Painful Ophthalmoplegia

Vignette

A 32-year-old pediatric nurse was brought to your attention because of right eye pain. Apparently 4 weeks previously she started complaining of throbbing pain involving the right eye, accompanied by severe frontal and periorbital headache. She then developed double vision and drooping of her right eyelid, which persisted without fluctuations. The neurological examination showed a large, nonreactive pupil on the right, right ptosis, and loss of right eye movement in all directions. Motor and sensory examinations were intact.

Summary

A 32-year-old woman with right eye pain and ophthalmoplegia. Clinical findings include right eye pain, ptosis, dilated pupil, and complete ophthalmoplegia, indicating a lesion of the third, fourth, and sixth cranial nerves.

Localization

The first consideration is to decide whether the lesion involves the peripheral nerve or if it is due to dysfunction of the muscle or the neuromuscular junction. Following are common localizations for multiple infranuclear nerve involvement:

- Cavernous sinus/parasellar area/superior orbital fissure region.
- Subarachnoid space.
- Brainstem/posterior fossa.
- Orbital area.

In a patient presenting with multiple ocular nerve palsy, a lesion involving the cavernous sinus should be highly suspected particularly because of the anatomical composition of the sinus. The carotid siphon, oculosympathetic complex, and cranial nerves III, IV, V₁, V₂, and VI are important structures located within the cavernous sinus. Therefore disorders affecting the cavernous sinus may cause multiple cranial nerve involvement. Another important feature is the occurrence of pain which is attributed to trigeminal nerve dysfunction. Different disorders of the cavernous sinus can cause painful ophthalmoplegia, such as infectious, inflammatory vascular disorders, and primary and metastatic tumors (see later discussion on cavernous sinus syndrome).

Infectious and neoplastic infiltration of the subarachnoid space can also manifest with multiple cranial nerve paresis, including the ocular motor nerves. Leptomeningeal metastasis can affect the sixth, third, and fourth oculomotor nerves and cause diplopia. Facial paralysis and visual and hearing loss can also occur in combination with headache and altered level of consciousness. Leptomeningeal metastasis represents a late manifestation of systemic cancer.

An intrinsic parenchymal brainstem process can cause dysfunction of ocular cranial nerves and their nuclei, but signs of involvement of the long motor and sensory tract are also present. Lesions extrinsic to the brainstem, such as ruptured aneurysms of the posterior communicating artery, can present with painful ophthalmoplegia particularly affecting the oculomotor nerve, usually with pupillary involvement. Basilar artery aneurysms can be responsible for progressive cranial nerve palsies and hydrocephalus.

Pathological processes involving the orbital area are due to inflammatory pseudotumor infections, such as mucormycosis, particularly in patients with diabetes, inflammation of the contiguous sinuses, and so on (Glaser). Painful ophthalmoplegia can be associated with proptosis and, in the case of mucormycosis, can cause fatal complications.

Disorders of the muscles include acute orbital myositis, which is an inflammatory process localized to the extra-
ocular muscles and responsible for the occurrence of orbital pain and limitation of eye movements, that usually resolves over a few weeks. Ocular myopathies (e.g., thyroid myopathy and progressive external ophthalmoplegia) can also be differentiated. In dysthyroid myopathy, pain is not common. Bilateral involvement, pupillary sparing, proptosis, and restrictive ophthalmoplegia are other features.

Disorders of the neuromuscular junction, such as myasthenia gravis and botulism, can also be easily excluded. Myasthenia gravis is characterized by fatigable weakness that improves with rest, and asymmetrical painless ophthalmoplegia with ptosis and without pupillary involvement. Botulism is responsible for acute onset of dysphagia, ophthalmoplegia with dilated pupils, and rapidly progressing limb weakness and respiratory distress.

Cavernous Sinus and Its Disorders

The cavernous sinus is a venous structure localized on either side of the sella turcica that expands from the superior orbital fissure to the petrous portion of the temporal lobe and is connected with the opposite sinus via the intercavernous space. Disorders affecting the cavernous sinus can be vascular, neoplastic, infectious, and inflammatory.

Vascular disorders include intracavernous aneurysms, cavernous sinus fistulas, and thrombosis of the cavernous sinus. Aneurysms of the internal carotid artery present with progressive diplopia, varying degrees of ocular paralyses, Horner’s syndrome, exophthalmus, and peribital pain that can be severe. Aneurysmal rupture may cause subarachnoid, intraventricular, or parenchymal hemorrhage with fatal complications.

Carotid-cavernous sinus fistulas that can be spontaneous or may follow a trauma are characterized by an abnormal communication between the ICA or its branches and the cavernous sinus. Clinical manifestations are characterized by chemosis, pulsating exophthalmus, ophthalmoplegia that more commonly affects the sixth nerve, and visual loss.

Cavernous sinus thrombosis is caused by spreading of infections of the ethmoid, sphenoid, or maxillary sinuses, or the skin around the eyes and nose. Symptoms are unilateral but may become bilateral if the opposite sinus becomes involved. They include exophthalmus, edema of the eyelids, ophthalmoplegia preferentially involving the sixth nerve, retinal hemorrhages, papilledema, and severe orbital pain.

Neoplastic disorders involving the cavernous sinus can be primary or metastatic. Pituitary adenomas may invade the cavernous sinus by lateral extension resulting in progressive ophthalmoparesis preferentially involving the third nerve. A dramatic picture of severe headache ophthalmoplegia and rapid neurological deterioration is caused by pituitary apoplexy due to spontaneous hemorrhage into a pituitary adenoma.

Other tumors such as intracavernous meningiomas can cause slowly progressive cranial nerve palsies and ophthalmoparesis.

Metastatic tumors can involve the cavernous sinus by direct extension, such as nasopharyngeal carcinoma, via perineural routes, such as squamous cell carcinoma of the face or neck or through the hematic and lymphatic systems in patients with cancer of the lung, breast, or prostate, or malignant lymphoma.

Inflammation within the cavernous sinus may result from infectious causes or may be idiopathic. Infectious processes may be due to bacterial, viral, or fungal organisms, such as those responsible for bacterial sinusitis or herpes zoster and fungal mucormycosis. Granulomatous inflammatory disorders are typically represented by the Tolosa-Hunt syndrome and sarcoidosis.

Tolosa-Hunt Syndrome

The Tolosa-Hunt syndrome is an idiopathic inflammatory disorder of the cavernous sinus that clinically manifests with orbital and peribital pain and varying degrees of ophthalmoplegia due to dysfunction of the third, fourth, and sixth cranial nerves in various combinations. Pupils can be spared or involved and be dilated or small. Horner’s syndrome can occur if the sympathetic fibers are affected. The course can be acute or subacute and the treatment is based on the use of steroids.

Pituitary Apoplexy

Pituitary apoplexy, which is due to hemorrhagic infarction of the pituitary gland, is an acute event characterized by abrupt onset of excruciating headache, epistaxis, or cerebral fluid rhinorrhea, visual loss, nausea, vomiting, and ophthalmoplegia. The headache is frontal or retroorbital and is often the initial manifestation. A superior expansion of the blood may cause compression of the optic chiasm and bitemporal hemianopia, visual loss, or junctional scotomas. A lateral expansion may be responsible for a cavernous sinus syndrome. Sphenoid sinus involvement causes epistaxis or cerebrospinal fluid rhinorrhea. Signs of hypopituitarism can be present. The course is usually acute but a subacute evolution is also described with symptoms occurring over days or weeks.

Pituitary apoplexy has been described in patients who have large adenomas and factors such as pregnancy, bleeding disorders, hypertension, trauma, radiation therapy, adrenalectomy may increase the risk. Neuroimaging studies may show evidence of hemorrhage. Lumbar puncture may increase the risk of herniation and should not be performed. The treatment is based on corticosteroid
and supportive therapy as well as decompression through the sphenoid sinus.

**Subdural Hematoma**

**Vignette**

A 42-year-old successful editor started complaining of throbbing generalized headache. At work she seemed more irritable and at times forgetful and apathetic, making a few mistakes. She woke up a couple of times at night with headache and vomiting. There was no history of alcohol consumption or drug abuse and previous medical history was unremarkable. She seemed to notice that the headache began after returning from a ski trip in Switzerland with friends six weeks before. During the examination she had trouble with memory and calculation and was uncooperative. Absence of venous pulsation on fundoscopic examination and a left pronator drift were noted.

**Summary**

A 42-year-old previously healthy woman with chief complaints of headache associated with vomiting and cognitive impairment. The neurological examination shows signs of increased intracranial pressure (early papilledema) and a left pronator drift. The headache started after returning from a ski trip with friends (underlying the possibility of a trauma).

**Localization and Differential Diagnosis**

The differential diagnosis in a patient with headache, cognitive impairment, and focal neurological signs is extensive. Space-occupying lesions should be ruled out first. Intracranial tumors may manifest with intermittent headache exacerbated by positional changes, coughing, or straining, and associated with mental status abnormalities, such as irritability, apathy, forgetfulness, and signs of increased intracranial pressure or focal neurological findings.

Inflammatory disorders such as central nervous system vasculitis are also a consideration in the differential diagnosis. Isolated aneuritis of the CNS, for example, is characterized by the occurrence of headache, changes in mental status, focal neurological findings, and seizures, in the absence of signs of systemic involvement. Subarachnoid hemorrhage, cranial nerve involvement and myelopathy can also occur. The diagnosis is mainly based on angiographic findings of diffuse segmental narrowing of the cerebral vessels and on the results of brain biopsy.

Infectious and parainfectious processes include bacterial, fungal, parasitic, and viral causes.

Chronic meningeal processes can manifest with headache, confusion, stiff neck, fever, seizures, and focal lateralizing signs. CSF findings include mononuclear pleocytosis, hypoglycorrachia, and decreased protein level. The responsible organisms include *Mycobacterium tuberculosis* and *Cryptococcus neoformans*. Tuberculous meningitis is more common in immunosuppressed individuals, such as AIDS patients, organ transplant recipients, or patients who undergo chronic corticosteroid treatment. High-risk groups also include immigrants from areas where tuberculosis is highly endemic. Clinically it is manifested with intermittent headache, confusion, low-grade fever, multiple cranial nerve involvement, and progressive deterioration, often in absence of meningeal signs. CSF shows lymphocytic pleocytosis, increased protein level, and hypoglycorrachia. Cryptococcal meningitis can present with subacute onset of headache, mental status and behavioral changes, increasing intracranial pressure, and in some cases meningeal signs and seizures.

Toxic, metabolic, or endocrine disorders can be associated with encephalopathies, but without focal or lateralizing signs.

Chronic subdural hematomas frequently manifest with moderate to severe headache, mental status changes, and focal deficits. Headache occurs in 30 to 90 percent of patients (Stein et al.). The diagnosis of chronic subdural hematoma can present some difficulties when the patient is confused or cannot recall a minor head trauma.

**Clinical Features**

Subdural hematomas can be traumatic when due to the effects of penetrating or nonpenetrating trauma to the head, or spontaneous when not related to trauma but due to aneurysmal rupture, bleeding disorder, use of anticoagulants, infections, low intracranial pressure due to removal of CSF, and so on.

Traumatic subdural hematomas can be acute, subacute, and chronic based upon the time of clinical presentation that varies between a maximum of 72 hours to over 20 days after the trauma.

In acute subdural hematoma, presenting signs are related to the area where it is located and the size of the hematoma, and include changes in mental status, such as confusion, lethargy, stupor, and coma; pupillary abnormalities with dilatation of the pupil ipsilateral to the hematoma; and focal signs, such as hemiparesis. Cranial nerve paralysis may preferentially affect the third and sixth cranial nerves. Other findings include hypertension, bradycardia, papilledema, decerebrate posture, and so on (Stein et al.).

In chronic subdural hematoma, the history of trauma is less recognizable and can be represented by a minor...
injury often forgotten, particularly in elderly confused patients. Stein et al. describe the most frequent presenting symptoms as headache, changes in mentation, and hemiparesis. The headache can be intermittent, mild or severe and may be associated with nausea or vomiting. It can be precipitated by straining, coughing, or physical activity. Mental status and behavioral changes vary and manifest with drowsiness, confusion, forgetfulness, personality changes, and apathy, and can typically fluctuate. Focal signs are never a prominent feature and are mainly represented by hemiparesis. Transient neurological deficits and seizures also occur in some cases.

**Diagnosis**

The diagnosis of traumatic subdural hematoma is based on neuroimaging studies. Subdural hematomas are due to tearing of bridging veins, causing signs of brain compression. Venous bleeding is usually arrested by the rising intracranial pressure. Acute subdural hematoma can be clearly diagnosed by CT scan of the brain, which will demonstrate a hyperdense lesion with concave inner margins. The hyperdense lesion gradually becomes isodense over two weeks and can still be easily diagnosed if signs of mass effect or brain compression are recognized, such as obliteration of the sulci or compression of the ventricles. Chronic subdural hematomas result in a hypodense collection on CT scan.

On MRI, acute subdural hematomas present with decreased signal on T2 due to the presence of deoxyhemoglobin. As deoxyhemoglobin converts to methemoglobin, high signal appears on T1 around the periphery of the collection, later filling in completely. Chronic hematomas show isointensity on T1 and hyperintensity on T2.

**Treatment**

The treatment of subdural hematoma can be medical and surgical. Medical therapy is based on controlling intracranial hypertension and prevention of seizures as well as electrolyte imbalance. The surgical intervention is based on the evacuation of the hematoma, particularly in order to prevent cerebral compression and temporal lobe tentorial herniation.

**Migraine Headache**

**Vignette**

A 20-year-old waitress had a six-month history of several episodes that she described as "pins and needles" in the right fingers that advanced to involve the whole hand, right mouth, lips, and tongue. Occasionally she felt clumsiness of her right arm for 30 minutes, or mumbled or jumbled correct words. By this time a slight right-sided headache had developed, which increased in intensity over a few minutes to become throbbing and severe. Her past history included a heart murmur since childhood and cigarette smoking (one pack per day) for five years.

**Summary**

A 20-year-old female experiencing episodes of paresthesias and clumsiness of the right arm spreading from the fingers to the right mouth, lips, and tongue, associated with occasional speech difficulties and followed by headache.

**Localization**

The vignette points to a cortical localization particularly the frontoparietal area.

**Differential Diagnosis of These Transitory Episodes**

The differential diagnosis includes
- Migraine with aura: cheirooral migraine.
- Epileptogenic event.
- Transitory vascular event.

Migraine with aura can manifest with sensory phenomena such as paresthesias that may involve the fingers of one hand and then advance to involve the forearm up to the elbow and the tongue (cheirooral migraine). This usually occurs in a slowly progressive march evolving over several minutes rather than in a simultaneous manner. Speech difficulties or dysphasia may also occur in a left-dominant patient. Motor weakness can also be present and if prolonged may be consistent with hemiplegic migraine.

Somatosensory seizures may originate in the postcentral or precentral area and are characterized by localized paresthesias or numbness that may progress in a Jacksonian march within seconds as opposed to the slow march of migraine. Postictal numbness can occur corresponding to a sensory Todd’s phenomenon (Engel).

The spread of paresthesias as seen in the case presented is rarely seen in cerebrovascular attacks, where the advance of the paresthesias is much quicker than in migraine (Campbell and Fumihiko). Sensory phenomena in migraine usually consist of a pins and needle sensation that gradually spreads over different areas. TIAs are more often described as numbness and heaviness rather than a positive phenomenon of paresthesias. Also, true paresis is rare in migraine with aura according to some authors who rather describe the weakness as sensory ataxia. Pure hemiplegic migraine is a rare syndrome reported in 0.3
percent of migraine patients (Varelas). Headache can also
develop in cerebrovascular disorders, sometimes preced-
ing the stroke or being associated with transitory attacks.
According to Marks and Rapoport, ischemia in the ter-
ritory of the posterior cerebral arterial system is more
likely to cause headache than anterior circulation cerebral
ischemia.

Secondary disorders that may cause migraine-like ep-
isodes, seizures, or TIAs include

- Vascular disorders, such as venous thrombosis, sub-
arachnoid hemorrhage, Moya-Moya, vascular malfor-
mations, cardiac embolism, carotid dissection, and
so on.
- Blood abnormalities, such as protein C, S, and anti-
  thrombin deficiency, antiphospholipidic antibodies,
  sickle cell disease, and so on.
- Infectious and inflammatory disorders responsible for
  arteritis and arteriopathies, such as syphilis, tubercu-
  losis, herpes zoster, collagen vascular disorders, and
  so on.
- Space-occupying lesions, such as tumors, abscess, cyst,
  and so on.
- Familial disorders such as MELAS (mitochondrial en-
  cephalopathy, lactic acidosis, and stroke), familial
  hemiplegic migraine, and so on.
- Drug-induced/toxic disorders due to cocaine, heroin,
  estrogens, or associated with particular situations such
  as pregnancy or puerperium.

Clinical Differential Diagnosis of
Migraine Headache

There are important clinical clues that help support the
diagnosis of migraine headache in this patient such as age
of presentation usually during youth, typically between
ages 6 and 25 (Marks and Rapoport), slow development
of symptoms, recurrent similar attacks, focal neurological
deficits that do not follow a vascular distribution, tem-
poral association of the aura that can precede or manifest
simultaneously with the headache, family history of mi-
graine, and normal neurovascular examination.

Diagnosis

The diagnosis of migraine headache is based on a com-
prehensive medical and family history and neurological
examination. The characteristic of the headache should
be emphasized, such as age of onset, quality, location,
frequency, duration, triggering or exacerbating factors,
premonitory symptoms, aura if present, and associated
symptoms, such as nausea, vomiting, diarrhea, photo-
phobia or phonophobia, lightheadness, vertigo, and so on.

Neuroimaging studies are indicated if the pain is severe
and different from previous attacks in terms of frequency
and persistence and also if it is the first and worst episode
of migraine mimicking the headache of SAH. The oc-
currence of seizures or neurological deficits on exami-
nation are also an indication for further investigations,
such as MRI of the brain and EEG. MRA and cerebral
angiography are not routinely performed unless there is
a high index of suspicion for certain pathology, such as
arteriovenous malformations, cerebral aneurysm, or
vasculitis.

CSF examination is obtained only in selected cases
when SAH is suspected but neuroimaging studies are nor-
mal, or if an infectious process needs to be ruled out.
Cardiac studies are useful in selected cases to exclude the
possibility of cerebral embolism as a cause of the head-
ache or neurological deficits. Laboratory investigations
are particularly important in all elderly patients where an
elevated ESR can be an indication of temporal arteritis or
to exclude anemia, electrolyte imbalance, systemic infec-
tions, and so on.

Clinical Features

Migraine Headache

Migraine headache is defined as an episodic disorder
characterized by gradual onset of pain that is described
as throbbing, pulsating, or pounding of different intensity
and duration. According to the International Headache
Society, diagnostic criteria for migraine without aura in-
clude the occurrence of five or more episodes of moderate
to severe unilateral headache described as pulsating and
exacerbated by physical activity and with a duration that
varies from 4 to 72 hours (untreated or unsuccessfully
treated). The headache is accompanied by at least one of
the following:

- Nausea and/or vomiting.
- Photophobia and phonophobia.

Also there should be no indication based on history
and general and neurological examination of organic pa-
thyology or, if there is suggestion of this possibility, it
should be ruled out by appropriate studies. If there is an
underlying organic pathology, the migraine attacks do not
manifest for the first time in close temporal relation to
the disorder.

Migraine with Aura

The auras are characterized by transient focal neurolog-
al symptoms that may precede or occur during the head-
ache but can also represent the only symptom. The visual
type of aura is very common and consists of positive phe-
nomena, such as visual hallucinations that consist of a
flashing light, stars, or lines moving across the visual
field, or negative phenomena (scotoma) with different vi-
usal field defects. Sensory and motor phenomena can also occur as well as distortion of perception with alterations of size, contour, and shape of objects.

The International Headache Society has established criteria to differentiate migraine with aura. They include the occurrence of two or more episodes characterized by at least three of the following:

- One or more aura symptoms that resolve completely and suggest focal cerebral cortical or brainstem dysfunction, or both.
- At least one aura symptom that occurs gradually over more than four minutes, or two or more symptoms that develop in succession.
- The symptoms related to the aura should not last more than one hour unless there is more than one aura symptom.
- The headache can precede, occur at the same time, or follow the aura with a free interval of less than 60 minutes.

Also, there should be no indication of an underlying structural pathology or if there is it should be ruled out by appropriate investigations. If organic disease is present, migraine attacks do not manifest for the first time in close temporal relation to the disorders (Silberstein 1995).

**Treatment**

The therapy of migraine headache is based on treatment of the acute attack and prevention of recurrent headaches.

**Prevention**

The need for a preventive approach is based on the frequency of the attacks (at least two per month or more), the duration or significant disability produced by the headache, or if patients experience prolonged auras with risk of permanent neurological deficits. Preventive treatment is also indicated in cases refractory to the acute treatment due to overuse or intolerable side effects.

Several medications have been used for migraine prevention, particularly beta-adrenergic blockers, antidepressants, calcium channel antagonists, antiserotonergic agents, anticonvulsants, nonsteroidal antiinflammatory drugs, and so on. Beta blockers have been extensively used for migraine prevention. Propranol, a nonselective beta blocker, can be started at a dose of 40 mg a day and gradually increased to a maximum of 240 mg a day. Adverse effects have been described such as depression, bradycardia, nausea, dizziness, impaired sexual function with impotence, and so on. Contraindications include congestive heart failure, asthma, insulin-dependent diabetes, and Raynaud’s disease. Other beta blockers used in migraine prevention include atenolol, nadolol, metoprolol, and timolol.

The antidepressants have been widely used for migraine prevention, particularly tricyclics. Amitriptyline, the prototype, is considered a first line drug in patients who suffer from migraine and are depressed or have a sleep disorder, or in the treatment of tension headache and chronic daily headache. Adverse effects are characterized by dry mouth, blurred vision, sedation, weight gain, cardiac arrhythmias, urinary retention, sexual dysfunction, and so on. Tricyclic antidepressants should not be used in patients with glaucoma, heart block, or urinary retention. The dose of amitriptyline is individualized from 10 to 150 mg a day. Fluoxetine (Prozac) a selective serotonin reuptake inhibitor has also been used in migraine associated with depression with a dose that varies from 20 to 80 mg a day and is usually well tolerated except for the occurrence of agitation, anxiety, insomnia, and nausea in some cases.

Calcium channel blockers also need to be considered for prophylactic treatment of migraine, and verapamil has been considered particularly in patients with frequent migraine attacks with auras. The dose varies from 80 to 480 mg a day and usual side effects include constipation, edema of the hands and feet, and cardiac abnormalities.

Anticonvulsant medications represent an important treatment in migraine prevention. Valproic acid has been effective in preventing migraine with and without aura. Adverse effects include gastrointestinal symptoms, such as nausea and vomiting, anorexia, and also tremor, hair loss, and weight gain. Absolute contraindications are pregnancy and liver disease. Divalproex sodium is a stable coordination of sodium valproate and valproic acid in 1:1 molar ratio. The dose varies from 500 to 1000 mg a day. Other anticonvulsants include gabapentin (Neurontin), which has good tolerance and has been used in doses that vary from 300 to 1800 mg with different results. Side effects are drowsiness, dizziness, and, rarely, a rash. Topiramate (topamax) has also been utilized for migraine prevention with improvement in headache frequency in some studies. The dosage varies from 25 to 400 mg a day and adverse effects include fatigue, dizziness, paresthesias, nausea, and anorexia.

Serotonin antagonist drugs used for prophylaxis of migraine include methysergide and cyproheptadine, the latter particularly in pediatric cases. Side effects are gastrointestinal symptoms, drowsiness, and weight gain. Retroperitoneal, pulmonary, or endocardial fibrosis has rarely occurred in patients treated with methysergide.

Nonsteroidal antiinflammatory drugs, such as naproxen sodium, tolfenamic acid, mefenamic acid, ketoprofen, and aspirin, are also part of preventive treatment.

**Acute Attack**

The acute treatment of migraine is based on the use of several medications, some specific, such as triptans and
ergot alkaloids, and some not specific, such as nonsteroidal antiinflammatory agents (naproxen, ketoprofen, diclofenac, and so on) or analgesics (aspirin, acetaminophen) and narcotic analgesics (codeine and meperidine).

Triptans are effective drugs for migraine and include sumatriptan and the new “second-generation triptans” — zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan. They are considered 5-HT–receptor agonists with activation of both 5HT1B and 5-HT1D. Their mechanism of action consists of vasoconstriction, inhibitory action on inflammatory substance released by trigeminal fibers, and inhibition of central pain processing. Sumatriptan has been widely used in the form of subcutaneous injection (6 mg), oral (25, 50, and 100 mg), nasal, and rectal preparations. Injectable sumatriptan (6 mg) has shown higher efficacy than any other form in some studies. The recommended dose is 6 mg subcutaneously that can be repeated without exceeding 2 doses within 24 hours. The oral administration can be repeated up to a dose of 200 mg within 24 hours. Adverse effects include injection site reactions, chest discomfort, a feeling of warmth, and paresthesias. Contraindications to the use of tryptans are the presence of cardiac disorders, such as ischemic heart disease or uncontrolled hypertension, and cerebrovascular disorders. Patients with basilar or hemiplegic migraine should also avoid the use of tryptans.

Ergot alkaloids are represented by ergotamine and its derivative dihydroergotamine. Ergotamine can be administered orally or through a suppository form during the early stage of the headache. Dihydroergotamine can be given intravenously for a rapid relief of pain in association with an antiemetic. Adverse effects include diarrhea, nausea, cramps, and paresthesias. Due to their strong vasoconstrictive effect, they are contraindicated in patients with coronary or other systemic vascular disorders, uncontrolled hypertension, renal or hepatic failure, and so on.

Cluster Headache

Vignette

A 50-year-old airline pilot was taken to the emergency room by his distressed wife in the middle of the night because of left orbital pain that lasted approximately 60 minutes and was so severe that it made him cry. In the emergency room conjunctival injection, edema of the left eyelid, ptosis, and miosis are noted. For the last six weeks, the pilot had experienced similar episodes and the pain had occurred suddenly without warnings. He had a history of hypertension and coronary artery disease and quit smoking two years ago.

Summary

A 50-year-old man with several episodes of severe left orbital pain lasting approximately 60 minutes, associated with other signs: left conjunctival injection, edema, ptosis, miosis, and lacrimation.

Localization and Differential Diagnosis

The differential diagnosis includes primary and secondary headaches.

Among the primary headaches, cluster headache should be considered first. Its clinical features are represented by brief, intermittent episodes of excruciating unilateral pain localized in the orbital and retroorbital area usually on the same side that last from 15 minutes to 3 hours and occur from one every other day to a maximum of eight times a day (Nappi and Russell). The pain is associated with autonomic signs, such as lacrimation, miosis with a partial Horner’s syndrome, conjunctival injection, rhinorrhea, and so on. The episodes of severe, intermittent left orbital pain and associated features experienced by the patient described in the vignette are highly suggestive of cluster headache.

Chronic and episodic paroxysmal hemicrania that manifests with brief episodes of severe unilateral pain localized in the frontotemporal area that recur frequently is also a consideration in the differential diagnosis. Paroxysmal hemicrania, which predominantly affects females as opposed to cluster headache that occurs mainly in males, typically presents with frequent daily attacks (more than five times a day) of shorter duration than cluster headache (5 to 45 minutes) (Goadsby). Signs of autonomic dysfunction also occur and the treatment of choice is indomethacin that causes a rapid relief of the pain.

Migraine headache can also be differentiated from cluster headache. Migraine patients complain of unilateral pain that sometimes extends to the opposite side, associated with nausea, vomiting, photophobia, and phonophobia, as well as focal neurological symptoms that may precede, accompany or follow the headache. Patients suffering from cluster headache have marked autonomic symptoms on the side of the pain, such as conjunctival injection, lacrimation, rhinorrhea, and so on, but nausea, vomiting, and signs of focal cerebral and brainstem neurological dysfunction are not usually observed.

Trigeminal neuralgia typically manifests with paroxysmal, brief attacks of intense electric-like pain that is not accompanied by focal neurological or autonomic symptoms. The pain is very short in duration lasting less than a minute, occurs in the distribution of one or more divisions of the trigeminal nerve, and can manifest spontaneously or be induced by stimulation of trigger areas localized on the skin or mucous membrane. Therefore, it can easily be differentiated from the typical attacks of cluster headache.
Cluster headache can also be secondary to an underlying intracranial organic pathology, such as space occupying and vascular lesions, trauma, and viral infections. Meningioma of the parasellar area, pituitary adenoma, vertebral artery aneurysm or dissection, head injury, facial injury, and so on have been described with symptomatic cluster headache. Patients usually present with clinical features that do not correspond to the ones commonly found in the typical cluster headache, and have more persistent pain that does not respond to the usual treatment and focal neurological findings other than Horner's syndrome.

**Diagnostic Criteria**

The International Headache Society has established some criteria for various types of cluster headache.

**Cluster Headache**

Cluster headache should be characterized by five or more episodes of severe, unilateral pain localized in the orbital, supraorbital, and/or temporal area of a duration that varies from 15 to 180 minutes if not treated and occurring at a frequency that varies from one every other day to eight per day. At least one sign of autonomic dysfunction should occur on the side of the pain, such as rhinorrhea, lacrimation, conjunctival injection, nasal congestion, ptosis, myosis, increased sweating in the forehead and facial area, and edema of the eyelid.

There should be no evidence of organic pathology.

**Episodic Cluster Headache**

Episodic cluster has been characterized as headache manifesting with periods that last seven days to one year separated by pain-free intervals lasting 14 days or more; cluster periods usually last between two weeks and three months. There should be two cluster periods or more with a duration that varies from seven days to one year (untreated), separated by remission of at least 14 days.

**Chronic Cluster Headache**

Chronic cluster headache is characterized by attacks that may last more than one year without remission or with remission of less than 14 days’ duration. Also, there can be no remission phases for one year or more, or remissions lasting less than 14 days.

**Diagnosis**

The diagnosis of cluster headache is based on a comprehensive history and neurological examination and also on neuroimaging studies CT and MRI of the brain if atypical features are present and an underlying organic pathology needs to be ruled out.

**Treatment**

Therapy involves treatment of the acute attack and prevention of recurrent headache. The treatment of the acute attack consists of the use of 100 percent oxygen inhalation for 15 minutes at the onset of headache, sumatriptan, dihydroergotamine, instillation of lidocaine nasal drops, corticosteroids, and so on. Prophylactic treatment is usually prescribed in patients with frequent, severe attacks, particularly those suffering from chronic cluster headache.

The therapy includes several medications such as methysergide, which is preferred in younger patients and has several adverse effects including the rare retroperitoneal fibrosis, and ergotamine that can be given at bedtime to prevent nocturnal attacks, keeping in mind the contraindications in patients with cardiac and cerebral vascular disorders. Other medications include corticosteroids that can be very effective as a short treatment because the side effects prevent prolonged use.

Verapamil is now considered the treatment of choice for prevention of chronic and episodic cluster headache. The dose varies from 80 to 240 mg a day and more based on individual patients. Side effects are constipation, limb edema, and heart block. Lithium carbonate is also effective particularly in patients with chronic cluster headache but has side effects such as gastrointestinal symptoms, CNS toxicity with tremor, confusion, seizures, etc. and needs careful monitoring of the blood level. Valproic acid, gabapentin, and topiramate are also considered prophylactic agents.

**Trigeminal Neuralgia**

**Vignette**

A 44-year-old housewife has a four-week history of lancinating pain involving the right cheek occurring about 30 times a day and lasting several seconds. The pain is quite severe and often precipitated by chewing. There is no nausea, vomiting, or photophobia, but the husband volunteered and she confirmed tearing of the eyes without redness or nasal congestion. General, physical, and neurological examinations are normal.

**Summary**

A 44-year-old woman with right facial pain that occurs 30 times a day, of brief duration (several seconds), without other associated symptoms. Neurological examination is normal.

**Differential Diagnosis**

The differential diagnosis includes disorders characterized by facial pain. Trigeminal neuralgia needs to be con-
considered first due to its features of abrupt, paroxysmal, excruciating pain described as a stabbing, electric-like sensation localized in the distribution of one or more divisions of the trigeminal nerve (usually the second and/or third division) of very brief duration (from seconds to less than 2 minutes). The pain can be triggered by touch or movements of the face, such as when talking or eating. In order to make a diagnosis of trigeminal neuralgia there should not be any focal deficit, particularly any facial area of sensory loss or any abnormality of the corneal reflex unless prior surgery has been obtained.

Postherpetic neuralgia, which is related to acute herpes zoster infection, tends to affect the ophthalmic division of the trigeminal nerve, which is not commonly involved in trigeminal neuralgia. The characteristics of the pain are described as a constant burning, sharp, itchy sensation, without a remitting pattern typical of trigeminal neuralgia.

Other neuralgic syndromes include glossopharyngeal neuralgia and atypical facial pain. Glossopharyngeal neuralgia is less common and has a different distribution of pain from trigeminal neuralgia, manifesting with paroxysmal attacks of severe stabbing or electric shock-like sensation localized in the posterior part of the tongue and tonsil area that recurs many times a day and lasts one minute. The pain can be precipitated by chewing, talking, coughing, swallowing, or yawning. The distribution of pain represents an important factor in the differentiation from trigeminal neuralgia. Atypical facial pain is characterized by a constant, unilateral pain of different intensity that does not follow any anatomical distribution. The pain does not occur in combination with any sensory abnormality.

Cluster headache manifests with severe, unilateral, excruciating pain of longer duration (15 to 180 minutes according to the International Headache Society Criteria) than the typical attacks of trigeminal neuralgia (seconds to less than two minutes) and associated with significant autonomic features. Conjunctival injection, lacrimation, and nasal congestion are accompanying signs of cluster headache. A partial Horner’s syndrome may also manifest.

Trigeminal neuralgia may be indicative of structural lesions, such as tumors, aneurysms, infections, or demyelinating disorders. Impaired sensation, other cranial nerve involvement, and corneal reflex abnormalities may suggest an underlying organic pathology.

Treatment

The medical management of trigeminal neuralgia is based on the use of pharmacological agents such as carbamazepine, phenytoin, valproic acid, and baclofen, with carbamazepine being the first line of treatment. Gabapentin, lamotrigine, and oxycarbazepine have also been used with varying results. Surgical techniques have different approaches, from alcohol or glycerol injection to microvascular decompression that removes aberrant blood vessels from the trigeminal nerve root, to stereotactic radiosurgery.

Facial Palsy: Ramsey Hunt Syndrome

Vignette

A 62-year-old dry cleaning worker started complaining of severe pain and unpleasant loudness in his left ear. During the next 24 hours he became unable to close his left eye and noticed an unusual taste sensation on the tip of his tongue. In the ER, the neurology resident noticed a complete left facial paralysis and redness and tenderness of the left ear canal. The rest of the cranial nerves were normal as well as motor and sensory functions. His previous history was significant for heart disease and diabetes and he was fearful that he’d suffered a stroke.

Summary

A 62-year-old man with left facial paralysis. Associated findings are severe left ear pain, redness, and tenderness; hyperacusia (unpleasant loudness); and taste dysfunction.

Localization

The first consideration is that this is a lower motor neuron lesion because the entire left face is affected. Taste dysfunction over the anterior two thirds of the tongue and hyperacusis (abnormal loudness of sounds due to paralysis of the stapedius muscle) help localize the lesion.

Lesions involving the facial nerve within the facial canal proximal to the exit of the nerve to the stapedius muscle can explain the ipsilateral facial paralysis, taste dysfunction over the anterior two thirds of the tongue, and hyperacusis. When the geniculate ganglion is affected, pain in the region of the eardrum may occur (Brazis).

Differential Diagnosis

In the differential diagnosis, disorders to be considered are idiopathic facial paralysis (Bell’s palsy) and secondary processes affecting the facial nerve, such as infections, tumors, and trauma.

Bell’s palsy, characterized by a nonprogressive peripheral facial paralysis, has been linked to different etiological processes particularly involving a viral inflammatory-immune mechanism. Some studies point to a herpes simplex virus-I infection. The presentation is usually acute and predisposing factors include diabetes, hypertension, or pregnancy. Infectious and parainfectious
disorders causing facial paresis include herpes zoster cerephalicus (Ramsey Hunt syndrome), acute inflammatory demyelinating polyradiculopathy (Guillain-Barré syndrome), infectious mononucleosis, Lyme disease, and others (chickenpox, mumps, influenza, HIV, leprosy, mucormycosis, and so on).

Ramsay Hunt syndrome (RHS) caused by herpes zoster virus infection, is characterized by excrecuting ear pain accompanied by a vesicular eruption involving the external canal and pinna that can precede, accompany, or follow the onset of the facial paralysis. The ear can become red and tender. The paralysis is often severe and complete and postherpetic neuralgia may occur. The patient in the vignette with ear redness and tenderness and complete left VII nerve peripheral palsy may well represent a case of RHS. The diagnosis does not present difficulty in the presence of the typical skin rash. Oral acyclovir is the preferred treatment.

Facial weakness can be an important manifestation of Guillain-Barré syndrome and Lyme disease where it is often bilateral. In GBS cardinal features include symmetrical proximal weakness and hypo-areflexia. Lyme disease is also characterized by generalized weakness, fatigue, headache, fever, and so on.

Infectious mononucleosis rarely is responsible for unilateral, recurrent, or bilateral facial paralysis.

Complicated infections of the middle ear with involvement of the petrous apex, particularly in children, can be responsible for the so-called Gradenigo’s syndrome characterized by severe ear pain and involvement of multiple cranial nerves, such as the ophthalmic division of the trigeminal nerve, the abducens, and facial nerve.

Primary and metastatic tumors may cause facial nerve dysfunction along its course but usually there are other signs and symptoms that suggest a more widespread involvement of other organs and neurological structures. Nuclear and fascicular pontine lesions involving the facial nerve due to vascular processes or tumors also affect other structures and cause long tract signs and gaze abnormalities.

Cerebello-pontine angle lesions, such as acoustic neuromas, facial neuromas, meningiomas, or metastatic processes, can cause facial nerve dysfunction in combination with other signs and symptoms, such as hearing loss, vertigo, tinnitus, diminished corneal reflex, and facial hypoesthesia.

Other causes of facial nerve abnormality include trauma, vasculitis, granulomatous disorders, and so on.

References

**Painful Ophthalmoplegia**


**Subdural Hematoma**


**Migraine and Cluster Headaches**


**Trigeminal Neuralgia**


**Facial Palsy**