The use of infrared oculography to study disturbances of eye movements in patients with autoimmune diseases and suspected neuropsychiatric involvement

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Summary

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Although a wide range of diagnostic tools have been used to assess CNS involvement in autoimmune disease, no single technique has proven to be reliable. Patients with these diseases often underwent detailed neurocognitive test batteries which are extremely time consuming and quite expensive. The cognitive deficits of these individuals are sometimes unspecific. Nevertheless, patients suffering from intracerebral affection of autoimmune diseases are extremely handicapped in their daily activities and work. These diseases are often associated with a depressive syndrome in many cases resistant to therapeutic efforts. Psychiatric treatment is not infrequent and the clinical picture is dominated by impaired intellectual performance, poor concentration, mental fatigue and depression, often related to emotional stress. For these reasons cognitive deficits in individuals being suspected for neuropsychiatric symptoms in autoimmune diseases are often misdiagnosed. Imaging techniques like MRI and CT only sometimes show pathological results. Electroencephalography (EEG) is not specific for the disease and adds little to diagnosis. Even the positron emission tomography (PET) does not always reveal pathological findings. With the aid of the non-invasive eye movement measurement technique it is possible to detect eye movement disturbances in individuals being suspected for intracerebral affection with autoimmune diseases.

10 patients (5 with SLE, 5 with other autoimmune diseases) and 10 healthy controls were examined using infrared oculography to measure disturbances of eye movements in order to determine whether this method is useful in the assessment of CNS involvement. For smooth pursuit eye movements (SPEM) there was a significantly higher number of correction saccades ($p < 0.01$) and a non-significant trend towards a fixation deficit in patients compared to controls.

Keywords: SLE; autoimmune disease; CNS involvement; saccadic eye movements; smooth pursuit eye movements; infrared oculography

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Introduction

Neuropsychiatric symptoms occur during the course of systemic lupus erythematosus (SLE) in 24–51% of patients and are often difficult to ascribe to the underlying disease with certainty [1]. Major manifestations include stroke, epileptic seizures and psychoses. Headaches, often migrainous in character, occur in up to 40% [1, 2] and psychiatric symptoms in up to 71% of patients with SLE [3]. Minor cognitive deficits such as impaired intellectual performance, poor concentration, mental fatigue and depressed mood which are not usually related to emotional stress or medication are common [4, 5]. The minor cognitive deficits are often present at an early stage of the disease. Even if formal psychiatric disease is excluded by detailed mental state examination, the symptoms often persist and lead to a decrease in performance that can cause major disability. No single diagnostic method is generally applicable in suspected CNS involvement from SLE or other autoimmune diseases. Serum antibodies, complement and circulat-

ing immune complexes lack sensitivity and specificity although serum antiribosomal P protein [6] and antineuronal antibodies [7] may be useful.

Analysis of routine CSF parameters revealed elevated protein in only 22–50% and pleocytosis in only 6–34% of 250 patients with CNS lupus [1] but CSF antineuronal antibodies may be more sensitive [8]. Of the imaging techniques, cranial MRI is superior to CT but both lack sensitivity and specificity [9]. Recently it has been shown that positron emission tomography (PET) [10, 11] and single-photon emission computed tomography (SPECT) [12, 13] may detect lesions not apparent in MRI.

Impaired visual-spatial intelligence [14] has been demonstrated using neuropsychological testing in patients with SLE. Eye movement abnormalities might be expected in cerebral involvement from an autoimmune disease such as SLE. Saccadic eye movements (SEM) are induced by ocular fixation of a rapidly alternating target whereas smooth pursuit eye movements (SPEM) involve fixating and following a slowly moving target. Eye movements (SEM and SPEM) have recently been studied in patients with proven or suspected CNS lupus without conclusive results. To address this, we used a non-invasive, highly sensitive testing method, the infrared oculography [15], to investigate whether eye movements are affected in patients with suspected CNS involvement from autoimmune diseases compared to healthy controls.

Methods

Patients

The inclusion criterion for this study was suspected or proven CNS involvement from SLE or another autoimmune disease. Ten patients (all female, mean age 48.3 years, range 26 to 75 years) and 10 age-matched controls were examined using infrared oculography.

Five patients were suffering from systemic lupus erythematosus diagnosed according to the ACR criteria [16] and 5 from other systemic autoimmune diseases (one patient had primary Sjögren's syndrome diagnosed according to published criteria [17] with accompanying myositis, 3 patients an undifferentiated connective tissue disease as described by Black and Isenberg [18] and one a microscopic polyangiitis as defined by the Chapel Hill Consensus Conference criteria [19]). With the exception of one patient (LM) who developed left-sided Horner's syndrome, no patient had clinical evidence of a focal neurological deficit (table 1 and 2).

Table 1 Patients with systemic lupus erythematosus (SLE) (n = 5).

patient	diagnosis	clinical and laboratory features	serological parameters	CSF	imaging	medication
SM 26 years, ♀	SLE	leucopaenia, thrombopaenia, autoimmune haemolysis	ANA (speckled) 1:640, anti-RNP positive	–	MRI: left-sided frontoparietal arachnoidal cyst SPECT: marked inhomogenous perfusion	cyclophosphamide therapy, prednisone, aspirin
BC 27 years, ♀	SLE	diffuse segmental proliferative glomerulonephritis, anaemia, leucopaenia, thrombopaenia	ANA (speckled) 1:160, anti-ds-DNA positive, anticardiolipin positive	–	MRI: multiple lesions, old lesion in the right superior parietal region, new lesion in the left fronto-parietal region	prednisone, phenprocoumon
GG 29 years, ♀	SLE	polymyalgia, polyarthritis, pericarditis, renal involvement (IgA nephropathy), rapid fatiguability, headaches, vertigo, concentration deficit	ANA >1:640, anti-ds-DNA positive	normal	MRI: normal	prednisone, azathioprine, hydroxychloroquine
WD 31 years, ♀	SLE	polyarthralgia, polymyalgia, pleuropericarditis, photosensitivity, oral ulceration	ANA (speckled) 1:640, anti-ds-DNA and RNP positive	–	MRI: normal	prednisone, plaquenil, methotrexate
MV 50 years, ♀	SLE	polyarthritis, perimyocarditis, shrinking-lung syndrome, acute confusional state with aggressiveness, focal vasculitis of retina	ANA (speckled) >1:640, anti-ds-DNA and RNP positive	normal	MRI: normal	azathioprine, prednisone, previously: cyclophosphamide, hydroxychloroquine

Table 2 Patients with other autoimmune conditions (n = 5).

patient	diagnosis	clinical features	serological parameters	CSF/histology	imaging	medication
RM 75 years, ♀	PSS	polyarthritis, kerato-conjuctivitis sicca, proximal muscle weakness	ESR 46 mm, CRP 50 mg/l, ANA speckled 1:640, anti-Ro + anti-La positive	CSF: normal cell count, normal total protein, oligobands positive lip biopsy: lymphocytic infiltration	–	prednisone
MM 70 years, ♀	UCTD	CIDP, rapid fatiguability, concentration deficit, history of thyroiditis	ESR 50 mm, CRP 90 mg/l, ANCA negative, ANA 1:80	CSF: raised protein with normal cell count sural nerve biopsy: lymphocytic endoneural	MRI: generalised cortical atrophy, multiple subcortical white-matter lesions infiltration	prednisone
LM 55 years, ♀	UCTD	left-side frontal headaches, Horner's syndrome, polyarthralgia, mild renal involvement	ANA positive, anti-RNP positive	–	–	prednisone
IW 52 years, ♀	UCTD/RA overlap	erosive polyarthritis, concentration deficit	ANA 1:320, RF positive	normal	MRI: normal SPECT: reduced perfusion frontal and temporal lobes bilaterally	prednisone, methotrexate
ZO 65 years, ♀	mPA	renal involvement, rapid fatiguability, concentration deficit	ESR 80 mm, CRP 136 mg/l, p-ANCA 84 U/l, ANA 1:80, RF positive	normal, sural nerve biopsy: angiitis of the epineural vessels	–	prednisone

PSS = primary Sjögren's syndrome; UCTD = undifferentiated connective tissue disease; RA = rheumatoid arthritis; mPA = microscopic polyangiitis.

All patients suffered from minor cognitive deficits such as rapid fatiguability, concentration deficits and poor memory and/or depressive symptoms which, however, did not fulfil the ICD-10 diagnostic criteria for depression. The symptoms as determined by an experienced psychiatrist are shown in table 3 and 4. In two cases dementia was diagnosed, one with cortical predominance and one subcortical.

Table 3 Neuropsychological and neuropsychiatric features in patients with SLE.

SM 26 years	impaired concentration, rapid fatiguability, visual-spatial deficits
BC 27 years	confusional state, impaired concentration, attention deficits, deficits in cognitive flexibility and abstract problem solving
GG 29 years	low mood, attention deficit, rapid fatiguability
WD 31 years	low mood, attention and concentration deficits, rapid fatiguability, deficits in visual spatial problem solving
MV 50 years	concentration deficits, rapid fatiguability, confusional state with aggression

All patients had received treatments with systemic corticosteroids with or without other immunosuppressive agents. An examination of the cerebrospinal fluid had been performed in 7 of 10 patients, a cranial MRI examination in 7, a SPECT examination in 2 and a PET examination in one patient.

A group of 10 healthy probands with a comparable mean age served as controls. Exclusion criteria were significant binocular decrease in visual acuity, a former history of psychiatric disease or other significant medical conditions. Informed consent was obtained from all patients and probands.

Computer-driven infrared oculography was used to measure the eye movements non-invasively. The subject is seated in a darkened room and the head is fixed to avoid concomitant head movements. The stimulus for the eye movements is provided by a red light source on a screen which the patient is asked to fixate. In the case of saccadic eye movements a square-wave with an amplitude of ± 20° and in the case of smooth pursuit eye move-

Table 4 Neuropsychological and neuropsychiatric features in patients with other autoimmune conditions.

RM 75 years	low mood, impaired concentration, rapid fatiguability
MM 70 years	dementia, orientation deficit, confusional state
LM 55 years	low mood, hypomania, affective liability, impaired memory
IW 52 years	subcortical dementia, rapid fatiguability, orientation deficit
ZO 65 years	rapid fatiguability, impaired concentration

ments a sinusoidal stimulus with a frequency of 0.33 Hz and an amplitude of 30° appears on a translucent screen. The eye movements are registered by using an infrared system attached to the headgear worn by the patient during the examination. The recording system was calibrated before each experiment. The instructions were given uniformly to all subjects. With a software program, fixation, saccadic eye movements and smooth pursuit eye movements were displayed on a screen, numerically evaluated and compared with the reference values obtained from healthy controls. Fixation was measured by analogue online recording of the movement of the eye.

The Mann-Whitney test was used for statistical analysis. A p value of <0.05 was regarded as significant.

Results

Saccades

On comparison of amplitude, latency, duration and velocity of saccadic eye movements (square-wave with amplitude of ± 20°), there were no statistical significant differences between patients and controls but a significantly increased number of correction saccades ($p < 0.05$) following hypometric (undershooting) saccades in both groups of patients (systemic lupus erythematosus [SLE] and other autoimmune diseases [OAD]) compared to the controls (table 5, fig. 1).

Smooth pursuit eye movements and fixation

For smooth pursuit eye movements (sinusoidal at a frequency of 0.33 Hz and amplitude of 30°), there was a significantly higher number of correction saccades in both groups of patients compared to controls on analysis of six hemicycles ($p < 0.01$) (table 5). In controls there was a mean of 2.6 (range 0–9) correction saccades per 6 hemicycles whereas in the patients with SLE and other autoimmune diseases there was a mean of 7.5 (range 7–25) and 8.6 (range 14–25), respectively. This observation was independent of the direction of the gaze and there was no significant difference between the two groups of patients. The semi-quantitative analysis of the accuracy of fixation showed a trend towards a fixation deficit in the patients with autoimmune diseases and SLE compared to controls but this did not reach statistical significance (not shown here).

As an example figure 2 shows the recording of a patient (SM) with SLE and pathological SPECT examination, who had persistent deficits of alertness and concentration, and rapid fatiguability. Significantly more correction saccades were seen in the smooth pursuit eye movement programme (fig. 2B).

Discussion

We found significant impairment of smooth pursuit eye movement in patients with suspected CNS involvement from autoimmune diseases compared to controls. The impaired tracking was characterised by a significantly increased number of corrective saccades, meaning a reduced gain. In addition, there was a non-significant trend towards

Table 5 Number of corrective saccades.

	saccades 20° (n = 10)		smooth pursuit eye movement 6 hemicycles (0.33 Hz)		
	hypo corr	hyper corr	corr right	corr left	total
SLE	2.4 ± 2.07*	1.6 ± 2.61	8.0 ± 4.63**	7.0 ± 3.53**	7.5 ± 3.92**
OAC	3.6 ± 0.55*	0.8 ± 1.30	8.0 ± 2.73**	9.2 ± 2.77**	8.6 ± 2.67**
controls	0.5 ± 0.71	0.9 ± 0.99	2.0 ± 0.71	2.6 ± 1.67	2.6 ± 1.35

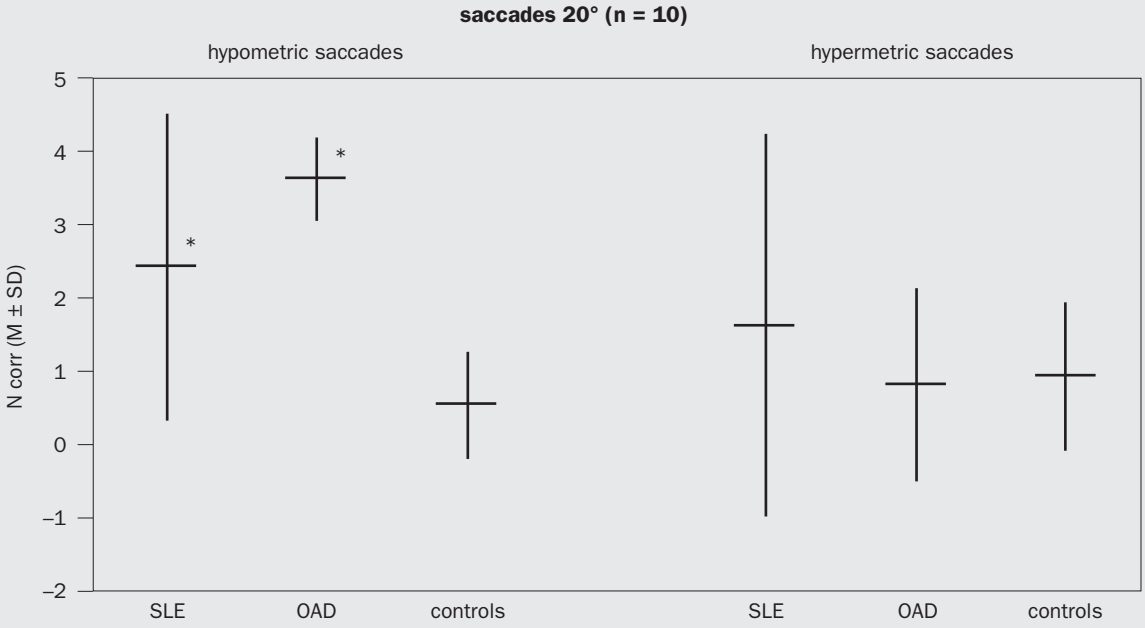
Mann-Whitney test *$p < 0.05$, **$p < 0.01$.

The number of corrective saccades following hypometric saccades was significantly higher in both groups of patients than in controls, the number of corrective saccades during smooth pursuit eye movements was significantly higher in all patients compared to controls independent of the direction of the gaze.

an impairment of fixation and a significantly increased rate of hypometric saccades with corresponding corrective saccades following a 20° visual stimulus which probably reflected a general instability of the oculomotor system. No significant differences were found between the patients with SLE and the patients with other autoimmune diseases.

Specific brain areas, e.g. the occipital cortex (area 17, 18), the mediotemporal area (MT), the

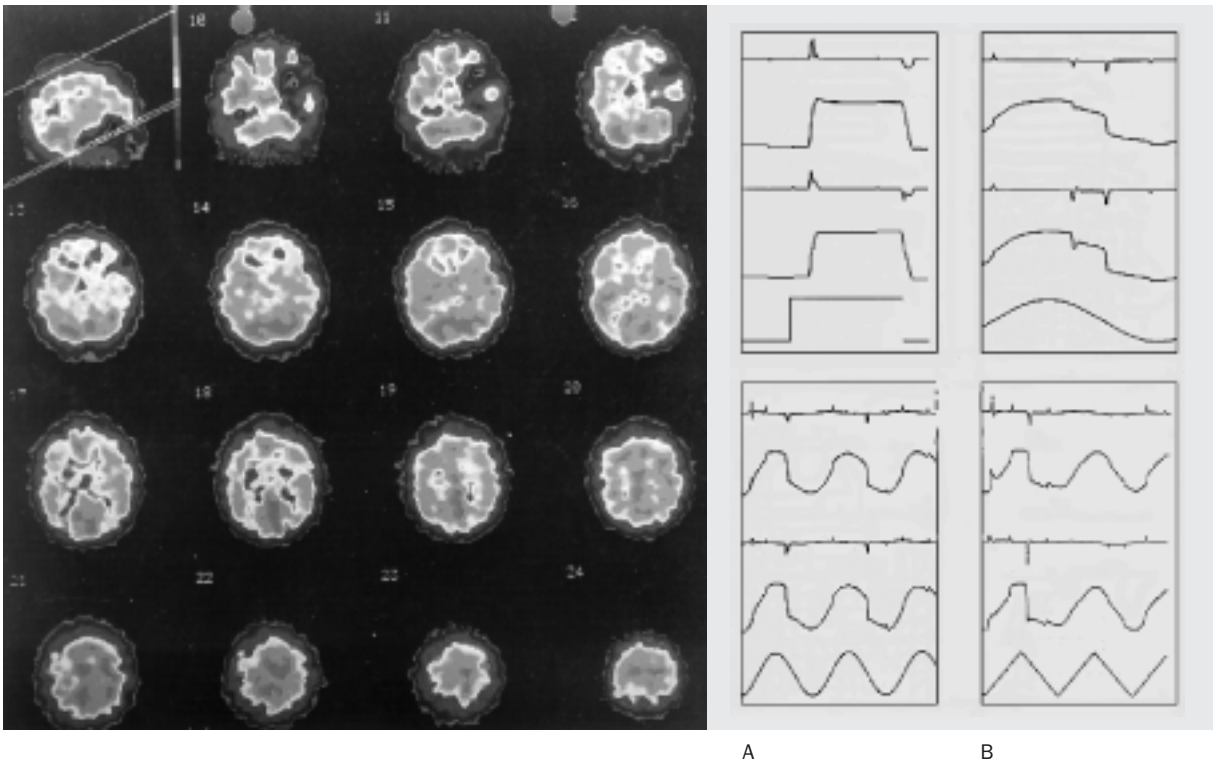
Figure 1 Number of correction saccades in the two groups of patients and controls.



Mann-Whitney test: *p <0.05;

only in hypometric saccades the number of corrective saccades reached significance (p <0.05).

Figure 2 On the left of figure 2 the SPECT of a patient with SLE being suspected for CNS involvement is shown. The left frontal and parietal cortex are hypoperfused. The patient's eye movement recordings are shown on the right. The saccadic movement is unaffected (A), however, the smooth pursuit eye movement is disrupted by corrective saccades (B).



A B

mediosuperior temporal area (MST) and frontal eye fields (FEF, area 8), control not only contralateral saccades but also ipsilateral smooth pursuit movements. Cortical lesions result in abnormalities of ipsilateral smooth pursuit movements. If the regulation of smooth pursuit movements is disturbed, the saccadic system can evoke substitute movements such as corrective saccades which lead to a reduced gain [20].

Studies with fMRI indicate that both saccades and smooth pursuit movements are generated in the same cortical fields, particularly the frontal eye fields, mediotemporal and mediosuperior temporal areas frequently leading to overlapping saccadic and smooth pursuit activity. Thus, when smooth pursuit movements or saccadic eye movements are disturbed, disturbances of the frontal and parietal cortical function are likely, especially if no significant deficit of fixation or nystagmus is present. The saccadic system may then be activated as an auxiliary mechanism leading to e.g. corrective saccades and reduced gain. In patients with suspected autoimmune disease, examination of eye movements, a not-invasive technique, can contribute to the assessment of CNS involvement. Giacomini et al. [21] found a significant delay in the initiation of saccadic eye movements in patients with SLE compared with controls. The velocity of saccades was unaffected but smooth pursuit eye movements were not studied in detail.

In some of the patients we examined, reduced perfusion of the parietal, frontal and prefrontal regions of the brain was seen in SPECT and PET, suggesting an anatomical correlate for the disturbance of smooth pursuit eye movement. Sanna et al. [22] describe that patients with neuropsychiatric manifestation in lupus erythematosus showed a high prevalence of headache, mood disorders and seizures. These symptoms seem to be associated with white-matter hyperintensity lesions on MRI.

The cerebellum and brain stem would appear less affected because our patients showed no signs of pathological nystagmus. It may be diagnostically useful to examine the saccadic and smooth pursuit eye movements, especially if the patients suspected of CNS involvement are suffering from cognitive deficits and the cranial MRI was non-diagnostic. In patients in whom CNS involvement from the underlying autoimmune disease is already known from other investigative modalities this screening method can be used as a follow-up parameter, perhaps as an alternative to detailed neuropsychological testing. However, it is not yet clear if deficits in eye movements are specific to CNS involvement in SLE or other autoimmune diseases. In addition, the patient's reaction might be influenced by the chronic nature of the disease or by other factors such as immunosupressive medication. It is necessary to confirm these observations in a larger number of patients with CNS involvement in autoimmune diseases.

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