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Ocular motor abnormalities in neurodegenerative disorders

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Abstract

Eye movements are a source of valuable information to both clinicians and scientists as abnormalities of them frequently act as clues to the localization of a disease process. Classically, they are divided into two main types: those that hold the gaze, keeping images steady on the retina (vestibulo-ocular and optokinetic reflexes) and those that shift gaze and redirect the line of sight to a new object of interest (saccades, vergence, and smooth pursuit). Here we will review some of the major ocular motor abnormalities present in neurodegenerative disorders.
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Neurodegenerative disorders are chronic conditions of the central nervous system that often lead to motor problems and dementia. With an ageing population, we are facing a rise in the incidence of these conditions. Studies have revealed that neurodegenerative conditions, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) have a presymptomatic phase that may be present for some years before the onset of the overt clinical syndrome. During this presymptomatic phase, considerable neuronal degeneration occurs; but the potential opportunity for preventative intervention is lost, because the diagnostic symptoms and signs have not yet appeared. Once the condition is manifest, there may still be diagnostic uncertainty, particularly in disorders such as PD, which is closely mimicked by the early stages of the so-called 'Parkinson's-plus' conditions.

Eye movement control is complex and involves many brain areas, including the brainstem, cerebellum, basal ganglia, and cerebral cortex.[1] Abnormalities of eye movements are a source of valuable information to clinicians and scientists. Identification of an abnormality during clinical examination may allow accurate localisation of a focal lesion in the nervous system, and may give clues as to the nature of the pathology causing it. Certain eye movement abnormalities may also reflect the presence of widespread disease affecting far more than just the ocular motor system, for example, the inability to voluntarily elevate the eyes seen in progressive supranuclear palsy (PSP). Oculometry—using sophisticated measuring instruments rather than simple clinical examination—has been increasingly used as an experimental tool to gain insights into a wide range of neurological disorders.[2–5]

Alzheimer's disease (AD)

Clinical ocular motor manifestations

Abnormalities of eye movements in AD, especially saccades, have been reported in a number of studies.[6] Hypometric saccades, prolonged saccade latencies,[7–11] reduced peak velocities,[8] and disorganized visual scanning[10,12] have been noted. However, an early observation suggesting that prosaccadic latencies might prove to be a reliable index of dementia severity[13] was not confirmed.[7] Furthermore, results from studies looking at the saccadic gain and velocity in AD are controversial; some studies found impairment,[8,14] whereas other studies did not.[9,15]

Research findings

Scinto *et al*[16] noted deficits in the generation of visually-guided saccades in AD, which they attributed to an attentional, rather than to an ocular motor source. However, two consistent impairments of saccades have emerged from AD research: (1) a high frequency of saccadic

intrusions during attempted fixation;[11] and (2) visual capture by the target in the antisaccadic paradigm,[14,17–19] in which the subject has to suppress a reflexive saccade to a peripheral target and execute an endogenously driven saccade to an equal and opposite location. Interestingly, inhibition errors in the antisaccadic paradigm could be predicted by measures of dementia severity.[14,17,18,20] Antisaccades may provide not only a functional index of the dorsolateral prefrontal cortex, which is damaged in the later stages of AD, but also a tool for monitoring the progression of AD.[6] A more recent study[21] used an antisaccadic paradigm as a way of testing inhibitory control in AD patients. The results showed that AD patients were impaired relative to the mild cognitive impairement in participants and healthy controls. The antisaccadic task, therefore, might be a useful and relatively easy way of measuring executive function in AD.

Smooth pursuit eye movements in AD are also usually abnormal. Increased frequency of saccades during pursuit[22] may result from a disturbance in the pursuit system, due to a reduced gain (eye velocity divided by target velocity).[23] However, large-amplitude saccadic intrusions in the direction of target motion are also observed, probably reflecting increased saccadic distractibility.

Recently, a study by Kapoula *et al*[24] has looked into measuring fixational eye movements and in particular microsaccades, in a group of AD, minimal cognitive impairment, and healthy individuals. Microsaccade direction differed significantly in patients *vs* controls, but no abnormalities were observed in microsaccade dynamics (such as duration, intersaccadic intervals, peak velocity, and the peak duration—magnitude relationship) that are more directly related to the function of the brainstem saccade generator.[25] Such studies lend support to the idea that microsaccadic metrics may be a useful tool for an accurate diagnosis, as well as for evaluating ongoing therapies in neurodegenerative disorders, such as AD.

Frontotemporal dementia (FTD)

Clinical manifestation

The majority of patients with FTD develop the condition in the presenium, with the onset usually occurring between 45 and 60 years of age.[26] About 50% of patients have a positive family history in a first-degree relative. An abnormality of chromosome 17 was present in affected members of a family with an autosomal dominant form of the disease.[27] The incidence of FTD in relation to presenile AD is estimated to be at least 1 : 5. FTD comprises three core clinical dementia syndromes, a behavioural and dysexecutive (or frontal) variant called frontotemporal lobar dementia and two forms of primary progressive aphasia, a temporal lobe variant, also called semantic dementia (SD), and a progressive nonfluent aphasia (PA).[28] The diagnosis of each of these FTLD clinical syndromes relies mainly on the combination of progressive behavioural and neuropsychological impairments and the exclusion of others.

Research findings

Studies of saccades in FTD have found normal reflexive saccades, but impairment in the ability to inhibit a reflexive saccade in the antisaccade task, that is, impaired reflexive saccade inhibition, except in the SD group.[29,30] However, they were able to self-correct the antisaccade errors as well as controls, in contrast to patients with AD, corticobasal degeneration (CBD), and PSP. Interestingly there was a positive correlation between antisaccade performance and the volume of a segment of the right frontal eye field using an unbiased voxel-based morphometric analysis of grey matter volume in their structural MRI images.[30] Findings in a recent study have shown that saccades are abnormal in FTD, reflecting reduced decision-making speed, and that these abnormalities related to atrophy of the left frontal eye field. In addition, patients with FTD had an increased incidence of early saccades, which may be due to reduced inhibition of primitive responses.[31]

Although FTLD, CBD, and PSP might present with similar pathology, they do represent distinct syndromes.[32] The results of the ocular motor studies so far suggest that saccadic analysis may be useful in differentiating these groups (saccadic gain and velocity, and antisaccade performance).[19,33]

Dementia with lewy bodies (DLB)

Clinical manifestation

DLB is now recognized as one of the most common dementias in the elderly after AD. It can be recognized on the basis of several clinical characteristics including progressive dementia with marked slowing and fluctuations, persistent visual hallucinations, and an extrapyramidal syndrome. Several other clinical and imaging features are highly suggestive, such as the presence of rapid eye movement sleep disorder, severe sensitivity to neuroleptics, and specific neuroimaging abnormalities.

Ocular motor manifestations

Research findings

In a comparison of saccades in patients with AD, DLB and PD dementia (PDD), and controls, those with DLB

and PPD were impaired in both reflexive saccade execution (gap and overlap latencies) and complex saccade performance (target prediction, error decisions,and antisaccades errors).[19] Patients with AD were only impaired in complex saccade performance, but not reflexive saccade execution. Impaired saccade execution in reflexive tasks allowed discrimination between DLB *vs* AD. It was concluded that impairments in reflexive saccades may be helpful for differential diagnosis and are minimal when either cortical (AD) or nigrostriatal neurodegeneration (PD) exists solely; however, they become prominent with combined cortical and subcortical neurodegeneration in PDD and DLB. The similarities in saccade performance in PDD and DLB underline the overlap between these conditions and underscore differences between AD and PD.[12]

Basal ganglia disorders

The basal ganglia have a vital role in the generation of saccades and it is not surprising that many of the diseases of the basal ganglia give rise to disturbances of saccades.

Parkinson's disease

Idiopathic PD (IPD) is a progressive neurodegenerative disorder that results in a loss of dopamine in the basal ganglia giving rise to tremor, rigidity, bradykinesia, and postural instability.

Clinical ocular motor findings

Ocular motor abnormalities that might be detected during a routine clinical examination include blepharospasm, paucity of blinking, apraxia of lid opening, visual neglect, reduced vergence, reduced upgaze, and blurred vision.[34]

Research findings

Abnormalities of eye movements, especially in saccades are known to occur in PD. To date, several studies have presented quantitative data from studying different types of saccadic eye movements in PD, but early results were conflicting. Although some authors found that saccadic velocity was preserved,[35,36] others did not.[37,38] As pointed out,[36] these discrepancies could have been attributed to methodological differences. In most studies, the patients were taking various antiparkinsonian drugs that we now know may have profound effects on eye movements.

Typically, even at the earlier stages of the disease, the most consistent ocular motor abnormality in PD is saccadic hypometria in which the primary saccade undershoots the target, especially vertically.[39–41] This was initially demonstrated in saccades executed to verbal command,[42] in the dark,[43] or to fixed targets.[37] Predictive saccades also show hypometria, in addition to difficulty in anticipating the stimulus,[36,44] and in unilaterally affected patients the abnormalities were found to be lateralized.[45] There are also deficits in initiation and performance of internally mediated tasks, including antisaccades and memory-tasks.[40,44,46–48] The memory-guided task seems to be the most sensitive, and performance gets worse as disease progresses.[46,47,49–51] Mild to moderate PD patients show a marked increase in saccade amplitudes.[52] Saccadic latency is typically normal or mildly increased compared with controls.[36,38,53]

Studies of scanpaths of saccades during visuospatial sorting tasks have provided insights into the cognitive changes in PD.[4] In the 'Tower of London' task, that tests working memory and planning, patients have to rearrange coloured balls to fit a particular pattern. After analysing the scanpaths of PD patients in this task compared with those of controls, it was suggested that PD patients kept forgetting the arrangement of the test objects,[54] implying a deficiency in their spatial working memory.[55]

Advanced PD patients may show greater abnormalities on particular tests as compared with mild PD patients.[5] For example, they make more directional errors in the antisaccade task and have increased mean latencies[53] that increase as the disease progresses;[48] this is more evident when patients are on anticholinergic medication.[56] It has been suggested that in advanced PD, brain structures other than the basal ganglia such as the frontal lobe,[57] might produce these saccadic deficits.

If endogenously and exogenously driven saccades are differentially affected in PD, a task such as the antisaccade paradigm that involves both should demonstrate impairment. Some studies have found no significant impairment in the performance of PD patients compared with age-matched controls,[47,58] and others have shown impaired performance.[48,53,56,59,60] It is difficult to draw firm conclusions from these studies because of methodological difficulties; however, the one study that employed a 'gap' paradigm and tested patients in their 'OFF' state, demonstrated more errors, increased latency, and reduced gain in patients with mild to moderate PD,[59] compared with controls. However, if reflexive (pro-) and antisaccade tasks are mixed up in a block, as opposed to the usual single-task blocks normally used, then PD patients showed a marked increase in prosaccade and antisaccade error rates in repeated trials.[61]

Response to treatment

Studies looking into the effect of L-dopa are not consistent and sometimes even conflicting, which may be owing to an inadequate number of subjects studied. A few studies have shown beneficial effects on the parameters of voluntary saccades,[39,42] and on the ability to perform sequences of MGS,[49] but none has ever demonstrated any improvement in the most characteristic abnormality in PD, the hypometria of MGS. Recent studies have agreed that L-dopa and dopamine agonists shorten the latency of these voluntary saccades,[62,63] whereas they prolong the latency of both externally guided or triggered saccades.[64]

Several studies have examined the effect of STN stimulation on saccades. Stimulation of the STN reduced reflexive saccadic latencies,[3,65] increased the amplitude,[66,67] and produced a marked improvement in the gain of MGS.[68] There is also a single case report of a similar improvement in MGS, as well as antisaccades, in a patient with a GPi electrode when the stimulator is turned on.[69] Depending on the location of the electrode fixation instability may occur.[70] A disruption of ocular fixation has also been reported after a unilateral pallidotomy.[71]

Differential diagnosis

Clinically obvious impairment in vertical eye movements is a characteristic of PSP, although it may be seen in other conditions such as diffuse Lewy body disease,[8] CBD,[72] amyotrophic lateral sclerosis,[73] post-encephalitic parkinsonism,[74] and Creutzfeld–Jacob disease.[75] In PSP, slowing of vertical saccades precedes ophthalmoplegia and is probably the earliest sign of ocular motor involvement. A supranuclear gaze palsy may be seen in CBD, but usually only when the disease is advanced.[76] Eye signs are rarely an early feature of MSA, but in some cases may mimic PD.

Several studies are using eye movements to differentiate parkinsonian-like syndromes, although it is still not clear to what extent eye movement recordings are helpful in discriminating among them. A couple of small studies have examined simple saccadic metrics in the horizontal, vertical, and diagonal planes in patients with PD, MSA, pure akinesia, PSP,[77] and CBD.[41] It was found that compared with age-matched controls only patients with PSP had slow saccades (in any direction), and only patients with CBD had increased saccadic latency. Other parameters such as hypometria, vestibulo-ocular responses, and smooth pursuit did not discriminate between groups, although deviation of oblique saccades towards the horizontal plane was more marked in patients with pure akinesia and PSP.

In another study,[58] patients with CBD had greater saccadic latency, and those with PSP more marked hypometria and worse antisaccade performance compared with patients with PD, however, there were no saccadic criteria by which patients with MSA could be differentiated from those with PD. Thus detailed eye movement analysis may be helpful in identifying patients with PSP and possibly CBD, but until there is more data on its sensitivity and specificity using large prospectively studied patient cohorts, it is difficult to recommend it for routine use in the diagnosis of parkinsonian disorders.

Huntington's disease (HD)

HD is a neurodegenerative disorder, due to an inherited autosomal dominant genetic mutation, characterized by chorea, cognitive impairment leading to dementia, and psychiatric disturbances with a clinical onset in the 30s.

Clinical ocular motor findings

For HD, the challenge is to predict disease onset given that we can test for the presence of the abnormal huntingtin gene on chromosome 4. Ocular motor impairment is among the first manifestations in HD,[78] and the main abnormality involves the saccadic system to a greater extent than the pursuit system. This has been attributed to the close involvement of the basal ganglia with the saccadic control circuit.[79,80]

Research findings

Impairment of both vertical and horizontal saccades was originally reported in patients suffering from manifest HD.[81] Contrary to earlier eye movement findings on premanifest HD individuals that reported intact performance,[82,83] a number of recent studies have reported deficits even in premanifest subjects. Initiation deficits of voluntary guided saccades, saccadic slowing, and delayed reflexive saccades were present.[84–86] When compared with controls, premanifest individuals also show impairment in the antisaccadic and memory-guided tasks and longer latencies, especially during the latter. Furthermore, the saccadometry research tool has proved valuable in separating premanifest, manifest, and controls who showed an increased incidence of early saccades with unusually short latencies.[84–89]

Manifest patients early in the course of their disease, exhibit reduced saccadic velocity,[78,81,90] impaired initiation of saccades, an increase in the frequency of square-wave jerks, and an increase in saccadic latencies, that is greater for voluntary than reflexive saccades. They have excessive distractibility during attempted fixation,

even when specifically instructed to maintain fixation on a centrally located target.[78,91] HD patients also increased distractibility in the antisaccade task.[91,92] Impaired initiation of saccades was manifested by increased latency and the inability to make a saccade without head thrust or blink.[78] This behaviour is similar to that of patients with congenital ocular motor apraxia. Volitional saccades are also often hypometric.[84,93,94] In addition, saccadic hypometria has been documented in mildly affected HD patients.[78,91–93,95–99]

Later on in the disease, manifest patients usually begin to show more prominent slowing of saccades, as well as smooth pursuit deficits. Eventually, a reduced range of eye movements is observed with vertical saccades affected more than horizontal ones.[5,78,96] Patients who become manifest at an earlier stage tend to have slower velocity saccades, and it has been suggested that those patients are more likely to have inherited the gene from their paternal side.[93] Longitudinal studies of saccadic eye movements have reported significant progressive slowing and prolongation of reaction times and despite the great individual variation, impairment of the initial saccadic velocity is more prominent in younger patients.[100]

All the findings mentioned above can be attributed to the malfunction in parallel pathways that are utilised for the various saccadic eye movement behaviours in different saccadic paradigms. As Hikosaka *et al*[79] have described, a neurodegenerative disease affecting the frontal lobes or the caudate nucleus that inhibits the substantia nigra, pars reticulata (SNpr), the major outflow centre for saccades in the basal ganglia, may lead to difficulties in initiating voluntary saccades in tasks that might require learned or predictive behaviour. Furthermore, HD also affects the SNpr[101] and as the SNpr inhibits the superior colliculus (SC), it could therefore affect saccades to visual stimuli. Two distinct pathways project to the SC, working sequentially to suppress planned eye movements. One of them may be disrupted in HD as shown in Figure 1.

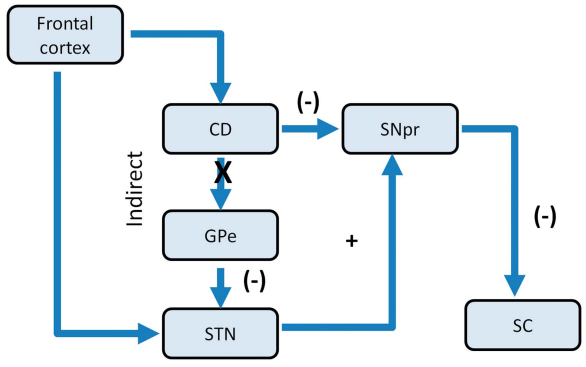

Figure 1 Schematic illustration showing two pathways projecting to superior colliculus (SC) via pars reticulate (SNpr), termed the direct and indirect pathways. Excitatory projections to the caudate from the frontal cortex trigger saccades via the indirect pathway. CD inhibits the SNpr, which tonically inhibits the SC. Excitation of CN could lead to disinhibition of SC and thus generation of saccades. The direct pathway may mediate saccade initiation by decreasing GABAergic connections within the SC. A possible mechanism by which HD interferes with saccades is by disruption of the indirect pathway as shown at the point marked X; (−) inhibitory, + excitatory.

The strong correlation between the worsening of saccadic performance and disease severity, particularly in later stages of the disease, indicates that abnormalities in eye movements might be a useful and sensitive clinical marker not only in assessing motor and functional changes in HD individuals, but also in separating manifest from premanifest individuals.

Conflict of interest

The authors declare no conflict of interest.

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