *biperiden* 30 µg/kg IVI or IMI and repeated every 30 minutes if necessary. The maximum daily dose is approximately 150 µ/kg.

Paracetamol and NSAIDs

These drugs may suffice for mild to moderate migraine attacks, but are always used for severe attacks. Except for naproxen, NSAIDs have a rapid onset of action. NSAIDs improve the 2-hour and 24-hour pain-free rate. Oral preparations should be used if possible.

Paracetamol on its own is suitable only for mild attacks, but is additive to the effect of NSAIDs. The dose is 15 mg/kg p.o. or 15 mg/kg IVI 4–6-hourly with a maximum of 60 mg/kg/day.

Ibuprofen is often used by migraineurs. A maximum effective and appropriate dose is approximately 7 mg/kg, which can be repeated 6-hourly.

Diclofenac can be given p.o. (diclofenac sodium tablets or diclofenac potassium powder for oral solution), IMI, IVI or rectally. The dose is 0.7 mg/kg p.o. 8-hourly, 1 mg/kg IMI, or IV infusion over at least 30 minutes (see postoperative pain), or 1–1.5 mg/kg per rectum. The maximum dose of diclofenac is approximately 2 mg/kg/day.

Ketorolac has been used with success for migraine headaches. It has a relatively long half-life of 5 hours. The dose is 0.5 mg/kg IVI, followed by 0.15 mg/kg 6-hourly with a maximum of approximately 1 mg/kg/day. The oral dose is 10 mg 4–6-hourly.

Naproxen is commonly used for acute migraine headaches. It is available as the base and the sodium salt. Naproxen sodium is preferred since it is absorbed quicker than the base. Naproxen has a half-life of 14 hours, but the 2-hour pain-free characteristic is inferior to that of ibuprofen and diclofenac. The long half-life of naproxen reduces the recurrence rate of migraine. Moreover, the CV and antiplatelet profile of naproxen is better than those of other NSAIDs. The dose is 3.5–7.0 mg/kg 12-hourly.

The triptans

During a migraine attack, intracranial arteries dilate on the side of the headache and to a lesser extent on the nonpainful side. *The extracranial arteries do not dilate.* The anti-migraine effect of the triptans is still unclear. Possibilities include extracranial vasoconstriction, suppression of neuropeptide release from trigeminovascular afferents, and antinociceptive activity in the brainstem. The triptans are agonists at 5-HT1B and 5-HT1D receptors, causing peripheral vasoconstrictors. These constrict extracranial arteries (making them less pulsatile with less release of neuropeptides from the hyperexcitable trigeminovascular afferents).

Sumatriptan does not cross the intact BBB, which also stays in tact during a migraine attack. Since the anti-migraine effect of sumatriptans does not rely on intracranial vasoconstriction and cerebral antinociceptive effects, it is also unlikely that the triptans drugs blunt the migraine generator (focus). This may explain the recurrence of headache once the extracranial vasoconstrictor effect of the triptans has worn off.

Owing to possible genetic factors, triptans are not equally effective in all patients. The adverse effects may also differ between patients. Therefore, a patient may prefer a particular triptan.

Subcutaneous sumatriptan has the best 2-hour pain-free rate. Regarding the *oral preparations*, eletriptan and rizatriptan are better after 2-hours, while eletriptan has the highest 24-hour pain-free rate. Oral eletriptan and zolmitriptan works faster than oral sumatriptan. *Nasal sprays* work faster than oral triptans, may offer relief if the oral dose has failed, and is useful in patients who cannot take tablets due to vomiting.

If a triptan is ineffective, a follow-up dose usually does not offer any additional relief. A triptan failure may be rescued by naproxen sodium 550 mg p.o.

Triptans are administered when paracetamol and an NSAID has failed to control the headache. All three of these are often co-administered for moderate to severe migraine. Both IV or oral metoclopramide and oral domperidone are antiemetic as well as prokinetic and promote the absorption of oral triptans.

Triptans are contraindicated in patients with vascular disease, namely hypertension, coronary artery disease, Prinzmetal angina, cerebrovascular disease and peripheral artery disease. Triptans and ergot alkaloids have additive vasoconstrictive effects and should be given more than 24 hours apart. These should not be given for ophthalmoplegic, basilar artery and hemiplegic migraines.

These are also contraindicated in patients on drugs that increase serotonin levels, including SSRIs and SNRIs. Sumatriptan and eletriptan contain a sulfur-containing moiety, which makes them contraindicated in patients allergic to sulfas. Zolmitriptan is sulfur-free. Triptans should be avoided in patients taking MAOIs and lithium.

The following triptans are available in SA: Sumatriptan, eletriptan, zolmitriptan, and naratriptan.

- Sumatriptan is administered by SC injection for a severe migraine attack, while oral tablets or wafers or IN sprays can be used for less severe attacks. The IN spray may be effective if the oral route fails to control the attack. The SC dose is approximately 80 µg/kg. SC sumatriptan may be effective if another triptan has failed to give adequate relief. The oral dose is 50 mg and the IN dose is 20 mg. The SC dose can be repeated after an hour and the oral and IN doses, after two hours.
- *Eletriptan* is a sulfur free triptan. It has a short onset of effect and a high 2-hour and 24-hour pain-free rate. The dose is approximately 0.5 mg/kg p.o. The metabolism of eletriptan is decreased by suppressors of liver CYP3A4, including erythromycin and its derivatives, the conazole antifungal agents, and the ARV ritonavir.
- *Naratriptan:* the dose is approximately 30 µg/kg p.o.
- *Zolmitriptan:* it is a fast-acting oral triptan. The dose is approximately 30 µg/kg p.o.
- *Rizatriptan:* the dose is approximately 0.15 mg/kg p.o.

The ergot alkaloids

These drugs should not be used any longer. These are non-selective vasoconstrictors affecting serotonin, adrenergic and dopaminergic receptors. This non-selectivity gives rise to several potentially long-lasting adverse effects, including hypertension, myocardial ischaemia, peripheral ischaemia (ergotism), and nausea and vomiting. These have several drug interactions,

including the erythromycin derivatives and the protease inhibitors, such as ritonavir (slower metabolism), and with other vasoconstrictors, non-selective beta-blockers, and the triptans.

Opioids

Opioids should not be used routinely for migraine headaches. It may also promote the development of MOHs, which may make the routine antimigraine agents less effective.

Corticosteroids

Although evidence is lacking regarding the efficacy of corticosteroids for the management of migraine headache, dexamethasone 4–16 mg IVI may prevent recurrence of headache for up to 72 hours.

Migraine during pregnancy and lactation

Acetaminophen, metoclopramide and codeine are safe during pregnancy. NSAIDs should be avoided. Prochlorperazine is not teratogenic, but should be avoided in the peripartum period since it can cause extrapyramidal effects in the neonate. An occipital nerve block (greater and lesser occipital nerves) may be helpful.

During lactation, paracetamol and the tNSAIDs are safe, but aspirin should be avoided. Sumatriptan and the antiemetics are safe. Opioids should be avoided if possible, especially if the mother breastfeeds an infant with a postconceptional age of less than 60 weeks or when the mother experiences drowsiness after taking an opioid. In the case of codeine, she may be an extensive metaboliser of codeine to morphine.

Thunderclap headache: sudden onset of severe headache

The onset of a severe headache may be abrupt with maximal intensity from the start. These headaches are not transient (seconds) and are repetitive in nature, such as neuralgic head pain. A thunderclap headache is severe, persistent and distressing. However, the severity does not correlate with the gravity of the underlying pathology. This group of headache-causing disorders is mentioned since patients with a known primary headache disorder may also present with a 'sudden severe different headache'.

Although these headaches occur infrequently (approximately 40 cases per 100 000 adults per year) it is essential to exclude possible deadly secondary disorders that have a potentially good prognosis if treated correctly and urgently.

It is important to exclude a *ruptured cerebral aneurism*. This lesion may present with rapidly deteriorating focal neurological signs and consciousness, or with the headache only. The diagnosis is facilitated by urgent imaging and lumbar puncture.

In the majority of these cases, a secondary cause is not identified and the diagnosis of a primary headache disorder is made. The most important secondary causes are neurovascular in origin, including SAH from a cerebral aneurism, arterial dissection, reversible cerebral vasoconstriction syndrome and dural sinus thrombosis. Other rare causes include MI, phaeochromocytoma, pituitary apoplexy, spontaneous intracranial hypotension (SIH), and idiopathic physical-activity-related thunderclap headache.

New-onset persistent headache

This is a person with no prior history of headache who presents with several days or weeks of a new headache. These patients may have a history of 'normal' headaches, but now presents with new headaches. Several of these patients visit the emergency department for help. These headaches do not present as abruptly as a thunderclap type headache, but is new in character and persists. These headaches have a wide differential diagnosis. As is the case with thunderclap headaches, it is important not to miss an important secondary cause.

Tension-type headache

TTH is a primary headache. It occurs commonly and is probably the kind of headache that occurs 'normally'. It is also referred to as a stress or muscle tension headache. Since there is an overlap in symptomatology, pathophysiology, as well as the co-occurrence of the two headaches in the same patient, migraine is often erroneously diagnosed as TTH, and vice versa.

A diagnosis (International Headache Society [IHS] diagnostic criteria for migraine without aura and episodic tension-type headache [ETTH]) of TTH is mainly based on the absence of certain other symptoms, while migraine is diagnosed by the presence of typical symptoms, namely nausea and vomiting, photo- and phonophobia, headache exacerbated by physical activity. However, the absence of differentiating characteristics of TTH contributes to the diagnosis of TTH instead of migraine. The overdiagnosis of TTH may explain its high prevalence of ETTH of approximately 40% in adults. The misdiagnosis may deprive the migraineur of appropriate therapy, which may cause suffering unnecessarily, and vice versa.

The nonspecific nature of TTHs must be investigated further for a secondary cause, especially if the pattern of headache changes (e.g. if starting during the night or if therapy does not give relief anymore). In this regard, the doctor must recommend a visit to the dentist to exclude temporomandibular pathology, bruxism and impacted wisdom teeth. Also consider cervical spine disorders, including cervicogenic headaches (CGHs).

For differentiation between these primary headache types, the reader is referred to the diagnostic criteria of the IHS for migraine without aura and ETTH.

TTH can be episodic (ETTH) or chronic (CTTH). In ETTH, the headache occurs for less than 14 days per month and typically last from 30 minutes to 7 days. In CTTH, the headache is experienced for more than 14 days per month and is present relatively continuously. The pathogenesis of ETTH and CTTH differ.

Headaches usually start during waking hours and get worse during the day. TTH is triggered by increased psychological (depression, anxiety and panic disorder), or physiological stress (including disturbed sleep patterns, overexertion, hunger, dehydration, female hormonal fluctuations and caffeine withdrawal). However, these stressors are also frequently present in migraineurs.

Pathophysiology

The pathophysiology of ETTH and CTTH differ, but there may be an overlap in patients. Both peripheral myofascial and CNS sensitisation are involved. Pericranial myofascial mechanisms are implicated in ETTH. Continuous stimulation of trigger points in the pericranium and cervical muscle cause sensitisation of peripheral nociceptors followed by sensitisation of second-order neurons in the spinal nucleus of the trigeminal nerve.

CNS sensitisation is involved in the pathogenesis of ETTH and CTTH, leading to decreased pain thresholds. These patients are hypersensitive to noxious stimulation of muscle, tendon, nerve, at cephalic and extracephalic points, and during and between headaches. Patients with CTTH also have decreased central nociceptive inhibition.

Management of tension-type headaches

Management consists of avoiding triggers (i.e. stressful situations), following a stress-avoiding lifestyle (get more sleep and apply sleep hygiene, physical exercise, regular healthy meals), psychological aspects (overcome depression and stress through CBT), physiotherapy and pharmacological management.

ETTH attacks are managed with paracetamol (15 mg/kg p.o. 6-hourly) combined with an NSAID such as ibuprofen (4 mg/kg p.o. 6-hourly) or naproxen (7 mg/kg bd; available with esomeprazole). Caffeine improves the efficacy of paracetamol and ibuprofen. It is available in several paracetamol combinations. To prevent the development of analgesic overuse headache, the use of these drugs should be limited to 3 days and opioids and sedatives should not be prescribed. Triptans are ineffective.

If a patient experiences headache more than twice a week (CTTH), preventative medication is indicated. Amitriptyline is the drug of choice. Start with a low dose (10 mg) at night and increase it gradually up to 75 mg at night. The effective dose is prescribed for 6–12 months.

Thereafter, the patient can be weaned from amitriptyline. Other TCAs may be used instead of amitriptyline. The SSRIs and botulinus toxin are ineffective.

13.9.3 Carbon monoxide poisoning

Most patients with chronic carbon monoxide (CO) poisoning present with the symptom of nonspecific headaches. These patients usually work close to internal combustion engines in poorly ventilated spaces. CO poisoning can cause permanent neurological impairment and even death. The diagnosis is made from the occupational history and an arterial blood gas analysis.

13.9.4 Temporal arteritis (giant cell arteritis)

Giant cell arteritis (GCA) is a rare disease (incidence of approximately 20/100 000/year). The disease affects elderly people, usually in their eighties, and women are affected more often than men. Although GCA is a rare cause of acute headache, it has a high morbidity if not treated promptly.

GCA is an autoimmune disease that affects large and medium size arteries. It is the most common systemic arteritis in elderly people. It usually affects the branches of the external carotid artery, namely the superficial temporal, maxillary, ophthalmic, posterior ciliary and vertebral arteries. These arteries supply the structures of the temporal, frontal (including the orbit), facial and temporomandibular joints.

Systemic signs of inflammation are often present, including fever, malaise and anorexia (flu-like symptoms). Less commonly, coronary arteries, cerebral arteries and the aorta are affected, causing MI, stroke and an aortic aneurism, respectively.

The typical symptoms form the triad of a severe, unilateral throbbing, temporal headache, jaw claudication and blindness. The painful areas are also hyperalgesic, and may be aggravated by chewing and swallowing. Patients may also complain of diplopia and both eyes are affected in > 50% of cases. The temporal arteries are tender and swollen. Patients may also present with ataxia, tinnitus and deafness.

The diagnosis is made by a raised erythrocyte sedimentation rate and biopsy of the temporal artery.

Management of acute giant cell arteritis

Once the diagnosis of GCA is suspected, treatment must be started *immediately* to prevent blindness or a stroke. Prompt administration of a corticosteroid before visual symptoms occur, decreases the prevalence of blindness from 50% to 1%. Corticosteroids are the only confirmed

treatment for GCA. Start with prednisone approximately 1.0 mg/kg/day p.o. In the presence of visual loss, start with methylprednisolone 15 mg/kg/day IVI for three days.

13.9.5 Disorders of abnormal intracranial pressure

These disorders include the following:

- Idiopathic intracranial hypertension (IIH) (pseudotumor cerebri)
- Low intracranial pressure headache (LPH): postdural puncture headache (PDPH) and SIH

Patients suffering from these disorders may present to the emergency department with severe persistent headaches.

Idiopathic intracranial hypertension

IIH is defined as elevated ICP, normal CSF composition, and the absence of intracranial pathology. It occurs in obese persons, more often in young women, but may also occur in children. It is also associated with a recent steep increase in BMI.

A wide range of conditions have been associated with IIH, including medication (hypervitaminosis A and retinoids [used for acne], growth hormone [GH], tetracycline, the quinolone antibiotics), OSA, and several endocrine disorders.

Patients complain of a persistent severe headache (> 90% of cases) accompanied by nausea, pulse-synchronous tinnitus (turbulent blood flow in cerebral venous sinuses), diplopia (loss of N. abducens), blurred vision, restricted visual fields, tunnel vision or even loss of vision. Visual loss correlates with increased BMI – in adults and children. Symptoms are exacerbated when the ICP is raised (e.g. by lying down).

Patients often present complaints similar to those of migraine, including headache, nausea, vomiting, and photo- and phonophobia. As is the case with other headaches, different headache disorders may occur in the same patient. IIH also occur in migraineurs.

As with all headaches, the doctor must be on the lookout for symptoms and signs of increased ICP (see above). Secondary causes of elevated ICP must be excluded, especially venous sinus thrombosis. Investigations include imaging, CSF pressure studies and biochemistry. The patient should be referred to a neurologist and ophthalmologist.

Management of acute IIH-related headache

Symptoms usually present acutely and are self-limiting, but the condition may become chronic. The aim of treatment of an acute headache is to alleviate pain and other symptoms and to prevent vision loss.

Although weight loss is the most important long-term treatment to improve the headache and the visual outcome, these patients need symptomatic treatment in the emergency setting. Headaches may be alleviated by an NSAID, an antiemetic, a glucocorticoid and a triptan. However, the most important component of acute therapy is to decrease CSF production and intracranial and intraocular pressure by the carbonic acid anhydrase inhibitor, acetazolamide and the antiepileptic agent topiramate. Acetazolamide may be combined with a loop diuretic such as furosemide. Acetazolamide causes a hypokalaemic metabolic acidosis. Furosemide also lowers the potassium. Therefore, serum electrolytes should be monitored.

The advantages of topiramate are that it is useful in preventing migraine and suppresses appetite. However, it has several adverse effects, including cognitive decline, dysgeusia, acral paraesthesiae, metabolic acidosis, acute narrow-angle-glaucoma, renal calculi and is **teratogenic**.

The following drug combination is useful for an acute attack of IIH:

- Acetazolamide 500 mg p.o. immediately, then bd, increased to 2–4 g/day
- Ketorolac 30 mg IVI
- Dexamethasone 8 mg IVI
- An antidopaminergic antiemetic such as *metoclopramide* 10 mg p.o. or IVI up to 6-hourly, or *domperidone* 10 mg p.o. 8-hourly, or *prochlorperazine* 20 mg p.o. followed by 5–10 mg 6-hourly if necessary or 12.5 mg IMI or 25 mg per rectum.

If the headache and visual loss do not respond to weight loss or medical treatment, surgery should be considered, including CSF diversion with a ventriculo- or lumboperitoneal shunt, optic nerve sheath fenestration, or venous sinus stenting. Bariatric surgery is indicated if dietary measures are ineffective.

Low intracranial pressure headache

PDPH is the most common cause of an LPH. This follows subarachnoid anaesthesia or analgesia and correlates with needle size used (< 25 G), number of attempts and age. PDPH occurs more commonly in young patients and rarely in the elderly.

SIH is a rare cause of LPH and usually follows a tear in the spinal dura or dural sheath of a spinal nerve. The tear is caused by known or unrecognised trivial trauma involving the spine. CSF leaks into the spinal epidural space resulting in LPH. Patients present with acute (thunderclap)

disabling headache, or the headache may develop over several days. The diagnosis of SAH is high on the differential diagnosis list in patients presenting with severe acute headache. If imaging does not confirm SAH or any cause of increased ICP, SIH should be considered.

Postural headaches can be relieved by lying down or by sitting up. A headache that is relieved on lying down (orthostatic headache) is typical of PDPH and SIH. In contrast to orthostatic headache, meningitis-associated headache is exacerbated by supine position.

Loss of SCF causes sagging of the brain in the upright position, resulting in traction on the pain-sensitive meninges, sensory cranial nerves V, VII, IX, and X, cervical spinal nerves C1–3, motor cranial nerves (VI, VII) and NVIII. Traction on these nerves explains the symptoms of frontal and occipital headache, nausea, vomiting, tinnitus, vertigo, muffled hearing, diplopia and cervical myelopathy; all which improve in the horizontal position.

LPH is treated with paracetamol, an NSAID and caffeine, but these drugs do not contribute to sealing of the CSF leak. LPH may disappear spontaneously over time (days to months), but intervention is often necessary. The most common remedy is an epidural blood patch (EBP).

The EBP may be done using the loss of resistance technique or with the help of a radiologist under fluoroscopic or computed tomography (CT) guidance. The EBP is a sterile procedure. The patient may sit or lie on the side. The epidural space is identified with an epidural needle (usually an 18 G). With the needle in place, the assistant draws 15–20 ml blood from the patient (also applying a strictly sterile technique). The blood is injected into the epidural space over approximately one minute. After the EBP, the patient must stay in bed for a day and avoid exercise for a few days. The EBP has a success rate of more than 90%, but may be repeated.

The EBP may be difficult in patients with SIH. The epidural space may be filled with CSF under pressure. When the needle is inserted, CSF may flow back through the epidural needle and it may seem as if the tip has perforated the dura. In these cases, fluoroscopy may facilitate the procedure.

PDPH may also be treated with neostigmine and atropine. *Neostigmine* increases CSF production and blocks CSF reabsorption by the cerebral vessels on the brain surface, which is the main reabsorption mechanism of CSF (not the subarachnoid villi). Both neostigmine and atropine cause cerebral vasoconstriction. The doses are neostigmine 20 µg/kg and atropine 10 µg/kg slowly IVI over approximately 5 minutes 8-hourly. Two doses are usually sufficient. Adverse effects are abdominal cramps (20%), muscle twitches (15%) and urinary bladder hyperactivity (12%).

13.9.6 Paranasal sinusitis

When the cause of headache cannot be identified clinically, the clinician should refer the patient for imaging, including the paranasal sinuses to exclude sinusitis. Pain management consists of antibiotics, paracetamol, an NSAID and decongestants.

Isolated sphenoid sinus pathology

Infection/inflammation is the most common pathology (bacterial and fungal sphenoiditis), followed by polyps and neoplasia.

Pathology of the sphenoid sinus should be considered in severe, refractory new-onset headaches. Isolated sphenoid sinusitis is an uncommon condition, which can often be overlooked. Patients may present with nonspecific symptoms and the clinical examination often do not reveal pathology. Different from pathology in the other paranasal sinuses, patients do not often present with nasal obstruction, rhinitis, tenderness or nasal secretions. Only approximately 20% of patients are febrile. The diagnosis is often missed even after the patients have developed neurological signs. Sphenoid sinusitis has a high morbidity and mortality (7–30%) if diagnosis and management are delayed.

Situated at the center of the skull, the sphenoid sinus is in contact with several structures, including the dura, cavernous sinus, internal carotid artery, optic nerve and optic chiasm, pituitary gland, and cranial nerves III, IV, VI, and all three divisions of V (V1 is the nerve supply of the sphenoid sinus), and is close contact with the sphenopalatine ganglion. These relationships explain the (non)specific symptomatology, variations in pain, the referred nature of the pain, and the wide range of complications.

All patients with inflammatory/infective pathology (usually pneumococcal or staphylococcal, and fungal) present with headache, while only 30% with neoplastic lesions experience headaches. The headache may present gradually or may present as an acute thunderclap headache. The pain is referred to any part of the head and is worse at night. It may involve any part of the head: pancephalic, hemicranial (migraine-like), retro- or periorbital, maxillary, frontal, fronto-occipital, vertex, parietal, temporal (arteritis-like) or postauricular.

Patients with cranial nerve involvement present with diplopia (NIII, NIV and VI), and pain or numbness over the distribution of the trigeminal nerve. Photophobia and loss of vision are caused by inflammation of the optic nerve and retinal ischaemia. The latter is caused by occlusion of the retinal artery and vein by thrombosis, oedema or vasculitis.

Other complications of sphenoiditis include osteitis, extra- and subdural empyema, meningitis, brain abscess, and cavernous and superior sagittal sinus thrombosis.

Sphenoiditis needs emergent surgery and antimicrobial therapy. Pain is managed by paracetamol, an NSAID and an opioid (e.g. buprenorphine).

13.9.7 Occipital neuralgia and cervicogenic headache

Occipital neuralgia (ON) and CGH present with occipital pain. Symptoms point to involvement of the upper cervical and trigeminal nerves. The upper cervical afferents and trigeminal afferents converge to form the *trigeminocervical complex*. Therefore, nociceptive stimuli from the upper cervical afferents (C1–3) are referred to areas that are innervated by trigeminal afferents, causing referred cervical, parietal, frontal or orbital pain.

The greater occipital nerve (C2) supply the skin overlying the posterior skull to the vertex. The lesser occipital nerve (C2 and C3) supply the skin overlying the posterior third of the temporal fossa, and the area of the neck superior and posterior of the ear. The third occipital nerve (C3) supplies the skin of the lower occipital scalp and upper neck.

Occipital neuralgia may be a primary headache disorder, or it may be caused by irritation of the occipital nerves. Patients complain of paroxysms of severe, usually unilateral, stabbing pain that last for seconds to minutes. The pain is in the distribution of the greater and lesser occipital nerves (i.e. occipital area) and radiates to the vertex and to the trigeminal areas, namely the temporal, frontal and orbital areas. In between attacks, patients may experience a dull pain and allodynia over the affected area.

Referred pain from cervical structures should be considered if the pain is persistent and allodynia is absent. Pain referred from the atlantoaxial or upper facet joints may point to CGH.

The diagnosis of *CGH* is made if a temporal relationship exists between the headache and disorders of the cervical spine or soft tissues. Clinical and/or imaging evidence may identify a disorder within the cervical spine and soft tissues of the neck, which are known causes of headache. In patients with CGH, neck mobility is limited and pain is aggravated by certain neck manoeuvres and pressure points on the nerve.

CGH may be caused by myelopathy involving C1, C2 and C3. Approximately 90% of patients suffering from a cervical myelopathy or radiculopathy, complain of headache. There may be an association between neck pathology and CGH, but the pathology is not necessarily the cause of the headache. Nevertheless, imaging may be necessary to exclude pathology such as tumours, fractures, spondylolysis, etc.

Both ON and CGH, as well as other primary headaches, such as migraine, CH, and TTH may improve with blockade of the occipital nerves. All these headache disorders may overlap clinically, including pericranial (periosteum of the skull) tenderness and neck pain. Connections

between the upper cervical nerves and cranial nerves VIII, IX, and X may explain tinnitus, dizziness and nausea.

Both ON and CGH respond to manual treatment (massage and manipulation of the neck). The value of pharmacological treatment is not clear but may be helpful. These include NSAIDs, amitriptyline, baclofen and an anticonvulsant such as gabapentin or carbamazepine. The cytokine TNF-α antagonist infliximab may also be helpful. Opioids should not be prescribed and doctors must be on the lookout for the development of MOH.

13.9.8 Hypnic headache

A hypnic headache (HH) is a rare primary headache. It usually occurs in persons older than 50 years and more commonly in women. It is a strictly sleep-associated headache, waking the patient up at approximately the same time, usually between 2:00 am and 4:00 am (*alarm clock headache*), and lasts for 2–3 hours. The headache is usually described as mild to moderate, is usually bilateral, frontotemporal, or diffuse. The headache improves after a few hours.

The clinical presentation and pathophysiology differ from other primary headaches, such as migraine. The strict association with sleep and the circadian nature suggest involvement of the hypothalamus, not the trigeminal nerve. It is not a REM sleep disorder, and not a manifestation of OSA, although OSA does occur more commonly in the elderly.

The acute attack is usually terminated by caffeine (a cup of strong coffee). Prophylactic treatment options are caffeine, indomethacin and lithium.

Caffeine (a cup of strong coffee at bedtime) is safe and promising. Patients do not usually complain of any sleep problems after taking caffeine.

The COX-1 inhibitor indomethacin may be an effective prophylactic drug. The dose is 0.3–2 mg/kg at bedtime. Since HH occurs more commonly in the elderly, the effect of NSAIDs on kidney function should be considered. A combination of indomethacin with a PPI prevents gastric mucosal effects.

Lithium carbonate may be effective. The dose is 2–8 mg/kg/day (plasma levels of 0.5–1.0 mmol/l). However, lithium has several adverse effects, including worsening of the headache, sedation, tremor, nausea, vomiting, diarrhoea, nephrogenic diabetes insipidus resulting in polydipsia and polyuria, chronic renal failure, hypothyroidism, acne and psoriasis. It is contraindicated in patients with kidney disease and CV disease. It should not be used in combination with NSAIDs and diuretics since they decrease the clearance of lithium.

13.9.9 Cluster headache

A CH is a rare (about 4/10 000) primary headache, occurring more often in men. Headache recurs (clusters) within active periods. CHs usually occur at night during the first three hours of sleep. The attack starts within 5–10 minutes, and lasts between 15 minutes to 3 hours (usually less than an hour). At least five headaches occur during a cluster, with frequency ranging from one every other day to eight per day. CHs can be episodic or chronic. Patients with episodic CH (about 90% of patients) have a series of attacks lasting from weeks to months followed by pain-free periods lasting months to years.

CHs are intense, stabbing, strictly unilateral in the periorbital and temporal region, and are accompanied by agitation and restlessness (which is not typical of migraine). Attacks usually remain on the same side. Ipsilateral autonomic activation occurs in approximately 90% of patients. These present as nasal congestion, ptosis, lacrimation and conjunctival hyperaemia.

CHs should be differentiated from dissection of the internal carotid artery, venous sinus thrombosis, and C2 nerve root pain. Internal carotid artery dissection presents with headache, pulsatile tinnitus, aphasia, eye pain, neck pain, Horner syndrome, inability to swallow and hemiparesis.

Venous sinus thrombosis may present with a thunderclap headache or a new-onset headache. Venous sinus thrombosis occurs in patients with pro-thrombotic risk factors. They present with neurological symptoms, including headaches, which may appear gradually or suddenly (thunderclap), aphasia, hemiparesis or bilateral weakness, seizures, depressed consciousness and coma. On examination, there are signs of severe increased ICP, including papilloedema, decreased level of consciousness, abnormal posturing, and a Cushing response.

Pathophysiology of cluster headache

The pathophysiology of CH is unclear. The circadian and seasonal nature of CH suggests a role of the hypothalamus in the pathophysiology. Neuroendocrine changes also point to hypothalamus dysfunction, including decreased melatonin levels; especially during attacks. Headaches can be provoked by vasodilatation in the hypothalamus. Nitroglycerin causes vasodilatation in the ipsilateral inferior hypothalamus during a nitroglycerin provoked attack.

Fibres from the hypothalamus to trigeminal nuclei can activate the trigeminovascular and cranial parasympathetic systems, which may explain the ocular autonomic symptoms.

Management of the acute cluster headache attack

Primary analgesics are ineffective.

Oxygen

When the patient seeks help while still experiencing a headache, the first step is the administration of 100% oxygen at 10 l/minute using a nonrebreathing mask for 25 minutes. The attack can recur after discontinuation of oxygen. Oxygen therapy is more effective in men.

The triptans

Sumatriptan 6 mg SC is the most effective treatment to abort a CH and is effective in more than 70% of patients within 15 minutes. Higher doses are not more effective. Sumatriptan 20 mg via nasal spray is effective in approximately 55% of patients within 30 minutes. The other triptans are also effective, especially when administered via nasal spray (see the section on migraines). For adverse effects and contraindication for triptans, see the section on migraines. Ergotamine and dihydroergotamine are not recommended.

Octreotide

Octreotide (somatostatin analogue) may be considered to improve the headache. The dose is octreotide100 µg subcutaneously. However, the patient must be monitored for adverse effects, including bradycardia or tachycardia, and hyper- or hypoglycaemia. Minor adverse effects include urticaria at the injection site, nausea, flatulence, diarrhoea and lethargy. It should not be administered with calcium channel blockers.

Sphenopalatine ganglion topical anaesthesia

The sphenopalatine ganglion is situated posterior to the middle nasal turbinate. Lignocaine and cocaine swabs have been applied to the mucosa covering this area. Using lignocaine 4% spray, the pain relief was moderate or poor in 54% of patients, with no relief in the rest.

Prophylactic therapy

Only small studies have evaluated the use of drugs in the management of CH, and are used off-label. Patients suffering from CH should be monitored for the development of analgesia overuse headache.

Verapamil

Verapamil is the drug of choice and is tolerated well. It can be used in combination with other agents (except octreotide) during the acute attack. The prophylactic oral dose is approximately 4.5–9.0 mg/kg/day p.o. divided into three doses (i.e. approximately 1.5–3.0 mg/kg p.o. 8-hourly). The long-acting tablet (240 mg daily) may also be used. Verapamil is effective after approximately one week. Common adverse effects are constipation, hypotension and dizziness.

An electrocardiogram must be done to exclude conduction defects. The vascular selective calcium blockers nifedipine and nimodipine have been used.

Lithium carbonate

Lithium carbonate may be used for the long-term prophylaxis of CH. The dose is 4 mg/kg p.o. bd. The trough plasma concentration is measured 12 hours after the last dose and should not exceed 1.0 mmol/l. It may be used in conjunction with verapamil. For adverse effects and monitoring of lithium therapy, see hypnic headache.

Melatonin

Melatonin levels are controlled by the suprachiasmatic nucleus of the hypothalamus. Levels increase at nighttime and decrease during daytime. In patients suffering from CHs, melatonin levels are reduced, especially during headache. The dose is 2–10 mg/day p.o. Melatonin causes drowsiness and must be taken at bedtime.

Civamide

Civamide is a capsaicin receptor modulator. It depresses activity in type-C nociceptive fibres, and releases with repeated application, depletes neuropeptides algesic peptides, such as substance P and CGRP. Substance P and CGRP may trigger episodic CH. Civamide nasal spray has been effective in improving headache response.

Baclofen

The $GABA_B$ receptor agonist baclofen has been used with some success. The dose was 5 mg three times per day. The drug has several adverse effects, including drowsiness, hallucinations, depression, hypotension, dizziness and urinary retention.

No evidence supports the use of triptans and corticosteroids for prophylaxis in CHs.

13.9.10 Chronic headache because treatment is not working: medication overuse headache

These patients suffer from a chronic headache *of known diagnosis* and start to present more often because their medication does not give relief anymore. Although these patients may suffer from a primary headache, the doctor must be vigilant not to miss a new headache, or secondary headache where the underlying pathology is changing. This is especially true for patients with intracranial hypertension. The headache of intracranial hypertension may be ascribed to TTH, migraine, or MOH.

Patients presenting for medication failure suffer from chronic migraine. They experience headache almost daily and triptans do not give complete relief. It is important to look for a

new headache, but also to review their medication consumption. Very often, patients overuse tramadol and OTC analgesic combinations containing codeine and a sedative, such as meprobamate, doxylamine, promethazine and diphenhydramine. If patients use analgesics for headache for more than ten days per month, the diagnosis of MOH should be considered.

The reason for the MOH may be that the primary headache has not been addressed adequately. If the patient is in pain when presenting, the primary headache should be managed with a triptan, a neuroleptic (dopamine antagonist) and an IV NSAID. The doctor must ensure that the patient receives appropriate prophylactic medication. Lifestyle and psychological interventions may assist in addressing the drug overuse.

13.10 Acute neuropathic pain

13.10.1 General considerations

Owing to its severity and persistence (considered as chronic pain), neuropathic pain has a high morbidity and often results in disability.

Nociceptive pain differs from neuropathic pain. Neuropathic pain is usually described as being sharp, aching or throbbing. It usually occurs in the area of injury, is proportional to the extent of injury, and decreases as healing takes place.

Neuropathic pain may remain constant, but usually changes in character (i.e. distribution, triggers, severity, duration and frequency of attacks). It often persists even after healing or after the original stimulus has disappeared. The pain is dysfunctional since it no longer has a protective role, namely to protect the person from real or potential tissue harm:

- The person experiences pain in a body part that is not present anymore (*phantom pain*).
- Pain may be experienced in the absence of a stimulus (*dysaesthesia*).
- Pain may be experienced in response to nonharmful stimuli, such as touch (*allodynia*).
- The pain may be a disproportionate response to a stimulus that is painful (*hyperalgesia*).
- Pain may be accompanied by inappropriate sensations, such as pins and needles, crawling and tingling (*paresthesia*).
- Pain or other sensations are experienced in a different part than the part that is stimulated (*alachaesthesia*).
- Pain is experienced in a numb area (*anaesthesia dolorosa*).

Neuropathic pain is caused by lesions in the CNS or the peripheral nervous system (PNS). Injury of the CNS and PNS cause severe acute neuropathic pain (ANP) and may evolve into chronic pain complex regional pain syndromes.