Clinical and ocular motor analysis of the infantile nystagmus syndrome in the first 6 months of life

R W Hertle, V K Maldanado, M Maybodi, D Yang

Background/aims: The infantile nystagmus syndrome (INS) usually begins in infancy and may or may not be associated with visual sensory system abnormalities. Little is known about its specific waveforms in the first 6 months of life or their relation to the developing visual system. This study identifies the clinical and ocular motor characteristics of the INS and establishes the range of waveforms present in the first 6 months of life.

Methods: 27 infants with involuntary ocular oscillations typical of INS are included in this analysis. They were evaluated both clinically and with motility recordings. Eye movement analysis was performed off line from computer analysis of digitised data. Variables analysed included age, sex, vision, ocular abnormalities, head position, and null zone, neutral zone characteristics, symmetry, conjugacy, waveforms, frequencies, and foveation times.

Results: Ages ranged from 3 to 6.5 months (average 4.9 months). 15 patients (56%) had abnormal vision for age, nine (33%) had strabismus, five (19%) had an anomalous head posture, 13 (48%) had oculographic null and neutral positions, nine (33%) had binocular asymmetry, and only two showed consistent dysconjugacy. Average binocular frequency was 3.3 Hz, monocular frequency 6.6 Hz. Average foveation periods were longer and more "jerk" wave forms were observed in those patients with normal vision.

Conclusions: Common clinical characteristics and eye movement waveforms of INS begin in the first few months of infancy and waveform analysis at this time may help with both diagnosis and visual status.

Involuntary ocular oscillations have been classified in many ways, resulting in some confusion and disagreement among clinicians, physiologists, psychologists, and bioengineers.7 The recently sponsored national eye institute workshop on classification of eye movement abnormalities and strabismus (CEMAS) has attempted to resolve some of these issues.8 The CEMAS working group publication outlining a definition of infantile nystagmus syndrome (INS) is used in this study.9 Nystagmus in infancy may also be due to structural disease of the brainstem and cerebellum, much the same as nystagmus in adulthood. Other common types of infantile nystagmus in addition to INS include latent/manifest latent nystagmus (LMLN), now classified as fusion maldevelopment syndrome (FMS) and spasms nutans, now defined as the spasms nutans syndrome (SNS).1-7

This study examines those infants from birth through 6 months of age with INS. The aetiology of this oscillation remains elusive. In many patients with INS, a sensory system abnormality can be detected. Gelbart studied 152 patients with congenital nystagmus and found 119 patients to have a diagnostically significant sensory system defect.10 Spierer studied 14 patients with congenital nystagmus and decreased vision due to amblyopia.11 Gibb studied 105 patients with clinical nystagmus and found electroretinographic abnormalities in 56% of patients.12 Numerous reports on the ocular motor behaviour in human albinos, patients with retinal disease, and visual deprivation amblyopia have shown INS to be the predominant ocular oscillation.13-16 There are also groups of isolated patients or those with familial INS, whose visual system shows no clinically detectable sensory abnormality.

The ocular motor systems of patients with INS and no strabismus (with or without associated sensory deficits) are otherwise normal, showing normal smooth pursuit, saccadic, and vestibulo-ocular systems.17-22 Since this oscillation usually begins in the first few months of life, a better understanding of its clinical and ocular motor system characteristics during that time may help in explaining the common aetiology of the oscillation in those patients, both with and without visual sensory system abnormalities. A previous report showed that clinical and oculographic characteristics of INS were present in infants and children with INS in the first 18 months of life.23 This report further studies the developmental phenomenology of this disease in the first 6 months of life.

METHODS
All families signed informed consent and all testing was approved by the institutional review boards of the National Eye Institute (NEI), the National Institutes of Health (NIH), and the Children’s Hospital of Philadelphia. Significance of mean differences and p values calculated for major analytical variables were performed using a two tailed paired Student’s t test.

Clinical data
Between August 1995 and July 2000, we studied 564 patients with involuntary ocular oscillations. Twenty seven of these patients (5%) were infants in the first 6 months of life who had involuntary oscillations typical of INS. These 27 infants were evaluated both clinically and with motility recordings. Ten were evaluated at the ocular motor neurophysiology laboratory of the Children’s Hospital of Philadelphia and 17 were evaluated at the laboratory of sensorimotor research, NEI/NICHD. All patients underwent a complete ophthalmic examination by a paediatric ophthalmologist. The clinical variables analysed included age, sex, visual behaviour (fixation and following with central, steady, and maintained gaze), ocular abnormalities (eye disease), head position, null or neutral zone characteristics, and other ocular motor disease. In patients with clinical visual loss, additional testing included...
photodetectors for each eye. This system does not monitor the visual information. This system uses goggles with an array of mobil Meditech, Inc, Woburn, MA, USA). It measures, records, was 0–500 Hz and drift was less than 10 mV/h (0.03°/h) (Per-

recordings of all patients were made using a system employing GX1, Intel Pentium II Microprocessor, internal speed of 400 
MHz and external speed of 100 MHz). The eye movement


The presentations of stimuli, and the acquisition, display, and storage of data were controlled by a PC (Dell OptiPlex 
GX1, Intel Pentium II Microprocessor, internal speed of 400 MHz and external speed of 100 MHz). The eye movement 
recordings of all patients were made using a system employing the infrared reflection method; the infrared system bandwidth was 0–500 Hz and drift was less than 10 mV/h (0.03°/h) (Per-
mobil Meditech, Inc, Woburn, MA, USA). It measures, records, files, displays, and prints binocular and monocular eye move-

ment information. This system uses goggles with an array of pulsed light emitting infrared diodes, along with an array of photodetectors for each eye. This system does not monitor the

position of the eyes continuously, but uses short pulses of infrared light at chosen frequencies to record the horizontal and vertical eye position intermittently. Accurate measure-
ments of eye movements of both eyes are obtained in a hori-
nzontal direction to within plus or minus 1 degree and vertical movements within plus or minus 2 degrees. The analogue 
signals from the infrared goggles are digitised at frequencies ranging from 10 Hz to 1 KHz. These digitised data can be 
stored on disk for future viewing and analysis. Eye movement 
data are also displayed on a computer screen from digitised 
 analogue signals along an axis represented by time. Patient 
information, recording date, stimulus presented, event mark-
ers, time, and horizontal and vertical eye position are dis-
played. Eye movement calibration was attempted using 
stimuli generated by the PC system software at a distance of 1 metre from the patient to targets plus or minus 15° 
horizontally. Eye position signals were digitised online at each 400 or 500 samples per second and simultaneously dis-
played on the computer. Data files for each 30–300 second 
recording interval were stored in binary format with 16 bit 
resolution for later analysis.

**Ocular motility recordings**

The previously described 12 INS waveforms represent various combinations of fast and slow phases. The motility based 
diagnosis of INS included in this study were oscillations that displayed waveforms consistent with INS, specifically increasing 
exponential slow phases with jerk fast phases. In pure jerk 
INS (J) a slow phase eye movement is followed by a fast phase, 
giving rise to a typical sawtooth waveform. While in pendular 
INS (P) the eyes exhibit a within beat (slow phase-fast phase) 
periodic regular motion and in asymmetric pendular (AP) 
they exhibit a within beat irregular motion. These two wave-
forms give rise to approximately sinusoidal waveforms. Dual 

jerk waveforms (DJ) show small, rapid oscillations superim-
posed on a jerk-like waveform, thus being a mixture of jerk 
and pendular congenital nystagmus (CN). The mature INS 
waveforms of all patients are some combination of the same 
12 waveforms, independent of the presence or type of visual 
sensory system abnormalities. In this study we included all 
patients with oculographically diagnosed INS regardless of 
their other associated ocular or systemic conditions to more 
fully establish early waveform characteristics. Our main 
purpose was to demonstrate the rich variability of waveforms 
and foveation abilities present at an early age.

The presentations of stimuli, and the acquisition, display, and storage of data were controlled by a PC (Dell OptiPlex 
GX1, Intel Pentium II Microprocessor, internal speed of 400 MHz and external speed of 100 MHz). The eye movement 
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recording interval were stored in binary format with 16 bit 
resolution for later analysis.

**Ocular motor recording protocol**

The infant was seated in a comfortable position in a parent or caretaker's lap. The infrared goggles rested comfortably on the infant's face in front of the visual axis and the head was held steady by the examiner. After 2.5–3.0 minutes of binocular 
recordings the left and then the right eyes were occluded with 
an opaque trial lens placed in a holder attached to the front of the 
goggles. At all times during recording, attempts were made 
to pacify the child and obtain their attention to the fixation 
screen at 1 metre. When possible, attempts were made to have 
the child look to the right and left (the infrared goggles have a 
monocular viewing aperture of plus or minus 20 degrees at 1 metre distance) as well as near while recording the oscil-
lation's response to gaze and vergence changes.

This method, in use for more than two decades, produces clear, artefact-free records of INS waveforms in infants and

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The clinical characteristics of the 27 infants included in this study at the time of their ocular motor recordings. (NL = normal, ABNL = abnormal, M = male, F = female, FH = foveal hypoplasia, OCA = oculocutaneous albinism, ET = esotropia, ONH = optic nerve hypoplasia, XT = exotropia, CVI = cortical visual impairment, OND = optic nerve dysplasia, SSN = seesaw nystagmus, OA = ocular albinism, CD = cone dystrophy, FD = foveal dysplasia, Y = Yes, N = No.)
young children. Although the amplitude of the INS in either
was not always accurately determined (that is, all the data are
not calibrated), all phase and timing information (for
example, interocular foveation time, asymmetry) can be accu-
rately measured.

Data analysis
Eye movement data analysed for this study included the aver-
age binocular (and monocular) frequencies that were com-
puted from at least 60 seconds of data. Interocular conjugacy
and amplitude symmetry were analysed directly from the
recordings by comparing the right eye and left eye positions
throughout the same periods used for frequency and foveation
analysis. If the two eyes were moving in the same direction
during this time, the movement was considered conjugate.
The type of waveforms present were classified according to the
previously described 12 waveforms associated with horizontal
INS.

Because of the sensitivity of these recording
techniques, foveation periods and fast and slow phases could
be identified during almost all cycles. In the absence of accu-
rate calibration, a foveation period was defined as a relatively
constant eye position that occurred during an oscillatory cycle,
usually followed a fast phase, and lasted for at least 40 ms.
This approximation to foveation period durations yielded
values that were higher than those determined by accurate
position and velocity criteria. However, interpatient compar-
sions could still be made. For foveation periods to be included
in data analysis, a minimum of 40 cycles that contained
foveation periods were required. All eye movement data were
analysed off line. Waveform percentages were calculated using
the following formula; waveform% = (No of cycles waveform
present/No of total cycles) × 100. Mathematical and statistical
analysis was done on a computer spreadsheet.

RESULTS

Clinical characteristics
All patients in this study met two inclusion criteria: (1) they
were all younger than 7 months of age, and (2) they had
motility recording evidence of involuntary ocular oscillations
with typical waveforms characteristics of INS. Seventy per-
cent were male, with ages ranging from 3 to 6.5 months
(average 4.9 months). Vision was abnormal in at least one eye
in 15 patients (56%). All of these 15 patients had associated
eye disease. Nine (22%) patients had strabismus, 13 (48%) had
a clinical null or neutral position, and five (19%) had an
anomalous head posture due to the null position being in an
eccentric position of gaze. Clinical findings are reported in
Table 1.

Ocular motility characteristics
The average binocular frequency was 3.3 Hz and monocular
frequency 6.6 Hz. There were occasional episodes of dysconju-
gate oscillations in many patients associated with divergence
and convergence that were inconsistent and probably reflected
voluntary vergence movements, as stimulus parameters were
difficult to control. There was evidence of interocular
asymmetry manifested by calibrated amplitude differences in
five (19%) patients. Average binocular foveation time was sig-
ificantly longer in those patients with normal vision (158

Table 2 Oculographic characteristics

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<td>5</td>
<td>35</td>
<td>ABNL</td>
</tr>
</tbody>
</table>

The oculographic characteristics of the 27 infants included in this study at the time of their clinical examination. (AP = asymmetric pendular, JEF = jerk with extended foveation, P = pendular, J = jerk, D/J/B = dual jerk/bidirectional jerk, NL = normal, ABNL = abnormal).

Figure 1. The percentage of patients exhibiting individual waveforms at any time during ocular motility recordings. A high percentage of patients displayed the more developed waveforms of jerk and jerk with extended foveation. (P = pendular, AP = asymmetric pendular, J = jerk, JEF = jerk with extended foveation, D/J/B = dual jerk/bidirectional jerk.)
ms) than those with abnormal vision (61 ms) (p <0.001). Asymmetry (one eye with a more intense oscillation) was seen in five (19%) patients. Two patients had consistent periods of dysconjugate oscillations unrelated to spontaneous vergence movements (Table 2).

Different waveform types could be clearly distinguished on tracings from all eye movement recordings (see Fig 3). The recordings displayed mixtures of pendular (P), asymmetric pendular (AP), jerk (J), jerk with extended foveation (Jef), and bidirectional jerk/dual jerk (DJ/BDJ) waveforms. As shown in Figure 1 all types of waveforms are represented in this age population including Jef and DJ/BDJ, which are mature types of waveforms. Further analysis showed that a higher percentage of patients with abnormal vision had pendular and asymmetric pendular waveforms than patients with normal vision, whereas a higher percentage of patients with normal vision had jerk waveforms than those with abnormal vision (Fig 2). In addition to horizontal oscillations, occasional vertical oscillations were noted. They were characterised by P and occasionally AP waveforms of the same frequency as the horizontal oscillation. Asymmetric recording characteristics between the eyes, either under binocular or monocular viewing conditions, often reflected clinical afferent visual system asymmetry. A latent component was present in six (22%) patients.

**DISCUSSION**

There are many distinguishable types of involuntary ocular oscillations. Nystagmus is an oscillation caused by a disorder of the slow eye movement system. It may either be a purely pendular or jerk waveform. Ocular oscillations caused by disorders of the saccadic system, necessarily containing saccades, are classified as fast eye movement or “saccadic” oscillations. It is well documented that these differences may be difficult, if not impossible, to differentiate clinically. Electrophysiological analyses using precise eye movement recordings have provided a new basis for eye movement abnormality classification, aetiology, and treatment. Recent advances in this technology have increased its application in infants and children who have clinical disturbances of the ocular motor system. By only including those infants with the 12 previously described INS waveforms we have excluded all forms of nystagmus in the first few months of life caused by structural disease of the brain and brainstem—for example, acquired nystagmus.

“Congenital” means, by definition, “present at birth.” Strict application of this term to the range of nystagmus types possible in infants has led to confusion by all disciplines involved in the care or study of these patients. Nystagmus in infancy and childhood has been classified as one of three types, based solely on associated clinical conditions. One was “pathological,” if a central nervous system abnormality was found that “explained” the oscillation—for example, tumour. The second was “sensory” nystagmus, if the patient also had an ocular abnormality associated with decreased vision—for example, retinal dysplasia. The third, by process of exclusion, was “motor” nystagmus, if no associated vision abnormality was clinically evident. Confusion in disease terminology was one
of the major factors leading to a recent NEI/NIH sponsored workshop and publication on the classification of eye movement abnormalities fixed strabismus (CEMAS). We chose the term infantile nystagmus syndrome (INS) and its CEMAS definition for the patients reported in this study. INS is but one of a number of types of nystagmus which are generally observed in the first few months of life (for example, fusion maldevelopment or spasms nutans syndromes). Estimates of its incidence range from 1 in 350 to 1 in 6550.  

Infantile nystagmus is an eye sign; its direct cause may be an increase in the normal oscillation of the pursuit system. It is quite simply, a motor oscillation, whether present in isolation or in conjunction with any number of sensory disorders, each deserving of a specific, descriptive diagnosis (for example, INS plus aniridia or INS plus albinism). Neither is the direct cause of the other and both patients share the same INS (as one with idiopathic or hereditary INS) regardless of the type of (or presence of a) sensory disorder.

The oscillation as part of the INS does have well described, but not diagnostic, clinical characteristics. These include, in varying degrees, onset in infancy, conjugacy, uniplanar movements (usually horizontal), increased intensity in eccentric gaze and with increased fixation effort and, sometimes with monocular cover, disappearance with sleep, decreased intensity with eyelid closure and convergence. Well defined null and neutral positions of gaze and associated head posturing and/or head oscillations may also be present. These characteristics are based largely on descriptions of INS in its mature form in older children and adults.

This clinical examination of 27 infants in the first 6 months of life with ocular motility documentation of INS, revealed 70% of the total were male (and 66% of the 12 patients with normal vision were male) with an average age of 4.9 months. Strabismus was present in 22%. Vision was abnormal in at least one eye in 56% of patients. The most common visual abnormalities were due to congenital optic nerve or retinal anomalies. Other visual abnormalities occurred in patients as a result of central visual impairment and strabismic amblyopia. Associated clinical characteristics included intermittent head or face posturing in 19% and a null and neutral zone other than primary position in 13% of patients. It should be noted that the absence of a head turn could indicate either of two things, a null position in primary position or no null position at all. The high incidence of these associated clinical conditions may reflect bias in that these patients were selected for referral to the ocular motor neurophysiology laboratory. Even if the proportion of INS associated characteristics is not this high in all infants with INS, this analysis shows that the clinical spectrum of INS is well developed in the first few months of life. The high incidence of ocular abnormalities and visual disturbance may also reflect the referral nature of our patient population. The fact that normally sighted as well as visually disturbed patients had typical ocularographic evidence of INS is not a new finding.

Accurate diagnosis of INS depends on objective motility system waveforms, some of which display an “increasing velocity exponential” movement. Most of the specific waveforms identified in INS are diagnostic, being found in no other type of nystagmus. Even increasing velocity exponential slow phases, with no other distinguishing characteristics, are unique to INS, having only been noted in one other form of phases, with no other distinguishing characteristics, are present most commonly (70%) under 6 months, with 18% pendular and 12% jerk. This evolved so that at 18 months of age only 7% of waveforms was triangular with pendular and jerk predominating. These triangular waveforms disappeared by 2 years of age. In two previous studies it was also shown that the predominant waveforms change with age. For our patients under 7 months of age, the predominant waveforms were pendular and asymmetric pendular. The absence of purely triangular waveforms (that is, with linear slow phases) in our patients may be due to the use of different recording methods. It is possible that such waveforms might have been observed if our recording apparatus was linear at amplitudes greater than plus or minus 20 degrees. In the earlier study, contact electro-oculography was used; this is less able to depict waveform details than infrared oculography. The triangular waveform noted in the previous study may appear as a result of central visual impairment and strabismic amblyopia.

Although pendular waveforms did not disappear, by 18 months of age, jerk waveforms predominated. More subtle changes in waveform with age (for example, breaking and foveating saccades and extended foveation periods) reflect the effect of visual system maturation on the oscillation. Many parallel visual processes such as, but not limited to, acuity, contrast, colour, fusion, and motion perception may influence the clinical and motility maturation of INS.

Attempts have been made to correlate visual function with clinical, oculographic and waveform characteristics in patients with INS. Mature INS represents developmental modification of an ocular motor instability by the afferent visual system. The integrity of the afferent visual system may ultimately determine the clinical characteristics and waveforms in any one patient. A sensitive measure of vision is presented in motility recordings by “foveation” periods. These are periods during an INS cycle when the eyes are more stable. This period of time corresponds to maximum afferent attention (visual fixation) and is the period of time when a patient with INS sees most clearly. Patients with more normal visual sensory function exhibit “well developed” foveational strategies (that is, beat to beat accuracy). In a previous study on infants and toddlers up to 18 months of age, the average foveation time viewing binocularly was considerably greater (158 ms) in patients with clinically normal vision than those patients with abnormal vision (61 ms).

This study demonstrates that clinical and motility patterns of “mature” INS are present in early infancy and that accurate diagnosis of INS in infancy can be easily accomplished using standard ocular motor recording techniques. This study also confirms an “early” age dependent evolution of waveforms during infancy from pendular to jerk. This is consistent with the theory that jerk waveforms reflect modification of the INS oscillation by growth and development of the visual sensory system.

Although numerous studies have described INS pathophysiology and its effect on the visual system, its aetiology remains elusive. Defects involving the saccadic, optokinetic, smooth pursuit, and fixation systems as well as the neural integrator for conjugate horizontal gaze have been proposed. Biomedical control system models have reproduced this oscillation and it has been attributed it to a “high gain instability” in the ocular motor system. This loosely translates as an error in “calibration” of the eye movement system during attempted fixation. Including genetic predisposition, many clinical conditions are associated with the INS oscillation. Regardless of the clinical associations, nearly all patients with INS have infantile onset in common; we can deduce that this oscillation is most likely to occur in an immature ocular motor system. The aetiology is probably multifactorial but the final common pathway may be interference with ocular motor calibration (neural “cross talk”) between the developmentally (7) and motor systems during a period of developmental sensitivity, at which time an insult results in irreversible changes.
This study also suggests that if an infant is diagnosed with INS, ocular motility analysis may be helpful in understanding the visual status of the affected infant and possible interocular differences. Ocular motor recordings can provide a prediction of the potential best corrected visual acuity. Such a measure is the nystagmus acuity function (NAF) and its recent improvement, the expanded nystagmus acuity function (NAFX). Using this function on eye movement data taken under low stress conditions helps to eliminate both intrasubject and intersubject variability and facilitates comparisons under different viewing conditions or before and after therapy. The inherent assumption of the NAFX is that acuity is solely limited by the CN waveform. It is calculated using both eye position and velocity data to determine a “foveation window” within which the data most important for acuity reside. The method is independent of the methodology used to gather the data (presuming that they are accurate and noise free) and of the nystagmus type or waveform.

Analysis of binocular or monocular differences in waveforms and foveation periods reflect development of the afferent visual system. Pure pendular or jerk waveforms without foveation periods are associated with poorer vision while waveforms of either type with extended periods of foveation are indicators of good vision. Significant interocular differences in a patient reflect similar differences in vision between the two eyes. Ocular motility analysis in infants also accurately determines nystagmus changes with gaze (null and neutral zones).