Clinical Reasoning: An unusual cause of multiple cranial nerve impairment

SECTION 1

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In January 2009, an 89-year-old Caucasian man was referred to our hospital for progressive multiple cranial neuropathies. His past medical history included arterial hypertension, acute pancreatitis, heart failure, and in situ cutaneous squamous cell carcinoma (SCC) in the left temporal scalp, which was treated with total local excision (negative margin) in 2001. Two years later (2003), a right temporal SCC was diagnosed and treated with surgery and local radiotherapy (54 gray). In June 2006, a recurrence occurred on the same side, and pathology from the surgical excision revealed negative margins. In September 2007, he was admitted to the otolaryngology department for right facial nerve palsy; Bell palsy was diagnosed and treated with oral steroids, but this regimen was ineffective. To avoid eye complications, botulinum toxin was injected in the right levator

palpebrae muscle. The patient progressively complained of right crawling paresthesias and numbness only of the right cheek. In January 2009, the right eyelid was still closed, despite the disappearance of botulinum toxin effects. A thorough neurologic examination revealed the following: hypesthesia and pain in the territory of the right V1 cranial nerve (CN), right peripheral facial palsy (CN VII), right deafness (CN VIII), complete right ophthalmoplegia, and right unreactive mydriasis (CNs III, IV, and VI). The examination was otherwise unremarkable.

Questions for consideration:

1. Which anatomic structures could explain the clinical presentation?
2. Which syndrome is observed?
3. What etiologies might explain this case?

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SECTION 2

Topographic reasoning to explain multiple CN involvement requires knowledge of anatomic structures where CNs are closely bundled. Focal lesions of such structures define clinical syndromes involving multiple CNs (table e-1 on the *Neurology*[®] Web site at www.neurology.org).

Our observations indicate that none of the previously described syndromes can explain the full spectrum of CN impairment described above; therefore, the pathology is likely multifocal. Garcin syndrome is a rare condition that results in unilateral impairment of all or nearly all CNs. It is a progressive syndrome that affects the base of the skull but not the brain itself, and it is typically characterized by a lack of intracranial hypertension (IHT). The most commonly involved CNs are V and VII.

From the midbrain to distal nerve ending, CNs cross meninges, subarachnoid space, the skull, and its foramina. Their complex path explains why only a few possibilities could account for the lesion's localization: tumors (30%), vascular disease (12%), trauma (12%), infection (10%), inflammatory processes (5%), and diabetes mellitus (2%).¹

Multiple CN impairment could reveal an extra- or intra-axial process. Etiologies are listed in the table.

Question for consideration:

1. According to the possible etiologies, which complementary investigation would you propose for this patient?

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Table Etiologies and clinical symptoms of extra- and intracranial process

Etiologies	Clinical symptoms
Intracranial process	
Vascular: midbrain stroke	Acute onset Bilateral facial palsy, motor or sensitive hemicorporal dysfunction
Inflammatory: multiple sclerosis	Internuclear ophthalmoplegia, facial nerve palsy, pain in the territory of CN V
Tumoral: anaplastic astrocytoma, lymphoma, glioblastoma	Insidious and progressive CN palsy, intracranial hypertension
Degenerative diseases: amyotrophic lateral sclerosis (bulbar form: 25% of initial onset)	Dysarthria, dysphonia, deglutition, and mastication disorder Fasciculation and amyotrophy of the tongue
Extracranial process	
Tumoral	Cavernous sinus syndrome: Horner syndrome, ophthalmoplegia, facial sensory loss
Local tumor extension (e.g., nasopharyngeal carcinoma, pituitary adenoma)	
Primary metastatic tumor (e.g., lymphoma, meningioma)	
Vascular: carotid aneurysms, cavernous thrombosis and fistulas	Cavernous sinus syndrome, pulsating exophthalmos
Inflammatory: sarcoidosis (neurologic manifestations in about 5% of cases, secondary to meningitis infiltration)	Multiple, relapsing, and alternating CN involvement (all CNs could be targeted): facial nerve palsy is more frequently observed
Behçet disease (neurologic manifestations in about 5% of cases)	Anosmia, hearing loss, tinnitus, nystagmus, ocular inflammation (iritis, uveitis), skin lesions (oral and genital ulcers)
Wegener granulomatosis (neurologic manifestation in 34%, and CN involvement in 19% of cases)	Anosmia, facial nerve palsy ± pain in the territory of CN V, peripheral neuropathy, seizure, and stroke
Other: rheumatoid arthritis, scleroderma, systemic lupus, periarteritis nodosa, amyloidosis type IV, Gougerot-Sjögren disease	Multiple nerve involvement without specificity
Infection: tuberculosis (CN palsy in 30% to 50% of tuberculous meningitides, between 6 months and 2 years after the primary infection)	Ophthalmoplegia: CN VI (40%) > CN III (5% to 15%); facial nerve palsy (10% to 20%)
Lyme disease (neurologic manifestation in 15% of infected patients during the second stage of infection)	Facial nerve palsy (75% of cases) sometimes bilateral, anosmia, pain in the territory of CN V, hearing loss, tinnitus, nystagmus; radicular pain and cardiac abnormalities
Whipple disease (CNS involvement in 20% to 40% of cases)	Ophthalmoplegia, facial nerve palsy, hearing loss, tinnitus, nystagmus; cognitive impairment, myoclonus, arthralgia, diarrhea, asthenia, weight loss, and fever
Other: HIV, mycoplasma, botulism, leprosy, diphtheria, listeria, VZV infection, cysticercosis, aspergillus, candida	
Neuromuscular junction disorder: myasthenia, botulism	Diplopia, ptosis, dysarthria and dysphagia; fluctuating muscle weakness and fatigability
Peripheral neuropathies: Guillain-Barré and Miller Fisher syndrome	Ophthalmoplegia, ptosis, dysarthria, dysphonia; acute ascending symmetric weakness with ataxia and areflexia

CN = cranial nerve; VZV = varicella-zoster virus.

SECTION 3

The first brain MRI was taken 1 month before admission (December 2008) and did not reveal any abnormality (figure e-1A). A second MRI taken in February 2009 revealed an isolated enhanced signal in the area of CNs V, VII, and VIII on the right side (figure e-1B). A lumbar puncture (LP) did not show meningitis (4 leukocytes without malignant cells and 1 hematia); the amount of protein in CSF was increased (0.73 g/L). CSF glucose and lactate were normal. Viral PCR (including herpes simplex and varicella-zoster virus) in CSF was negative. Routine blood test, angiotensin-converting enzyme, $\beta 2$ microglobulin levels, immunologic tests, CT of the skull, and histologic examination of a duodenal biopsy were normal. Serologies for hepatitis, HIV, syphilis, and Lyme disease; PCR for Whipple disease; tuberculin test reaction; antineural antibodies; and tumoral blood markers were negative. We continued to manage the patient's symptoms, but the CN palsy worsened, and newer examinations were performed. A third cerebral MRI (September 2009) showed bone lysis of the clivus area, infiltration from the right cavernous sinus to the superior orbital fissure, pterygopalatine fossa and right inferior temporal fossa, and an enhancement of CNs V, VII, and VIII on the right side. A second LP was negative for meningitis but did show evidence of hyperproteinorrachia at 1.10 g/L with oligoclonal distribution. In February 2010, a cerebral MRI revealed an extension of the tumoral process with infiltration and erosion of the occipital basilar process, the right petrous apex, the Meckel cave, and the right pterygoid process with gadolinium enhancement (figure e-1C). Whole-body PET-fludeoxyglucose fixation did not reveal any abnormalities with the exception of the skull.

We performed a surgical biopsy in the target area and pathologic analysis revealed a metastasis of an SCC.

Question for consideration:

1. Which diagnosis would you make in this case?

DISCUSSION

We gave a diagnosis of perineural infiltration (PNI) of CNs by facial SCC.

SCC and basal cell carcinomas (BCC) are the most common human cancers. The incidence of SCC in France is about 30/100,000.² The mean age at diagnosis is 76 years (74.4 years in men and 77 years in women), almost 10 years higher than for BCC, with a higher incidence in men (sex ratio around 2). SCC and BCC are traditionally considered to be superficial malignancies and generally require localized treatment. Unfortunately, when they are undetected, untreated, or incorrectly managed, they may cause morbidity.

PNI describes tumor growth in or around peripheral nerves, and it enables these tumors to extend from the most distal nerve termination to the proximal

subarachnoid space of the CNS with catastrophic consequences.³ The propensity for tumors to penetrate the perineural fascial plane is attributed to the lower resistance of these distensible spaces.³ Furthermore, the rich vascular environment of the perineurium may provide growth factors, and tumor cells could produce matrix metalloproteinases that degrade extracellular matrix and facilitate metastasis.

Neumann⁴ described the first cutaneous tumor with PNI in 1862. The frequency of PNI varies with histology; the incidence in SCC is between 2.5% and 5% and could approach 80% in microcystic adnexal carcinoma.⁵ About 5% of all cutaneous carcinomas have nerve involvement.⁶ Factors associated with PNI include tumor size >2 cm, facial localization, male gender, recurrence of tumor, and previous lesion treatment.⁷ These considerations may explain why the PNI occurred on the right side in our case, despite an antecedent of bilateral facial SCC. PNI is asymptomatic in 60% to 70% of patients. Symptoms generally occur late in the disease course. The main symptoms are paresthesias, feelings of tingling and crawling, facial pain, anesthesia, burning and numbness, ptosis, diplopia, facial weakness or paralysis, ophthalmoplegia, and fasciculations.³ Tumor progression may cause ophthalmoplegia, blindness, sensory loss, and meningeal carcinomatosis. Seizures, IHT, and cognitive impairment occur less often. Suspicion of neoplastic etiology is established when there is insidious, slowly progressive CN involvement, no return of function after 6 months, and recurrent symptoms; increased pain severity and unremitting characteristics are also signs of malignancies. Symptoms may precede the diagnoses of PNI or primary or recurrent skin carcinomas by months or years. CNs that are most often invaded are V and VII because of their extensive distribution.⁸ Clinical examinations fail to diagnose PNI because of a lack of signs and symptoms in most patients.

One should consider "red flags" (e.g., progressive facial weakness) and conduct appropriate neurologic testing in patients with SCC with recurrent, aggressive skin cancer. Imaging could expedite the correct diagnosis; in fact, CT or MRI give some radiographic features, such as bone erosion, enlargement of skull foramina, loss of fat pad in the pterygopalatine fossa, muscle atrophy, mass along the nerve, and enhancement of the neural foramen, Meckel cave, or the nerves themselves.⁹

MRI detection sensitivity is 95% (62% for complete, accurate mapping of perineural spread).⁹ Thus, MRI detection could fail to depict PNI and underestimate the extent of PNI.

LP could provide evidence of tumor cells or hyperproteinorrachia in CSF in 50% of cases at the first LP and 90% at the third LP. Biopsies allow the histologic diagnosis of PNI and must be performed if there is clinical evidence of a tumor. Unfortunately, biopsies are often difficult because malignant cells usually present

exclusively in the perineural space and may be missed by routine sectioning, as in our case. PNI is easier to identify with Mohs micrographic surgery, which yields horizontally cut frozen section and allows tissue margin examination. It seems to be the most common therapeutic approach to these complex lesions because it allows small areas of PNI to be identified. This procedure decreases the rates of recurrence and metastasis and increases the survival rate.¹⁰ The use of adjuvant localized radiotherapy remains controversial with conflicting results, but it is largely used for palliative care and seems to be commonly used postoperatively.¹⁰ Prognosis varies and depends on the type of malignancy and the nerves that are involved. PNI clearly increases the rates of recurrence and metastasis and decreases survival rate.

Perineural invasion is uncommon but not rare, occurring in about 5% of SCC. Our case demonstrates the necessity of testing for PNI during the course of SCC with CN involvement, even if specific blood assessments and radiologic examinations are normal.

AUTHOR CONTRIBUTIONS

V. Roubeau drafted the manuscript. C. Diard-Detoeuf helped acquire data. S. Moriniere helped acquire data. J.-P. Cottier helped acquire data and interpreted MRI. N. Limousin managed the patient. B. de Toffol helped acquire data. C. Hommet helped acquire data. K. Mondon supervised the study, developed the idea, and corrected the manuscript.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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