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Diplopia: A Diagnostic Challenge with Common and Rare Etiologies

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Case series

Patient: Male, 71 • Female, 41 • Female, 67
Final Diagnosis: Diabetic neuropathy • meningioma • drug-induced diplopia
Symptoms: Diplopia
Medication: —
Clinical Procedure: Clinical and imagiologic study
Specialty: Ophthalmology

Objective: Challenging differential diagnosis
Background: Diplopia is a symptom with very different etiologies. It may be caused by pathology in the eye, orbit, extraocular muscles, neuromuscular junction, or in the central nervous system.
Case Reports: Three clinical cases of hospitalization due to isolated diplopia are presented here, illustrating different etiologies.
Conclusions: The present article aims to address the differential diagnosis of this clinical condition and to warn of less frequent causes of diplopia, such as adverse effects of commonly used drugs.

MeSH Keywords: Diabetic Neuropathies • Diplopia • Neurologic Manifestations

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/893134>

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Background

Diplopia, or double vision, is a symptom resulting from the perception of 2 images of a single object (Figure 1). The diplopia mechanism (monocular or binocular), its type (horizontal, vertical, or oblique), and its temporal progression and accompanying symptoms are important for its etiological diagnosis [1,2]. Conducting a detailed history-taking and physical examination often reveal the underlying disease of this symptom [3]. Binocular diplopia is the most frequent (89%) and is characterized by the disappearance of the double image when 1 eye is closed [1,2,4]. The main cause of this symptom is a misalignment of the visual axes. Monocular diplopia differs from binocular diplopia by the persistence of the symptom when the eye is closed; it is normally caused by intraocular pathology [1,2]. In adults, the most common cause of diplopia is oculomotor nerve palsy due to ischemia. However, other important and common causes of diplopia should be considered, such as stroke, intracerebral aneurysms, brain tumors, and giant cell arteritis. [3]

Case Reports

Case 1

A 71-year-old man, with a history of poorly controlled type 2 diabetes mellitus (T2DM) and hypertension, was admitted due to sudden onset horizontal binocular diplopia, isochoric pupils, and ptosis due to left third cranial nerve palsy, without evidence of other neurological defects. About 6 months earlier, he had shown transient paresis of the right fourth cranial nerve, with subsequent spontaneous resolution of the symptoms. No changes were detected in the brain diffusion-weighted magnetic resonance imaging (MRI); therefore, neuropathy of ischemic etiology of the third cranial nerve was assumed, in the context of his vascular risk factors. Transthoracic echocardiography (TTE) and carotid ultrasound (CU) showed no significant pathology. During the follow-up period these changes regressed spontaneously within 2 months.

Case 2

A female patient, 41 years old and healthy, was admitted due to isolated horizontal binocular diplopia with a 2-week evolution. Clinically, she had paresis in the right sixth cranial nerve without presenting any other changes in the neurological examination. She was tested for serum and cerebrospinal fluid evaluation and underwent brain computed tomography (CT) scanning, which showed no alterations. However, diffusion-weighted MRI revealed meningioma of the lateral wall of the right cavernous sinus, with extension and mass effects towards the inner part. She was referred for neurosurgery

Figure 1. Diplopia – example.

consultation, and is due to undergo Gamma-knife surgery. TTE and CU were normal.

Case 3

A 67-year-old women, with a known history of T2DM, hypertension, and dyslipidemia, was admitted due to isolated horizontal binocular diplopia that had started about 3 days earlier. She reported having started taking Zolpidem recently for insomnia, emphasizing a chronological association between these 2 events. Upon admission, she stopped taking Zolpidem and the diplopia regressed. The analytical and imaging study (CT and diffusion-weighted MRI) showed no type of neurological injury or any other etiology. TTE and CU showed no significant pathology. She is being followed at medical consultation with no disease recurrence.

Discussion

The etiologic diagnosis of a patient with diplopia is a clinical challenge. Binocular diplopia is referred to in the literature as the most common type – 89% in some studies [4]. The 3 cases described above present clinical situations of binocular diplopia with distinct etiologies. There are several binocular diplopia etiological mechanisms: (1) orbital disorder; (2) extraocular muscle disorder; (3) neuromuscular junction dysfunction; (4) third, fourth, and sixth cranial nerve palsy; and (5) injury of the central nervous system (Table 1) [2,5].

Another less frequent cause, yet mentioned in the binocular diplopia literature, is diplopia caused by drugs, such as our third presented case. Table 2 shows a list of drugs associated

Table 1. Common causes of binocular diplopia.

Orbital disorder	Trauma, tumor, infection, thyroid-associated ophthalmopathy
Extraocular muscle disorder	thyroid-associated ophthalmopathy, extraocular muscle injury or hematoma due to ocular surgery, congenital myopathies, mitochondrial myopathies, muscular dystrophy
Neuromuscular junction dysfunction	Myasthenia gravis, botulism
Palsies of the third, fourth or sixth cranial nerves	Microvascular ischemia – diabetic neuropathy, hemorrhage, tumor, vascular malformation, aneurysm, meningitis, multiple sclerosis
central nervous system injury (pathways and cranial nerve nuclei)	Ischemia, hemorrhage, tumor, vascular malformations, multiple sclerosis, hydrocephalus, syphilis, Wernicke's encephalopathy, neurodegenerative disease

with diplopia, some of which are commonly taken (e.g., amlodipine, sertraline, ciprofloxacin, and antiepileptics) [6].

The onset of diplopia is usually sudden, but this does not necessarily indicate vascular pathology. The temporal evolution of the clinical situation is more useful for the etiological diagnosis [1]. Diplopia with intermittent evolution and diurnal variations should alert the clinician to the possibility of neuromuscular junction disease.

The presence of accompanying symptoms may also help in the investigation of diplopia. Periorbital pain or pain associated with eye movement points to inflammatory causes. Constant or intermittent pain and defects in visual acuity should be investigated and may correlate with neuromuscular dysfunction, third cranial nerve injury, or orbital disease.

Other diseases and history of eye surgery are important in the evaluation of these patients. The presence of cardiovascular risk factors (e.g., hypertension, diabetes, and T2DM) supports the hypothesis of vascular lesion of the central nervous or microvascular systems (diabetic neuropathy) [2].

Diabetic neuropathy, as in our first presented case, is sometimes neglected in investigating the diplopia, although it is one of the most frequent causes; it usually has a sudden onset and may affect cranial nerves (third and sixth cranial nerves more often than the fourth). It normally resolves spontaneously within 3–12 months [5]. A factor important in the differential diagnosis in these situations is that in ischemia of the third nerve, the pupil is normal and there is no mydriasis, because the constriction of the pupil is spared. Conversely, if the etiology is compressive due to tumor or aneurysm, mydriasis is normally present.

Monocular diplopia is less frequent (11%) and may be caused by refractive errors, corneal disease (e.g., irregular astigmatism), iris lesion, cataracts, and macular disease. Primary or secondary visual cortex diseases are rarely associated with monocular diplopia or cerebral polyopia (seeing more than 2 images) [1,4].

Table 2. Drugs associated with diplopia.

Lacosamide	Very common ($\geq 1/10$)
Zonisamide	Very common ($\geq 1/10$)
Eslicarbazepin	Common ($\geq 1/100$ a $< 1/10$)
Botulinum toxin	Common ($\geq 1/100$ a $< 1/10$)
Rufinamide	Common ($\geq 1/100$ a $< 1/10$)
Pregabalin	Common ($\geq 1/100$ a $< 1/10$)
Perampanel	Common ($\geq 1/100$ a $< 1/10$)
Temozolomide	Common ($\geq 1/100$ a $< 1/10$)
Zicotinamide	Common ($\geq 1/100$ a $< 1/10$)
Sildenafil	Common ($\geq 1/100$ a $< 1/10$)
Gabapentin	Common ($\geq 1/100$ a $< 1/10$)
Topiramate	Common ($\geq 1/100$ a $< 1/10$)
Zaleplon	Uncommon ($\geq 1/1000$ a $< 1/100$)
Levetiracetam	Uncommon ($\geq 1/1000$ a $< 1/100$)
Bortezomib	Uncommon ($\geq 1/1000$ a $< 1/100$)
Amlodipine	Uncommon ($\geq 1/1000$ a $< 1/100$)
Adalimumab	Uncommon ($\geq 1/1000$ a $< 1/100$)
Pravastatin	Uncommon ($\geq 1/1000$ a $< 1/100$)
Lamotrigine	Uncommon ($\geq 1/1000$ a $< 1/100$)
Capecitabine	Uncommon ($\geq 1/1000$ a $< 1/100$)
Telithromycin	Rare ($\geq 1/10000$ a $< 1/1000$)
Voriconazole	Rare ($\geq 1/10000$ a $< 1/1000$)
Dextromethorphan/ Quinidine	Rare ($\geq 1/10000$ a $< 1/1000$)
Sertraline	Rare ($\geq 1/10000$ a $< 1/1000$)
Ciprofloxacin	Rare ($\geq 1/10000$ a $< 1/1000$)

Conclusions

This paper aims to draw attention to the various causes of diplopia, whose diagnosis requires a clinical study and detailed imaging. The high prevalence of chronic diabetic patients is an important factor and should always be considered as a possible etiology. The temporal correlation between the onset of

symptoms and introduction of new drugs is important to investigate when taking the clinical history of the patient.

Statement

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