SHORT COMMUNICATION

The use of eye-movement recording in patients with anti-Hu antibody–associated paraneoplastic neurological syndromes to objectively determine extent and course of disease

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Abstract

Background and purpose: Paraneoplastic neurological syndromes with Hu-antibodies (Hu-PNS) are immune-mediated disorders in patients with malignancies, most frequently small cell lung cancer, affecting both the peripheral and central nervous system (CNS). In Hu-PNS, brainstem and cerebellar involvement are common. Here, we assessed whether eye-movement disturbances can be used for diagnosis and monitoring of CNS involvement in Hu-PNS.

Methods: Twenty-nine patients with Hu-PNS (17 females; mean age, 63.2 years,) and 14 healthy age-matched controls (seven females; mean age, 60.2 years) were included. Saccadic and smooth pursuit eye movements in response to visual stimuli were recorded with video-oculography. Eye movements were scored quantitatively (number of correction saccades, saccadic intrusions, and saccades during fixation period) and qualitatively by two eye-movement experts. In 20 patients, up to three follow-up measurements were made during subsequent hospital visits with fixed 4-week intervals. Disease course was assessed using the modified Rankin Scale.

Results: Eye movements were disturbed in 26 of 29 Hu-PNS patients, with horizontal eye movements being in general more impaired. Moreover, in 12 of the 14 Hu-PNS patients without clinical CNS involvement, eye movements were disturbed. Changes in eye-movement control over a period of up to 12 weeks were significantly correlated with the clinical response to treatment ($\rho = 0.52, p = 0.02$).

Conclusions: Hu-PNS often affects eye-movement control, also in the absence of CNS signs or symptoms. Eye-movement recordings in Hu-PNS patients might be a useful tool to objectively monitor progression and treatment efficacy in Hu-PNS patients.

Keywords
eye-movement control, modified ranking scale, paraneoplastic neurological syndromes, saccadic eye movement, smooth pursuit
INTRODUCTION

Paraneoplastic neurological syndromes with Hu antibodies (Hu-PNS) are severely disabling disorders associated with various types of cancer, most commonly small cell lung cancer [1–4]. Because the Hu antigen is expressed by all neurons, all parts of the nervous system can be affected in Hu-PNS. The poor prognosis of paraneoplastic neurological syndrome (PNS) patients and the presumed autoimmune etiology have led to several open-label prospective trials of various immunotherapies [5,6]. In these studies, the outcome is usually defined by changes in the modified Rankin Scale (mRS) score and disorder-specific rating scales assessing neurological symptoms. At present, no objective measures of disease activity are available.

In Hu-PNS, the brainstem and cerebellum are often affected [7]. In addition, the Hu antigen is expressed ubiquitously throughout the brain, increasing the likelihood of eye-movement disturbances in Hu-PNS [8,9]. Therefore, we previously assessed motor disturbances in 11 Hu-PNS patients using video-oculography. In eight of 11 patients, prominent saccadic changes were demonstrated, whereas only five of these patients had clinical cerebellar signs [10]. Here, we expand upon these data by including more patients and by analyzing vertical eye movements. Finally, we studied in a subset of patients whether longitudinal data by including more patients and by analyzing vertical eye movements. Finally, we studied in a subset of patients whether longitudinal measurements of eye movements are correlated with clinical outcome.

METHODS

Subjects

In total, 29 patients (12 males; 17 females; mean age, 63.2 years; range, 46–77 years) with Hu-PNS were included (Table 1). Part of the data of 11 of these 29 patients has been described previously [10]. All patients participated in prospective, phase II, open-label clinical trials evaluating the beneficial effect of immunomodulatory agents (human chorionic gonadotropin and sirolimus) in the treatment of PNS [5,11]. Two patients experienced blurred vision, probably caused by unilateral or bilateral tonic pupil(s), and in one patient, monoculocerous vision was decreased due to optic neuritis. Eye movements of 20 patients were measured during subsequent hospital visits with 4-week intervals. These patients were included in the second analysis studying change over time and correlation with clinical disease course (Table 2). Thirteen of these 20 patients received concurrent chemotherapy.

Fourteen age- and gender-matched healthy controls without neurological history and with (i.e., corrected to) normal vision participated in this study. The study was approved by the institutional review board of the Erasmus University Medical Center. Informed consent was obtained from all patients.

Eye-movement measurements

Eye movements were recorded as described previously [10]. Participants were placed 50 cm from a monitor, and visual stimuli were generated using MATLAB (MathWorks, Natick, MA, USA). Eye movements were recorded using 50-Hz video-oculography (ViewPoint Eye Tracker; Arrington Research, Scottsdale, AZ, USA and EasyGaze EyeTracker; Design Interactive, Orlando, FL, USA). Data were pooled because analysis showed no effect of apparatus on outcome. Twelve different types of eye-movement measurements were performed for saccades and smooth pursuit three amplitudes/speeds, both horizontal and vertical. Analyses were done automatically by custom-written software in MATLAB and inspected manually. Numbers of saccadic intrusions determined the smooth pursuit quality [12]; for saccades, the number of correctional saccades and saccades during fixational periods were determined. Statistical analyses were performed using repeated-measurement analysis of variance.

Eye movements were rated independently by two experts (M.F. and J.v.d.G.), who were blind to patient details and functional outcome. All 12 eye movements were scored between 0 and 4. The concordance in rating between the two experts was high (Spearman ρ, 0.76). For each examination, an overall eye-movement score (EMS) was calculated. The EMS consisted of the average rating of all 24 eye-movement recordings (12 ratings per expert). EMS was considered impaired when <3.5, because this results in impairment of at least half of the eye movements judged by both experts. Improvement or deterioration in EMS was determined (ΔEMS) by comparing the first and last EMS score.

Disease course was determined using changes in the mRS score [13], rated by another expert (P.S.S.), who was unaware of the eye-movement results. Successful outcome was defined as mRS score ≤3 remaining stable or improving or when the mRS score ≥4 improved. Correlations between mRS score and EMS were assessed by Spearman rank correlation and Fisher exact test. All statistical analyses were performed in SPSS (version 20), and significance levels were set at 5%.

Data availability

The raw data are available from the corresponding author upon reasonable request.

RESULTS

We compared the baseline eye movements in 29 patients with 14 healthy controls. Typical eye movements have been published previously [10].

Smooth pursuit

Horizontal pursuit yielded more saccadic intrusions than vertical ones (p = 0.04). In both horizontal and vertical pursuit, patients had significantly more intrusions per movement cycle than healthy
### TABLE 1  Patient characteristics at baseline, treatment, and initial eye-movement scores

| No. | Sex | Age, years | Syndrome | Presenting symptoms | CNS | Cerebellum | Clinical eye-movement symptoms, type (severity) | Eye-movement score, start | Treatment | Time from symptoms to diagnosis, weeks | Tumor type | Tumor treatment | Tumor response | mRS, start |
|-----|-----|------------|----------|--------------------|-----|------------|---------------------------------------------|-----------------|-----------|------------------------------------------|------------|----------------|----------------|-----------|
| 1   | M   | 61         | PCD      | x                  | x   | x          | Saccadic pursuit, nystagmus (1)             | 2.31            | HCG       | 4                                        | SCLC       | Chemo/RT      | PD             | 2         |
| 2   | F   | 51         | PEM      | x                  |     |            |                                               | 1.18            | HCG       | 31                                       | SCLC       | Chemo/RT      | CR             | 3         |
| 3   | F   | 68         | PSN      |                   |     |            |                                               | 2.96            | HCG       | 2                                        | SCLC       | Chemo/RT      | CR             | 2         |
| 4   | M   | 66         | PSN      | x                  |     |            |                                               | 2.67            | HCG       | 2                                        | NSCLC      | Chemo          | CR             | 3         |
| 5   | M   | 75         | PSN      | x                  |     |            | Nystagmus (2)                                | 2.04            | HCG       | 2                                        | SCLC       | Chemo/RT      | CR             | 4         |
| 6   | M   | 61         | PSN      |                   |     |            |                                               | 3.88            | HCG       | 2                                        | SCLC       | Chemo/RT      | CR             | 3         |
| 7   | F   | 66         | PSN      |                   |     |            |                                               | 2.92            | HCG       | 11                                       | NSCLC      | Chemo/RT      | CR             | 2         |
| 8   | M   | 64         | PSN      |                   |     |            |                                               | 2.61            | HCG       | 16                                       | Prostate   | Chemo          | PR             | 3         |
| 9   | F   | 53         | PSN      |                   |     |            |                                               | 2.96            | HCG       | 3                                        | SCLC       | Chemo/RT      | CR             | 2         |
| 10  | F   | 70         | PSN      |                   |     |            |                                               | 2.46            | HCG       | 1                                        | SCLC       | Chemo          | CR             | 3         |
| 11  | F   | 55         | PSN + ON | x                  |     |            |                                               | 2.85            | HCG       | 7                                        | SCLC       | Chemo/RT      | CR             | 3         |
| 12  | F   | 66         | PLE      | x                  |     |            |                                               | 1.80            | Sirolimus | 7                                        | Lung a     | No            | NA             | 3         |
| 13  | F   | 77         | PSN      |                   |     |            |                                               | 1.75            | Sirolimus | 5                                        | No b       | NA            | NA             | 4         |
| 14  | M   | 64         | PLE      | x                  | x   |            |                                               | 2.19            | Sirolimus | 0                                        | SCLC       | Chemo/RT      | PR             | 3         |
| 15  | F   | 64         | PSN      |                   |     |            |                                               | 3.50            | Sirolimus | 0                                        | SCLC       | Chemo/RT      | CR             | 4         |
| 16  | F   | 51         | PSN      |                   |     |            |                                               | 2.81            | Sirolimus | 1                                        | SCLC       | Chemo          | CR             | 5         |
| 17  | F   | 59         | MN       |                   |     |            |                                               | 3.04            | Sirolimus | 2                                        | SCLC       | Chemo/RT      | CR             | 3         |
| 18  | F   | 52         | PSN      |                   |     |            |                                               | 3.19            | Sirolimus | 11                                       | SCLC       | Chemo/RT      | CR             | 2         |
| 19  | M   | 66         | PCD      | x                  | x   |            | Nystagmus (1)                                | 2.25            | Sirolimus | 5                                        | Lung a     | No            | NA             | 4         |
| 20  | F   | 65         | PSN/PNP  |                   |     |            |                                               | 1.92            | Sirolimus | 4                                        | Chondrosarcoma | NA         | NA             | 4         |
| 21  | F   | 61         | MN       | x                  |     |            | Saccadic pursuit (1)                          | 1.94            | HCG       | 0                                        | SCLC       | Chemo          | PR             | 5         |
| 22  | M   | 75         | PCD      | x                  | x   |            | Saccadic pursuit, nystagmus, poor fixation (3)| 1.85            | HCG       | 7                                        | Lung a     | No            | No             | 5         |
| 23  | M   | 66         | PCD      | x                  | x   |            | Saccadic pursuit (1)                          | 1.85            | HCG       | 3                                        | SCLC       | No            | No             | 3         |
| 24  | F   | 69         | PEM      | x                  |     |            |                                               | 3.50            | HCG       | 5                                        | SCLC       | Chemo          | PR             | 3         |
| 25  | M   | 67         | BE       | x                  | x   |            | Bilateral INO (3)                             | 3.38            | Sirolimus | 9                                        | SCC parotid | Chemo/RT      | PD             | 2         |
| 26  | M   | 60         | PCD      | x                  | x   |            |                                               | 3.08            | Sirolimus | 4                                        | No a       | No            | No             | 3         |
| 27  | F   | 46         | PEM/PSN  | x                  |     |            | Nystagmus (1)                                | 2.19            | Sirolimus | 1                                        | Lung a     | No            | No             | 3         |
| 28  | M   | 62         | PSN      |                   |     |            |                                               | 2.85            | Sirolimus | 2                                        | SCLC       | Chemo/RT      | CR             | 3         |

(Continues)
controls (8.03 ± 0.48 vs. 4.01 ± 0.72, p < 0.00 for horizontal and 6.54 ± 0.39 vs. 2.91 ± 0.56, p < 0.00 for vertical, respectively). Only in horizontal pursuit, an effect of target velocity was observed for all subjects combined, with slower moving targets resulting in more intrusions: 6.90 ± 0.67 for 10°, 5.85 ± 0.48 for 15°, and 5.31 ± 0.38 for 20° (p = 0.01).

**Saccades**

In all subjects, horizontal saccades yielded more correctional saccades compared to vertical ones (0.54 ± 0.04 vs. 0.47 ± 0.03; p = 0.03, respectively). In both directions, patients needed more corrections than healthy controls (0.63 ± 0.04 vs. 0.47 ± 0.06, p = 0.04 for horizontal and 0.60 ± 0.05 vs. 0.36 ± 0.06 for vertical saccades, p < 0.00, respectively). Patients made more saccades during fixation periods than healthy controls for both horizontal (p = 0.01) and vertical (p = 0.00) directions.

**Eye-movement deficits in relation with clinical presentation**

The clinical findings at presentation and EMSs are presented in Table 1. Eight patients had clinical eye-movement symptoms, all accompanied by abnormal EMSs. In these patients, the mean EMS was significantly lower than in the other 21 patients (2.12 ± 0.04 vs. 2.85 ± 0.06, p = 0.04, respectively). The EMS was abnormal in 26 of the 29 patients (90%). Fifteen patients had signs or symptoms indicating central nervous system (CNS) involvement, including cerebellar symptoms in seven. Of these 15 patients with clinical CNS involvement, all but one had impaired EMSs. All seven patients with cerebellar signs had impairment of eye movements. Intriguingly, eye-movement control was also affected in 12 of the 14 patients without clinical CNS involvement. Of these 12 patients, 11 had paraneoplastic sensory neuronopathy (PSN), and one had motor neuropathy.

Two of the three patients with a normal EMS had PSN without any clinical CNS signs or symptoms, whereas the other one suffered paraneoplastic encephalomyelitis (PEM). The patient with PEM had sensory neuropathy and limbic encephalitis presenting with seizures, diminished attention, and short-term memory loss.

**Correlation of evolution of eye-movement score with functional outcome**

For the 20 patients who were measured multiple times, ΔEMS and functional outcome were determined (Table 2). The functional outcome was successful in nine and unsuccessful in 11 patients. Of the nine patients with successful outcome, three showed an overall improvement of their EMS, whereas six were stable, and none
## Table 2: Evolution of eye-movement score and functional outcome

| No. | Sex | Age, years | Syndrome | Concurrent chemotherapy | Treatment | Follow-up period, weeks | Eye-movement score<sup>a</sup> | Functional outcome, mRS<sup>b</sup> |
|-----|-----|------------|----------|-------------------------|-----------|-------------------------|-----------------------------|----------------------------------|
|     |     |            |          |                         |           |                         | Start | Change       | Evolvement       | Start | Final | Successful? |
| 1   | M   | 61         | PCD      |                         | HCG       | 12                      | 2.31  | 0.53         | Improved        | 2     | 3     | No          |
| 2   | F   | 51         | PEM      |                         | HCG       | 12                      | 1.18  | 0.36         | Stable          | 3     | 2     | Yes         |
| 3   | F   | 68         | PSN      | x                       | HCG       | 8                       | 2.96  | 0.04         | Stable          | 2     | 3     | No          |
| 4   | M   | 66         | PSN      | x                       | HCG       | 8                       | 2.67  | −0.09        | Stable          | 3     | 3     | Yes         |
| 5   | M   | 75         | PSN      | x                       | HCG       | 12                      | 2.04  | 0.67         | Improved        | 4     | 3     | Yes         |
| 6   | M   | 61         | PSN      | x                       | HCG       | 12                      | 2.92  | 0.29         | Stable          | 2     | 2     | Yes         |
| 7   | F   | 66         | PSN      | x                       | HCG       | 12                      | 2.96  | 0.37         | Stable          | 2     | 3     | No          |
| 8   | M   | 64         | PSN      | x                       | HCG       | 12                      | 3.88  | −1.09        | Declined        | 3     | 4     | No          |
| 9   | F   | 70         | PSN      | x                       | HCG       | 8                       | 2.92  | −0.27        | Stable          | 3     | 4     | No          |
| 10  | F   | 55         | PSN/ON   | x                       | HCG       | 12                      | 2.85  | 0.20         | Stable          | 3     | 3     | Yes         |
| 11  | F   | 66         | PLE      |                          | Sirolimus | 4                       | 1.80  | 0.35         | Stable          | 3     | 3     | Yes         |
| 12  | F   | 77         | PSN      |                          | Sirolimus | 8                       | 1.75  | −0.60        | Declined        | 4     | 4     | No          |
| 13  | F   | 66         | PLE      | x                       | Sirolimus | 8                       | 2.19  | 0.62         | Improved        | 3     | 1     | Yes         |
| 14  | M   | 64         | PSN      |                          | Sirolimus | 8                       | 3.50  | −0.92        | Declined        | 4     | 4     | No          |
| 15  | F   | 64         | PSN      |                          | Sirolimus | 8                       | 2.81  | −0.54        | Declined        | 5     | 5     | No          |
| 16  | F   | 59         | MN       | x                       | Sirolimus | 4                       | 3.04  | −0.69        | Declined        | 3     | 4     | No          |
| 17  | F   | 52         | PSN      | x                       | Sirolimus | 12                      | 3.19  | −0.04        | Stable          | 2     | 2     | Yes         |
| 18  | F   | 51         | PSN      | x                       | Sirolimus | 8                       | 2.25  | −0.17        | Stable          | 4     | 5     | No          |
| 19  | M   | 66         | PCD      |                          | Sirolimus | 8                       | 1.92  | 0.27         | Stable          | 4     | 4     | No          |
| 20  | F   | 65         | PSN/PNP  |                          | Sirolimus | 8                       | 1.92  | 0.27         | Stable          | 4     | 4     | No          |

Abbreviations: F, female; HCG, human chorionic gonadotropin; M, male; MN, motor neuropathy; ON, optic neuritis; PCD, paraneoplastic cerebellar degeneration; PEM, paraneoplastic encephalomyelitis; PLE, paraneoplastic limbic encephalitis; PNP, paraneoplastic polyneuropathy; PSN, paraneoplastic sensory neuronopathy.

<sup>a</sup>Eye-movement score was considered stable when the absolute difference between the first and final measurement was <0.5.

<sup>b</sup>The functional outcome was considered successful when the mRS score ≤3 remained stable or improved and when mRS score ≥4 improved.
declined. In the 11 patients with unsuccessful clinical outcome, we observed declined EMS in six, stable EMS in four, and improved EMS in one.

The correlation between EMS evolvement and functional outcome was significant ($\rho = 0.52, p = 0.02$). Most patients with improving EMS had a successful functional outcome (75%).

DISCUSSION

This study shows that eye-movement control is disturbed in most patients with Hu-PNS. The observed disturbances are present in smooth pursuit and in saccades in both horizontal and vertical directions, indicating the necessity to measure all four movement types.

Given the central origin of the eye-movement disturbances studied here [12], it is remarkable that 12 of the 14 patients with a clinically purely peripheral presentation had impaired eye-movement recordings at baseline. These findings indicate that eye-movement recordings can detect subclinical involvement of the CNS in Hu-PNS.

Due to the expression of Hu antigens in all neurons, all areas of the central and peripheral nervous system can be affected in Hu-PNS [14,15]. Autopsy studies showed T-cell infiltrates with associated neuronal loss [16–18]. Although the location and severity of the neuronal loss correlates with the clinical syndrome, the pathological changes are much more extensive than expected based on the patient’s clinical symptoms [7,17]. Our findings confirm the more widespread distribution of abnormalities than clinically predicted in Hu-PNS.

We observed a correlation between disease course and changes in EMS. Therefore, eye-movement recordings offer the possibility to objectively measure disease development in patients with Hu-PNS. These recordings could be used to evaluate and optimize treatment.

Our study has several limitations. We did not study disconjugate eye movements (eg, convergence, divergence). The wide range of clinical presentations in our small cohort hampered detailed analysis of associations of specific signs and symptoms with affected eye movements. Finally, this study consisted only of patients with Hu antibodies.

We conclude that deficits in eye-movement control are commonly found in Hu-PNS patients, even in those who do not present clinically with symptoms or signs of CNS deficits. Given the moderate correlation between changes in eye-movement control and disease course, eye-movement recordings may provide an objective tool to aid in monitoring treatment responses in Hu-PNS patients.

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CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Concept and design: P.S.S., M.F., and J.v.d.G. Acquisition, analysis, or interpretation of data: M.J., F.v.B., P.S.S., M.F., J.v.d.G. Drafting of the manuscript: M.J., P.S.S., J.v.d.G. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: M.J., J.v.d.G. Obtained funding: not applicable. Supervision: M.F., J.v.d.G., P.S.S. M.F. and J.v.d.G. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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