

Acquired pendular nystagmus in multiple sclerosis and oculopalatal tremor

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ABSTRACT

Objective: Acquired pendular nystagmus occurs mainly in multiple sclerosis (MS) and focal brainstem lesions. In the later case, it is part of the syndrome of oculopalatal tremor. Even though pathophysiology of acquired pendular nystagmus has been clearly characterized experimentally in both etiologies, there is a persisting ambiguity in clinical literature, which leads one to consider both clinical conditions as a common entity. The objective of our work was to compare in a prospective study clinical features, eye movement recording, and functional consequences of acquired pendular nystagmus in 14 patients with oculopalatal tremor and 20 patients with MS.

Methods: Besides complete neurologic evaluation, evaluation of visual function, 3-dimensional eye movement recording, and functional scores of the Visual Function Questionnaire were recorded.

Results: One patient with oculopalatal tremor and 15 patients with MS disclosed signs of optic neuropathy. The nystagmus in the oculopalatal group showed significant larger mean amplitude (8 deg vs 1 deg), higher mean peak velocity (16 deg/s vs 6 deg/s), lower mean frequency (1–3 Hz vs 4–6 Hz), and larger asymmetry and irregularity of ocular oscillations compared to the MS group. The vision-specific health-related quality of life was more deteriorated in the oculopalatal tremor group than in the MS group.

Conclusions: This study emphasizes the need to consider acquired pendular nystagmus in MS and oculopalatal tremor as 2 different clinical entities. This is of particular importance regarding the future evaluation of potential specific effects of pharmacologic agents. *Neurology*® 2011;76:1650–1657

GLOSSARY

APN = acquired pendular nystagmus; **ION** = inferior olivary nucleus; **MS** = multiple sclerosis; **OPT** = oculopalatal tremor; **VFQ-25** = 25-item National Eye Institute Visual Function Questionnaire.

Pendular nystagmus corresponds to an enduring to and fro eye oscillation without resetting quick phases. The most common causes of acquired pendular nystagmus (APN) are multiple sclerosis (MS) and focal brainstem lesions. In the later case, APN arises as a feature of the oculopalatal tremor (OPT) syndrome. OPT develops weeks, months, or even years after a single brainstem or cerebellar lesion,^{1–3} in most cases a hemorrhagic stroke. It results in synchronized low-frequency tremor of the eyes and palate or other orofacial motor territories and is associated with an hypertrophic degeneration of the inferior olivary nucleus (ION),² leading to T2 hypersignal on MRI.¹ This condition is triggered by interruption of the Guillain-Mollaret triangle.^{2,4}

Even though both etiology and clinical aspects appear different in APN associated with MS or OPT,⁵ many neurologists are not familiar with the distinct pathogenesis and characteristics of nystagmus in these 2 syndromes. Furthermore, some pharmacologic studies and nystagmus treatment reviews did not differentiate their results according to the underlying etiology.^{6–10}

In this study, we aimed to compare clinical features, eye movement recordings, and functional consequences of APN in patients with MS or OPT. The main objective was to empha-

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size the different clinical aspects associated with these 2 etiologies and the need to consider APN in MS or OPT as 2 different entities with different underlying mechanisms. This is particularly important for evaluating potential specific effects of pharmacologic agents.

METHODS Patients. Starting in 2007, we prospectively included 14 patients with APN in the context of OPT syndrome and 20 patients with APN in the context of MS (table e-1 on the *Neurology*[®] Web site at www.neurology.org).

OPT group. This group consisted of 10 men and 4 women with a mean age of 50. As seen from the MRI data (figure 1A), all patients had a focal brainstem lesion at the pontine level. The visual impairment and accompanying ION hypersignal (figure 1B) developed 1 month to 10 years after the initial neurologic event. The examination disclosed nystagmus of pendular form, irregular in amplitude, of low and irregular frequency, predominantly in the vertical direction, which was clinically asymmetric between the 2 eyes in all cases.

MS group. This group consisted of 11 men and 9 women with a mean age of 44. All patients were tested at least 3 months after an acute phase. The median EDSS score was 6 (range 1–8). The examination disclosed pendular nystagmus of regular quasi-sinusoidal form, high frequency, mainly in the horizontal direction, that was clinically symmetric in 17 patients, and asymmetric in 3 patients. MRIs in 10 out of the 20 patients showed multiple areas of patchy hypersignal at the level of the pontine tegmentum (figure 1C) without ION hypersignal (figure 1D).

Standard protocol approval, registrations, and patient consent. Approval was received from the National French ethical committee on human experimentation, in agreement with French law (March 4, 2002) and the Declaration of Helsinki (no. 2007-008B). Written informed consent was obtained from all patients participating in the study.

Evaluation of visual function. All patients underwent a thorough ophthalmic examination including fundi and best-corrected visual acuity measurement. Monocular visual acuity was determined with the Monoyer scale for far vision and the Parinaud scale for near vision. The results were converted in logMAR. In the MS group, the presence of underlying chronic optic neuropathy was tested by evaluating automatic visual field and static contrast sensitivity (Metrovision, Pénchenies, France) and the Farnsworth-Munsell D-15 Hue test was used to test color vision. The diagnosis of optic neuropathy was established according to the criteria detailed in appendix e-1.

Eye movements. Eye movement recordings. A quantitative recording of eye movements for each eye in the 3 axis dimensions was performed in all 34 patients using infrared video-oculography (25 Hz frequency; Synapsys[®], Marseille, France). Details of the eye movement software analysis and calibration are given in appendix e-2.

Eye movement analysis. Based on the trajectories of each eye projected in the 3 planes, the following values were extracted: the dominant plane (H, V, or T) was the plane in which the largest amplitude of eye oscillation was measured; the mean amplitude and the mean peak velocity were calculated on 20 consecutive cycles of nystagmus in the dominant plane; the frequency of pendular nystagmus was manually calculated over a

30-second period (for the purpose of analyzing more precisely the frequency of nystagmus, we also performed a fast Fourier transform of 2D eye position data [200 Hz frequency recording] in 15 patients with MS and 5 patients with OPT); the symmetry index was defined by the absolute value of the following equation: $(100 \times [A_{RE} - A_{LE}] / [A_{RE} + A_{LE}])$, where A_{RE} and A_{LE} are the mean amplitude of the right and left eye in the dominant plane.¹¹

VFQ-25. To examine vision-specific health-related quality of life, we used the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25), which has been validated in patients with optic neuritis.¹² The VFQ-25 consists of a set of 24 vision-targeted questions (and one general health question) generating a global score between 0% and 100% and 10 vision-related subscores.

Statistics. All statistics were performed by the STATISTICA software package (Statistica 9, Statsoft Inc., 1984–2010). Student *t* tests were performed to compare different variables in the 2 groups of patients (MS vs OPT).

RESULTS Ophthalmologic evaluation. Mean far visual acuity measured in each eye was significantly higher in the OPT group (0.33 ± 0.21 logMAR, 20/40) than in the MS group (0.55 ± 0.28 logMAR, 20/80) ($t[32] = 2.5, p < 0.05$). Near visual acuity, obtained in 13 out of 14 patients in the OPT group and all patients in the MS group, did not differ significantly between the OPT (0.41 ± 0.21 logMAR, P3) and the MS groups (0.51 ± 0.29 logMAR, P4) ($t[31] = 1.7, p > 0.05$).

With the exception of one patient (OPT10), none of the patients in the OPT group had clinical signs of ocular or optic nerve dysfunction. In the MS group, 15 patients had chronic signs of bilateral optic neuropathy and one patient (MS17) of unilateral optic neuropathy. In the 4 remaining patients with MS without any sign of optic neuropathy, mean far visual acuity was 0.35 ± 0.27 logMAR (20/40).

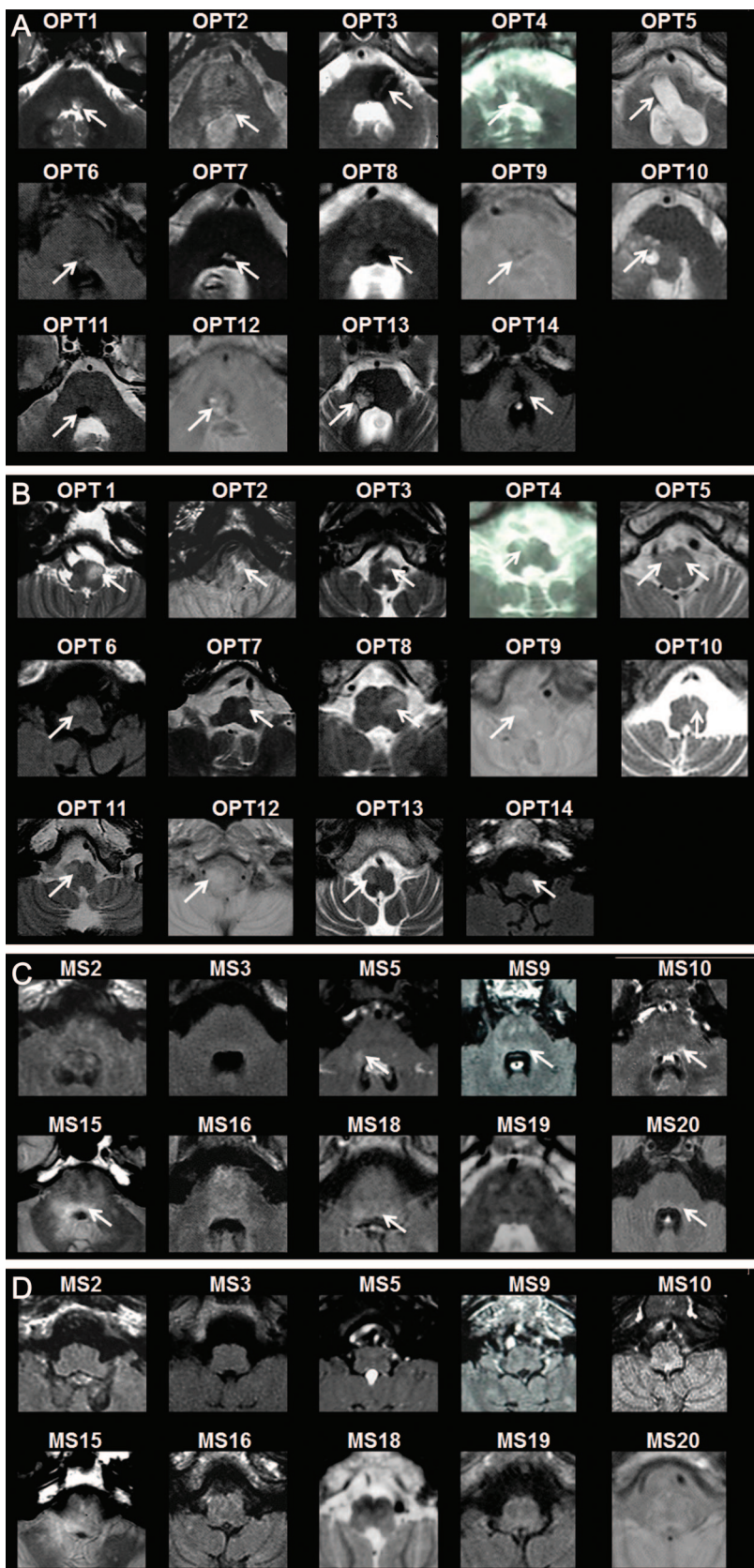
Visual acuity was poor in both groups of patients, and far visual acuity was significantly more impaired in the patients with MS with signs of optic neuropathy than in the patients with OPT.

Eye movements. Figure 2 shows eye movement recordings from, respectively, one patient with OPT and one patient with MS, while figure 3 shows the results of eye movement recordings in the 2 patient groups. Table 1 gives the values of each eye movement parameter in individual patients.

Nystagmus was predominantly in the torsional and vertical planes in the OPT group and the torsional and horizontal planes in the MS group.

Mean amplitude and mean velocity were significantly higher in the OPT group (8.00 ± 7.02 deg, 16.00 ± 13.71 deg/s) compared with the MS group (1.03 ± 0.88 deg, 6.35 ± 5.05 deg/s) (respectively $t[32] = 4.4, p < 0.001, t[32] = 2.9, p < 0.01$) (figure 3, A and B). Furthermore, the amplitude of

Figure 1 MRI data



Axial fluid-attenuated inversion recovery or T2 MRI (1.5-T GE scanners) at midpontine tegmentum level (A and C), inferior olive level (B and D), and in the patients with oculopalatal

nystagmus was more variable in patients with OPT than patients with MS.

The fast Fourier transform showed a narrow frequency peak in the patients with MS that matched with the frequency obtained from manual measurements. However, in the patients with OPT, the peak was wide, less visible, and did not match with the manual measurement. As a consequence, frequency was measured manually for subsequent statistical analysis. The mean frequency was significantly lower in the OPT group (1.76 ± 0.72 Hz) than the MS group (4.65 ± 0.59 Hz) ($t[32] = 12.9$, $p < 0.001$) (figure 3C). The frequency in the OPT group never exceeded 3 Hz and in the MS group always exceeded 4 Hz. Furthermore, for individual OPT patients the frequency of nystagmus was highly irregular (see figure 2).

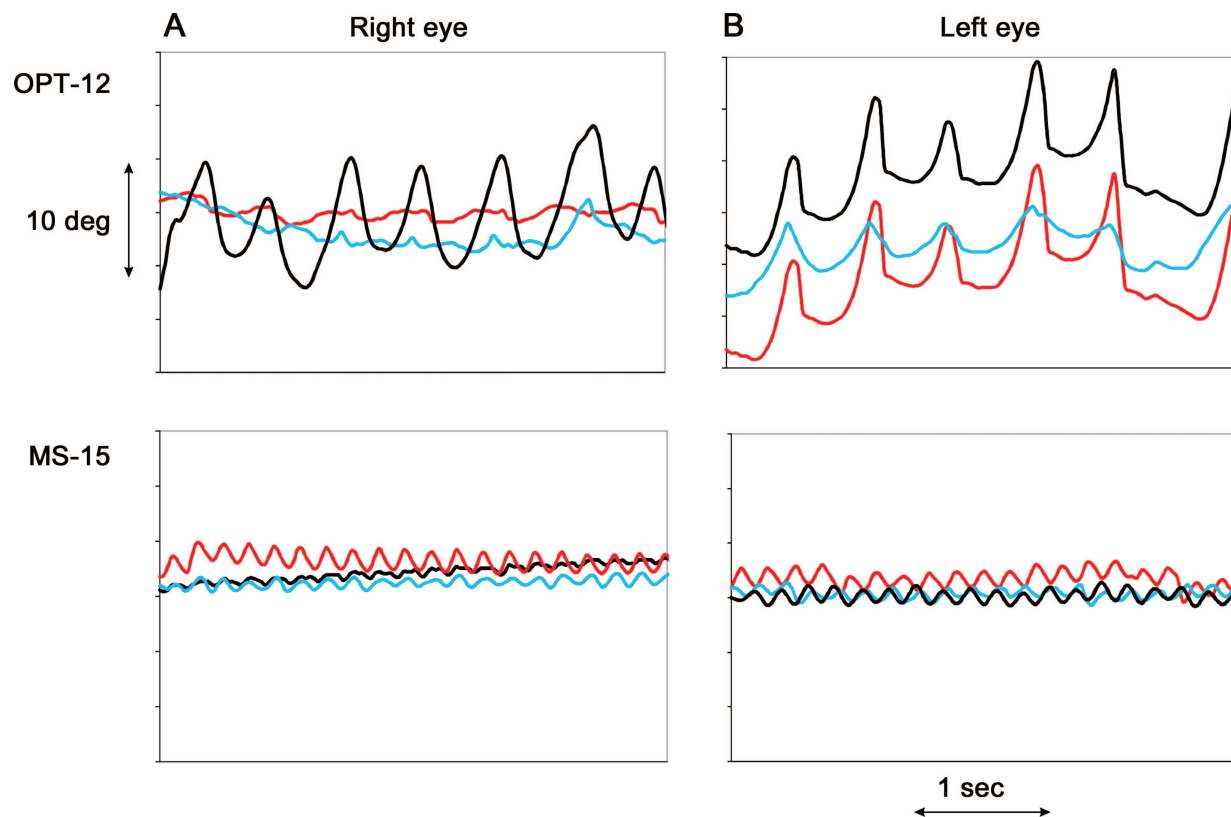
The mean symmetry index of all 34 patients was $33.3\% \pm 28.2\%$. It was significantly higher in the OPT group ($44.6\% \pm 28.7\%$) than the MS group ($25.4\% \pm 25.6\%$) ($t[32] = 2.05$,³² $p < 0.05$) (figure 3D). Furthermore, while 13/14 OPT patients had a symmetry index above 10%, this was only the case in 13/20 patients with MS.

The pendular nystagmus had a higher amplitude, velocity, and symmetry index and lower frequency in the OPT group than the MS group. Furthermore, the nystagmus in individual patients with OPT was more variable in amplitude and irregular in frequency.

VFQ-25. VFQ-25 answers were obtained from 12 of the 14 patients with OPT and 17 of the 20 patients with MS. The global score was lower (30.39 ± 9.09) in patients with OPT than patients with MS (54.26 ± 19.76) ($t[27] = 3.9$, $p < 0.001$) (figure e-1). The subscores for pain, near, far, and peripheral vision, social life, mental state, and dependency on

tremor (OPT) (A and B) and patients with multiple sclerosis (MS) (C and D). White arrows indicate abnormal hypersignals. In all patients with OPT, we observed a unique focal lesion at the level of the pontine tegmentum (A). The lesion was right-sided in 5 patients, left-sided in 4 patients, and paramedian in 5 patients. When lateralized, the lesion was ipsilateral to T2 inferior olivary nucleus (ION) hypersignal. We observed a hypersignal at the level of the ION in all patients in the OPT group (B). The hypersignal was right-sided in 6 patients, left-sided in 7, and bilateral in 1 patient. Unilateral hypersignal was associated with asymmetric nystagmus in 8 cases out of 13, predominant in the contralateral eye in 7 out of 8 cases. The only case of bilateral hypersignal showed asymmetric nystagmus predominant on the left eye. In 6 out of 10 patients in the MS group, we observed multiple areas of patchy hypersignals at the level of the pontine tegmentum (C). These hypersignals likely corresponded to demyelinating lesions. None of the patients in the MS group presented ION hypersignal (D).

Figure 2 Recording of nystagmus in one patient with oculopalatal tremor (OPT) and one patient with multiple sclerosis (MS)



Eye position traces (in degrees) with time (in seconds) for right eye (A) and left eye (B) in one patient with OPT (upper panels) and one patient with MS (lower panels). Red line: horizontal position; black line: vertical position; blue line: torsional position.

others were all significantly lower in the patients with OPT than the patients with MS (all $p \leq 0.05$).

Correlations were performed on data from all 34 patients (both MS and OPT). We found no significant correlation between the global VFQ-25 score and mean amplitude ($r = 0.26$), peak velocity ($r = 0.26$), or symmetry index ($r = 0.03$) of eye oscillations, nor between the global VFQ-25 score and far visual acuity ($r = 0.03$).

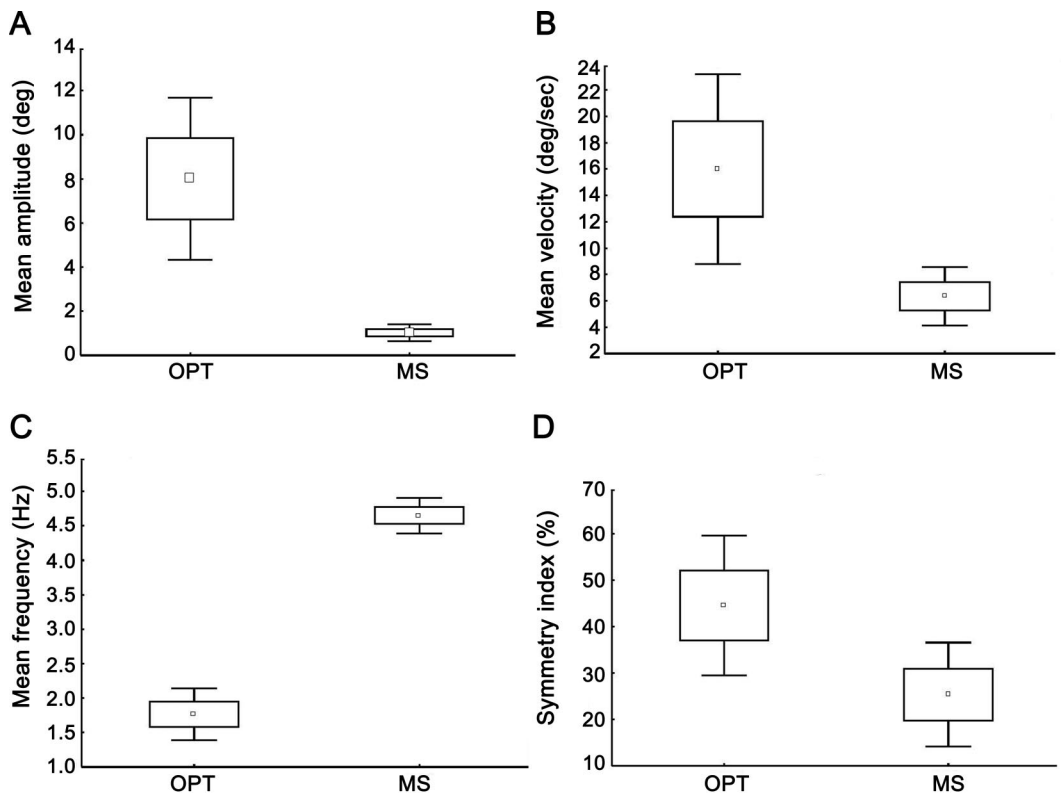
The vision-specific health-related quality of life was more deteriorated in the OPT group than the MS group. There was no correlation between the global score on the VFQ-25 scale and nystagmus characteristics, nor with visual acuity.

DISCUSSION This study shows clear differences in the features of nystagmus and in the functional consequences of APN in patients with OPT compared to patients with MS.

Here we demonstrate that APN in the context of OPT is of low frequency (maximum 3 Hz) and high amplitude (up to 30 deg), while in MS it is of high frequency (minimum 4 Hz) and low amplitude (maximum 3–4 deg). Some caution is needed in interpreting the results of our frequency analysis because of our low sampling rate. However, these data

are consistent with previously published data in patients with MS reporting a nystagmus of 2–5 deg amplitude^{13,14} and of 3.6 Hz mean frequency^{6,13–15} and in patients with OPT a nystagmus of 2–10 deg amplitude^{11,16} and of 1–3 Hz frequency.^{11,16,17} In addition, we found that the velocity of eye oscillations was higher in patients with OPT than patients with MS, but the cutoff point was not as clear as for frequency. In our study, the main direction of nystagmus was in the torsional and horizontal planes in the MS group and the vertical and torsional planes in the OPT group. This is consistent with previous recordings of 3-dimensional eye motion in APN.^{11,15,18,19} Even if the predominant horizontal plane in MS and vertical plane in OPT is a frequent observation, the direction of the nystagmus cannot strictly differentiate between the 2 etiologies. Previous studies that tested APN asymmetry in a subjective way found an equivalent percentage of patients with asymmetric APN (30%–50%) in both MS and OPT groups.^{1,11,13–15,18–21} In contrast, our eye movement data show that OPT is more frequently associated with asymmetric pendular nystagmus, and this feature may help distinguish patients with MS from patients with OPT. It should be noted that in those patients with MS with INO, impaired adduction

Figure 3 Results of eye movement recordings in the 2 patient groups



Mean amplitude (A), peak velocity (B), frequency (C), and symmetry index (D) of pendular nystagmus in the oculopalatal tremor (OPT) group (left side) and the multiple sclerosis (MS) group (right side). In each figure, the central squares represent the mean, the boxes the standard error, and the error bars the 95% confidence interval.

could influence the symmetry index. We found that the waveform and the frequency of the nystagmus in OPT was more variable and less sinusoidal than in patients with MS. While these observations have already been reported in patients with either APN due to OPT^{11,22} or MS,^{15,19} by comparing the 2 patient groups in the same study we show that this feature may be important for establishing a differential diagnosis between MS and OPT.

These data provide evidence of different underlying mechanisms in APN due to OPT or MS.

The most recent model of the mechanisms responsible for these oscillations in MS suggests abnormal delays in the oculomotor feedback loops due to central demyelination. This hypothesis is supported by the sinusoidal aspect of APN associated with MS, its frequency of around 4–5 Hz as well as its small amplitude.²³ Abnormal feedback loops could involve the oculomotor neural integrator which normally guarantees stable gaze through mathematical integration of preculomotor signals.¹⁹ This idea is mainly supported by the saccadic resetting of nystagmus and by the predominant location of lesions in the pontine tegmentum that could include cell groups of the paramedian tract involved in the oculomotor neural

integrator feedback loops.¹⁵ Abnormal feedback could also arise from an impairment in visual feedback secondary to a demyelination of the optic nerve.¹⁵ An abnormal visual feedback is supported by the frequent association of APN and optic neuropathy^{20,24,25} and the observation of larger oscillations in the eye with the more severe optic neuropathy.²⁰ However, this abnormal visual feedback hypothesis is challenged by the APN insensitivity to darkness or to experimental change of visual feedback delay.¹⁹

The more influential model of OPT suggests a dual mechanism involving inferior olivary hypertrophy and cerebellar plasticity.^{22,26} First, disruption of inhibitory cerebellar modulation of the ION leads to the development of somato-somatic gap junctions between neurons, generating periodic oscillations that are transmitted to the cerebellar cortex. The second mechanism would be a superimposed cerebellar “smoothing” of the output signal leading to smoother and less periodic eye movements. This model is supported by the irregular aspect of APN associated with OPT, its low frequency of around 1–3 Hz, and its asymmetry.⁵

The ambiguity of combining MS and OPT in the etiologies of APN is reinforced by the publications of

Table 1 Dominant plane (DP), amplitude (A), velocity (V), frequency, and symmetrical index (SI) of acquired pendular nystagmus in oculopalatal (OPT) and multiple sclerosis (MS) groups^a

Group	Patient	Nystagmus						Frequency, c/s	SI, %
		RE			LE				
		DP	A, deg	V, deg/s	DP	A, deg	V, deg/s		
OPT	1	T	12	20	V	4	8	1	50
	2	VT	5	15	VT	8	15	1	23
	3	V	10	10		0	0	0.7	100
	4	T	6	10	T	5	10	1.65	9
	5	V	2	5	V	4	10	2.5	33
	6		0	0	VT	2	5	1.15	100
	7	T	7	11	HVT	2	4	0.9	56
	8	V	3	10	V	2	10	2.5	11
	9	T	3	10	H	4	10	2.5	33
	10	VT	3	7	T	10	16	2.4	54
	11	V	3	10	V	2	10	1.95	20
	12	T	12	28	T	30	60	1.35	60
	13	T	2	4	V	3	6	1.65	50
	14	T	8	17	T	5	12	1.3	25
MS	1	HT	1.5	10	H	1.5	10	5	20
	2	T	1	5	H	0.5	5	5	33
	3	H	1	8	H	1	6	4	0
	4	T	1	6	HV	0.5	5	5	33
	5	H	1.5	8	H	2	16	5	14
	6	H	0.5	3	H	0.5	3	5	0
	7	T	4	20	T	2	18	4	33
	8	T	0.3	2	T	0.3	2	5	9
	9	H	1.5	10	H	2	10	5	14
	10	T	0.5	5		0	0	4	100
	11	HV	0.25	2	HT	0.3	2	5	9
	12	H	1	7	T	0.5	4	6	33
	13	VT	0.5	4	VT	0.5	4	4	0
	14	H	0.25	3	T	0.5	5	5	33
	15	T	0.5	2	T	0.5	2	5	0
	16	T	0.5	2.5	T	0.5	3	4	0
	17	T	0.3	1	T	0.5	2	5	33
	18	H	1	4	VT	0.5	2	4	33
	19	T	0.5	2	T	1	3	4	33
	20	V	2	13	T	0.3	3	4	74

Abbreviations: c = cycle; H = horizontal; T = torsional; V = vertical.

^a In the OPT group, the dominant plane of nystagmus was torsional in 11 eyes, vertical in 9 eyes, mixed vertico-torsional in 4 eyes, horizonto-vertico-torsional in 1 eye, horizontal in 2 eyes (2 different patients). The dominant plane of eye movement in the MS group was torsional in 18 eyes, horizontal in 13 eyes, mixed vertico-torsional in 3 eyes, mixed horizonto-torsional in 2 eyes, mixed horizonto-vertical in 2 eyes, vertical in 1 eye, and absent in 1 eye.

observations of OPT in MS. Indeed, old articles suggest some rare cases of OPT or palatal tremor secondary to MS.^{16,27,28} The features of nystagmus, its frequency and association with palatal tremor, suggested OPT. However, most of the time, the diagnosis of MS was only based on the young age of the

patient. Critical reading of these publications suggests that some cases could correspond to brainstem hemorrhage or even essential palatal tremor. A notable exception is the report of a patient with clinical, biological, and MRI criteria for MS, developing OPT associated with ION hypersignal on MRI.²⁹

The nystagmus had a pendular aspect, 3–4 deg amplitude, 2 Hz frequency, and was in the horizontal and vertical planes. Therefore, OPT might exceptionally develop after an inflammatory focal lesion due to MS. In this case, the nystagmus may present the features of ocular tremor associated with OPT instead of the high-frequency, low-amplitude pendular nystagmus usually observed in MS.

Visual acuity was poor in both groups of patients, and far visual acuity was significantly more impaired in the patients with MS than the patients with OPT. Patients with MS had associated signs of optic neuropathy in 15 out of 20 cases, which could explain the differences in terms of visual acuity. Conversely, vision-specific health-related quality of life was more deteriorated in the OPT group than the MS group. In our study, correlation analyses suggested that the visual functional score was not related to visual acuity, amplitude, velocity, or frequency of APN. Interestingly, a recent study comparing patients with pontine hemorrhage showed that global functional scores were more severe in patients with ION hyper-signal, even though motor paresis, sensory disturbance, and ataxia were comparable,³⁰ but they did not attempt to correlate functional scores with eye movement impairments. One explanation for the lower scores on the vision-specific quality of life scale in the OPT group could be the fact that the deficit in horizontal eye movements is more profound in patients with OPT than in patients with MS. Another explanation could be that APN in MS develops slowly whereas it develops rapidly in patients with OPT. Finally, patients with MS show progressive cognitive impairment in which anosognosia might lead to them ignoring part of the visual functional consequences of the disease. We suggest that the visual functional consequences of APN should be taken into consideration in future therapeutic trials.

In the first double-blind, controlled study performed in 15 patients with APN, 9 were patients with MS and 3 had stroke suggesting the presence of OPT.⁶ Gabapentin was efficient in the treatment of APN but the published data do not allow a comparison of the results in patients on the basis of different underlying etiologies. In a second trial showing that gabapentin was more successful than vigabatrin in improving APN, only patients with MS were tested.³¹ In contrast to the results of a recent study in a small group of patients,¹⁰ Shery et al⁸ found that gabapentin and memantine were both effective in treating APN secondary to MS but not to other neurologic diseases, which is in accordance with our personal clinical experience. Finally, the studies from Starck^{21,32} showing improvement of APN with gabapentin and memantine only tested patients with MS.

On the basis of this literature and our personal clinical experience, gabapentin and memantine appear to be effective in APN associated with MS but not OPT. Based on the dual-model hypothesis of OPT (see above), it was recently proposed that treatments should combine drugs acting on cerebellar modulation (clonazepam, alprazolam, primidone, topiramate, memantine) and drugs reducing the electrotonic coupling between the hypertrophied inferior olive neurons by blocking connections (quinine, carbenoxolone, mefloquine).^{22,26} To date, none of these combinations of drugs have been tested in patients with APN arising from OPT.

The results of this study emphasize the different clinical aspects of these 2 etiologies of APN, the fact that the functional consequences of APN are more severe in patients with OPT, and the need to differentiate both etiologies in future textbooks, reviews, and pharmacologic trials.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Caroline Tilikete.

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DISCLOSURE

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