VISUAL PATHWAYS INVOLVEMENT IN MULTIPLE SCLEROSIS FROM PATHOLOGICAL PROCESS TO NEURO-OPHTHALMOLOGIC ASSESSMENT

Adriana Bulboaca, Corina Ursu, Ioana Stanescu, Dafin Muresanu, Angelo Bulboaca
"Iuliu-Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca

ABSTRACT

Multiple sclerosis (MS) is a demyelinating disease associated with a myriad of visual pathways pathology. These pathologies need to be assessed, even when asymptomatic, because they may represent an important index of disease course, severity and treatment response. This is a review of the importance of different visual pathways assessment methods such as classic ophthalmologic examination, cerebrospinal fluid analysis, Doppler ultrasonography of the orbital vessels, magnetic resonance imaging, optical coherence tomography, visual evoked potential, evaluating which may contribute to elucidate the pathophysiological process, structural and functional damage. The modern medical technology developed multiple methods which are trying to link their results to the overall brain damage in MS. A global analysis of these methods is needed, in order to a better evaluation of visual pathways damage associated with multiple sclerosis.

Keywords: multiple sclerosis, visual pathways, optical coherence tomography, visual evoked potentials

INTRODUCTION

Multiple sclerosis (MS) is an immune mediated demyelinating disease of the central nervous system in which there are multiple associated neuro-ophthalmologic pathologies. Considering that the approximately 40% of the brain is devoted to visual function, MS (which is associated with an immune inflammation of central nervous system, with various localizations) commonly affects the visual function in a myriad of neuro-ophtahlmologic symptoms, depending of localization and pathological process (demyelination or axonal degeneration) (1). The visual function may be affected by various disorders such as uveitis and periphlebitis retinae, neuroretinitis, nerve palsy, nystagmus, conjugate eye movement disorders and visual pathways pathology. There are no satisfactory clinical, anatomical and functional assessment methods in order to make a complete evaluation of visual pathways involvement in multiple sclerosis. Therefore a presentation of the diagnosis methods in neuro-ophthalmologic examination of visual disabilities in multiple sclerosis may be useful background for clinical practice.

Associated neuro-ophthalmologic disorders in multiple sclerosis

Uveitis usually manifests as bilateral, intermediates uveitis (pars planitis) and is associated with MS patients in 1% of cases (2). Retinal periphlebitis with microcystic macular edema (consequence of neuroretinitis) is a rare manifestation associated with MS (3). Nystagmus or internuclear ophthalmoplegia are frequent signs in MS and their pathophysiological process is relatively well known. On the contrary, isolated cranial palsy is a rare finding in MS occurring in 1,6% of patients, and in order of their frequency we can find palsies of cranial nerves VI, III, and IV (4). Less commonly, MS may cause horizontal and vertical gaze palsies, upbeat and downbeat nystagmus, and optokinetic abnormalities (5,6,7). There are reports of oscillopsia (illuso-

Author for correspondence:
Conf. Dr. Adriana Bulboaca, "Iuliu-Haţieganu" University of Medicine and Pharmacy, 16 Pasteur St., Cluj-Napoca
e-mail: adriana_bulboaca@yahoo.com

ry motion of visual perception) without nystagmus in patients with MS (8).

Posterior (retrobulbar) pathways involvement occur by prechiasmatic, chiasmatic and retrochiasmatic lesions. Usually it is unilateral at onset, but involvement of bilateral optic pathways is common during the course of disease. The visual pathways involvement leads to specific clinical picture such as anopsia (prechiasmatic optic nerve structure involvement leading to anterior or posterior optic neuropathy), heteronimous hemianopsia (chiasmatic lesions) and homonimous hemianopsia/ qvadranopsia (retrochiasmatic lesions). Despite of high frequency of pathological involvement of retrochiasmatic pathways, homonymous hemianopsia or qvadranopsia are uncommon clinical signs in MS (0.5-3.5% of MS cases) (9). There are some reasons for this fact: the lesions affect only the peripheral visual field, resulting small scotomas that do not impair visual acuity, and they are difficult to be detected by the patient ; the other fact is their occurrence in the late stage of disease and, consequently, are masked by optic neuropathy already onset. The optic neuropathy is associated with considerable decreasing of visual acuity, therefore, the retrochiasmatical visual pathways involvement is difficult to be assessed in such cases (10). Heteronymous hemianopsia is a more rare clinical presentation in MS. There are few cases reports of bitemporal field defects assumed to plaques within the chiasma (11,12). There are recent studies which show the involvement of occipital cortex due to chronic inflammation process associated with autoimmunity in MS patients. (13).

Optic neuritis is the most common visual pathway pathological process and is associated with 40% of MS cases (40% of MS patients suffer an optic neuritic attack during the course of disease) (14). It may be due to anterior optic neuropathy (optic papillitis), and posterior optic neuropathy. Optic papillitis may occur in approximately 25% of cases of optic nerve involvement due to MS (15). Retrobulbar optic neuropathy is the most common clinical presentation of visual pathway involvement in MS (16).

The injury in visual pathways specifically reflects central nervous system effects of pathological process in MS patients (demyelination or axonal degeneration) (17).

The pathophysiological mechanism of lesions in MS

The involvement of visual system in MS consists in two separate processes. The first one is the demyelination process (demyelinated optic neuritis – MS-ON), and the second one consists in loss of retinal ganglion cells (non-optic neuritis – MS-NON). MS-ON is an inflammatory process and MS-NON is a neurodegenerative process. The pathological basis of MS-NON remains unclear. There are strong evidences that MS is accompanied by intrathecal production of antibodies against various proteins of CNS myelin including myelin basic protein (MBP), proteolipid protein (PLP), myelin oligodendrocytes protein (MOG) and myelin-associated glycoprotein. These antibodies may play a role in induction and perpetuation of inflammation in MS (18). Chronic demyelination or diffuse CNS inflammation may potentially contribute to the axonal loss (19). There are evidences for retrograde retinal damage after optic tract lesions in MS. These lesions are associated with retinal fibres layer thickness (RFLN) modification (20).

Demyelination process is the first pathological process, followed by remyelination. There is a question whether the remyelination is associated with restauration of visual function or demyelination leads to retinal ganglion cell loss and optic nerve atrophy despite of remyelination.

Neuro-ophthalmological assessment in multiple sclerosis

The examination methods comprise the structural damage, functional consequences and pathophysiological process assessment. Often, there is not a perfect correlation between the structural damage size and functional consequences. Different methods asses from different point of views the optical pathways involvement in MS. Some of them measure the structural damage and others the functional consequences.

Beside the classical ophthalmological examination, in order to prove retinal and optic nerve involvement in multiple sclerosis, determination of visual acuity, color perception, pupillary reflexes, visual field assessment and ophthalmoscopy, there are some modern methods that proved (in the last years) their utility in neuro-ophtalmological assessment of MS lesions. Such methods are focused on etiopathogenic mechanisms detection (cerebrospinal fluid analysis, Doppler ultrasonography of orbital vessels), structural damage assessment (magnetic resonance imaging, optical coherence tomography), and functional consequences evaluation (contrast sensitivity assessment – Pelli-Robson visual chart, visual evoked potentials determination).

Ethiopathogenetic mechanism detection

Cerebrospinal fluid in MS

Some cerebrospinal fluid (CSF) features are associated with MS. The analysis evolved from cytological, protein – cytological dissociation and immunoglobulin G index assessment to more sophisticated immunological descriptions (21). Although de CSF features associated with multiple sclerosis primary reflects the blood brain barrier permeabilization by inflammatory process, there are more etiopathogenic mechanism information which can be obtained by CSF analysis. The presence of oligoclonal IgG bands in CSF is a consequence of immune reactions in MS. Recently, newly occurring of oligoclonal bands or oligoclonal bands loss in CSF were associated with new symptoms onset or disease remission. Both positive and negative oligoclonal bands in CSF may change over the disease course and are often parallel with clinical condition (22).

Multiple CSF inflammatory biomarkers have prognostic potential for MS risk after clinically isolated syndrome as in MS associated demyelinated optic neuropathy. The CSF biomarkers of leukocytes infiltration (CXCL 13, matrix metalloproteinase-9, CXCL 10, myelin basic protein and neurofilament light chain) are strongly associated with MS risk. The others, osteopontin and CHI3L1 are related to tissue damage due to chronic immune inflammation and residual disabilities after MS attack (23). The CSF analysis due to initial attack and due to disease course may constitute a value predictor for MS risk and clinical outcome and may offer data about treatment efficacy.

Neuromyelitis optica spectrum disorders (Deviq's syndrome) are possible to be differentiated from MS by the presence of aquaporin-4 autoantibodies and other imuno-markers in CSF (24). Neuromyelitis optica is caused by autoantibodies to astrocytic aquaporin-4 (AQP4), the most abundant water channel in the CNS. Recently, an association between elevated level of lactate and neuromielitis optica attack was found. Lactate elevation and consequently CSF acidosis have been shown to cause astrocytic swelling and to affect astrocytic viability, potentially lead to more susceptible astrocytes to AQP4-antibodies-mediated damage (25).

Orbital vessels Doppler ultrasonography in MS

The evaluation of blood flow in ophthalmic artery (OA), central retinal artery (CRA) and short posterior ciliary artery (SPCA) revealed important changes associated with MS, having a great role in understanding the involvement of the retrobulbar hemodynamics in the pathogenesis of ON. In these arteries the following parameters have been assessed: peak systolic velocity (PSV), end-diastolic velocity (EDV), mean flow velocity (MV), indicators of peripheral vascular resistance such as Gosling Index (PI) and Pourcelot Index (RI). In MS patients with past optic neuritis, disturbances of ocular circulation were observed. These disturbances consist in increased resistance in the peripheral circulation in the orbit, within few days from ON onset, with normalisation of the parameters in the chronic phase (26,27). This may indicate serious disturbances in the retinal circulation due to demyelination and enlargement of the optic nerve compressing the OA, or due to vasoconstrictors released such as endothelin-1 and consequently vasospasm (27,28).

Assessment of visual pathways structural damage in MS

Magnetic resonance imaging

The role of magnetic resonance imaging (MRI) in multiple sclerosis diagnosis is well established. There are two processes revealed by brain MRI in multiple sclerosis: brain atrophy which reflects axonal degeneration, and white matter lesions which reflect the demyelination process. There are a number of magnetic resonance imaging-based methods for determining the posterior visual pathways damage by volumetry of visual cortex, lesion localisation, and lesion volume within the optic radiations. Although these methods are sensitive and reproducible, interpreting brain volume data has to be made with caution in order to exclude other factors (e.g. pseudoatrophy) which may create confusion, especially in a disease with complex pathological substrates such as MS. However, these findings demonstrate the presence of white matter demyelination and trans-synaptic degeneration as a contributor to chronic CNS damage in MS. (29, 30, 31).

Optical coherence tomography in MS

Optical coherence tomography (OCT) evaluates the anterior optic pathway damage by assessement the reduction of peripapillary retinal nerve fiber layer (RFLN) thickness, and by measurement of macular volume. The histological changes in these regions reflect the axonal degeneration in MS. The axonal degeneration is anterograde and retrograde. Retrograde retinal damage occurs after optic tract lesions in MS (29). These abnormalities were identified in all MS types. (32).

OCT is a noninvasive imaging technique and provides high resolution, cross-sectional images of the retina, the retinal nerve fiber layer (RNFL) and the optic nerve head. With axial resolution in the 5–7 μm range, OCT provides close to an in-vivo „optical biopsy" of the retina. The correlation of RFLN with MS stage is a point of considerable interest. The RFLN assessment may be used as a neurodegeneration marker. OCT could improve understanding the relation between structure and function in MS pathophysiology and include spectral or Fourier domain OCT technology, polarisation-sensitive OCT, fluorescence labelling, structural assessment of action-potential propagation, and segmentation algorithms allowing quantitative assessment of retinal layers (33).

Contrast sensititvity acuity assessment

In patients with MS with apparently normal high-contrast visual acuity, measurement of low-contrast letter acuity and visual evoked potentials may uncover previously undetected visual deficits. Low-contrast testing identifies the minimum size at which letters of a particular contrast level (i.e., shade of gray on white background) can be perceived. Measures of low-contrast letter acuity have a greater sensitivity to changes in visual function in patients with MS compared with assessments of high-contrast visual acuity. Low-contrast letter acuity is predictive for the presence of MS and is significantly correlated with other disease markers (e.g., disability scores, MRI findings, and RNFL thickness) (34, 35).These findings suggest that low-contrast letter acuity testing is useful to determinate the visual disability in MS.

Visual evoked potentials in MS

Visual evoked potential (VEP) determination play an important role in evaluation of demyelinated optic neuritis associated with MS. The method reflects functional consequences on optic nerve in MS patients. Optic neuritis was defined by an acute loss of visual acuity or scotoma associated with extended visual evoked potential latencies (> 120 ms) and/or an MRI T2 hypersignal of the optic nerve (36). Therefore the VEP measurement is important for optic neuritis diagnosis in patients with MS attack and visual symptoms. Subclinical optic pathway involvement may also be demonstrated by pattern VEP assessment (PVEP). Patients with normal visual acuity test shows modification of P100 wave latency on PVEP. PVEP, a functional test, is more severely and frequently affected than OCT that assesses the RFLN thickness in MS patients (37). For this reason VEP determination is an important test in neuro-ophthalmologic assessment of optic neuritis.

Demyelinated optic neuropathy is possible to be demonstrated by low contrast VEP. VEP latencies were found significantly increased in response to low, compared with high contrast stimuli in MS patients with optic neuritis (38).

The involvement of visual system in MS optic consists in two separate processes. The first one is the demyelination process (demyelinated optic neuritis – MS-ON) and the second one consists in loss of retinal ganglion cells (non-optic neuritis – MS-NON). MS ON is an inflammatory process and MS NO is a neurodegenerative process. The pathological basis of MS-NON remains unclear. Recent studies demonstrate that there is a correlation between thinning of RFLN **(**measured by OCT) and latency delay of the multifocal VEP in non-optic neuritis associated with MS (39).

mfVEp can measure the local response amplitude and latency in the field of vision. Increased latency demonstrated the demyelination process and reduced amplitude revealed neural degeneration. Comparison between multifical VEP (mfVEP), standard automated perimetry and OCT, emphasized that the mfVEP revealed more abnormalities than automated perimetry or OCT in MS patients (40).

CONCLUSIONS

Visual dysfunction is one of the most common pathology in MS patients. The assessment of the relationship between structure and function is a difficult task and requires correlation between different methods. The evaluation methods described have multiple important roles such as: prediction value, diagnostic value, and the possibility to apply the correct therapeutic measures. No single test can identify all lesions but studies made in this field area demonstrated the correlation between the MRI findings, OCT results, contrast sensitivity test and VEP measurement. The visual function affected in the beginning of the MS or worsening during the disease course or, even subclinical visual pathways involvement, is an ideal clinical model for testing novel agents for neuroprotection and neurorepair.

REFERENCES

1. **Kaur P., Bennett J.L.** Optic neuritis and the neuro-ophthalmology of multiple sclerosis. *Int Rev Neurobiol,* 2007, 79:633-63.
2. **Thouvenot E., Mura F., De Verdal M. et al.** Ipsilateral uveitis and optic neuritis in multiple sclerosis. *Mult Scler Int.* 2012, 2012:372361, doi: 10.1155/2012/372361.
3. **Ortiz-Pérez S., Martínez-Lapiscina E.H., Gabilondo I. et al.** Retinal periphlebitis is associated with multiple sclerosis severity, *Neurology.* 2013, 81(10):877-81. doi: 10.1212/WNL.0b013e3182a3525e.
4. **Thömke F., Lensch E., Ringel K. et al.** Isolated cranial nerve palsies in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1997, 63(5):682-5.
5. **Milea D., Napolitano M., Dechy H. et al.** Complete bilateral horizontal gaze paralysis disclosing multiple sclerosis. *J Neurol Neurosurg Psychiatry,* 2001, 70(2):252-5.
6. **Baloh R.W., Yee R.D.** Spontaneous vertical nystagmus. *Rev Neurol (Paris),* 1989,145(8-9):527-3.
7. **Todd L., King J., Darlington C.L. et al.** Optokinetic reflex dysfunction in multiple sclerosis. *Neuroreport*, 2001, 12(7):1399-402.
8. **Proudlock F.A., Gottlob I., Constantinescu C.S.** Oscillopsia without nystagmus caused by head titubation in a patient with multiple sclerosis. *J Neuroophthalmol*, 2002, 22(2):88-91.
9. **Frederiksen J.L., Larsson H.B., Nordenbo A.M. et al.** Plaques causing hemianopsia or quadrantanopsia in multiple sclerosis identified by MRI and VEP. *Acta Ophthalmol (Copenh)*. 1991, 69(2):169-77.
10. **Hawkins K., Behrens M.M.** Homonymous hemianopia in multiple sclerosis. With report of bilateral case. *Br J Ophthalmol.* 1975, 59(6):334-7.
11. **Sacks J.G., Melen O.** Bitemporal visual field defects in presumed multiple sclerosis. *JAMA*. 1975, 234(1):69-72.
12. **Wilhelm H., Grodd W., Schiefer U. et al.** Uncommon chiasmal lesions: demyelinating disease, vasculitis, and cobalamin deficiency. *Ger J Ophthalmol*. 1993, 2(4-5):234-40.
13. **Popescu B.F., Pirko I., Lucchinetti C.F.** Pathology of multiple sclerosis: where do we stand? *Continuum (Minneap Minn)*. 2013, 19(4Multiple Sclerosis):901-21. doi: 10.1212/01.CON.0000433291.23091.653077.100628.
14. **Sørensen T.L., Frederiksen J.L., Brønnum-Hansen H. et al.** Optic neuritis as onset manifestation of multiple sclerosis: a nationwide, long-term survey. *Neurology.* 1999, 53(3):473-8.
15. **Pedro-Egbe C.N., Fiebai B., Ejimadu C.S.** Visual outcome following optic neuritis: a 5-year review. *Niger J Clin Pract.* 2012, 15(3):311-4. doi: 10.4103/1119.
16. **Toosy A.T., Mason D.F., Miller D.H.** Optic neuritis. *Lancet Neurol.* 2014, 13(1):83-99. doi: 10.1016/S1474-4422(13)70259-X.
17. **Trapp B.D., Peterson J., Ransohoff R.M. et al.** Axonal transection in the lesions of multiple sclerosis. *N Engl J Med.* 1998, 338(5):278-85.
18. **Söderström M., Link H., Xu Z. et al.** Optic neuritis and multiple sclerosis: anti-MBP and anti-MBP peptide antibody-secreting cells are accumulated in CSF. *Neurology.* 1993, 43(6):1215-22.
19. **Trapp B.D., Ransohoff R., Rudick R.** Axonal pathology in multiple sclerosis: relationship to neurologic disability. *Curr Opin Neurol.* 1999, 12(3):295-302.
20. **Gabilondo I., Sepúlveda M., Ortiz-Perez S. et al.** Retrograde retinal damage after acute optic tract lesion in MS. *J Neurol Neurosurg Psychiatry.* 2013, 84(7):824-6. doi: 10.1136/jnnp-2012-304854.
21. **Schmidt R.M., Neumann V.** Liquor-cytological investigations in multiple sclerosis. *Schweiz Arch Neurol Neurochir Psychiatr.* 1980, 127(2):237-42.
22. **Haertle M., Kallweit U., Weller M., Linnebank M.** The presence of oligoclonal IgG bands in human CSF during the course of neurological diseases, *J Neurol.* 2014.
23. **Modvig S., Degn M., Horwitz H. et al.** Relationship between cerebrospinal fluid biomarkers for inflammation, demyelination and neurodegeneration in acute optic neuritis. *PLoS One*. 2013, 8(10):e77163. doi: 10.1371/journal.pone.0077163.
24. **Kitley J., Waters P., Woodhall M. et al.** Neuromyelitis Optica Spectrum Disorders With Aquaporin-4 and Myelin-Oligodendrocyte Glycoprotein Antibodies: A Comparative Study. *JAMA.* 2014, doi: 10.1001/jamaneurol.2013.5857.
25. **Jarius S., Wildemann B.** Aquaporin-4 antibodies, CNS acidosis and neuromyelitis optica: a potential link. *Med Hypotheses*. 2013, 81(6):1090-5. doi: 10.1016/j.mehy.2013.10.011.
26. **Modrzejewska M., Karczewicz D., Wilk G.** Assessment of blood flow velocity in eyeball arteries in multiple sclerosis patients with past retrobulbar optic neuritis in color Doppler ultrasonography. *Klin Oczna.* 2007, 109(4-6):183-6.
27. **Hradílek P., Stourac P., Bar M.** Colour Doppler imaging evaluation of blood flow parameters in the ophthalmic artery in acute and chronic phases of optic neuritis in multiple sclerosis. *Acta Ophthalmol*, 2009, 87:65-70.
28. **Karami M., Janghorbani M., Dehghani A. et al.** Orbital Doppler Evaluation of Blood Flow Velocities in Optic Neuritis. *Rev Diabet Stud.* 2012, 9(2-3):104-11. doi: 10.1900/RDS.2012.9.104.
29. **Gabilondo I., Martínez-Lapiscina E.H., Martínez-Heras E. et al.** Trans-synaptic axonal degeneration in the visual pathway in multiple sclerosis. *Ann Neurol.* 2013, doi: 10.1002/ana.24030.
30. **De Stefano N., Airas L., Grigoriadis N. et al.** Clinical Relevance of Brain Volume Measures in Multiple Sclerosis. *CNS Drugs.* 2014.
31. **Brinar V.V., Barun B.** Challenges in multiple sclerosis; how to define occurence of progression. *Clin Neurol Neurosurg.* 2013, 115 Suppl 1:S30-4. doi: 10.1016/j.clineuro.2013.09.017.
32. **Ratchford J.N., Quigg M.E., Conger A. et al.** Optical coherence tomography helps differentiate neuromyelitis optica and MS optic neuropathies. *Neurology.* 2009, 73(4):302-8. doi: 10.1212/WNL.0b013e3181af78b8.
33. **Petzold A., de Boer J.F., Schippling S.** Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurol*. 2010, 9(9):921-32. doi: 10.1016/S1474-4422(10)70168-X.
34. **Baier M.L., Cutter G.R., Rudick R.A. et al.** Low-contrast letter acuity testing captures visual dysfunction in patients with multiple sclerosis. *Neurology.* 2005, 64(6):992-5.
35. **Balcer L.J., Frohman E.M.** Evaluating loss of visual function in multiple sclerosis as measured by low-contrast letter acuity, *Neurology*, 2010, vol.74, no.17 Supplement 3 S16-S2.
36. **Thouvenot E., Mura F., De Verdal M. et al.** Ipsilateral uveitis and optic neuritis in multiple sclerosis. *Mult Scler Int*. 2012, 2012:372361. doi: 10.1155/2012/372361.
37. **Gundogan F.C., Tas A., Altun S. et al.** Color vision versus pattern visual evoked potentials in the assessment of subclinical optic pathway involvement in multiple sclerosis. *Indian J Ophthalmol.* 2013, 61(3):100-3. doi: 10.4103/0301-4738.9984.
38. **Thurtell M.J., Bala E., Yaniglos S.S. et al.** Evaluation of optic neuropathy in multiple sclerosis using low-contrast visual evoked potentials. *Neurology.* 2009, 73(22):1849-57. doi: 10.1212/WNL.0b013e3181c3fd43.
39. **Klistorner A., Garrick R., Barnett M.H.** Axonal loss in non-optic neuritis eyes of patients with multiple sclerosis linked to delayed visual evoked potential. *Neurology.* 2013, 80(3):242-5. doi: 10.1212/WNL.0b013e31827deb39.
40. **Laron M., Cheng H., Zhang B. et al.** Comparison of multifocal visual evoked potential, standard automated perimetry and optical coherence tomography in assessing visual pathway in multiple sclerosis patients. *Mult Scler.* 2010, 16(4):412-26. doi: 10.1177/1352458509359782.