Annals of Case Reports and Medical Images

Article Type: Case Report

Annals of Case Reports and Medical Images
Volume 2 Issue 1 - 2025
www.anncrmi.org

Isolated sixth cranial nerve palsy in a patient with new onset diabetes mellitus

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Received: Mar 17, 2025; **Accepted:** Apr 08, 2025;

Published: Apr 15, 2025

Citation: Charpuria PJ. Isolated sixth cranial nerve palsy in a patient with new onset diabetes mellitus. Ann Case Rep Med Images. 2025; 2(1): 1018.

Background

Diabetes mellitus, a notorious global health concern, presents with a broad spectrum of microvascular and macrovascular complications, of which peripheral neuropathy and diabetic retinopathy are well known; however, isolated sixth nerve palsy is a rare entity noticed in the diabetic population. Although cranial nerve palsy is an uncommon variant of diabetic neuropathy, it occurs 10 times more frequently in diabetics than in non-diabetics [1]. Long intracranial course exposes the sixth nerve to diverse pathologies ranging from benign vascular to sinister causes like tumor and aneurysm, making the etiological evaluation more tedious and the foremost thing. Usually the history and examination findings in the case of sixth nerve palsy reveal the associated potential risk factors and neurological signs or symptoms that help in tracing the underlying etiology. On the other hand, sometimes an isolated presentation of sixth nerve palsy, as mentioned in our case, poses more trouble in unfolding the diagnosis. ISNP in diabetes was typically seen in the elderly with vasculopathic risk factors on long-term disease progression [2]. This case highlights the diagnostic challenges encountered in disclosing the culprit of sixth nerve palsy when diplopia in a young adult is the solitary clinical manifestation with no known vasculopathic risk factors and inconclusive neuroimaging. This also focuses on the importance of considering diabetes as a differential diagnosis while evaluating an unexplained ocular nerve palsy. It emphasizes the role of early neurological consultation and neuroimaging in establishing the prompt and appropriate diagnosis and management that has influenced the course of sixth nerve palsy.

Case presentation

A 36-yr-old previously healthy male presented to the emergency department with complaints of double vision and pain in the right eye. He initially noticed a change in vision 3 days ago that appeared to worsen on right lateral gaze and was associated with dull right eye pain. There is no history of redness, watering, or vision loss. He denies a history of any trauma, vomiting, neck stiffness, fever, focal weakness, numbness or seizures. Vitals measured were normal. On ocular examination of the right eye, there was limited abduction on the right gaze, and other ocular movements were intact in both the eyes; bilateral pupils were equally reactive and showed no evidence of ptosis or proptosis. Other cranial nerves on examination revealed no functional impairment. He is devoid of any significant past medical ailments or surgery. No abnormal causative findings revealed on initial CT brain. Basic laboratory tests were ordered.

Given the persistent clinical manifestations, the neurology department was consulted and further evaluated with MRI of the brain, orbits, and MRI brain venogram. All the neurological workup turned out to be negative, thus ruling out tumors, aneurysms, cavernous sinus thrombosis, and other possible intracranial etiologies. On thorough investigation, the only remarkable finding was an elevated blood glucose level of 206 g/dl, noted on the basic metabolic panel. Hemoglobin A1C level was then tested and found to be elevated at 9.7%, concluding a diagnosis of new-onset diabetes mellitus. Abnormally elevated HbA1c with negative neurological workup implied that the undiagnosed diabetes could be the culprit, and hence the diag-

nosis was formed as diabetes-induced microvascular ischemic isolated sixth nerve palsy. Immediately he was started on metformin 1000 mg orally twice daily and sitagliptin 100 mg once daily with strict glycemic control, and other lifestyle modifications were advised, like regular physical activity, consumption of a diet rich in fiber, protein, fruits and vegetables, healthy carbs, and polyunsaturated or healthy fats, and avoidance of refined sugars and saturated fats. On his monthly follow-up, he was assessed for medication adherence, progression of symptoms, and blood sugar levels, also looking for any new-onset neurological manifestations. Blood glucose levels were normalized within one month, with noticeable improvement in abduction of the right eye. At a 3-month follow-up, his diplopia had completely resolved with return of ability to abduct his right eye to the full extent, and HBA1C was noted at 6%, confirming that diabetic cranial mononeuropathy involving the sixth nerve was the most likely cause of diplopia. Fundoscopy was done to rule out retinopathy, and peripheral sections were intact.

Discussion

Here we analyze a case of an adult male with sudden onset diplopia and restricted abduction of the right eye suggesting sixth nerve palsy. Diplopia in diabetes can be due to third, fourth, sixth ocular nerves affected either individually "cranial mononeuropathy" or all together "mononeuropathia multiplex". Sanders, in his study, stated that most of the ischemic recurrent cases of oculomotor mononeuropathy are preceded by abducens nerve palsy, showcasing the vulnerability of the sixth cranial nerve to vascular ischemia [3]. While the sixth nerve was the most commonly affected, trochlear involvement was the least noted [4]. Although etiologies are wide and diverse, sixth nerve palsy in the absence of other neurological symptoms and neuroimaging findings and elevated HbA1C points towards the undiagnosed diabetes as a potential cause of isolated sixth nerve palsy. Cranial mononeuropathy in the elderly with long-standing diabetes and associated cardiovascular risk factors like hypertension, hyperlipidemia, and smoking can be presumed to be vasculopathic in origin, and initial observation for spontaneous resolution with management of underlying risk factors would suffice unless symptoms persist beyond 3 months, development of other neurological symptoms, or the initial palsy worsens, which demands further investigation [1]. However, isolated sixth nerve palsy in an adult with new-onset diabetes and no other significant risk factors requires careful evaluation because of the usual presentation, and diabetes as a cause is generally a diagnosis of exclusion made only after investigating for all the potential causes.

Diabetic complications are usually noticed in the tissues where glucose uptake is independent of insulin action and hence exposed directly to serum glucose levels, likely seen in the retina, kidneys, and vascular endothelium [5]. Persistent hyperglycemia, reactive oxygen species, and advanced glycated end products induce microvascular changes that include thickening of the endothelial basement membrane, endothelial cell hyperplasia, pericyte degeneration, connective tissue deposition, and endothelial dysfunction producing hypercoagulable changes. All these underlying pathological changes in the vasa nervorum, together with various metabolic factors and genetic factors, lead to ischemia and axonal degeneration followed by demyelination of portions of the affected nerve and are known to play a major role in the pathophysiology of diabetic neuropathy. Prior studies recorded the presence of less intense microvascular changes even in diabetic patients without clinical neuropathy, suggesting the occurrence of pathological changes early in the disease, and also noticed more damage in endoneurial than epineural vessels [6]. The Oculomotor nerve has its motor fibers aligned centrally with parasympathetic pupillary fibers placed peripherally; oxygen and nutrients are diffused from outer to inner portions of the nerve by the vasa nervorum overlying the peripheral parasympathetic fibers, making the centrally placed motor fibers more prone to microvascular (vasa nervorum) changes. Most of the diabetic patients with third nerve palsy show peculiar pupillary sparing and primarily affect the motor fibers, which further supports the ischemic microvascular changes playing a crucial role in the pathogenesis of cranial nerve damage in diabetes.

Diabetic neuropathy can involve any of the systemic peripheral and autonomic nervous systems, most commonly manifesting as symmetric peripheral polyneuropathy and cranial nerve palsy; particularly isolated involvement is uncommon. Diabetic neuropathy can be divided into two distinct groups: one of peripheral neuropathy and autonomic neuropathy and the other consists of diabetic mononeuropathy based on mode of onset, progression, etiopathogenesis, and recovery. There is no evidence of association between diabetic mononeuropathy and peripheral autonomic neuropathies; they occur independently, thus validating the different underlying pathomechanisms [7]. Although our case does not show features of peripheral neuropathy, which is the most common complication seen in diabetic patients, diabetic cranial mononeuropathy can be present. Previous studies noticed the occurrence of peripheral neuropathy only in 22% of patients with diabetic mononeuropathy; hence, it emphasizes the need for investigating mononeuropathy even in the absence of the most commonly seen peripheral neuropathy in diabetics [1].

In our case, isolated sixth nerve palsy as the initial presentation of diabetes in the absence of cardiovascular risk factors in a 39-year-old is atypical and cannot be presumed to be vasculopathic in origin. Hence this brings up the necessity for early neuroimaging, because an isolated sixth nerve palsy may be the initial presentation of an underlying serious neuro-ophthalmological pathology. There is also documented evidence of MRI in young people without risk factors who are more likely to have underlying lesions leading to sixth nerve palsy [8]. Acute onset diplopia in an otherwise healthy patient induces anxiety, and performing early neuroimaging becomes beneficial and provides reassurance rather than wait-and-watch policy for resolution or other neurological symptoms to show up, particularly in our case where no other associated finding refers to a vasculopathic cause. Advances in treatment strategies and significant betterment in prognosis of non-microvascular neurological conditions highlight the need for early detection of underlying etiology in isolated cranial nerve palsy not presumed to be of vasculopathic origin [2]. The negative MRI brain and orbit eliminate tumor, aneurysm, demyelinating disorder, and brainstem ischemic lesion, and MRI venogram helps rule out cavernous sinus thrombosis. Nowadays MRI is more sensitive and preferred over computed tomography and has become a choice of imaging in abducens nerve palsy [2,8].

Moster studied isolated sixth nerve palsy in younger age groups (15-50 years) and postulated useful diagnostic guidelines stating that patients with no significant history should undergo investigations for the presence of any risk factors, and early imaging is mandatory because 27% of such cases are due

to underlying malignant lesions, which becomes highly significant [9].

This patient displayed complete resolution with control of blood glucose levels, reassuring the diagnosis of diabetic cranial mononeuropathy in a new-onset diabetes. The remyelination and repair of the involved nerve with return of normal blood supply might be the cause of recovery. Sixth nerve palsy due to vascular causes reported remarkably high rates of complete recovery up to 70% [4]. Few studies also noticed increased recovery rates when presented early in the disease and normal blood glucose levels [10]. However, there is no evidence of factors like specific risk factors, the number of associated risk factors, associated pain, or age on the prognosis and duration of the sixth nerve palsy [4,3]. This patient should be assessed carefully in case any recurrence or other neurological symptoms appear. He is also examined for other diabetic complications, and there is no evidence of other variants of diabetic neuropathy, retinopathy, or nephropathy.

Conclusion

Irrespective of vasculopathic age group and associated cardiovascular risk factors, diabetes should be evaluated in the context of isolated sixth nerve palsy with inconclusive neuroimaging. Acquired ocular nerve palsy contributes to 40-60% of cases of diplopia; systemic vascular causes account for a major portion (nearly 33%) of acquired ocular nerve palsy, with the most common being the sixth nerve [4].

Isolated sixth nerve palsy can be the initial presentation of diabetes, unlike the typical presentation of other microvascular diabetic complications that usually manifest years after uncontrolled diabetes. Ellenberg mentioned cases of diabetic neuropathy as the initial presentation of undiagnosed diabetes and highlighted that “diabetic neuropathy is a fundamental component of multifaceted crystal” rather than a mere complication of diabetes [11].

Sudden onset diplopia in a previously healthy adult provokes anxiety and also interferes with daily activities, which leads to intense psychological, social, and economic burden. Therefore, it’s wiser to choose early neuroimaging in presumed vasculopathic isolated sixth nerve palsy in younger age groups without a history of systemic vascular diseases or other vasculopathic risk factors for prompt diagnosis and management. A prospective study demonstrated that most of the sixth nerve palsy cases with intracranial causative lesions on initial MRI belong to the younger age groups and showed comparatively very low rates of vasculopathic risk factors [8].

In such atypical presentations of isolated sixth nerve palsy that are diagnosed as diabetic in origin and resolved spontaneously, patients must be followed for any recurrence or emergence of newer neuro-ophthalmological symptoms, because there are many known cases of sixth nerve palsy presumed to be vasculopathic that resolved completely but later on were diagnosed to be neoplastic after a recurrence [8].

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