ELSEVIER

Journal of the Neurological Sciences 188 (2001) 37–41

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Pupillary disturbances in multiple sclerosis: correlation with MRI findings

J. de Seze [a,*], C. Arndt [b], T. Stojkovic [a], M. Ayachi [c], J.Y. Gauvrit [c], M. Bughin [b], T. Saint Michel [c], J.P. Pruvo [c], J.C. Hache [b], P. Vermersch [a]

[a] *Department of Neurology, Hôpital R. Salengro, CHRU de Lille, 59037 Lille Cedex, France*
[b] *Department of Neuro-ophthalmology, Hôpital R. Salengro, CHRU de Lille, 59037 Lille Cedex, France*
[c] *Department of Neuroradiology, Hôpital R. Salengro, CHRU de Lille, 59037 Lille Cedex, France*

Received 15 February 2001; received in revised form 10 May 2001; accepted 11 May 2001

Abstract

Autonomic nervous system disturbances such as pupillary abnormalities have rarely been evaluated in multiple sclerosis (MS). However, pupillary impairment is not uncommon in MS and its origin is still unclear. The aim of this study was to investigate pupillary disturbances in MS and to try to correlate pupillary defects with spinal cord and brainstem magnetic resonance imaging (MRI) findings. We prospectively studied 45 MS patients and 30 normal subjects. *Methods*: The pupillary contraction latency and the amplitude of contraction were recorded by pupillometry. We also determined afferent and efferent pathway defects by comparing the direct and consensual pupillary reflexes. We evaluated brainstem and spinal cord demyelinating lesions and spinal cord cross-sectional area on MRI. At least one pupillometric parameters were significantly impaired in 60% of patients and in none of the controls. We did not find any correlation between pupillary defect and demyelinating lesions on MRI. The most frequent abnormality was efferent pathway shift and this was correlated with spinal cord atrophy ($P < 0.02$). These results confirm that the autonomic nervous system, and especially pupillary function, is frequently impaired in MS. The parasympathetic system is most commonly affected and this is most likely linked to axonal loss (demonstrated by spinal cord atrophy) rather than to demyelinating lesions.

Keywords: Pupillary disturbances; Multiple sclerosis; MRI

1. Introduction

Autonomic nervous system (ANS) disturbances have been studied in several neurodegenerative disorders such as multiple system atrophy [1], but have also been reported in multiple sclerosis (MS) [2]. Many MS patients develop disturbances of sexual functions or urinary bladder and bowel functions. In addition, simple bedside tests have demonstrated abnormalities of sweating and cardiovascular tone [2]. Furthermore, pupillary impairment, irrespective of the presence of optic neuritis (ON), seems to be underestimated in MS [3]. Both afferent and efferent pupillary defects have been reported in MS [4,5]. The latter disturbances are clearly less frequent than visual evoked potential (VEP) abnormalities, and appear to be due to a different mechanism, which still remains unclear [3,5]. In the studies by Pozzessere et al. [3] and Van Diemen et al. [5], no correlation was found between VEP abnormalities and pupillary defects, suggesting that pupillary dysfunction could be independent of demyelinating lesions. Moreover, individual categories of MS such as primary progressive were not studied. The few studies comparing pupillometric disorders and magnetic resonance imaging (MRI) findings [3,6] failed to demonstrate a clear relationship between demyelinating lesions and pupillometric disturbances.

A recent neuropathological study highlighted the high level of axonal loss in MS [7]. MRI techniques are now available to assess the degree of axonal loss [8]. Magnetic resonance spectroscopy, diffusion MRI and brain or spinal cord atrophy are the best markers of axonal loss in MS [8–11]. We recently confirmed the interest and the reproducibility of spinal cord area assessment [12]. A reduction in spinal cord area is clearly correlated with the level of disability [9,12].

The aim of this study was to investigate pupillary disturbances in the different forms of MS, and to try to

* Corresponding author. Fax: +33-3-20-44-44-84.
E-mail address: j-deseze@chru-lille.fr (J. de Seze).

0022-510X/01/$ - see front matter
PII: S0022-510X(01)00540-8

correlate these abnormalities with brainstem or spinal cord MRI findings.

2. Methods

2.1. Patients and control subjects

We prospectively studied 45 patients with clinically and laboratory definite MS according to Poser's criteria for relapsing–remitting and secondary progressive MS [13], and Thompson's criteria for progressive forms [14]. We included 27 women and 18 men with a mean age of 44.1 years (range = 30–60). Fifteen patients had relapsing–remitting MS, 15 had secondary progressive MS and 15 had primary progressive MS, according to the criteria of Lublin and Reingold [15] for the various forms of the disease. Disability as scored by the Expanded Disability Status Scale (EDSS) was 4.9 (range = 2–7) [16]. Best corrected visual acuity in all MS patients was superior to 6/9. Several patients had a history of ON defined as an acute or subacute loss of vision lasting more than 24 hours with partial or total recovery. The interval between ON and the pupillometric study was greater than 6 months. We excluded patients with other diseases that might have influenced the visual system or the ANS such as diabetes mellitus. Any treatment involving drugs affecting the pupillary function were withdrawn at least 1 week prior to the test. All patients and controls were non-smokers. All tests were performed at the same time of day to decrease any pupillary diurnal variations.

A group of 30 healthy age-matched volunteers without optic signs was used as a control group. Best-corrected acuity was 9/9 in all controls. Their mean age was 42.6 years (range = 25–60). Results of the control group were used as normal values (mean $\pm$ 2 S.D.). Informed consent was obtained from both patients and controls.

2.2. Visual examination

A complete routine ophthalmologic examination was performed in all patients and controls. Visual acuity was determined on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Slit lamp anterior segment biomicroscopy was performed. Tonometry was performed after pupillometry and prior to diagnostic mydriasis for retinal biomicroscopy by indirect ophthalmoscopic examination.

2.3. Pupillometry and VEPs

Pupillary parameters were recorded with a pupillometer (Vision Monitor system, Métrovision, France) that induced a near infrared illumination (880 nm). Patients were placed 160 cm from a screen with an angular size of 40°. After 20 min of dark adaptation, eight uniform flashes of white light with a duration of 1 s and a mean luminance of 30 candela/m^2 were produced at 8-s intervals. The first response was excluded and the following seven responses were averaged. The amplitude of pupillary constriction and the pupillary light reflex latency (PLRL) were recorded. The PLRL was defined as the time interval between the onset of the stimulation and the beginning of the constriction. The direct PLRL was recorded after stimulating the ipsilateral eye, and the indirect PLRL was recorded on the ipsilateral eye with the eye occluded with a near infrared filter while stimulating the contralateral eye. Both eyes were stimulated separately. To determine afferent and efferent pupillary latency responses, we used the method described in a previous study [5,17]. Briefly, this method allows an impairment of the afferent pupillary pathway to be evaluated by determining the difference between the direct PLRL and the indirect PLRL in the same eye (e.g. right eye: [Direct PLRL right eye − Indirect PLRL right eye]). The efferent pupillary pathway is evaluated by the difference between the direct PLRL in one eye and the indirect PLRL in the other eye (e.g. for the right eye: [Direct PLRL right eye − Indirect PLRL left eye]). When averaging these responses for both eyes, the mean afferent latency becomes: ([Direct PLRL right eye − Indirect PLRL right eye] + [Direct PLRL left eye − Indirect PLRL left eye])/2 and the mean efferent latency becomes: ([Direct PLRL right eye − Indirect PLRL left eye] + [Direct PLRL left eye − Indirect PLRL right eye])/2 [5].

Pattern reversal VEPs were elicited by square wave slow reversal (1.25 Hz) high-contrast check stimulation. We used two sizes of checks (15 and 60 min of arc, respectively). The VEPs were recorded by epicranial surface electrodes. The positive electrodes were placed opposite Brodman's area 17.3 cm on either side from the middle, 4 cm above the inion. The reference, negative electrode, was placed on the vertex (Cz), and the ground electrode on the forehead (Fz). The amplification was 12 500. A high pass filter at 1 Hz and a low pass filter at 35 Hz were used. A minimum average of 64 sweeps was used. We considered the first positive response registered more than 100 ms after stimulation onset (P100).

2.4. MRI

All imaging was carried out on a 1.5-T MRI unit (Vision, Siemens, Erlanger, Germany). A detailed description of the spinal cord MRI evaluation is given in a previous report [12]. MRI of the brainstem and the spinal cord included sagittal T2-weighted turbo spin-echo sequences with the following parameters: TE = 130 ms, TR = 4336 ms, flip angle = 180°, section thickness = 4 mm, intersection gap = 4.4 mm, field of view = 300 × 300 and matrix = 300 × 512. The acquisition time was 5.31 min. We also performed axial T2-weighted gradient-echo sequences with the following parameters: TE = 11 ms, TR = 75 ms, flip angle = 30°, section thickness = 4 mm,

intersection gap = 4.4 mm, field of view = 236 × 270 and matrix = 224 × 512. The acquisition time was 5 min 38 s. The number and location of demyelinating lesions were evaluated blindly in both the brainstem and the spinal cord. The axial plane was divided into four parts (anterior, posterior, lateral and central).

A volume-acquired inversion-prepared fast-spoiled gradient-echo acquisition was performed in an axial plane at the level of the C2 vertebral body to assess the spinal cross-sectional area. Sixty-four partitions in the sagittal plane of 1-cm-thick equivalents were acquired in a three-dimensional volume centered on the cervical spine with the following parameters: TE = 4.9 ms, TR = 11.6 ms, flip angle = 8°, matrix = 256 × 256. The imaging time was 10 min 49 s. From the data set, a series of five contiguous 3-mm pseudoaxial slices were reformatted using the center of the C2/C3 intervertebral disc as a caudal landmark with the slices perpendicular to the spinal cord. In view of the cord position and the strong signal intensity, the gradient between the cord (bright) and the surrounding cerebrospinal fluid (dark) was obtained. Measurement of the cord area was performed blindly using a semi-automated contouring technique. We established the reliability of this method in a previous study [12].

2.5. Statistical analysis

Pupillometric results in normal subjects and in MS patients were presented as mean ± 2 S.D. (Table 1). A statistical comparison of the results was performed using a Mann–Witney *U*-test. Correlations between pupillometric values and clinical parameters (age, duration of the disease and EDSS score) or MRI findings were calculated using Spearmann's Rank Correlation (SRCC). Past history of ON or VEP abnormalities was evaluated with regard to pupillometric values using a Kruskall–Wallis test.

3. Results

Compared to controls, 60% of MS patients showed pupillary abnormalities (on average, one value higher than normal ±2 S.D.). We found no correlation either in controls or patients between pupillometric parameters and age. The results of pupillometry are reported in Table 1. PLRL was increased in MS patients compared to controls ($P < 0.01$). The amplitude of contraction was lower in MS patients than in controls ($P < 0.01$). Afferent and efferent pupillary pathways were also significantly affected in MS compared to the control group ($P < 0.001$).

The most significant difference was found in primary progressive MS for three of the studied parameters (Table 1). We found a statistical difference between primary progressive and relapsing–remitting MS for the PLRL ($P < 0.01$), the contraction amplitude ($P < 0.01$) and the afferent pathway ($P < 0.02$). VEP latencies were increased (more than 2 S.D.) in 80% of MS patients and in none of the controls. A past history of ON was found in 16 patients (36%). Clinical or laboratory visual abnormalities (past history of ON or increased VEP latencies) were not correlated with pupillometric abnormalities. Pupillometric abnormalities were not correlated with disability evaluated by the EDSS score or with disease duration. There was no correlation between pupillometric abnormalities and MRI findings (brainstem and spinal cord demyelinating lesions). Furthermore, there was no correlation between spinal cross-sectional area and age in either patients or controls. Only efferent pathway defects and spinal cord cross-sec-

Table 1
Clinical and pupillometric values in MS patients and controls
For the latencies and the amplitude of contraction, the results are shown in milliseconds and millimeters, respectively, ± standard deviation (S.D.). Afferent and efferent pathways are expressed in terms of variation (absolute value) from 0.

	Patients				Controls
	Total	Relapsing–remitting	Secondary progressive	Primary progressive	
Number	45	5	15	15	30
Age: mean (range)	44.1 (30–60)	41.5 (30–57)	44.2 (30–57)	46.2 (30–58)	42.6 (25–60)
Sex ratio (women/men)	27/18	9/6	11/4	7/8	19/11
Disease duration: mean (range)	11.9 (3–35)	12.3 (3–35)	14.1 (4–20)	9.1 (3–22)	
EDSS: mean (range)	4.9 (2–7)	3.6 (2–5.5)	5.8 (4–7)	5.6 (4–7)	
PLR latency (ms): mean ± S.D.	334.8 (±80.5)*	304.7 (±83)*	338.6 (±65.5)*	360 (±62.5)**,##	260.3 (±62.1)
Contraction amplitude (mm):mean ± S.D.	180.3 (±53)*	182.5 (±38)*	200.3 (±59)*	156.6 (±69)**,##	234.7 (±32.5)
Afferent pathway: absolute value (± S.D.)	45 (±27)*	31.2 (±15.1)*	36.8 (±15)*	52.8 (±37.2)**,#	6.2 (±10)
Efferent pathway: absolute value (± S.D.)	54.4 (±24.4)**	51.3 (±21.3)**	51.9 (±32)**	60 (±17.9)**	18.7 (±18)

PLRL = pupillary light reflex latency.
* $P < 0.01$ (versus controls).
** $P < 0.001$ (versus controls).
$P < 0.01$ (versus relapsing–remitting multiple sclerosis).
# $P < 0.02$ (versus relapsing–remitting multiple sclerosis).

tional area reduction were significantly correlated ($P < 0.02$).

4. Discussion

Previous studies on pupillary dysfunction in MS have shown that abnormalities are frequent [5,18]. Our results confirm the high frequency of pupillary abnormalities in MS, as 60% of the patients had abnormal values in one or more parameters compared to controls.

Pupillometry might appear to be of little interest as a diagnostic tool because VEP abnormalities are more frequent in MS, as demonstrated by our results and previous studies [5]. However, our study shows that pupillometry is of particular interest in the primary progressive form of MS. In accordance with Van Diemen et al. [5] and others [3,18,19], we found no correlation between VEP and pupillometric abnormalities. Bos et al. [17] found a correlation between the VEP latencies and pupillary reflex latency but they included patients within 6 months after ON. These two visual defects could be secondary to different pathophysiological mechanisms. Increased VEP latencies in MS could be linked to optic nerve demyelination. This appears to have been confirmed by a recent study demonstrating that VEP changes are not correlated with optic nerve fiber layer thickness evaluated by optical coherence tomography [20].

There appeared to be no significant link between pupillary reflex latency delays in our MS patients and hyperintensities in the brainstem and the spinal cord. Moreover, we found a correlation between spinal cord atrophy and efferent pathway defects. These two results, taken together, suggest that pupillary abnormalities are related to axonal loss rather than to demyelination [3]. The fact that the more significant results are observed in the primary progressive form, where demyelinating lesions are less common, supports this hypothesis. A primary involvement of the ANS and predominantly, the parasympathetic system, may be frequent in MS as shown by the efferent pupillary pathway defect in our study and others [5], and by cardiovascular dysfunction in MS [2,21–23]. Recent magnetic resonance spectroscopy studies have shown that axonal loss occurs early in the course of MS [24–26]. It would be of interest to correlate these abnormalities with ANS disturbances and especially pupillary abnormalities.

5. Conclusions

As far as we are aware, this is the first demonstration that pupillary abnormalities are frequent in primary progressive MS. This finding could be of particular interest in the diagnosis of this rare form where demyelination is poor. However, further studies will be needed to confirm the predictive value of pupillometric abnormalities with regard to disability and the potential role of axonal loss in the pathophysiology of this disorder in MS.

References

[1] Micieli G, Tassorelli C, Martignoni E, Marcheselli S, Rossi F, Nappi G. Further characterization of autonomic involvement in multiple system atrophy: a pupillometric study. Funct Neurol 1995;10:273–80.
[2] Linden D, Diehl RR, Berlit P. Sub-clinical autonomic disturbance in multiple sclerosis. J Neurol 1995;242:374–8.
[3] Pozzessere G, Rossi P, Valle E, Froio CP, Petrucci AF, Morocutti C. Autonomic involvement in multiple sclerosis: a pupillometric study. Clin Auton Res 1997;7:315–9.
[4] Cox TA. Relative afferent defects in multiple sclerosis. Can J Ophthalmol 1989;24:207–10.
[5] Van Diemen HAM, Van Dongen MM, Nauta JJP, Lanting P, Polman CH. Pupillary light reflex latency in patients with multiple sclerosis. Electroencephalogr Clin Neurophysiol 1992;82:213–9.
[6] Rossi P, Colombo B, Martinelli V, et al. Pupillary light reflex abnormalities in multiple sclerosis. Ital J Clin Neurophysiol 1993; 2:243–8.
[7] Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mörk S, Bö L. Axonal transection in the lesions of multiple sclerosis. New Eng J Med 1998;338:275–8.
[8] Liu C, Edwards S, Gong Q, Roberts N, Blumhardt LD. Three dimensional MRI estimates of brain and spinal cord atrophy in multiple sclerosis. J Neurol, Neurosurg Psychiatry 1999;66:323–30.
[9] Losseff NA, Webb SL, O'Riordan JI, et al. Spinal cord atrophy and disability in multiple sclerosis. Brain 1996;119:701–8.
[10] Lycklam a Nijeholt GJ, van Walderveen MAA, Castelijns JA, et al. Brain and spinal cord abnormalities in multiple sclerosis. Correlation between MRI parameters, clinical subtypes and symptoms. Brain 1998;121:687–97.
[11] Stevenson VL, Leary SM, Losseff NA, et al. Spinal cord atrophy and disability in MS. A longitudinal study. Neurology 1998;51:234–8.
[12] de Seze J, Ayachi M, Stojkovic T, et al. IRM médullaire et sclérose en plaques: intérêt du calcul d'atrophie comme marqueur d'évolutivité de la maladie. Rev Neurol 2000;156:491–6.
[13] Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–31.
[14] Thompson AJ, Montalban X, Barkhof F, et al. Diagnostic criteria for primary progressive multiple sclerosis: a position paper. Ann Neurol 2000;47:831–5.
[15] Lublin FD, Reingold SC. For the National Multiple Sclerosis Society defining the clinical course of multiple sclerosis: results of an international survey. Neurology 1996;46:907–11.
[16] Kurtzke J. Rating neurologic impairment in multiple sclerosis. Neurology 1983;33:1444–52.
[17] Bos JE, Fock JM, Reulen JPH, Van Lith GHM. Pupil constriction and visual evoked potential latency in optic neuritis. Neuro-ophthalmology 1990;10:187–96.
[18] Jacobsen J. Pupillary function in multiple sclerosis. Acta Neurol Scand 1990;82:392–5.
[19] Ellis CJK. The afferent pupillary defect in acute optic neuritis. J Neurol, Neurosurg Psychiatry 1979;42:1008–17.
[20] Parisi V, Manni G, Spadaro M, et al. Correlation between morphological and functional retinal impairment in multiple sclerosis patients. Invest Ophthalmol Visual Sci 1999;40:2520–7.
[21] Vita G, Fazio MC, Milone S, Blandino A, Salvi L, Messina C. Cardiovascular autonomic dysfunction in multiple sclerosis is likely related to brainstem lesions. J Neurol Sci 1993;120:82–6.

[22] Drory VE, Nisipeanu PF, Korczyn AD. Test of autonomic dysfunction in patients with multiple sclerosis. Acta Neurol Scand 1995;92:356–60.
[23] de Seze J, Stojkovic T, Gauvrit JY, Saint Michel T, Ayachi M, Pruvo JP, Vermersch P. Cardiac repolarization abnormalities in multiple sclerosis: spinal cord correlates. Muscle Nerve 2000;23: 1284–6.
[24] Davie CA, Barker GJ, Thompson AJ, McDonald WI, Miller DH. Magnetic resonance spectroscopy of chronic cerebral white matter lesions and normal appearing white matter in multiple sclerosis. J Neurol, Neurosurg Psychiatry 1997;63:736–42.
[25] Fu L, Matthews PM, De Stefano N, et al. Imaging axonal damage of normal-appearing white matter in multiple sclerosis. Brain 1998; 121:103–13.
[26] Leary SM, Davie CA, Parker GJM, et al. ^{1}H magnetic resonance spectroscopy of normal appearing white matter in primary progressive multiple sclerosis. J Neurol 1999;246:1023–6.