Introduction

This article includes discussion of multiple cranial neuropathies, cranial polyneuropathy, and Garcin syndrome, hemibase syndrome, and polyneuritis cranialis. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

There are several syndromes of multiple cranial nerve involvement. One syndrome described by Garcin was a step-by-step ipsilateral involvement of all 12 cranial nerves unilaterally. This term is now used for multiple cranial nerve palsies that do not fit into any of the other named syndromes. This article describes the various pathologies associated with multiple cranial nerve palsies and their differential diagnoses. Neurologic diagnosis is helpful in the early detection of the lesions and their management by the appropriate specialists. Cancer detected early may be amenable to surgery and radiotherapy.

Key points

- Multiple cranial nerve palsies are a part of several neurologic syndromes.
- The original Garcin syndrome was described as unilateral involvement of all the cranial nerves, usually due to malignancy at the base of skull.
- A large number of diseases besides cancer, such as benign tumors, infections, traumatic brain injury, and vascular lesions, can cause multiple cranial nerve palsies and should be considered in the differential diagnosis.
- Treatment and prognosis of multiple cranial nerve palsies depends on the cause.

Historical note and terminology

Galen (131 AD to 201 AD) was the first to classify cranial nerves but counted only 7 pairs of nerves (Major 1961). This classification was employed until the 17th century. Galen demonstrated the existence of 11 cranial nerves of the 12 cranial nerves (he regarded the olfactory nerve as an extension of the brain) but combined several and arrived at a total of 7. Although Vesalius followed the classification of Galen, his excellent dissections of the brain show 9 pairs of cranial nerves (Vesalius 1543). Willis described the arteries at the base of the brain and showed 10 pairs of cranial nerves (Willis 1664). This was the first reclassification of cranial nerves since the time of Galen, and it provided the correct numbering up to cranial nerve X. He described the accessory nerve but did not give it the number it has now: XI. Complete classification of all 12 cranial nerves did not take place until a century later in Germany (Soemmerring 1788). Cranial nerve palsies were not described adequately for still another 100 years. The best description of cranial nerve disorders in the 19th century was in Gower's manual of diseases of the nervous system. This manual was considered to be the bible of neurology at that time, as it devoted 150 pages to cranial nerve disorders (Gowers 1886). Several of the syndromes of multiple cranial nerve palsies were described toward the end of the 19th century and at the beginning of the 20th century. These include the syndromes of Jackson (Jackson 1872), Avellis (Avellis 1891), Tapia (Tapia 1905), Collet (Collet 1915), Villaret (Villaret 1916), and Sicard (Sicard 1917).

Knowledge of cranial nerve lesions is a cornerstone of neurology, and numerous names have been attached to syndromes of various combinations of cranial nerve palsies. One syndrome described by Garcin was a step-by-step ipsilateral involvement of all 12 cranial nerves unilaterally, without the rise of intracranial pressure and long-tract signs (Garcin 1927). Most of the original patients had radiologically demonstrated infiltration of the base of the skull by malignant disease and, in some cases, inflammatory process. Unilateral involvement of all 12 cranial nerves is rare; all of the original cases did not have this. The syndrome has since been modified to include cases with involvement of 7 cranial nerves ipsilaterally as well as a few contralaterally (Roger et al 1969). In Europe, many cases of multiple cranial nerve palsies (even less than 7) that do not fit into any of the other named syndromes are described as Garcin syndrome. Another term used for multiple cranial nerve palsies due to lesions of the skull base is “hemibase syndrome” (Schiffer 1951). Some reported cases have other symptoms such as headaches and signs such as hypopituitarism (Abe et al 1988). One case has been reported with papilledema (Agoni and Prencipe 1968). Another
The term used to describe multiple cranial nerve palsies is “polyneuritis cranialis.”

**Clinical manifestations**

**Presentation and course**

Clinical features depend on the cranial nerves involved. Some of the syndromes associated with tumors at the base of the skull are shown in Table 1.

**Table 1. Multiple Cranial Nerve Syndromes Associated with Lesions at the Base of the Skull**

<table>
<thead>
<tr>
<th>Location of lesion</th>
<th>Cranial nerves involved and clinical manifestations</th>
<th>Eponym</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior orbital fissure</td>
<td>III, IV, V (1st division), VI; ophthalmoplegia, pain and hypoesthesia in the first division of V, exophthalmos, vegetative disturbances</td>
<td>Rochon-Duvigneaud</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>III, IV, V, VI; ophthalmoplegia, exophthalmos</td>
<td>Foix-Jefferson</td>
</tr>
<tr>
<td>Apex of petrous temporal</td>
<td>V and VI; neuralgia, sensorimotor disturbances, diplopia</td>
<td>Lannois-Lannois</td>
</tr>
<tr>
<td>Petrosphenoidal region</td>
<td>II, III, IV, V, VI; ophthalmoplegia, amaurosis, trigeminal neuralgia</td>
<td>Jacod</td>
</tr>
<tr>
<td>Jugular foramen</td>
<td>IX and X; loss of gag reflex</td>
<td>Avellis</td>
</tr>
<tr>
<td>Jugular foramen &amp; hypoglossal canal</td>
<td>IX, X, XI; dysphagia, loss of gag reflex, weakness of sternocleidomastoid and trapezius muscles</td>
<td>Vernet</td>
</tr>
<tr>
<td>Occipital condyles</td>
<td>Foramen jugular syndrome plus XII; unilateral paralysis of tongue muscles with disturbance of tongue movements</td>
<td>Sicard-Collet</td>
</tr>
<tr>
<td>Cerebellopontine angle</td>
<td>V, VII, VIII, IX to XII; deafness, vertigo, nystagmus, raised intracranial pressure, brainstem symptoms</td>
<td>NA</td>
</tr>
<tr>
<td>One half of the base of the skull</td>
<td>I to XII on 1 side; usually the sparing of some nerves and involvement of contralateral nerves also; usual lack of pyramidal signs or any rise of intracranial pressure</td>
<td>Garcin</td>
</tr>
</tbody>
</table>

Cavernous sinus syndrome is often used as a working diagnosis of signs and symptoms related to the 4 cranial nerves passing through the cavernous sinus. One study made an interesting observation that there was an approximately linear correlation between the number of cranial nerves affected by a lesion and the percentage of lesions located within the cavernous sinus (Lin and Tsai 2003). The likelihood of a lesion to be in the cavernous sinus increases to 77.8% with involvement of all 4 nerves, as compared to 17.7% if only 1 nerve is involved.

**Prognosis and complications**

Prognosis depends on the pathology of the primary lesions. Prognosis is poor with infiltration of the base of skull by malignant processes. Many of these tumors are inoperable and are treated with radiation therapy. Five-year survival of nasopharyngeal carcinoma with radiation therapy lies between 25% and 50%. Early detection of a tumor at the base of the skull in an operable stage may improve the prognosis.

**Biological basis**

**Etiology and pathogenesis**

Various causes of multiple cranial nerve palsies are shown in Table 2.
Table 2. Causes of Multiple Cranial Nerve Palsies

**Neoplasms at base of skull**
- Anaplastic ependymoma with intracranial meningeal carcinomatosis
- Benign tumors at the base of the skull
  - acoustic neurinoma
  - sphenoid ridge meningioma
- Chordomas
- Glomus jugulare tumors
- Parapharyngeal branchial cleft cyst
- Leptomeningeal carcinomatosis
- Malignant extracerebral tumors infiltrating the base of the skull
- Metastatic tumors involving the base of the skull

**Lower cranial neuropathy after radiotherapy for oropharyngeal cancer**

**Paraneoplastic syndrome with multiple cranial nerve palsies**

**Inflammatory lesions at the base of the skull**

**Fractures of the base of skull**

**Complications of surgery and radiofrequency lesions**

**Vascular diseases**
- Dissection of internal carotid artery
- Giant aneurysms of the circle of Willis
- Giant cell arteritis
- Venous sinus thrombosis: cavernous, sigmoid
- Vertebrobasilar occlusive disease

**Pseudotumor cerebri/idiopathic intracranial hypertension**

**Infections**
- Bacterial meningitis
- *Brucella melitensis* (Sahin et al 2009)
- Malignant otitis externa
- Rhinocerebral mucormycosis, aspergillosis
- Cryptococcal meningitis
- Cephalic tetanus (Chebel et al 2010)
- Tuberculosis
- Viral infections
- Viral infections

**Pachymeningitis**

**Granulomatous diseases**
- Infectious granulomas
- Sarcoidosis
- Wegener granulomatosis

**Hyperostosis of the skull**
- Paget disease
- Hyperostosis cranialis interna

**Multiple sclerosis**

**Moebius syndrome**

**Melkersson-Rosenthal syndrome**

**Idiopathic cranial neuropathy**

**Complication of Ramsay Hunt syndrome**

**Guillain-Barré syndrome**

**Metabolic disorders**
- Renal osteodystrophy with multiple cranial nerve palsies
- Diabetes mellitus with multiple cranial nerve palsies

Cranial nerves pass through distinct passages at the base of the skull to innervate various structures in the head and
the neck. They are vulnerable to lesions that involve the base of the skull. They are also liable to be involved after exit from the skull base to the structures in the neck. Other parts of the cranial nerves that are susceptible to discrete lesions are those between the brain and the base of the skull. In addition to lesions at the bony base of the skull, the nerves in this portion are liable to be involved in inflammatory processes involving the meninges, trauma and vascular malformations, and intracranial aneurysms. Giant intracranial aneurysms can involve multiple cranial nerves. Cranial nerves may also be affected due to vascular disturbances, such as those that result from vasculopathies involving the cerebral arteries and their branches.

Cranial nerve palsies due to cancer. The most frequent cause of cranial nerve palsies is malignant disease involving the base of the skull. Histology and primary location of the tumor do not play a decisive role in the causation of the cranial palsy. Damage to cranial nerves occurs during the infiltration by the tumor without intradural extension and rise of intracranial pressure. For example, malignant nasopharyngeal tumors expand in 2 directions: (1) through the foramen lacerum into the middle cranial fossa, then into the cavernous sinus and the superior orbital fissure with involvement of cranial nerves III to VI; and (2) to the lymph nodes behind the parotid gland with compression of the cranial nerves IX to XII.

A case of adenoid cystic carcinoma arising from the right salivary gland presented with right multiple cranial nerve palsies without any mass formation (Inose et al 2012). The neurologic manifestations were considered to be attributed to the perineural spread of cancer.

Cranial nerve palsies as a sequel of radiotherapy for cancer. Although cranial nerves are considered to be relatively resistant to radiotherapy, late radiation-associated dysphagia is a rare delayed toxicity after radiotherapy and/or chemotherapy for oropharyngeal cancer, and a study reported that lower cranial neuropathies were present in 10 of 12 cases (Awan et al 2014). Mean dose delivered to superior pharyngeal constrictor, but not the regions of interest containing cranial nerve paths, significantly predicted late-radiation-associated dysphagia and related cranial neuropathies.

Cranial nerve palsies as a complication of surgical procedures. Injuries to the auditory and facial nerves are well-known complications of removal of acoustic neuroma. Procedures involving cavernous sinus are associated with cranial nerve injuries. Internal carotid artery injury during endoscopic endonasal surgery, particularly if it involves the cavernous segment, can be associated with multiple cranial nerve palsies (Chin et al 2016).

Cranial neuropathies due to infections. Although involvement of skull base producing multiple cranial nerve palsies is usually from a malignant process, infections may also involve the base of skull. Four cases of infective skull-base lesions causing multiple lower cranial nerve palsies in elderly patients have been described (Patmore et al 2010). With history of otitis externa in an immunocompromised or diabetic patient presenting with multiple cranial nerve palsies, a diagnosis of osteomyelitis of base of the skull should be considered. A patient with skull base osteomyelitis with septic pulmonary embolism who presented with multiple cranial nerve palsies was treated successfully with antibiotics and anticoagulants (Lee et al 2011).

Epidemiology

Multiple intracranial nerve palsies are frequent, but due to the multiplicity of disease processes involved, no figures are available on the incidence or prevalence. Of the 20 cases of Garcin syndrome published between 1970 and 1988, 16 were due to malignant disease, 1 was due to compression from a benign intracranial tumor, and 3 were due to an infectious process (Greulich et al 1992). If one drops the definition of multiple cranial nerve lesions to involvement of 2 or more nerves, the number of cases may be impossible to record. In 1 series alone there were 979 such cases, of which one fourth were due to malignancy (Keane 2005).

Differential diagnosis

The differential diagnosis of multiple cranial nerve palsies involves 2 important steps:

(1) Localization of the cranial nerves involved and the allocation of an eponym, if it fits.
(2) Determination of the pathology of the lesion.

Various pathological processes that can be identified are as follows:
Primary malignancies at the base of skull. These include tumors of the nasopharynx, cylindromas, and osteosarcomas.

- Garcin syndrome. Chouza and colleagues reported a case of Garcin syndrome with involvement of all the cranial nerves on 1 side due to jugular chemodectoma (Chouza et al 1981). Practically all the possible ways of spreading were followed by the tumor, with involvement of the posterior, middle, and anterior fossae of the skull base, and also the orbit, middle ear, and neck. These were demonstrable by CT.

- Primary osteosarcoma. This has been reported to produce unilateral paralysis of several cranial nerves within a period of 5 months. Diagnosis was based on CT of the skull base (Ratfisch 1984). Other cases have been reported of osteosarcomatosis involving craniofacial bones and presenting with cranial nerve palsies (Sato et al 2000).

- Lymphoma presenting with isolated diffuse infiltration of the skull. This can manifest with multiple cranial nerve palsies (Erlich et al 1996). MRI of the head shows an abnormal signal from the diploic space of the calvarium and skull base on both T1- and T2-weighted images, infiltration of the temporalis muscles and clivus, and diffuse meningeal enhancement encroaching on the cavernous sinus bilaterally. Biopsy of temporalis muscle and skull shows a diffuse large cell lymphoma in such cases. Primary non-Hodgkin lymphoma of the skull base has been reported to present as Garcin syndrome with MRI showing lesions at the skull base (Nakamura et al 2009). In this patient, the diagnosis was established by biopsy of the tumor in the cavernous sinus.

- Leukemia may be associated with multiple cranial nerve palsies. This usually occurs due to infiltration of the cranial nerves. However, there are cases where no infiltrations are demonstrated on brain imaging studies, and the diagnosis and treatment decisions are both based on clinical examination.

- An atypical extra-axial teratoid rhabdoid tumor with extension and bony expansion of the jugular foramen was demonstrated by MRI in a boy who presented with nausea, weight loss, and hoarseness of voice associated with multiple lower cranial nerve palsies (Udaka et al 2015). After near total excision, neuropathological examination showed the absence of INI-1 gene expression that is consistent with a diagnosis of atypical teratoid rhabdoid tumors.

- In a patient presenting with dysphagia and multiple cranial nerve palsies, a past history of radiotherapy for nasopharyngeal carcinoma should be considered in the differential diagnosis.

Metastatic tumors involving the base of the skull. A case of Garcin syndrome due to metastasis to the skull from breast carcinoma has been described (Benedetti 1989). The patient presented with a unilateral abducent paralysis 12 years after mastectomy for breast carcinoma. Multiple unilateral cranial nerve involvement (V to XII) developed over a period of 6 months. CT scan showed the unilateral destructive lesion at the base of the skull on 1 side. In another case of Garcin syndrome with progressive cranial nerve palsies, MRI revealed an intracranial extension of a tumor from the skull base, which had metastasized from carcinoma of the lung (Fujii et al 2007). Cranial nerve palsies in metastatic prostate carcinoma usually occur late in the course of the disease, but a case is reported where diagnosis of prostate cancer was made following investigation of multiple cranial nerve palsies (Mitchell et al 2008).

Benign tumors at the base of the skull. Acoustic neurinomas, and sphenoid ridge meningiomas may present with multiple cranial nerve palsies. Often, with large tumors, there will be signs of raised intracranial pressure as well as other localizing signs. Diagnosis of these treatable lesions can be made both clinically and radiologically. Parapharyngeal branchial cleft cyst can manifest as multiple, lower cranial nerve palsies (Shin et al 2001).

Pituitary carcinoma. Pituitary carcinomas usually originate by transformation of benign invasive macroadenomas. A pituitary macroadenoma that invaded into the right cavernous sinus presented with abducent nerve palsy that resolved following transsphenoidal surgery plus Gamma Knife® radiation, but tumor recurred with malignant change producing right lower cranial nerve palsies, which resolved following repeat Gamma Knife radiation (Ono et al 2011). Multiple cranial nerve palsies in this patient indicated malignant transformation of the tumor.

Giant cell tumor. This is a primary bone tumor rarely affecting the skull base. There is a case report of an 8-year-old child who presented with unilateral cranial nerve palsies of the 5th cranial nerve to the 12th cranial nerve and fulfills
the criteria of Garcin syndrome (Bonet et al 2003).

**Meningeal carcinomatosis.** The cranial nerves involved are usually II, III, IV, VI, and VII. The involvement may be bilateral. There are headache and signs of raised intracranial pressure. Malignant cells can be demonstrated in the cerebrospinal fluid. Rarely, multiple cranial nerve palsyes present as a manifestation of leptomeningeal involvement by glioblastoma multiforme (Trivedi et al 2000).

An extramedullary anaplastic ependymoma has been reported that presented with bone metastases and intracranial leptomeningeal carcinomatosis (Perez-Bovet et al 2013). MRI scan revealed leptomeningeal carcinomatosis in the brainstem, the cerebellum, and along the whole spinal cord.

**Paraneoplastic syndrome with multiple cranial nerve palsyes.** One patient with small-cell lung cancer developed multiple cranial nerve palsyes, including palsyes of the left 5th nerve through 10th nerve and both 12th nerves in the course of paraneoplastic sensory neuronopathy (Fujimoto et al 2002). There were no metastasis or direct invasion of malignancy, but there was gliosis and perivascular inflammation throughout the brainstem, indicating paraneoplastic encephalomyelitis. A paraneoplastic syndrome with involvement of multiple cranial nerves has been reported and may precede diagnosis of testicular cancer (Morelli et al 2007).

Multiple cranial nerve palsies may result from paraneoplastic effect of a tumor rather than local compression. There is a case report of an immunocompetent patient who presented with facial palsy, and then progressively developed other cranial nerve palsyes over several months and was later diagnosed with diffuse large B cell lymphoma originating from the frontal sinus (Kim et al 2011).

**Inflammatory lesions at the base of the skull.** Inflammatory myofibroblastic tumor of the orbit has been reported to manifest as multiple progressive cranial nerve palsyes involving II, V1 to V3, and X with orbital and infraorbital masses and diffuse dural enhancement demonstrated on MRI (McKinney et al 2006). Diagnosis of inflammatory myofibroblastic tumor was confirmed by biopsies of the orbital lesion; the manifestations quickly improved with steroid administration. A case of isolated sphenoiditis presented with unilateral multiple cranial nerve palsyes and was treated successfully with functional endoscopic sinus surgical drainage, and histological confirmation of diagnosis was obtained by biopsy (Shukla et al 2007).

**Fractures of the base of skull.** Fractures of the base of the skull can damage cranial nerves on 1 side. Diagnosis can be made by history or by radiological demonstration of fracture. There may be cerebrospinal fluid rhinorrhea. Unilateral IX, X, XI, and XII cranial nerve palsyes (Collet-Sicard syndrome) have been reported after sustaining a closed head injury with linear fractures of the occipital bone traversing through the right occipital condyle (Wani et al 1991). A case of Collet-Sicard syndrome presented following a traumatic atlas fracture in a patient with congenital basilar invagination. Such a fracture can compromise the space and make cranial nerves IX through XII more vulnerable to compression injury (Hsu et al 2004). Delayed glossopharyngeal nerve, vagus nerve, and facial nerve palsyes have been reported after a head injury with fracture of the petrous part of the temporal bone (Yildirim et al 2005).

Mild head injuries without fracture of the base of the skull may be associated with multiple cranial nerve palsyes. In one series of head injuries with Glasgow Coma Scale scores of 14 to 15, multiple nerve injuries were observed in 22.4% of cases; the most frequent association was between cranial nerves VII and VIII (Coello et al 2010). After 1 year, cranial nerve deficit was present in only 30% of mild head injury cases without CT abnormalities as compared to 81.2% of the cases with a skull base fracture.

**Complications of surgery and other procedures at base of skull.** Multiple cranial nerve palsyes are recognized as complications of surgery on tumors around skull base, some of which already present with cranial nerve involvement. A patient developed multiple cranial nerve palsyes following radiofrequency ablation for trigeminal neuralgia and improved over a period of 4 months (Madhusudan Reddy et al 2008).

**Vascular diseases.** Giant aneurysms of the circle of Willis can cause pressure on cranial nerves. Jugular bulb diverticulum, a rare condition, has been reported in association with lower cranial nerve palsyes and multiple intracranial aneurysms in a patient who presented with dysphagia and hoarseness (Kobanawa et al 2000). The patient recovered after repair of the aneurysms.

Cavernous sinus thrombosis can involve the cranial nerves traversing the sinus and can produce a cavernous sinus syndrome. Multiple cranial nerve palsyes (III to VIII), without evidence of other signs and symptoms, have been
Documented in patients with thrombosis of the ipsilateral transverse and sigmoid sinus (Kuehnen et al 1998). The diagnosis was supported by MRI with the application of a newly developed subtraction technique.

The usual presentation of spontaneous internal carotid artery dissection includes ipsilateral hemicranial headache, oculosympathetic paresis, and contralateral focal cerebral ischemic deficits. Multiple cranial nerve palsies are reported in more than 10% of patients with spontaneous dissection of the internal carotid artery. Two cases with multiple cranial nerve involvement ipsilateral to the dissection as the principal feature have been described (Panisset and Eidelman 1990). One of these patients had involvement of the IX, X, XI, and XII cranial nerves, and the other showed abnormalities of the V, VII, IX, X, and XII cranial nerves. In both, MRI revealed a ring-like area of abnormal signal intensity surrounding the carotid artery at the skull base. Carotid angiography was consistent with the suggestion of dissection on the magnetic resonance studies in both cases. Another patient with right internal carotid artery dissection developed ipsilateral II, V, VII, VIII, IX, X, and XII cranial nerve deficits, which resolved as the internal carotid artery recanalized following conservative treatment (Mattioni et al 2007). The acute onset of cranial nerve palsies IX through XII, mostly accompanied by pain in the head, neck, or ear, should prompt consideration of a diagnosis of internal carotid artery dissection (Peltz and Köhrmann 2011). Internal carotid artery dissection, presenting multiple cranial nerve palsies, could be mistaken for an infiltrating tumor of the skull base, and MRI is useful in correctly identifying the condition.

Vertebrobasilar occlusive disease may produce multiple cranial nerve palsies but is easy to distinguish clinically because of the involvement of other structures in the brain stem.

Collet-Sicard syndrome with paralysis of cranial nerves IX to XII due to internal carotid artery dissection was observed (Smith et al 2013).

Infections. Any subacute or chronic meningitis may involve the cranial nerves. Well-recognized causes are pneumococcal, tubercular, cryptococcal, mycoplasmal, and treponemal infections. Craniovertebral junction tuberculosis has been reported as a cause of multiple cranial nerve palsies, and diagnosis is confirmed on histopathological examination (Mohindra et al 2006). One patient with AIDS who developed cryptococcal meningitis had involvement of 5 cranial nerves, resulting in the complete loss of vision and hearing as well palsies of cranial nerves III, VI, and VII, which improved following treatment with multiple antifungal medications (Mohan et al 2006).

Another patient with AIDS presented with neurosyphilis as the initial manifestation of HIV infection with acute bilateral hearing loss and bilateral facial droop multiple cranial nerves palsies caused by direct invasion of the central nervous system by the spirochete Treponema pallidum (Alqahtani 2014). Basal meningoencephalitis resolved with recovery of cranial nerves after a course of treatment with penicillin, and antiretroviral therapy was started later.

Multiple cranial nerve palsies may occur in viral infections. Unilateral IX, X, and XI have been reported in a rare case of laryngeal herpes zoster where the mucosal lesions were discovered during upper gastrointestinal endoscopy, and the patient recovered with antiviral therapy (Van Den Bossche et al 2008).

Varicella zoster. Virus infections such as varicella zoster may rarely cause multiple cranial nerve palsies. These can be recognized by cerebrospinal fluid examination, serology, or molecular diagnostics. Unilateral cranial neuropathy involving cranial nerves VII to X has been associated with serological evidence of varicella zoster infection (Mayo and Boos 1989). A case of multiple cranial nerve palsies (left VIII, IX, X, XI and right VII, IX, X) has been reported to be due to varicella zoster infection (Kikuchi et al 1995). Multiple lower cranial nerve palsies due to the reactivation of varicella zoster virus may be present without skin lesions; this is known as zoster sine herpete. There is a case report of a patient with unilateral involvement of the cranial nerves VIII, IX, X, and XI without skin lesions and mononuclear pleocytosis in the cerebrospinal fluid with antibodies against Herpes zoster (Terborg et al 2001). Another patient with varicella zoster, who initially presented with Ramsay Hunt syndrome, later developed multiple cranial nerves palsies mimicking Garcin syndrome but improved following treatment with intravenous acyclovir and corticosteroids (Nishioka et al 2006).

Malignant otitis externa. This syndrome consists of an antibiotic-resistant Pseudomonas aeruginosa infection of the external auditory meatus with osteomyelitis of the temporal bone. It usually affects patients with long-standing diabetes mellitus and a weakened immune system. The incidence of multiple cranial nerve palsy was reported to be 24% of one series of cases of malignant otitis externa (Ali et al 2010). Malignant external otitis often spreads inferiorly from the external canal to involve the subtemporal area and progresses medically toward the petrous apex leading to multiple cranial nerve palsies. CT findings in malignant external otitis include obliteration of the normal fat planes in...
the subtemporal area as well as patchy destruction of the bony cortex of the mastoid. The point of exit of the various cranial nerves can be identified on CT scans, and the extent of the inflammatory mass correlates well with the clinical findings. Multiple cranial nerve palsies have been described as a complication of infectious mononucleosis due to inflammatory lesion in the jugular foramen (Joki-Erkkila et al 2000).

**Fungal infections.** Aspergillosis of the CNS should be considered in those with clinical features of headache, multiple cranial nerve palsies, and alteration of consciousness accompanied by sinusitis, especially in elderly and diabetic patients (Pongbhaesaj et al 2004). Mucormycosis is a devastating fungal disease that occurs most commonly in immune-suppressed patients who have burns, are on long-term corticosteroid therapy, or present with diabetic acidosis. Cases of Garcin syndrome have been reported with unilateral palsy of all cranial nerves in patients with rhinocerebral mucormycosis (Hanse and Nijssen 2003; Mutsukura et al 2004). The disease is often fatal when cerebral extension occurs with multiple cranial nerve involvement. One patient with malignant lymphoma was reported with an acute rhinocerebral infection after chemotherapy that manifested initially as a stuffy nose and intractable headache. Ptosis, proptosis, and multiple cranial nerve palsies appeared later (Tsai et al 1994). Rhinocerebral mucormycosis should be ruled out in patients with diabetes mellitus or immunosuppressed patients presenting with rapid onset of multiple cranial nerve palsies (Kikuchi et al 1998).

**Pseudotumor cerebri.** Multiple cranial nerve palsies have been described as a complication of pseudotumor cerebri, presumably due to stretching of the cranial nerves due to raised intracranial pressure. These usually recover following measures to reduce intracranial pressure. A 13-year-old boy who presented with papilledema as well as an acute-onset paresis of the left abducens and facial and vagus nerves was diagnosed with pseudotumor cerebri and recovered following acetazolamide therapy (Antoun et al 2013).

**Granulomatous diseases.** Granulomas can be due to diverse causes such as infections and vasculitis, or due to unknown causes.

**Granulomatous infections.** There is a case report of a patient with multiple cranial nerve palsies of V, VII, VIII, IX, X, XI and spastic paraparesis due to hypertrophic cranial pachymeningitis extending into the spinal epidural space and originating from a bacterial infection secondary to the secretory otitis media (Adachi et al 1995). MRI revealed hypertrophy of the dura of the posterior fossa and a spinal epidural mass that showed chronic granulomatous change on biopsy.

**Sarcoidosis.** Sarcoidosis is a multisystem granulomatous disorder of unknown cause. There is a predilection for the lungs, with up to 90% of cases displaying pulmonary sarcoidosis. Neurosarcoidosis is relatively rare and accounts for approximately 5% to 15% of cases. Sarcoidosis typically produces unilateral or bilateral facial palsies and less commonly involves the II and VIII nerves. In a series of patients with neurosarcoidosis, 72% of the patients presented with cranial nerve palsies (Zajicek et al 1999). One case of neurosarcoidosis presented with multiple cranial nerve palsy manifested by hyposmia, visual loss, facial hypoesthesia, facial weakness, dysphagia, and gustatory disturbance (Uzawa et al 2009). A case has been reported with the involvement of cranial nerves V, VII, VIII, IX, and X following a viral-like illness (Rose et al 2014). Biopsy of lymph nodes showed granulomatous lymphadenopathy, and the diagnosis was made on the basis of combined clinical, radiological, and histological findings. The patient recovered following corticosteroid therapy.

**Wegener granulomatosis.** This is a systemic granulomatous vasculitis involving multiple organs. The neurologic complications are due to vasculitis, but it may encroach on the base of the skull and involve cranial nerves (Keni et al 2005). Palsies affecting cranial nerves VII to XII were manifestations of a case of Wegener granulomatosis due to refractory sinus disease, and it was successfully treated with immunosuppressive therapy (Kim et al 2013).

**Hyperostosis of the skull.** Paget disease of the bone may narrow the exit foramina of the skull and affect any of the cranial nerves. The VIII nerve is affected with progressive loss of hearing. Involvement of the V and VI nerves are associated with trigeminal neuralgia and hemifacial spasm respectively. Lower cranial nerves are involved if there is associated platybasia. Diagnosis can be established by plain x-rays of the skull and CT of the skull base. Serum alkaline phosphatase is elevated.

**Hyperostosis cranialis interna.** This is a genetic bone disorder with intracranial hyperostosis and otosclerosis of the calvaria and the base of the skull. The rest of the skeleton is normal. A case has been described where this disorder led to variable involvement of cranial nerves I, II, VII, and VIII from late childhood onward (Manni et al 1990). The
diagnosis was made on the basis of the appearance of the skull on x-rays. Among the 8 members of the family who had this lesion of the skull, only a single member has remained asymptomatic on follow-up. The age of onset ranged from 9 years to 32 years.

**Multiple sclerosis.** The multiplicity of neurologic signs in multiple sclerosis include those due to lesions of visual pathways, disturbances of eye movements, and brainstem manifestations, including facial palsy. These patients may also present with trigeminal neuralgia that may resemble the idiopathic form. History, clinical neurologic examination, and MRI of the brain help to distinguish this disease from most of the other pathologies mentioned in the differential diagnosis.

**Hypertrophic pachymeningitis.** Multiple cranial nerve palsies can occur in intracranial hypertrophic pachymeningitis (fibrosclerosis of the meninges) with normal cerebrospinal fluid findings. Many of these cases are idiopathic. Gadolinium-enhanced MRI is essential in identifying meningeal inflammation and locating suitable sites for biopsy. The causes in reported cases, however, include tuberculosis, Lyme disease, and sarcoidosis. One case report is that of an old man who presented with multiple cranial nerve palsies, central diabetes insipidus, and had an elevated serum titer of perinuclear antineutrophil cytoplasmic antibody (Takuma et al 2001). MRI showed thickening of the dura and an intrasellar mass. The etiology could not be determined, but corticosteroid and oral cyclophosphamide therapy improved his neurologic symptoms. Another patient with hypertrophic pachymeningitis and multiple cranial nerve palsies of the left II and III, bilateral VI and VII, and right IX, X, and XII cranial nerves had hypopituitarism due to hypothalamic failure (Manabe et al 2001). The patient was seropositive for rheumatoid factor, but there were no symptoms of rheumatoid arthritis. In a patient with hypertrophic pachymeningitis, presenting features were bilateral loss of vision, left hearing loss, and right IX, X, and XI nerve palsies (Tsugawa et al 2014). Dural biopsy showed inflammatory thickening of the dura mater with infiltration by plasma cells that were immunoreactive to an anti-IgG4 antibody. There was some improvement following corticosteroid therapy.

**Melkerson-Rosenthal syndrome.** This is complex neuromucocutaneous disorder with recurrent facial edema, facial palsy, and fissured tongue, which can be associated with multiple cranial nerve palsies in complete form (Zeng et al 2010).

**Moebius syndrome.** This is a rare congenital anomaly due to intrauterine hypoxia and is characterized by multiple cranial nerve palsies, orofacial malformations, and limb anomalies. Children with this syndrome also drool saliva.

**Idiopathic cranial polyneuropathy.** The diagnosis is usually made after exclusion of other causes. This term is also used for an unusual syndrome of pain in the face and head followed by the onset of multiple cranial nerve palsies occurring days to weeks later (Juncos and Beal 1987). Cranial nerves III to VII are involved in various degrees. Involvement of the lower cranial nerves (VIII to XII) is less common. Fifty percent of these patients have mild cerebrospinal fluid lymphocytosis or protein elevation.

**Complication of Ramsay Hunt syndrome.** Ramsay Hunt syndrome is associated with varicella zoster virus infection along the distribution of the sensory nerves innervating the ear, which usually includes the geniculate ganglion and is associated with facial paralysis unilaterally. Rarely, other cranial nerves may be affected. One case of Ramsay Hunt syndrome evolved into multiple cranial nerve palsies involving cranial nerves V, VII, VIII, IX, X, XI, and XII unilaterally (Morelli et al 2008). A retrospective study reviewed 11 patients with Ramsay Hunt syndrome who presented with cranial polyneuropathy between 1999 and 2009; all of these were treated with systemic steroids and antiviral agents resulting in improvement of cranial nerve functions except hearing loss in most patients (Kim et al 2010).

**Guillain-Barré syndrome.** About half of the patients with this syndrome develop cranial nerve palsies following the ascending limb weakness. Facial palsy is the most common; bulbar palsy and weakness of the muscles of mastication follow close behind in frequency. Ocular palsy occurs in 10% of the patients. In 80% of Guillain-Barré syndrome cases, spinal cord involvement, clinical course of the disease, and cerebrospinal fluid findings of protein elevation with normal cell count help to distinguish it from other cranial neuropathies. An atypical case of Guillain-Barré syndrome presented only with multiple cranial nerve palsies (Ohi et al 1998).

**Metabolic disorders.** Renal injury impairs skeletal anabolism, decreasing the osteoblast compartment of the skeleton and consequent bone formation. There is a case report of bilateral deafness and recurrent episodes of bilateral facial nerve palsy that were caused by renal osteodystrophy, and it was suggested that this condition be considered in the differential diagnosis of multiple cranial nerve palsies (Abid et al 2007).
Diabetes mellitus is usually associated with peripheral neuropathies and rarely with cranial nerve palsies. In a large series, cranial nerve palsies were identified in 0.75%, which were mostly isolated III, VII, or VI nerve palsies, and multiple palsies in only 0.04% of these (Greco et al 2012). A 55-year-old diabetic woman developed simultaneous right VII and left III, IV, VI cranial nerve palsies that responded to treatment with intravenous immunoglobulin (Uluduz et al 2006).

**Diagnostic workup**

The following diagnostic procedures are recommended in a patient who presents with multiple cranial nerve palsies:
- Appropriate diagnostic procedures according to general physical examination for establishing or excluding the diagnosis of cancer.
- Neurologic examination with special emphasis on testing the cranial nerves.
- Blood count and routine chemistry tests with measurement of the erythrocyte sedimentation rate.
- Lumbar puncture with cerebrospinal fluid examination and culture as well as cytology for tumor cells.
- Imaging: CT and MRI of the base of the skull are considered to be the most important diagnostic procedures. High-resolution MRI is the preferred modality for evaluating most lesions involving the orbital apex.
- Cerebral angiography for detection of arterial aneurysms and venous sinus thrombosis.
- Ear, nose, and throat examination to search for nasopharyngeal carcinoma, as it is a common cause of Garcin syndrome.
- A meningeal biopsy may be necessary in some cases.

**Management**

Management depends on the cause because the condition may be treatable or untreatable. Neurologic diagnosis is helpful in early detection of the lesions and their management by the appropriate specialists.

**Treatment of the cause of nerve palsies.** Cancer detected early may be amenable to surgery and radiotherapy. In 1 retrospective study, brain irradiation was found to be effective in reversing the cranial nerve palsies in leukemic patients with no radiological evidence of intracranial leukemic infiltration (Ha et al 1999). Corticosteroids have been used with improvement of inflammatory lesions. Calcitonin may be used in Paget disease with cranial nerve compression; however, the response is not as good as in cases of spinal cord compression.

Some of the infectious granulomas are amenable to appropriate antibiotic therapy. Malignant otitis externa requires intensive management with antibiotics, surgery, and hyperbaric oxygen therapy (Jain 2016). This condition should no longer be malignant for the majority of the patients where the disease is diagnosed early and treated adequately. The mainstay of the treatment of rhinocerebral mucormycosis is surgery for eradication of the underlying cause, amphotericin B, and hyperbaric oxygen.

Recovery in a case of multiple cranial nerve palsies due to varicella zoster infection was reported following acyclovir therapy (Terborg et al 2001). However, a previously reported similar case did not respond to acyclovir and steroid therapy (Funakawa et al 1999).

**Management of cases in which cause is not known.** In cases of idiopathic multiple cranial nerve palsy, where no cause is discovered despite extensive investigations, good response may be obtained by use of corticosteroids. A case of multiple cranial neuropathy with positive antinuclear antibody but no established diagnosis responded to steroids even though there was no change in titer of antinuclear antibody (Ogawa et al 2000). Marked improvement was reported following 2 cycles of intravenous immunoglobulin therapy in a child with multiple palsies involving cranial nerves III, IV, V, VI, VII, IX, X, XI, and XII after initial, unsuccessful treatment with corticosteroids and acyclovir (Pavone et al 2007).

**Surgical procedures.** Although surgical procedures are performed for correction of sequelae of lesions of some of the individual cranial nerves, patients with multiple cranial nerve palsies are usually considered for surgical procedures...
only for removal of the causative lesions, such as skull base tumors. In a case of dysphagia due to palsies of cranial nerves V and VII after radiotherapy for nasopharyngeal carcinoma, anastomosis of the functioning XII nerve to the buccal branch of the VII nerve in an end-to-side fashion, and direct implantation of a nerve graft from the spinal XI to the masseter muscle, failed to restore masticatory function (Alcon et al 2015).

**Outcomes**

Outcome of treatment depends on the cause of nerve palsies and the method of treatment.

**Special considerations**

**Pregnancy**

None of the reported cases of multiple cranial nerve palsies have been associated with pregnancy.

**Anesthesia**

Problems can arise during anesthesia in children with Moebius syndrome. There is a high incidence of difficult or failed intubation with potential for problems with aspiration of oral secretions. Use of premedication to reduce salivary secretion is recommended. Children with Moebius syndrome have a high incidence of other anomalies, including congenital heart disease. A careful preoperative assessment should be done.

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**References especially recommended by the author or editor for general reading.

**ICD and OMIM codes**

**ICD codes**

ICD-9:
Cranial polyneuropathy: 352.6

ICD-10:
Disorders of multiple cranial nerves: G52.7

**Profile**

**Age range of presentation**

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance**

male=female

**Family history**

family history may be obtained

**Heredity**

none

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

tumors of the nasopharynx
tumors of the cylindromas
tumors of the osteosarcomas
leukemia
metastatic tumors at the base of the skull
benign tumors at the base of the skull
pituitary tumors
acoustic neurinomas
sphenoid ridge meningiomas
parapharyngeal branchial cleft cyst
meningeal carcinomatosis
paraneoplastic syndrome
diffuse large B cell lymphoma originating from the frontal sinus fractures at the base of the skull
aneurysms
cavernous sinus thrombosis
internal-carotid-artery dissection
vertebrobasilar occlusive disease
subacute or chronic meningitis
Collet-Sicard syndrome
varicella zoster infection
malignant otitis externa
rhinocerebral mucormycosis
pseudotumor cerebri
granulomatous infections
sarcoidosis
Wegener granulomatosis
hyperostosis cranialis interna
Paget disease of the bone
multiple sclerosis
pachymeningitis
Moebius syndrome
idiopathic cranial polyneuropathy
Guillain Barré syndrome
Diabetes mellitus

Associated disorders

Avellis syndrome
Cancer
Cerebellopontine angle syndrome
Foix-Jefferson syndrome
Gradenigo-Lannois syndrome
Inflammatory disorders
Jacod syndrome
Jugular bulb diverticulum
Leukemia
Lyme disease
Ramsay Hunt syndrome
Sarcoidosis
Sicard-Collet syndrome
Superior orbital fissure syndrome
Tapia syndrome
Tuberculosis
Varicella zoster infection
Vernet syndrome

Other topics to consider

Combined third, fourth, and sixth nerve palsies
Diabetic neuropathies
Guillain-Barre syndrome in children
Leptomeningeal metastasis
Leukemia: neurologic complications
Neurolymphomatosis
Ophthalmoplegic migraine
Sjogren syndrome: neurologic complications
Toxic peripheral neuropathies
Traumatic cranial neuropathy
Vestibular schwannoma

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