Quantitative Analysis of the Ocular Motor Deficit in Progressive Supranuclear Palsy (PSP)

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Despite extensive descriptions of the clinical and pathologic features of progressive supranuclear palsy (PSP), there is no systematic analysis of the cardinal abnormality characterizing the syndrome, namely the progressive disorder of eye movements. We present the results of quantitative infrared horizontal eye movement recordings on 8 patients with PSP.

Case Material and Methods

The patients, 7 men and 1 woman, ranged in age from 60 to 75. Each had axial rigidity, mild to moderate dementia, and ophthalmoparesis. Whereas some had total paralysis of vertical movements, none had completely lost the ability to perform voluntary horizontal movements. The eye movements were recorded by infrared reflection with analogs pen-written on rectilinear graph paper. Vertical eye movements cannot be measured quantitatively with this technique. The patients sat in a modified dental chair with a chin rest and head band for stabilization. None had been taking sedatives, hypnotics, or anticonvulsants, and none was being treated with L-dopa. Following calibration, the following parameters were recorded: *fixation, voluntary refixations* to and from targets 5°, 10°, 20° and 30° from primary position, and *pursuit* of ramp and sinusoidally moving visible targets. We checked the calibration after each series of refixations or pursuit attempts; periodic verbal encouragement and frequent rest periods ensured alertness. The position analog could be read to an accuracy of 0.5°, and the electronically differentiated signal read to the nearest 10°/sec for peak velocity. We recorded *vestibulo-ocular* responses in 2 patients during sinusoidal rotation in a chair with the head and eye positions measured simultaneously.

Results

All 8 patients had frequent square wave jerks (SWJ) during *fixation,* a defect previously undescribed in PSP. SWJ or "Gegenrucke" are ½°–3° conjugate horizontal saccades with normal velocity-amplitude characteristics, occurring

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at a frequency of 1–4 Hz. They move the eyes away from the point of fixation for about 200 msec, followed by a return to the initial position.

Analysis of *refixation saccades* demonstrated the following: (1) a velocity-amplitude relationship near the "pathologically slow" limits previously established in this laboratory (Boghen et al., 1974); (2) hypometric saccades for almost all refixation attempts greater than 5°. The multiple-step hypometric saccades (MSHS) were of both types (normal and slow velocity steps) previously described (Troost et al., 1974); (3) prolonged duration of saccades greater than 5°. For example, refixations of 5° averaged 50–60 msec with an expected normal duration of 30–35 msec, and saccades of 25° amplitude had durations reaching 150 msec (normal 80–90 msec).

The primary *visual pursuit* dysfunction, characterized clinically by the appearance of "cogwheel" eye movements, was the inability of patients to match eye velocity to target velocity. The pursuit gain (G_p), defined as the ratio of peak eye velocity to target velocity, was usually 0.4–0.5. (Normal gain approaches unity for ramp target speeds less than 40°/sec.) Despite the use of very slowly moving stimuli (velocity 5°/sec), G_p remained low and relatively constant in all patients.

Defects in the *vestibulo-ocular reflex* (VOR) were manifest by: (1) inability to increase the gain of the reflex (ratio of peak eye velocity to head velocity), G_{vor}, during viewing of a visible stationary target; and (2) failure to suppress the VOR when viewing a target rotating with the head.

Discussion

All aspects of ocular motor function are quantitatively abnormal in PSP by the time clinical diagnosis is possible. We have demonstrated defects in fixation, saccadic refixation, and both pursuit and compensatory (vestibular) slow eye movements. The defect in fixation is primarily characterized by frequent SWJ. These saccadic intrusions may occur in normals behind closed lids and previously have been recorded in patients with brainstem or cerebellar dysfunction. All patients with PSP had virtually constant SWJ, often unappreciated clinically or by inspection of film strips.

Refixation saccades have previously been studied by others primarily for abnormalities in velocity or the velocity-amplitude characteristics. In our patients, some pathologically slow values were obtained, especially in those severely affected clinically. Hypometric saccades, the most striking saccadic abnormality, may be regarded as a decrease in the gain of the saccadic system (G_s = ratio of saccadic amplitude to desired refixational distance). Thus defective gains emerged as analogous defects in saccadic, pursuit, and vestibulo-ocular functions in patients with PSP. The small individual saccadic steps which composed the hypometric refixations usually had peak velocities in

the normal range for amplitude. However, the durations of these saccades were distinctly long as a consequence of markedly prolonged deceleration times, the latter not previously reported as an eye movement abnormality.

None of the patients could normally pursue moving targets. As a consequence of the inability to match target velocity, the eyes constantly fall behind the intended target and required a saccade to reattain the stimulus, thus producing "cogwheel" or "saccadic" pursuit. The pursuit dysfunction was also shown by the inability of the patients to maintain fixation on a stable target during head rotation, a task easily accomplished in normal subjects. This task requires suppression of the vestibulo-ocular reflex and depends upon steady fixation, a process that has been conceptualized as "pursuit at zero velocity." The SWJ intrusions upon fixation and the defective pursuit both contributed to the VOR suppression failure.

We have determined that the earliest abnormalities of horizontal eye movements in PSP are square wave jerks during fixation, cogwheel pursuit, and hypometric saccades with prolonged-duration saccadic steps. As the pursuit gain gradually drops toward zero, the saccadic velocity gradually slows. Then both pursuit and refixation are accomplished by slow multistepped saccades. As the disease progresses further, the amplitudes become gradually limited. When voluntary eye movements are totally paralyzed, vestibular compensatory eye movements remain. Ultimately, if the patient survives a sufficient time, all reflex as well as voluntary eye movements are lost.

DISCUSSION

LAWRENCE STARK (*San Francisco, California*): The authors are to be congratulated on this very interesting paper and especially on its quantitative analysis. Indeed, they go below the surface to look at the control system abnormality in brain control of eye movements. It is natural for neurologists to be interested in control theory, because we see clinical abnormalities in neurological control systems all the time.

In 1962, at MIT, with Young and Navas, I put forward two sampled data models —one for saccadic eye movements and the other for hand movement. Four essential features of the engineering models match the neurologic systems. One is discontinuity in control seen in saccadic eye movements, and that I'll show you later in hand movement. Second is the 150-200 millisecond refractory period, a consequence of the sampling process. Third is the fact that saccadic oscillations are flat-topped between saccades, demonstrating that smooth pursuit is not involved. And fourth, that it is a visual feedback control system.

Recently, Jack Selhorst, William Hoyt, Al Ochs and I studied deficits in cerebellar patients with vermal lesions that, not surprisingly to a neurologist, are the inverse of the hypometric saccadic picture. The first slide (*SLIDE*) shows "saccadic overshoot dysmetria." Here, saccades are not too small, but rather too big. It appears as an unsustained clonus; notice the clonus is not sinusoidal, but square-waved.

(*SLIDE*) An even more severe abnormality is continual "macrosaccadic oscillation" showing enormous saccades in patients with severe cerebellar insult. Notice the oscillations or waves are square-topped with 200 millisecond refractory periods. The next slide (*SLIDE*) shows the sampled data model which simulates "macrosaccadic oscillation"

and also "hypometric saccades" such as shown to you by Drs. Troost, Daroff and Dell'Osso. You can see, as gain increases, less and less convergence of oscillation is obtained. As gain is further increased, the square-wave clonus gets worse and worse.

The next slide (*SLIDE*) shows the sampled data model Young and I put forward in 1962, simulating in normal subjects similar hypometric saccades, hypermetric saccades and square-waved oscillations. Oscillations are increasing in the bottom corner, the normal record is in the upper left-hand corner, and hypometric saccades are shown next to that.

(*SLIDE*) Back to our patient with macrosaccadic oscillations. If we turn off the lights we open the loop—we stop visual feedback. Then oscillation stops because they are dependent on a visual feedback control system with an abnormal gain, as Dr. Troost explained for his patient with decreased gain.

(*SLIDE*) The last slide shows normal hand movement to be saccadic or sampled data. Voluntary, skilled movement—controlled, not through stretch reflexes, but from higher levels—is saccadic movement! This has been partly confirmed in animals by Brooks and Everts, but not many clinical studies have been preoccupied by the saccadic nature of voluntary movements.

There are many other interesting phenomena discussed by Dr. Troost in his patients. The eye movement control system is a multilevel control system and at each level of control there is a beautiful brain control mechanism—shaping the saccades, controlling their amplitude, controlling positioning of the eye in random searches for visual information processing. I'm sure, in the future, clinical cases will illustrate defects in many aspects of this control system. Thank you.

WILLIAM LANGSTON (*Stanford, California*): I would like to know how the proposed theory of defective gain would account for the presence of square-wave jerks which apparently was a very common finding in these patients.

DAVID A. PRINCE (*Stanford, California*): How do these findings relate to the discrepancy between initiation of a voluntary saccadic shift and following or pursuit in some of these patients? There is often a very pronounced discrepancy.

DR. TROOST (*closing discussion*): I would like to thank Dr. Stark for his remarks. We have also recently reported a patient with macro square-wave jerks in *Neurology* in which the eye movements were seen clinically to be a sinusoidal oscillation but which, on recording, did have flat tops.

As far as the abnormal gain concept goes, I'm not certain that that explains everything abnormal that we see in progressive supranuclear palsy. We believe that pursuit and fixation are very intimately linked, and that fixation is an active process, perhaps pursuit of a target with zero velocity. If the gain is abnormal then there may be oscillations in the system resulting in the square-wave jerks.

I'm not certain whether our theory of gain would explain the difficulty with initiation of eye movement. I believe that loss of neurons, particularly in the paramedian pontine reticular formation, may lead to a defective pulse and a defective sustaining of that pulse which might result in prolonged duration. I believe that actually the pursuit abnormality comes much earlier than the saccadic abnormality, and despite previous reports that pursuit was normal in patients that had abnormal saccadic eye movements, I think when they are recorded and looked at carefully, the pursuit will almost always be abnormal at the time when clinical diagnosis can be made. Thank you.