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► To cite this version:

Ailsa E Ritchie, Philip Griffiths, Patrick F Chinnery, Adrian W Davidson. Eye movement recordings to investigate a supranuclear component in CPEO: a cross sectional study. *British Journal of Ophthalmology*, 2010, 94 (9), pp.1165. 10.1136/bjo.2009.165639 . hal-00557328

HAL Id: hal-00557328

<https://hal.science/hal-00557328>

Submitted on 19 Jan 2011

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Eye movement recordings to investigate a supranuclear component in CPEO: a cross sectional study

Ailsa E Ritchie*, Philip G Griffiths+, Patrick F Chinnery% Adrian W Davidson^

^ corresponding author

Regional Medical Physics Department, Royal Victoria Infirmary, Queen Victoria Road
Newcastle upon Tyne, NE1 4LP

Adrian.davidson@nuth.nhs.uk

Tel 0191 2824954

Fax 0191 2820887

*Centre for Professional Postgraduate education, St Thomas' Hospital, Westminster
Bridge Road, London SE1 7EH

+ Department of Ophthalmology Royal Victoria Infirmary
Queen Victoria Road, Newcastle upon Tyne. NE1 4LP.

% Mitochondrial Research Group, Institute of Ageing and Health, Newcastle University,
NE2 4HH, UK

Key words

Vestibuloocular reflex

Chronic progressive external ophthalmoplegia

Supranuclear

Number of words 2147

ABSTRACT

Background: It has been postulated that eye movement disorders in CPEO have a neurological as well as a myopathic component to them.

Aim: To investigate whether there is a supranuclear component to eye movement disorders in CPEO using eye movement recordings.

Methods: We measured saccade and smooth pursuit characteristics together with vestibulo-ocular reflex (VOR) gain and VOR suppression (VORS) gain in 18 patients with CPEO and 34 normals using Eyelink II video-oculography.

Results: The asymptotic values of the peak velocity main sequence curves were reduced in the CPEO group compared to normals, with a mean of 161 deg/sec (95% CI 126-197 deg/sec) compared to 453 deg/sec (95% CI 430-475 deg/sec) respectively. Saccadic latency was longer in CPEO (263ms; CI 250-278), compared to controls (185ms; CI 181-189). Smooth pursuit and VOR gains were impaired in CPEO although this could be explained by non-supranuclear causes. VORS gain was identical in the two groups.

Conclusions: This study does not support a supranuclear component to the ophthalmoplegia of CPEO, although the increased latencies observed may warrant further investigation.

INTRODUCTION

Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial disorder characterised by progressive restriction of eye movements, ptosis and orbicularis weakness. Although myopathy accounts for a major part of the restriction of eye movements seen in CPEO some authors have suggested that there may be a supranuclear component to the ophthalmoplegia.[1] The distinction between myopathic and supranuclear components is not purely academic because the success of strategies to regenerate normal extraocular muscle, by stimulating endogenous satellite cells,[2] or by using embryonic stem cells, is dependent on CPEO being primarily a myopathy.

Suppression of the vestibulo-ocular reflex (VORS) measures central aspects of eye movement control since if VOR suppression is complete no actual eye movement has to be generated, thus isolating out the myopathic component of the eye movement problem. Impaired suppression of VOR has been cited as evidence of supranuclear involvement in myotonic dystrophy.[3, 4]

METHODS

Ethical approval was gained from the local research ethics committee before starting the study. Patients were recruited into the study if they had a slowly progressive ophthalmoplegia, cytochrome c oxidase negative fibres on muscle biopsy and had given written, informed consent.

Eye movement recordings

Eye movements were recorded using an EyelinkII video-oculography system (SR Research, Canada) at 500 samples per second. Calibration, saccadic and smooth pursuit stimuli were produced at a distance of approximately 1100mm from the subject. The distance was measured and stimulus angle calculated individually for each subject.

All tests were done with the subject seated in a MiniTorque Barany chair (Difra, Belgium). A chinrest was mounted on the chair, which substantially reduced but did not completely eliminate head movements. Eyelink long-range infra-red markers for head movement compensation were mounted on the fixation board and used during the Eyelink internal calibration. Eyelink head referenced data was used in the analysis and the head movement markers were turned off during VOR testing. Saccades and smooth pursuit were recorded in low level lighting, and VOR was measured in total darkness.

Eyelink calibration was done at an angle suitable for the range of movements of the subjects' eyes. This ranged between +/- 7 degrees and +/-26 degrees horizontally and +/- 5 and +/-20 degrees vertically, using a 5 point calibration. Some subjects had ptosis, in which case the eyelids were taped up. Where the ptosis still interfered with calibration a horizontal 3 point calibration was employed. The best possible Eyelink calibration was obtained, but in addition, up to 9 horizontal fixations were used to derive a third order polynomial which was retrospectively used as a secondary calibration and applied to the horizontal signals. Where the subject had limited eye movements, only those fixations within the range of valid movements were used for secondary calibration. Subjects with tropias were calibrated monocularly. Ideally, all subjects should have been calibrated monocularly. Calibration was difficult for some subjects in the CPEO group.

Saccades

Saccades were measured using an LED board. A zero-gap paradigm was used with stimulus amplitude up to a maximum of 26 deg left or right. Direction and timing were randomized. Leftward and rightward primary centrifugal saccades were used in the analysis. The start and end of saccades was defined at the points where velocity dropped below 20 deg/s. We excluded saccades contaminated by blinks, artefacts or with a latency less than 100ms.

Smooth pursuit

Smooth pursuit was generated with a laser spot projected via a galvanometer mirror, with a sinusoidal profile of +/- 10 degrees at 0.4, 0.6 and 0.8 Hz (peak velocities of 25, 38 and 50 deg/s), the amplitude being chosen with the expectation that most CPEO patients would have that degree of eye movement.

VOR and VOR suppression

VOR was generated using the Barany chair, using sinusoidal stimulation of +/-80 deg at 0.1 and 0.2Hz (peak velocities of 50 and 100 deg/s). Subjects were asked to imagine viewing a distant object and to perform mental arithmetic to maintain alertness. The VOR suppression stimulus was an LED mounted on a moveable stalk, positioned in front of the subject at a distance of approximately 50 to 60cm, depending on the size of the subject.

Statistical analysis

For each subject, only the “best eye” data was used, and this was determined from consideration of the Eyelink calibration reports and subjective examination of the quality of the signals.

Peak saccadic velocity main sequence curves were derived for each subject by fitting data to an equation of the form

$$PV = PV_{max} * (1 - e^{-A/c})$$

where PV_{max} is the asymptotic value of the curve, A is the amplitude of the saccade, and C is a constant relating to the slope. The mean and 95% confidence interval (CI) of the mean were then derived for PV_{max} .

Saccade latencies from all studies were pooled for the control and CPEO groups. Only the first 13 primary saccades for each study were used, to ensure that the mean was not biased due to uneven numbers of saccades per study. Because the distribution of latencies was skewed, the reciprocal of the latencies were taken, mean and CI were calculated, and the values transformed back.[5]

We hypothesised that VORS gain may be related to VOR gain such that subjects with a lower VOR gain would find it easier to suppress their VOR, and therefore would be more likely to have a lower VORS gain. We plotted VORS gain against VOR gain, to see if there was any relationship.

If the VOR was perfect, that is, the countermovement of the eyes perfectly matched the rotation of the chair we would expect a VOR gain of one. If VORS was perfect we would expect a gain during chair rotation, while fixating the suppression LED, of zero.

RESULTS

18 patients with CPEO were tested (median age 59 years). All patients had cytochrome c oxidase negative fibres in skeletal muscle biopsies and slowly progressive ophthalmoplegia. 7 patients had multiple deletions, 7 had single deletions, 2 had point mutations and in 2 cases no mutation could be identified. We could not reliably perform all of the measurements on all of these patients, and therefore the numbers for the different measurements differ slightly. Thirty four control patients were tested (median age 36 years).

Saccades

As expected, peak saccadic velocity was slow in CPEO in comparison with controls. Figure 1 shows the peak velocity for each saccade plotted against its amplitude (the peak velocity main sequence). The mean asymptotic peak velocity (PV_{max}) was 453 deg/s for controls (CI 430-475) and 161 deg/s for CPEO (CI 126-197).

For analysis of latency we used the same number of saccades from each subject in order to avoid biasing the results. Studies with a minimum of 13 primary centrifugal saccades

suitable for measuring latency were used and the results are shown in figure 2.

Mean saccadic latency in CPEO (263ms, CI 250-278) was increased in relation to controls (185, CI 181-189), although many saccades made by patients with CPEO had short latency times which overlapped with those of the control group.

Smooth pursuit

Participants who were unable to maintain smooth pursuit at all frequencies were excluded. Some controls had measurements made at different frequencies during the early stages of data collection and their data is excluded from the statistical calculations, however, the measurements at these frequencies are plotted on Figure 3. There was some impairment of smooth pursuit in patients with CPEO compared to normal controls at all frequencies. At 0.4Hz mean gain for controls was 0.89 (0.85-0.92) compared to 0.71 (0.59-0.83) in the CPEO group. At 0.6Hz the means were 0.80 (0.72-0.89) in controls and 0.53 (0.39-0.66) for CPEO. Finally, at 0.8Hz the control group mean was 0.65 (0.54-0.77) compared to 0.37 (0.25-0.49) in CPEO.

VOR and VORS

VOR gain was lower in the CPEO group than in controls. At 0.1Hz, mean VOR gain was 0.65 (0.58-0.72) in the control group and 0.48 (0.39-0.57) in the CPEO group. At 0.2Hz, mean VOR gain was 0.61 (0.55-0.67) in controls and 0.34 (0.25-0.44) in the CPEO group. Means and 95% confidence intervals were almost identical for VORS gains. At 0.1Hz both groups had a mean of 0.06, but the CPEO group had a slightly larger confidence interval of 0.05-0.08 compared to 0.05-0.07 for controls. At 0.2Hz both means were 0.09, with a control CI of 0.07-0.12 and a CPEO CI of 0.07-0.11. Figure 4 shows that there is no relationship between VOR gain and VORS gain.

DISCUSSION

Interpretation of results should always take account of the limitations of the measurements. In our case this mainly concerns the inherent inaccuracy of subject fixation, small head movements, and potential errors in calibration. These will introduce some variability into the measurements.

There is no doubt that there is a major myopathic component to CPEO. Evidence for this includes loss of muscle bulk on MRI scans,[6] findings on muscle biopsy [7] and the appearance of muscles at surgery. It has been proposed that eye muscles are uniquely vulnerable in mitochondrial myopathies because of their functional and ultrastructural properties.[8] However, these findings do not preclude an underlying supranuclear component. Some previous studies point in this direction. There have been isolated case reports of patients with a greater range of eye movements to oculocephalic testing than ductions.[1] Magnetic resonance imaging has shown abnormal metabolic profiles of the brain in patients with mitochondrial myopathies including CPEO [9] and brain stem reflexes have been found to be abnormal in patients with mitochondrial myopathies.[10] The observed reduced saccadic velocities in CPEO are well documented [11] and most likely muscular in origin. Increased latency might be taken as evidence of supranuclear pathway dysfunction, so that it takes longer to generate the pulse required to move the

eyes. Latency is easier to measure reliably in CPEO subjects than other parameters, since it is less influenced by calibration errors and ptosis. However, we hesitate to argue for abnormal supranuclear function from this data alone, since other factors may be involved. One factor is the difference in age distribution of the two groups, although this is unlikely to account for all the difference. Irving et al [12] found that subjects below the age of 50 had mean latencies of around 195ms, and this rose in each decade to around 265ms in those 80 or older. Using the mean values from their chart, we estimated the effect on our group means that each subject would have made due to the age difference with a nominal reference age. Depending on the reference age, we could account for 25 to 30ms of the observed 78ms difference in means between the groups.

VOR is responsible for maintaining images steady upon the retina while the head moves. It is a brain stem reflex mediated by the vestibular apparatus, vestibular nuclei and oculomotor nuclei. The maintenance of steady gaze while reading in a moving vehicle, for example, requires the ability to suppress the VOR. VORS is mediated by the pursuit pathway [13,14] and the cerebellum.[15] In the ophthalmoplegia of myotonic dystrophy, parallel impairment of SP and VORS has been taken as evidence of a supranuclear component to the ophthalmoplegia.[3, 4] We found impairment of SP (although there is large variability and considerable overlap with controls) and VOR, but no impairment of VORS. If the impaired VOR is due to peripheral ocular muscle weakness, then there would likely have been adaptive changes in the internal VOR gain, which nevertheless may have been insufficient to overcome the peripheral muscle weakness. The closed loop nature of the SP control system, along with parallel adaptation in the SP system, [16,17] may enable continued suppression of the VOR. However, as with the VOR, this may still be insufficient to overcome the peripheral weakness, so that SP is still impaired. This would explain our observations of impaired VOR and SP, but preserved VORS. This suggests a peripheral rather than central pathology

CONCLUSION

While the observed increase in latency is consistent with a possible supranuclear component, there are other potential contributing factors. Although we found that the VOR gain was reduced in CPEO, VORS gain and confidence intervals were almost identical in the two groups. Since VORS is mediated by the pursuit pathway this supports our view that the reduction in smooth pursuit gain in CPEO is not supranuclear in origin. We did not observe any relationship between VORS gain and VOR gain. We considered VORS to be the more robust indicator in subjects with ophthalmoplegia and it therefore seems unlikely from our data that supranuclear dysfunction is the primary event in CPEO. However, the increased latency observed may warrant further investigation.

Because of the small numbers it not possible to make distinctions between CPEO due to single or multiple deletions.

Acknowledgements

PFC is a Wellcome Trust Senior Fellow in Clinical Science who also receives funding from the Medical Research Council (UK), the UK Parkinson's Disease Society, and the

UK NIHR Biomedical Research Centre for Ageing and Age-related disease award to the Newcastle upon Tyne Foundation Hospitals NHS Trust.

Competing interests: None declared

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Figure Legends

Figure 1: Peak saccadic velocity of primary centrifugal saccades in controls (crosses, n=34) and CPEO patients (circles, n=18)

Figure 2: Saccade latencies in controls (crosses, n=34) and CPEO patients (circles, n=16)

Figure 3: Sinusoidal smooth pursuit gain at +/- 10 degrees amplitude and 0.4, 0.6 and 0.8Hz. Means and 95% confidence interval for the means are also shown. Control data represented by crosses, CPEO by circles. Offsets were used when plotting for clarity.

Figure 4: VORS gain vs VOR gain at 0.1Hz (a) and 0.2Hz (b). Controls represented by crosses and CPEO by circles.

Fig 1

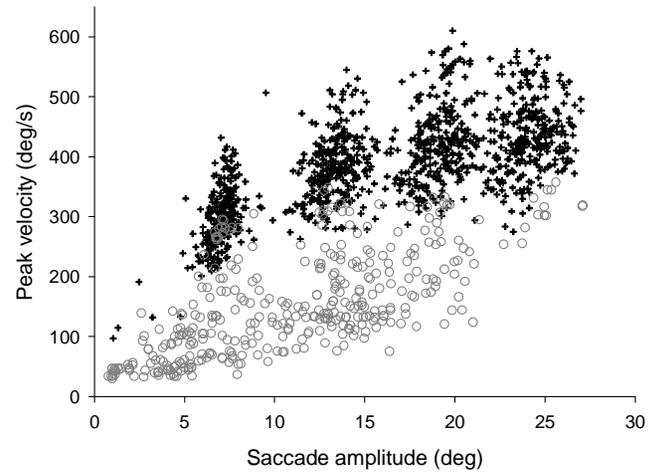


Fig 2

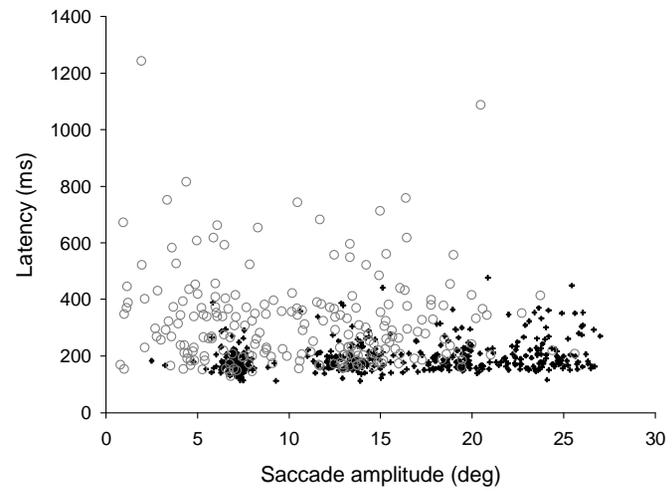


Fig 3

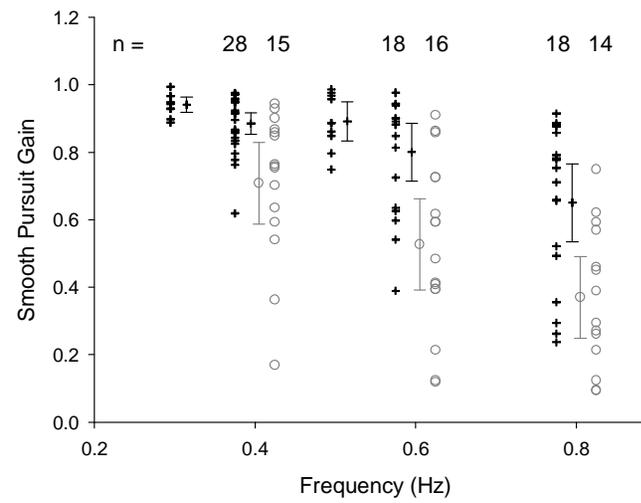


Fig 4a

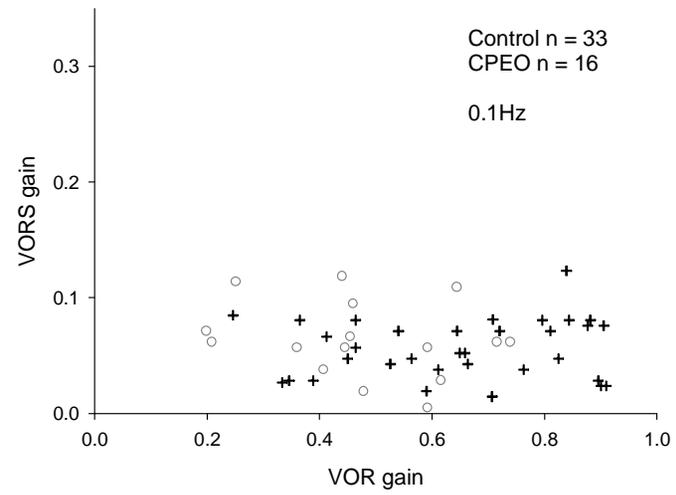


Fig 4b

