Congenital Esotropia - an overview

Robin Wilkinson

Abstract

This paper looks at congenital esotropia, its phenotypic expression and the current theories on the neural mechanisms underlying the disorder. The clinical spectrum of the disorder is outlined and current research on latent nystagmus, asymmetries of optokinetic nystagmus and defects in visual motion perception are discussed. The aetiology of the disorder is unknown but recent studies on the macaque monkey which has naturally occuring congenital esotropia provides the first neuroanatomic evidence for cerebral cortex maldevelopments associated with the disorder.

Key Words: congenital esotropia, nystagmus, motion processing, neuroanatomical defect.

Introduction

Congenital or Infantile Esotropia has been defined as esotropia occurring in the first 6 months of life[1]. The incidence of the disorder has in the past been reported as1%[2]. However recent studies have disputed this and put the incidence as low as 0.27%[3].The disorder has a variable phenotype but commonly there is a constant large angle of deviation with associated anomalies such as latent nystagmus, dissociated vertical deviation , asymmetry of pursuit and optokinetic nystagmus and poor potential for normal binocular vision to develop.

Aetiology-theories

There are two main theories on the aetiology of congenital esotropia and they largely shape the various terminologies used for the disorder.

Worth postulated the aetiology of congenital esotropia was a congenital defect of the fusion faculty and that restoration of normal binocular single vision was therefore not possible[4].Chevasse later postulated that congenital esotropia developed as a result of interference with the development of the conditioned reflexes which in normal development lead to binocular single vision[5].

In a sense both were correct for certain phenotypes of the disorder but neither explain the complete clinical spectrum of congenital esotropia. Worth's theory would explain congenital esotropia which fails to develop any signs of binocularity in spite of surgical intervention in early life. Chevasse's theory on the other hand would explain congenital esotropia which develops albeit imperfect binocular single vision after early surgical intervention.

Terminology : Congenital vs Infantile

There has been much discussion regarding the correct terminology for esotropia occuring early in life. Congenital esotropia is a term we are all familiar with and it implies the disorder is present from birth. Neonate studies dispute this; Nixon and co-workers examined 1219 neonates in an attempt to discover whether esotropia is truly present at birth and found that 49% were orthotropic, 33% were exotropic, 3% were esotropic, and 15% were not sufficiently alert to permit classification. None of the 40 esotropic neonates demonstrated typical signs of congenital esotropia but rather 17 had intermittent esotropia, 14 varied from esotropia to exotropia and 9 had variable esotropia[6]. Three infants did go on to develop infantile esotropia. Another study by Archer, Sondhi and Helveston came to similar conclusions that normal infants and those with congenital esotropia or exotropia could not be distinguished on neonatal examination[7].

Lang summarises the situation thus; "does the term congenital really mean the defect must be both present and visible at birth?" At birth the visual system is anatomically and functionally immature and birth in a way is a premature event for the visual system thus congenital esotropia only manifests itself when the visual system matures and the binocular system becomes functional at 4 to 6 months of age[8].

While the aetiology remains unknown the terminology will remain largely a debate of words.

Clinical Spectrum of Congenital Esotropia

There are several syndromes that fall within the spectrum of congenital or infantile esotropia and it may be that they are simply the same basic disorder varying in expression. These are:
Essential Infantile Esotropia
Lang's Congenital Esotropia Syndrome
Ciancia Syndrome
Adelstein -Cuppers Nystagmus Blocking Syndrome

Essential Infantile Esotropia(Von Noorden)[9].
Onset birth to 6 months of age
Large stable angle which exceeds 30 prism dioptres
Defective abduction
Overaction of the Inferior Obliques
Dissociated Vertical Divergence (DVD)
Manifest/Latent nystagmus
Asymmetry of Optokinetic Nystagmus (OKN)
AHP

Lang's Congenital Esotropia Syndrome - concentrates on the four characteristics of a condition he labelled "alternating sursumduction"[10].

Early onset
DVD
Nystagmus - latent in most cases
Excyclodeviation of the non fixing eye
Abnormal head posture (AHP)

Ciancia Syndrome - this emphasises nystagmus as the most crucial component characterising the syndrome[11].
Early onset
Bilateral limitation of abduction
Jerk nystagmus increasing in abduction and decreasing in adduction
AHP with the face towards the side of the fixing eye
DVD
Asymmetric optokinetic nystagmus

Nystagmus Blocking Syndrome. Adelstein and Cuppers - proposed that the esotropia resulted from hypertonicity of the medial recti caused by sustained adduction of each eye and that the convergence impulse dampens the nystagmus[12].
Nystagmus increases on abduction
AHP with the face towards the side of the fixing eye
There is a straightening of the eyes under general anaesthetic.

Thus the clinical correlation of early onset or congenital esotropia with DVD, asymmetry of OKN and latent/manifest nystagmus is well documented.The pathogenesis is unknown and as stated it may be that the various syndromes are simply phenotypic variations of the same basic disorder.

Before discussion of the current research on congenital esotropia, the following is a brief review of the visual pathway and the mechanism of fusion.

Visual Pathway

Axons from the ganglion cells of the retina group together and travel as the optic nerve to the optic chiasm where the nasal fibres decussate. From the chiasm the fibres then travel via the optic tract to the lateral geniculate nucleus (LGN).

The LGN is a six layered structure. It is divided into two ventral

magnocellular laminae and four dorsal parvocellular laminae. Magnocellular cells appear to be concerned with movement, while parvocellular cells are concerned with stereopsis, colour and form discrimination[13]. Lamina 1,4 and 6 receive axons from the ganglion cells of the retina of the contralateral eye and lamina 2,3 and 5 receive from the ipsilateral retina[14].

The LGN is a 'sorting station' and from here the highly organised fibres travel via the optic radiations to the visual cortex (Brodmans area 17) which is also referred to as visual area 1 or V1.

The axons of the LGN project essentially to layer IV of the cortex where there is an alternation of ocular dominance areas receiving fibres from left or right eye but not both[15]. In layers just above and below area IV about half of the cells are binocularly driven from corresponding regions in the two retinas. The striate cortex is layered into parvocellular and magnocellular recipient lamina. The axons of the corpus callosum link the cerebral hemispheres.

The Fusion Mechanism

In congenital esotropia fusion deficits range from impairment to total lack of fusion so it is important to understand the neural mechanism of fusion. Essentially there are two components, sensory and motor fusion. Sensory fusion results from the detection of two similar images, one with each eye, and interprets them as one. Motor fusion aligns the visual axes and ensures a single fused image during vergence movements[16]. The extent of the disparity that motor fusion can respond to is measured by prisms and is called the fusion amplitudes.

At the retina visual input as light energy is transformed into electrical energy and travels the visual pathway to the occipital cortex.

Following decussation at the optic chiasm the input from both eyes is sorted at the level of the lateral geniculate nucleus and relayed to the visual cortex. Here recognition of retinal image disparity generates two different responses to disparity - motor fusion and stereopsis (three dimensional perception).

Central stereopsis(fine) is a highly specific pattern matching process operating over a narrow range of horizontal spatial disparities. Peripheral stereopsis (coarse) is a much less specific process which uses retinal disparity cues outside Panum's area[17].

Current Research Relating to Congenital Esotropia

The Onset of Binocularity.

Current research has given us a clear insight into the anatomical and physiological events that take place postnatally in the development of binocular single vision. Anatomically the visual system is immature at birth in particular with regard to the retina, lateral geniculate nucleus and visual cortex.

A morphological study on an 8 day old normal full term infant has yielded important information on the retina in the immediate post natal period[18]. The study confirmed the maturity of the peripheral retina at this stage compared to the very immature macula.

The fovea is so poorly developed that the authors suggested neonatal visual acuity must be extra foveal.

The lateral geniculate nucleus undergoes a doubling of volume between birth and six months of age.after which it remains stable into adult life[19].

In the visual cortex synapse development, synaptogenesis, occurs rapidly between 2- 4 months.The total volume of striate cortex reaches adult size at 4 months.

There is evidence that binocular interactions appear during this period. Such interactions include stereopsis, equalisation of optokinetic nystagmus responses, and binocular summation of pupillary light reflexes[20].

In the visual cortex there is initially a massive growth spurt resulting in an over production and redundancy of synaptic connections which reaches a maximum between 4 and 8 months. The connections are unspecified in terms of their function. Neuronal circuits emerge in response to afferent stimulation and stabilise and persist. There is a subsequent 'pruning' of non utilised synapses. Synapse elimination occurs between the ages of 8 months and 11 years.

This evidence of initial exhuberant synaptic connections support the hypothesis of an anatomical substrate for plasticity in the developing cerebral cortex.

Animal Models for Congenital Esotropia

Macaque Monkey

The macaque monkey is considered the best non human model for investigation of the neural mechanisms of strabismus. Some macaque monkeys have been found to develop early onset esotropia with abnormal temporally directed horizontal pursuit and latent nystagmus similar to those documented in strabismic humans[21].

Tychsen and Burkhalter and others have investigated functional and structural abnormalities in the visual cortex of squinting macaque monkeys in a bid to provide an insight into human congenital esotropia. They have demonstrated that there is a structural anatomical basis for functional deficits in infantile esotropia. Macaques with early onset strabismus were found to have maldevelopment in connections in ocular dominance columns in the upper V1 layers of the visual cortex . Binocular horizontal connections were reduced an average of 50/60% in strabismic monkeys compared to normal monkeys. Ocular dominance columns also showed greater activity in nasally driven columns in each V1 area - that is the contra lateral neurons inhibited the ipsilateral neurons and this may explain alternate suppression[22,23]. This study provides the first neuroanatomic evidence for cerebral cortex maldevelopments in natural infantile esotropia. They postulate that the defect could be congenital or that the esotropia itself could cause excessive pruning of connections early in life because of abnormal binocular experience.

Siamese cat

The Siamese cat, like the macaque monkey, has a naturally occuring esotropia. Studies by Hubel and Wiesel have investigated the visual pathway in the Siamese cat and have found it to be abnormal[24].They showed that the temporal fibres also decussate at the optic chiasm. In turn the lateral geniculate nucleus has anomalous layering patterns which suggest that at this early level the substriates for fused binocular single vision have been largely lost. Hubel and Wiesel found that in the visual cortex of the Siamese cat the area that would normally receive inputs from central vision have projections from retinal areas up to 30 degrees from central vision. In addition they have found that the vast majority of striate cortex units investigated were only activated by monocular contralateral eye stimulation.

An experiment by Cool and Crawford conducted on Siamese cats involving three subgroups - orthophoric, moderate angle esotropia and large angle esotropia, yielded results that were interesting. Basically they found that none of the cats had binocular or ipsilaterally activated cells in the visual cortex. They hypothesised that as two cats were orthophoric this supported the theory that the squint is primary and does not develop from a central defect of coding mechanism for fusion[25].

The development of esotropia in Siamese cats mimics that of humans in that initially the eyes diverge in the neonate stage and converge at three months. Moreover the degree of misalignment varies greatly.

Siamese cats present a model that the abnormal pattern of decussation at the chiasm that is an abnormal anatomical condition can lead to anomalous projections in the geniculostriate pathway that prevent the development of normal binocular single vision[26].

Asymmetries of optokinetic nystagmus and motion perception.

Optokinetic Nystagmus (OKN) Asymmetry.

Optokinetic nystagmus is an oscillatory response to moving targets. It consists of a slow phase (pursuit) followed by a rapid refixation (saccade). The pretectal nucleus of the optic tract contains direction selective neurons that are believed to be involved in OKN responses.

In a normal neonate, monocular optokinetic nystagmus is asymmetrical; - the response to a stimulus moving in the nasal-temporal direction is significantly reduced compared to the response in the temporal - nasal direction[27]. This asymmetry decreases with age and becomes symmetrical at around 6 months of age when the binocular reflexes are established.

In congenital esotropia it has been found that the reduced temporally directed monocular horizontal OKN persists. Mein studied this asymmetric OKN and concluded that only patients with the triad of early onset strabismus, nystagmus and DVD consistently demonstrated asymmetry of uniocular OKN[28].

However a more recent study suggested that the OKN response was directly related to the age of onset of the strabismus. The earlier the onset the more likely the OKN response will be asymmetric[29]. This was confirmed in a study which found that OKN responses remained asymmetric in a group of congenital esotropes even though they were aligned before 5 months and went on to achieve good stereopsis[30].

A recent study by Westall and others looked at a group of 14 infants and toddlers with congenital strabismus and found none of them developed symmetric monocular OKN. However 45% did elicit sensory-cortical fusion. They concluded that

optokinetic nystagmus asymmetry may not be associated with a deficit in cortical fusion but rather with deficits in binocular pathways projecting to OKN control centres[31].

In summary, current research supports the theory that monocular optokinetic nystagmus asymmetry is related to the age of onset of strabismus and not to the potential for binocularity.

Defects in Visual Motion Processing

Recent work has shown that smooth pursuit movements are driven by visual inputs from the cortical pathways for motion processing.

Congenital esotropes have been found to have a number of abnormalities of ocular motor responses that imply asymmetry of the motion processing mechanism with nasal to temporal motion being defective.

These studies have found that in congenital esotropes:

1. Monocular OKN is defective in nasal to temporal direction, as previously mentioned.
2. Pursuit eye movements are defective with failure to track smoothly from nasal to temporal direction unioculary.
3 There is failure to judge velocity of targets moving in the nasal to temporal direction[32].

These deficits are considered to be due to maldevelopment in the motion processing of the visual cortex although whether the strabismus being present at a critical developmental period causes the defect or whether the strabismus is a result of an abnormal emphasis on nasally directed motion is not clear.

A study by Norcia, Hamer, Jampolsky and Orel-Bixter found that motion processing showed plasticity in the critical developmental period and the magnitude of directional bias improved after early surgery in a group studied[33]. They felt that there was a critical period for the development of binocular direction selective mechanisms during which accurate alignment may be effective in promoting recovery of response.

Latent Nystagmus

Latent nystagmus (LN) is a congenital jerk nystagmus which manifests on covering one eye or reducing image brightness in one eye. The term manifest latent nystagmus was introduced by Dell'Osso to describe manifest nystagmus with the same characteristics as latent nystagmus that is, the nystagmus increases on reducing input to one eye[34]. He felt this was the same as nystagmus associated with congenital esotropia and that it only appeared as latent nystagmus because the very low amplitude wiyh both eyes open was not observed clinically. Essentially the characteristics of latent nystagmus and manifest latent nystagmus are the same with a fast phase (jerk) to the temporal side on the fixing eye and a slow nasal movement or slip.

Kommerell has postulated that latent nystagmus is due to the same defect in naso-temporal symmetry that affects pursuit and optokinetic systems. Normals employ two controls to pursue, foveation or position of the image in relation to the fovea, and retinal slip. He hypothesised that the asymmetry of smooth pursuit and LN are due to maldevelopment of retinal slip He argues that the key factor in producing these asymmetries is the reduced binocularity rather than monocular or binocular deprivation.[35]

Current Genetic Studies

Strabismus Inheritance Study in Tasmania (SIST)

The SIST study is a genetic study looking for the genes that predispose individuals to congenital esotropia. The study hypothesises that congenital esotropia is a genetic disorder which results in anatomical changes which affect the development of the binocular reflexes and normal binocular single vision. The expression of the gene varies in severity and the milder phenotypes do have the anatomical structure to develop subnormal binocular vision if the eyes are aligned surgically at at an early age. The more severe phenotype will never have the structure in place to develop any form of binocularity.

The study is currently looking at several candidate genes looking for mutations that segregate with affected individuals in 25 sibling pairs with congenital esotropia. The initial candidate genes under investigation are genes that relate to the development of axonal direction in the visual pathway.

CONCLUSION

The aetiology of congenital esotropia is unknown. Current research on the clinical manifestations of the disorder and anatomical studies on the macaque animal model have done much to enlighten us on the neural mechanisms underlying the disorder.

ACKNOWLEDGEMENT

The author and the Strabismus Inheritance Study in Tasmania would like to acknowledge the support of the Clifford Craig Foundation, Ophthalmic Research Institute of Australia, Alcon and the Orthoptic Association of Australia.

REFERENCES

1. Von Noorden G. Bowman Lecture. Current concepts of infantile esotropia. Eye 1988; 2 :343-357.

2. Graham PA. Epidemiology of strabismus. Br J Ophthalmology 1974; 58:224-231.

3. Mohney B, Erie J, Hodge D, Jacobsen S. Congenital esotropia in Olmstead County Minnesota Ophthalmology 1988; Vol 105, 5 :846-850.

4. Worth C. Squint, its causes pathology and treatment. 6th ed. London: Balliere, Tindall and Cox. 1929.

5. Chavasse FB. Worth's Squint. The binocular reflexes and the treatment of strabismus. 7th ed. Philadelphia: P Blakiston's Son and Co Inc. 1939. 117-163.

6. Nixon RB, Helveston EM, Miller K, Archer SM, Ellis FD. Incidence of strabismus in neonates. Am J Ophthalmology 1985; 100: 6: 798-801.

7. Archer S, Sondhi S, Helveston E. Strabismus in early infancy. Ophthalmology 1989; 96: 133-137.

8. Lang J. Congenital or infantile that is the question? Binocular Vision 1998; 3 :116-117.

9. Von Noorden F. A reassessment of infantile esotropia. Am Journal of Ophthalmology 1998; 105;1-10.

10. Lang J. Squint dating from birth or with early onset. Transactions 1st International Congress of Orthoptics. London: Kimpton; 1968:231-237.

11. Ciancia A. On infantile esotropia with nystagmus in abduction. J Pediatr Ophthalmol Strabismus 1995;32:280-288.

12. Adelstein F, Cuppers C. Zum problem der echten und der scheinbaren abducents ishmung (Das sogenannte blockierungasyndrom) Buch Augenarzt 1966; 46:271-278.

13. Guillery RW. Normal deprived and congenitally abnormal geniculocortical pathways Strabismus Proc Third Meeting International Strabismological Assoc 1978 Kyoto Japan. ed Reinecke R. Grune and Stratton New York.

14. Kupfer C. The laminar pattern and distribution of cell size in the lateral geniculate nucleus of man J Neuropathol and Exp Neurol 1965; 24; 645-652.

15. Weisel TN, Hubel DH, Lam DMK. Autoradiographic demonstration of ocular dominance columns in the monkey striate cortex by means of transneuronal transport. Brain Res 1974; 79:273-279.

16. Mein J, Trimble R. Diagnosis and management of Ocular Motility Disorders. 2nd ed Blackwell 1991 Oxford. 132.

17. Bishop PO, Henry GH. Spatial vision. Ann Rev Psychol 1971; 22:119.

18. Abramov I, Gordon J, Hendrickson A, Hainline L, Dobson V, LaBoissiere E, The retina of the newborn human infant. Science 1982; 217; 265-267.

19. Huttenlocher PR, de Courten C, Garey LJ, Van der Loos H. Synaptogenesis in human visual cortex. Evidence for synapse elmination during normal human development. Neurosci 1982; Lett 33: 247-252.

20. Huttenlocher PR, de Courten C. The development of synapses in striate cortex of man. Human Neurobiology 1987; 6:1-9.

21. Tychsen L, Boothe R. Latent fixation nystagmus and nasotemporal asymmetries of motion visually evoked potentials in naturally strabismic primates. J Pediatr Ophthalmol Strabismus 1996; 33:3:148-52.

22. Tychsen L, Burkhalter A. Functional and structural abnormalities in the cortex in early childhood strabismus. Klin Monatsbl Augenyheilkd 1996; 208 :1:18-22

23. Tychsen L, Burkhalter A. Nasotemporal asymmetries in V1: ocular dominance columns of infant, adult and strabismic macaque monkeys. J Comp Neurol 1997; 388:1:32-46

24. Hubel D, Wiesel T. Aberrant visual projections in the Siamese cat. J Physiol, 1971; 218: 33-62.

25. Cool S, Crawford M. Absence of binocular coding in striate cortex units of Siamese cats. Vision Res 1972; 12:1809-1814.

26. Blake R, Crawford M. Development of strabismus in siamese cats. Brain Research 1974;77: 492-496.

27. Mein J. The OKN response and binocular vision in early onset strabismus. Australian Orthoptic Journal 1983; 20: 13-17.

28. Naegele J, Held R. The postnatal development of monocular optokinetic nystagmus in infants. Vision Res 1982; 22; 341-346.

29. Hooper A. Optokinetic nystagmus and the age of onset of strabismus Br Orthop J 1990; 47:44-47.

30. Aiello A, Wright K, Borchert M. Independence of optokinetic nystagmus asymmetry and binocularity in infantile esotropia. Arch Ophthal 1994;112:1580-1583.

31. Westall C,Eizenmann M, Kraft S, Panton C, Chatterjee S, Siesmund D. Cortical binocularity and monocular optokinetic asymmetry in early onset esotropia. Invest Ophthal and Vis Sci 1998; 39:8 1352-1359.

32. Tychsen L, Lisberger S. Maldevelopment of visual motion processing in humans who had strabismus with onset in infancy. Journal Neuroscience 1986; 6:9: 2495-2508.

33. Norcia A, Hamer R, Jampolsky A, Orel-Bixler D. Plasticity of human motion processing mechanisms following surgery for infantile strabismus. Vision Res 1995; 35:23-24 ;3275-3296.

34. Dell'Osso L, Schmidt J, Darroff R. Latent, manifest latent and congenital nystagmus. Archives of Ophthalmology 1979; 97: 1877-85.

35. Kommerell G. The relationship between infantile strabismus and latent nystabmus. Eye 1996; 10:274-281.