Periodic alternating nystagmus and the shifting null

R. B. DAROFF, M.D.* and L. F. DELL'OSSO, Ph.D.** Miami, Florida

Abstract. The characteristics and etiologies of periodic alternating nystagmus (PAN) are reviewed briefly. This eye movement disorder and congenital nystagmus share many similar features, the most important being prominent neutral zones and null regions. The phenomenology of PAN can be explained by omnipresent periodic shifts of the null region.

Periodic alternating nystagmus (PAN) is perhaps the most dramatic of the cyclic ocular phenomena which also include periodic alternating lid retraction, cyclic oculomotor palsy, periodic skew deviation, cyclic esotropia, and periodic alternating gaze deviation[1-3]. Since PAN has attracted multi-disciplinary interest from neurologists, neuro-ophthalmologists, and neuro-otologists, it seems an appropriate subject for review in this special issue.

REBOUND NYSTAGMUS

Before discussing PAN, we will comment upon "pseudo-PAN". The last two patients which the senior author, after several minutes of clinical observation, had thought had PAN, actually had "rebound nystagmus"[4]. This form of nystagmus is usually of first degree and noted initially during lateral gaze deviation to one side; when the eyes are returned to primary position (straight-ahead), a brief "rebound" nystagmus in the opposite direction develops. These same patients may also shift directions during maintenance of lateral gaze. Primary position jerk nystagmus occasionally rebounds and might mimic PAN. Our first such experience was in a patient with right-beating third-degree nystagmus who was observed clinically for about 10 minutes during a conference presentation. Shortly thereafter, he developed left-beating nystagmus which lasted only several seconds before reverting again to a seemingly persistent rightward beating. We considered the diagnostic possibility of PAN with a cycle of minutes to hours in the rightward direction and only seconds to the left. However, electronystagmography (ENG) indicated that the right-beating nystagmus damped on gaze to the right, and upon refixation back to primary position a few seconds of rebound left-beating emerged. The second patient had primary position jerk nystagmus which shifted directions irregularly without definite periodicity.

From the Miami Veterans Administration Hospital and the Department of Neurology, University of Miami School of Medicine, Miami, Florida.

**Director, Ocular Motor Neurophysiology Laboratory, Veterans Administration Hospital, Miami; Professor of Neurology, University of Miami School of Medicine.*

***Co-Director, Ocular Motor Neurophysiology Laboratory, Veterans Administration Hospital, Miami; Assistant Professor of Neurology, University of Miami School of Medicine.*

Requests for reprints should be sent to Dr. R. B. Daroff, Veterans Administration Hospital, Miami, Florida 33125, U.S.A.

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We thought he had an atypical PAN but ENG recordings disclosed that the directional shifts were the results of rebounding. One must therefore consider and rule out rebound nystagmus in those patients whose nystagmus suggests PAN but with asymmetrical or irregular periods.

PAN CHARACTERISTICS

The usual cycle of PAN is 90 to 100 seconds in one direction, five to 10 seconds of neutrality (i.e., no nystagmus), and 90 to 100 seconds in the opposite direction. The time period of neutrality, called the *neutral phase,* may be free of any nystagmus, consist of pendular nystagmus, or even manifest downbeating nystagmus. The directional periods may be somewhat asymmetrical with one phase consistently longer in duration than the other. The duration of the neutral phase may differ with shifts between right-left and left-right. The changes consequent to eye closure and darkness are quite variable. In some cases eye closure and/or darkness leads to a complete cessation of the nystagmus, whereas in others the effects are minor or contrary. Sleep typically abolishes PAN.

Another interesting feature is the effect of eye closure suppression upon the duration of a cycle. We recorded a patient whose PAN in both directions was completely abolished by eye closure. During the left-beating phase, eye closure lengthened the cycle by an amount equivalent to the suppression, but the right-beating cycle was not prolonged. Furthermore, the right-ward cycle was increased by darkness even though the nystagmus was only reduced in amplitude and not totally damped.

PAN can be supplanted by caloric-induced nystagmus but the ultimate outcome of the PAN cycle is variable[5]. In so-called dominant cases, the PAN will always return to the appropriate place in the cycle after the caloric response is over. By contrast, the timing of the cycles in stimulus-dependent cases can be drastically altered by calorics. Intermediate forms are probably most frequent. We have seen a patient with dominant PAN in one direction and stimulus-dependent in the other. Moreover, even dominant PAN can be altered by prolonged and repeated caloric stimulation in the same ear. The situation would seem too complicated for simplistic classifications. Unfortunately, there has never been a detailed ENG study of repetitive caloric stimulation over many hours to delineate precisely the effects upon timing of the cycle.

ETIOLOGY

The etiologies of PAN have included head trauma, chronic otitis (?), brain stem vascular disease, brain stem encephalitis, spino-cerebellar degenerations, central nervous system syphilis, syringobulbia, multiple sclerosis, fourth ventricular tumors, cerebellar tumors, Arnold-Chiari malformations, extra-medullary cysts, and aqueductal stenosis[6-8]. Some patients are born with PAN as the only congenital manifestation of neurological dysfunction.

The disease states and structural abnormalities associated with PAN are generally no more specific than for almost all other types of acquired central nystagmus. The first pathologically reported case, by Towle and Romanul[9] in 1970, described an arachnoidal cyst ventral to the cerebellum which compressed the underlying medulla. Since then, we have been impressed that lower brain stem dysfunction, such as with Arnold-Chiari malformations, is more strongly linked to PAN than pathological alterations in the rostral stem. In addition, the causative disturbances are more likely to be chronic in nature than acute events.

MECHANISM

The PAN studies of the Freiburg neurophysiological group[10,11] are the most detailed and widely quoted. Based upon investigations

of post-rotary nystagmus, they concluded that 200 seconds was the fundamental constant of the central vestibular system in humans. PAN, which generally has a 200 second duration, was considered to be the manifestation of extreme vestibular hyper-responsiveness representing the "release" of the normal physiological periodicity of post-rotary nystagmus.

SHIFTING NULL

We will conclude with an exposition of our conceptualization of the phenomenology of PAN. Firstly, PAN and congenital nystagmus seem to share many of the same features; indeed, some cases of PAN are actually forms of congenital nystagmus. Sleep abolishes both. Many cases of PAN have developed after the patients became blind; there is an obvious relationship between poor vision and congenital nystagmus[12,13]. PAN and congenital nystagmus are often damped during eye closure (when fixation attempt is lowered) and both are usually horizontal in direction even with the eyes deviated vertically. The most important similarity between PAN and congenital nystagmus is the existence of a prominant neutral zone and null region in both entities.

Strictly speaking, the *null* is that specific gaze region where the nystagmus intensity is minimum. The *neutral zone* is the region where there is equality of drift forces, on either side of which is jerk nystagmus; within this zone the nystagmus may be absent or mimic a pendular form. With congenital nystagmus, the null is usually within the neutral zone, and in PAN the null and neutral zones are identical. For that reason, and to avoid confusion with the *neutral phase* of PAN, we will regard the terms as synonymous and utilize "null" to signify both in PAN.

In some cases of congenital nystagmus, the extent of the neutral zone may be only a few degrees and be fixed in position; whereas in others, it extends over a larger region whose bounds vary at different times. The neutral zone in congenital nystagmus may therefore shift, and this is best demonstrated by the influence of latent nystagmus.

Latent nystagmus vera is a specific variety of congenital nystagmus in which the eyes are stable during binocular vision, but when either eye is covered, jerk nystagmus in the opposite direction develops (Figure 1). At times, manifest congenital jerk nystagmus may demonstrate remarkable shifts in the neutral zone consequent to the superimposition of a latent nystagmus influence. In some patients, eye closure shifts the neutral zone toward the covered eye, as demonstrated in Figure 2. Also shown is the progressive increase in nystagmus amplitude as gaze is directed from the neutral zone. Thus it is apparent that the neutral zone of congenital nystagmus need not be hardwired, but instead may represent a plastic region capable of movement and shifting.

Examination of the cycling of PAN reveals that following a neutral *phase*, the nystagmus begins gradually and continues to increase in intensity until a maximum is reached; there is then a gradual decrease until the eyes stop during the next neutral phase. Nystag-

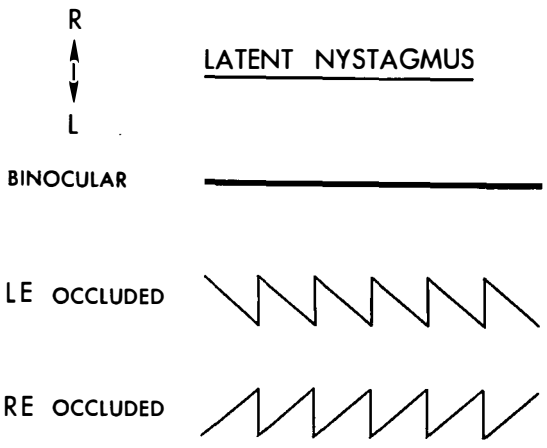

Fig. 1. Diagramatic electronystagmogram (ENG) demonstrating latent nystagmus. With both eyes open, there is no nystagmus. Closure of either eye results in jerk nystagmus with the fast phase directed away from the occluded side.

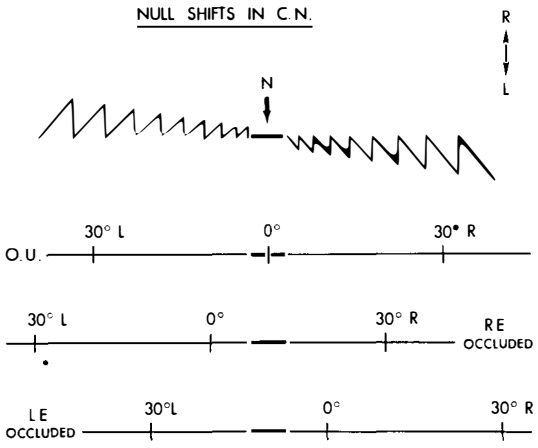

Fig. 2. Depiction of the shifts of the neutral zone or null (N) in congenital nystagmus (CN). ENG tracing demonstrates an idealized nystagmus pattern with both eyes open (O.U.). The neutral zone extends over several degrees on either side of 0°. When gaze is directed laterally, nystagmus of increasing amplitude develops with the fast phase in the direction of gaze. Occlusion of the right eye (RE) shifts the zone to the right; at 0° there is left-beating nystagmus. Occlusion of the left eye (LE) shifts the zone to the left; at 0° there is right-beating nystagmus.

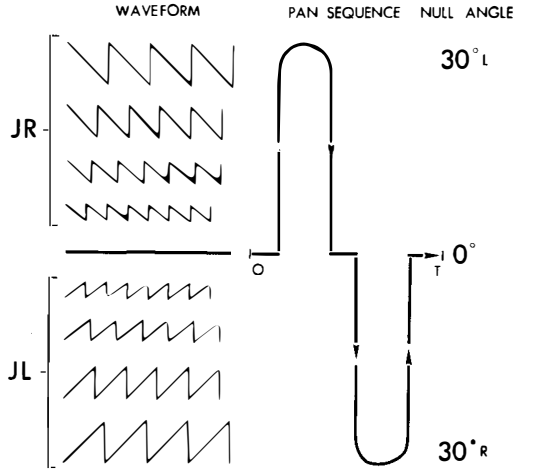

Fig. 3. Periodic alternating nystagmus (PAN) sequence is depicted in relation to waveform and null angle. The sequence reflects one PAN period (from O to T). The period begins in a neutral phase; the null is at 0°. As the null shifts to the left, jerk right (JR) nystagmus develops and gradually increases in amplitude to a maximum when the null is at the extreme left (e.g., 30°L). The null then shifts back toward 0° and the JR nystagmus decreases, finally stopping and forming the next neutral phase when the null reaches 0°. The same sequence of the null shifting to the right and back accounts for the jerk left (JL) phase.

mus *intensity* is the product of frequency and amplitude[6,13]. ENG recordings indicate that the amplitude of PAN, but not the frequency, increases and decreases in such a graded and predictable fashion during a particular directional phase.

What PAN seems to represent is a horizontal jerk nystagmus with omnipresent periodic shifts of the null region which result in corresponding reversals of the jerk direction[6]. When the null is at 0°, there is no primary position jerk nystagmus and the PAN is in the neutral phase. The null then begins to shift in a given direction (for example, to the left), a right-beating nystagmus gradually builds up and reaches maximum amplitude when the null is furthest to the left. The null then begins to return to center and the nystagmus amplitude decreases until the null is again at 0°, when another neutral phase begins. This sequence is graphically demonstrated in Figure 3.

Theoretically, a gradual turning of the head from side to side, away from the direction of the null shifting, should keep the null in the straight-ahead position and permit nystagmus-free viewing. In fact, some patients with PAN learn to do just that, particularly children with the congenital variety. Unfortunately, many patients with acquired PAN have less than optimal head control because of cerebellar ataxia and cannot utilize the technique comfortably. If the null region is narrow, the head turn must be quite accurate to avoid overshifts into the nystagmus region beyond the null. The problem is analogous to other acquired forms of nys-

tagmus where the patients, even in the absence of ataxia and incoordination, do not develop or employ the compensatory techniques seen in patients with congenital nystagmus. These include head nodding and wave form distortion designed to extend target foveation time[13].

Precise explanations of the pathophysiology of periodic alternating nystagmus seem distant at the present time. We need considerably more information about nystagmus oscillations in general, and particularly the brain stem firing patterns which delimit the null regions, before we can fully understand the mechanisms responsible for the periodic shifting of the null — the underlying basis for the extraordinary phenomenon of periodic alternating nystagmus.

Résumé. Une brève revue est faite des caractéristiques et de l'étiologie du nystagmus alternant périodique (NAP). Ce désordre oculo-moteur et le nystagmus congénital revêtent plusieurs similitudes dont les plus importantes sont les zones neutres et les régions nulles. La phénomènologie du NAP peut s'expliquer par le décalage périodique de la région nulle.

REFERENCES

1. Goldberg, R. T., Gonzalez, C., Breinin, G. M. et al. Periodic alternating gaze deviation with dissociation of head movement. *Arch Ophthal 73:* 324-330, 1965.
2. Friendley, D. S., Manson, R. A. and Albert, D. G. Cyclic strabismus — a case study. *Docum Ophthal 34:* 189-202, 1973.
3. Susac, J. O. and Smith, J. L. Cyclic oculomotor paralysis. *Neurology 24:* 24-27, 1974.
4. Hood, J. D., Kayan, A. and Leech, J. Rebound nystagmus. *Brain 96:* 507-526, 1973.
5. Duensing, F. and Pfander, F. Reizwiderstandsfähiger (dominanter) und reizabhängiger Nystagmus alternans nach Hirntrauma. *Arch Ohr Nas u Kehlkopfheilk 168:* 349-370, 1956.
6. Kestenbaum, A. *Clinical Methods of Neuro-Ophthalmologic Examination.* Grune and Stratton, New York, 1961, 2nd Ed.
7. Dufour, A., Lazzaroni, M. and Zibordi, F. Ulteriore contributo elettronistagmografico allo studio del nistagmo spontaneo alternante. *Arch Ital Otol 79:* 739-742, 1968.
8. Davis, D. G. and Smith, J. L. Periodic alternating nystagmus. *Amer J Ophthal 72:* 757-762, 1971.
9. Towle, P. A. and Romanul, F. Periodic alternating nystagmus: First pathologically studied case. *Neurology (Minneap.) 20:* 408, 1970.
10. Kornhuber, H. H. Der periodisch alternierende Nystagmus (Nystagmus alternans) und die Enthemmung des vestibulären Systems. *Arch Ohr-, Nas-, u. Kehlkopfheilk: 174:* 182-209.
11. Jung, R. and Kornhuber, H. H. Results of electronystagmography in man: The value of optokinetic, vestibular, and spontaneous nystagmus for neurologic diagnosis and research. In *The Oculomotor System,* edited by M. B. Bender, Harper and Row, New York, 1964, pp. 428-482.
12. Cogan, D. G. Congenital nystagmus. *Can J Ophthal 2:* 4-10, 1967.
13. Dell'Osso, L. F., Flynn, J. G. and Daroff, R. B. Hereditary congenital nystagmus: An intrafamilial study. *Arch Ophthal.* In press.