# Multiple Cranial Neuropathies in a Patient with Diabetes Mellitus

Sir,

A 54-year-old female presented with complaints of impaired vision, binocular double vision, both horizontal and vertical, and drooping of the left eye for 1-week duration. There was no diurnal variation. She had no headache, fever, eye pain, or facial asymmetry. Seven months previously, she had been diagnosed, elsewhere, with left lateral rectus palsy which had resolved over time. She was detected to have diabetes but had discontinued medication 1 month before the onset of her present symptoms.

On examination, she had partial ptosis, impairment of adduction, and elevation and depression of the left eye with preserved abduction. Her pupils were bilaterally equal in size and constricted to light and accommodation. She had no other neurologic deficits. The clinical features suggested a pupil-sparing partial third nerve palsy of the left eye. The etiology was thought to be microvascular ischemia due to diabetes. Brain magnetic resonance imaging (MRI) showed only small-vessel ischemic changes. Random blood sugar was 200 mg/dL, total cholesterol 202 mg/dL, low-density lipoprotein cholesterol 149 mg/dL, and high-density lipoprotein 38 mg/dL. Aspirin 150 mg OD and atorvastatin 20 mg HS were instituted, and oral hypoglycemic drugs were restarted.

Two weeks later, her symptoms had worsened with complete drooping of the left eye, numbness of the left cheek and forehead, a change in voice, and progressive difficulty in swallowing. Physical examination revealed complete third nerve palsy with pupillary involvement. The fourth and sixth cranial nerves were unaffected. Touch and pinprick perception over the left side of the face was impaired, but the trigeminal motor function was preserved. The corneal reflex, both direct and consensual, was normal. She had no facial or auditory involvement but was found to have left palatal weakness, absent gag reflex, and left vocal cord palsy on laryngoscopy. There was no sternocleidomastoid or trapezius muscle weakness, and tongue movements were normal. She had no limb weakness, incoordination, sensory deficits, long-tract signs, or autonomic dysfunction. Lymph nodes were palpable in both axillae and a nodule was detected in the right lobe of thyroid, but systemic examination was otherwise normal. In view of subacute, progressive, unilateral, and sequential involvement of the third, fifth (sensory), ninth, and tenth cranial nerves, a neoplastic or granulomatous compressive lesion or infiltrative pathology such as carcinomatous meningitis was suspected. Apart from uncontrolled diabetes (fasting and postprandial sugars 223 and 321 mg/dl, respectively, HbA1C 10.2%), routine serum chemistry and hematology showed no abnormalities. ANA and ANCA, HIV, VDRL, HBsAg, and HCV serology were all negative. The biopsy of the axillary lymph node and FNAC thyroid was noncontributory. Routine nerve conduction study of the peripheral nerves was within normal limits. Cerebrospinal fluid (CSF) showed normal protein and sugar, no pleocytosis, negative malignant cytology, and VDRL. Repeat contrast-enhanced MRI of brain, nasopharynx, and skull base was negative, and her MR angiogram showed no evidence of vasculitis or other abnormalities in the cerebral vasculature. Screening for systemic malignancy with contrast-enhanced computed tomography chest and abdomen and mammogram were all negative. Indirect laryngoscopy and nasal endoscopy ruled out any upper airway pathology such as nasopharyngeal carcinoma.

Nasogastric feeds were instituted and glycemic control optimized. She gradually improved; after 4 weeks, she could swallow some food and her voice had normalized. Her visual complaints, ptosis, and extraocular movements improved over the next 2 months, but the left pupil continued to react sluggishly to light at 3 months.

The affected nerves were all on the left and were affected sequentially although the seventh and eighth cranial nerves were spared. A compressive or infiltrative multifocal pathology such as carcinomatous meningitis was, therefore, strongly considered, but a thorough evaluation for underlying malignancy was unyielding. Systemic malignancies include breast, ovary stomach, lungs, and lymphoma, while locally advanced malignancies are nasopharyngeal carcinoma, clival neoplasm, glomus jugulare tumor, etc., Malignant infiltration can cause sequential affection of multiple cranial nerves in a "pick and choose" manner,[1] but the gradual resolution of the disease without specific intervention precluded this possibility. Nasopharyngeal carcinoma is of particular concern in this patient, as it can extend superiorly into the middle cranial fossa and cavernous sinus through the foramen lacerum and involve the third, fourth, fifth, and sixth cranial nerves. It may erode the pharyngobasilar fascia and invade the base of the skull causing lower cranial nerve palsies.[2]

The normal CSF formula did not favor an infective or inflammatory pathology, and vasculitic workup was also negative. Polyneuritis cranialis or Guillain–Barré syndrome variants may present in a similar manner, but the seventh cranial nerve is usually the most commonly involved in these patients.[3] There was no antecedent febrile illness, CSF showed no albuminocytologic dissociation, and the patient improved without any immunomodulatory therapy. Neurosarcoidosis may also manifest with multiple cranial nerve palsies, the facial and optic nerves being the most commonly affected.[4] The

absence of hilar lymphadenopathy, normal CSF, and recovery without steroids makes this an unlikely etiology in our patient.

The only significant abnormality identified was the uncontrolled diabetes. Worsening glycemic status could conceivably have led to complete oculomotor palsy, but the involvement of the trigeminal, glossopharyngeal, and vagus nerves is very unusual as manifestations of diabetic neuropathy. Oculomotor paresis in diabetes is thought to be due to microvascular ischemia affecting the central fibers predominantly; the peripherally located pupillomotor fibers are commonly but not invariably spared.[5] Pupillary involvement is more often seen with compressive or infiltrative lesions of the oculomotor nerve such as aneurysms, neoplasms, or granulomata. Our patient had presented initially with third nerve palsy sparing the pupils, but 3 weeks later developed pupillary involvement and other cranial neuropathies. The impairment of pain and touch in the trigeminal territory without motor deficits and preservation of corneal reflex suggested trigeminal sensory neuropathy, which has been associated with infiltrative or connective tissue disorders.[6] These conditions were excluded by clinical and serological evaluation.

Dysphagia and dysphonia are unusual symptoms of diabetic neuropathy, but it is unlikely that the lower cranial involvement was related to a separate etiology as they occurred contiguously and simultaneously with the oculomotor palsy and resolved with no intervention apart from glycemic correction and stabilization. Vagal mononeuropathy may occur with postinfectious states or compressive lesions such as aneurysms, abscess, and neoplasms in the mediastinum or at the base of the skull. It has been described rarely in diabetes but is most often idiopathic.[7,8] Diabetes mellitus and the accompanying microvascular disease are, therefore, the most likely explanations for her cranial palsies. The cause of the strict lateralization of the cranial nerve involvement in this patient, which provoked extensive evaluation for a structural cause, remains enigmatic.

Diabetes mellitus causes neuropathy mostly through microvascular ischemia. However, other mechanisms are also described like sorbitol and fructose accumulation due to hyperactivity of the polyol pathway with the consequent depletion of myoinositol, activation of protein kinase Cβ isoform causing microvascular damage, advanced glycation end products resulting from nonenzymatic glycosylation of structural nerve proteins such as laminin, and buildup of toxic free radicals. Lack of neurotrophins such as nerve growth factor, ciliary neurotrophic factor, and insulin-like growth factor (IGF-1 and IGF-2) along with an increased concentration of tumor necrosis factor–alpha and interleukins plays an important role in the pathogenesis of diabetic neuropathy.[9,10] An immune mechanism in the pathogenesis of certain types of diabetic neuropathy, including cranial neuropathy, has also been postulated with a possible role for immunomodulatory treatment.[11,12] Nerve biopsy has shown perivascular collections of mononuclear lymphocytes surrounding the epineurial microvasculature in diabetic patients. The reason for the sparing of lower cranial nerves and the more frequent involvement of the ocular, optic, and facial nerves in diabetes is not well appreciated. Variations in the microanatomy and the pattern of myelination may influence the vulnerability of these nerves to hypoxia and microvascular disease.[13]

Correction of the glycemic status is the cornerstone of the treatment of diabetic neuropathy, although immunomodulation may have a role in selected situations where an immune mechanism is suspected.

This case is highlighted for the possible rare association between diabetes and the involvement of trigeminal, glossopharyngeal, and vagal nerves.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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## References

1. Grossman SA, Krabak MJ. Leptomeningeal carcinomatosis. Cancer Treat Rev 1999;25:103-19.
2. Patel S, Patel A, Majmundar M, Madabhavi I, Shah R, Soni J, *et al.* Nasopharyngeal carcinoma presenting as Garcin's syndrome: A rare case report. Iran J Neurol 2015;14:228-30.
3. Polo A, Manganotti P, Zanette G, De Grandis D. Polyneuritis cranialis: Clinical and electrophysiological findings. J Neurol Neurosurg Psychiatry 1992;55:398-400.
4. Lim SH, Puvan K, Cheah ES. A case of sarcoidosis presenting as cranial polyneuritis. Singapore Med J 1989;30:400-3.
5. Dhume KU, Paul KE. Incidence of pupillary involvement, course of anisocoria and ophthalmoplegia in diabetic oculomotor nerve palsy. Indian J Ophthalmol 2013;61:13-7.
6. Lecky BR, Hughes RA, Murray NM. Trigeminal sensory neuropathy. A study of 22 cases. Brain 1987;110 (Pt 6):1463-85.
7. Berry H, Blair RL. Isolated vagus nerve palsy and vagal mononeuritis. Arch Otolaryngol 1980;106:333-8.
8. Flowers RH 3rd, Kernodle DS. Vagal mononeuritis caused by herpes simplex virus: Association with unilateral vocal cord paralysis. Am J Med 1990;88:686-8.
9. Kelkar P, Parry GJ. Mononeuritis multiplex in diabetes mellitus:

Evidence for underlying immune pathogenesis. J Neurol Neurosurg Psychiatry 2003;74:803-6.
10. Uluduz D, Bozluolcay M, Ince B, Kiziltan M. Simultaneous multiple cranial nerve neuropathies and intravenous immunoglobulin treatment in diabetes mellitus. Neurol India 2006;54:308-9.
11. Yagihashi S, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: Where are we now and where to go? J Diabetes Investig 2011;2:18-32.
12. Llewelyn JG. The diabetic neuropathies: Types, diagnosis and management. J Neurol Neurosurg Psychiatry 2003;74 Suppl 2:ii15-9.
13. Hoffman HH, Kuntz A. Vagus nerve components. Anat Rec 1957;127:551-67.



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