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Pupillary dilatation test and Fourier analysis of pupillary oscillations in patients with multiple sclerosis

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Abstract Recently we investigated 29 patients aged between 31 and 60 years with multiple sclerosis by means of two new techniques. The first technique was based on pupillary dilatation response to the topical application of the cholinergic antagonist tropicamide. The second technique was the Fourier analysis of pupillary oscillations for measurement of central activation, carried out without and under the influence of a cognitive task. The multiple sclerosis group had a pupillary dilatation of 31.9% after 40 min. Under the influence of a cognitive task the patient group revealed lower amplitudes of pupillary oscillations reflecting a decreased capacity for cognitive activation.

Key words Multiple sclerosis · Tropicamide · Pupillary dilatation · Pupillary oscillations · Cognitive task · Central activation

Introduction

Multiple sclerosis (MS; also known as encephalomyelitis), is characterized by the onset in early and adult life of progressive diffuse neurologic disturbances with an irregular fluctuating period of exacerbation and apparent improvement or quiescence. Irregular gray patches of degeneration occur in the brain and spinal cord with a predilection for the white matter, varying in size from a few millimeters to several centimeters. Signs of multiple involvement of the central nervous system (CNS) may include slurred speech, intention tremor, nystagmus, retrobulbar neuritis, incontinence, spastic paralysis, pallor of the temporal halves of the optic disks, increased deep tendon reflexes, and bilateral extensor plantar responses. Late in the course of the disease the mental state is characterized by euphoria with little insight into condition or disability and further by dementia. Excited and even maniacal states may occur.

Our assumption was that MS patients exhibit slight to moderate cognitive deficits which are related to a reduction of acetylcholine and to a central nervous deactivation, respectively. Therefore, the aim of the study was to answer the questions concerning whether patients with MS reveal a wider pupil dilatation after application of tropicamide, an antagonist of acetylcholine transmission, and whether the patients show central nervous deactivation and lower cognitive activation as compared with normal controls.

Two new techniques were used in the investigation of patients with MS: The first technique was based on a pupillary dilatation response to the topical application of the cholinergic antagonist, tropicamide. The second technique included Fourier analysis of pupillary oscillations reflecting central nervous activation without and under the influence of a cognitive task, i.e. cognitive pupillary oscillations hypothesis. The reticulo-thalamo-cortical axis plays an important role in central nervous activation, because parts of its systems seem to control differential activation processes in ascending direction (Schandry 1981). There is a relationship between central activation and pupillary oscillations because the oscillations reflect the physiological cortico-diencephalic activity: The frequencies and amplitudes of the pupillary oscillations are modulated cortico-diencephalically.

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Subjects and methods

The patients were investigated by means of a computer-assisted video pupillometer 1050 from the Whittaker Corporation. For "static" measurement the subject had to adapt, for 3 min, to the illumination (160 Lux) of a sound-attenuated room measuring 3 × 4 m. The pupillometric technique consisted of positioning the subject's head comfortably on a chin-rest and forehead-rest with his/her gaze directed at a black dot positioned 1.60 m in front of the eye. The subject was then instructed to fix the dot to avoid accommo-

dation on the one side and to warrant a precise recording of the pupil on the other side. We used distance of 1.6 m, because the fixation of a nearer dot (16 cm) causes a smaller pupil than a wider fixation point (1.60 m). Subsequent to adaptation and adjustment of the pupillometer, the computer-assisted measurement lasted for 25.6 s. Afterward, mean pupil diameter and standard deviation were calculated.

Recently, we tried to determine central activation by means of Fourier analysis of pupillary oscillations. We analyzed pupillary oscillations during the recording periods of static pupillometry (Grünberger et al. 1992), which lasted 25.6 s. A sampling frequency of 40 Hz was used. Before calculating the Fourier analysis blinks have to be identified and eliminated by means of a new technique called smoothing: Each problematic value has to be compared with the subsequent value and the difference is calculated until they are again within the limit. The two values marking the start and the end of the blink have to be linked, whereas the blink is eliminated. Using the Fourier analysis the spectrum was divided into five frequency bands (0.0–0.2; 0.21–0.4; 0.41–0.6; 0.61–0.8; 0.81–1.0 Hz). We were also interested in the total spectrum. Under the influence of a cognitive task (simple calculations: 100 minus 7, minus 3, minus 7, minus 3, etc.). Amplitude changes of pupillary oscillations can be expected (Grünberger et al. 1994, 1995, in press).

Description of patients

A total of 29 patients (males and females) aged between 31 and 60 years diagnosed (and well defined) as MS patients participated in the study and their results were compared with those of 18 normal controls with only small differences in age. All patients had to pass a complete ophthalmological exam to exclude any anterior-segment disease.

Design of study

The pupillary diameter (left eye) of the MS patients and of the normal controls was measured eight times. The first measurement was the baseline value. After 3 min the second measurement was carried out (under cognitive activity). The third was taken 20 min after the first measurement, and the fourth to the seventh were taken at 20-min intervals. Measurement time points were: 0 min (baseline), 3 min, 20 min, 40 min, 60 min, 80 min, and 100 min. At these time points each measurement value is the mean value of 40 scourments per second of the left eye. The patients with multiple sclerosis (n = 29) received by topical application 0.01% tropicamide solution in the left eye and their pupil diameter was measured at the time points mentioned previously.

Statistical analysis

For statistical data analysis ANOVA, the Duncan test, the Newman-Keuls test, and discriminant analysis were used.

Results

Both groups showed pupillary dilatation after application of tropicamide. The MS patient group had a pupil dilatation of 31.9% after 40 min as compared with their baseline value, the control group showed at the same measurement time point only 16.5% dilatation: The MS group had a baseline value of $\bar{x}$ = 4.04 mm; s = 0.82 and the maximum dilatation $\bar{x}$ = 5.32; s = 0.91. In the normal controls a baseline $\bar{x}$ = 4.57; s = 0.76 and the maximum dilatation $\bar{x}$ = 5.33; s = 0.52 could be observed. By means of the Newman-Keuls test significant differences between the MS group and the normal controls were found: 20 min (n.s.), 40 min ($P < 0.05$); 60 min ($P < 0.05$), 80 min (n.s.), and 103 min (n.s.) after application of tropicamide (Fig. 1).

After calculation of the Fourier analysis in the frequency bands 0.21–0.4; 0.41–0.6; 0.61–0.8; and 0.81–1.0 Hz significant differences of changes to the baseline between the patients with MS and healthy normals were found. Furthermore, during the cognitive task the changes of the power (sum of the frequency bands) revealed a significant difference between patients with MS and normal controls. After 20 min the changes of the amplitudes in the frequency bands 0.0–0.2 Hz and 0.81–1 Hz differed significantly between the patients and the control groups (Fig. 2). However, the patients with MS showed 40 min af-

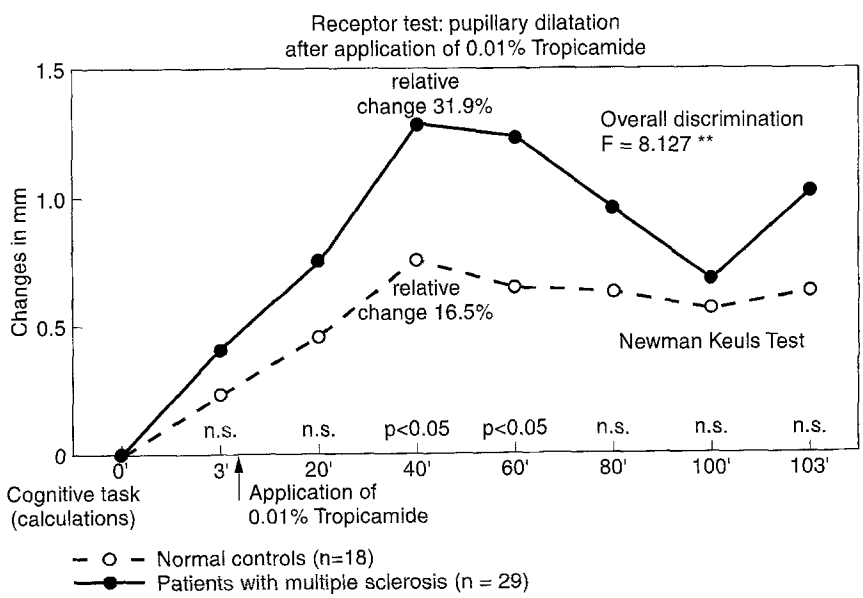

Fig. 1 Forty minutes after application of 0.01% tropicamide solution in the patient with multiple sclerosis, a relative change of 31.9% in pupillary diameter was found, whereas normal controls revealed a change of only 16.5%

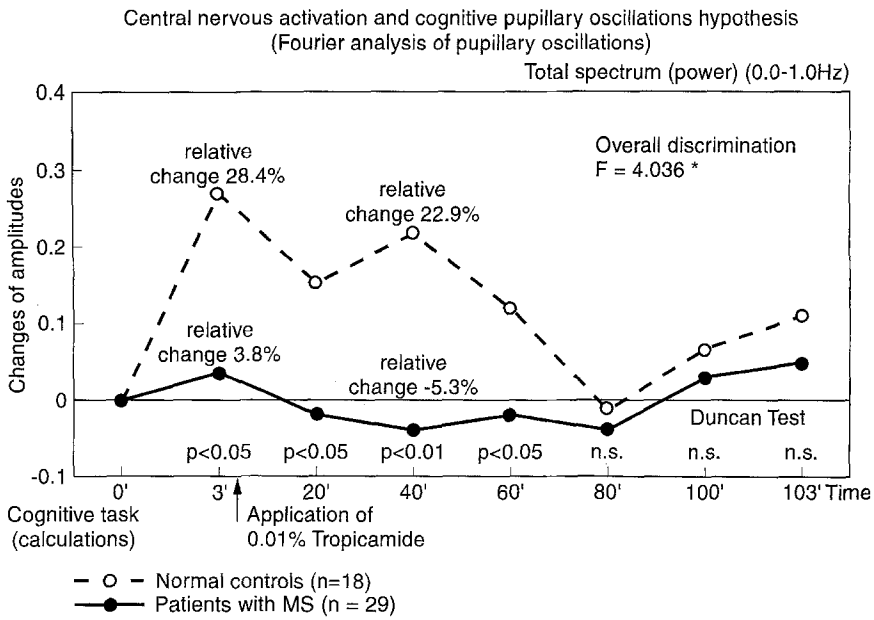

Fig. 2 Whereas the patients with MS were characterized by a lower central nervous activation as measures by Fourier analysis of pupillary oscillations, the normal controls showed a significant higher activation during a cognitive task and 20, 40, 60 min, respectively, after topical application of tropicamide

Table 1 Receptor test: changes (%) in pupillary oscillations after administration of 0.01% tropicamide solution. (MS multiple sclerosis; $n = 29$; Norm healthy normals; $n = 18$)

Time point pupillary oscillations (Hz)	Cognitive task							
	3 min	20 min	40 min	60 min	80 min	100 min	103 min	
0.0–0.2	13.48	2.37	2.05	1.44	– 2.33	4.37	10.78	MS
	29.43	18.80*	28.96**	23.07*	3.10	8.22	14.86	Norm
0.2–0.4	7.51	–5.32	– 7.90	– 3.40	0.02	–1.21	4.51	MS
	31.22**	12.83	20.51**	4.04	2.66	9.11	2.21	Norm
0.4–0.6	–3.30	–5.45	–15.09	–10.65	– 6.91	0.78	0.19	MS
	25.79**	4.27	5.63*	1.04	– 9.81	3.45	12.67	Norm
0.6–0.8	–2.13	–8.94	–25.27	– 9.25	–16.07	7.12	–9.81	MS
	16.56*	9.92	13.42**	– 6.78	–13.70	3.35	5.52	Norm
0.8–1.0	–8.54	–7.65	– 6.03	– 4.18	–17.04	14.34	3.94	MS
	33.16*	31.53*	26.92	7.98	– 2.87	13.20	21.19	Norm
0.0–1.0	3.77	–2.24	– 5.28	– 2.61	– 4.83	3.59	5.54	MS
	28.43*	15.69	22.92**	13.06*	– 1.45	7.67	11.58	Norm
Dilatation of pupil	10.16	18.53	31.85	30.83	23.65	16.82	25.36	MS
	5.10	10.09*	16.52**	14.52**	13.85*	12.27	13.73*	Norm

NOTE: Cognitive task means calculations during recording of pupillary oscillations. (From J. Grünberger 1994)
Multiple t-test; Duncan test: * $P < 0.05$; ** $P < 0.01$

ter application of tropicamide changes in all frequency bands apart from the frequency band 0.81–1.0. These changes reached the level of statistical significance as compared with normal controls. Thus, the patient group was characterized by a lower activation. After 60 min only significant differences of the changes in the frequency band 0.0–0.2 and in the sum (power) of the frequency bands between healthy normals and the patients could be found. The latter were more deactivated (Table 1).

Conclusion

In contrast to Scinto et al. (1994, 1995), we could demonstrate that the response to an antagonist of acetylcholine is not specific for Alzheimer patients only, but could also be found in patients with MS. The results of the Fourier analysis of pupillary oscillations demonstrated the most significant changes between MS patients and normal controls during the cognitive task and 40 min after application of tropicamide. From this result we conclude that the MS group has a lower capacity for cognitive activation. Furthermore, a central nervous deactivation could be observed in the patient group until the 100th min.

Especially 40 min after administration of tropicamide a marked deactivation was found in the patient group while at this time the pupil reached the maximum dilatation. These findings support our observation that there is no relationship between pupillary diameter and pupillary oscillations.

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