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SHORT REPORT

Neuropsychological and quantitative oculometric study of a case of sporadic Creutzfeldt–Jakob disease at predementia stage

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A quantitative assessment of eye movements and a detailed neuropsychological profile were conducted at predementia stage in a patient who later had histological confirmation of sporadic Creutzfeldt–Jakob disease (CJD). The patient was a middle aged man who presented with abnormal eye movements and poor balance. Neuropsychological deficits suggested orbito-mesial dysfunction, resembling progressive supranuclear palsy. Oculometry showed accurate but dramatically slowed saccades, with normal pursuit movements. Neuropsychology and quantitative oculometry may be of value in the differential diagnosis and earlier detection of dementia-akinetic-rigid syndromes; in particular, because of the highly stereotyped nature of saccades, routine quantitative oculometry can reveal significant impairment at a very early stage in some cases and could thus facilitate earlier diagnosis.

Creutzfeldt–Jakob Disease (CJD) is a fatal prion disease characterised by spongiform changes in brain tissue, neural loss and astrocytic reactions,¹ and a rapidly progressive dementia. To our knowledge this report is the first quantitative oculometric study of a patient with CJD at predementia stage. Abnormal eye movements are rarely the main presenting complaint in prion diseases; they are usually found at the later stages, when dementia and other neurological signs are evident,² and secondary to cerebellar³ and vestibular⁴ involvement. The pattern of dementia in CJD has not been extensively studied, largely because of practical difficulties in performing neuropsychological assessments on mentally debilitated patients. Early symptoms—such as deficits in concentration, memory, and problem solving, apathy, labile emotions, asthenia, altered sleep patterns and appetite, weight loss, and loss of libido—are non-specific and can be readily attributed to depression, for which extensive neuropsychological assessment is rarely indicated. In the present study both quantitative oculometry and neuropsychological assessment were carried out before the emergence of cognitive symptoms, shedding light on early patterns of impairment in CJD and raising the hope of earlier diagnosis. As well as obvious implications in terms of planning care and handling bodily fluids, specimens and tissues, there is potential therapeutic benefit, as emerging neuroprotective drugs for slowing neurodegeneration require an early diagnosis for early treatment to be instituted.

CASE REPORT

A 55 year old non-smoking man, a previously healthy company manager, presented with progressive difficulty in maintaining balance and tracking moving objects, and diplopia for distant targets. There were no sensory, motor, or cogni-

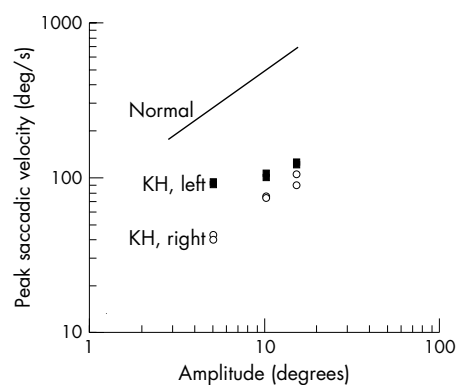


Figure 1 Peak saccadic velocity as a function of amplitude, for movements in the two directions. The line shows a typical normal human velocity-amplitude relation.⁷

tive symptoms. Physical examination on admission was unremarkable and the Addenbrooke's cognitive examination score⁵ was normal (97/100), with no frontal lobe release or cortical signs. He had facial hypomimia with mild rigidity in the right upper limb, and was also bilaterally ataxic with dysdiadokokinesia: his gait was unsteady with poor postural reflexes. Saccades appeared sluggish while ocular pursuit and oculo-cephalic reflexes were intact. Haematological, biochemical, and immunological tests—including paraneoplastic markers, serum caeruloplasmin, autoimmune profile, serology for Whipple's disease, and routine cerebrospinal fluid (CSF) examination—were all normal, as was neuroimaging (magnetic resonance imaging and single photon emission computed tomography).

In view of the unusual eye movements, the oculomotor system was examined quantitatively within days of presentation, using an infrared oculometer,⁶ with the head immobilised on a bite bar and appropriate visual stimuli presented at a distance of 57 cm. Visually evoked saccades and OKN quick phases were dramatically slowed to around 12% of typical normal values. Leftward saccades were significantly faster than rightward ($p < 0.02$), and their latencies were higher but not abnormal (mean (SEM): 231 (6) v 181 (14) ms; $p < 0.01$). The relation between peak saccadic velocity and amplitude (fig 1) was similar to that of a normal subject, albeit with much lower velocity values. Neither smooth pursuit nor slow phases of optokinetic nystagmus were affected, and there was no obvious abnormality of the accuracy of saccades in either direction.

To assess any subclinical cognitive impairment, we carried out an extensive neuropsychological assessment of memory, attention, language, visuo-perceptual function, and executive ability (table 1). General intellectual function, attention, naming, visual perception, and recall of stories and designs were all

Table 1 Results of neuropsychological examination

Test	Age scaled scores	Age matched control scores or patient's centile
<i>General intellectual function (WAIS-R)</i>		
Picture completion	13	
Digit span	12	
Block design	14	
Arithmetic	11	
Similarities	13	
*Digit symbol substitution	9	
<i>Memory</i>		
Logical memory (WMS-R)		
Immediate	26	(67th centile)
Delayed	24	(79th centile)
Visual reproduction (WMS-R)		
Immediate	40	(99th centile)
Delayed	30	(74th centile)
Rey auditory verbal learning test		
Total 5 trials	38	47.6 (8.5)
*Recall list A	8	9.6 (2.9)
*20 Min delayed recall list A	6	10 (2.6)
<i>Executive function</i>		
*Trail making test		
Part A	60 s	(10th to 25th centile)
Part B	115 s	(25th to 50th centile)
*Letter fluency (FAS)	31	(19th centile)
*Wisconsin card sorting test (WCST)	3 categories	5.6 (1.1)
<i>Language</i>		
Graded naming test	22	(50th centile)

Control values are mean (SD).

*Tests on which performance was considered abnormal. Published norms used for comparisons.

WAIS-R, Wechsler adult intelligence scale-revised; WMS-R, Wechsler memory scale-revised.

intact, but retrieval of unstructured verbal information was impaired in comparison with recognition memory, with deficits on several specific tests of executive ability, including completion of only three of six categories on the Wisconsin card sorting test. Psychomotor speed was reduced.

Rapid deterioration raised the possibility of CJD, and examination of CSF showed very high titres of S-100b (5.92 ng/ml *v* less than 0.38 in normal cases), neurone specific enolase (310 ng/ml *v* less than 20), and 14-3-3 proteins. These made CJD a very likely diagnosis. Towards the end, the patient developed fasciculations and myoclonic jerks, became verbally unresponsive, and died of bronchopneumonia six months after presentation. Necropsy examination confirmed the diagnosis of sporadic CJD, with a diffuse pattern of lesions involving many areas of the brain including the brain stem, and no clear focus of degeneration.

DISCUSSION

These findings emphasise the importance of considering CJD in the differential diagnosis of progressive supranuclear palsy, from which it is at times differentiated by a "wait and see" policy because unlike other dementia-akinetic-rigid syndromes such as corticobasal degeneration and multisystem atrophy, CJD progresses much more rapidly and death ensues within a few months. Neuropsychological assessment in progressive supranuclear palsy shows deficits of attention, executive function, memory retrieval, visual and auditory perception, and language production.³ In this case, however, early

neuropsychological impairment was limited to an executive deficit, although it was followed by further cognitive impairment which we were unable to assess fully at later stages of the disease. Interestingly, in progressive supranuclear palsy, there is a strong correlation between abnormal eye movements and neuropsychological deficit, particularly in sustained and divided attention.⁸ It is yet to be shown whether abnormal oculometry in other dementia-akinetic-rigid syndromes is also correlated with the severity of cognitive impairment. A study of the eye movements of 23 patients with akinetic-rigid syndrome (idiopathic Parkinson's disease, multisystem atrophy, pure akinesia, progressive supranuclear palsy, and corticobasal degeneration) showed that, though impairment of pursuit movement was a common finding and could not differentiate between subgroups, only those with corticobasal degeneration showed prolonged saccadic latency, and only patients with progressive supranuclear palsy had slowed saccades.⁹ This suggests that quantitative oculometry may be useful in the routine assessment of such patients. The oculomotor control system has a wide anatomical distribution and is composed of numerous different cell types. Many neurological diseases therefore leave characteristic signatures on its performance, as they damage different and sometimes selective parts of its widely distributed neural circuitry.¹⁰

We believe that the pattern of neuropsychological impairment and quantitative oculometric abnormalities described in this paper may be useful in the early diagnosis of CJD. In particular, as saccades are highly stereotypic and can be recorded easily, consistently, non-invasively, and precisely, with appropriate quantitative analysis, relatively small deviations from normality can be very significant and have high diagnostic value, if specific patterns of impairment are demonstrated for different diseases. At the time the oculometry was performed in our patient the saccadic slowing was already dramatic; it seems probable that significant slowing, probably indiscernible without quantitative examination, would have been found had we made the measurements some months earlier. Given the very low incidence of CJD, the chances of making quantitative eye movement measurements in a patient before the diagnosis is clear are necessarily small, and previous reports of saccadic slowing have been at a relatively late stage in the disease.¹¹

We were fortunate in having the opportunity to make these measurements at such an early stage, quantitative oculometry not being a routine neurological procedure. We hope that as a result of our serendipitous discovery, others will be encouraged to undertake speculative quantitative oculometry in similar circumstances.

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