Frequency of Naturally Occurring Strabismus in Monkeys

Lynne Kiorpes, Ph.D.
Ronald G. Boothe, Ph.D.
Melvin R. Carlson, M.D.
Dalia Alfi, B.S.
Seattle, Washington

ABSTRACT

A colony of *Macaca nemestrina* monkeys was screened for naturally occurring strabismus. Thirteen cases of naturally occurring strabismus were documented, 12 esotropes and one exotrope. The characteristics of the strabismus in these monkeys were similar to those of human clinical cases. Four of the affected monkeys showed interocular differences in grating acuity. We estimated the incidence of strabismus in the monkey colony to be 4%.

Introduction

Until recently it was thought that primates other than humans do not naturally develop strabismus.[1] In 1981, we first documented the existence of naturally strabismic nonhuman primates.[2] The occurrence of natural strabismus in monkeys is important for several reasons. First, the causes underlying the development of strabismus can be studied directly in naturally strabismic monkeys. Previous research on strabismus in monkeys has been restricted to studying experimentally produced strabismus and thus precluded studying causes of the disorder. Second, the potential exists for studying genetic contributions to the development of strabismus. The monkeys described were born into a large breeding colony with well-documented genealogies. Third, information about the development of sensory deficits that are associated with strabismus, which is not available from the clinical setting, can be made available through the study of the monkey. Thus, the utility of the macaque as a model system for studying visual development under abnormal clinical conditions is increased.

Following our initial report of natural strabismus in monkeys, several important issues remained to be addressed. For example, we needed to establish the frequency of occurrence of natural strabismus in our colony. We were particularly interested in determining whether the naturally strabismic monkeys described in our first report[2] were representative of a larger population. Further, it was of interest to know whether the incidence was similar to that found in humans. Also, it was important to determine whether we could find, or produce, enough naturally strabismic monkeys to allow experimental studies. For these reasons we implemented a screening program to look for additional naturally strabismic monkeys in our colony. The results of our screening efforts to date are described herein. In addition, we describe the characteristics of the strabismus found in some of our monkeys.

Methods

Approximately 1000 monkeys were screened from the general population of the Washington Regional Primate Center. The population screened consisted primarily of *Macaca nemestrina* (Pigtails), as those were most available. However, two other species, *Macaca fascicularis* (Crab-eaters) and *Papio cynocephalus* (Baboons), were also screened when possible. The monkeys were located in one of two branches of the Primate Center, either the Field Station Breeding Colony (FS) in Medical Lake, Washington, or the Infant Primate Research Laboratory (IPRL) in Seattle, Washington. Screening was conducted between 1980 and 1983.

From the Department of Ophthalmology, University of Washington, Seattle.

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Requests for reprints should be addressed to Lynne Kiorpes, Ph.D., Department of Ophthalmology RJ-10, University of Washington, Seattle, Washington 98195.

Screening was accomplished by two primary methods: home cage observation and a series of eye alignment tests. Home cage observation, as described previously,[2] involved observing the eye alignment of each animal as it moved freely about its home cage. This procedure was used both at the FS and IPRL. At the FS it was the only feasible method to use as there are generally five or more animals per cage or room, and the animals are rarely handled by humans. On the other hand, the animals at the IPRL are singly caged and handled frequently. Thus, it was possible to do the eye alignment tests with those animals.

At the IPRL eye alignment tests were applied to all presumptively normal infant monkeys and to monkeys who were identified as having abnormal eye alignment on the basis of the home cage screening. Any monkeys who had been subjected to invasive experimental procedures were excluded from the screening. Eye alignment was assessed by five tests, performed by one of the authors, while the animal was hand-held by another person. The tests involved observation of the corneal light reflexes while the animal:

1. fixated an object at two distances, 0.3 meter and 1 meter, in the primary position.
2. tracked a target in both directions along both the horizontal and vertical meridia.
3. converged on an object brought steadily in towards the monkey's nose from a distance of 1 meter.
4. fixated an object in each of the nine diagnostic positions of gaze.
5. fixated targets during the cover-uncover test.

Throughout the eye alignment test series, the positions of the corneal light reflexes in the two eyes were compared. Asymmetries were noted. Tests showing abnormalities were always repeated within the same session. In order to maintain the interest and cooperation of the animals, a wide variety of small toys were used as targets, and the targets were changed frequently during each test session. Judgments were made only when the tester was confident that the animal was fixating.

The IPRL animals were scheduled to be tested at 4, 8, 12, and 16 weeks, however, it was not always possible to test every animal at each age. Also, it was not always possible to complete all five tests within each test session because the animals sometimes became agitated or uncooperative.

In cases where screening documented a misalignment of the visual axes, cycloplegic refractions and examinations of the fundi were conducted. Pupils were dilated and accommodation paralyzed by instilling 1 drop each of 1% Cyclopentolate and 10% Phenylephrine in each eye every five minutes for 15 minutes. The last drops were given at least one-half hour prior to examination. Most animals were lightly anesthetized with ketamine hydrochloride for the period of the examination. The extent of the strabismus was either measured by the Krimsky Prism Test or estimated by the Hirschberg method from photographs.

In some of the affected animals, visual resolution was also assessed. Methods used for obtaining acuity estimates from the animals were those commonly used in our laboratory: forced-choice preferential looking[3-5] and operant methods.[6,7] In both cases, a grating stimulus is discriminated from a homogenous field of equal average luminance, and resolution estimates are derived from the animal's performance on a large number of trials.

Results

We found 13 monkeys who demonstrated a clear misalignment of the visual axes with no concurrent neurologic abnormalities. The 13 monkeys are listed in the Table, with the relevant information for each animal. Five of these animals were noted in a previous report.[2] Most of the affected animals were Pigtails. Two exceptions were M81434-YO, a Crabeater, and M82100-ER, a Baboon. Eight were screened from the IPRL population and five from the FS. Of those found at the IPRL, three were first identified with the eye alignment tests. The rest were obvious from home cage screening.

As shown in the Table, most of the affected monkeys had esodeviations. Sample photographs of an esotropic monkey and the exotropic monkey appear in the Figure. All of the strabismic monkeys were able to hold fixation with either eye although there was often a preference for one or the other eye. The refractive errors tended to be hyperopic and in some cases were quite large. Normal macaque monkeys in our colony tend to be within 3.00 D of emmetropia by six months of age (from F.A. Young, unpublished data). For seven of the 13 monkeys the spherical equivalent of the refractive error for both eyes was greater than +3.00 D (T81008-KF, T79139-KY, M75038, T79380-SY, M81434-YO, M82100-ER, T82327-LM). With the exception of F82366-MS, all of the animals were found to have clear media and normal fundi. F82366-MS was noted to have lens opacities, as is described later.

The age at which the deviation was first noted, shown in the Table, is in most cases the age at which we saw the animal for the first time. However, in three cases, T81008-KF, M79434-UN and F82366-MS, "age noted" is known to correspond to the age of onset of the strabismus. Those animals were observed to have straight eyes at earlier ages. At least eight of the monkeys can be considered to have infantile strabismus, that is, they were noted to have strabismus by 12 postnatal weeks. In humans, the appearance of strabismus prior to 12 months characterizes infantile strabismus.[8] Since one week of visual development in this species is approximately equivalent to one month of human visual development,[6,9] 12 weeks in the monkey would be approximately equivalent to 12 months in the human.

Seven of the affected monkeys were tested at least once, monocularly and binocularly, for visual resolution. Of these monkeys, four showed interocular differences in acuity that exceeded 0.5 octave: T81008-KF, T79139-KY, T81345-VP, M79434-UN. The grating acuity data, shown in the Table, are those obtained closest in time to the refractions. These data are representative of the current visual status of all except one monkey, M79434-UN. His more

TABLE

CHARACTERISTICS OF NATURALLY OCCURRING STRABISMUS IN MONKEYS

Animal-ID	Age Noted	Refraction (Age)	Fixation Pattern* (Age)	Acuity (Age) (min arc)
T81008-KF	12 wks	OD +4.00S (23 mos) OS +4.25×0.50×80	25-30 LE(T) (7 mos)	OD 1.3 (28 mos) OS 2.0
T79139-KY	15 wks	OD +4.00+0.50×90 (13 mos) OS +5.00S	25-30 RE(T) (20 wks)	OD 7.5 (16 mos) OS 5.0
M75038	5 yrs	OD +6.50+0.50×180 (5 yrs) OS +6.00S	25-35 ALTERNATING ET (5 yrs)	
T79325-RF	10 wks	OD Plano (4 yrs) OS −1.00+0.50×60	RE(T) (never measured or photographed)	
T79380-SY	6 mos	OD +8.00S (9 mos) OS +8.00S	20-25 RE(T) (6 mos)	
M79434-UN	5 wks	OD 0.0+0.75×180 (20 wks) OS −0.25+0.50×180	30-35 ALTERNATING ET (20 wks)	OD 1.4 (10 mos) OS 2.2
T81345-VP	4 wks	OD +3.00+1.50×150 (7 mos) OS +2.00+1.00×30	40-50 ET; ALTERNATES BUT PREFERS OS (17 wks)	OD 2.0 (11 mos) OS 1.0
M81434-YO	6 mos	OD +6.75S (14 mos) OS +4.50+0.50×90	20-25 ALTERNATING ET (6 mos)	
M82100-ER	18 wks	OD +5.00+1.00×75 (9 mos) OS +4.50+1.50×120	20-25 ET; ALTERNATES BUT PREFERS OD (20 wks)	
T82250-JF	1 wk	OD +1.00S (20 mos) OS +1.25S	15-20 ALTERNATING XT (4 wks)	OD 6.1 (8 wks) OS 6.4
T82327-LM	12 wks	OD +4.00+1.00×90 (18 wks) OS +5.00+1.50×90	40-50 ALTERNATING ET (16 wks)	OD 3.2 (14 mos) OS 2.9
T82265-JO	5 wks	OD +5.00S (20 mos) OS +3.00S	20-30 LE(T) (6 mos)	
F82366-MS	5 wks	OD +6.00S (16 mos) OS −1.00S	20-25 LET (6 mos)	OD 2.9 (16 mos) OS 3.4

**ET — Esotropia*
E(T) — Intermittent esotropia
XT — Exotropia
Measurement in Prism Diopters

recent data show less than 0.5 octave difference between the eyes. The other three monkeys who were tested for visual resolution (T82250-JF, T82327-LM, F82366-MS) had 0.2 octave or less difference between their eyes. None of the seven monkeys tested showed evidence of binocular summation, a measure of binocularity that can be demonstrated in normal monkeys.

In addition to the 13 cases listed in the Table, there were several other animals identified during the screening that are less well-documented but are worthy of note. Two additional monkeys demonstrated a manifest esotropia; one had an alternating esotropia (M80220-CH) and one had a constant left esotropia (T79320-RB). Unfortunately, they both died before further evaluations could be made. Six monkeys demonstrated abnormalities on the eye alignment tests but failed to complete cover testing. They all appeared to have intermittent esodeviations on some tests.

In order to arrive at an estimate of the incidence of strabismus in our colony we considered only the population at the IPRL, where we conducted the eye alignment tests. From the time screening began in mid-1980 until mid-1983, 130 monkeys were evaluated. Five (4%) were confirmed as

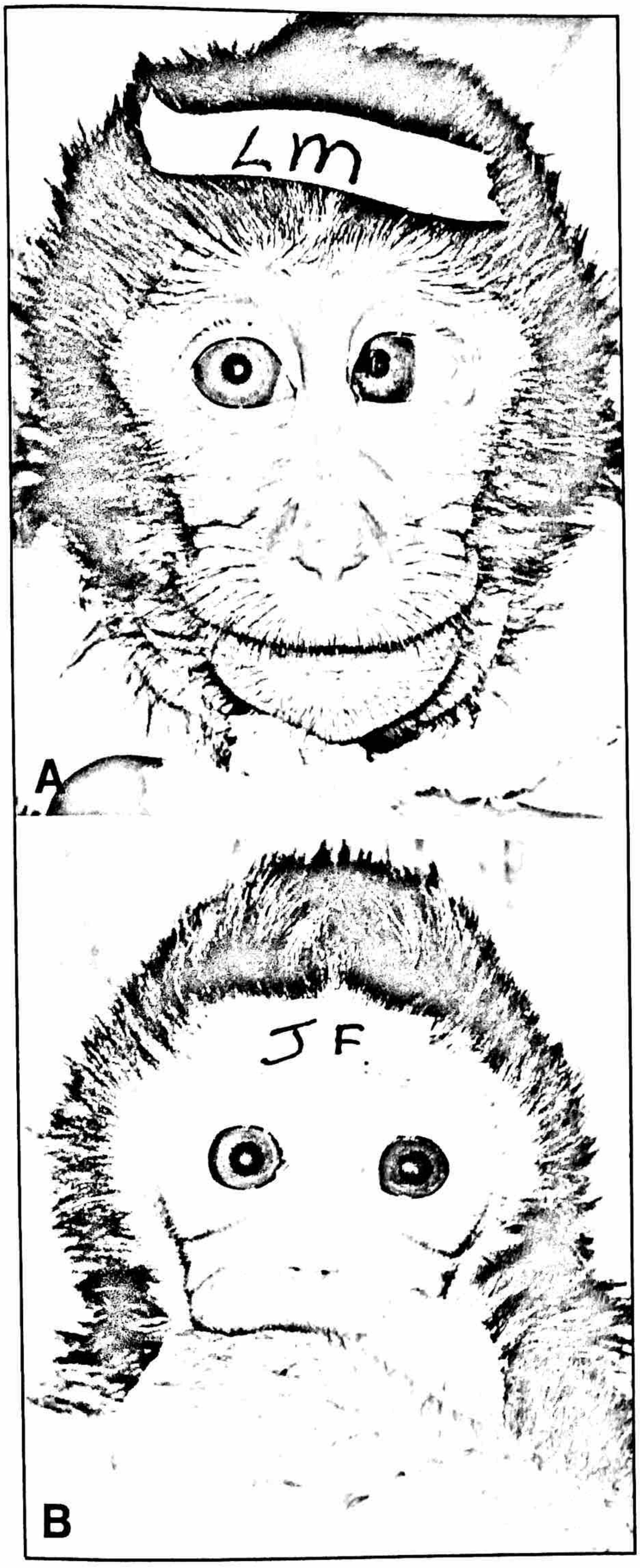

FIGURE: Sample photographs of naturally strabismic monkeys. (A) Esotropic monkey LM, shown fixating with her right eye. (B) Exotropic monkey JF, shown fixating with his right eye.

strabismic and are among those listed in the Table (T81008-KF, T81345-VP, T82250-JF, F82265-JO, F82366-MS). The incidence of 4% is similar to that reported for human clinical surveys.[10,11]

Discussion

The results of our screening suggest that there are many similarities between human and monkey strabismus. Our estimated incidence of strabismus in monkeys is 4%, which is within the 3-5% range estimated for human populations.[10] Also, many of the affected monkeys demonstrated hyperopic refractive errors that are also associated with strabismus in humans.[12,13] The characteristics of the strabismus in some of the individual monkey cases resemble those of the strabismus in more common human clinical cases. A few cases that are most similar to human cases are described below.

Two monkeys have what resembles an infantile esotropia syndrome that, in humans, is characterized by a large-angle, constant esotropia and is documented prior to six postnatal months. M79434-UN and T81345-VP were both found to have constant, fairly large-angle esotropia that appeared within the first six postnatal weeks. Acuities for the two eyes of each monkey were similar, i.e., there was no amblyopia, at the time the strabismus was first noted. Fundus examinations were unremarkable and retinoscopy showed their refractive errors to be within the normal range for monkeys their age. Both monkeys showed interocular differences in visual resolution at various times during development. T81345-VP continues to demonstrate amblyopia, to date, whereas by the age of two years, M79434-UN had similar acuity in his two eyes.

Another interesting case is that of F82366-MS. His strabismus may have developed as a result of early diffuse occlusion. He had a bilateral anterior chamber hemorrhage, most likely as a result of birth trauma, that was noted at two days postnatal. Both pupils were clear by about 10 days postnatal and there was no obvious misalignment at that time. Over the next several weeks he was tested for visual resolution and was found to consistently have poorer than normal vision, tested binocularly. At five weeks he was first noted to have a misalignment, that first appeared as an intermittent exotropia. By about 12 weeks, a constant esotropia had developed. Examination at 12 weeks revealed lens opacities in both eyes with the left eye more involved than the right. By 14 months the lenses had cleared but a substantial anisometropia was present (Table).

In summary, our findings indicate that strabismus occurs in nonhuman primates with reasonable frequency. Some of the cases studied are similar to common human clinical cases. The incidence also seems to be similar to that reported for humans. Given that strabismus in humans is thought to be familiar,[14,15] we are attempting selective breeding with the hope of producing more affected animals. In the near future we hope to have sufficient numbers of subjects to begin studying mechanisms underlying the development of strabismus and amblyopia in primates.

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