

Recurrent Multiple Cranial Neuropathies in a Diabetic Patient

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Abstract-

Purpose: Multiple cranial neuropathies is one of the neurological complications among diabetic patients.

Symptoms of multiple cranial neuropathies may cause great anxiety for these patients and often appear to be a serious problem from a diagnostic and therapeutic point of view. A correct and timely diagnosis of the underlying cause of cranial nerve palsy in these patients is crucial because of the realistic threat of devastating neurologic conditions.

Case report: Recurrent cranial neuropathies involving different cranial nerves are unusual. In this case report, we present a diabetic patient with four episodes of recurrent cranial neuropathies including two times of facial neuropathies and two episodes of external ophthalmoplegia within 2 years.

Conclusion: Diabetic cranial neuropathies may appear in a recurrent pattern; spontaneous remission is the rule.

Key Words: diabetes mellitus, ophthalmoplegia, recurrent cranial neuropathies.

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INTRODUCTION

Diabetic cranial neuropathies is one of the neurological complications among diabetic patients. It usually involves cranial nerves III, IV, and VI, causing acute onset of ophthalmoplegia⁽¹⁾. Paralysis of the third, fourth, or sixth cranial nerve as a complication of diabetes mellitus (DM) was first recognized as a clinical entity by Ogle in 1866⁽²⁾. The diabetic patients have 10-fold increase in the incidence of cranial nerve palsies, with an incidence of 0.97 % among diabetics compared with an incidence of 0.13% of the non-diabetic population⁽³⁾. Symptoms of diabetic cranial neuropathies usually occur suddenly and can cause great anxiety. A proper

clinical evaluation is important for the diagnosis, treatment strategy, and prognosis prediction. In the diabetic cranial neuropathy, the prognosis is relatively benign and spontaneous recovery is expected within three months in most patients⁽⁴⁾. Among these patients, multiple cranial neuropathies are less common. Although the incidence is unclear on recurrent events involving the same nerve or some other cranial nerve based on literature review. Clinically, recurrent cranial neuropathies can be of greater impact to the patients and deserves detail discussion. Here we report a diabetic patient presented with four episodes of recurrent cranial neuropathies within 2 years.

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CASE REPORT

A 56-year-old woman suffered from acute onset of the left eye ptosis and binocular double vision. Her past medical history was notable for DM for five years without known hypertension or hyperlipidemia. She had received oral antihyperglycemic agents for 5 years and had fasting sugar record ranging from 100 to 250 mg/dl. Over the past two years she had had two episodes of transient facial palsy, the right and the left respectively. In addition, she once hospitalized for similar ptosis event of the right eye two months prior to this admission. Paresis over the right medial rectus, superior rectus, and inferior rectus, and equivocally decreased pinprick sensation over right ophthalmic division of the trigeminal nerve (V1) area were recorded. The right oculomotor nerve palsy was diagnosed, which completely resolved one month later.

On admission, physical examination showed mild left periorbital edema. No chemosis, ecchymosis or vessel engorgement was scrutinized over her both eyes and nearby. Neurological examination showed a normal mental status. The visual acuity, color vision, and visual field were normal. The pupils were isocoric and reacted properly to both direct and indirect light stimulations. There was 3 mm of the left upper lid ptosis; and when the lid was lifted, extropia of the left eye were noted in natural position. A complete limitation of the left eye movement except for the lateral gazing was witnessed. No voluntary intorsion was observed. The motility test of the right eye was normal. Hypesthesia over the left V1 area in the pinprick modality was also identified. Examination of the other cranial nerves was normal. Tendon reflexes of the four limbs showed normoreflexia. No evidence of abnormal pyramidal, extrapyramidal, cerebellar sign was found. There was no gait disturbance or sensory dysfunction in the limbs and trunk.

A complete blood cell count, liver and renal function, electrolytes, lipid profile, thyroid and adrenal function were all within normal limits. Tests of the fasting blood glucose ranged from 100 to 250 mg/dl and the index of glycosylated hemoglobin was 7.8%. The erythrocyte sedimentation rate (ESR) was 15 mm/hour.

Tests of antibodies to the human immunodeficiency virus 1+2, human T lymphocyte virus 1 and mycoplasma as well as reagin plasma response and cryptococcus antigen were all negative. Tests of antibodies for autoimmune diseases including antinuclear antibody (Ab), anti-beta 2 glycoprotein Ab, anti-double strand DNA Ab, and anticardiolipin Ab were all negative. Serial immunologic survey showed C3 98mg%, C4 13.9mg%, IgG 1170 mg%, IgM 98.7mg%, IgA 256mg%, and no paraprotein in the serum or CSF. Tumor markers including carcinoembryonic antigen, carbohydrate antigen (CA) 125, CA 15-3, CA 19-9, and squamous cell carcinoma antigen were not elevated. The cytological and biochemical analyses of CSF were within normal limits.

The blink reflex was essentially normal. Cranial magnetic resonance imaging (MRI) with gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA) enhancement and magnetic resonance angiography (MRA) did not reveal any lesion in the intrinsic brainstem, subarachnoid space, cavernous sinus, and posterior orbit. Clinically diabetic multiple cranial neuropathies, involving the left oculomotor, trochlear nerve, and possible V1 division were impressed. Complete recovery was documented 2 months after admission.

DISCUSSION

In our patient, the clinical constellation indicated that the palsy was involved in the left third and fourth cranial nerve with sparing of pupil paralysis. A possible irritation of the V1 was also found. The culprit of above identified multiple cranial nerve palsy may happen onto anywhere in the course from intrinsic brainstem, subarachnoid space, cavernous sinus to their peripheral course. Some of etiologies in the differential diagnosis list are highly risky; therefore, to exclude life-threatening conditions is crucial.

Several caveats are offered to help us avoid the traps that may lead to delay and misdiagnosis. First at all, we lay interest onto sign of pupillary involvement, which had been ominous for compressive lesions abutting ocular nerve. Of 4278 cases with ophthalmoplegia collected from Mayo Clinic, 26 oculomotor nerve palsies were

caused by aneurysm with pupillary involvement in only 19⁽⁵⁾. Kissel et al. reviewed the clinical course of 51 patients with third nerve palsy caused by angiographically-proven aneurysm at the junction of the posterior-communicating and internal carotid arteries⁽⁶⁾. Seven (14%) of their patients with incomplete ophthalmoplegia but normal reactive pupils initially proved having aneurysm⁽⁶⁾. Five of them developed complete oculomotor nerve palsy thereafter⁽⁶⁾. Concerning the reliability of pupillary sparing in non-compressive ophthalmoplegia, according to Zorrilla and Kozak's series, pupillary sparing occurs in 16 of 20 cases of diabetic ophthalmoplegia, leaving the other four patients with pupillary involvement⁽⁷⁾. A similar observation was reported in patients with ischemic third nerve palsy evaluated by other investigators⁽⁸⁾. Therefore, pupillary sparing is not an unfailling sign to tell whether the lesions compressive or not.

In our patient, absent truncal ataxia, long tract signs or brainstem irritation signs make anatomical localization in the brainstem less likely. The lack of vessel engorgement of sclera, pupillary involvement, and signs of aberrant regeneration does not favor the lesions around cavernous sinus. Persistent neurological symptoms without diurnal change and limited involvement on ocular movement control have made the possibility of neuromuscular junction disease and myopathy unlikely. Moreover, the histories of recurrent peripheral facial palsy also provide additional diagnostic support of multiple cranial neuropathies in our case (Table 1). Repeated

neuroimage with emphasis on arachinoid space and CSF study were all unremarkable. Considering all the aspects from the patient history, neurological findings, laboratory and neuroimage data, recurrent diabetic multiple cranial neuropathies would be favored. However, the possibility of Bell's palsy in terms of the first and second event still could not be totally excluded as recurrent peripheral facial palsy is also commonly seen in diabetic patients.

Multiple cranial nerve neuropathies can occur simultaneously in diabetic population and sometimes it may be a presenting sign of newly diagnosed diabetes or glucose intolerance⁽⁹⁾. Based on a large retrospective study from institute for Diabetes Care and Research in Tokyo, diabetic patients had 10-fold increase in the incidence of cranial nerve palsies, with an incidence of 0.97% in the diabetics compared with an incidence of 0.13% of non-diabetic population⁽³⁾. In regarding to patients with external ophthalmoplegia, the incidence of diabetic multiple cranial neuropathies is also relative rare, ranging from 0.4-0.97%^(5,10). In a case series study reported by Keane JR⁽¹¹⁾, among 979 multiple cranial neuropathies patients collected in 34 years, DM was identified as its etiology in 25 cases only. However, studies concerning the incidence of recurrent diabetic multiple cranial neuropathies are limited except for some case report series. Ross AT demonstrated three cases with DM had recurrent cranial nerve palsies, with variable combination of the third, fourth, fifth, sixth, and seventh cranial nerve⁽¹²⁾. Those

Table 1. Clinical information of 4 episodes of cranial nerve palsy in this case

	Symptoms	Signs	CrN involved	Duration
1 § Nov.2006	Drooling from right mouth angle	Right peripheral facial nerve palsy	Right CrN. VII	1 month
2 § May.2007	Left face drooping	Left peripheral facial nerve palsy	Left CrN. VII	1 month
3 Oct.2008	Right eyelid lag Blurred vision	Incomplete right oculomotor nerve palsy and equivocal hypesthesia over ophthalmic branch of right trigeminal nerve	Right CrN. III and possible CrN V-1.	1 month
4 Dec.2008	Left eyelid drop Double vision Cheek swelling.	Complete left oculomotor nerve palsy, trochlear nerve palsy, and hypesthesia over ophthalmic branch of trigeminal nerve	Left CrN III, IV, and V-1	2 months

Note: § indicates history reported by patient and collateral information CrN.: Cranial nerve

cases have variable sugar control. One hospital-based case series enrolling 29 patients with diabetic ophthalmoplegia demonstrated only 4 patients had recurrent or alternate cranial nerve involvement on retrospective review⁽¹³⁾. In our patients, four recurrent episodes including two peripheral facial palsies, one right oculomotor and another left external ophthalmoplegia occurred within two years draw us extra attention. From literature review of diabetic cranial neuropathies, spontaneous recovery is expected within five months in most patients^(4,5). In our patient, the complete recovery of the right oculomotor nerve palsy, followed in two months by a similar external ophthalmoplegia on the opposite side, militates against aneurysm and favors relatively reversible pathology in subarachnoid space.

The pathogenesis of diabetic cranial neuropathy remained obscured due to paucity of pathological reports. Although there's no unanimity on the direct relationship of vascular lesions with neuropathy, there had been more attention directed to the probable existence of diabetic angiopathy⁽¹⁴⁾. Dreyfus et al. postulated ischemic neuropathy as the likely pathological change, although no occluded arterioles or venues and no evidence of hemorrhage or inflammation were found⁽¹⁴⁾. In their pathology report, they remarked that only one-fourth to one-fifth of the nerve fibers disappeared microscopically, yet almost all of the function of the oculomotor nerve had been affected. Combing with clinical self recovery trait, a functional rather than an irreversible structural change was proposed. Asbury et al. identified hyalinization of the intra-neural arterioles (30-80 μm) with endothelial proliferative degeneration and resultant stenosis in the lesioned nerves that provided additional support of ischemic pathology⁽¹⁵⁾. Focal non-inflammatory demyelination in the intracavernous portion of third cranial nerve was also observed in autopsy⁽¹⁴⁾. This may provide explanation of pupillary sparing as the oculomotor parasympathetic fibers are small myelinated or unmyelinated.

Variable cranial nerve palsy may happen onto subjects with DM or glucose intolerance. Associated periorbital aching commonly happens. The "pupil sparing rule" is not an unfailing sign in a diabetic patient with

incomplete third nerve palsy or multiple cranial neuropathies. Exception does occur. Thus, prudent neurological assessment and appropriate imaging study should be performed in these patients. Recurrence of diabetic ophthalmoplegia may occur occasionally, albeit its prognosis is relatively benign.

REFERENCES

1. Said G. Focal and multifocal diabetic neuropathies. *Arq Neuropsiquiatr* 2007;65:1272-1278.
2. Ogle JW. On disease of the brain as a result of diabetes mellitus. *St George's Hospital Rep* 1866;1:157.
3. Watanabe K, Hagura R, Akanuma Y, Takasu T, Kajinuma H, Kuzuya N, Irie M. Characteristics of cranial nerve palsies in diabetic patients. *Diabetes Res Clin Pract* 1990; 10:19-27.
4. Eshbaugh CG, Siatkowski R, Smith JL, Kline LB. Simultaneous, multiple cranial neuropathies in diabetes mellitus. *J Neuroophthalmol* 1995;15:219-224.
5. Richards BW, Jones FR, Younge BR. Causes and prognosis in 4278 cases of paralysis of oculomotor, trochlear, and abducens cranial nerves. *Am J Ophthalmol* 1992;113:489-496.
6. Kissel JT, Burde RM, Klingele TG, Zeiger HE. Pupil-sparing oculomotor palsies with internal carotid-posterior communicating artery aneurysms. *Ann Neurol* 1983;13:149-154.
7. Zorrilla E, Kozak GP. Ophthalmoplegia in diabetes mellitus. *Ann Intern Med* 1967;67:968-976.
8. Jacobson DM. Pupil involvement in patients with diabetes-associated oculomotor nerve palsy. *Arch Ophthalmol* 1998; 116:723-727.
9. Goldstein JE, Cogan DG. Diabetic ophthalmoplegia with special reference to pupil. *Arch Ophthalmol* 1960;64:592-560.
10. Greco D, Gambina F, Maggio F. Ophthalmoplegia in diabetes mellitus: a retrospective study. *Acta Diabetol* 2009; 46:23-26.
11. Keane JR. Multiple cranial nerve palsies: analysis of 979 cases. *Arch Neurol* 2005;62:1714-1717.
12. Ross AT. Recurrent cranial nerve palsies in diabetes mellitus. *Neurology* 1962;12:180-185.

13. Shih MH, Huang FC, Tsai RK . Ischemic ophthalmoplegia in diabetic mellitus. *Neuro-Ophthalmology* 2001;26:181-191.
14. Dreyfus PM, Hakim S, Adams RD. Diabetic ophthalmoplegia. Report of case, with postmortem study and comments on vascular supply of human oculomotor nerve. *Arch Neurol Psychiatry* 1957;77:337-349.
15. Asbury AK, Aldredge H, Hershberg R, Fisher CM. Oculomotor palsy in diabetes mellitus: a clinico-pathological study. *Brain* 1970;93:555-566.