Periodic Alternating Nystagmus in Humans With Albinism

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Purpose. To quantify the spatial and temporal nature of congenital periodic alternating nystagmus (PAN) and to test the hypothesis that PAN results from a temporal shift in the null zone.

Methods. Twenty-five subjects with oculocutaneous albinism (16 tyrosinase negative and 9 tyrosinase positive) and 7 with ocular albinism (5 x-linked and 2 autosomal recessive) participated in the study. Using infrared oculography, five features of the nystagmus were examined: amplitude, frequency, waveform, beat direction, and temporal nature of the cycle.

Results. Twelve subjects (37.5%) exhibited a PAN. The nystagmus waveforms encountered during the PAN active phases were either jerk-with-extended-foveation or pseudocycloid, whereas a variety of oscillations (including triangular and bidirectional) were evident during the quiet phases. For most of the 12 subjects, there was an asymmetric variation in nystagmus intensity during each PAN cycle. None of the 12 demonstrated a convergence null or an abnormal head posture.

Conclusions. PAN is not an uncommon oscillation among humans with albinism. Changes in gaze position markedly influenced the periodicity of the ongoing nystagmus, thus supporting the hypothesis that PAN is the result of a temporal shift in the null zone. Invest Ophthalmol Vis Sci. 1994; 35:4080-4086.

Periodic alternating nystagmus (PAN) is a rare but well-recognized form of involuntary nystagmus. Essentially, it is a conjugate, horizontal jerk oscillation in which regular reversals in the direction of the fast component are separated by brief "quiet" intervals. The time period of each cycle is variable (60 to 360 seconds) and may be asymmetric, such that the nystagmus beating in one direction is of longer duration than that beating in the opposite direction. Within each "active" phase, the amplitude, frequency, and slow-phase velocity progressively change, whereas during the quiet phase (the null zone), the eye movements are often pendular and of low intensity.

In PAN, the null zone may be considered to be equivalent to the neutral zone (i.e., the position where there is a change in beat direction) as long as there is not a high-amplitude pendular nystagmus present during the neutral zone of the nystagmus.

Current literature indicates that the majority of people with PAN have acquired this ocular motor instability after disease of the caudal brainstem or cerebellum. In comparison, there have been very few published reports of congenital PAN and in only five cases has PAN been described in association with albinism.

In recent years, we have had the opportunity to study the oculomotor behavior of a large number of people with albinism and have been surprised to discover that a significant portion exhibited PAN. It is the purpose of this paper to quantify for the first time the nature of the periodicity and explore the factors that influence beat direction and other characteristics of the nystagmus. More specifically, we carried out experiments to test the hypothesis that PAN could be explained on the basis of continuous and regular shifts in the null zone over time. Thus, at the start of a typical cycle, with the null zone located in central gaze, the PAN would be in its quiet phase. Thereafter, as the null zone moves off in one direction, (for example, to the right), a left-beating nystagmus should develop. It should be therefore possible to bring about a reemergence of the quiet phase by either looking to the right or turning the head to the left. Our experiments, using step changes in gaze position and prolonged, eccentric-fixation extended gaze, do indeed suggest that PAN results from both a spatial and temporal shift in the null zone.
MATERIALS AND METHODS

Binocular, horizontal eye movements were recorded using infrared oculography. Subjects were instructed to fixate on a stationary circular white target (0.5°) projected onto a large uniform field (172° horizontal × 50° vertical). The target had a luminance of 4.1 candelas per m², and low internal room illumination provided background screen illuminance of approximately 0.4 cd/m². Five directions of gaze were examined (−20°, −10°, 0°, +10°, and +20°) for time periods of up to 8 minutes for each gaze position. In addition, the subjects were instructed to change gaze position in response to step changes in target position. During recording sessions, head movements were minimized by the use of a chin rest and forehead restraint. Four features of the nystagmus were examined: amplitude, frequency, waveform, and beat direction. Amplitude of the nystagmus was defined as the peak-to-peak slow-phase displacement, frequency as the number of oscillations per second, and intensity as amplitude × frequency. The velocity components of the slow phases were analyzed, using methods that have been described previously, so that a profile of the constituent slow-phase velocities could be built up. A cover test was carried out on each subject to determine if a strabismus was present and also to detect the presence of either a latent or manifest latent nystagmus.

The subject sample was comprised of 32 people with albinism 8 to 57 years of age, 14 males and 18 females (see Table 1). There were four pairs of siblings and one group of three sisters. Within this sample, 16 subjects had tyrosinase-negative oculocutaneous albinism (TNOCA), nine had tyrosinase-positive oculocutaneous albinism (TPOCA), five had x-linked ocular albinism (XOA) and two had autosomal-recessive ocular albinism (AROA). All the subjects underwent full assessment to ensure exclusion of subjects with other ocular disorders associated with congenital nystagmus. Biochemical tests and clinical examination, in combination with personal and family history details, were used to aid diagnosis. Binocular visual acuities were recorded using a high-contrast (90%) Bailey–Lovie chart located in the primary position. Visual acuity was recorded as the log of the minimum angle of resolution (logMAR) from 1.0 (Snellen equivalent 6/60) to 0.0 (Snellen equivalent 6/6).

The tenets of the Declaration of Helsinki were followed in this research. Informed consent was obtained from all subjects after the nature and possible consequences of the study had been explained.

RESULTS

Periodic Alternating Nystagmus

Twelve of the 32 subjects with albinism exhibited a PAN (Table 1). These subjects came from all four major categories of albinism (four TNOCA, four TPOCA, two XOA, and two AROA). Although there was a 100% incidence of PAN in the AROA group, the small number of subjects here makes any conclusions premature. None of the 12 exhibited a convergence null or an abnormal head posture. The waveforms encountered during the PAN active phases were either jerk with extended foveation or pseudocycloid, although two of the subjects also demonstrated dual jerk oscillations on occasions. This in itself is not surprising because the jerk with extended foveation and pseudocycloid waveforms are the ones most commonly found in adults with congenital nystagmus. All subjects with PAN had strabismus, and none exhibited a latent or manifest latent nystagmus. The use of binocular eye movement recordings and the cover test excluded the possibility that the change in beat direction of the nystagmus was due to a change in eye fixation. The PAN was a genuine time-varying change in the nystagmus beat direction during primary position fixation. Visual acuities among the 12 subjects ranged from 0.90 to 0.54 logMAR.
Periodic Alternating Nystagmus Cycle

Eye movement recordings from these 12 subjects revealed many differences in the nystagmus parameters. The duration of each PAN cycle displayed both intersubject and intrasubject variation. For all 12 subjects, mean cycle length was 271 seconds, with maximum and minimum times of 141 and 430 seconds. Examination of our subjects on more than one occasion highlighted individual variation; for example, one TNOCA exhibited PAN cycles lasting 164, 225, 240, and 301 seconds during central gaze on four separate visits. Some PAN cycles were also markedly asymmetric, with one active phase being of longer duration than the other. This was particularly true for one subject with ocular albinism who had a right-beating phase of 282 seconds and a left-beating phase of 126 seconds.

Previous reports have claimed that, within one active phase, the nystagmus amplitude and frequency progressively change. Typically, the intensity is low at the start of each jerk phase, gradually builds up to a midcycle maximum, and decreases until the quiet phase is reached. This periodicity was exhibited by most of the subjects and is illustrated in Figure 1.

Mean slow-phase velocity, which is closely linked to intensity, has also been shown to vary during PAN, but not in a simple sinusoidal fashion. Instead, temporal velocity profiles of those with congenital and acquired PAN have revealed that slow-phase velocity builds up more quickly than it declines in each half cycle. Figure 2a illustrates the variation in intensity and mean slow-phase velocity over time during a complete PAN cycle, for a subject with TNOCA. The cycle is relatively symmetrical with mean slow-phase velocity increasing rapidly at the start of each half cycle, reaching the peak value after approximately 40 seconds, and then declining gradually in the subsequent 80 seconds. A slightly greater maximum velocity was found during the left-beating phase: 65°/second compared with 51°/second for the right-beating phase.

The temporal variation in intensity paralleled that of the slow-phase velocity but was consistently lower in value. Investigation of the velocity components of the slow phases revealed that the percentage of slow phase time spent at low retinal slip velocities also varied dur-
ing each PAN cycle. Figure 2b shows that this particular subject had longer "foveation" periods (defined as the percentage of the slow phase spent at velocities ≤10°/second) during her right-beating phase, as compared with her preceding left-beating phase. This difference is clearly illustrated in the velocity histograms that were constructed from data recorded on a separate occasion (Fig. 3). Here it can be seen that during the right-beating phase, up to 7.4% of the cycle was made up of velocities ≤10°/second, whereas this was only true of 0.6% of the left-beating phase. In addition, the mean slow-phase velocity was less during the right-beating phase.

Eleven of the 12 subjects with albinism with PAN did not have completely motionless eyes during their quiet phases but exhibited a variety of oscillations such as triangular, bidirectional, and pendular waveforms (Fig. 4). The duration of the three phases of PAN were found to be subject to the same external influences as a nonperiodic congenital nystagmus. For instance, when the subject felt tired or anxious, the intensity of the oscillations increased, and the length of the quiet phase shortened. In contrast, if the subject was relaxed, the quiet phase tended to lengthen, resulting in the eyes remaining virtually stationary for several seconds.

**Effect of Gaze Changes on Periodic Alternating Nystagmus**

To test the hypothesis that PAN results from a temporal shift in the null zone, eye movements were monitored at different gaze positions, in an attempt to "track" the null zone. For example, if a subject had gone into the quiet phase after a period of right-beating nystagmus, then looking into right gaze (i.e., to where the null should then move) ought to prolong the quiet phase. Similarly, it should also be possible either to abolish completely or to alter significantly the PAN cycle (such that one active phase is much longer than the other) by instructing the subject to maintain fixation on a horizontally eccentric stimulus. Examination of the resulting eye movement traces revealed that it was indeed possible to interrupt the ongoing PAN cycle and "chase" the null zone on some occasions (Fig. 5).

To explore this effect further, the eye movements of seven subjects with albinism and one with idiopathic congenital PAN were recorded at three gaze positions (0°, +20°, and −20°). At each gaze, position fixation was maintained until a complete PAN cycle had been recorded or until it became clear that the involuntary oscillations were not going to change direction—usually after a period of 6 minutes. The subjects were given a short rest after each period of fixation.
The percentages of time spent in the right-beating, left-beating, and quiet phases were then calculated for every PAN cycle. Figure 6 illustrates that, for all eight subjects who participated in this part of the study, gaze position influenced the proportions of right-beating and left-beating nystagmus compared to primary gaze. In four of the cases, there was an increase in the duration of the centrifugally beating nystagmus (i.e., right-beating on right gaze, left-beating on left gaze) at the expense of the other phase, whereas in others, the PAN cycle disappeared. Two subjects “lost” the periodicity of their nystagmus in both directions of gaze, and two others exhibited an asymmetrical PAN in right gaze and a left-beating nystagmus in left gaze. As a general rule, holding an eccentric gaze position biased the directionality of the nystagmus beat for each complete cycle. Thus, during right gaze, the time given to a right-beating nystagmus was far greater than that seen during central gaze. This would suggest that it is predominantly the movement of the null zone that is responsible for the nature of the periodicity.

**DISCUSSION**

Our recent investigations have indicated that PAN may not be uncommon in humans with albinism. This study has established that this is indeed the case: 37% of our subjects exhibited a PAN. Despite the small size of our sample (n = 32), it is unlikely that this was a chance finding because the relative number of subjects with albinism with PAN was large. In addition, those subjects with PAN did not have particularly poor acuity or other apparent visual problems that might have led to a greater level of referral to our laboratory. One possible explanation for such a high incidence is that in our laboratory we routinely monitor fixation eye movements over long continuous periods. In other published studies of people with albinism, any PAN may have been missed because recording sessions were too short to reveal the spontaneous changes in nystagmus beat direction. A larger sample of people with albinism would need to be investigated to establish the real frequency of congenital PAN in people with albinism.
Periodic Alternating Nystagmus

TABLE 1. Summary of the Eye Movement Behavior of the Original 32 Subjects with Albinism

<table>
<thead>
<tr>
<th></th>
<th>TNOCA</th>
<th>TPOCA</th>
<th>XOA</th>
<th>AROA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>16</td>
<td>9</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Age range</td>
<td>12-57 years</td>
<td>13-52 years</td>
<td>8-40 years</td>
<td>15-38 years</td>
</tr>
<tr>
<td>VA range</td>
<td>0.52-1.00</td>
<td>0.34-0.92</td>
<td>0.70-1.12</td>
<td>0.80-0.86</td>
</tr>
<tr>
<td>Strabismus</td>
<td>16</td>
<td>9</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Cn Waveform

- **Jef**: 4* 3* 2** 1*
- **PC**: 5** 3** 1 1*
- **Jdv**: 1 — — —
- **P**: 1 — — —
- **Pfs**: 2 — — —
- **DJ**: 1 1 — —
- **AP**: 1 — — —
- **PC + P**: — — 2 —
- **Jef + DJ**: — 1* — —
- **PC + DJ**: 1* — — —
- **Torsion**: 1 — — —

PAN

- **Spatial null zone**: 4 4 2 2
- **Convergence null**: 4 2 1 0
- **Abnormal head posture**: 3 2 1 0
- **Abnormal head posture**: 10 6 5 2
- **Head nodding**: 4 3 1 1

* Identifies 12 subjects with periodic alternating nystagmus (PAN). Visual acuity is given in logMAR.

The dominant waveforms on primary gaze were either Jef (jerk with extended foveation), PC (pseudocycloid), Jdv (jerk with decreasing velocity), P (pendular), Pfs (pendular with foveating saccades), DJ (dual jerk), or AP (asymmetric pendular). Some subjects exhibited a combination of waveforms, and one subject had a jerk with decreasing velocity slow phase (Jdv) waveform.

Although the variation in PAN timing with gaze position has been mentioned in several other smaller studies, this has often been in a qualitative manner. Our present research conclusively supports the hypothesis originally put forward by Daroff and Dell'Oso6 that PAN results from a temporal shifting of the null zone. It is also of interest that accurate foveation during the minimum velocity period of the slow phase of each waveform can still be achieved even with this form of nystagmus periodicity.14 Theoretically, a slow rotation of the head away from the direction of the null zone should bring the null back to center again. This head-turning strategy is sometimes adopted by a PAN subject but was not evident in our sample. This is not surprising because the adoption of an alternating head posture would require not only the precise control of the head posture, but also a regular periodicity in the shifting of the null zone. Moreover, even subjects with a congenital nystagmus and a static null zone may not adopt predictable head postures.23

In a parallel study, we also examined subjects with idiopathic congenital PAN, and the spatial and temporal nature of their involuntary oscillations appear to be indistinguishable from those of the albino group.24 Thus, any attempt to elucidate the mechanisms behind PAN cannot rely on features that are unique to albinism. For example, the suggestion that PAN or nystagmus in general in albinism is a result of visual pathway misrouting seems improbable.10,11,22

To date, there has been only one report of a PAN in an albino animal. Guillery and his colleagues, who were principally studying the aberrant visual pathways in a single albino green monkey, described a periodic nystagmus but gave no further details of the spatial or temporal characteristics of the oscillations.25 Although it is tempting to suggest that this is further evidence of the close relationship between congenital PAN and albinism, the possibility of the PAN being secondary to central nervous system disease cannot be excluded.1-4

The etiology of PAN, both acquired and congenital, has received some attention, but as yet no firm conclusions have been reached. Although the shifting null may represent a valid interpretation of these periodic oscillations and could account for the influence of gaze position on the PAN cycle found in this and other studies, it does not explain how or why the periodicity develops. Some years ago, Leigh and colleagues21 described a hypothetical model of PAN that relied on an instability in the neural mechanisms that generate vestibular and optokinetic slow phases, combined with an inability to process retinal velocity error signals. Based on physiological data, this model generated linear slow-phase oscillations with characteristics similar to acquired PAN and could predict a critical rotational stimulus that temporarily stopped the PAN...
of one individual. This model may not be fully appropriate to explain a congenital PAN, because in the congenital form, the slow phases are not linear but are almost always of an increasing velocity type.

More recently, Harris26 proposed that congenital nystagmus was due to an excess gain in the internal efference copy, positive feedback loop of the smooth pursuit system. The efference copy is a velocity feedback signal from the output of the common neural integrator of the oculomotor system (i.e., the position signal output of the neural integrator is differentiated and fed back). He further hypothesized the notion of two nulls, a velocity null and a positional null, to account for the null shifting found in PAN. The next stage of our work is to explore whether either model can successfully mimic congenital PAN, including features such as the typical waveforms and the changes in cycle with gaze angle, and also take into account the fact that these subjects with congenital nystagmus still have operational vestibular, optokinetic, and pursuit systems, within the confines of each foveation period.

Key Words
albino, periodic alternating nystagmus, null zone

References