Ocular motor dysfunction in total and hemicerebellectomized monkeys

RONALD M. BURDE, MALCOLM H. STROUD, G. ROPER-HALL, FREMONT P. WIRTH, AND JAMES L. O'LEYAR* 
From the Departments of Ophthalmology, Otolaryngology, Neurology and Neurosurgery, Washington University School of Medicine, St Louis, Missouri, USA

Recent reports (Kornhuber, 1971; Robinson, 1974; Westheimer and Blair, 1973) have implied conflicting roles for the cerebellum in the control of eye movements. Recently, as part of a large multispecies study to determine the effects of cerebellectomy on power and co-ordinating functions (Wirth and O'Leary, 1974), we had the opportunity to study prospectively the effects of this surgery on the ocular motor system in primates. Altogether 21 monkeys (Macaque mulatta) were observed both during the acute stage (the first postoperative 8 weeks) and during the compensated stage (as late as 6 months after surgery). Our observations on the ocular motor function of these primates are reported in this paper and an attempt is made to draw some pathophysiological correlations with human ocular motor dysfunction.

Material and methods
The details of animal preparation have been reported separately (Wirth and O'Leary, 1974). The extent of cerebellar removal was confirmed in each animal with a thorough neuroanatomical study at the conclusion of each experiment. These findings are also reported in detail elsewhere (Wirth and O'Leary, 1974) and will be referred to here only when relevant to specific ocular movement disorders.

The animals were studied in a primate chair with or without head restraint. Motion pictures (16 mm) were taken of all animals during the tests. Electro-oculography was performed in three animals and frame projection comparisons were made to estimate speed of movement in all animals. The following ocular motor functions, for the most part, were routinely studied:

1. Movements during spontaneous gaze (that is, the presence or absence of nystagmus, strabismus, skew deviation, conjugate gaze weakness, or deviation)

2. Horizontal and vertical saccades
3. Following movements
4. Convergence function
5. Horizontal and vertical optokinetic nystagmus
6. Doll's head manoeuvre
7. Cold water calorics (30°C).

Warm water calorics (44°C) were performed when indicated. A special canaliculus extension earpiece of Teflon tubing (1 mm internal diameter) was inserted into the external auditory meatus of each animal and threaded into the bony canal to ensure adequate stimulus delivery. Then 15 cm³ water was flushed into the external ear in approximately 15 seconds.

Animals were divided arbitrarily into two groups. Acute—examined within the first 8 weeks of surgery. Compensated—examined in the ninth week or later.

Results
Adequate data were available in 10 animals which underwent total cerebellectomy and in two animals that underwent hemicerebellectomy. The results are summarized in Tables I and II.

In animals that underwent total cerebellectomies and which were studied during the acute period the following eye movement abnormalities were noted:

1. Spontaneous gaze

Spontaneous nystagmus was noted constantly in two of seven animals. This was an upbeating nystagmus (fast phase up). An additional four animals had intermittent nystagmus, usually horizontal, but occasionally with an oblique component.

Gaze-paretic nystagmus (that is, nystagmus in conjugate lateral gaze with a small amplitude and high frequency) was present in four of six monkeys. This was a horizontal movement in lateral gaze (fast phase right in right gaze and vice versa), and a vertical movement in vertical gaze, usually upbeating when looking up and downbeating when looking down. Generally the nystagmus was bilateral and symmetrical. In one animal (No. 13), that underwent first a left cerebellectomy followed by a right cerebellectomy, the gaze-paretic nystag-
Table I  Summary of pertinent findings in monkeys with acute cerebellectomies (less than 8 weeks)

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Monkey no.</th>
<th>Nystagmus</th>
<th>Pursuit</th>
<th>Cold caloric</th>
<th>Skew deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Spontaneous</td>
<td>Gaze-fixation</td>
<td>To right</td>
<td>OKN abnormal</td>
</tr>
<tr>
<td>Left hemi-cerebellectomy</td>
<td>13</td>
<td>Absent</td>
<td>Present</td>
<td>Normal</td>
<td>Micro-saccade</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>Upbeating</td>
<td>Absent</td>
<td>Normal</td>
<td>Micro-saccade</td>
</tr>
<tr>
<td>Total cerebellectomy</td>
<td>8</td>
<td>Present intermittently</td>
<td>Present</td>
<td>Normal</td>
<td>Micro-saccade</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Absent</td>
<td>Not recorded</td>
<td>Normal (apparently)</td>
<td>Not recorded</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>Upbeating</td>
<td>Present</td>
<td>Left gaze</td>
<td>Right gaze</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>Present intermittently</td>
<td>Present</td>
<td>Impersistence of gaze</td>
<td>Left and right</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>Present intermittently</td>
<td>Present</td>
<td>Left gaze</td>
<td>Right gaze</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>Absent</td>
<td>Impersistence of gaze</td>
<td>Left and right</td>
<td>Normal</td>
</tr>
<tr>
<td>Sequential left cerebellectomy followed by a right cerebellectomy</td>
<td>13</td>
<td>Upbeating</td>
<td>Present</td>
<td>Left gaze</td>
<td>Right gaze (R &lt; L)</td>
</tr>
</tbody>
</table>

1. Hydrocephalus
2. Animal would not move eyes—doll's head manoeuvre induced vestibular nystagmus
3. Violent animal. Calorics impossible; seemed to have impersistence of gaze with wide amplitude
4. Larger amplitude to left

Table II  Summary of pertinent findings in monkeys with compensated cerebellectomies (after more than 8 weeks)

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>Monkey no.</th>
<th>Spontaneous nystagmus</th>
<th>Gaze-paretic nystagmus</th>
<th>Abnormal</th>
<th>Cold caloric</th>
<th>Skew Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemi-cerebellectomy</td>
<td>13</td>
<td>Absent</td>
<td>Present Left gaze</td>
<td>Normal</td>
<td>Micro-saccade to left</td>
<td>Present</td>
</tr>
<tr>
<td>Total cerebellectomy</td>
<td>4</td>
<td>Absent</td>
<td>Present Left gaze</td>
<td>Normal</td>
<td>Micro-saccade to left</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Downbeating</td>
<td>Present Left gaze</td>
<td>Normal</td>
<td>Micro-saccade to left</td>
<td>Not recorded</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Present intermittently</td>
<td>Present Left gaze</td>
<td>Normal</td>
<td>Micro-saccade to left</td>
<td>Pendular response</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Periodic alternating nystagmus</td>
<td>Present Left gaze</td>
<td>Normal</td>
<td>Micro-saccade to left</td>
<td>Micro-saccade to left</td>
</tr>
</tbody>
</table>

1. Hydrocephalus—minimal damage to lateral vestibular nuclei
2. Massive hydrocephalus—minimal damage to lateral vestibular nuclei—fibrous occlusion of lower end of fourth ventricle
3. Gliosis of superior vestibular nuclei
4. Vestibular nuclei damaged medially. Marked obstructive hydrocephalus
mus was greater in right conjugate gaze. The other two animals demonstrated a gaze-holding failure (drifts of large amplitude from the lateral gaze position towards the midline) with infrequent corrective fast movements (large amplitude low frequency gaze-paretic nystagmus). Skew deviation was constantly present in two animals and was seen intermittently in an additional two monkeys. The skew was usually manifested by a left hypertropia in right gaze or a right hypertropia in left gaze. The skew deviation was often exaggerated by caloric stimulation.

2. Saccadic movement
In all six animals the speed (400–600 arc degrees/s (Fig. 1)) and amplitude of conjugate movements was normal.

3. Following movements
In six of seven animals in which adequate recordings were available microsaccadic or cogwheeling movements were noted (Fig. 2) instead of smooth following movements.

4. Convergence
In six of seven animals a normal convergence response could be obtained.

5. Optokinetic nystagmus (OKN)
In order to assess lateralizing differences in the slow and fast phases the OKN drum or tape was held to the right or left of the midline. In this position the eyes were still without gaze-paretic nystagmus. The animals, in general, showed no response when the stripes were rotated away from the midline, but a demonstrable, albeit inconsistent, response could be obtained when the drum was rotated so that the slow phase was towards the midline and the fast or corrective phase was away from the midline. Five of seven animals demonstrated cogwheeling or large saccadic movements instead of smooth following movement. The animal (no. 13) which had undergone a sequential total cerebellectomy had a questionable left internuclear ophthalmoplegia on OKN testing. Of these five animals only two demonstrated a normal corrective fast movement. Animal 16 showed a better response when the stripe moved to the right in either gaze position.

6. Doll's head manoeuvre
Data were available on three of seven animals. Two animals responded normally. One substituted cogwheel movements for smooth slow movement, and tended to develop gaze-paretic jerks on lateral gaze.

7. Calorics
Good responses were obtained in six of seven monkeys. There was an immediate induction of nystagmus with no latency. Five of the six animals had a normal response; that is, the eyes deviated towards the side stimulated with a corrective fast phase contralaterally. The amplitude (excursion) was increased and the frequency decreased when gaze was directed towards the side of the tonic deviation, and vice versa. One animal developed convergence retraction nystagmus intermittently superimposed on a normal response (Table I). All animals demonstrated a sustained post-stimulatory response compared with normal animals. Animal 16 developed an asymmetric response. Cold water stimulation of the right ear led to a horizontal nystagmus of the right eye and a vertical nystagmus of the left eye. Stimulation of the left ear led to an oblique nystagmus with the major horizontal fast phase component in the appropriate direction, that is, to the right.

Data were available in the chronic or compensated stage of recovery for four animals that underwent total cerebellotomies.

1. Spontaneous gaze
Only one animal had totally normal ocular movements. One animal demonstrated down beating nystagmus in the primary position and downgaze. Another animal had periodic alternating nystagmus. The remaining animal had an intermittent upbeating nystagmus. Three of the four animals had gaze-
paretic nystagmus. One of these animals also had an accompanying head thrust in the direction of the conjugate gaze movement. The fourth animal had gaze-paretic nystagmus in left gaze only. In addition, two of the animals had mild bilateral convergent squint (esotropia) secondary to bilateral partial sixth cranial nerve palsies. One of these animals also had a constant skew deviation, and the other demonstrated a skew intermittently.

2. Saccadic movements
All four animals had normal saccadic movements in terms of velocity and amplitude.

3. Following movements
Three of four animals demonstrated symmetric cogwheel or microsaccadic movements in both directions.

4. Convergence
Normal convergence could be elicited in only two of the four animals.

5. Optokinetic nystagmus (OKN)
All four animals had abnormal OKN responses. In one animal cogwheeling replaced the smooth slow movement. The animal which had gaze-paretic nystagmus only in left gaze also had an asymmetric OKN response. With the stripes moving to the right there was microsaccadic following associated with an extremely slow corrective fast phase to the left. There was no response when the stripes moved to the left. The two remaining monkeys had grossly abnormal responses to the OKN stimuli (one developed a pendular nystagmus to movement in either direction and the other ocular flutter-like movements on each attempted fixation).

6. Calorics
Three of the four animals responded normally to caloric stimulation except for a decrease in latency of onset and the presence of a prolonged post-stimulatory effect. The fourth animal (no. 9) developed an intermediate contralateral deviation without a corrective fast phase movement. There was evidence of a bilateral internuclear ophthalmoplegia with a lag of the activated adducting eye and a few beats of nystagmus in the abducting eye.

Adequate records were available on two animals which had hemicerebellectomies in the acute stage of recovery and in one animal in the chronic or compensated period. The results from both of these periods are superimposable in this small sample and are summarized together.

1. Spontaneous gaze
Animal 13, which was seen in both the acute and compensated periods, did not have any nystagmus in spontaneous gaze. Animal 19 intermittently had an upbeating nystagmus in primary position. Both of the animals had gaze-paretic nystagmus in left gaze only, and neither had a skew deviation.

2. Saccadic movements
The speed and amplitude of conjugate movements were normal.

3. Following movements
Both animals 13 and 19 had microsaccadic pursuit movements only in moving from right to left gaze. Animal 19 at times would make small saccadic corrective movements in left to right gaze, but for the most part the pursuit was normal.

4. Convergence
A normal convergence response was obtained in all testing conditions.

5. Optokinetic nystagmus
The only consistent response was recorded in animal 13 in the compensated period. There was microsaccadic following when the stripes moved to the left with a normal fast recovery movement.

6. Calorics
All animals responded symmetrically to the caloric stimulus. When the right ear was stimulated there was an immediate response to the stimulus without latency, an increased frequency and decreased amplitude of the induced movement, and a prolonged post-stimulatory response. Stimulation of the left ear produced a completely normal response including the expected latency and damping of movement.

Discussion
As previously reported (Westheimer and Blair, 1973) cerebellectomized animals demonstrated:
1. Loss of smooth pursuit function
2. Normal saccadic function.

Unlike the previous report our animals also exhibited, for the most part:
1. Gaze-fixation nystagmus
2. Normal convergence
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3. An abnormal response to vestibular stimulation (a decreased latency in onset and prolonged continuation of calorically induced nystagmus).

Only one animal demonstrated gaze-holding failure as described by Westheimer and Blair (1973). In general, the two animals which had hemicerebellarlectomies demonstrated similar defects but limited to systems dealing with ipsilateral tone: gaze-paretic nystagmus, loss of smooth pursuit ipsilaterally, and abnormal vestibular response when the induced tonic deviation was to the ipsilateral side. In spite of the meticulous microsurgical technique performed by a trained neurosurgeon, many of these animals demonstrated ocular movement disorders associated either with induced brainstem dysfunction or with pathology.

Serial section examination of the nervous systems of the animals studied in this series indicated only an occasional remnant of the dentate and interpositus nuclei, or flocculi demonstrating the total removal of cerebellum. After total cerebellectomy (Wirth and O’Leary, 1974) many of the animals examined late (that is, in the compensated stage) demonstrated hydrocephalus. Many animals were also found to have some damage, although minimal, to the vestibular nuclei on one side.

Interestingly, monkey 9, which was found to have bilateral damage to the medial vestibular nuclei, exhibited periodic alternating nystagmus. This finding is compatible with previous reports (Kornhuber, 1966; Walsh and Hoyt, 1969) implicating intrinsic brainstem damage or damage to the cerebellar connexions as a cause of periodic alternating nystagmus. Recently, Karp and Rorke (1975) have also reported the involvement of central vestibular nuclei in a case with this type of nystagmus. It is of note that Kornhuber (1966) reported a distinctive prolongation of post-rotatory nystagmus in his patients with periodic alternating nystagmus which was also recorded in this experimental situation.

The demonstration of intrinsic brainstem damage makes it difficult, if not impossible, to relate the presence of spontaneous nystagmus to isolated cerebellar lesions in our animals. Bender (1969) has proposed that pure cerebellar disease does not produce spontaneous nystagmus, although the opposite view is held by Duke-Elder and Scott (1971). Walsh and Hoyt (1969) avoid the distinction and state that the interconnexions of the cerebellum and brainstem are so tightly assembled that it is impossible to differentiate the true origin of nystagmus when present. Ron and Robinson (1973) have recently produced nystagmus in alert animals by stimulating the lobules IX and X of the cerebellum and the flocculi. In spite of these observations and our data (that is, a limited number of animals demonstrating consistent spontaneous nystagmus) and that of Westheimer and Blair (1973), it is our view that lesions isolated to the cerebellum do not produce spontaneous nystagmus.

The presence of gaze-fixation nystagmus in our animals is certainly compatible with the clinical findings of gaze-fixation nystagmus reported by Hood, Kayan, and Leech (1973) and Jung and Kornhuber (1964) in patients with chronic cerebellar disease. The findings of gaze-fixation nystagmus appear to stand in contradiction to the lack of persistence of gaze reported by Robinson (1974) and Westheimer and Blair (1973), a movement of larger amplitude and slower frequency.

The results of Westheimer and Blair (1973), wherein no abnormality of the vestibulo-oculoreflex arcs could be demonstrated, are surprising in face of well-documented clinical (Ellenberger, Keltner, and Stroud, 1972; Hood and others, 1973; Jung and Kornhuber, 1964) and experimental evidence (Dow and Manni, 1964; Jung and Kornhuber, 1964) of a hyperactive or exaggerated response to vestibular stimulation. Our animals demonstrated a definite decrease in latency and a prolonged response to caloric stimulation. One animal developed vestibular nystagmus with gentle doll’s head maneuvering.

The physiological role of the cerebellum, vis-à-vis the generation and control of eye movements, remains speculative. If, as Kornhuber (1971) has postulated, the cerebellum acts as a spatio-temporal translator in saccadic movements (determining the length of the burst activity in the parapontine reticular formation for any given saccadic movement), absence of the cerebellum would be expected to produce abnormalities in the amplitude of a given saccadic movement. Ellenberger and others (1972) have recently invoked this hypothesis in explaining the findings of dysmetria, flutter-like oscillations, and opsoclonus in patients with cerebellar dysfunction. The almost universal findings of normal saccadic movements in cerebellar disease and, in the absence of the cerebellum in humans and subhuman primates, certainly excludes this structure from having a primary role as the generator or neural integrator involved in saccadic movements. Westheimer and Blair (1973) link gaze-holding failures with pursuit abnormalities as manifestations of a single defect indicating failure of a selective suppression of the oculomotor apparatus. This statement is broad enough to appear correct, but it does not add significantly to our understanding of cerebellar function.

It would appear that the most acceptable hypothesis for the role of the cerebellum, at this time, would be that offered by Robinson (1974). It is now apparent that all horizontal eye movements are modulated through neural integrators in the pons (Cohen, 1971; Cohen and Komatsuzaki, 1972;...
Goebel, Komatsuzaki, Bender, and Cohen, 1971) the substrate being the nucleus reticularis magnocellularis (parapontine reticular formation). All models of the ocular motor control system include a position-holding function as a parameter of the saccadic integrator. Robinson postulates that this neural integrator in the pons is inherently 'leaky' and therefore dependent upon a cerebellar influence to have its output precisely proportional to eye position. When cerebellar tone is removed (for example, by cerebellectomy), the pontine integrator accepts a certain fixed range of error, and therefore eye drift occurs after repositioning. If, as in our experiments observing alert monkeys, visual elicited stimuli cause an immediate discharge through the pulse generator in response to any drift, an immediate corrective saccade would be instituted and a small amplitude high frequency gaze-fixation nystagmus would be apparent. This is, of course, compatible with the clinical findings in patients with chronic cerebellar disease (Hood and others, 1973; Kornhuber, 1964). If one observed animals that were not fully alert or that were observed in subdued lighting, a decrease in processing of visual input would result in larger amplitude slower frequency drifts similar to those reported by others (Robinson, 1974; Westheimer and Blair, 1973). It would thus appear that there is no contradiction between our findings and those reported by others, and again this is certainly compatible with the known clinical fact that there is an increase in amplitude and decrease in frequency of gaze-evoked nystagmus in patients with cerebellar disease when visual fixation is impeded.

Similarly, the absence of cerebellar tone on the saccadic integrator can explain the decreased latency in damping noted in response to caloric stimuli, as the fast phase of vestibulo-ocular reflexes is also monitored by the same saccadic integrator. A similar analogy can be drawn for the smooth pursuit system, postulating the need for cerebellar tone to modulate the action of a saccadic integrator in order to produce smooth pursuit movements with a closed loop continuous feedback system precisely controlling eye fixation and position at all times.

It would appear that the experimental clinical findings are compatible with Robinson's hypothesis that the cerebellum has a modulating tone upon an inherently 'leaky' neural integrator in the pons. The stability of precise eye positioning and movement (pursuit) is dependent upon a functioning cerebellum.

Summary

Studies of ocular motor function in monkeys undergoing either total or hemicerebellectomies has revealed the following abnormalities which can be attributed to cerebellar dysfunction:

1. Loss of smooth pursuit movements
2. Gaze-fixation nystagmus
3. Loss of inhibitory input on the vestibular apparatus reflected in a decreased latency and prolonged response to caloric stimuli.

It is intimated that the role of the hemicerebellum deals with ipsilateral tone and its effect on eye movements.

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