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Eye movements in canine hemichiasma: does human hemichiasma exist?

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Abstract *Purpose:* We wished to compare the eye movements seen in two Belgian sheepdogs whose crossing retinal fibers from *one eye* were interrupted at the optic chiasm (hemichiasma) with those seen in dogs lacking any crossing fibers (achiasma). In the latter condition, congenital nystagmus (CN), see-saw nystagmus (SSN), and strabismus result; also, unyoked or uniocular eye movements (saccades and nystagmus) are possible. *Methods:* Eye movements during fixation were measured using infrared reflection. Data were digitized either at 250 Hz with 8-bit resolution or 200 or 400 Hz with 16-bit resolution. *Results:* One dog behaved normally, indicating good stereopsis, and had no nystagmus. However, unyoked and uniocular saccades were recorded and the number of fibers from the good eye were close to normal. The other dog mimicked the behavior of dogs with achiasma, including CN and SSN and there was a reduced number of fibers from the good eye and an increased number of fibers to the ipsilateral lateral geniculate. *Conclusions:* Although *bilateral* redirection of retinal fibers that would normally cross may be strongly associated with the CN and SSN seen in achiasmatic canines and humans, *unilateral* redirection is not. The preservation of one 'binocular' representation of the central visual field seems to be sufficient to calibrate both horizontal and vertical ocular motor subsystems, thereby preventing the development of CN and SSN; hemichiasma may not result in strabismus. Dogs with either achiasma or hemichiasma make uniocular saccades. The discovery of canine achiasma led to the identification of its human counterpart and canine hemichiasma now raises the possibility of a similar syndrome in humans. Human hemichiasma may mimic achiasma, with CN and SSN, or, unlike achiasma, it might not be associated with CN, SSN, or strabismus, preserving stereopsis. Thus, it might easily go

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undetected in the human population. However, human hemichiasma may be differentiable from achiasma by imaging the chiasm, or possibly, using VEP.

Key words Hemichiasma; achiasma; nystagmus

Introduction In the early 1990s, a remarkable new visual system abnormality (canine 'achiasma') was described in dogs in which optic nerve fibers fail to cross at the optic chiasm.[1-4] Experimental analysis of these achiasmatic mutants demonstrated that the entire nasal hemiretina with its misdirected ipsilateral projection made functional connections in the thalamus and in primary visual cortex. A critical finding was that input from nasal and temporal sides of the same retina were integrated at the cortical level. Adjacent neurons often responded to visual stimuli that were far apart, often on opposite sides of the vertical meridian. Given this radical misarrangement of maps of visual space, it is not surprising that the ocular motor system of these achiasmatic dogs did not develop normally, and the syndrome is associated with congenital nystagmus (CN) see-saw nystagmus (SSN), and strabismus. This is now also known to be the case in achiasmatic humans.[5]

We have recently discovered a variant mutant phenotype in which fibers from only one eye fail to decussate: canine *hemichiasma.* This incomplete form has, if anything, more dramatic effects on visual system anatomy than does the bilateral phenotype.[6-8] For example, optic tracts differ more than threefold in size, patterns of lamination in the dorsal lateral geniculate nucleus are severely altered and asymmetric, and maps of visual space in the cortex can be inverted. However, the *uniocular decussation* error does not invariably result in obvious ocular motor abnormalities. In this report, we examine the eye movements in two hemichiasmatic animals and consider anatomical, physiological, and genetic factors that contribute to the development of ocular motor abnormalities in this family of dogs. The marked similarity in ocular motor abnormalities in achiasmatic dogs and humans, combined with findings reported in this study, raises the possibility that hemichiasma may also exist in humans.

Methods All applicable N.I.H. guidelines and regulations regarding the care and handling of dogs were followed at the kennel and were adhered to in this study.

RECORDING We designed and constructed a sling apparatus to comfortably hold and restrain the heads of untrained dogs. Details of the apparatus may be found elsewhere.[4] The sling was used to record one of the dogs with hemichiasma (M6). The other dog with hemichiasma (MP1) was recorded using our previous protocol.[2]

For M6, horizontal and vertical eye movement recordings were made using a mobile system employing the IR reflection method; the IR system bandwidth was 0-100 Hz and drift was less than 10 mv/h (0.03°/h). Eye movements were calibrated using simultaneous light and sound sources at ±15° or ±20° horizontally and ±10° vertically. Eye position signals were digitized on-line at either 200 or 400 samples/sec and

simultaneously displayed on the computer screen using the ViewDac data acquisition software (Keithley, Taunton, MA, USA). Data files for each 20- or 40-second recording interval were stored in binary format with 16-bit resolution for later analysis.

For MP1, horizontal eye movement recordings were also made using the above mobile system employing the IR reflection method. Eye position signals were digitized on-line at 250 samples/sec and displayed by a Tektronix TDS 420 digitizing oscilloscope. The oscilloscope was interfaced to a Macintosh IIci via the IEEE 488.2 protocol. Data files for each 20-second (5000 samples) recording interval were stored in ASCII format with 8-bit resolution for later analysis.

Constant monitoring of each dog, by placing a hand on the back of their head, allowed us to note any movement that might occur during the 20- or 40-second record; such movement was rare and, when it occurred, the data were excluded.

Due to the nature of the recording apparatus (i.e., one channel for each eye), simultaneous measurements could be made from both eyes in either the horizontal or vertical plane but not in both planes simultaneously. However, *either* eye could be recorded in *either* plane, allowing simultaneous recordings of one eye in the horizontal plane and the other in the vertical plane. Thus, we were able to make waveform, amplitude, frequency, and phase comparisons between the eyes in either plane when recording both eyes in that plane and, using that information plus simultaneous horizontal and vertical data, imply interplane waveform, frequency, and phase differences for each eye. Simultaneous recordings of both eyes in both planes, made with an Ober system on an achiasmatic canine, verified the phase relationship between the horizontal and vertical motion of the eyes.[4]

PROTOCOL Eye movements were recorded in a quiet examination room at the kennel where these untrained dogs were housed. The dogs were encouraged to view LEDs, blinking and noise-making toys at known gaze angles. Either horizontal, vertical, or a combination of horizontal and vertical eye movements were made from the two eyes simultaneously under binocular or monocular viewing conditions. Because of the cooperative nature of most sheepdogs, we were able to obtain eye-movement records from dogs without the use of sedatives. The absence of a chiasm in the mutant dogs was verified by anatomical postmortem studies.[1,9] All mutant dogs with nystagmus in this family who had been studied anatomically, either lacked a chiasm or, in M6, had a severely maldeveloped chiasm. The pedigree of this family is shown in Figure 1.

ANALYSIS Data analysis (and filtering, if required), statistical computation of means and standard deviations, and graphical presentation were performed using either the ASYST (Keithley) or MATLAB (The MathWorks, Natick, MA, USA) software for scientific computing. Eye velocities were obtained by digital (2-point, central-difference algorithm) differentiation of position signals. Further details on ASYST may be found elsewhere.[10]

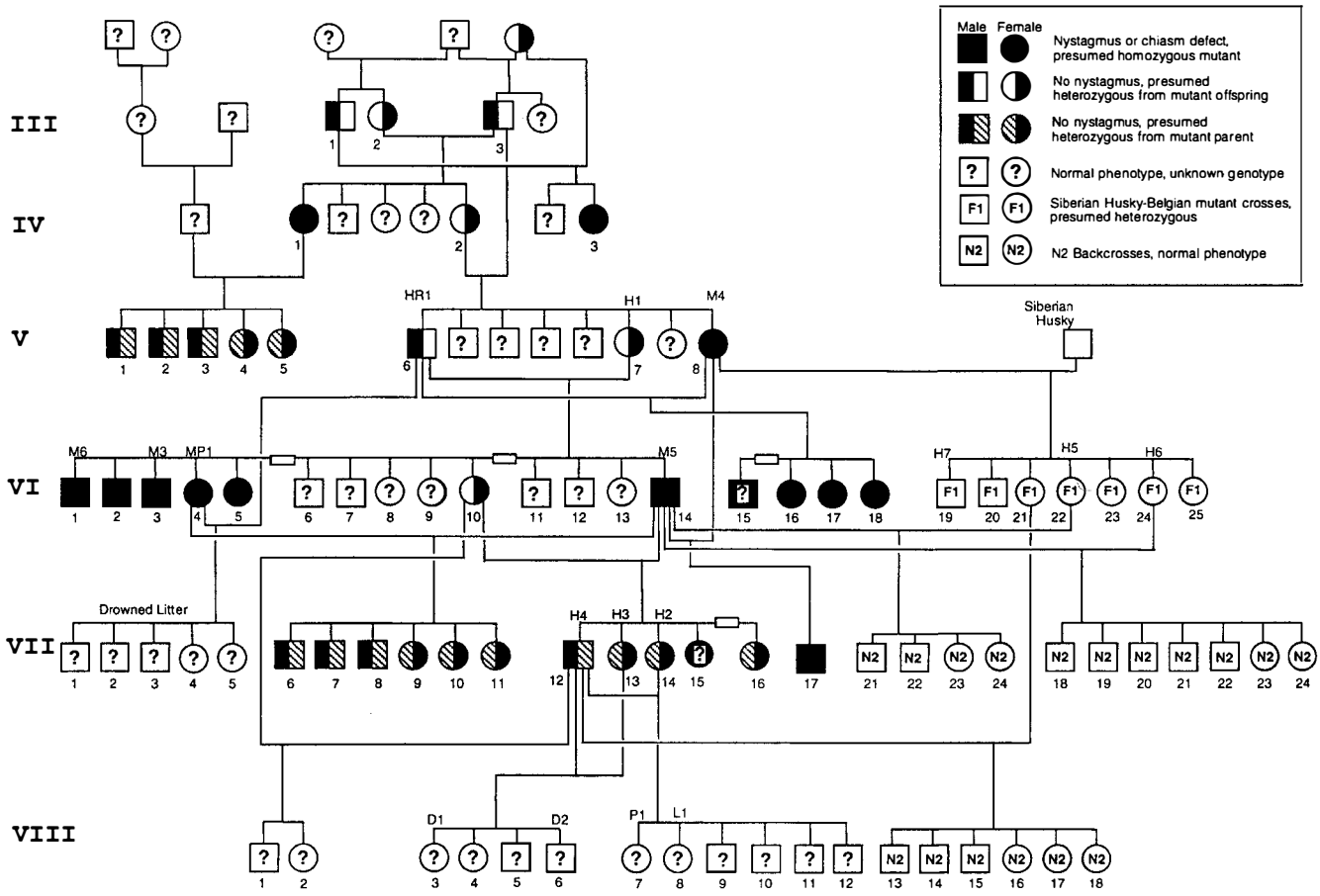


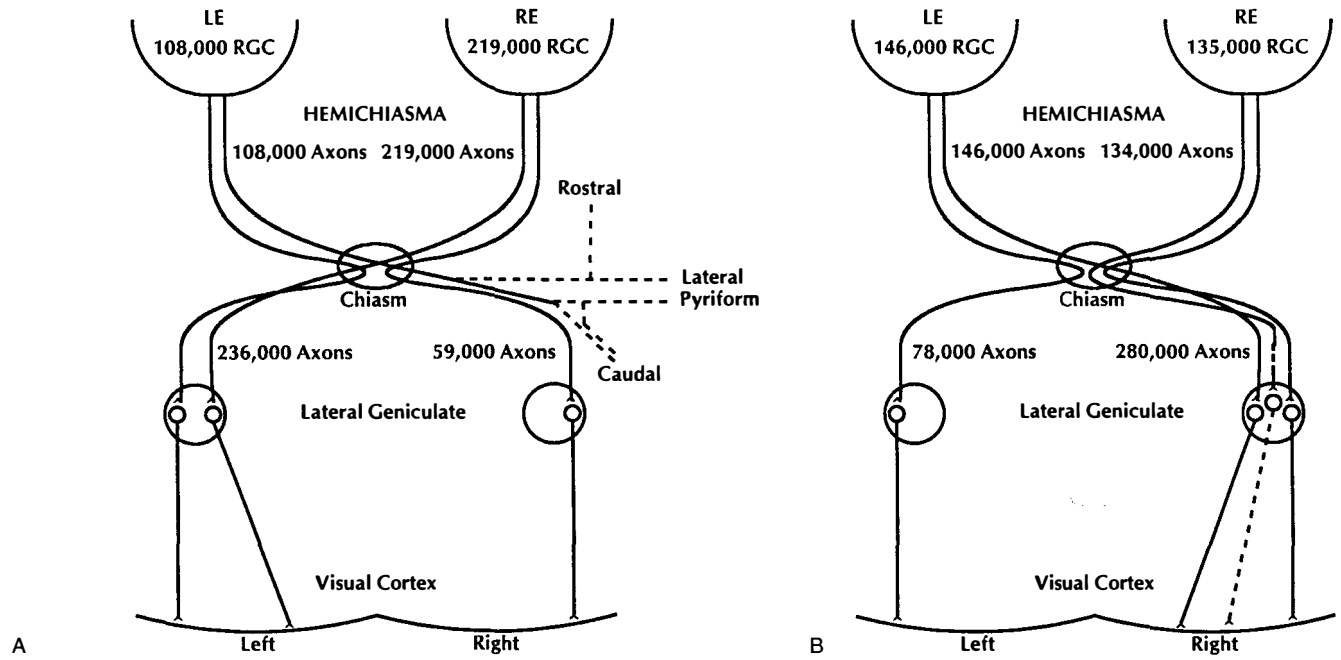
Fig. 1. Illustration of the pedigree of this family of Belgian sheepdogs containing the achiasmatic mutation. Family members from this and previous studies are identified by their alphanumeric labels.

Results We will divide the presentation of our studies of these two dogs into the following areas: behavioral characteristics; an anatomical synopsis of retinal projections and the structure of retinotopic maps; and, finally, ocular motility characteristics.

BEHAVIOR The behavior of MP1 was entirely normal. The dog was able to jump onto and off of raised platforms with ease, indicating good stereopsis and depth perception. MP1 was attentive to all visual stimuli and appeared to have normal vision.

The behavior of M6 mimicked that of the achiasmatic members of this family. He was not very attentive to his visual surroundings, was tentative and fearful when presented with new situations, and did not jump onto or off raised platforms spontaneously.

RETINAL FIBERS In normal dogs, 80% of the retinal fibers decussate at the optic chiasm, with 20% remaining ipsilateral.[9] In MP1, only fibers from the right eye decussated, with a near normal 73% crossing; none of the fibers from the left eye crossed into the contralateral optic tract (see Fig. 2a). Although there was unequal input from both eyes to the optic chiasm, the input from the right eye (whose fibers decussated) was normal. A small aberrant fascicle exited the left side of the chiasm, crossed the midline rostrodorsal to the chiasm, and split into five misdirected branches. None of the fibers from the left eye entered the right



optic tract. The left tract contained 3-4 times more fibers than the right. Thus, MP1 had hemichiasma with the number of fibers from the good eye being closer to normal than those of M6, who had a reduced number of fibers from the good eye.

In M6, only fibers from the left eye decussated, with 58% crossing; none of the fibers from the right eye crossed into the contralateral optic tract (see Fig. 2b). There was equal but reduced input from both eyes to the optic chiasm. The 'near-normal' (58% vs. 80%) right optic tract contained 3-4 times more fibers than the left.

CORTICAL MAPPING The left lateral geniculate nucleus of MP1 (with a larger than normal projection) was innervated by both nasal hemiretinas and possibly by both temporal hemiretinas; it contained duplicates of both the A and the A1 laminae.[6] The right LGN was probably innervated by only the ipsilateral retina and had no interlaminar zones. The asymmetry was reflected in the right retina, where the temporal hemiretina was expanded (3% in area), the peak ganglion cell density was 20% higher than that of the left retina, and the number of ganglion cells higher by a factor of two; the area centralis was larger.[9] Mapping in the striate cortex showed a vertical inversion in the map of visual space compared to normal dogs. Superior fields were located rostrally and inferior fields caudally. Binocular fields were recorded in the central 25° of visual space, with peripheral monocular fields located contralaterally. Ipsilateral fields were recorded to 10° and were all binocular.

The left LGN of M6 was unlaminated and not uniformly innervated, despite receiving input from only the left eye.[7] The right LGN was also poorly laminated, despite its binocular innervation. Only the caudodorsal tail of the LGN was laminated. The right superior colliculus received binocular but patchy input. The left colliculus, innervated by only the ipsilateral eye, was very poorly innervated only in one restrict-

Fig. 2. Illustrations of uniocular decussation at the optic chiasm of the retinal fibers in two Belgian sheepdogs. (A) Left hemichiasma [MP1]. (B) Right hemichiasma [M6]. In (A), an unequal number of fibers from the two eyes reach the chiasm where those from the right eye decussate normally, while those from the left do not; the decussating fibers from the left eye formed rostral, lateral, pyriform, and two caudal branches (see text). In (B), a reduced but equal number of fibers reach the chiasm from the two eyes. Those from the left eye decussate normally and those from the right eye remain ipsilateral, resulting in a superinnervated lateral geniculate. In both cases, the normal optic tract is larger than the other; the connections between both hemiretinas indicate that fibers from both decussate and remain ipsilateral. RE, right eye; LE, left eye; RGC, retinal ganglion cells. The total numbers of axons in the retinas, optic nerves, and tracts from both eyes are indicated.

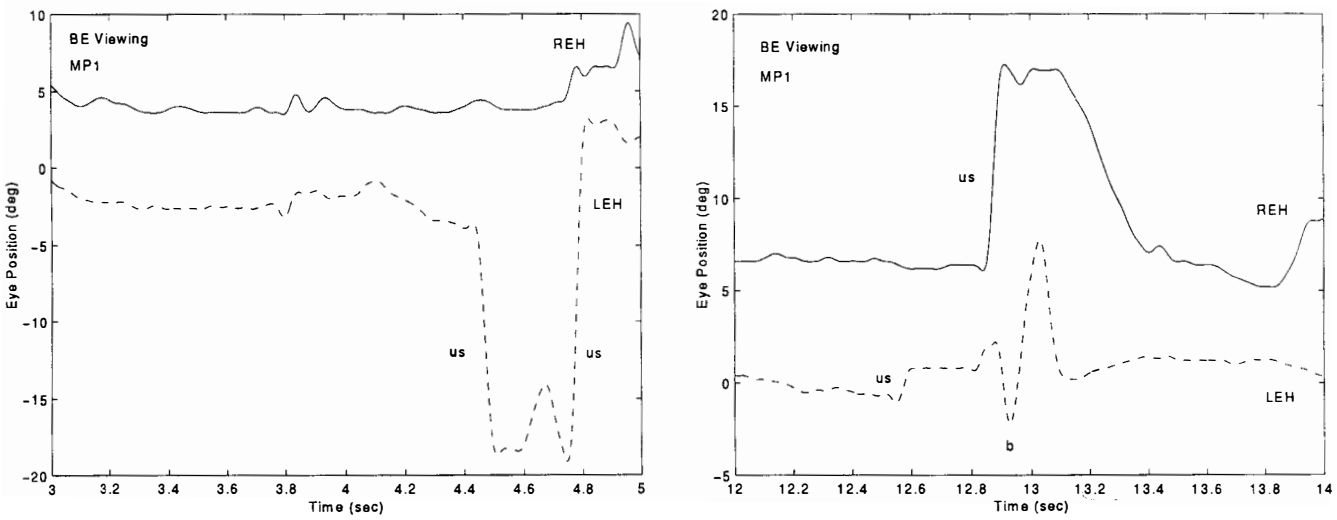


Fig. 3. Horizontal eye movements of the right (REH) and left (LEH) eyes of MP1 during binocular fixation. (A) Two large uniocular saccades interrupt fixation in the left eye. (B) Fixation in both eyes is interrupted by uniocular saccades. In this and Fig. 4 BE, both eyes; us, uniocular saccade; b, a blink; solid trace is RE (binocular viewing) or fixating eye (monocular fixation); dashed trace is LE or nonfixating eye, respectively.

ed area. Recordings in the visual cortex showed globally appropriate topography, with regional anomalies. Near the horizontal meridian, mirror-image reversals in field azimuths were mapped. Also mapped was a cell with bilateral receptive fields in mirror-image positions across the vertical meridian. Most units lacked orientation selectivity and responded well to all orientations.

OCULAR MOTILITY The ocular motility of MP1 was normal, both clinically and as determined by ocular motor recordings. Neither CN nor SSN was present and the animal made conjugate saccades. The only unusual eye movements recorded were occasional uniocular saccades, similar to those reported in canine achiasma.[2,4,11] Figure 3 shows these saccades, which could occur in either the left (Fig. 3a) or the right (Fig. 3b) eye and could be quite large.

The eye movement recordings of M6 were indistinguishable from those of achiasmatic dogs, with both CN and SSN; uniocular saccades were also present.[4] The CN waveforms were either pendular or jerk with extended *centralisation*, the latter being the canine equivalent of the human waveform, jerk with extended *foveation*. The pendular CN varied from 1° to 4° at 5-6 Hz and the jerk varied from 12° to 16° at 1 Hz. Figure 4a shows the pendular CN of M6, which exhibited interocular amplitude variability. In addition, the record contained conjugate and uniocular saccades along with slow (1 Hz) vergence variations. The horizontal CN of both eyes was usually conjugate, with occasional phase shifts of 90-180°. The SSN of M6 was pendular, varying from 1° to 6° and 3 to 6 Hz; typical of SSN, the two eyes oscillated 180° out of phase. Figure 4b shows his pendular SSN, vertical saccades (typical of the fast phases of jerk SSN), and a disconjugate vertical saccade.

Discussion In this study, we have presented ocular motor and neuroanatomic data from two canines with differing manifestations of a newly discovered abnormality: *hemichiasma*, decussation of the retinal fibers of only one eye. The presence of this abnormality in a mammal,

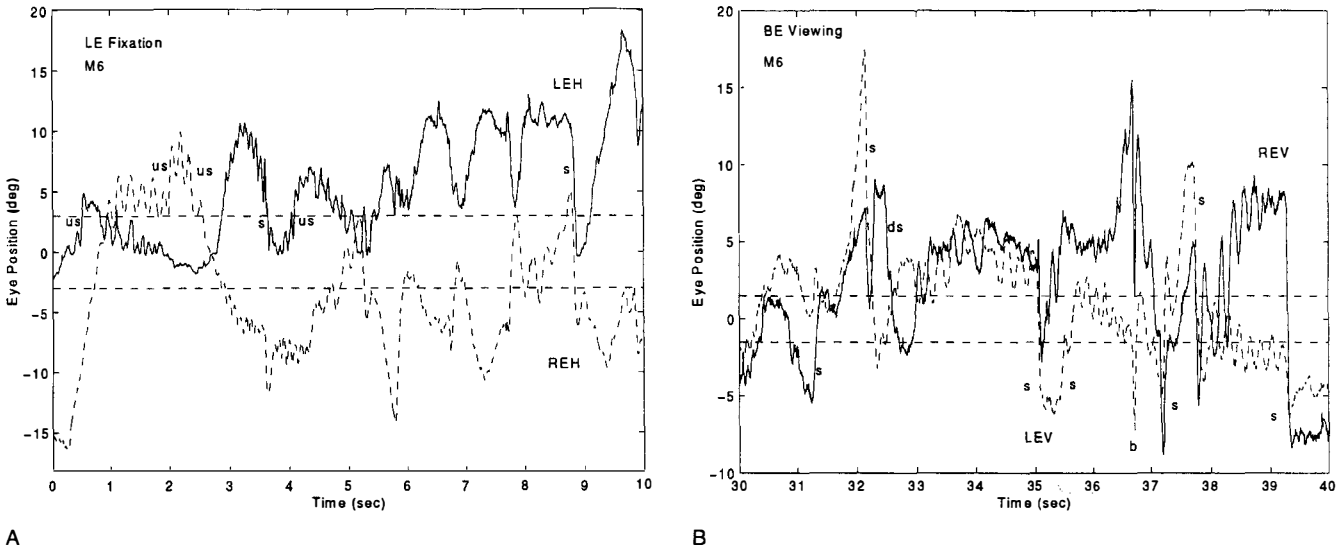


Fig. 4. Horizontal and vertical eye movements of the right (REH and REV) and left (LEH and LEV) eyes of M6 during binocular fixation. (A) Pendular congenital nystagmus during left-eye fixation with both conjugate and uniocular saccades and with slow (~1 Hz) vergence variations. (B) Pendular see-saw nystagmus during binocular viewing with both time-locked and uniocular saccades. s, time-locked (conjugate) saccade; ds, disconjugate saccade; dashed lines indicate the extent of the horizontal (A) and vertical (B) area centralis. For other abbreviations, see Fig. 3.

not unlike the discovery of canine achiasma, raises the possibility of its existence in humans. The ability of hemichiasma to present without either ocular motor or visual abnormalities increases the probability that it might go undetected.

BEHAVIOR AND GENETIC VARIABILITY For several years prior to anatomic study, MP1 was considered a perfectly normal dog and M6 an achiasmatic mutant. These initial classifications were based on both their behavior and ocular motor signs, as well as the breeding pattern of MP1 (see Fig. 1). MP1 was bred to a known carrier (HR1) and to a mutant (M5) – *no* mutant pups resulted.

Clearly, normal behavior, the absence of ocular motor dysfunction, or apparent breeding pattern have proved to be insufficient grounds to correctly assess the genotypes of members of this family of sheepdogs. The anatomical identification of MP1 as a mutant, albeit with incomplete penetrance (i.e., not a total lack of an optic chiasm), contributes to our understanding of the genetic transmission in this family of Belgian sheepdogs. The pattern of inheritance of the achiasmatic mutation in Belgian sheepdogs was initially thought to be most consistent with the segregation of an autosomal recessive mutant allele.[1] That simple interpretation is no longer tenable. An outcross of a mutant female (M4) to a wildtype Siberian husky (N1) produced a litter of six F1 obligate heterozygotes, all of whom had normal ocular motor and visual behavior (D. Goldowitz and R. Williams, unpublished observations). This is consistent with a recessive model. However, a subsequent backcross of one of the F1 females (H6) to a mutant Belgian male (M5) produced a litter of seven behaviorally normal dogs (see Fig. 1). If the mutation behaved as an autosomal recessive with complete penetrance, then each offspring would have had a 50% probability of being mutant. The probability of all seven being normal is only 0.0078. This result indicates that the penetrance of the mutation is compromised by the presence of alleles at other gene loci, inherited from the Siberian husky sire. There are, in other words, strong epistatic interactions that suppress the achiasmatic phenotype. But, as shown in

the present paper, even in a pure Belgian sheepdog background, the achiasmatic mutation leads to variable phenotypes. Belgian sheepdogs are far from being inbred[12] and it is therefore possible that the variation among Belgians is due to polygenic factors. However, many mutations have variable phenotypes even when placed on a fully inbred background. It is therefore possible that the cascade of genetic and developmental miscues that results in an achiasmatic phenotype is inherently variable.

RETINAL FIBERS The functional significance of a reduced number of retinal fibers or of the percentage that decussate from a given eye may be greater than previously appreciated. In M6 (the more seriously affected dog), the right optic tract contained 3-4 times the number of fibers as the left, although it was only 1.5 times larger in area and in MP1, the left optic tract contained four times as many axons as the left and was 3.5 times larger in area. It is possible that either the number of axons or the percentage that decussate might contribute to the failure of the ocular motor system to develop into a stable control system with the result being nystagmus, either CN or SSN.

CORTICAL MAPPING The inability to map the visual world into a meaningful cortical representation may also have deleterious effects on ocular motor-system calibration and stability. In M6, areas of contralateral innervation were arranged in groups or islands, surrounded by ipsilaterally driven regions (complete details of the anatomical and physiological methods and data are in preparation by Hogan, Garraghty, and Williams). Binocularly driven units were found at the borders of these islands. The mirror-image receptive fields found were similar to those found in the LGN of achiasmatic dogs and albino cats.[1-3] Thus, both the achiasmatic dogs and M6 had conflicted cortical maps and they all developed CN and SSN. Conversely, the normal horizontal mapping of MP1 (whose deficit was milder) coincided with a stable ocular motor system (i.e., no nystagmus).

OCULAR MOTOR STABILITY Our previous studies of achiasma suggested that total failure of the retinal fibers from both eyes to decussate at the optic chiasm allowed the development of both CN and SSN in dogs and humans.[2,4,13] Both of the canine subjects of this report had uniocular failure of the retinal fibers to decussate, but only one developed the characteristic instabilities of achiasma. There were several differences between these two animals that our studies uncovered. First, the dog with CN and SSN (M6) had reduced retinal fiber input to the chiasm from both eyes with a reduced percentage of crossing fibers, while the dog with no instabilities (MP1) did not; instead, she had normal retinal input from one eye and reduced input (50%) from the other. The contralateral LGN was markedly smaller (25% of the normal number of fibers) as a result (see Fig. 2a). Second, M6 also had a superinnervated LGN and confused cortical mapping with mirror-image reversals, similar to those found in the achiasmatic dogs studied,[1] whereas MP1 had relatively normal mapping. Third, M6 was monocular and MP1 had at least some binocularity. We can dismiss this latter

finding as a possible factor because strabismus and monocularity are not causal factors for either CN or SSN. Remaining possibilities are that either the number or percentage of decussating retinal fibers or the resulting cortical mapping are critical to developmental ocular motor stability. Perhaps both are necessary. Finally, it is possible that the asymmetry between the retinas of MP1 and the resulting asymmetries of the LGN allowed one map to 'take over' (i.e., dominate the visual system) and ocular motor stability resulted as a result of the absence of conflict.

There are many afferent conditions associated with human CN that are not its direct cause. Similarly, hemichiasma is not causally related to either CN or SSN; that is, it is not the direct cause of either (or, MP1 would have had CN and SSN). Hemichiasma is a condition that may interfere with the proper calibration of the developing motor control system (as in M5). Motor oscillations, such as CN and SSN, are the direct result of unstable gain and phase relationships in their respective control systems.

Previously, uniocular saccades were found in achiasmatic dogs,[2-4] and the ability to make them led to the suggestion that the architecture for individual ocular motor control of each eye (indeed, each eye muscle) existed in dogs.[11] Recent evidence supporting this hypothesis has now been found in normal monkeys, where *uniocular* burst-cell populations have been identified.[14-16] The presence of uniocular saccades in both these dogs, especially in MP1, who had no ocular motor abnormalities, raises the possibility that even *normal* dogs may be able to generate unyoked saccades. It might be advantageous for them to have this ability because they have large monocular peripheral fields. We are presently evaluating the eye movements of several normal dogs, unrelated to this family of Belgian sheepdogs, to address this question.

HUMAN HEMICHIASMA At the time the condition of achiasma in Belgian sheepdogs was identified, its counterpart in humans, or in any other species, was unknown. Although abnormalities of crossing fibers can be determined using VEP, the absence of an optic chiasm in humans can only be definitively diagnosed from postmortem anatomic studies or images of the chiasm. It was only after the identification of SSN from a videotape of the eye movements of a human with achiasma (later diagnosed by MRI), that the significance of SSN as a possible diagnostic tool in human infants was appreciated.[5] Now, because of our identification of hemichiasma in canines, the possibility is raised that this condition may also exist in humans. In hemichiasma, even good imaging studies of the chiasm might not reveal a structural abnormality. Furthermore, it could present in either a mild form (as in MP1) with no ocular motor signs or a more severe form (as in M6) mimicking achiasma. In the former instance, it is likely that the condition would go undiagnosed because of the lack of ocular motor instabilities or other ophthalmological symptoms. In the latter instance, it could easily be confused with the recently recognized condition of human achiasma; only clear images of the optic chiasm may be able to differentiate the two. If the images of any of the four currently identified 'achiasmatic' humans show only structural abnormalities of the chiasm

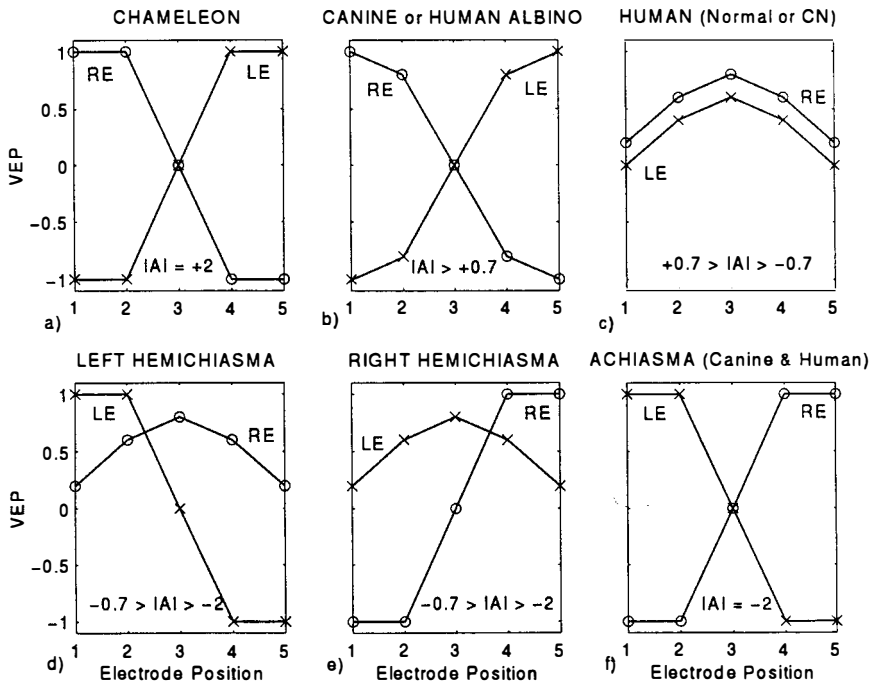


Fig. 5. Schematic, idealized, and hypothetical (a, d, and e, respectively) illustrations of monocular pattern-onset VEPs of (a) total decussation from both eyes (chameleon), (b) greater than 55% decussation (canine or human albino), (c) approximately 50% decussation (human – normal or with CN) with LE VEP shifted downward for clarity, (d) right uniocular decussation (left hemichiasma – canine [MP1]/human?), (e) left uniocular decussation (right hemichiasma – canine [M6]/human?), and (f) 0% decussation from both eyes (achiasma – canine or human). In (d) and (e), the illustrations are for human data. Also shown (here and in Fig. 6) are the expected values of the interocular asymmetry index (IAI) in each case. X-axis: electrode position (left=1, right=5). Y-axis: peak values of C1 component in arbitrary units. RE, right-eye stimulation; LE, left-eye stimulation.

rather than its total absence, it is possible that the correct diagnosis for those individuals is 'hemichiasma with associated CN and SSN' – that is, the more severe form of hemichiasma.

The above possibility leads to the question of whether VEP could be helpful in distinguishing human hemichiasma from achiasma. Figure 5 illustrates schematically the monocular pattern-onset VEP of (a) total decussation (as in the chameleon), (b) greater than 55% decussation (normal canines and human albinism[17]), (c) approximately 50% decussation (normal humans and those with CN[18]), (d) and (e) left and right uniocular decussation (canine/human? hemichiasma), and (f) no decussation (canine and human achiasma); parts a, d, and e are theoretical extrapolations based on the existing data represented schematically by illustrations b, c, and f. The VEP for total decussation was created by extrapolating the trends shown from c to b and opposite to f. Similarly, interpolation between the illustrations in c and f yielded the expected VEP profiles for uniocular decussation shown in d and e.

The interocular asymmetry index (IAI) is the difference between the left- and right-eye lateralization values, where the lateralization value is the difference between trace 2 from the left and trace 4 from the right occiputs, respectively. For total decussation, the VEP profiles show contralateral asymmetry with an IAI of approximately +2. When there is greater than 55% decussation (e.g., in normal canines or due to albinism in humans), the amount of contralateral asymmetry is indicated by an IAI that is greater than +0.7.[17] Normal humans, with 53% decussation, exhibit small amounts of asymmetry (either ipsilateral or contralateral) and are illustrated with an IAI of 0 (±0.6). At the opposite end of the spectrum from total decussation is achiasma, with 0% decussation with and IAI of approximately -2. Canine hemichiasma (or human, if it exists) would be expected to exhibit VEP profiles similar

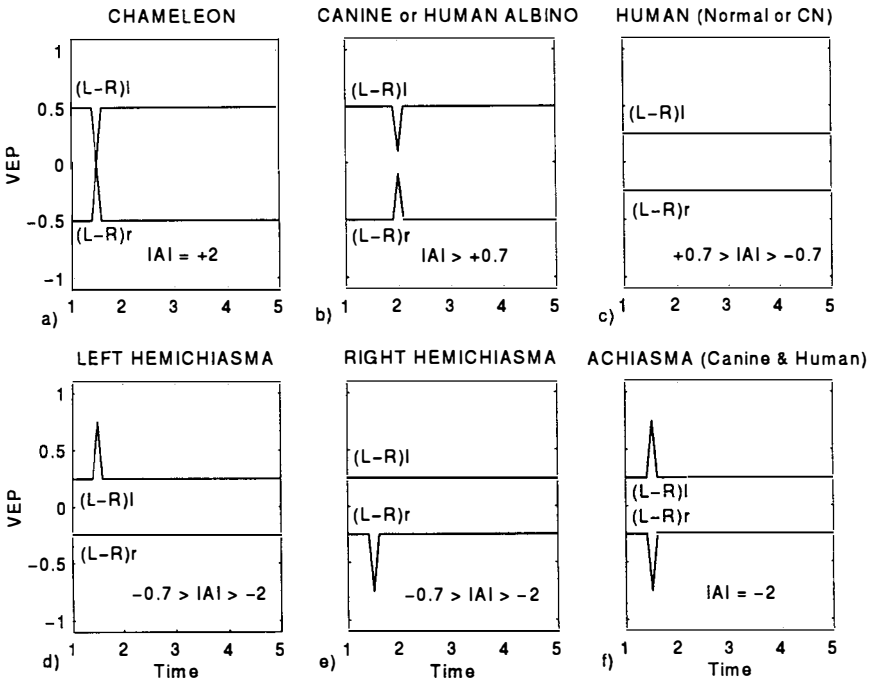


Fig. 6. Schematic, idealized, and hypothetical (a, d, and e, respectively) illustrations of difference potentials (L-R = trace 2-trace 4) from monocular pattern-onset VEPs. (a) through (f) are as described for Fig. 5. X-axis: time in arbitrary units. Y-axis: difference potentials for stimulation of left (l) and right (r) eyes. All tracings are shifted for clarity.

to those shown in d (for left hemichiasma) or e (for right hemichiasma). The IAI would be less (i.e., more negative) than -0.7 and greater than -2. Using the difference potentials illustrated in Figure 6, the tracings associated with hemichiasma are also shown in d and e. These difference potentials are distinguishable from those of 100% decussation (a), greater than 55% decussation (b), 53% decussation (c), or 0% decussation (f).

Thus, if a patient had an abnormal image of the optic chiasm that did *not* clearly establish the total absence of a chiasm and their VEP was type d or e (Figs 5 and 6) with an IAI between -0.7 and -2, the diagnosis of hemichiasma could be entertained. If they also had CN and SSN, most diagnoses other than the severe form of hemichiasma would be precluded. It is, therefore, possible that the mild form of hemichiasma has been overlooked in humans with neither CN nor SSN and the severe form may be misdiagnosed as achiasma in those with both types of nystagmus and inconclusive images of the chiasm. Given the strong association between chiasmatic abnormalities and the presence of nystagmus, VEP might prove useful in making the correct diagnosis.

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