Intermittent Anisocoria as a Presenting Sign of Relapsing-Remitting Multiple Sclerosis

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Abstract

A 36-year-old male reported intermittent episodes of different pupil sizes (right pupil always larger than the left pupil) that had been noted for one week. Over a one-month period, ocular findings consisted of intermittent and variable anisocoria, diplopia, and torsional nystagmus. Neurology made a diagnosis of relapsing-remitting multiple sclerosis (MS) using the McDonald criteria based on brainstem syndrome, optic neuropathy, transverse myelitis symptoms, multifocal areas of demyelination in the spinal cord on MRI, and the absence of MS mimickers in lab findings. This case report alerts eye care providers to the possibility of intermittent anisocoria as a presenting sign of relapsing-remitting multiple sclerosis.

KEYWORDS:
anisocoria, nystagmus, multiple sclerosis

INTRODUCTION

Multiple sclerosis is a chronic, demyelinating autoimmune disease of the central nervous system. This condition typically manifests in adults between the ages of 20 and 40 years .[1] While the pathogenesis is not completely understood, it is largely believed to be an autoimmune disease in which T-cell mediated inflammation attacks the nerve myelin sheath. If the myelin becomes damaged, the nerve cell's ability to transmit the signal effectively is hindered or impaired. Depending on where in the nervous system this damage occurs, patients may present with an array of neurological signs and/or symptoms. A common ocular manifestation of multiple sclerosis is optic neuritis. However, nearly any portion of the visual system can be affected resulting in diplopia, inflammatory reactions, and painful eye movements, among other signs and symptoms. In this case report, eye care providers help identify previously undiagnosed multiple sclerosis through a collection of transient and uncommon ocular findings.

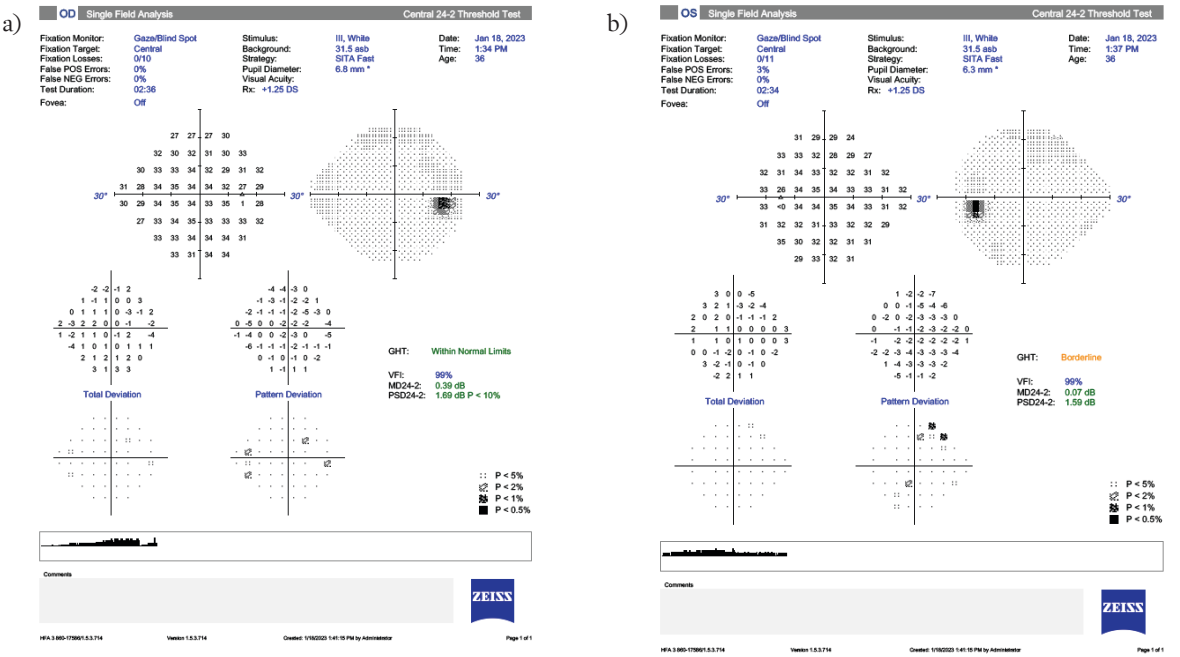
CASE REPORT

A 36-year-old male presented for an ocular examination reporting intermittent differences in pupil size (with the pupil of the right eye always larger than that of the left eye) of one week duration. One week prior, after the initial onset of anisocoria and mild dizziness, he went to a local urgent care facility that recommended he go to the local emergency department, but the anisocoria resolved prior to his arrival at the emergency department. The emergency department performed a computed tomography scan, a sinus X-ray, and electrocardiogram . He reported that all testing was unremarkable. At discharge, he was prescribed an oral steroid and meclizine for dizziness.

At the present visit, he reported headaches, dizziness, and double vision only in the mornings. His medical history was significant for ulcerative colitis, hypertension, and anxiety. His uncorrected visual acuities were 20/20 in both eyes. Pupils were equal, round, and reactive to light; however, the patient showed the provider a photo of an episode of anisocoria from earlier in the week. The extraocular muscles showed a full range of motion without any report of pain or double vision. A unilateral cover test showed no strabismus and an alternating cover test revealed orthophoria at distance and near.. The anterior segment exam and dilated fundus examination were unremarkable. A 24-2 SITA-Fast Humphrey visual field showed insignificant scattered defects of both eyes. He was instructed to return to the clinic

for a follow-up in one week or sooner if he experienced any recurrence or worsening of his symptoms. This initial eye exam occurred in the afternoon, while the follow-up appointment was scheduled for first thing in the morning.

Figure 1: *Humphrey 24-2 visual field results*



At the one-week follow-up, the patient reported still having episodes of unequal pupil size but no double vision. He also reported lightning sensation of the shoulders and thighs that started on the left side and spread to the right side, a swirling sensation when in fluorescent lights, and dizziness if he turned his head too quickly or when he was assessing the left side while driving. His uncorrected visual acuities were 20/15 in both eyes. Pupils were equal, round, and reactive to light. He reported double vision during extraocular muscle testing in right gaze, and torsional nystagmus was observed in all secondary gazes, especially in left gaze. He appeared orthophoric during initial cover testing but reported double vision as testing progressed, although no deviation was observed. In the phoropter, he reported fusion with one prism diopter base down over the left eye and two prism diopters base out. By the end of the examination, the patient had developed marked anisocoria, with the right pupil significantly larger than the left. At this point, the leading differential diagnoses were believed to be demyelinating disease, migraine headaches, and cluster headaches. Neuro-ophthalmology was consulted for further examination.

During the neuro-ophthalmology consultation one week later, in addition to the previous symptoms mentioned at the prior examinations, the patient reported shaking after warm showers which is consistent with possible Uhthoff phenomenon, a worsening of neurological symptoms in demyelinating disease during overheating or increased body temperatures. The uncorrected visual acuities were 20/15 in both eyes. Pupils were equal and round with no afferent pupillary defect. Color vision was normal in both eyes by the Ishihara test. Confrontation visual fields were full in both eyes. Torsional nystagmus was noted in horizontal gazes but was worse in left gaze. In right gaze, he initially had diplopia with mild exotropia, but that finding had dissipated before re-evaluation by the attending neuro-ophthalmologist during the same examination. Dilated fundus examination was normal. Humphrey 24-2 SITA-Standard visual field was full in both eyes. An MRI of the brain and orbit with and without contrast with fat suppression was ordered, and a neurology consult was scheduled.

MRI demonstrated bilateral optic nerve enhancement/enlargement and a T2 FLAIR lesion in the left cerebellar peduncle without contrast enhancement. Since the extraocular muscles did not appear to be enlarged/inflamed, there were no findings to suggest an ocular myopathic process or neuromuscular junction disorder, such as myasthenia gravis. Neurology ordered an MRI of the cervical and thoracic spine with and without contrast, lab work (serum ANA, SSA/B, ACE, MOG Ab, AQP4 Ab), and CSF studies (basic studies plus IgG index and MSP3 panel), and referred the patient to neuroimmunology.

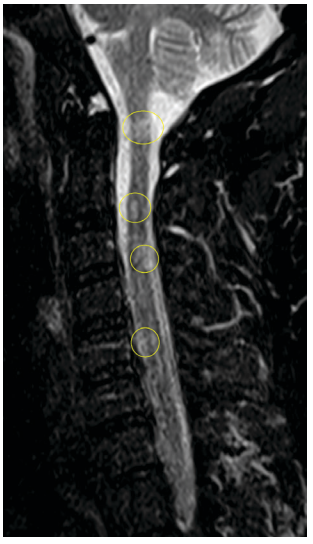
The neuroimmunology clinic gave a diagnosis of relapsing-remitting multiple sclerosis using the McDonald criteria for diagnosis based on the brainstem syndrome caused by demyelination in the white matter of the brainstem (nystagmus and diplopia in this case), transverse myelitis symptoms, and multilevel patchy T2 hyperintensity with partial

contrast enhancement in some places in the cervical and thoracic spinal cord seen on MRI. The lab work for MS mimics was unrevealing. The treatment plan was to initiate natalizumab infusions based on his spinal disease burden.

Figure 2: *Copy of lab results for MS mimickers. Negative results were obtained in neuromylitis optica testing for aquaporin 4 antibodies. The patient was also negative for MOG antibodies which allows for the exclusion of myelin oligodendrocyte glycoprotein disease.*

Test Name	In Range	Out of Range	Reference Range	Lab
AQP4 Ab,w/rfl Titer,Serum				AMD
AQP4 Ab,w/rfl Titer,Serum				
Aquaporin 4 Ab, CBA, Serum	NEGATIVE		NEGATIVE	
	This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute San Juan Capistrano. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.			
MOG Ab w/refl Titer, Serum (Continued)				
MOG Ab CBA, Serum	NEGATIVE		NEGATIVE	
	This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute San Juan Capistrano. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.			

Figure 3: *Sagittal STIR MRI image showing hyperintense lesions (circled in yellow) involving the corticomedullary junction, cervical spine, and thoracic spine. These lesions are indicative of demyelination.*



DISCUSSION

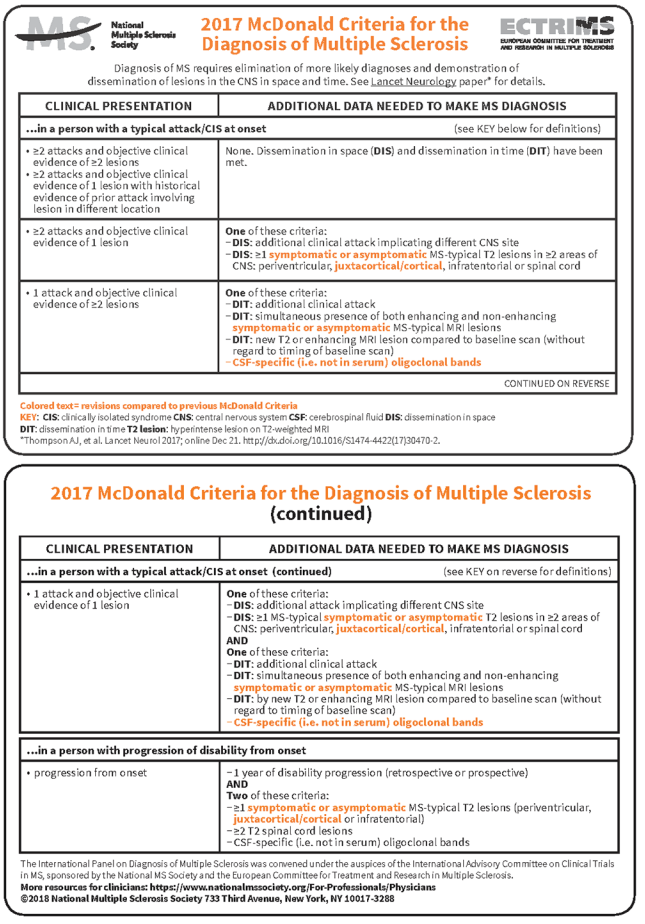
Multiple sclerosis is an autoimmune neurological disease that generally affects females more frequently than males, with onset between ages 20 and 40 years. Diagnosis can be difficult due to the range of symptoms, the remitting nature, and overlapping symptoms with other conditions. MS can affect the visual, motor, sensory, cerebellar, genitourinary, and neuropsychiatric systems. The most common ocular manifestation is optic neuritis, but other ocular signs and symptoms include blurred vision, unilateral loss of vision, pain with eye movements, afferent pupillary defect, oscillopsia, diplopia, nystagmus, and internuclear ophthalmoplegia. Other symptoms include changes in gait, fatigue, loss of balance or coordination, muscle weakness, and tingling or numbness.

A review of the literature identified only one report of anisocoria as the initial presentation of MS.[2] The estimated occurrence of isolated cranial nerve palsies in MS ranges from 1.6% to 10.4%, with CN VI palsies accounting for half of those cases.[3,4] Cranial nerve III palsy in MS is rare because of the relative lack of myelination surrounding the CN nuclei compared with the extensive myelination seen in other portions of the brainstem, and it is even more rare to have isolated anisocoria as the initial presentation.[5,6]

Ocular motor disturbances in MS are prevalent, with the most frequent being internuclear ophthalmoplegia. Common ocular motor disorders include saccadic hypermetria, gaze-evoked nystagmus, and impaired vestibulo-ocular

reflex suppression.[7] Gaze-evoked nystagmus is also a rare initial presentation of MS.[8,9] Damage to the cerebellar peduncle may result in ipsilesional gaze-evoked nystagmus, as was the case with this patient.[7]

Figure 4: *2017 McDonald Criteria Revision*



2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis

National Multiple Sclerosis Society

ECTRIMS European Committee for Treatment and Research in Multiple Sclerosis

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time. See Lancet Neurology paper* for details.

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset	(see KEY below for definitions)
• ≥2 attacks and objective clinical evidence of ≥2 lesions • ≥2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space (**DIS**) and dissemination in time (**DIT**) have been met.
• ≥2 attacks and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS:** additional clinical attack implicating different CNS site – **DIS:** ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord
• 1 attack and objective clinical evidence of ≥2 lesions	**One** of these criteria: – **DIT:** additional clinical attack – **DIT:** simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT:** new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**
	CONTINUED ON REVERSE

Colored text= revisions compared to previous McDonald Criteria
KEY: CIS: clinically isolated syndrome **CNS:** central nervous system **CSF:** cerebrospinal fluid **DIS:** dissemination in space **DIT:** dissemination in time **T2 lesion:** hyperintense lesion on T2-weighted MRI
*Thompson AJ, et al. Lancet Neurol 2017; online Dec 21. http://dx.doi.org/10.1016/S1474-4422(17)30470-2.

2017 McDonald Criteria for the Diagnosis of Multiple Sclerosis (continued)

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED TO MAKE MS DIAGNOSIS
...in a person with a typical attack/CIS at onset (continued)	(see KEY on reverse for definitions)
• 1 attack and objective clinical evidence of 1 lesion	**One** of these criteria: – **DIS:** additional attack implicating different CNS site – **DIS:** ≥1 MS-typical **symptomatic or asymptomatic** T2 lesions in ≥2 areas of CNS: periventricular, **juxtacortical/cortical**, infratentorial or spinal cord **AND** **One** of these criteria: – **DIT:** additional clinical attack – **DIT:** simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions – **DIT:** by new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) – **CSF-specific (i.e. not in serum) oligoclonal bands**
...in a person with progression of disability from onset	
• progression from onset	– 1 year of disability progression (retrospective or prospective) **AND** **Two** of these criteria: – ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions (periventricular, **juxtacortical/cortical** or infratentorial) – ≥2 T2 spinal cord lesions – CSF-specific (i.e. not in serum) oligoclonal bands

The International Panel on Diagnosis of Multiple Sclerosis was convened under the auspices of the International Advisory Committee on Clinical Trials in MS, sponsored by the National MS Society and the European Committee for Treatment and Research in Multiple Sclerosis.
More resources for clinicians: https://www.nationalmssociety.org/For-Professionals/Physicians

The McDonald multiple sclerosis diagnostic criteria use clinical, radiographic, and laboratory data to facilitate a diagnosis.[10] There are four main types of MS diagnosed based on the progression of symptoms: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS). CIS refers to the first episode of neurologic symptoms caused by demyelination that must last at least 24 hours. RRMS is the most common type and is defined by relapses of neurological symptoms with periods of remission. If the disease progressively worsens or disability accumulates, it is classified as secondary progressive MS. PPMS involves a gradual worsening of symptoms without remission.

There is no specific lab test available to diagnose MS, but lab work is important in ruling out other diseases that can mimic MS. A serum antinuclear antibody test can look for antinuclear antibodies that could indicate autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome, among others. SS-A and SS-B antibodies can test for connective tissue disease such as Sjogren's and lupus. Angiotensin converting enzyme can be used to monitor for sarcoidosis. Testing for anti-myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP4) can be used to delineate neuromyelitis optica from MS in combination with clinical symptoms. Cerebrospinal fluid and serum can be tested for IgG and albumin quantitation including oligoclonal banding as a way of detecting increased intrathecal immunoglobin synthesis as an adjunct in the clinical diagnosis of MS. As an alternative to CSF oligoclonal band testing, serum can be tested for Kappa/Lambda light chains.

There is no cure for MS and treatment focuses on the management of symptoms, speeding up recovery, and slowing the progression of the disease. Attacks can be treated with oral or intravenous corticosteroids or plasmapheresis.

Disease-modifying therapies include injectable treatments, oral medications, and infusion treatments. Natalizumab was selected for this patient due to its rapid onset with full efficacy achieved immediately with the first infusion, a paucity of side effects, and a good safety profile for patients who are JCV-Ab-negative so that the risk of progressive multifocal leukoencephalopathy is negligible. In addition, it also does not impair systemic immune functions like many immune suppressives. Treatments for symptoms include physical and occupational therapy, muscle relaxants, antidepressants, and medications for fatigue, sexual dysfunction, insomnia, and bladder or bowel control.

CONCLUSION

Multiple sclerosis can present with a wide array of systemic and ocular symptoms. Eye care providers should be knowledgeable of these possibilities to help facilitate timely diagnosis and treatment which can result in improved long-term outcomes. ●

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