Neonatal ocular misalignments reflect vergence development but rarely become esotropia

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Background: 214 orthoptists’ infants have been followed for up to 15 years, relating neonatal misalignment (NMs) behaviour to onset of convergence and 20 Δ base out prism response, and also to later childhood ocular abnormalities.

Methods: In a prospective postal survey, orthoptist mothers observed their own infants during the first months of life and regularly reported ocular behaviour and alignment, visual development, and any subsequent ocular abnormalities.

Results: Results confirm previously reported characteristics of NMs. Infants who were misaligned more frequently were misaligned for longer periods (p <0.01) and were later to achieve constant alignment (p <0.001) but were earlier to attempt first convergence (p = 0.03). Maximum NM frequency was usually found at or before the onset of first convergence (p = 0.0002).

Conclusions: NMs occur in the first 2 months of life and usually reflect a normally developing vergence system. They appear to represent early attempts at convergence to near targets. Emerging infantile esotropia is indistinguishable from frequent NMs before 2 months.

Ocular behaviour in early infancy is immature. Acuity and contrast sensitivity are low (for reviews see Atkinson and Held) and refractive error common until later childhood. There is a consensus that binocular vision is not required, most infants’ eyes appear broadly aligned and largely unresponsive to varying target demand. There is no clear evidence that any reliable accommodation/vergence link is present at this time, and if present, convergence accommodation may be just as, or more, influential than accommodative convergence. Nevertheless, when active convergence is not required, most infants’ eyes appear broadly aligned (once corrections for the large angle lambda of infancy have been made) and studies suggest that a primitive vergence system may exist before 12 weeks that is not dependent on cortical binocularity.

Parents of visually normal children often comment that their eyes had been “all over the place” in their first weeks. In a booklet issued to all new parents in the United Kingdom, the advice is given “at birth a baby’s eyes may roll away from each other occasionally”. General practitioners and health visitors only refer intermittent squinting if it persists after about 3 months of age. However, if the intermittent “strabismus” reaches an ophthalmologist before the infant is 4 months of age, these misalignments may be considered pathological. Two recent papers suggest that early intermittent esotropia resolves in 27% of referred cases, especially if they present under 12 weeks of age. The relatively small numbers reported (175 subjects provided by 137 investigators at 104 clinical paediatric ophthalmology sites) suggest that these early deviations form a very small part of the clinical ophthalmology caseload. But perhaps, instead of being rare, early squinting is so common and normal that it rarely reaches eye professionals.

A longitudinal study by the author of a group of 75 normal infants of orthoptists found that most neonates’ eyes were briefly periods of intermittent squinting. The deviations were overwhelmingly short lived, convergent, large angle, unilateral, and alternating. I term these “neonatal misalignments” (NMs) because “esotropia” implies an abnormality that may not be present. Although the time scale sometimes falls outside the 1 month limit of “neonatal,” the majority of NMs do occur within the first month and are generally reducing by 2 months of age.

In later infancy, intermittent strabismus is always pathological, but the 1993 data, along with anecdotal reports, suggested that NMs are of little significance. It is possible that instead of being part of a pathological spectrum of esotropia, intermittent misalignment is normal behaviour that may “tip over” into, or overlap with, pathology, especially if excessive in early infancy, or abnormally persistent.

A second, longitudinal cohort study of 1150 children showed that there were subtle consequences of NMs. There was a small but significant association of frequent NMs in the first 8 weeks with later hyperopia and myopia, as well as with clinically significant esotropia or esophoria at 4 years of age, while never showing NM was significantly associated with later astigmatism.

This paper reports the orthoptists’ infants study in more detail, including additional data on the nature and frequency of NMs in an extended group that was not analysed in the original publication. The original group now also includes a number of infants who developed pathological strabismus and refractive error, who were excluded from the 1993 report. Unreported data on the development of convergence in relation to NMs and later refractive error are also presented. A companion paper reports in more detail the NM behaviour of those children who went on to develop referable abnormalities.
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Transient esodeviations are common in months 1–4. In month 1, 73.2% were misaligned at some time (21.6% less than once a day, 15% once a day, 23.2% up to 10% of the time, 7.8% for 11–30% of the time, and 4.7% for more than this). They were reducing by 2 months (when only 49% of subsequently normal infants showed any deviation at all) and, in the visually normal infants, gone by 4 months.

The only infants (n=2) still misaligned at 4 months were in the process of developing true infantile esotropia, confirming the findings of The Pediatric Eye Disease Investigator Group.25 26 All other infants were constantly aligned at 4 months. Those destined to develop subsequent manifest deviations of later onset were all aligned, with normal binocular and acuity responses, until at least 2 years of age.

The two infants destined to be infantile esotropes were indistinguishable from the subsequently normal children in the first 2 months with frequent, but not constant, esodeviation. However, when the “normals” started to show fewer NMs at around 2 months, these infants were becoming more constantly misaligned. Although constantly misaligned for 4 months, the angle of deviation continued to increase until strabismus surgery on both infants was undertaken at around 9 months. Two further infants with similar characteristics have been observed in the infant vision laboratory in a group to be reported separately. One infant who needed frequent general anaesthetics was misaligned for 48 hours after each anaesthetic during her first year but at no other time and is now visually normal.

A one way ANOVA showed a highly significant effect of frequency of NMs on age at which NMs ceased (F5,205= 6.662, p<0.001). Those with most frequent NMs were later to cease squinting (Fig 2).

Of the infants who squinted in the first month, 29.3% squinted momentarily, 59.6% for a few seconds, 8.8% for a few minutes, and 0.6% (two infants) for 10–60 minutes at a time (neither of whom later proved to be infantile esotropes). There was a weak, but significant, correlation between frequency and duration of misalignment when it occurred (Spearman’s rho: r=0.18, p<0.01). Infants who squinted most frequently generally squinted for longer—for example, only 0.05% of infants who squinted only once daily did it for more than a few seconds, whereas 19% of those who squinted 11–30% of the time squinted for a few minutes. There were no sex differences in severity of any squint (t = 0.037, p = 0.7), age to start squinting (t = 0.2, p = 0.8), age at time of worst squinting (t = −0.93 p = 0.3), or age to stop squinting (t = 0.6, p = 0.5).

In week 1, 48.6% of NMs were unilateral (one eye fixing), 13.7% were bilateral (neither eye fixing the target) and 37.7%
There is a highly significant logarithmic trend \( (r^2 = 0.95, p < 0.001) \) for a rapid increase to unilaterality in the first month. Even if NMIs are merely inappropriate convergence, the infants generally fix with one eye; 64% of the deviations freely alternated, 33% showed slight fixation preference, and only 3% were consistently in the same eye.

The vast majority (87.1%) of NMIs were convergent, with a few (7.4%) showing both convergent and divergent deviations at different times. Only 5.2% were always divergent. Over the past 5 years, the orthoptist parents have been asked to estimate of the size of the deviation. Most report angles of >30Δ eso. Many parents of infants tested before this question was included enclosed photographs of their babies with similarly large angles.

At first, many NMIs (30.7%) were not associated with any specific stimulus or behaviour. Later, attempting near fixation rapidly becomes the most common precipitating stimulus (53.8% at 3 months of age).

Many mothers commented on how surprised they had been at the size and frequency of the deviations, and their later complete resolution. Those reporting on second or third children commented on how one infant’s behaviour was often very different from that of earlier siblings.

Seventeen (7.9%) parents noticed transient nystagmus in the first 2 weeks, which subsequently resolved completely. This was usually jerky, intermittent, and on lateral gaze. Most of the mothers commented that it did not look like the end positional nystagmus commonly seen in older children, but occurred nearer to the primary position. No question had been asked about this on the questionnaire, the parents adding it as a spontaneous comment, so the true incidence cannot be established. Further details were unavailable. This appears to be the first time that this has been reported in normal neonates.

**Relation to convergence**

The mothers were asked when their infants first attempted reliable and repeatable convergence to near targets. This was similar to the “first vergence” assessed by Thorn et al., and did not specify a specific near point or quality of movement. The target was whatever the mothers found most successful, generally the mother’s face. Convergence was generally more delayed in many infants than was steady fixation or following, which were usually elicited by the second week of age; 42.9% attempted convergence in week 1, with the percentage rising logarithmically with age \( (r^2 = 0.97) \) (Fig 3). By month 4, only four infants (2%) were still not seen to converge. There were no sex differences \( (t = -0.4, p = 0.6) \).

Figure 4 appears to illustrate that both frequent and rare NMIs are associated with later first convergence. However, the data from the seven infants with NMIs for >30% of the day (not shaded in Fig 4) have been excluded as unreliable. The wording of the question was “Is normal convergence attempted?” NMIs are usually reported to occur at the time of attempted near fixation. An orthoptist could easily interpret very frequent NMIs, which occurred on attempted near fixation, as “abnormal” convergence and so would answer “no” to the question. A “yes” response would only be used once NM had stopped when older. Secondly, if NMIs occurred every time convergence was attempted, it is impossible to differentiate NM from attempted convergence. They would therefore answer “no” to the normal convergence question. These few children may not have been genuinely later to start to converge; indeed their frequent NMIs might have been a sign of very early, but inaccurate, convergence.

If these seven infants (3%) are excluded, one way ANOVA showed a significant effect of neonatal frequency group \( (F_{2,13}, df 4,203, p = 0.03) \) with a highly significant linear trend \( (F_{1,129}, df 1203, p = 0.006) \) for the more frequently squinting infants (in the groups up to 30% of the time) to be earlier to converge.
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Change in frequency of NMs over the first 3 months of life may be a more important diagnostic clue than age of onset or time spent misaligned per se. Misalignments that are worsening at 2 months are likely to develop into infantile esotropia, while non-pathological NMs generally reduce from 1 month of age, but may still be seen until 3 months.

The orthoptists reported overwhelmingly large, intermittent exodeviations, not exodeviations as reported by Archer et al.\textsuperscript{14} It is improbable that these are pseudo-deviations because the angles are generally very large and orthoptists, unlike lay parents, are unlikely to be misled by epicanthus. If pseudostrabismus were to be the cause of an apparent squint, the large angle lambda of early infancy,\textsuperscript{14} 15 if anything, creates a significant bias towards pseudo-esotropia if corneal reflections are used to assess alignment.\textsuperscript{14} 17

Convergence was reported from the very first weeks, earlier than previously reported by some authors,\textsuperscript{14} 15 17 but not others.\textsuperscript{14} 15 17 NMs appear to occur at or just before the time that convergence emerges and rapidly cease once vergence becomes stable. If vergence develops early, infants are initially likely to spend more of their waking hours misaligned, but unless these misalignments are very frequent and worsening after the first month, they are less likely to go on to have a later abnormality (see companion paper).

NMs also appear to provide a useful research tool for the study of the emerging vergence system because they are large and easy to detect. The relation of NMs to accommodation measured objectively in a laboratory setting will be the subject of a future paper. In a clinical setting, awareness of what parents are describing when they say their babies’ eyes are “all over the place” or “unfocused” can help to differentiate pathology more accurately in the few, and avoid anxiety for many others.

REFERENCES