EPIDEMIOLOGY AND CLINICAL STUDY OF NYSTAGMUS

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Doctor in Medicine

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Abstract

Introduction

Nystagmus is a repetitive to and fro movement of the eyes and can affect vision and involve individuals of all ages. Previous research into the pathophysiology of this disease has been based on case series or small numbers of patients. Improvements in and standardisation of electrodiagnostics and eye movement recordings have enabled scientists to diagnose and characterise the different nystagmus types more accurately.

Purpose

The research into nystagmus carried out at the University of Leicester had several aims. The first population-based study on the prevalence of nystagmus was carried out within the county of Leicestershire. The second study was aimed at examining the clinical features of patients with different types of infantile and neurological nystagmus in order to characterise any specific features associated with this groups of patients. The final study was carried out with the aim of investigating the distribution of refractive errors in patients with nystagmus and to determine if the process of emmetropization in ocular development is influenced by the presence of nystagmus.

Methods

Ethical approval was obtained. Patients were recruited for the epidemiological study from both the community and hospitals within Leicestershire. Patients for the clinical and refractive error studies were additionally recruited from outside the county. A further 602 normal subjects volunteered to participate in the refraction study.

Results

The epidemiological study estimates the prevalence of nystagmus to be 16.6 per 10 000 (under 18 population) and 26.5 per 10 000 (over 18 population). The clinical study showed differences in visual acuity, stereopsis, anomalous head posture and conjugacy of nystagmus amongst different clinical groups. Finally, the refractive errors study suggests that the process of emmetropization is influenced by the presence of nystagmus.

Conclusion

These studies provide previously unknown data about nystagmus and provide a platform for further research into this condition.

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Chapter 1

Introduction

Chapter 1: Introduction

1.1. Nystagmus – Definition and historical perspective

Nystagmus is defined as a repetitive to-and-fro movement of the eyes that prevents steady fixation and leads to disruption of normal vision (Leigh and Zee, 1999). Historically, the term 'nystagmus' has been derived from the Greek words *'nystagmos'*, meaning to nod or drowsiness, and *'nystazein'*, which means to doze. The slow downward drift and brisk upward head movement seen when sleeping is similar to the 'jerky' movements seen in some nystagmus forms. There are no comprehensive historical reviews providing the first description of nystagmus. However, it is known that nystagmus was observed as early as 1794 by Erasmus Darwin (the grandfather of Charles Darwin) who first described vestibular nystagmus; in1820 when Jan Evangelista Purkinje described optokinetic nystagmus seen in people looking out of train windows, and in 1861 when the French physician Prosper Ménière described Ménière's disease and its association with nystagmus (Pryse-Phillips, 2003). Other milestones in the description of nystagmus included the development of the caloric test by Robert Barany, a Nobel Prize winner in 1906, through his purely clinical observation of eye movements.

Dr A. Samelson (1869), in his description of two patients with 'absence of iris', described one patient who is the 'eldest of four sisters and the only one in whom the eyes are imperfect'. 'There is slight rotatory nystagmus and the whole of the space within the corneoscleral junction reflects a red light under the ophthalmoscope' which appears to be a description of a case of aniridia and infantile nystagmus. Interestingly,

he concluded that 'the mother refers to the defect in the child's eyes, to a fright she had when pregnant, from a cat leaping at her' (Samelson, 1869). One of the earliest accounts of treatment for nystagmus described how surgical treatments for 'strabismus, closed pupil and nystagmus' had resulted in a reduction in 'the tremulous condition in the eyes' (listed, 1861).

Historically, a very interesting form of neurological nystagmus was 'miners' nystagmus' which in 1920 was thought to have affected 6,000 men every year since 1913 and was at the time costing the government £1,000,000 a year in compensation (listed, 1920)! By 1948, it was well established that there was a psychosomatic element to this condition in some patients, as the incidence rapidly decreased from 1930 onwards when miners were asked to sign a statement of good ocular health prior to work and the compensation for the disease was far less than the income earned by working. Miners' nystagmus has not been described recently in the medical literature.

1.2. Classification of nystagmus

Numerous classification systems for nystagmus have been proposed. The 'simplest' classification of nystagmus is into physiological and pathological which can be divided into congenital and acquired forms of nystagmus, although most authors argue that congenital nystagmus should be replaced with the term 'infantile nystagmus' as it is often not present at birth and develops in early infancy (Gottlob, 2000, Neely and Sprunger, 1999). Physiological nystagmus includes optokinetic, vestibular and end-

point nystagmus. Infantile nystagmus can be subdivided into six main types: idiopathic (IIN), associated with albinism, latent/manifest latent, spasmus nutans, sensory nystagmus (or associated to afferent pathway disease) and neurological forms of childhood nystagmus (Gottlob, 2000).

Adult onset nystagmus appears to be best classified based on pathogenesis into: nystagmus associated with disease of the visual system and its projections to the brainstem and cerebellum, nystagmus caused by vestibular imbalance and nystagmus due to abnormalities of the mechanism for holding eccentric gaze (Miller et al., 2005). In practice, most clinicians would group neurological nystagmus into vestibular nystagmus, nystagmus associated with neurological diseases such as multiple sclerosis, cerebrovascular ischaemia and gaze evoked nystagmus.

There are several other eye movement abnormalities which are often described in conjunction with nystagmus. Saccadic intrusions are characterised by an initial rapid eye movement which take the eyes off the object being observed as compared to nystagmus which is an initial slow movement (Abadi, 2002). Rapid oscillations can also be seen in diseases affecting ocular motoneurons and extraocular muscle such as superior oblique myokymia but are distinguished from nystagmus by irregular oscillations of small amplitude and variable frequency. Eyelid nystagmus is a phenomenon in which eyelid movements occur in association with nystagmus, most frequently upward movements of the eyelid with upward movements of the eye in vertical nystagmus (Miller et al., 2005).

Clinically, the simplest way to distinguish infantile from neurological nystagmus is through history, asking the patient about the time of onset of nystagmus, symptoms

of oscillopsia or the illusion of the entire world moving (usually absent in infantile nystagmus) and family history of nystagmus. Infantile nystagmus tends to be conjugate with horizontal or mixed (combination of horizontal, vertical or torsional) planes of oscillation but rarely, there can be pure vertical nystagmus. The presence of a null point (a region of gaze where the nystagmus is reduced) and dampening of the nystagmus on convergence also points towards a diagnosis of infantile nystagmus.

In 1967, Cogan classified congenital nystagmus into four types: sensory-defect nystagmus, motor-defect nystagmus, latent nystagmus and periodic alternating nystagmus (Cogan, 1967). Nystagmus was considered 'sensory' if it was associated with a defect in the afferent visual system, e.g. achromatopsia and 'motor' if the defect was in the efferent visual system, e.g. idiopathic infantile nystagmus.

Eye movement recordings have revolutionised the characterisation and discrimination of different types of nystagmus and more recently the CEMAS (Committee for eye movement disorders and strabismus) classification of nystagmus has reflected this (Figure 1) (http://www.nei.nih.gov/news/statements/cemas.pdf).

Table 1.1: *Classification system for nystagmus and other oscillations based on the*

committee for eye movement disorders and strabismus recommendations.

CEMAS classification for nystagmus and other oscillations
(http://www.nei.nih.gov/news/statements/cemas.pdf, 2001)

A. Physiologic fixational movements

B. Physiological nystagmus -   1.Vestibular
                              2. Eccentric
                              3. Optokinetic

C. Pathological nystagmus -   1.Infantile nystagmus syndrome
                              2. Fusion maldevelopment nystagmus syndrome
                              (previously called latent/manifest latent nystagmus)
                              3. Spasmus nutans syndrome
                              4. Vestibular nystagmus
                              5. Gaze-holding deficiency nystagmus
                              (e.g. cerebellardisease, intoxication diseases)
                              6. Vision loss nystagmus – chiasmal, prechiasmal and post
                              chiasmal
                              7. Other pendular nystagmus associated with diseases of
                              central myelin
                              8. Ocular bobbing – typical and atypical
                              9. Lid nystagmus

D. Saccadic oscillations and intrusions -   1. Square wave jerks and oscillations
                                              2. Square wave pulses
                                              3. Saccadic pulses
                                              4. Induced convergence retraction
                                              5. Dissociated ocular oscillations
                                              6. Hypermetric saccades
                                              7. Macrosaccadic oscillations
                                              8. Ocular flutter
                                              9. Flutter dysmetria
                                              10. Opsoclonus
                                              11. Psychogenic (voluntary) flutter
                                              12. Superior oblique myokymia

E. Generalised disturbance of saccades

F. Generalised disturbance of smooth pursuit

G. Generalised disturbance of vestibular eye movements

However, the CEMAS classification of nystagmus is controversial as it does not allow

clinicians to easily distinguish nystagmus based on aetiology and diagnosis of different

nystagmus types, for example not indicating whether there is visual loss due to associated diseases such as albinism or retinal dysfunction, which often have overlapping waveforms (Kuppersmith, 2008). The group of patients with 'infantile nystagmus' includes, for example, patients with idiopathic infantile nystagmus, albinism, congenital stationary night blindness and achromatopsia. The prognosis and management of these patients vary greatly. The classification also relies on analysis of eye movement recordings and the lack of availability of this equipment and expertise in interpreting these recordings means that only a minority of clinicians would be able to use this in daily practice.

1.3. Mechanisms causing nystagmus

There are three main mechanisms which enable an individual to maintain steady gaze: (i) fixation, (ii) the vestibulo-ocular reflex, and (iii) the gaze-holding system, also known as the neural integrator (Abadi, 2002). Fixation occurs when the retinal drift and unwanted saccades are suppressed, while the vestibulo-ocular reflex is the compensatory mechanism allowing fixation to be maintained during head and body movements. The neural integrator system enables fixation to occur on an object in eccentric positions of gaze (Neely and Sprunger, 1999). When the eye is turned in an extreme position of gaze, the tonicity of the extraocular muscles prevents the elasticity of the ligaments and fascia from pulling the eye back into the primary position. This tonicity is maintained by impulses which are received from the neural integrator system of which the nucleus prepositus hypoglossi is the main structure.

Disruption of any of these three control mechanisms results in either nystagmus or saccadic intrusions/oscillations and this can be differentiated through clinical examination of the patient by looking for the initial slow phase movement seen in nystagmus or the initial fast component seen in saccadic intrusions as described in section 1.2 (Leigh and Zee, 1999). The characteristics of the nystagmus (e.g. jerk, pendular, upbeat, see saw nystagmus), associated symptoms (e.g. oscillopsia) and signs (e.g. dampening with convergence) allow the clinician to establish a possible aetiology for nystagmus. For example, patients with idiopathic infantile nystagmus tend to have a conjugate, pendular or jerk, horizontal nystagmus with dampening of the nystagmus at near (Abadi and Dickinson, 1986, Dell'Osso and Daroff, 1975). In achromatopsia, another form of infantile nystagmus, patients have a conjugate, often initially pendular nystagmus of high frequency and small amplitude which evolves into a jerk nystagmus as the child becomes older and no convergence dampening is seen (Gottlob and Reinecke, 1994). Neurological pendular nystagmus which is seen in multiple sclerosis can show a disconjugate form in patients with unilateral signs of optic neuropathy (Barton and Cox, 1993a, Chen and Gordon, 2005). Unlike idiopathic infantile nystagmus, convergence in patients with multiple sclerosis could result in an induced or increased nystagmus (Barton et al., 1999).

1.4. Clinical assessment in nystagmus

The clinical assessment of a patient with nystagmus is very important in establishing a possible cause for the disease, prognosis and possible therapeutic measures, in addition to providing opportunities for genetic counselling in inherited forms of the disease. When confronted with a patient with nystagmus, the history, examination and clinical investigations, including eye movement recordings and electrodiagnostic testing, often provide most clinicians with a possible differential diagnosis or aetiology of the disease.

During history taking, family history, the duration of nystagmus, effects on vision (e.g. symptoms of oscillopsia) and association with other neurological symptoms are important initial questions (Serra and Leigh, 2002). Other information should include whether symptoms are worse in any position of gaze, e.g. whether there is a horizontal null point (causing a head position) or worsening, for example on down gaze. A history of previous and current medications is also useful. In children with nystagmus, parents should be asked about the exact nature of the eye movements in nystagmus, such as change since onset, direction, intermittency and conjugacy. It is also important to establish whether the abnormal eye movements could be opsoclonus, which are multidirectional bursts of rapid eye movements, rarely seen in normal infants in the first three months of life, but could be a presenting sign of occult neuroblastoma in an older child (Willshaw, 1993). Another rare form of nystagmus seen in children is periodic alternating nystagmus, where the parents may report seeing the direction of nystagmus change in a 'cyclical' manner with each cycle lasting up to three minutes. Often in these children, alternating head turns to each side are

observed. Again, this form of nystagmus can be idiopathic, associated with albinism or also be associated with pathology in the craniocervical junction or over dosage of anticonvulsants (Serra and Leigh, 2002, Willshaw, 1993).

Examination of a patient with nystagmus includes general examination, examination of head and neck, and ophthalmological assessment (Lueck et al., 2004). A good general examination could aid in diagnosis of conditions such as hypopigmentation of skin and hair (in cutaneous albinism). Neurological examination could aid in the diagnosis of multiple sclerosis and cerebrovascular disease. The head and neck assessment could help to localise neurological disease, for example hearing loss and facial muscle weakness seen in patients with nystagmus where the aetiology of disease is in the cerebellopontine angle.

The ophthalmological assessment of any patient with nystagmus should include measurement of visual acuity, colour vision, depth perception or stereoacuity, visual fields, pupil reactions, examination of ocular movements, slit lamp examination and finally, dilated fundus examination.

1.4.1. Investigations in patients with nystagmus

The investigation of any patient with nystagmus includes investigation of the associated systemic disease and specific ophthalmic investigations.

1.4.1.1. Haematological investigations

Haematological investigations are useful in both infantile and neurological nystagmus. For example, a newly diagnosed infant with oculocutaneous albinism may have electron microscopy of platelets to exclude Hermansky-Pudlak syndrome. Toxicology screening could identify over dosage of alcohol or anticonvulsants. Blood samples may be taken for clinical genetic testing either for diagnostic testing or carrier testing in inherited forms of nystagmus, for example in spinocerebellar ataxia. In patients with neurological nystagmus, toxicology tests in suspicious over dosage and full blood count, serum glucose, cholesterol and autoantibody testing in patients with associated cerebrovascular events can provide useful information to allow initiation of treatment for diabetes, hypercholesterolaemia or autoimmune diseases. In suspected multiple sclerosis, exclusion of Lyme disease, AIDS and autoimmune diseases through blood tests is important in cases where the diagnosis is not definitely established.

1.4.1.2. Radiological investigations

Neuroimaging forms an integral part of the assessment of both infantile and neurological forms of nystagmus and is particularly important in neurological diseases (Slamovits and Gardner, 1989, Bose, 2007). The main forms of imaging used in patients with nystagmus are magnetic resonance imaging (MRI), computed tomography (CT) and B-scan ultrasound. These investigations could, in some cases, help in anatomically localising the cause of the nystagmus, monitoring progression, treatment and prognosis of the condition. For example, in cases of internuclear ophthalmoplegia secondary to vascular disease (dorsal infarction), MR angiography has shown that the pathophysiology in these cases is large vessel artherosclerotic occlusion and not perforating vessel obstruction as previously thought (Kim, 2004). In children where there are difficulties with clinical assessment, neuroimaging may help to provide a clinical diagnosis of rarer diseases such as Pelizaeus-Merzbacher syndrome (see Table 1.2)-(Shen et al., 1994, Slatkowski et al., 1997). Newer imaging modalities such as magnetic resonance angiography, computed tomography angiography and contrast enhancement have improved the detection of lesions either vascular or solid and enabled clinicians to decide early appropriate treatment. .

Magnetoencephalography (MEG) is another imaging technique used to detect human neuronal activity of the brain mainly in research centres. In MEG, the active brain areas are detected by recording the weak magnetic field caused by activation of neuronal populations at the cortex. This is in contrast to fMRI where the images are related to blood flow. Real-time analysis of activation and localisation of visual signals in MEG is recorded by visual evoked magnetic fields (VEFs) which represent neuronal

activity in the primary visual cortex of both cerebral hemispheres. Its use has been demonstrated in albinism, where patients with albinism showed maximum response to both nasal and temporal field stimulation in the contralateral cortical area, in contrast to normal subjects where maximal contralateral cortical response was only seen in temporal half-field stimulation (Lauronen et al., 2005). This method of imaging remains primarily a research tool.

1.4.1.3. Electrodiagnostics

Electrodiagnostic testing is an important part of clinical investigation of any patient with nystagmus. In an infant presenting with nystagmus, it may be the first objective assessment of visual function carried out which provides the aetiology of the disease (Breceji and Stirn-Krancj, 2004). Electroretinography and visual evoked potential testing are the most commonly used tests in nystagmus and from these investigations the aetiology of nystagmus can be localised to retina, anterior visual pathway or a non-organic cause.

Electroretinography

These tests can be subdivided into full field, focal, multifocal and pattern electroretinography (ERG), with full field being the most commonly used test. The test can differentiate between abnormalities in rod, cone, inner retinal and outer retinal function. Testing using ISCEV (International Standards for Clinical Electrophysiology of

Vision) standards involves recording of photopic and scotopic waveforms of the patient with pupil dilation, dark and light adaptation (Marmor et al., 2009b). This can identify diseases such as congenital stationary night blindness, achromatopsia and a normal ERG may aid the diagnosis of idiopathic infantile nystagmus, particularly cases of idiopathic infantile nystagmus with atypical vertical or asymmetric nystagmus (Shaw et al., 2001, Shawkat et al., 2000). Carriers of diseases such as congenital stationary night blindness may have abnormal electroretinograms, aiding geneticists with counselling of patients (Rigaudiere et al., 2003).

Figure 1.1: I. *Normal ERG and* ***II.*** *ERG for congenital stationary night blindness with abnormal scotopic waveforms.*
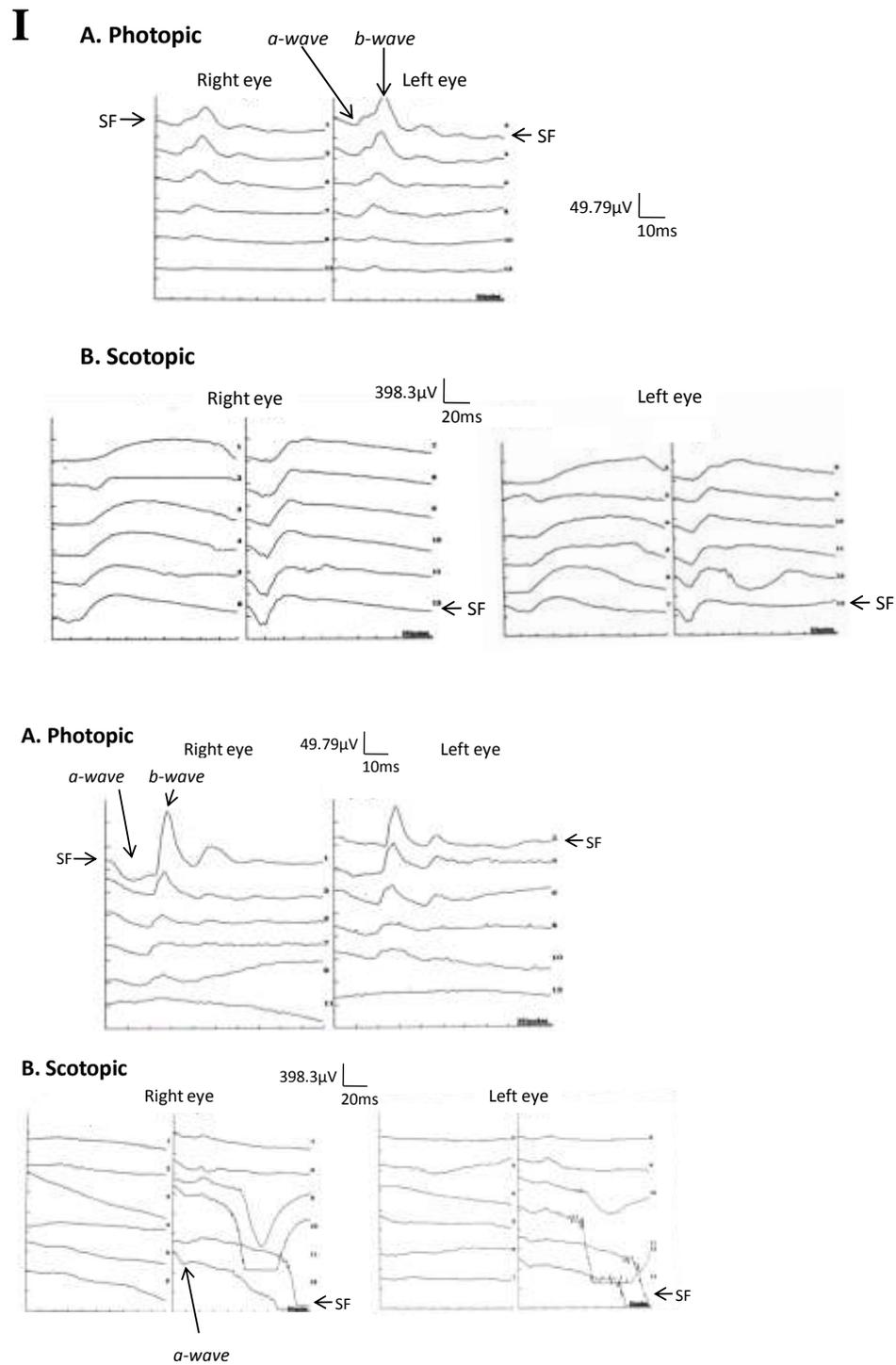
Visual evoked potential

The visual evoked potential (VEP) is recorded by averaging electroencephalographic activity at the scalp and can be used to differentiate between optic nerve, chiasmal and cerebral hemisphere abnormalities in adults and children with nystagmus (Shaw et al., 2001, Odom et al., 2004b). The stimulus used in recording VEP is either flash or pattern-onset stimulation. The most frequent use of this investigative tool in nystagmus is in detecting abnormal lateralisation or uncrossed asymmetry of retinal visual pathway. This can be seen in albinism or rarer conditions such as achiasma (Hoffmann et al., 2005). Flash stimulation appears to be more reliable than pattern-onset stimulation in detecting asymmetry in infants and children (Kriss et al., 1990) and flash stimulation only is advocated for children less than three years of age whilst both flash and pattern stimulation is suggested for children between three and six years of age (Apkarian, 1992). VEP testing remains the initial investigation of choice in patients with suspected ocular or oculocutaneous albinism (Figure 1.2), although as discussed previously, functional MRI (which is not currently in clinical use) may have an increasing future role in doubtful cases. In neurological nystagmus, visual evoked potential testing, in conjunction with MRI and cerebrospinal fluid analysis, can aid in the diagnosis of multiple sclerosis.

Figure 1.2: *Visual evoked potentials demonstrating misrouting seen in albinism compared to a normal patient. A flashing stimulus is applied with one eye open. Normal responses in the left hemisphere (O1 –FZ) and right hemisphere (O2-FZ) should be similar as optic chiasm distributes fibres to both sides (therefore, O1-O2 response almost flat). In albinism, asymmetric responses are seen leading to bigger O1-O2 response. (Picture produced by Dr Frank Proudlock, University of Leicester).*
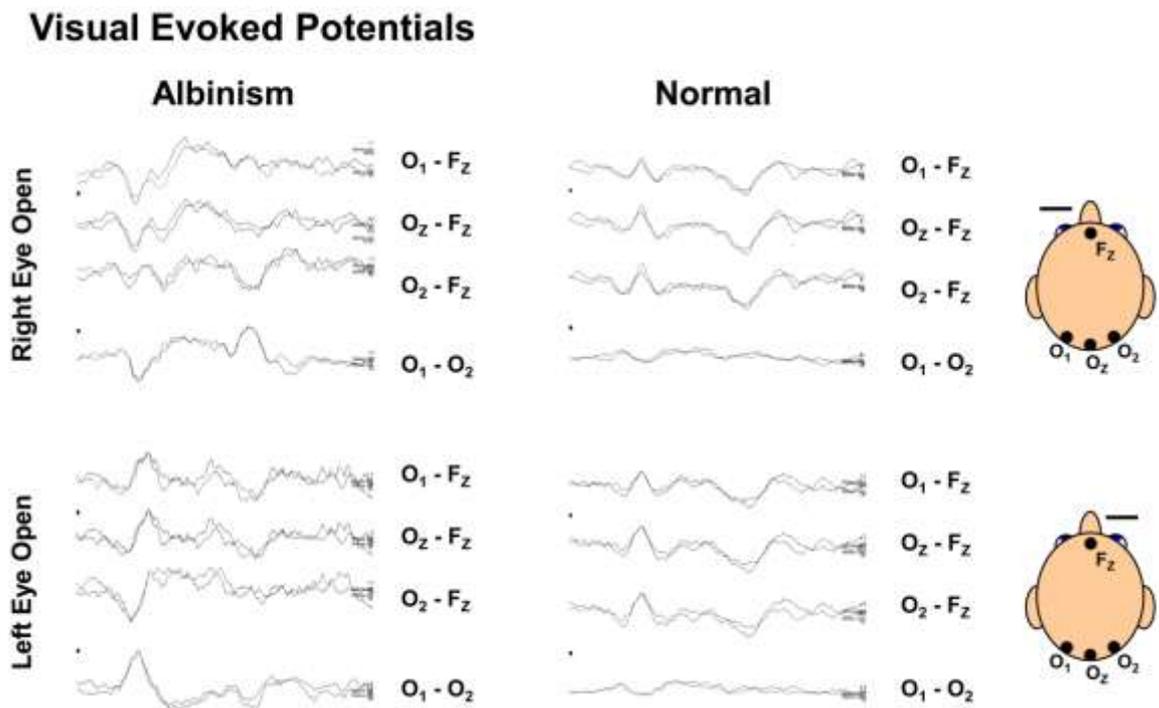
1.4.1.4. Eye movement recordings

Eye movement recordings enable clinicians and scientists to classify, provide a possible aetiology and monitor treatment of nystagmus. The main types of eye movement recording equipment are: electrooculography, infrared reflectance oculography and scleral contact lens/ magnetic search coils. Electrooculography relies on the fact that the eyes have a relatively positive potential of cornea due to the negative potential generated by the retinal pigment epithelium. It is available as part of routine electrodiagnostic testing in larger ophthalmology units. It enables recording of fast and slow phases of nystagmus but has limitations from calibration, interference from noise especially for vertical recordings, nonlinear recording and drifts (Taylor and Hoyt, 2005). Magnetic search coils are another technique and requires the patient to sit within a magnetic field whilst wearing a scleral contact lens with an embedded electrode (Figure 1.3. A). When the eyes move, an electrical current is generated and can be recorded. The main advantage of this equipment is its ability to record three dimensional eye movements (horizontal, vertical and torsional). Its use in younger children is limited due to difficulties with fitting and cooperation. Adults, too, often find it difficult to wear the search coil and tend to dislike frequently repeated measurements. There is also a risk of corneal damage.

Figure 1.3: *Eye movement recording techniques (A) sclera search coil where a scleral contact lens with an embedded electrode is inserted into the eye, and (B)* infrared reflectance videooculography *which monitors eye and head movements.*

Scleral Search Coil Technique

Infrared Video-oculography (EyeLink I system, SR Research, Canada)
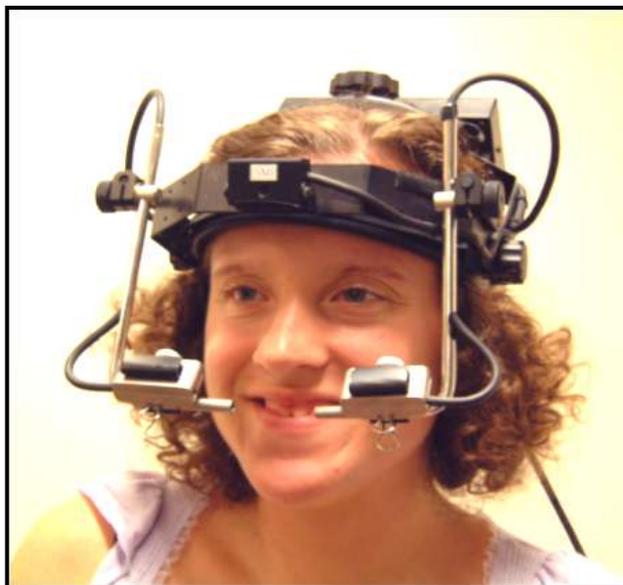
Head Camera view
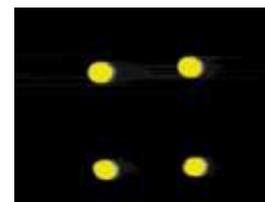
Eye Camera view
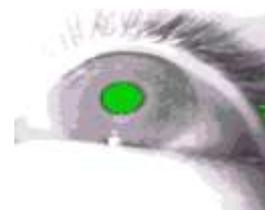
Infrared reflectance oculography is widely used in clinical and research laboratories. A typical tracker (e.g. the eye tracker shown in figure 1.3.B) consists of two infra-red video cameras which record each eye during the study. Some systems also monitor head monitor head movements to give gaze rather than eye position. With good calibration, the recordings obtained can be used in diagnosing nystagmus and monitoring the effects of therapy. The recordings provide continuous traces of the nystagmus waveform over time. This examination technique is non invasive, usually well tolerated and patients usually agree to participate in sequential or repeat examinations. Children from the age of about six year can usually be examined with this method.

Dell'Osso and Daroff have provided a classification system for infantile nystagmus waveforms based on detailed recordings from sixty five patients with an age range of thirty three to sixty seven years (Dell'Osso and Daroff, 1975). They described the four main groups as pendular, unidirectional jerk, bidirectional jerk and dual jerk waveforms. Within three of the main groups – pendular, unidirectional jerk and bidirectional jerk, there was a further subdivision of the waveforms as further illustrated in figure 1.4. This paper also discussed the concept of foveation periods (periods where the eye move at a lower velocity at the fovea), which were seen in patients with infantile nystagmus and found to be longer in patients with idiopathic infantile nystagmus, which could explain the better visual acuities in these patients.

Figure 1.4: The 12 different waveforms used to describe eye movement recordings in infantile nystagmus (Dell'Osso and Daroff, 1975).
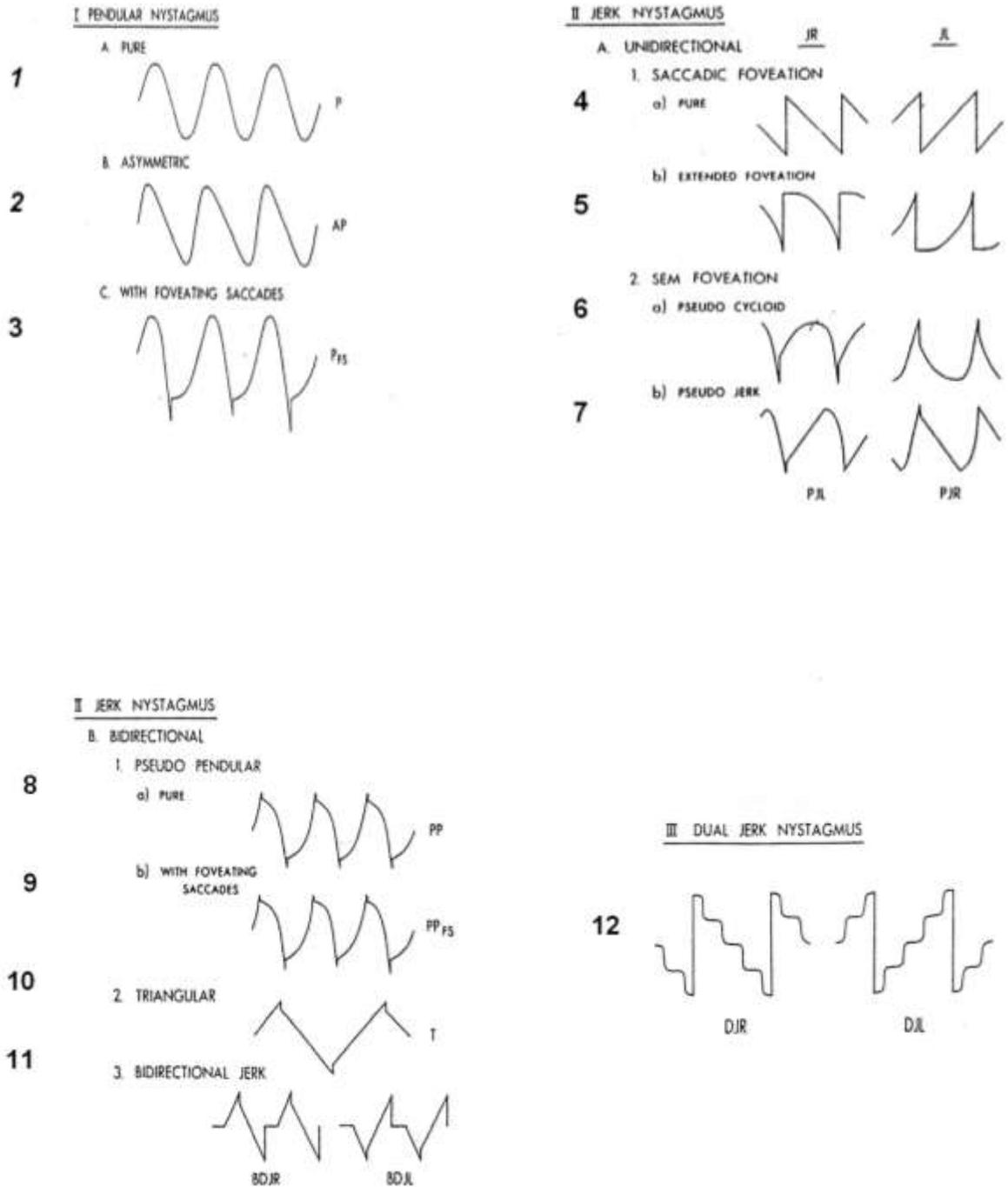
Further eye movement recordings carried out on 150 subjects with various forms of infantile nystagmus demonstrated patients with idiopathic infantile nystagmus and nystagmus associated with albinism could not be distinguished using foveation periods (Abadi and Dickinson, 1986). They suggested the importance of clinical assessment to be used in conjunction with eye movements in order to establish a clinical diagnosis. Another study on 27 infants found that infrared oculography carried out in younger infants with infantile nystagmus demonstrated longer foveation periods in patients with better visual acuity (Hertle et al., 2002). Despite limitations in clinical specificity, eye movement recordings have helped to provide important clinical information including the absence of nystagmus in at birth in some forms of infantile nystagmus (Gottlob, 1997), with later development at approximately six to seven weeks. Also, eye movements have been used to identify the presence of sub-clinical nystagmus in some carriers of genetically inherited forms of infantile nystagmus (Thomas et al., 2008, Gottlob, 1994) and characteristic features seen in diseases such as achromatopsia (Gottlob and Reinecke, 1994).

More recent phenotyping work, carried out on patients with known genetic mutations in conjunction with eye movement recordings, have shown that subtypes of idiopathic infantile nystagmus display differences in eye movement characteristics. For example, patients with idiopathic infantile nystagmus and FRMD7 mutations are more likely to have pendular nystagmus waveforms and lower amplitude of nystagmus in the primary position with resulting lower incidence of anomalous head postures (Thomas et al., 2008). There was a low prevalence of strabismus in patients with idiopathic infantile nystagmus with and without the FRMD7 mutation (7.8 to 10%) and both

groups of patients had visual acuities of 6/9 or better. Further delineation of the

nystagmus waveforms may enable clinicians to provide patients with a more reliable

initial diagnosis and prognosis for visual development.

Eye movement recordings have an important role in diagnosis of patients with

neurological nystagmus as they can assess the saccades, binocular and monocular

smooth pursuit, and binocular and monocular optokinetic nystagmus (Jacobs et al.,

1992). Eye movement recordings can demonstrate slow saccades seen in oculomotor

nerve paralysis or internuclear ophthalmoplegia (Leigh and Zee, 1999). Eye movement

recordings also aid in monitoring of treatment of neurological nystagmus by

demonstrating a reduction in the intensity of nystagmus in addition to an

improvement of symptoms experienced by patients and could help in dosage

adjustment or deciding when to try alternative treatments (McLean et al., 2007).

Figure 1.5: Eye movement recordings in a patient with internuclear ophthalmoplegia and multiple sclerosis showing the abducting nystagmus and slow adducting saccade waveform.
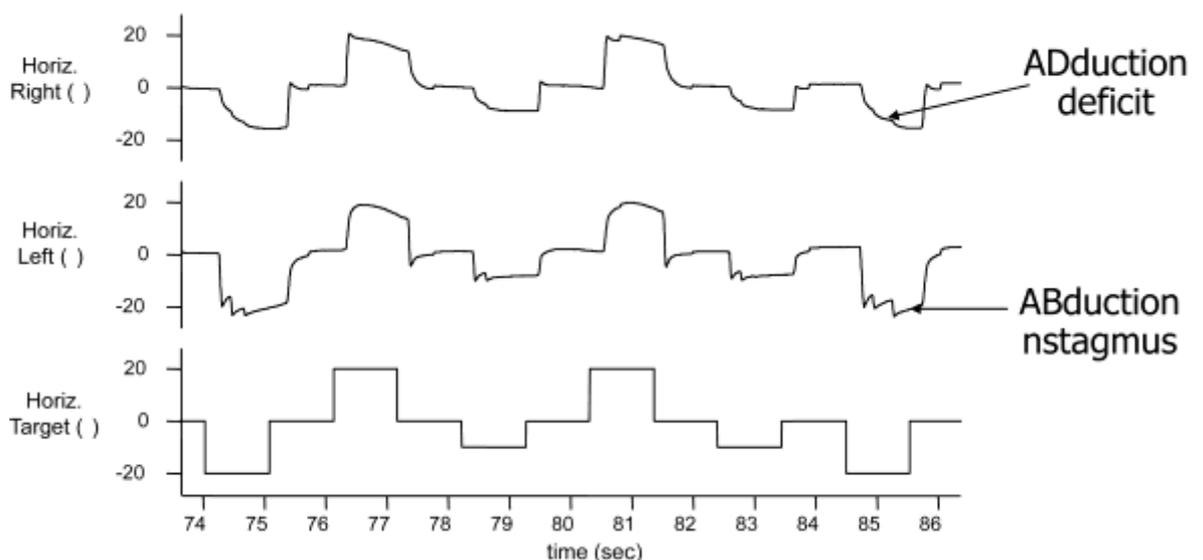
1.4.1.5. Optical coherence tomography

Optical coherence tomography (OCT) is a relatively new diagnostic tool which allows non-invasive, ultra high resolution imaging of the retina. Its use has been well established in diseases such as age related macular degeneration and macular oedema, where quantification of retinal thickness allows monitoring for disease progression. Within the clinical area of nystagmus, research has been performed in assessing foveal architecture in patients with albinism (Chong et al., 2009). Patients with albinism (Figure 1.6) show enhanced transillumination of the choroidal layer and absence of a foveal depression (Seo et al., 2007). Visual acuity in patients with albinism appears to correlate with the amount of foveal hypoplasia documented on OCT (Chong et al., 2009, Seo et al., 2007).

Figure 1.6: OCT of two patients with albinism showing absent and abnormal foveal depression.
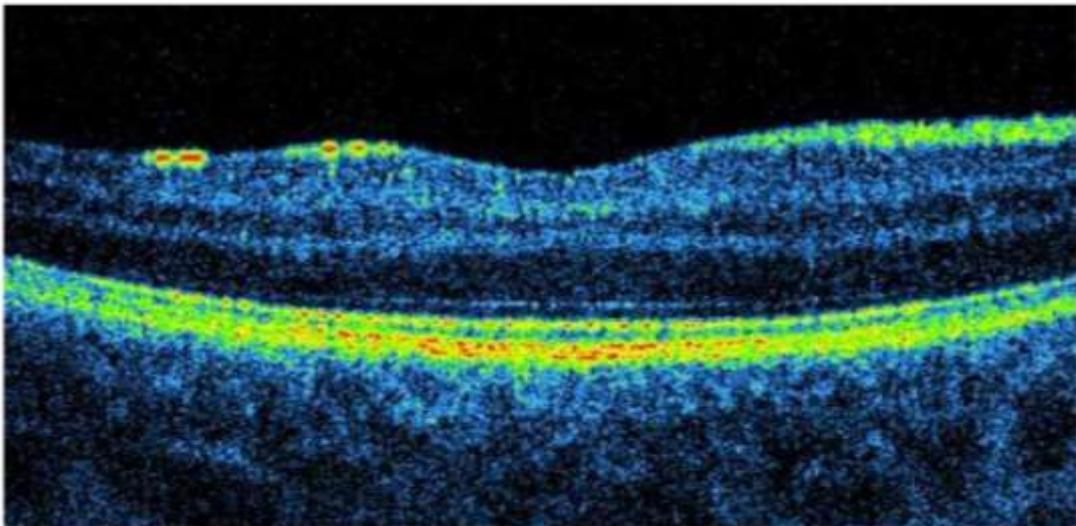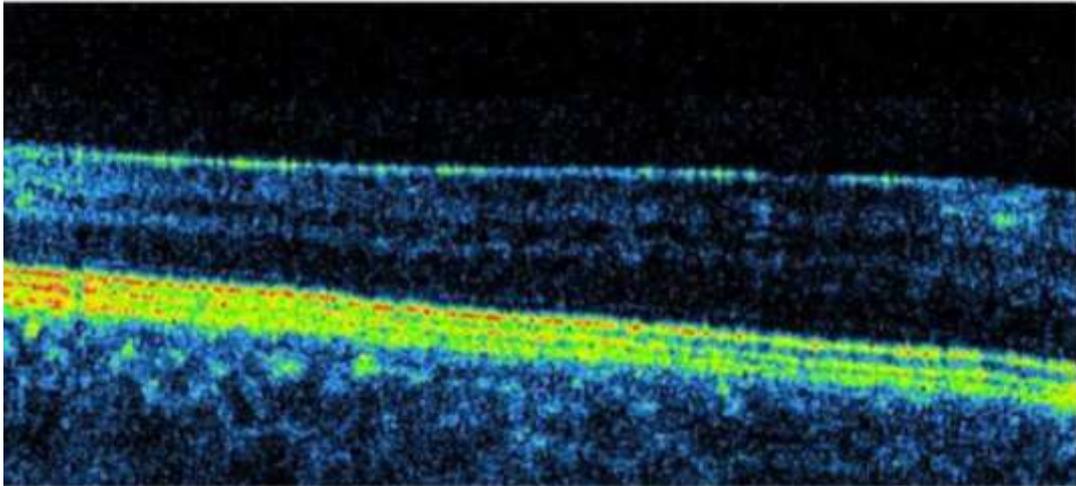
1.5. Epidemiology of nystagmus

Although the clinical diagnosis and investigation of patients with nystagmus have been well described, the prevalence of nystagmus in the general population is unknown. No published studies have been carried out with the primary aim of estimating the prevalence of nystagmus in the general population. The Royal College of Ophthalmologists estimates that 'nystagmus is believed to affect 1 in 1000 individuals' (http://www.rcophth.ac.uk/docs/publications/patient-info-booklets/UnderstandingNystagmus.pdf). In terms of infantile nystagmus, previous studies of the prevalence of nystagmus have been obtained among 220802 army recruits in Netherlands (Hemmes, 1927), from a cohort of partially-sighted and blind children in Denmark (Norn, 1964), in a special eye clinic available to children attending elementary schools of Malmo, Sweden (Forssman and Ringner, 1971) and in a representative sample of 1500 ten year old children in the United Kingdom (Stewart-Brown and Haslum, 1988):

- **Hemmes, 1927 (Netherlands):** The first prevalence study, carried out in1924 in the Netherlands, looked at recruits who had been 'discharged from service' on medical grounds and estimated the prevalence of nystagmus to be 1 in 5032 among males and 1 in 10,596 among females. Through calculations which are not clearly presented, Hemmes predicted a prevalence of 1 in 6500 individuals with nystagmus in the Netherlands. However, this was a select group of individuals who had been excluded from joining the army due to visual impairment (Hemmes, 1927).

- **Norn, 1964 (Denmark):** In a second study in 1964, all children over the age of 15 who attended The Danish Institute for the Blind and Partially Sighted were examined and 71 cases of nystagmus were diagnosed within a population of 3.7 million in 1937 (prevalence 1 in 500 000). However, this was a group of children with visual acuities of 6/36 or worse, which would have excluded infantile nystagmus patients with better visual acuities. In fact, the author appeared to label the study children with a diagnosis of 'idiopathic nystagmus' with no mention of other common infantile forms of nystagmus such as nystagmus associated with albinism (Norn, 1964).

- **Forssman and Ringner, 1971 (Sweden):** Between 1941 and 1959, 61 680 pupils attending elementary schools in Malmo, Sweden were examined on entry to the first grade. The families of all individuals found to have nystagmus were then examined and the prevalence of nystagmus was calculated as 1 in 1000 for males and 1 in 2800 for females.(Forssman and Ringner, 1971).

- **Stewart-Brown and Haslum, 1988 (UK):** In the United Kingdom, a study of all children with visual acuities worse than 6/24, born in 1970, found the prevalence of nystagmus to be 1 in 1000 (Stewart-Brown and Haslum, 1988). However, these were children with poorer vision and did not include children with nystagmus who had visual acuities better than 6/24 and the results of our work in Chapter 3 show that there are many patients with nystagmus and visual acuities better than 6/24.

All the previous studies looked at the prevalence of infantile forms of nystagmus and no data currently exists on the prevalence of neurological nystagmus in both children and adults. The patients in all previous studies had their diagnoses made based on

clinical examination only and there was no mention in all the papers about the use of electrodiagnostics, eye movement recordings and neuroimaging to aid in clinical diagnosis of the nystagmus form. Within the United Kingdom the prevalence of nystagmus is likely to vary between the multiracial communities with infantile nystagmus being more prevalent within communities with a higher rate of consanguineous marriages resulting in a higher incidence of inherited congenital ocular anomalies (Pardhan and Mahomed, 2002, Schwarz et al., 2002).

In the neurological forms of nystagmus, there is no published data on how common this disease is within a population. Pathological neurological nystagmus is seen in well described diseases such as multiple sclerosis (Barton and Cox, 1993b) and cerebrovascular disease (Gresty et al., 1982). Although epidemiological data exists on the incidence of multiple sclerosis (Robertson et al., 1995), there is very little information about the frequency of nystagmus in this disease. One paper quotes the incidence of internuclear ophthalmoplegia in multiple sclerosis to vary between 17 to 41% of patients (Tsuda et al., 2004).

The study in Chapter 2 is an epidemiological study carried out in Leicestershire to more accurately estimate the prevalence of nystagmus within a population. Individuals with both infantile and neurological nystagmus (with the exception of transient vestibular nystagmus) were included in this study. Capture-recapture statistical analysis was used to calculate the prevalence of nystagmus after individuals with nystagmus living in Leicestershire were identified through three independent sources of recruitment. The capture-recapture method provides an estimate of number of missing data not captured from the three sources.

1.6. Clinical features of infantile and neurological nystagmus

1.6.1. Infantile nystagmus

Infantile nystagmus may be idiopathic or associated with systemic or ocular disease (including retinal disease and strabismus). Infantile nystagmus is defined by onset of nystagmus within the first two months of life.

1.6.1.1 Idiopathic infantile nystagmus

This condition usually presents within the first two months of life (Gottlob, 1997). Both sporadic and familial forms occur. Patients characteristically have a horizontal, conjugate nystagmus with a null point and dampening on convergence (Abadi and Dickinson, 1986, Dell'Osso and Daroff, 1975). The waveform typically evolves from a slow, large pendular nystagmus in infancy into a smaller amplitude jerk nystagmus of higher frequency (Hertle et al., 2002). It can be associated with an anomalous head posture or strabismus (Abadi and Bjerre, 2002). Normal electrodiagnostic testing is important to exclude any retinal disease or optic nerve disease but most previous studies on idiopathic infantile nystagmus have not included this information. The recent discovery of genes involved in idiopathic infantile nystagmus have resulted in more recent phenotypic characterisations, for example patients with FRMD7 mutations having more pendular waveforms of nystagmus, significantly lower amplitudes of nystagmus in the primary position and significantly less anomalous head

postures than patients with idiopathic infantile nystagmus with no FRMD7 mutations

(Thomas et al., 2008)

1.6.1.2. Infantile nystagmus associated with albinism

One of the most common forms of infantile nystagmus associated with more generalised disease is albinism. Albinism is a heterogenous, inherited condition associated with hypopigmentation of skin, hair and eyes or eyes alone (Kriss et al., 1992). Characteristic ocular features include iris transillumination (Figure 1.7), foveal hypoplasia and optic nerve misrouting at the chiasma which is detected through visual evoked potential testing. The visual evoked potential abnormality appears most likely to be present in patients with foveal hypoplasia and who demonstrate virtually all the ocular features of albinism (Dorey et al., 2003).

Figure 1.7: Anterior segment and fundus photographs of patient with albinism demonstrating iris transillumination and fundus hypopigmentation.

The visual acuities of patients with albinism also show a wide variation ranging from 6/9 Snellen acuity to 6/60 Snellen acuity and gross stereopsis is demonstrable in patients with better visual acuities (Lee et al., 2001) suggesting a possible correlation

between increased melanin (less iris transillumination and less marked foveal hypoplasia) and better visual function.

1.6.1.3. Infantile nystagmus associated with retinal disease

Congenital stationary night blindness is an inherited disorder characterised by night blindness, mild to severe visual loss and normal fundus examination. Diagnosis is made with electroretinography testing which shows variable predominantly rod and some cone dysfunction.

Achromatopsia is another retinal dystrophy with abnormal cone function seen on electroretinography. There is usually reduced central vision, day-blindness, absent or poor colour vision, photophobia and a characteristic fine amplitude nystagmus (Michaelides et al., 2004). Complete achromatopsia is the typical form with poorer visual acuity and total colour vision loss in comparison to incomplete forms such as blue cone monochromatism where visual acuity may be slightly better and colour vision may be present for blue colours (Gottlob, 1994, Michaelides et al., 2004).

Leber congenital amaurosis is a rod-cone dystrophy with clinical presentation of poor vision from birth, nystagmus and absent or poor pupillary responses to light. It can be associated with eye poking or the 'oculodigital' sign (Taylor and Hoyt, 2005). Optic disc pallor, arteriolar attenuation and a subtle pigmentary retinopathy may be present on fundoscopy.

1.6.1.4. Manifest latent nystagmus (Fusion maldevelopment nystagmus syndrome)

Manifest latent nystagmus is characterised by a mainly horizontal, jerk nystagmus which changes in amplitude with occlusion of one eye. It is caused by a slow drift towards the covered eye with corrective quick phases towards the open eye which is fixing (Abadi and Scallan, 2000). Eye movement recordings in manifest latent nystagmus (Figure 1.8) typically show 'decreasing velocity' or decelerating slow phases with increasing intensity in abduction of the fixing eye. It is associated with congenital squint syndrome (Dell'Osso, 1985, Gradstein et al., 1998) and is seen in many patients with esotropia and Down syndrome (Averbuch-Heller et al., 1999).

Figure 1.8: *Eye movement recordings from a patient with manifest latent nystagmus showing slower velocity nystagmus towards the covered (occluded) eye with higher velocity corrective movements towards the uncovered eye. There is reversal of the nystagmus direction with covering alternate eyes.*
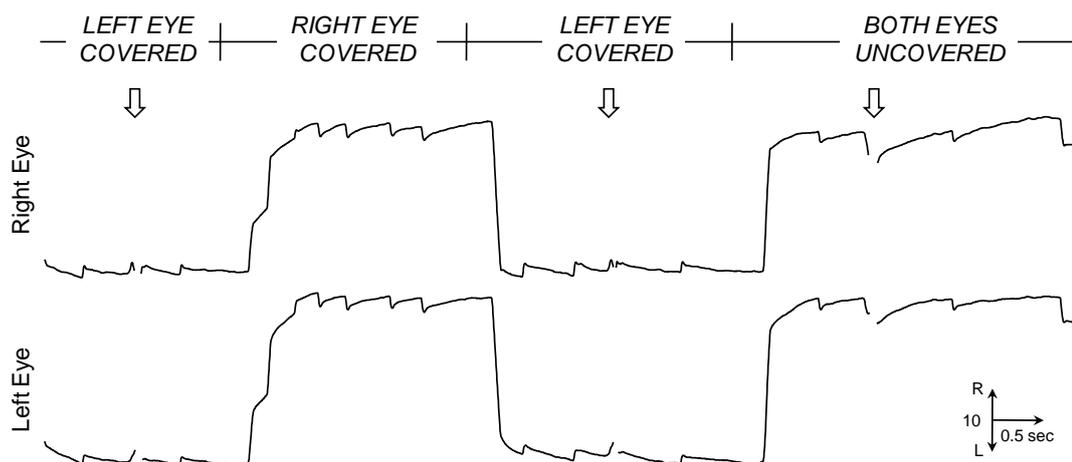
Disruption of binocular vision during visual development is thought to result in manifest latent nystagmus. The nucleus of the optic tract, which receives visual information from the contralateral retina and from the motion sensitive cortex which projects to the vestibular nuclei, is thought to play a role in the development of manifest latent nystagmus. Disruption of binocular information to the motion sensitive cortex results in a monocular nasotemporal eye movement preference with resulting asymmetrical output to the vestibular nuclei leading to manifest latent nystagmus (Brodsky and Fray, 1997).

1.6.1.5. Spasmus nutans

This disorder is characterised by a triad of nystagmus, head nodding and anomalous head posture. The nystagmus is fine, fast and pendular and dissociated between the two eyes. Unlike the other infantile forms of nystagmus, onset is usually later either just before or after the first birthday. Head nodding suppresses the nystagmus and signs and symptoms improve with time, by two to four years of age, although subclinical nystagmus may be seen up to thirteen years of age (Gottlob et al., 1995). It is important to exclude tumours or other neurological diseases e.g. optic nerve gliomas, encephalitis, empty sella and hydrocephalus in these patients through clinical assessment and neuroimaging. Eye movement recordings are unable to distinguish between benign spasmus nutans and spasmus nutans associated with intracranial disease (Gottlob et al., 1990). Spasmus nutans has not been shown to be hereditary and is associated with a low socioeconomic strata (Wizov et al., 2002).

1.6.1.6. Infantile nystagmus associated with ocular disease

Ocular diseases associated with nystagmus include Peters anomaly (Figure 1.9), optic nerve hypoplasia, congenital cataracts and aniridia. These diseases are further discussed in the genetics section. Other ocular diseases which have been associated with nystagmus in the study of patients in Chapter 3 are microphthalmos and persistent hyperplastic primary vitreous. Microphthalmos is a rare condition occurring in 1.5 per 10 000 births and is defined by a reduced size of one or both eyes. The condition is not known to be inherited and possible causes include maternal infection (rubella, syphilis, toxoplasmosis, and cytomegalovirus) and other environmental teratogens (Taylor and Hoyt, 2005). The condition is unilateral in three quarters of cases and can be associated with nystagmus. Persistent hyperplastic primary vitreous represents a wide spectrum of disease within the globe with features ranging from a retrolental fibrovascular plaque, prominent iris blood vessels, elongated ciliary processes, shallow anterior chamber and secondary vitreous haemorrhage or raised intraocular pressure. Nystagmus and strabismus may be present in unilateral cases.

Figure 1.9: Colour photograph of two month old infant with Peters anomaly showing shallow anterior chamber and cornea haze. The infant had several irido-corneal adhesions seen through the operating microscope.
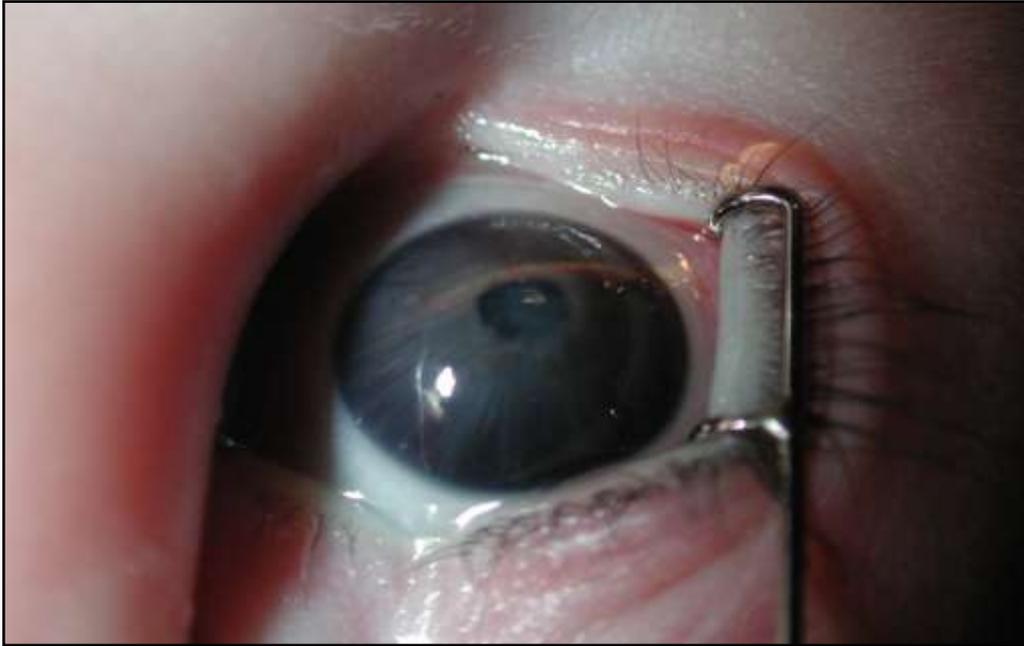
1.6.2. Neurological nystagmus

There are three main mechanisms for the development of neurological nystagmus: the first is disorder of the vestibulo-ocular reflex, secondly interruption to the brain's gaze holding mechanism and thirdly any interruption to the visual stabilisation process which involves the visual system's ability to detect and correct retinal image drift and the suppression of unwanted saccades which would take the eye off viewing the target (Leigh and Zee, 1999).

Nystagmus which occurs as a result of vestibular disease can be divided into peripheral and central forms. The central forms are usually subdivided into upbeat, downbeat and torsional nystagmus. Periodic alternating nystagmus and see-saw

nystagmus are other forms of recognised nystagmus in this group. Upbeat nystagmus can occur as a result of disease (e.g. stroke, demyelination, tumour) in the pons, cerebellum, medulla or midbrain (Hirose et al., 1991) and is thought to be due to a combination of hypoactivity of the elevator muscles of the eye and damage to the inhibitory control mechanism for vertical eye movements (Pierrot-Deseilligny and Milea, 2005). Thiamine deficiency, lithium toxicity, multiple sclerosis and Chiari malformation can all cause downbeat nystagmus (Yee, 1989) and in these cases a combination of hyperexcitability of the elevator muscles and inhibitory controls of the vestibulocerebellar system are thought to result in the downbeat nystagmus seen (Pierrot-Deseilligny and Milea, 2005). Acquired periodic alternating nystagmus is caused by lesions in the cerebellar nodulus and uvula (Leigh et al., 2002), and can be seen in disease such as multiple sclerosis, cerebellar tumour or degeneration, Chiari malformation and lithium or anticonvulsant toxicity (Leigh and Zee, 1999).

Abnormalities of the gaze holding mechanism can result in gaze-evoked nystagmus, Brun's nystagmus, convergence-retraction nystagmus, centripetal and rebound nystagmus.

The third group of neurological nystagmus is associated with disease of the visual system and its connections to the cerebral cortex, brainstem and cerebellum. This could be as a result of diseases involving the anterior segments of the eye, retina, optic nerve, optic chiasm and postchiasmal pathway. Acquired pendular nystagmus and oculopalatal myoclonus are other specific examples of this third group (Miller et al., 2005). Pendular nystagmus can be associated with multiple sclerosis (Chen and Gordon, 2005), Whipple's disease, encephalopathy, spinocerebellar degeneration and

brainstem stroke. Instability of the neural integrator has been postulated as the cause

of pendular nystagmus seen in multiple sclerosis (Das et al., 2000).

Neurological nystagmus in children can be seen in foetal alcohol syndrome,

developmental delay, hydrocephalus, Joubert syndrome, Cockayne syndrome and

Pelizaeus-Merzbacher syndrome. As part of our study, we have classified children with

nystagmus secondary to neurological diseases separately from infantile nystagmus.

This group of patients with nystagmus have not been well researched and one of our

aims in all our studies was to see if there were any specific characteristics in this group

of patients. All these patients have additional neurological systemic features in

addition to their nystagmus, and although the onset of nystagmus may have been

during the first two to three months of life, we believe that they represent a different

group of patients with nystagmus compared to infants with no known associated

central nervous system disease. The clinical study in chapter 3 found nystagmus in

other rare neurological diseases such as Stiff Person syndrome, Pallister Killian

syndrome and celiac disease.

Although understanding the pathogenesis and clinical features of different diseases

associated with nystagmus have advanced rapidly in the last two decades, most

studies have been case series or have involved small numbers of patients. We carried

out a study with the aim of looking at clinical characteristics of patients with both

infantile and neurological nystagmus to see if there were particular clinical features,

for example, visual acuity, stereoacuity, convergence dampening or other features which could help clinicians to accurately establish the aetiology of nystagmus in individual patients. This study involving three hundred and ninety one patients with nystagmus is described in detail in Chapter 3.

1.7. Genetics in nystagmus

The largest development in nystagmus in the last two decades has been in establishing the genetic basis of congenital or infantile nystagmus. The three most common inherited forms of nystagmus are idiopathic infantile nystagmus, albinism and nystagmus associated with inherited retinal diseases such as achromatopsia and congenital stationary night blindness. The inheritance mode and genetic mutations for the commonest inherited forms of nystagmus is listed below in Table 1.2. Nystagmus is also seen in ocular diseases such as congenital cataracts (Figure 1.10), optic atrophy and familial exudative vitreretinopathy which can all have various modes of inheritance.

Table 1.2 *Summary of phenotypic and genotypic characteristics of inherited nystagmus diseases*.

Disease group	Clinical subgroups/ diseases	Inheritance mode	Genetic mutations identified	Role of gene mutation	Other information
Idiopathic infantile nystagmus		Autosomal dominant (MIM608345, MIM193003, MIM300242) (Dichigans and Kornhuber, 1964, Kerrison et al., 1996, Klein et al., 1998) Autosomal recessive (MIM257400) (Waardenburg, 1953) X-linked (Kerrison et a.l, 1999, Tarpey et al, 2006, Kerrison et al., 2001, Cabot et a.l, 1999)	*FRMD7,*Xq26.2 (MIM300628)(Tarpey et al., 2006)	Affects neurite growth (Toyofuku et al., 2005, Betts-Henderson et al., 2010, Thomas et al., 2008)	50% of female carriers of *FRMD7* are affected (Thomas et al., 2008)
Infantile nystagmus associated with albinism	Oculocutaneous albinism type 1 (OCA1)	Autosomal recessive	Type 1A (complete absence tyrosinase activity, MIM203100), Type 1B (partial reduction tyrosinase activity, MIM606952)	Tyrosinase activity	
	Oculocutaneous albinism type 2	Autosomal recessive (MIM 203200)			Individuals acquire small amounts of pigment with age
	Oculocutaneous albinism type 3	Autosomal recessive (MIM203290)	Mutation in tyrosinase-related protein-1, *TYRP-1* on chromosome 9		Initially discovered in South African blacks
	Oculocutaneous albinism type 4	Autosomal recessive (MIM606574)	Mutation in *MATP* gene on chromosome 5 (Grosnskov et al., 2007)		Seen most commonly in Japan

| Disease group	Clinical subgroups/ diseases	Inheritance mode	Genetic mutations identified	Role of gene mutation	Other information
	Ocular albinism type 1	X-linked (MIM300500)	Mutation in *GPR143* gene (chromosome Xp22.3)	Pigment production affected through defective intracellular transport and glycosylation in melanosomes in eye (Oetting, 2002)	
Infantile nystagmus associated with ocular disease	Peters anomaly	Autosomal dominant or autosomal recessive (Hanson et al., 1994)	Mutation in *PAX6* gene (MIM607108), *PITX2* gene (MIM601542), *CYP181* gene (MIM601771) or *FOXC1* gene (MIM601090)		
	Aniridia	Autosomal dominant, autosomal recessive or sporadic (Nelson et al., 1984)	Mutation in *PAX6* gene (Jordan et al., 1992)		One third of cases are sporadic
	Congenital cataract (Figure 1.10)	Autosomal dominant (MIM123580), X-linked	Mutations in alpha-crystallin gene, *CRYAA* (chromosome 21q22.3) (Litt et al., 1998). Mutation in gamma-D-crystallin gene, *CRYGD* (2q33-q35)and *PAX6* gene (Hanson et al., 1999)		
	Oculocerebrorenal syndrome of Lowe	X-linked	Mutations in the *OCRL* gene (Xq26.1) (MIM309000) (Suchy and Nussbaum, 2002)		Characterised by congenital cataracts, renal tubular dysfunction, vitamin D resistant rickets, nystagmus and mental retardation

Disease group	Clinical subgroups/ diseases	Inheritance mode	Genetic mutations identified	Role of gene mutation	Other information
	Optic nerve hypoplasia	Autosomal dominant (MIM165550)	Mutation in *PAX6* gene (MIM607108), homeobox gene HESX1 (3p21.2-p21.1) (Dattani et al, 1998)		Can be associated with endocrine abnormalities
Infantile nystagmus associated with retinal disease	Congenital stationary night blindness (CSNB)	Autosomal dominant, autosomal recessive or X-linked	CSNB1 (MIM310500) associated with mutations in *NYX* (Xp11.4) (Bech-Hansen et al., 2000); CSNB2 (MIM300071) associated with mutations in CACNA1F (Xp11.23) (Strom et al., 1998); Autosomal recessive CSNB (MIM613216, MIM25720, MIM610427) associated with mutations in *TRPM1* gene (15q13-q14) (Li et al, 2009), *GRM6* gene (5q35) and *CABP4* gene (11q13.1) (Zeitz et al., 2006); Autosomal dominant CSNB (MIM610445, MIM163500, MIM610444) is caused by mutations in *RHO* gene (3q21-q24), *PDEB* (4p16.3) or *GNAT1* gene(3p21) (Gal et al., 1994)		
	Aland island disease	X-linked (MIM300600)	Mutations in *CACNAF1* gene		Abnormal dark adpatometry and electroretinography help to distinguish from ocular albinism (Jalkanen et al., 2007)

Disease group	Clinical subgroups/ diseases	Inheritance mode	Genetic mutations identified	Role of gene mutation	Other information
	Achromatopsia	Autosomal recessive	Complete and incomplete variants phenotypically. Complete achromatopsia due to mutations in genes *CNGA3* (2q11.2) (MIM216900)(Kohl et al., 1998), *CNGB3* (8q21.3) (MIM262300) (Sundin et al., 2000) and *GNAT2* (1p13) (MIM139340) (Kohl et al., 2002); Incomplete caused by mutations in *CNGA3 gene* (2q11) (MIM600053) (Moradi and Moore, 2007)		
	Blue cone monochromatism	X-linked (MIM303700)	Mutation on chromosome Xq28 or chromosome 7 (Nathans et al., 1989)		
	Leber congenital amaurosis	Autosomal recessive (MIM204100)	Mutations in *RPE65* gene (1p31) (Ahmed and Lowenstein, 2008, Kaplan, 2008)		
Nystagmus associated with chromosomal disorders	Down syndrome (RRRRRREF) (MIM190685)	Trisomy of chromosome 21	Variable ocular phenotypes (Berk et al., 1996, Da Cunha & Moreira., 1996)		Nystagmus seen in up to 16% of patients (Stephen et al.,2007)
	Turner syndrome (MIM300706)	Females have only one X chromosome instead of two.	Second X chromosome can also be partially missing or rearranged		Periodic alternating nystagmus may be present (Chrousos et al. 1984)

Figure 1.10: *Anterior segment photograph of congenital posterior polar cataract.*
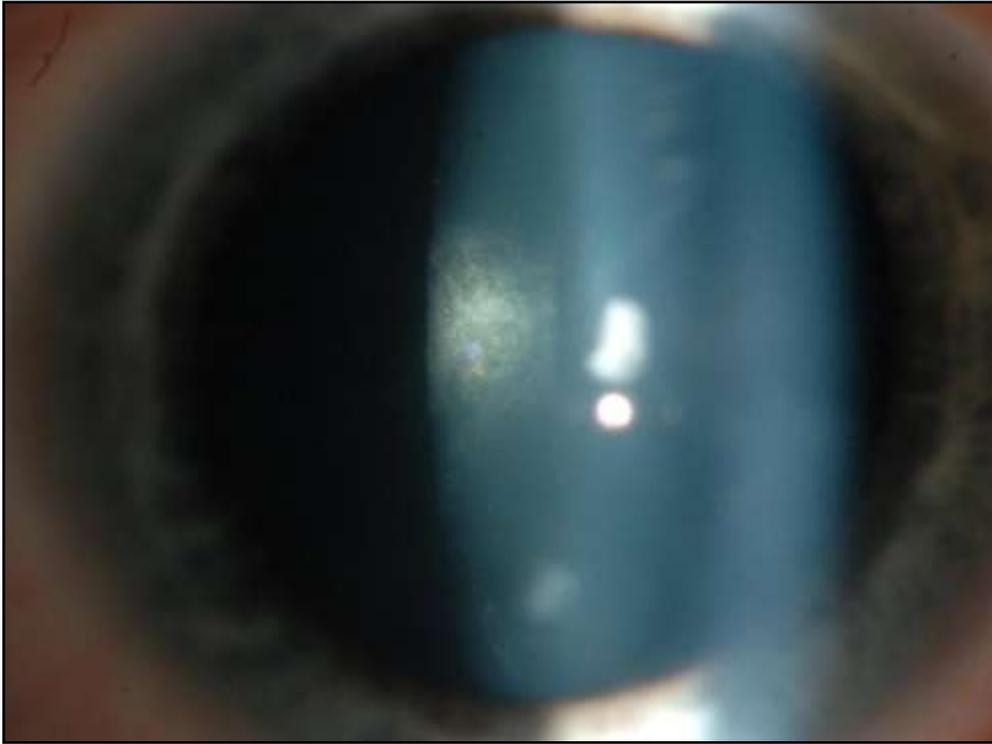
1.8. Treatment of nystagmus

Nystagmus was once regarded as a disease for which there were little, if any, treatment options. This has rapidly changed over the last two decades. The main aims of treatment are to provide symptomatic relief from oscillopsia (mainly in neurological forms) improve vision, correcting an anomalous head posture by moving the null position to the primary position, correction of any squint and reduction in amplitude and frequency of nystagmus. There is considerable overlap in these aims as reduction in amplitude and frequency of nystagmus or treatment of oscillopsia can often result in improvement in vision.

The types of treatment currently available are:

1. Pharmacological
2. Surgical
3. Social and rehabilitation
4. Optical

1.8.1. Pharmacological treatment

The initial work carried out into pharmacological treatment of nystagmus was for neurological forms of nystagmus. The main reasons for treating patients with drugs such as baclofen, clonazepam, 3,4-diaminopyridine,gabapentin,memantine and cannabis were to treat symptoms of oscillopsia and improve visual function in these patients (Averbuch-Heller et al., 1997, Strupp et al., 2003, Schon et al., 1999). In these studies, the numbers of patients were small ranging from one patient (Schon et al., 1999) to seventeen (Strupp et al., 2003) and twenty one cases (Averbuch-Heller et al.,

1997). There were no control group of nystagmus patients and there was heterogeneity in the causes of the acquired nystagmus. In all these studies, there was no assessment of long term safety or efficacy, although one study suggested that four patients were unable to tolerate the therapeutic dosage (Averbuch-Heller et al., 1997). However, these studies showed potential for improvement in both symptoms of oscillopsia and visual acuity with medical treatment.

In the United Kingdom, the commonest drugs used to treat neurological nystagmus are gabapentin and baclofen (Choudhuri et al., 2007). Most of the reported treatments have been based on case series or individual case reports and few randomised-controlled studies have been published. Baclofen is mainly used to treat periodic alternating nystagmus.

More recently, the emphasis has moved into medical management of infantile nystagmus. The author has published a case of infantile nystagmus associated with corneal dystrophy whose vision and amplitude of nystagmus improved after treatment with gabapentin (Sarvananthan et al., 2006). A further series of two patients with idiopathic infantile nystagmus and five with nystagmus associated with ocular disease showed a similar improvement when treated with gabapentin (Shery et al., 2006). This was a retrospective study but provided more information on longer term treatment with gabapentin for acquired and congenital nystagmus as one third of patients carried on with treatment for over twelve months. All except four patients had gabapentin dosages which were higher than 900mg described previously (Averbuch Heller et al., 1997). However, the numbers of patients recruited were small and for patients on memantine, the duration of treatment was less than six months.

The first randomised, controlled, double-masked trial in the treatment of infantile nystagmus divided forty-eight patients into three groups to receive either gabapentin, memantine or placebo (McLean et al., 2007). For the first time, both objective assessment of nystagmus using visual acuity and eye movement recordings and subjective assessment using visual function (VF-14) and social function questionnaires were used to evaluate response to treatment. Analysis of results in infantile nystagmus was separated for idiopathic and sensory forms of infantile nystagmus. Both treatment groups with memantine and gabapentin showed a significant reduction in nystagmus intensity and improvement in visual acuity (see Figure 1.11). Although the effect of visual acuity improvement in patients with sensory forms of infantile nystagmus was small compared with idiopathic infantile nystagmus, these patients reported subjective improvement and chose to continue with treatment after the study, suggesting a possible improvement in peripheral vision. The study did not evaluate optimal dosage of treatment for both drugs and further studies to assess duration of effect of these medications are needed. It was also interesting to note that patients with nystagmus in the placebo group showed significant subjective improvement in visual and social functions and the authors hypothesise that participation in the study environment itself may improve well-being in this group of patients.

Figure 1.11: *A. Original eye movements from a pharmacological trial (McLean et al (2007)) showing the wide range of eye movement waveforms in congenital (idiopathic) infantile nystagmus and secondary nystagmus (associated with sensory deficits). Figure B, C and D illustrate the change in nystagmus with eccentricity illustrating the null region, i.e. where the nystagmus is at its lowest intensity.*

From McLean et al Ann Neurol (2007) ; 61 (2): 130-8
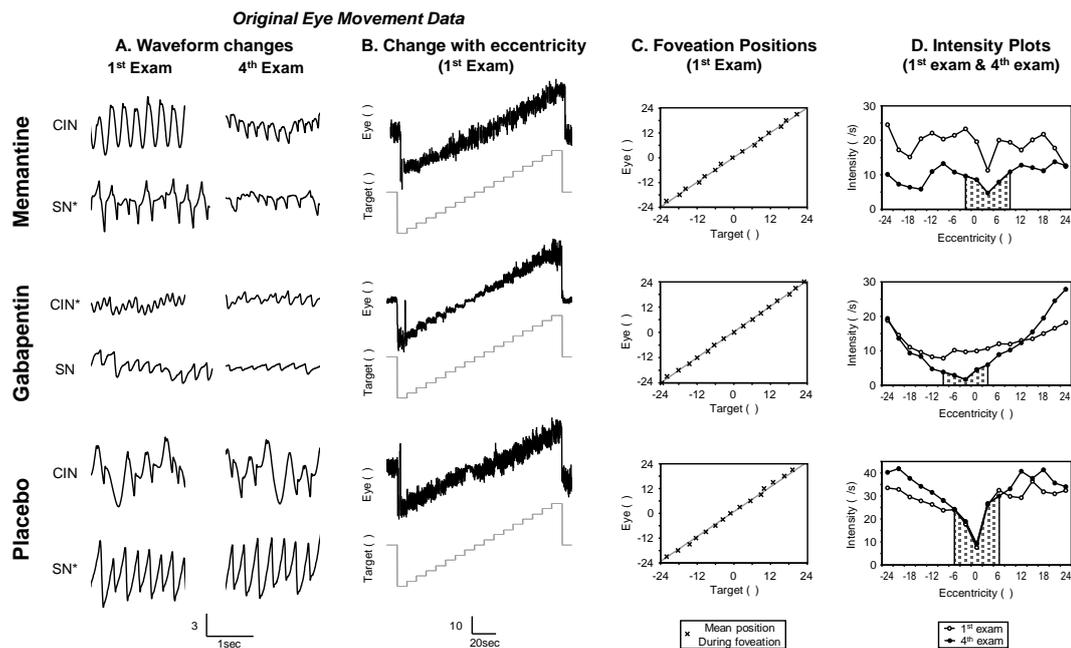
Gabapentin has been used in the treatment of epilepsy in children, while memantine has been used to treat Alzheimer's disease. Both have a common antiglutamatergic action and in addition, memantine is an N-methyl D-aspartate (NMDA) receptor antagonist. All these treatments have recognised side effects, which is why they may not be suitable for all individuals. However, they are usually well tolerated by patients who are otherwise systemically well. The long term efficacy and safety of the usage of the treatment at this dosage remains to be fully evaluated.

1.8.2. Surgical treatment

Surgical treatment in nystagmus is aimed at correction of an anomalous head posture, strabismus or a combination of both. The 'pioneers' of surgery in infantile nystagmus were Anderson and Kestenbaum (Anderson, 1953, Kestenbaum, 1953) with Anderson advocating recession of two yoke muscles and Kestenbaum carrying out a combination of resection and recession of all four horizontal extraocular muscles. Parks (Parks, 1973) modified this procedure and more recent procedures have included strabismus correction as part of the surgical procedure. The aim of all of these procedures is to realign the null region into the primary position.

Artificial divergence surgery is a procedure used in patients showing convergence dampening of nystagmus. An exodeviation is produced which results in fusional convergence and therefore reduces the nystagmus amplitude (Zubcov et al., 1993).

Retroequatorial recession of all four horizontal rectus muscles has also been reported to result in improved head posture and vision in some patients (Boyle et al., 2006).

Dell'Osso noted that any procedure which detached and reattached extraocular muscles tended to suppress infantile nystagmus particularly in cases with inconsistent anomalous head posture and absent convergence dampening (Dell'Osso, 1998). Trials in patients with nystagmus have shown improvement in binocular visual acuity in 5 out of 10 patients in the first study and 4 out 5 patients in the second study (Hertle et al., 2003, Hertle et al., 2004). The National Institute for Health and Clinical Excellence (NICE) recommends that tenotomy surgery should be carried out at ocular motility

centres with careful evaluation and preoperative counselling of patients (http://guidance.nice.org.uk/IPG299, 2009).

Surgical treatments have been reported to be successful in individual cases of patients with neurological nystagmus. Combined treatment with gabapentin and vertical Kestenbaum procedure in a patient with multiple sclerosis and nystagmus resulted in improvement in visual acuity from 6/60 and 6/24 in each eye to 6/9 in both eyes (Jain et al., 2002). Combined tenotomy and recession procedure in another case improved symptoms of diplopia, oscillopsia and visual acuity in another patient (Wang et al., 2007). Again, these represent individual cases and there is a need to carry out a randomised, controlled study to see if surgical treatment could be effective in improving the debilitating symptoms experienced by this group of patients.

1.8.3. Ancillary treatments

Accupuncture (Blekher et al., 1998), biofeedback (where the patient hears a sound which represents and varies with the intensity of nystagmus)(Sharma et al., 2000) and botulinum toxin A injection into horizontal rectus muscles (Carruthers, 1995) have all been used in the treatment of infantile nystagmus with transient success in isolated cases.

1.8.4. Social rehabilitation

The diagnosis of nystagmus in an otherwise healthy infant can be devastating to parents (Pilling et al., 2005). At the same time, neurological nystagmus can result in significant morbidity to the affected individual and his/her family. Various support networks exist to provide counselling, advice and rehabilitation advice to affected individuals and their family and this has proven invaluable in the medical management of these patients (Sanders, 2006).

1.8.5. Optical treatment

1.8.5.1 Prisms

Base-out prisms were initially prescribed to improve visual acuity by inducing fusional convergence in patients with congenital nystagmus (Metzger, 1950). This treatment does require the patient to demonstrate the presence of binocular vision. Its use as a permanent treatment for nystagmus is relatively unknown now but it is used as a temporary tool for preoperative assessment of correction of anomalous head posture, strabismus or in patients recovering from strokes with associated neurogenic palsies and neurological nystagmus.

1.8.5.2 Low vision aids

Low vision aids enable children and adults with nystagmus to carry out normal daily activities such as reading and watching television. Large print books, computers with

large fonts and tinted screens and telescopes are several examples of visual aids which have helped patients with nystagmus (Hertle, 2000, Hoeft, 1991). In young children (aged four to five years)with nystagmus, the use of magnifiers in conjunction with careful training has been shown to improve fine motor skills, accuracy in writing and better use of any head posture to optimise vision (Reimer et al., 2011). However the numbers of children studied was small (16 children). In adults, the use of an amblyoscope in addition to optimising refractive error (using prisms and bifocals) appeared to improve the visual acuity in five out of six individuals studied (Leung et al., 1995).

1.8.5.3 Correction of refractive error and amblyopia

Spectacles and contact lenses are used to optimise visual acuity in patients with nystagmus. With improving contact lens materials and better hospital optometry services, contact lenses are increasingly used in patients with high refractive errors or anomalous head postures (where the patient is unable to look through the optical lens of the spectacles). Contact lenses have been shown to improve visual function further compared to spectacles and it is thought that this may be due to a reduction in spherical and chromatic aberration (Abadi, 1979, Allen and Davies, 1983). The induced convergence and accommodative effort may reduce the amplitude of nystagmus and there is another hypothesis that the reduction in intensity may also occur through sensory feedback through the eyelid (Abadi, 1979). In addition to correction of refractive error, visual acuity can be improved further in children with amblyopia with the use of optical penalisation, occlusion or atropine occlusion.

1.9. Refractive error in patients with nystagmus

Although spectacles and contact lenses remain one of the most important and least interventional treatments in terms of visual improvement in patients with nystagmus, there are few studies into the distribution of refractive errors in these patients. The development of a refractive error is dependent on the presence of a difference between the focal length of the cornea and lens, and the length of the eye with resulting hypermetropia or myopia. A large early epidemiological study on healthy young men called up for National Service has shown that over 80% of individuals have unaided visual acuities of 6/6 or better and only 20% of the population have astigmatism greater than 0.5 dioptres (Sorsby et al., 1960). The results of this study were used to show that the distribution of refractive errors in normal individuals follows a leptokurtic distribution, which means there is an acute peak in the distribution curve around the mean (Sampath and Bedell, 2002). This is in contrast to patients with idiopathic infantile nystagmus and albinism who were found to have more refractive errors. However, the latter study only included two groups of nystagmus diagnoses.

Chapter 4 describes a large study in which the distribution of refractive errors of patients with various infantile and neurological nystagmus is compared to a large age-matched group of normal individuals. The aim of our study was to see if the presence of nystagmus affected the process of emmetropization in different clinical nystagmus groups, which would result in higher amounts of spherical and astigmatic refractive errors in these individuals. This was the first study including patients with neurological nystagmus and using normal age-matched controls from the same population. The

information from this study would help clinicians and optometrists recognise and treat

refractive errors early in order to treat or prevent the development of amblyopia and

enable optimal use of vision in patients with nystagmus.

Chapter 2

Epidemiology of nystagmus:

The Leicestershire Nystagmus

Survey

2.1 Introduction

Nystagmus consists of rhythmic involuntary oscillations of the eyes. It can occur in early childhood (infantile nystagmus) or be acquired later in life (acquired nystagmus, AN). The main groups of infantile nystagmus are unassociated/pure infantile nystagmus syndrome (INS) (which was widely known as idiopathic infantile nystagmus), INS associated with albinism, fusion maldevelopment nystagmus syndrome (which has previously been described as latent/manifest latent nystagmus), spasmus nutans syndrome and nystagmus associated with ocular disease (Gottlob, 2000).

Acquired nystagmus occurs mainly in neurological and vestibular diseases.

With the exception of vestibular nystagmus, which is most frequently due to inner ear semicircular canal dysfunction, nystagmus is likely to be due to abnormal development or pathological malfunction of areas in the brain controlling eye movements and gaze stability or afferent pathway disorders (Jacobs and Dell'Osso, 2004). New pharmacological (Averbuch-Heller et al., 1997, Bandini et al., 2001, Jain et al., 2002, Leigh, 1996, McLean et al., 2007, Sarvananthan et al., 2006, Schon et al., 1999, Shery et al., 2006, Starck et al., 1997, Strupp et al., 2003) and surgical (Del Monte and Hertle, 2006, Hertle et al., 2004) treatments for nystagmus are emerging. The understanding of pathological mechanisms in nystagmus is improving. In X-linked unassociated INS, we have recently identified mutations in a novel gene (FRMD7) (Tarpey et al., 2006). By analogy with other FERM proteins, loss of FRMD7 may alter neurite growth and branching in neuronal tissue.

The impact of nystagmus on vision can be significant, with visual function in many patients scoring worse than age-related macular degeneration (Pilling et al., 2005). However, the prevalence of nystagmus in the general population is unknown. No other studies have had the primary aim of estimating the prevalence of nystagmus in the general population. Previous estimates of nystagmus prevalence have been obtained from a cohort of partially sighted or blind children over the age of 15 years in Denmark (Noon, 1964), among 220802 army recruits (excluded from service due to poor vision) in the Netherlands (Hemmes, 1927), in all children attending the first grade of the elementary schools of Malmö, Sweden between 1941 and 1959, with further examination of family members of affected children(Forssman and Ringner, 1971), and in a representative sample of 15000 ten-year old children in the UK(Stewart-Brown and Haslum, 1988). Two of these studies looked at the incidence of all varieties of infantile nystagmus within a selected group of individuals with poor vision (Norn, 1964, Hemmes, 1927), whilst one study examined only the children and family members of affected children with nystagmus thus excluding adults with non-familial forms of nystagmus (Forssman et al., 1971). A further study looked at a representative sample of 15000 children aged 10 years with visual acuities ranging from 20/20 to poorer than 20/200 (Stewart-Brown and Haslum, 1988). None of these studies provided data on adults or children with acquired nystagmus.

The aim of our study was to specifically estimate the prevalence of nystagmus including all nystagmus forms (with the exception of transient vestibular nystagmus) in Leicestershire and Rutland, UK, with a population of just fewer than 1 million people. We used capture-recapture statistics with three different sources of data. Leicestershire and Rutland are a good setting for an epidemiological study since

previous locally conducted ophthalmic research has shown that only a very small number of patients obtain their eye care outside the county (Deane et al., 1998, Thompson et al., 1991).

2.2. Methods

The study had ethical approval from the Leicestershire ethics committee. We performed a county wide survey within Leicestershire and Rutland which has a population of 925 000 people (HMSO Office of population census and survey, 2001) (1.88% of the total population of England). Leicestershire (including Leicester city) and Rutland are situated in the centre of the East Midlands of England. The land area of Leicestershire is 2553 km^2. The ethnic minority community of Asian/Indian origin accounts for 29.9% in Leicester city, 3.7% in Leicestershire (excluding Leicester city) and 0.4% in Rutland (HMSO Office of population census and survey, 2001). This corresponds to 11.5% of the total county's population.

For the capture-recapture statistics, data were collected for three following sources up to and including 14th August 2003.

1) Leicester Nystagmus Survey (LNS)

A countywide (Leicestershire and Rutland) recruitment formed a hospital-based survey whereby all hospital specialists, general practitioners, community optometrists and teachers for the visually impaired were invited to inform patients with nystagmus about the study and ask them to participate. All existing databases from the hospital

were searched and patients with nystagmus were invited to participate (GW had a database of all diagnoses of children he has seen since 1995, and IG had a database of all patients she has seen in paediatric and adult neuro-ophthalmology clinics since 1999). In addition, there was media publicity using local newspapers, radio channels and talks to the local optometry association.

All identified patients were invited for a detailed clinical examination including assessment of vision, refractive error and fundoscopy. Informed consent was obtained from all participants of the community and hospital-based survey. Video and eye movement recordings (n=198) and electrodiagnostic (n=62) testing were carried out, where indicated, to aid with clinical diagnosis. Some patients had all three investigations. Twenty-eight patients did not attend for clinical assessment but all consented to a review of their clinical notes and previous investigations to establish a clinical diagnosis. Seven patients who were referred by neurologists but who were not current ophthalmology patients were seen by an ophthalmologist to confirm the diagnosis, according to the protocol requirements. Patients who attended the local hospital services but were living outside the designated boundaries of the county were excluded from the study. In the LNS group each patient was asked to state their ethnicity using the same classification as in the national census of the U.K. We compared the ethnic distribution of patients with nystagmus from Leicester city to the distribution of ethnic groups within the population of Leicester city obtained from the last census (HMSO Office of population census and survey, 2001). People from White British and other White backgrounds were grouped together as the 'White population' group and compared to the 'Asian population' grouped together from Indian, Pakistani, Bangladeshi and a minority from other Asian backgrounds.

The final classifications of the different types of INS were based on a combination of clinical assessment, electrodiagnostics, eye movement recordings and radiological tests. Unassociated INS was diagnosed in patients with nystagmus, where the patients had normal ocular examination and electrodiagnostic testing. The diagnosis of INS plus albinism was made based on the presence of one or a combination of the following clinical features in addition to nystagmus – iris transillumination, macular hypoplasia, fundus hypopigmentation and visual evoked potential asymmetry. Fusion maldevelopment nystagmus was distinguished from unassociated INS by the reversal in direction and increase in amplitude of nystagmus on occlusion of either eye, and the presence of linear or decelerating velocity waveforms in the slow phase in FMNS in contrast to increasing velocity waveforms in unassociated INS. Spasmus nutans syndrome was diagnosed in patients with the triad of nystagmus, head nodding and anomalous head positions.

2) Society for Visually Impaired Individuals (VISTA)

An independent source of people with nystagmus was obtained from VISTA using blind and partially sighted registration details held by the society of all persons living within the county of Leicestershire and Rutland. Registration with VISTA is voluntary but carries with it benefits including practical support from social services, concessions and in some cases financial support. The criterion for registration is based on national standards which take into account visual acuity and field of vision (http://www.dh.gov.uk, 2009). There were 5885 individuals registered as blind or partially sighted within the county up to and including 14th August 2003. Before September 2005, blind and partially sighted registration forms were known as BD8

registration forms and contained information about the patient's ocular diseases. The final clinical diagnosis was obtained from 2358 individuals' registration forms. In the remaining 3527 registered individuals, there were 498 missing registration forms, 424 patients had recently deceased prior to 14th August 2003 (and were excluded) and 2705 forms did not contain any clinical information and hospital notes had been destroyed. Following this, the hospital records of all patients who had a possible diagnosis associated with nystagmus or where the diagnosis was poorly recorded (n = 1873) were examined to confirm the presence or absence of nystagmus. In cases where hospital records were not obtained (n=202), further information was obtained from correspondence letters sent to general practitioners by the hospital ophthalmologist. Records confirming the diagnosis were found for all patients.

3) Leicestershire Educational Services (Education)

Data were obtained from the education services for the visually impaired within the county. The teachers provided details of pupils with nystagmus who were under their care (including elective home education, EHE children) and their hospital notes were reviewed in order to verify the diagnosis of nystagmus and to classify their nystagmus. For all pupils in this group hospital notes were found. All individuals within this data collection group were aged 18 years or under on 14th August 2003.

2.2.1 Statistical Analysis

We identified people with nystagmus that had registered with only one source (e.g. hospital survey), two sources (e.g. hospital survey & VISTA) or all three sources. After identifying the overlaps (patients whose names appeared on more than one database

source), we used 'capture-recapture' (CRC) method (Hook and Regal, 1995) using GLIM (Aitkin et al., 1992) software to establish the number of nystagmus subjects that were not recorded by any of these three sources, i.e. 'uncaptured' individuals with nystagmus. In the under-18 years age group, analysis was carried out using three data sources - hospital, visually impaired registration and education services. For the over-18 years age group, capture-recapture analysis was carried out using two sources of data – the hospital survey and visually impaired registration groups.

CRC was also used to estimate prevalence of the most common forms of nystagmus (i.e. unassociated INS, INS associated with albinism, INS associated with retinal diseases, INS associated with low vision and neurological) and in under-18 year olds and over-18 year old individuals. It was not possible to use CRC in less common forms of nystagmus (INS associated with ocular disease, FMNS, other infantile forms, spasmus nutans, neurological nystagmus in children, other neurological nystagmus forms than multiple sclerosis and stroke in adults and unknown aetiology) as there was no overlap between sources.

Pearson's Chi-Square tests were carried out to compare the distribution of nystagmus within ethnic groups within the population of Leicester city (obtained from the last Census 2001)(2001) from the LNS database, where we had data from all participants from the questionnaire. We did not have data on ethnicity from the VISTA or education databases.

2.3 Results

The hospital-based survey (LNS) located 238 out of a total of 241 known individuals with nystagmus. One person withdrew after initial consent. There were two other participants who attended the survey after media publicity who were excluded from the study as they did not have nystagmus. Figure 1 shows the frequency of different clinical types of nystagmus in the LNS patients. There were 111 male and 127 female patients. The most common type of nystagmus identified by the survey was unassociated INS (50 patients).

The records of blind and partially sighted individuals registered within Leicestershire identified 414 individuals (242 males and 172 females) with various types of nystagmus. Unlike the hospital patients, the most common form of nystagmus seen here was from patients with nystagmus with associated ocular diseases such as congenital cataracts, optic nerve hypoplasia and nystagmus associated with retinal diseases, for example achromatopsia and congenital stationary night blindness, all of which cause variable but significant visual impairment (figure 1). Other congenital forms of nystagmus include cases of unilateral microphthalmos, bilateral aniridia and congenital syndromes.

The third source of independent information, the education services, found 193 individuals (111 females and 82 males) with nystagmus, with mainly infantile nystagmus forms, which were almost equally distributed between INS associated with albinism, unassociated INS, INS associated with low vision and retinal diseases (figure 1). Of the children with neurological nystagmus most were associated with

neurological syndromes such as Down's syndrome or septo-optic dysplasia, or had

congenital neurological anomalies such as hydrocephalus or microcephalus.
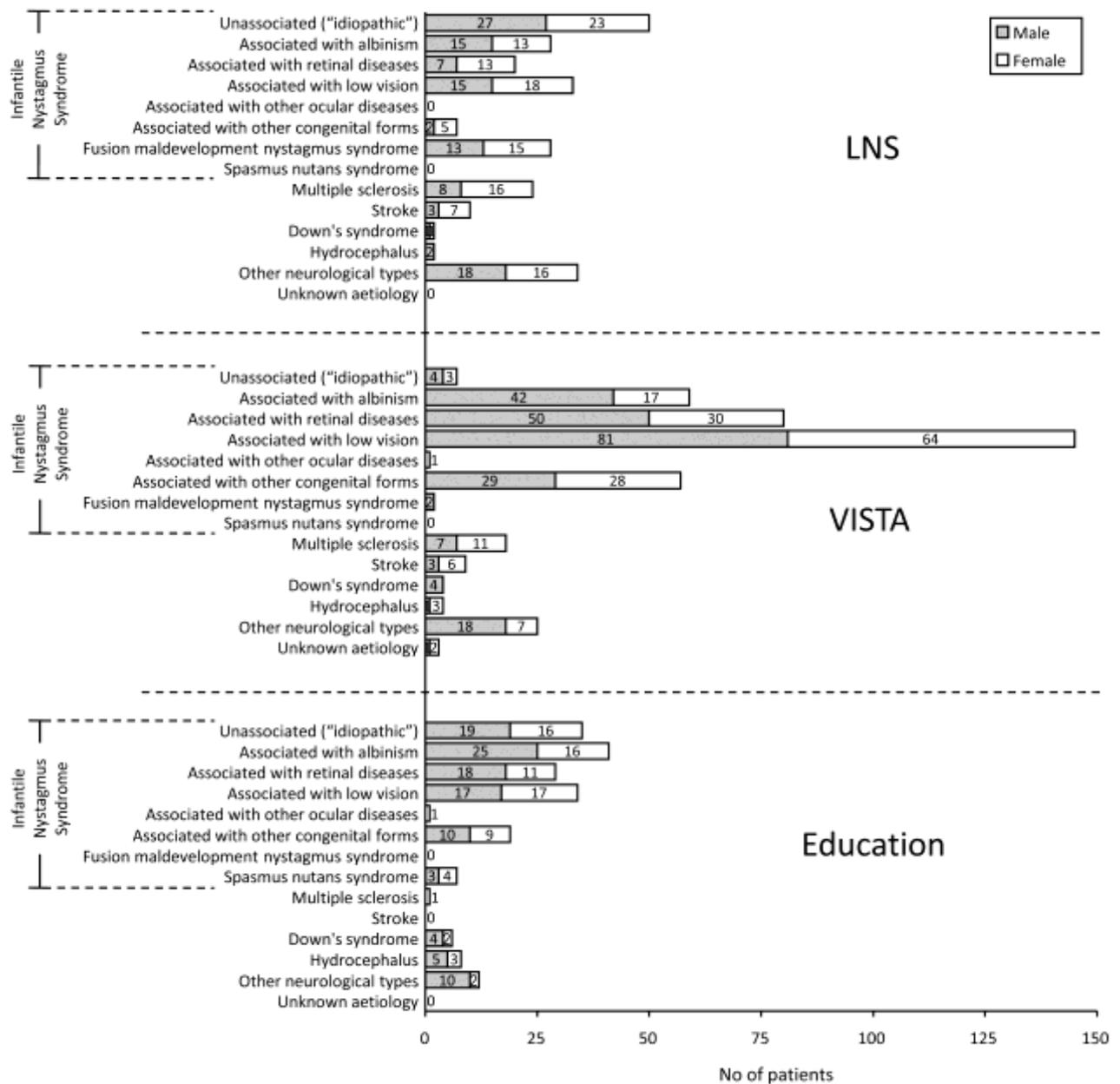
Figure 2.1: Bar plots representing the frequency of nystagmus forms in each of the

three sources. Grey filled bars indicate male patients and white filled bars, female

patients.

After independent ascertainment of patients with nystagmus from all three sources,

the overlapping patients in each source were identified (figures 2A and 2B).
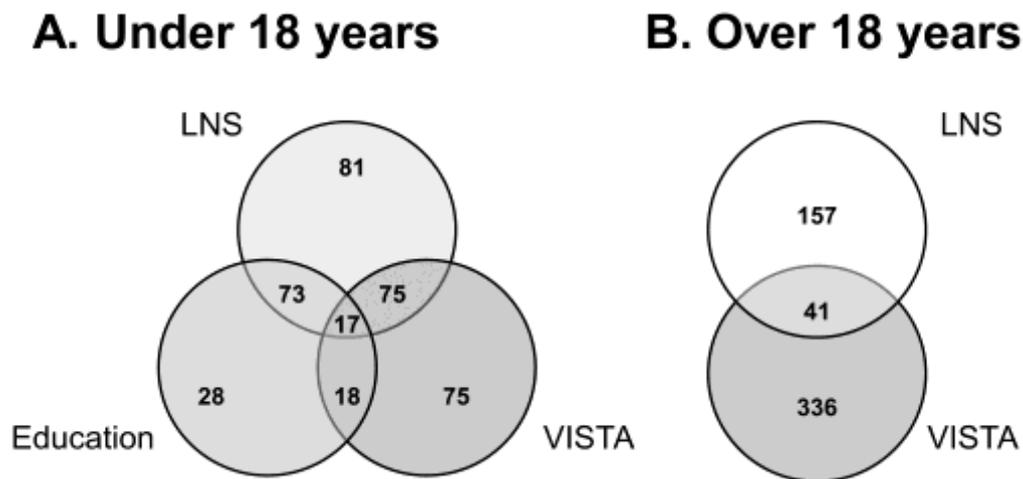
Figure 2.2: Venn diagrams of (A) patients under-18 years old identified through one or more of three data sources and (B) patients over-18 years old identified in either one or both data sources. The individuals present in two or more data sources are shown within the overlapping areas of the circles.

CRC analysis was used to estimate that 29 individuals were not identified by the three

data sources in the group below 18 years of age giving the total number of individuals

under 18 years with nystagmus as 396 (95% CI, +/-26). The population of under 18

year olds in Leicestershire is 238,100 (HMSO Office of population census and survey,

2001), giving an estimated prevalence of nystagmus at 16.6 per 10,000 (95% CI, +/-

1.1) population in this age group.

In the adult (over 18 years) age group, 1287 individuals were estimated as not being

captured by either data source giving a total of 1821 (95% CI, +/-473). With a

population of 685 900 over 18 year olds living in Leicestershire,(2001) the prevalence

of nystagmus in this age group is estimated at 26.5 per 10 000 population (95% CI, +/-

6.8). For the total population of Leicestershire and Rutland (924 000), the estimated

prevalence of nystagmus is 24.0 per 10 000 (95% CI, +/-5.3).

The clinical spectrum and frequency of patients with nystagmus was calculated

separately using CRC for the under 18 years age group and for the over 18 years

individuals (figure 3).
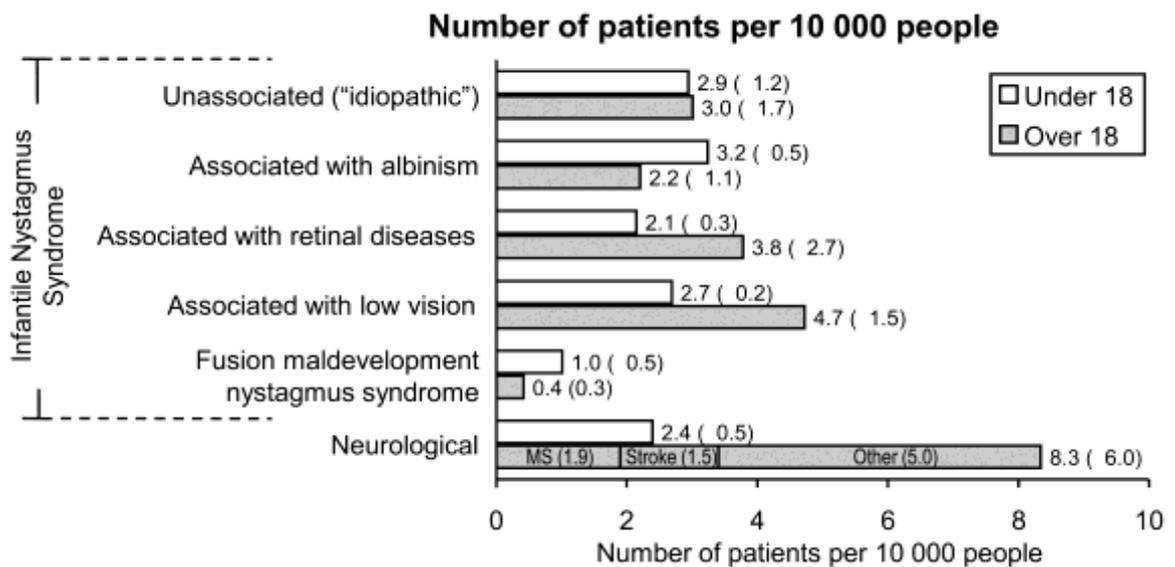
Figure 2.3: *Clinical diagnosis and frequency distribution of patients with nystagmus*

within Leicestershire calculated by CRC statistical method. The numbers beside the

bars represent prevalence per 10 000 (+/-95% CI) calculated separately for the under

and over 18 years age groups. For neurological nystagmus forms CRC statistics could

only be used for MS (multiple sclerosis) and stroke in adults as there was no overlap

between sources in children.

Using CRC analysis we calculated the prevalence of the more common nystagmus-

related diseases. For the total population (children and adults combined) the

prevalence of unassociated INS was 1.9 per 10 000 population (95% CI, +/-1.6), INS associated with albinism 2.5 per 10 000 population (95%CI, +/-0.9), INS associated with retinal diseases 3.4 per 10 000 population (95%CI, +/-2.1), INS associated with low vision 4.2 per 10 000 population (95%CI, +/-1.2) and FMNS 0.6 per 10 000 population (95%CI, +/-0.4). The total prevalence for INS was 14.0 per 10 000 population (95%CI, ±3.1: 12.0±0.9 per 10 000 in under 18 year olds and 14.7±3.8 per 10 000 in over 18 year olds). For neurological nystagmus the prevalence was 6.8 per 10 000 population (95%CI, +/-4.6) with 1.9 per 10 000 population in adults due to multiple sclerosis and 1.5 per 10 000 population due to stroke. For children there was no overlap between sources for neurological nystagmus and, therefore, CRC analysis was not possible.

Gender distribution for the different forms of INS was statistically analysed using Pearson's Chi-Square test and revealed that the higher prevalence of nystagmus in males was statistically significant in INS associated with albinism (p=0.001) and INS associated with retinal disease (p=0.048) but not in unassociated INS (p=0.34) or INS associated with low vision (p=0.26)

The distribution of nystagmus from the hospital survey was compared to the distribution of the main ethnic groups obtained from the last census in Leicester city (figure 4). There were proportionately fewer patients with nystagmus in the Asian population (Indian, Pakistani, Bangladeshi and a minority from other Asian backgrounds) compared to the White population group (White British and other White backgrounds). Statistical analysis using Pearson's Chi-Square test showed this difference to be significant (p=0.004).
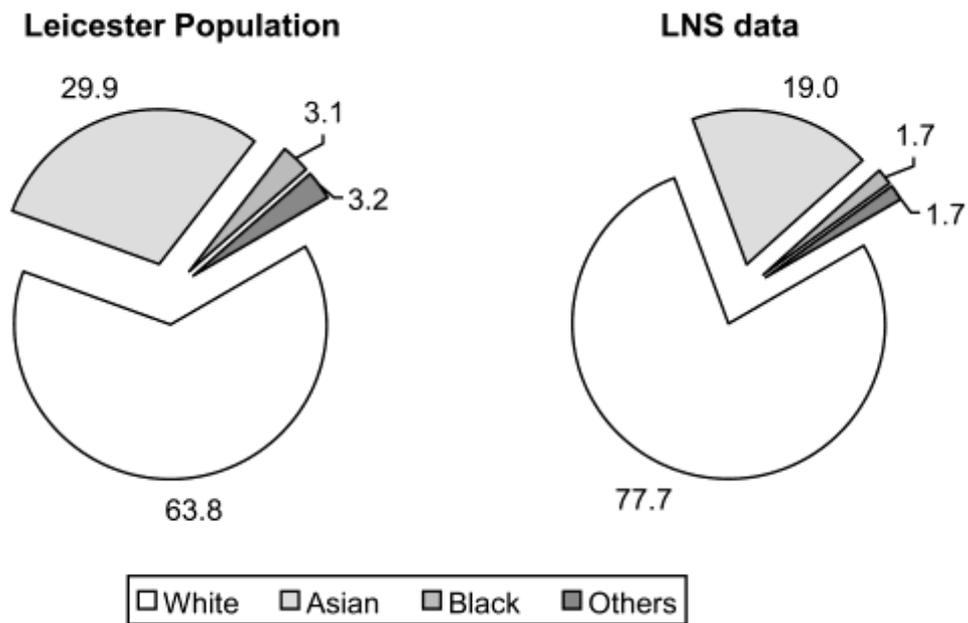
Figure 2.4: *Distribution of patients with nystagmus from different ethnic backgrounds living within Leicester city compared to the city's population demographics.*

2.4 Discussion

Our study shows the prevalence of nystagmus to be 24.0 per 10 000 population. In the under 18 age group the prevalence was 16.6 per 10 000 (95%CI, +/-1.1) population, with the most common form of nystagmus being due to INS associated with albinism. In the adult group the prevalence was estimated to be 26.5 per 10 000 (95% CI, +/-6.8) with the largest nystagmus group being associated with neurological disease.

The prevalence of nystagmus has previously only been estimated as part of larger scale epidemiological studies into low vision (Hemmes, 1927, Blohme and Tornqvist, 1997, DeCarlo and Nowakowski, 1999, Pardhan and Mahomed, 2002, Schwarz et al., 2002) or amongst children of a specific age group, without separating congenital and acquired forms of nystagmus (Forssman and Ringner, 1971, Stewart-Brown and Haslum, 1988). Estimates of nystagmus prevalence were 1/500000(Noon, 1964),

1/5032 among males and 1/10596 among females (Hemmes, 1927), 1/1000 in males

and 1/2800 in females (Forssman and Ringner, 1971) and 1/1000 (Stewart-Brown and

Haslum, 1988), respectively. Although not directly comparable, the prevalence of INS

in children and adults, from our study, has been found to be 14.0 per 10 000

population, which is higher than previous estimates. In terms of acquired nystagmus,

although the epidemiology of multiple sclerosis is well known, the prevalence of

ocular motor deficits in this condition has not been well established. The prevalence of

multiple sclerosis in neighbouring Cambridgeshire (latitude 52.2048 compared to

latitude 52.6335 in Leicestershire) is 126 per 100 000 (Robertson et al., 1995). The

prevalence of nystagmus among patients with multiple sclerosis in our study was

estimated to be 19 per 100 000. This is equivalent to 15% of patients based on the

Cambridge study. Although multiple sclerosis has different clinical characteristics in

Japan, a study suggests that the prevalence of internuclear ophthalmoplegia in

multiple sclerosis is between 17 to 41% of patients (Tsuda et al., 2004).

Our study provides the first hospital and community-wide estimate of the prevalence

of nystagmus. It includes patients with both good and poor vision who may or never

have had ophthalmic care within the hospital setting without being involved in this

study. Leicestershire has a population of 925,000 people and has a wide range of

ethnic minorities (11.5%) including patients from the Asian and African subcontinents.

Previous locally conducted ophthalmic research has shown that only a very small

number of patients obtain their eye care outside the county (Deane et al., 1998,

Thompson et al., 1991). This epidemiological study also enabled us to estimate for the

first time the prevalence of the most common nystagmus conditions and this

suggested that the most frequent form of nystagmus seen in the population is

neurological nystagmus, followed by nystagmus associated with low vision (seen in conditions such as optic nerve hypoplasia and congenital cataracts) and nystagmus associated with retinal diseases (for example, retinopathy of prematurity, achromatopsia and congenital stationary night blindness).

The distribution of nystagmus among the various ethnic groups shows a significantly higher proportion of patients having nystagmus in the Caucasian population compared to the Asian and Black ethnicity groups. Previous work looking at the distribution of visual impairment in children suggested a higher proportion of poor vision among the children of Pakistani heritage, with 44 % of the children having a family history of their ocular disease, and attributed this to a higher proportion of consanguineous marriages in this group of people (Pardhan and Mahomed, 2002). However, this survey included children with differing genetic ocular syndromes and our study incorporated both infantile and acquired nystagmus disorders in all age groups. It is possible that there may have been proportionately fewer Asian patients who attended our hospital survey, VISTA and educational services for various social reasons such as language barriers.

Capture-recapture statistical analysis is used in epidemiology to estimate or determine the 'extent of incomplete ascertainment using information from overlapping lists of cases from distinct sources' (Hook and Regal, 1995). The validity of CRC statistical analysis depends on several criteria being met, i.e. that the cases identified from each source must have an accurate diagnosis, the study population must be closed, subjects must be randomly captured, each source must be independent from other sources and the probability of being captured in each source is equal to that for the other sources (Hook and Regal, 1995, Rahi and Dezateux, 1999, Yip et al., 1995). These

assumptions may be difficult to prove and complete independence of reporting sources is unlikely (Rahi and Dezateux, 1999). We ensured the hospital and community sources of information were obtained independently and overlapping patients were only detected at final analysis. We also ensured accurate diagnosis for all sources and closed the study population of all sources at the same date.

Capture-recapture studies have been used to estimate the prevalence of other ocular diseases such as congenital cataract and developmental eye defects (Rahi and Dezateux, 1999, Campbell et al., 2002, Rahi and Dezateux, 2001). In these studies, use of independent sources of information, for example, National Congenital Anomaly Notification system (England and Wales) and independent hospital ophthalmology and paediatric surveillance shemes, showed a higher incidence of prevalence of the disease than was originally reported through passive notification.

In terms of commonality of ocular diseases, the prevalence of age-related macular degeneration (exudative and non-exudative forms) is significantly higher at 3680 per 10 000 population aged 75 or older (850 per 10 000 in those aged between 43 to 54 years age) (Klein et al., 1992) whilst at the other end of the spectrum the prevalence of mitochondrial DNA defects causing diseases is 0.657 per 10 000 population (Chinnery et al., 2000). Emphasis on screening and treatment have been placed on conditions such as retinopathy of prematurity with an estimated incidence of 11.7 per 10 000 live births (Mathew et al., 2002) and congenital cataracts, where the estimated incidence is 2.49 per 10 000 children in their first year of life (Rahi and Dezateux, 1999, Rahi and Dezateux, 2001). In the latter two conditions, incident figures were quoted suggesting a higher prevalence rate. The results of our study suggest that a similar

priority should be given to the detection and research into possible treatments and mechanism of nystagmus as other visual impairments with comparable prevalences.

2.5 Conclusion

We describe the first hospital- and community-wide survey of the prevalence of nystagmus. Although no similar previous studies exist, the higher prevalence of nystagmus than previously reported should alert health care providers to the need for allocation of resources for this largely under researched condition. Our epidemiological study has shown for the first time the prevalence of individual diseases associated with nystagmus and highlighted the significantly higher prevalence of this condition in the white European population. The information obtained from this study emphasizes the need for more research into nystagmus, especially with emerging new understanding of genetics (Tarpey et al., 2006) and new treatment modalities (Averbuch-Heller et al., 1997, Bandini et al., 2001, Jain et al., 2002, Leigh, 1996, McLean et al., 2007, Sarvananthan et al., 2006, Schon et al., 1999, Shery et al., 2006, Starck et al., 1997, Strupp et al., 2003, Del Monte and Hertle, 2006, Hertle et al., 2004).

2.6 Supplementary material to original publication

Epidemiological studies have provided information about the distribution of disease in specific populations for over 2000 years. Epidemiology is defined as the 'study of the distribution and determinants of health-related states or events in specified

populations, and the application of this study to control of health problems' (Last, 1988). The prevalence of a disease is the number of cases in a defined population at a specified point in time, while its incidence is the number of cases arising in a given population in a specified time period. In this study, the prevalence date was 14th August 2003.

Prior to our study, several epidemiological studies have been carried out locally to determine the prevalence of cataracts (Deane et al., 1997, Gibson et al., 1985) and macular degeneration (Deane et al., 1998). In all of these studies, it was calculated that most of the population of Leicester and Leicestershire obtained their eye care within the county. The population studied was also found to have similarities to the national average for social class, age structure and income (Deane et al., 1997).

The prevalence of nystagmus has not been estimated previously in large scale epidemiological studies of eye diseases, including the Framingham eye study (Leibowitz et al., 1980, Rosenthal, 1980), where more common ophthalmic diseases such as glaucoma, cataracts, diabetic retinopathy and macular degeneration were studied. Nystagmus does cause significant visual morbidity in some cases and more recently, the CVI forms for registration of visual impairment which replaced the old BD8 forms in England and Wales have enabled clinicians to record more than one cause of visual loss enabling epidemiological data on causes of visual impairment to have more specific causes of visual impairment (Bunce and Wormald, 2006, Bunce et al., 2010). The most recent epidemiological work into the cause of blind and partial sight registrations in England and Wales found that nystagmus was recorded as a main cause in 0.83% of forms. However, this small number is likely to be an underestimate

as not all clinicians record all different causes of visual loss and this group only represents people with visual impairment, whereas nystagmus can occur in individuals with near or near normal vision. V

The statistically significant difference in nystagmus prevalence between the White population groups and Asian population groups in Leicester, despite a study in Bradford showing higher numbers of Asian children with visual impairment (Pardhan and Mahomed, 2002), can be explained using the population census data on ethnicity distribution summarised in Table 2.1 below.

Table 2.1: *Demographic characteristics of Asian and White populations both nationally and in Bradford and Leicester based on population census data 2001*

	Location		
Ethnicity	**England and Wales**	**Leicester** (www.leicester.gov.uk)	**Bradford** (www.bmelearning.co.uk)
Asian or Asian British - Indian	1.99%	25.7%	2.7%
Asian or Asian British - Pakistani	1.37%	1.5%	14.5%
Asian or Asian British - Bangladeshi	0.54%	0.6%	1.1%
White -British	87.49%	60.54%	76.1%

The table demonstrates a difference in the Asian population living in Leicester where there are more Asians of Indian origin (Roberts-Thomson, 2008) who are Hindus and

therefore a lower incidence of consanguinity and related ocular diseases compared to Bradford where a higher proportion of Asians from Pakistani background where there is increasing consanguinity (Dhami and Sheikh, 2000). This has also been seen in studies looking at respiratory (O'Callaghan et al., 2010) and bowel diseases (Ali et al., 2010) in Asian communities in Bradford and Leiester respectively.

Previous large scale epidemiological studies into the causes of visual impairment in a population tended to focus on the more common causes i.e. cataract, glaucoma, diabetic retinopathy and macular degeneration.   All existing general ophthalmological databases within the hospital were searched. Another method of obtaining more accurate estimates of prevalence for some patient groups would have been to access disease specific databases. For example, a large multiple sclerosis database exists within the Hospital Trust which could have provided a more accurate estimation of nystagmus prevalence within this patient group.

Epidemiological studies into the incidence and prevalence of chronic neurological diseases have mainly focussed on multiple sclerosis but several studies exist for motor neurone disease, Huntington's disease and progressive supranuclear palsy (Hoppitt et al., 2011). Nystagmus has been reported in patients with progressive supranuclear palsy (Matsumoo et al., 2008 and Anderson et al., 2008) and abnormal optokinetic nystagmus, in particular the vertical waveforms has been recorded in patients with this condition (Garbutt et al., 2004). The prevalence of progressive supranuclear palsy in the United Kingdom has been estimated at 1.0 per 100,00 population based on a national study but a community based study showed that this was an underestimate and a prevalence of 6.5 per 100,000 population was found (Nath et al., 2001). This study used three methods of case ascertainment, as in our study, and showed that the

prevalence or prevalence of progressive supranuclear palsy was higher than initially

thought. As a result, a comprehensive review of death certificates found that the

number of deaths in south west England where PSP should have been recorded rose

from 57 to 1435 in the period 2002-2008 (Maxwell et al., 2010).

Chapter 3

**A clinical evaluation
of patients seen
within a tertiary nystagmus
referral service**

Chapter 3: A clinical evaluation of patients seen within a tertiary nystagmus referral service

3.1. Introduction

The evaluation of a patient presenting with nystagmus involves a detailed history taking into account the onset of nystagmus, effects on vision, presence or absence of oscillopsia and any associated ocular or systemic disease (Serra and Leigh, 2002). Examination of the patient should include assessment of visual acuity, strabismus, binocularity, colour vision, anomalous head posture, followed by external and slit-lamp examination of the anterior and posterior segments of both eyes. The nystagmus can be recorded in terms of direction, conjugacy, amplitude, frequency and whether there is dampening with convergence. The clinical assessment often provides sufficient information for a preliminary diagnosis to be made (Willshaw, 1993, Abadi and Bjerre, 2002) with further electrodiagnostic, eye movement recordings (Dell'Osso and Daroff, 1975) and radiological investigations confirming the final diagnosis and enabling a discussion of further management, including possible optical, pharmacological or surgical treatments and referral for genetic screening.

There have been several descriptions of methods of classifying nystagmus, including use of nystagmus waveforms from eye movement recordings (Abadi and Dickinson, 1986) and more recently, the CEMAS system have been used (http://www.nei.nih.gov/news/statements/cemas.pdf). A more commonly used system by clinicians incorporates information from eye movement recordings and

pathology and subdivides childhood nystagmus into idiopathic, associated with albinism, latent/manifest latent, spasmus nutans, 'sensory' (eg retinal or optic nerve diseases) and neurological or neurological forms (Gottlob, 2000, Neely and Sprunger, 1999).

3.2 Aims

The main aims of the following study was to characterise the visual deficit in nystagmus in terms of objective and subjective parameters, mainly (i) visual acuity, (ii) stereopsis, (iii) oscillopsia, (iv) strabismus and (v) anomalous head posture. Further analysis of visual impairment was made using United Kingdom driving licence visual standards and registration of partial sight or blindness.

3.3. Methods

3.3.1. Study population

Ethical approval was obtained from the local research and ethics committee. All patients with nystagmus attending the paediatric and adult neuroophthalmology service between January 2001 and July 2006 were invited to participate in the study. In addition, as part of the Leicestershire Nystagmus Survey (Chapter 2), a community-wide recruitment of patients was organised, involving local optometrists, general practitioners and visually impaired services recruited adults and children with nystagmus who were not current hospital patients. Subjects were recruited from

Leicestershire and throughout the United Kingdom after referral from their local

ophthalmologists, neurologists or general practitioners.

3.3.2. Clinical history

After informed consent was obtained, a detailed clinical history and examination was

obtained from each patient. In all patients, the clinical history included age of onset of

nystagmus, visual symptoms including oscillopsia, night blindness and photophobia.

Any family history of nystagmus was documented. The presence of amblyopia or

previous treatment in childhood for amblyopia was noted. All subjects were asked if

they had been placed on the partially-sighted or blind register.

3.3.3. Clinical examination

All patients underwent assessment of visual acuity, binocularity, ocular motility,

anomalous head posture, slit lamp examination and dilated fundoscopic examination.

Visual acuity was measured using Snellen acuity charts. The uniocular and binocular

best corrected visual acuity (BCVA) was recorded for each patient. In patients who

were too young, Keeler logMar visual acuity testing was used.

Stereopsis was assessed using either the TNO or Frisby stereotests in all patients.

Where the patient was too young or unable to perform the test, the Lang stereotest

(Test 1) was then attempted. The results were grouped into patients with no

stereopsis demonstrable (absent), poor stereopsis (>300" to 1500"), moderate

stereopsis (>170" to 300"), good stereovision (>55" to 170") and very good

stereovision (20" to 55"). In some patients with associated neurological disease or

developmental delay, the tests could not be performed and this was recorded

accordingly.

All patients were examined for the presence of a squint. The results of the strabismus

examination were subdivided into hypertropia, hyperphoria, exotropia, exophoria,

esotropia, esophoria or no deviation. Any mixed deviation was also documented.

The presence or absence of an anomalous head posture was confirmed in all patients

through clinical examination by asking patients to read a Snellen chart. Patients with

any head posture were grouped into a positive head tilt, chin elevation or depression

and a face turn. Often, combinations of these head postures were found and these

were recorded accordingly.

3.3.4. Eye movement recordings

Eye movement recordings were carried out, where possible, to collaborate the clinical

assessment. All eye movement recordings were made using the EyeLink I

(SensoMotoric Instruments, GmbH, Berlin, Germany) high-resolution infrared video

pupil tracker. It has a resolution of 0.005° and the eye tracking range for pupils is ±30°

horizontal and ±20° vertical. The tracker consists of two infra-red video cameras

suspended from a headband enabling eye movement recordings to be made both

uniocularly and binocularly. The eye movements carried out in this study were all carried out by researchers at the Department of Ophthalmology, University of Leicester using standardised protocols after callibration. Patients under six years of age or with severe cognitive problems were unable to carry out this test. Eye movements were used in this study to assist in diagnosis of patients. A detailed analysis of nystagmus waveforms was outside the remit of this study but much of the data was included in other studies carried out by the group.

3.3.5. Electrodiagnostics and radiological investigations

When the aetiology of nystagmus was unclear, further investigations including electroretinography and visual evoked potentials were carried out using ISCEV standards (Marmor et al., 2009a, Odom et al., 2004a). DTL electrodes were used in electroretinography and dilation of pupils with dark and light adaptation were performed as part of the standard protocol. The electrodiagnostics in this study was carried out by Dr.C.Degg, medical physicist at the University Hospitals of Leicester NHS trust.

In cases of nystagmus where the aetiology could not be made based on all of the above investigations, the results MRI or CT scanning and any other relevant investigations were requested and reviewed. The latter investigations were particularly useful in neurological nystagmus in both children and adults.

3.3.6. Diagnostic criteria

Once all relevant investigations had been carried out, patients were grouped into the appropriate clinical group. Patients with idiopathic infantile nystagmus had nystagmus with normal anterior segment and fundus examination and normal electrodiagnostic testing either as part of this study or at the time of initial diagnosis of nystagmus. In patients with albinism, the presence of at least one or more of the clinical signs – known cutaneous albinism, iris transillumination, foveal hypoplasia and visual evoked potentials showing optic nerve misrouting were used to confirm the diagnosis. In manifest latent nystagmus, the clinical presence of nystagmus which changes with occlusion of one eye and where possible, eye movement recordings showing decreasing velocity or decelerating slow phases with increasing intensity in abduction of the fixing eye was used to confirm this clinical diagnosis. Patients with neurological nystagmus were defined by the presence of associated neurological disease.

3.4. Results

Three hundred and ninety one patients participated in the study. One hundred and ninety eight patients had eye movement recordings and thirty four patients failed to attend for the test but had a full clinical assessment. Eighty seven electrodiagnostic tests were carried out and an additional thirty two patients failed to attend for the test but had a full clinical assessment.

Subjects with nystagmus were classified into a diagnosis of albinism, idiopathic infantile nystagmus, manifest latent nystagmus, nystagmus associated with ocular disease (e.g. Peter's anomaly), nystagmus associated with retinal disease (e.g. congenital stationary night blindness), other infantile nystagmus (e.g. Down syndrome) nystagmus secondary to multiple sclerosis, nystagmus secondary to CVA (cerebrovascular disease) and other neurological nystagmus (e.g. Arnold Chiari malformation). The distribution of diseases within the study group is shown in figures 3.1 and 3.2. Idiopathic infantile nystagmus represented the most commonly seen group of patients (81 patients), followed by manifest latent nystagmus (55 patients) and albinism (48 patients). 74.7% of patients had infantile forms of nystagmus and 25.3% had neurological diseases including multiple sclerosis and cerebrovascular disease.

Figure 3.1: Pie chart showing clinical spectrum of patients (n=391) seen within the tertiary nystagmus referral service.
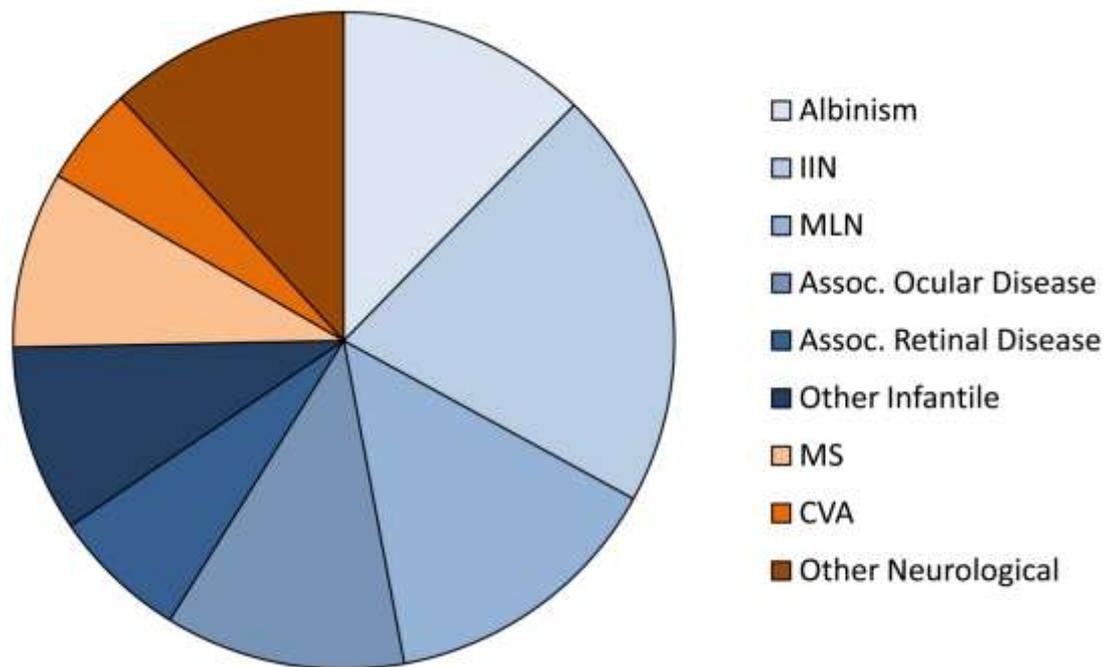
The gender distribution of patients with each group of diseases is shown in Figure 3.2. Statistical analysis (Chi Square) showed that the gender difference was only statistically significant in patients with idiopathic infantile nystagmus (*p=0.006*) where the disease was seen in more male patients.

Figure 3.2 *Proportion of female and male patients with each clinical type of nystagmus.*
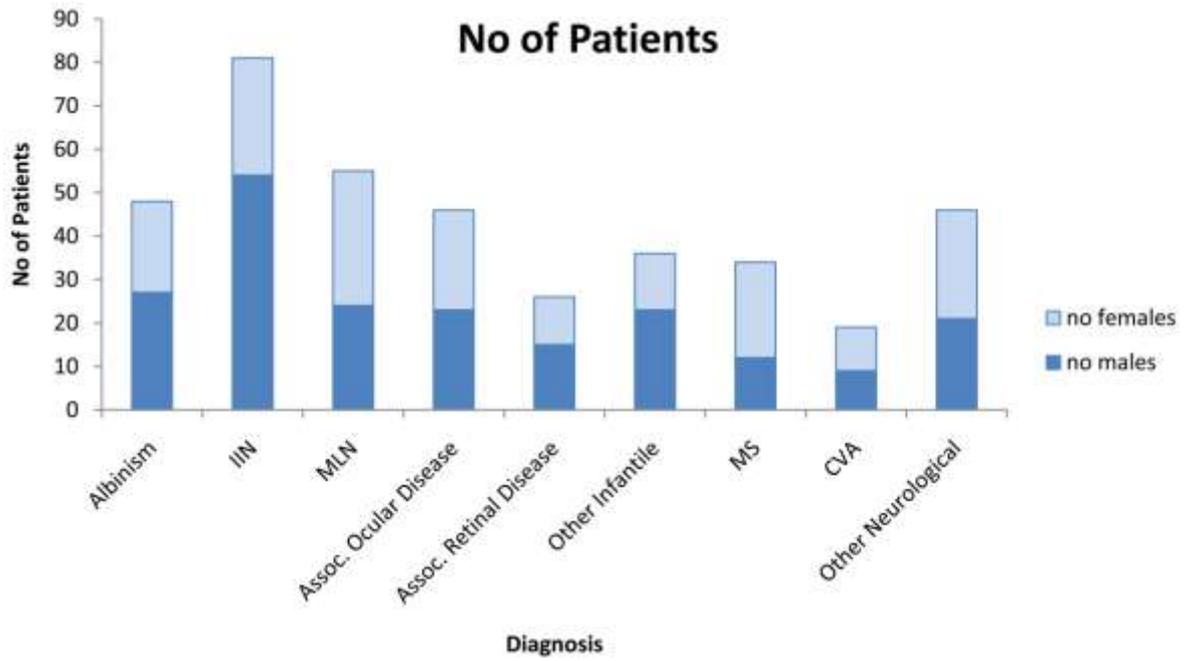
3.4.1. Disease types within subgroups

3.3.1.1. Nystagmus associated with ocular disease

There were 46 patients in this group with conditions such as congenital cataracts (19 cases), optic nerve hypoplasia (14 cases), aniridia (4 cases), microphthalmos (3 cases), congenital rubella (2 cases), Peters anomaly (2 cases) and persistent hyperplastic primary vitreous (PHPV- 2 cases).

3.4.1.2. Nystagmus associated with retinal disease

The 26 patients in this group were represented by patients with retinopathy of prematurity (9 patients), congenital stationary night blindness (6 patients), achromatopsia (4 patients), Leber congenital amaurosis (3 patients) and retinitis pigmentosa (4 patients - as part of Usher syndrome and Bardet-Biedl syndrome in some cases).

3.4.1.3. Other infantile nystagmus

Among the 36 patients in this group, there were 9 individuals with Down syndrome. This group also includes patients with infantile nystagmus who either did not attend for electrodiagnostic testing or in whom testing was technically unsuccessful due to poor cooperation and therefore could not be diagnosed as idiopathic infantile nystagmus or nystagmus due to albinism or secondary to retinal diseases. Patients with Down syndrome were grouped into the infantile nystagmus group as the onset of

nystagmus was before two months of age, all patients in this study had a conjugate, horizontal nystagmus and tended to be seen in the hospital service at a younger age.

3.4.1.4. Other neurological nystagmus

The 46 adults and children in this group had various diseases. Amongst the children there was hydrocephalus (4 patients), developmental delay (7 patients – in all cases no known associated systemic disease found), intraventricular haemorrhage (6 patients), and single cases of West's syndrome, Pallister-Killian syndrome, Shprintzen Goldberg syndrome, meningitis, fetal alcohol syndrome, carbamazepine toxicity, congenital myotonic dystrophy, cerebellar degeneration associated with celiac disease and Pelizaeus-Merzbacher syndrome. Details of the clinical presentation of these patients are discussed in Section 3.4.1. Cerebellar disease (7 patients) and Arnold-Chiari malformation (6 patients) were the commonest adult diseases. In addition there were tumours in 4 cases - cerebellar astrocytoma, neuroectodermal posterior fossa tumour, vascular malformation i.e. brain stem cavernous haemangioma and arteriovenous malformation. There were single cases of nystagmus seen in Stiff Person syndrome, Von-Hippel Lindau syndrome, progressive supranuclear palsy and Parkinson's disease.

3.4.2. Age distribution

Figure 3.3 shows the age range of patients with nystagmus and standard deviation for each group of patients. The age of the individual patient was defined by the age at which the patient was first seen for the study. The youngest group of patients with a mean age of 17.29 years (SD 18.87 years) were patients with other infantile nystagmus and the oldest group with a mean age of 75.72 years (SD 11.56 years) were patients with cerebrovascular disease (CVA).

Figure 3.3: Bar chart showing age range of patients with nystagmus.
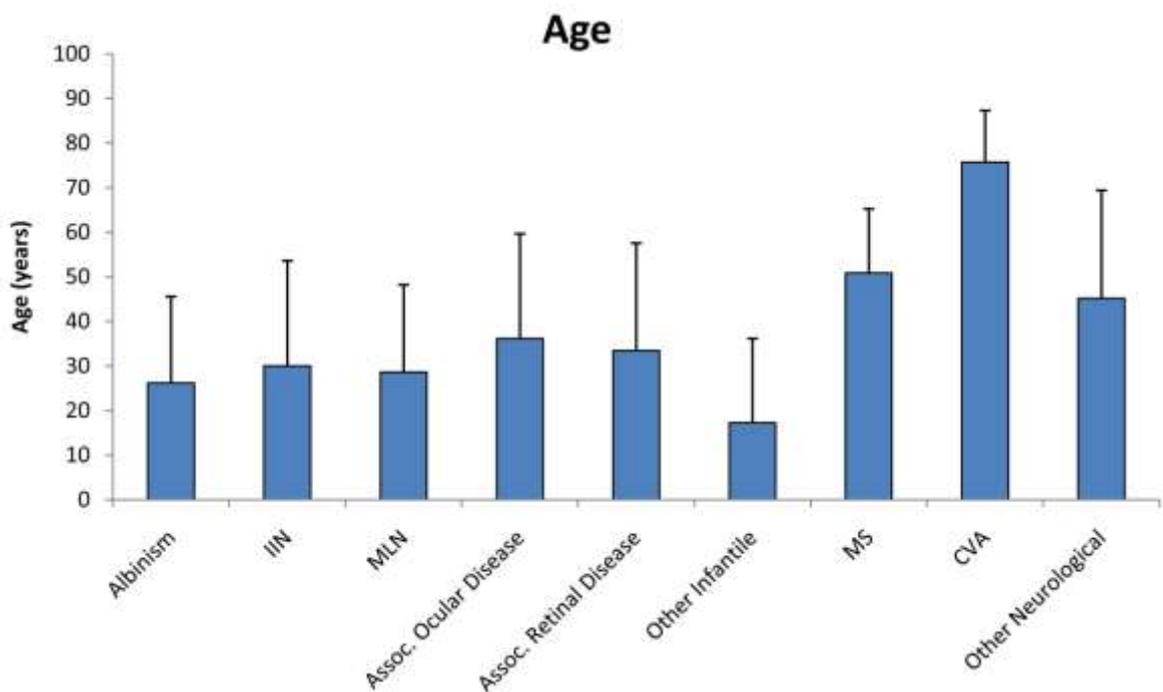
3.4.3. Visual acuity and binocularity

Both uniocular and binocular best corrected visual acuities for each patient were recorded and the results for binocular acuities are summarised in Figure 3.4. Patients with nystagmus and visual acuities better than 6/12 were seen mainly in idiopathic infantile nystagmus, manifest latent nystagmus, multiple sclerosis, cerebrovascular disease and other neurological forms of nystagmus. The current driving regulations in the United Kingdom requires an individual to read a number plate (with glasses or contact lenses if required) a number plate with symbols 79.4mm high at a distance of 20.5m (www.dft.gov.uk). This approximates to a binocular visual acuity 6/15 or better. The threshold for patients in this study for driving is shown in Figure 3.4

Severe visual deprivation of 3/60 or worse were seen predominantly in patients with nystagmus associated with retinal disease or nystagmus associated with other ocular diseases. Patients with this level of visual acuity qualify to be registered as severely visually impaired (blind registration) in the United Kingdom.

There was also another group of patients with moderate visual impairment (6/9 to 6/60 inclusive) and this affected mainly patients with infantile causes of nystagmus – albinism, other infantile nystagmus and nystagmus associated with ocular disease.

Figure 3.4: *Distribution of visual acuity amongst patients with nystagmus. Vertical dotted lines show proportions of patients within each diagnostic group who satisfy the legal limits for driving and patients who satisfy the criteria as being severely visually impaired.*
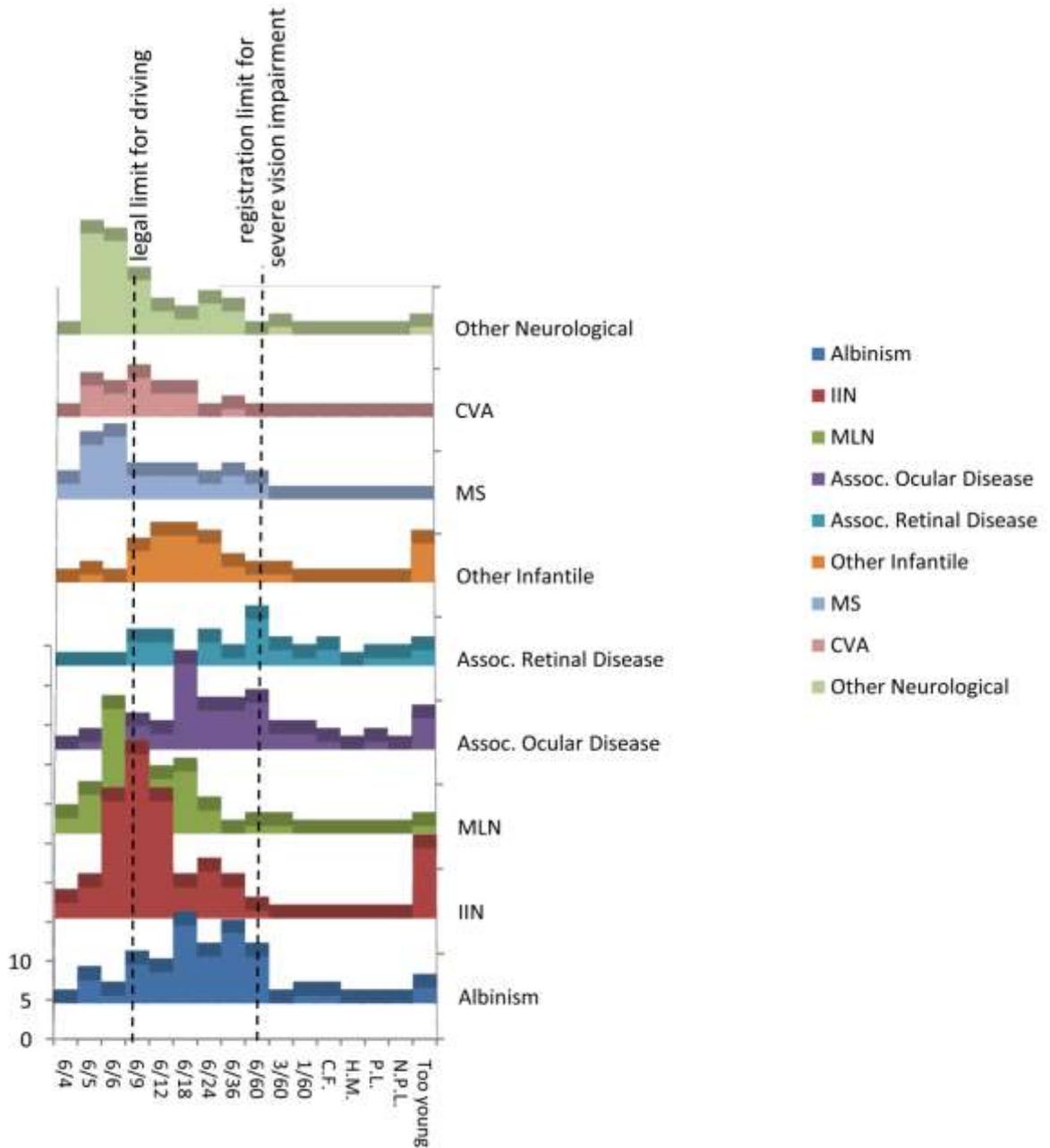
The variation in stereopsis of patients with nystagmus within each disease group and between different disease groups is summarised in Figure 3.5. The Lang Stereo Test

was positive in twelve patients who either tested negative with the Frisby stereotest or were unable to understand the latter test. Patients with the highest proportion (> 75%) of no demonstrable stereopsis were seen in manifest latent nystagmus, albinism, nystagmus associated with retinal disease, nystagmus associated with other ocular disease and other infantile nystagmus. Patients with idiopathic infantile nystagmus and neurological diseases such as multiple sclerosis and cerebrovascular disease and adults and children with other neurological types of nystagmus had better stereopsis and fewer patients with no demonstrable stereopsis within each group. The largest number of patients with very good stereopsis (35%) was seen in patients with idiopathic infantile nystagmus diseases group.

Figure 3.5: *Histogram showing quantification of stereopsis amongst patients with different clinical forms of nystagmus.*
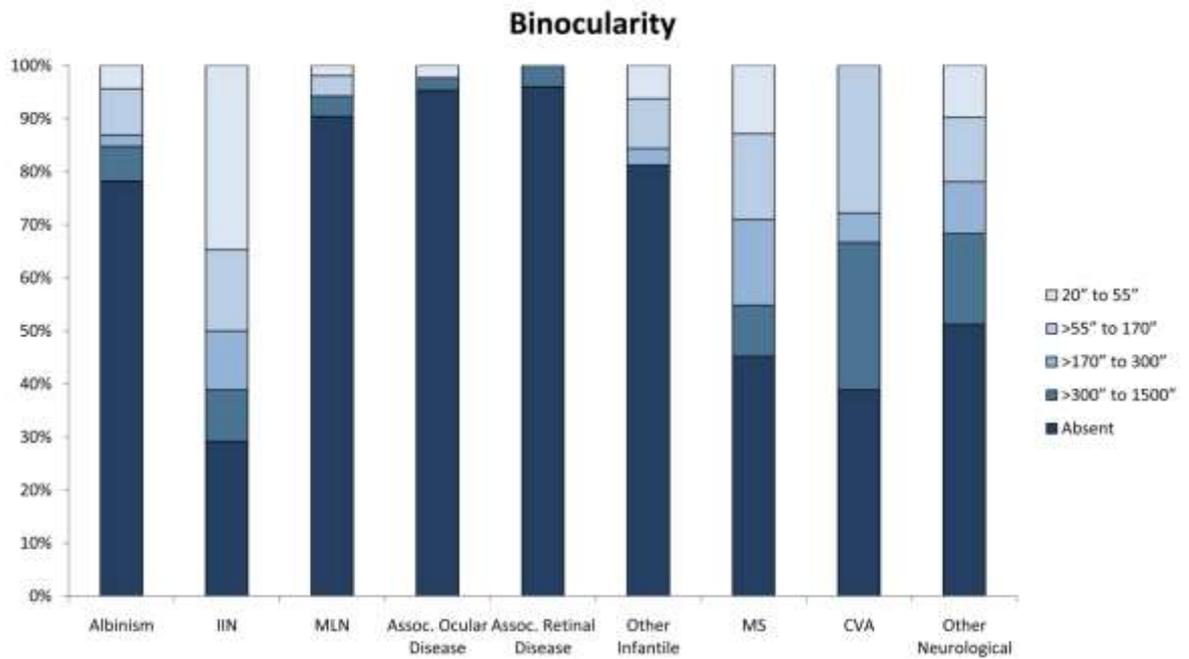
3.4.4. Strabismus and head posture

155 patients with nystagmus had no ocular deviation and the largest group of these patients had idiopathic infantile nystagmus (57 patients). The most common deviation seen in patients with nystagmus was esotropia (99 patients) and this was in the group of patients with manifest latent nystagmus (31 patients). 1 patient with manifest latent nystagmus who had an esophoria had had previous strabismus surgery with no previous clinical records available. The results for all groups of patients and all deviations are outlined in Figure 3.6. Exotropia was the next most frequent deviation (66 patients) and this was also most frequently seen in manifest latent nystagmus. Vertical deviations were seen in 21 patients either in combination with a horizontal

deviation (4 patients) or in isolation and were most commonly seen in cases of other

neurological nystagmus

Figure 3.6: *Variation in types of strabismus seen in clinical nystagmus.*
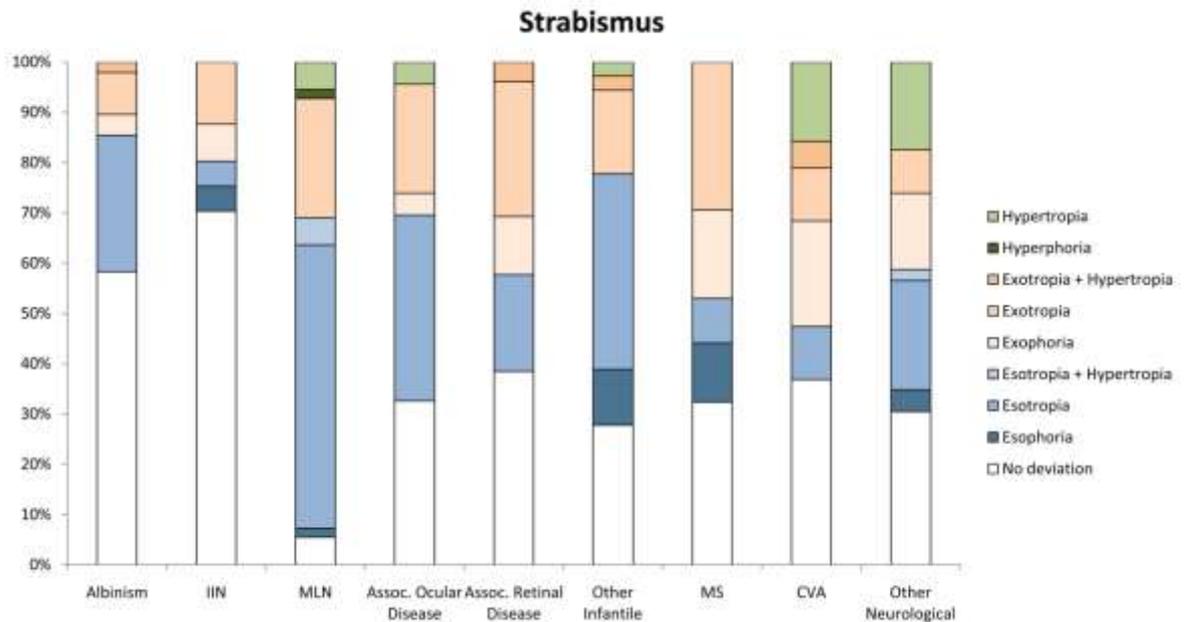
Figure 3.7 shows the distribution of anomalous head postures in the different groups

of patients with nystagmus. Anomalous head postures were most commonly seen in

patients with infantile forms of nystagmus, in particular the groups with idiopathic

infantile nystagmus (37% of patients) and other infantile nystagmus (39% of patients).

The frequency of anomalous head postures was least in the groups of patients with

neurological nystagmus (3% in multiple sclerosis and 5% in cerebrovascular disease).

Of the four groups used, i.e. head tilt, chin elevation, chin depression or face turn, the

commonest anomalous head posture adopted in patients with nystagmus with

infantile and neurological forms of nystagmus was a face turn in all groups of patients.

Chin elevation was the head posture seen least frequently in all groups of nystagmus

with the exception of nystagmus associated with ocular disease (11% of patients) and

other infantile nystagmus (14% of patients).

Figure 3.7: Variation in anomalous head postures seen in nystagmus.
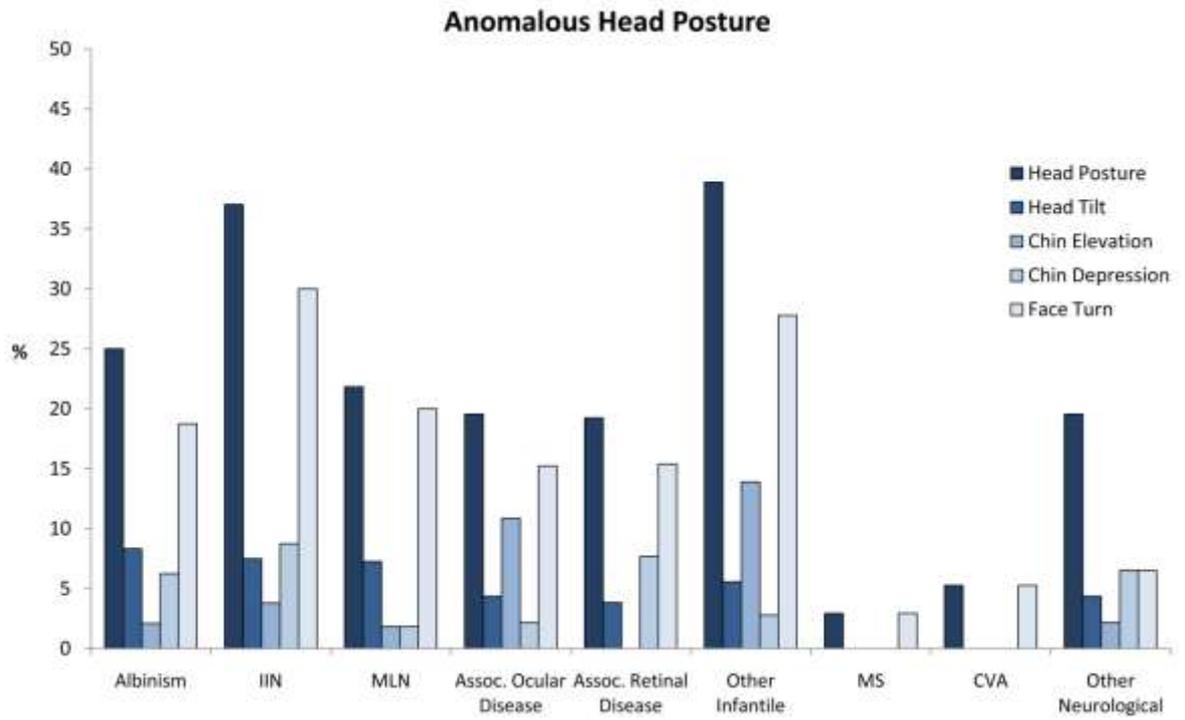
3.4.5. Monocular deficit and oscillopsia

Figure 3.8 shows the frequency of patients where there is a difference in visual acuity of greater than two Snellen lines – this has been classified as monocular deficit. In groups where there was no known retinal, ocular or brain disease i.e. the patients who had idiopathic infantile nystagmus or manifest latent nystagmus, this is most likely to be amblyopia. In albinism, the contribution of retinal disease to the monocular deficit is unknown and therefore the term amblyopia is not used. Amblyopia was most commonly seen in patients with manifest latent nystagmus (38% of patients).

Figure 3.8: Frequency of monocular deficit (difference in visual acuity of at least 2 Snellen lines) and oscillopsia in infantile and neurological nystagmus.
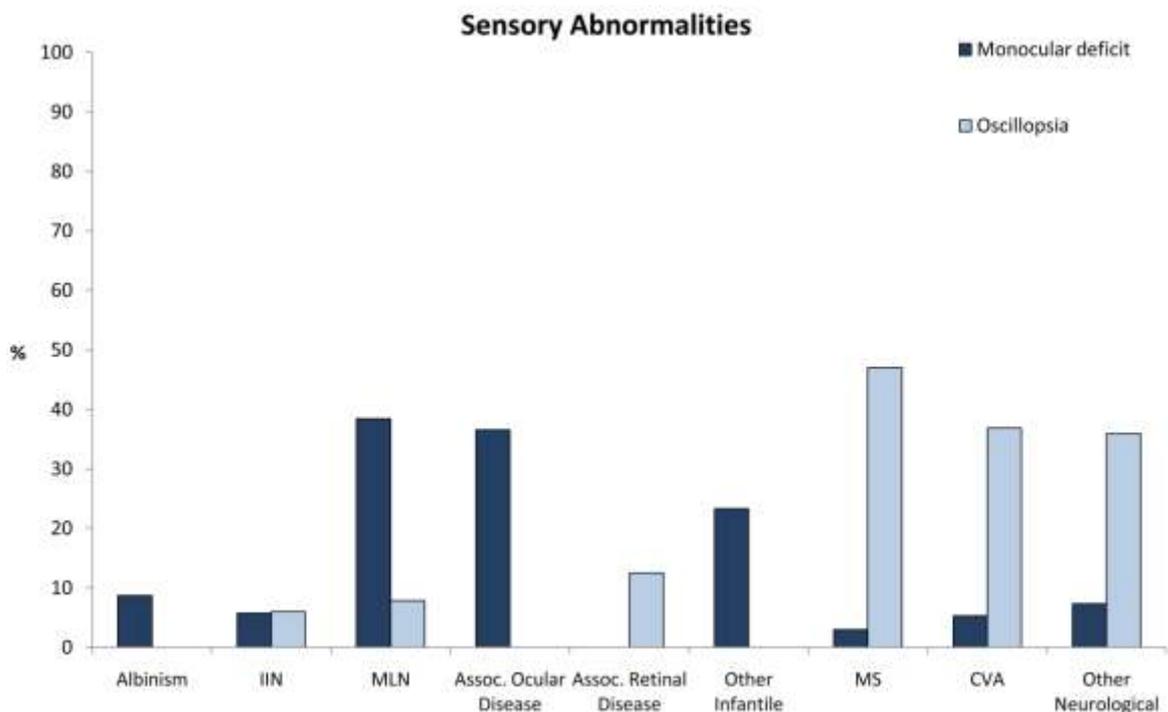
Symptoms of oscillopsia were most commonly reported by patients with neurological forms of nystagmus (47% of patients with multiple sclerosis, 37% of patients with cerebrovascular disease and 36% of patients with other neurological diseases).

Amongst patients with infantile nystagmus, oscillopsia was present in idiopathic infantile nystagmus (6% of patients), manifest latent nystagmus (8%) and nystagmus associated with retinal disease (13%).

3.4.6. Other nystagmus characteristics – conjugacy, null point and convergence dampening

Conjugacy of nystagmus was assessed clinically in this study where there was simultaneous nystagmus in the same direction for each eye. Patients with infantile forms of nystagmus had a predominantly conjugate form of nystagmus in more than 90% of cases (see Figure 3.9) apart from the groups with other infantile forms of nystagmus (86%), manifest latent nystagmus (83%) and infantile nystagmus associated with other ocular disease (80% of patients). Conjugacy of nystagmus in patients with neurological nystagmus was less common (35% of multiple sclerosis patients and 53% of patients with cerebrovascular disease).

Clinically, a null point was not found in the majority of patients (see Figure 3.9) with infantile and neurological forms of nystagmus. The groups of patients with the highest proportion with a null point were idiopathic infantile nystagmus (35% of patients) and albinism (21% of patients). The assessment for a null point was done purely on clinical examination and eye movement recordings were not used for this part of the study.

Convergence dampening was most commonly seen in patients with idiopathic infantile

nystagmus (46%) and albinism (21%). There was one patient with cerebrovascular

disease where dampening of nystagmus was seen with convergence and no cases

seen in multiple sclerosis.

Figure 3.9: *Histogram showing percentage of patients with demonstrable null point,*
convergence dampening and conjugate nystagmus.
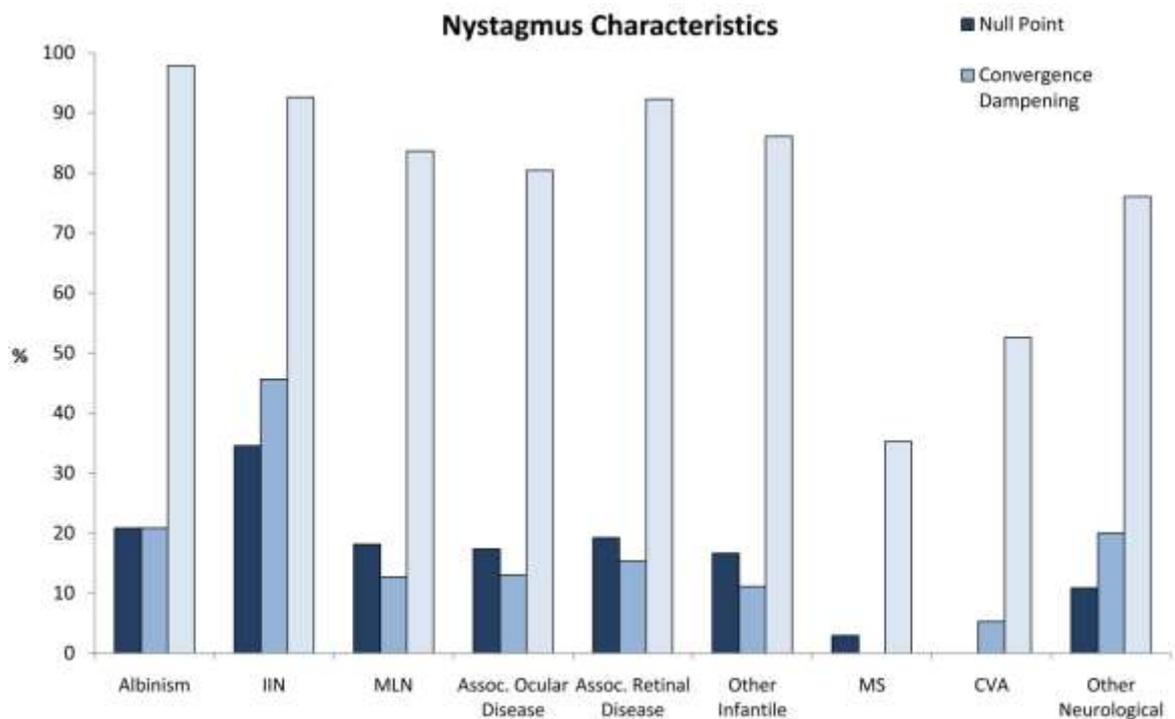
3.4.7. Visual impairment in common neurological diseases

Visual morbidity in patients with neurological diseases is summarised in Tables 3.1 and

3.2 for patients with multiple sclerosis and cerebrovascular disease.

Table3.1: *Summary of visual acuity, stereopsis and oscillopsia in patients with multiple*

sclerosis

No	logMAR VA			Binocularity		Oscillopsia
	RE open	LE open	BE open	Lang	Frisby	
1	6/6	6/9	6/6	negative	negative	Yes
2	6/6	3/60	6/6	550"	300"	Yes
3	6/24	6/6	6/6	550"	150"	No
4	6/4	6/4	6/4	550"	150"	Yes
5	6/36	6/36	6/24	negative	negative	Yes
6	6/36	6/36	6/36	negative	negative	No
7	6/5	6/24	6/5	Not Assessed		No
8	6/18	6/18	6/12	negative	negative	Yes
9	6/24	6/24	6/18	550"	110"	Yes
10	6/12	6/18	6/12	550"	300"	No
11	6/6	6/6	6/6	negative	negative	No
12	6/18	6/24	6/18	negative	negative	Yes
13	6/9	6/5	6/5	550"	300"	No
14	6/18	6/18	6/18	negative	negative	No
15	6/5	6/12	6/5	1200"	negative	No
16	6/5	6/5	6/5	Not Assessed		No
17	6/36	6/60	6/24	negative	negative	No
18	6/9	6/6	6/9	1200"	negative	No
19	6/5	6/5	6/5	550"	30"	Yes
20	6/9	6/9	6/9	550"	55"	No
21	6/60	6/60	6/60	negative	negative	Yes
22	6/6	6/5	6/5	550"	300"	No
23	6/60	6/60	6/36	550"	300"	Yes
24	6/6	6/6	6/6	550"	55"	Yes
25	6/5	6/6	6/6	550"	110"	No
26	6/5	6/5	6/5	negative	negative	Yes
27	6/5	6/5	6/6	550"	60"	No
28	6/4	6/6	6/4	negative	negative	No
29	6/6	6/6	6/6	550"	150"	Yes
30	6/12	C.F.	6/12	1200"	negative	No
31	2/60	3/24	3/24	negative	negative	No
32	6/9	6/9	6/9	Not Assessed		Yes
33	C.F	6/60	6/60	negative	negative	Yes
34	5/60	6/60	6/36	negative	negative	Yes

Table 3.2: *Summary of visual acuity, stereopsis and oscillopsia in patients with*

cerebrovascular disease

No	*logMAR VA*			*Binocularity*		
	RE open	**LE open**	**BE open**	**Lang**	**Frisby**	**Oscillopsia**
1	6/12	6/12	6/12	negative	negative	No
2	6/5	6/5	6/5	550"	300"	Yes
3	6/60	6/36	6/36	negative	negative	No
4	6/18	6/60	6/18	negative	negative	No
5	6/9	6/9	6/9	550"	110"	No
6	6/9	6/9	6/9	550"	110"	No
7	6/9	6/12	6/9	negative	negative	Yes
8	6/18	6/18	6/18	600"	negative	Yes
9	6/5	6/6	6/6	negative	negative	No
10	6/12	6/12	6/12	1200"	negative	No
11	6/18	6/18	6/18	negative	negative	No
12	6/5	6/36	6/5	negative	negative	No
13	6/5	6/5	6/5	550"	85"	Yes
14	6/5	6/5	6/5	550"	120"	No
15	6/12	6/6	6/6	1200"	negative	Yes
16	6/9	6/9	6/9	550"	110"	Yes
17	6/6	6/6	6/6	*Unable to assess*		No
18	6/9	6/9	6/9	1200"	negative	Yes
19	6/12	6/12	6/12	1200"	negative	No

41% of patients with multiple sclerosis and 54% of patients with cerebrovascular disease were outside the legal United Kingdom limit for driving. In both groups of diseases, approximately 1/3 of patients had absent stereopsis and just under one half of patients described symptoms of oscillopsia.

3.5. Discussion

This study shows the spectrum of diseases which can cause both infantile and neurological forms of nystagmus and the wide variation in visual acuity, stereopsis, presence of strabismus and anomalous head posture in the different conditions. The advantage of this prospective study was that careful clinical evaluation and requesting of additional investigations e.g. radiology, electrodiagnostics enabled a much more accurate final clinical diagnosis to be carried out.

There were some limitations to the study. Most of these patients were patients attending hospital services which would mean that there were fewer patients with better visual acuities or visual function who would be less likely to need hospital-based support. Younger patients were not able to carry out tests such as visual acuity testing, stereopsis measurements and eye movement recordings and their results were not included in these areas of investigation. Eye movement recordings were used as an adjunct to aid clinical diagnosis and no detailed analysis was carried out for the purposes of this study. We did not compare the patients to age-matched controls with no nystagmus and this was mainly a prospective, descriptive study with little statistical analysis.

A population based study on nystagmus in Leicestershire has shown that the commonest form of nystagmus within a population is infantile nystagmus (14.0 per 10 000 population) with nystagmus secondary to low vision e.g. congenital cataracts and optic nerve hypoplasia forming the majority of cases, followed by neurological nystagmus (6.8 per 10 000 population) where multiple sclerosis was the predominant

disease (Sarvananthan et al., 2009). The current study included patients who attended from areas outside Leicestershire and was limited to patients attending the hospital eye service. The commonest forms of nystagmus seen in this study were idiopathic infantile nystagmus and manifest latent nystagmus. These findings have been reported previously by a similar large scale hospital-based study of 224 subjects, where idiopathic infantile nystagmus was seen in 62% of patients (Abadi and Bjerre, 2002). However, the study was only limited to infantile forms of nystagmus and was a retrospective study where case records of patients were examined. The significantly higher numbers of male patients with idiopathic infantile nystagmus is due to the mode of inheritance of these diseases which can be X-linked in addition to autosomal recessive and dominant forms (Tarpey et al., 2006, Cabot et al., 1999, Preising et al., 2001, Bech-Hansen et al., 2000).

In terms of age distribution, the older patients were unsurprisingly patients with cerebrovascular disease. The youngest group of patients were represented by children and young adults with other infantile forms of nystagmus and this may have been due to a high number of children with Down syndrome attending the hospital ophthalmology service at an earlier age with nystagmus and other associated ocular abnormalities (Creavin and Brown, 2009).

Nystagmus can be an important cause of poor vision (DeCarlo and Nowakowski, 1999, Perez-Carpinell et al., 1992), however it can also be associated with good visual acuity and stereopsis (Thomas et al., 2008). The visual acuities of patients with nystagmus in this study showed wide variation as demonstrated in previous studies (Hanson et al., 2006, Abadi and Bjerre, 2002). The study also highlighted many patients with

nystagmus who had Snellen visual acuities better than 6/12, which satisfies the DVLA

regulations for driving cars and light vehicles (Group 1 drivers), particularly in

idiopathic infantile nystagmus, manifest latent nystagmus and other neurological

forms of nystagmus. Nystagmus is often associated with poor visual and social

function (Pilling et al., 2005) and parents of infants with nystagmus often associate the

disease with very poor vision. The results of this study provide some background

information to enable clinicians to provide parents with some level of visual prognosis

after careful clinical examination and investigations. The current level of visual

impairment registration enables a patient with 6/60 to 3/60 Snellen acuity and full

visual field to be classified as partially sighted. Figure 3.4 shows that this is seen most

frequently in patients with nystagmus associated with retinal diseases and ocular

diseases and this has been shown in much smaller studies than this study (Michaelides

et al., 2004, Nelson et al., 1984). This information enables the clinician to offer early

support to parents of these groups of patients through visual impairment registration

and involvement of education services when the diagnosis has been established.

Patients with idiopathic infantile nystagmus demonstrated the best level of stereopsis

and this is probably a reflection of the good level of visual acuity present in these

patients (Zaroff et al., 2003, Lee et al., 2001). We showed that 35% of our patients

with idiopathic infantile nystagmus had stereopsis better than 55 seconds of arc

whereas a previous similar study found this in only 14% of patients (Abadi and Bjerre,

2002). In patients with albinism, our study found 13% of patients had stereopsis better

than 170 seconds of arc whereas another study (Lee et al., 2001) found that 20% of

their patients had stereopsis better than 100 seconds of arc. The latter study used a different testing method (Titmus vectograph).

An interesting finding in this study was the presence of demonstrable stereopsis in 5 out of the 47 patients with manifest latent nystagmus in this study. The initial descriptions of this condition have strabismus as an essential component to diagnosis (Dell'Osso, 1985). However, our study found three patients had no measurable deviation and five patients had some measurable stereopsis. There are several possible explanations for this. Firstly, the patients with manifest latent nystagmus and no demonstrable strabismus may have been more appropriately classified as having idiopathic infantile nystagmus despite clinical observations of a latent nystagmus component. Secondly, more recent studies have shown that there is some variability in the waveforms of patients with manifest latent nystagmus (Abadi and Scallan, 2000, Gradstein et al., 1998). The latter study demonstrated one patient with mixed manifest latent nystagmus and idiopathic infantile nystagmus waveforms. In the latter study, seven out of fourteen patients showed dampening of nystagmus with convergence despite other clinical features of manifest latent nystagmus and it may be that our patients showed the same with improvements in visual acuity and demonstrable stereopsis for near. We did not assess stereopsis for distance but patients with manifest latent nystagmus with demonstrable stereopsis had visual acuities better than 6/12, similar to the seven patients in the other study (Gradstein et al., 1998). Further work correlating the amount of strabismus, nystagmus waveforms, visual acuity, distance and near stereopsis in patients with clinical findings of manifest latent nystagmus will help to confirm or refute our findings.

Strabismus in patients with nystagmus occurred most frequently in patients with manifest latent nystagmus, where less than 10% of these patients had no ocular deviation. The association between infantile strabismus and manifest latent nystagmus has long been recognised (Gradstein et al., 1998, Gresty et al., 1992, Sorsby, 1931) but these studies have also highlighted the need to find associated neurological or ocular diseases. This study group of manifest latent nystagmus represented patients in whom no other neurological or ocular diseases were found and the patients with any pathology were placed in the appropriate diagnostic groups. Figure 3.6 shows the high numbers of patients with strabismus and nystagmus in almost all diagnostic groups (including patients with neurological nystagmus) with the exception of idiopathic infantile nystagmus. Similar findings have been described by Brodsky et al, who found strabismus in over 50% of patients with all varieties of congenital nystagmus, particularly in albinism (53%) and bilateral optic nerve hypoplasia (85%) subgroups but a significantly lower prevalence in idiopathic infantile nystagmus (17%) (Brodsky and Fray, 1997). Other studies estimating the prevalence of strabismus have found rates of 16% (Forssman, 1964) and 33% (Dell'Osso, 1985) but the latter study included patients with manifest latent nystagmus within this prevalence rate. This study also highlights that patients presenting with vertical squints tend to have associated neurological disease and it is important for the clinician to be vigilant in patients with nystagmus from all age groups.

Anomalous head postures were most common in patients with other infantile and idiopathic forms of infantile nystagmus (39% and 37% of patients respectively) and least common in neurological nystagmus (8% of patients). Anomalous head postures

have been postulated to improve visual acuity in infantile nystagmus (Caldeira, 2000) but not in neurological forms of nystagmus (von Noorden, 1976, Gresty et al., 1984). Other theories underlying anomalous head posture, aside from a null point, have included improvement in symptoms of oscillopsia, compensation for A and V patterns of strabismus, and head posture due to structural abnormality of the head or central nervous system (Abadi and Whittle, 1991, Hertle and Zhu, 2000, Caldeira, 2000). The common theme in all of these studies is that an anomalous head posture is seen most frequently in idiopathic infantile nystagmus where patients have better acuities and stereopsis than their other infantile nystagmus counterparts (Abadi and Bjerre, 2002). This study, however, suggests that despite seeing a null point in only 17% of the patients with other infantile nystagmus compared with 35% patients with idiopathic infantile nystagmus, visual acuity may not be the primary reason for adopting an anomalous head posture. This is further confirmed by the work in this study which shows a predominance of chin elevation in nystagmus associated with other ocular diseases and other infantile foms of nystagmus. The lower prevalence of anomalous head postures seen in neurological nystagmus patients would also suggest that this does not help to improve symptoms of oscillopsia which was experienced by over one third of patients in each group of neurological diseases (Figure 3.8). Further detailed studies into anomalous head posture in patients with nystagmus would help in furthering our understanding of this very interesting clinical sign.

The high prevalence of amblyopia in patients with manifest latent nystagmus (38%) has been shown in other studies (Gradstein et al., 1998, Gresty et al., 1992). The latter study found just fewer than 50% of their patients had amblyopia.

3.5.1 Oscillopsia, conjugacy, null point and convergence dampening

Oscillopsia was reported by 47% of patients with multiple sclerosis and 37% of patients with cerebrovascular disease which represents over one third of patients with neurological nystagmus and is a well recognised symptom of this disease, (Gresty et al., 1982) with prevalence ranging between 28% (Yee, 1989) and 31% (Barton and Cox, 1993a). Various surgical and medical treatments have been used to try and reduce or eliminate this debilitating symptom (Leigh and Tomsak, 2003, Wang et al., 2007) but not all patients benefit. Further work into characterisation of the aetiology and nystagmus waveform may help to establish which patients could benefit from the differing treatments available. Amongst patients with infantile nystagmus, thirteen percent of patients with nystagmus associated with retinal disease reported symptoms of oscillopsia. It is interesting that rates as high as thirty nine percent has been quoted in previous studies in patients with infantile nystagmus (Abadi and Bjerre, 2002). This study and previous studies have not correlated visual acuity with symptoms of oscillopsia.

Another interesting finding from the study was the numbers of patients with clinically conjugate nystagmus in the neurological nystagmus group. Over one third and one half of patients with multiple sclerosis and cerebrovascular disease respectively had conjugate nystagmus waveforms. The traditional thinking that infantile nystagmus is predominantly conjugate with neurological nystagmus tending to be disconjugate may change as increasing numbers of patients have eye movement recordings carried out as part of their routine clinical assessment. Our study showed high rates of conjugate

nystagmus in the infantile nystagmus group. In all infantile forms of nystagmus, over 80% had conjugate form of nystagmus which compares to 78% in a previous study (Abadi and Bjerre, 2002).

The observation of a null point or 'position in which the nystagmus intensity is minimal' (Abadi and Dickinson, 1986) has been well recognised and is thought to be the position at which visual acuity is at its optimum (Gradstein et al., 1998, Dell'Osso and Daroff, 1975). This study showed that null point was most commonly seen in patients with idiopathic infantile nystagmus but the numbers were far lower (35%) compared with other studies showing null zones in up to 73% of patients with various forms of infantile nystagmus (Abadi, 2002). The latter study may have been more sensitive methodologically as the authors used eye movement recording data on all patients whereas this study relied on clinical assessment only. This may suggest that clinical assessment alone does not accurately detect the presence of a null point and highlights the importance of eye movement recordings to record this.

Convergence dampening is characterised by a reduction in nystagmus amplitude and frequency with adduction of both or the fixating eye. Patients in this study who demonstrated convergence dampening were predominantly infantile nystagmus patients and particularly, nearly half of the patients in the idiopathic infantile nystagmus group. Convergence dampening has been shown to improve visual acuity (Dell'Osso and Daroff, 1975, Abadi and Bjerre, 2002, Gradstein et al., 1998) and this may explain the highest number seen in our patients with idiopathic infantile nystagmus. Only 5% of patients with nystagmus and cerebrovascular disease and none

of the multiple sclerosis patients showed convergence dampening which may provide

a useful tool to differentiate between infantile and neurological forms of nystagmus.

3.6. Conclusion

This prospective study of patients both from within Leicestershire and outside the county has the following significance - firstly, the numbers of patients in this study is high for a rare condition like nystagmus. Only two other studies involving analysis of eye movement recordings has managed to recruit equivalent numbers of patients (Dell'Osso and Daroff, 1975, Abadi and Bjerre, 2002). Secondly, this is the first study to include both infantile and neurological forms of nystagmus and some recognised differences were shown, e.g. higher numbers of patients with oscillopsia in neurological nystagmus.Finally, this study looked at the proportion of patients with nystagmus with severe visual impairment and in contrast, the numbers of patients with good enough visual acuity to satisfy legal requirements for driving and more importantly showed there are a number of patients just outside the threshold of good vision who may benefit from treatment e.g. medical or surgical to improve their visual function in order to be eligible to drive and therefore improve their quality of life significantly.

Nystagmus is a condition with many different causes and differing clinical symptoms and signs and this study has helped to provide further information in helping to distinguish between the different and rarer forms of the disease, through assessment of visual acuity, stereopsis, stereopsis, monocular deficit, oscillopsia and conjugacy.

Chapter 4

The distribution of refractive errors in patients with infantile and neurological nystagmus

Chapter 4: The distribution of refractive errors in patients with infantile and neurological nystagmus.

4.1. Introduction

The previous chapters have shown that patients with nystagmus have best corrected visual acuities which range from very good, i.e. Snellen acuity of 6/6 or better to very poor, i.e. Snellen acuity of 6/36 or worse. In some cases, the presence of a refractive error contributes to poor vision in the uncorrected state. A refractive error is a difference between the focal length of the cornea and lens, and the length of the eye, resulting in myopia, hypermetropia and/or astigmatism. Correction of the refractive error often results in improvement of vision. The development of a refractive error in an individual relies on a combination of genetic and environmental factors which influence the axial length, corneal power and crystalline lens power (Hung and Ciuffreda, 1999, Mutti et al., 2005). Known environmental factors include smoking (Stone et al., 2006) or prolonged periods of near work (Young et al., 2007).

A spherical refractive error occurs when there is a difference between the axial length of the eye and the combined dioptric powers of the cornea and lens. At birth, the average refractive error is approximately one to two dioptres of hypermetropia. With increase in axial length and an increase in corneal diameter reduction in corneal curvature occurring throughout infancy and childhood, a process of emmetropization occurs resulting in most individuals having no significant refractive error by four years old(Troilo, 1992). Axial length appears to be the largest contributor to refractive error

and can be influenced by both genetic and environmental factors, with estimates for heritability ranging from 40% to 94% (Young et al., 2007).

Astigmatism is a refractive condition where parallel rays of light which enter the eye through the refractive media do not focus on a single point. This occurs due to an aspheric corneal surface or abnormal curvatures of the lens, irregular refractive index of the lens or an eccentric lens position (Gordon and Donzis, 1985). A large study of astigmatism in 328,905 individuals aged between 16 and 22 years of age in Israel showed that with the rule astigmatism was significantly associated with higher body mass index, higher refractive errors and lower intelligence scores (Mandel et al.). Unlike spherical refractive error, the role of genetics in development of astigmatism is under debate with studies suggesting some involvement (Clementi et al., 1998) whereas another Finnish twin study suggests environmental factors as the major contributor (Teikari et al., 1989).

In normal children, spherical refractive errors are common in infants under one year with a tendency towards low hypermetropia (Cook and Glasscock, 1951). By early school age, few children have significant refractive errors. Epidemiological studies have shown that over 80% of young adults have unaided vision of 6/6 or better - 10% have hypermetropia between 2 and 4 dioptres, 4% have higher degrees of hypermetropia, 9% have myopia under 4 dioptres, 2% have myopia over 4 dioptres and nearly 20% of the population have astigmatism of 0.5 dioptres or greater (Sorsby et al., 1960). This large scale study in 1033 young men called up for National Service aged between 18 to 22 years also showed the presence of squint in 4% of the study group and amblyopia in 0.5%.

The incidence of significant refractive errors in infantile nystagmus is thought to be as high as 85% (Hertle, 2000, Hertle and Zhu, 2000) with improvements in vision up to 6 lines of LogMAR vision seen in some cases with optical correction. The simple use of optical aids such as spectacles or contact lenses to achieve such improvement in visual acuity highlights the importance of a careful refractive examination in all patients presenting with nystagmus. Treatment of the refractive error (and any associated amblyopia) may sometimes require a longer period of visual adaptation before the optimal visual result is seen in patients with nystagmus compared with normal individuals (Bedell, 2006). Contact lenses have been shown to be particularly effective in improving visual acuity function in patients with nystagmus as most authors feel that the patient is looking along the visual axis of his/her correcting lens for a longer time than with spectacle lenses as the contact lens moves with the eye (Biousse et al., 2004, Allen and Davies, 1983). In addition, use of contact lenses result in additional convergence and accommodative effort, both of which can result in reduced amplitude and frequency of nystagmus in this position of vision. Contact lenses have also been used with biofeedback but evidence for the effectiveness of this method of treatment is controversial (Yaniglos et al., 2002).

The refractive errors in albinos with nystagmus has been studied in humans (Wildsoet et al., 2000), macaque monkeys (Repka and Tusa, 1995) and chicks (Rymer et al., 2007). The macaque monkeys had periods of occlusion of eyes after birth and developed exotropia and nystagmus. They showed higher hypermetropic refractive errors than their normal counterparts. The albino chicks, in contrast, had predominantly myopic refractive errors compared to their normal hyperopic

counterparts. There was a higher than normal against-the-rule astigmatism in albino chicks but no statistical analysis was carried out to test this. This study on 25 albino children and adults showed a high incidence of with-the-rule astigmatism, which has also been reported in another study (Dickinson and Abadi, 1984). There were also a high number of albino patients with both high myopic and high hypermetropic refractive errors but with an overall higher number of hypermetropes. Another study with smaller number of albino patients (nine patients in total) showed mainly high myopia and with-the-rule astigmatism greater than 1.50 dioptres in all the patients (Perez-Carpinell et al., 1992).

A further study compared the distribution of refractive errors in individuals with idiopathic infantile nystagmus (46 patients) and albinos (19 patients) (Sampath and Bedell, 2002). They found high numbers of patients who had with-the-rule astigmatism. Kurtosis (the distribution of data around the mean) of the refractive error data was analysed. In normal individuals, refractive errors show a leptokurtic distribution (i.e. a more acute peak in the distribution curve around the mean) whereas in this study, the distribution of refractive error in patients with albinism and idiopathic infantile nystagmus showed no significant kurtosis.

The aim of our study was to determine the distribution of refractive errors and degree and type of astigmatism in nystagmus subgroups compared to age-matched controls. In comparison to previous studies, we have used a larger sample size of 376 patients and 602 normal controls. Unlike a previous study, where army recruits from another study were used as normal controls (Sampath and Bedell, 2002, Sorsby et al., 1960), we used normal individuals who were from the same representative population. We

have also included a number of nystagmus subtypes that have not been previously investigated i.e. manifest latent nystagmus, other infantile nystagmus and neurological nystagmus.

4.2. Methods

4.2.1. Patients

After informed consent, 376 patients with infantile nystagmus, 96 patients with neurological nystagmus and 602 normal individuals without nystagmus agreed to participate in the study. Patients with infantile nystagmus were subdivided into diagnostic groups of albinism (n=43), idiopathic infantile nystagmus (IIN, n=108), manifest latent nystagmus (MLN, n=47) and nystagmus associated with low vision or retinal disease (n=82). The clinical diagnosis of nystagmus was established after careful clinical history, examination and investigations e.g. electrodiagnostics, eye movement recordings and radiological tests. These have been discussed in detail in chapter 3. Normal individuals were included in the study after a detailed ocular history and slit lamp examination to exclude any ocular pathology.

Patients with neurological nystagmus within this study were defined as adults or children with nystagmus and associated neurological diseases such as hydrocephalus, demyelination, cerebrovascular ischaemia , arteriovenous malformation or tumours. Infants with nystagmus who had associated neurological disease were also included in this group as the influences of neurological diseases on emmetropization in children in

this group of patients with central nervous system disorders has not been studied or established unlike the other infantile groups of diseases. There were also single cases of rarer neurological disease.

4.2.2. Refraction technique and recording

All children with and without nystagmus who were under 7 years of age underwent cycloplegic refraction after initial visual acuity measurement, using Cyclopentolate 1% (or 0.5% in infants under 6 months old) eye drops instilled into both eyes. A two dioptre working distance was subtracted from the objective refraction. All children over 7 years old and all adults had a subjective refraction carried out using retinoscopy and the best corrected visual acuity was recorded.

The author recruited and carried out the refractions on all 602 normal controls. In addition, the author carried out the refraction on 217 patients with nystagmus whilst the remaining 255 patients had refractions carried out by hospital optometrists using the above protocol. Statistical analysis was carried out with the assistance of Dr Frank Proudlock, University of Leicester.

The refractive error for each eye was recorded and calculations made for the spherical equivalent by adding half the cylindrical refractive error to the spherical refractive error. The axis of astigmatism for each eye was recorded in order to determine with or against the rule astigmatism values and the proportions for each clinical nystagmus group were compared to the control group using a criteria of $90^{\circ} \pm 15^{\circ}$ and $180^{\circ} \pm 15^{\circ}$ respectively.

Although the refractive errors for both eyes were recorded, measurements from the

right eye of each individual were used in the analysis.

4.3. Results

4.3.1. Spherical equivalent

The distribution of refractive errors of individuals with nystagmus and normal controls

is shown in Figure 4.1.

Figure 4.1: *Distribution of spherical equivalent refraction for patients with infantile and neurological nystagmus and a comparison with age-matched normal controls with no nystagmus.*
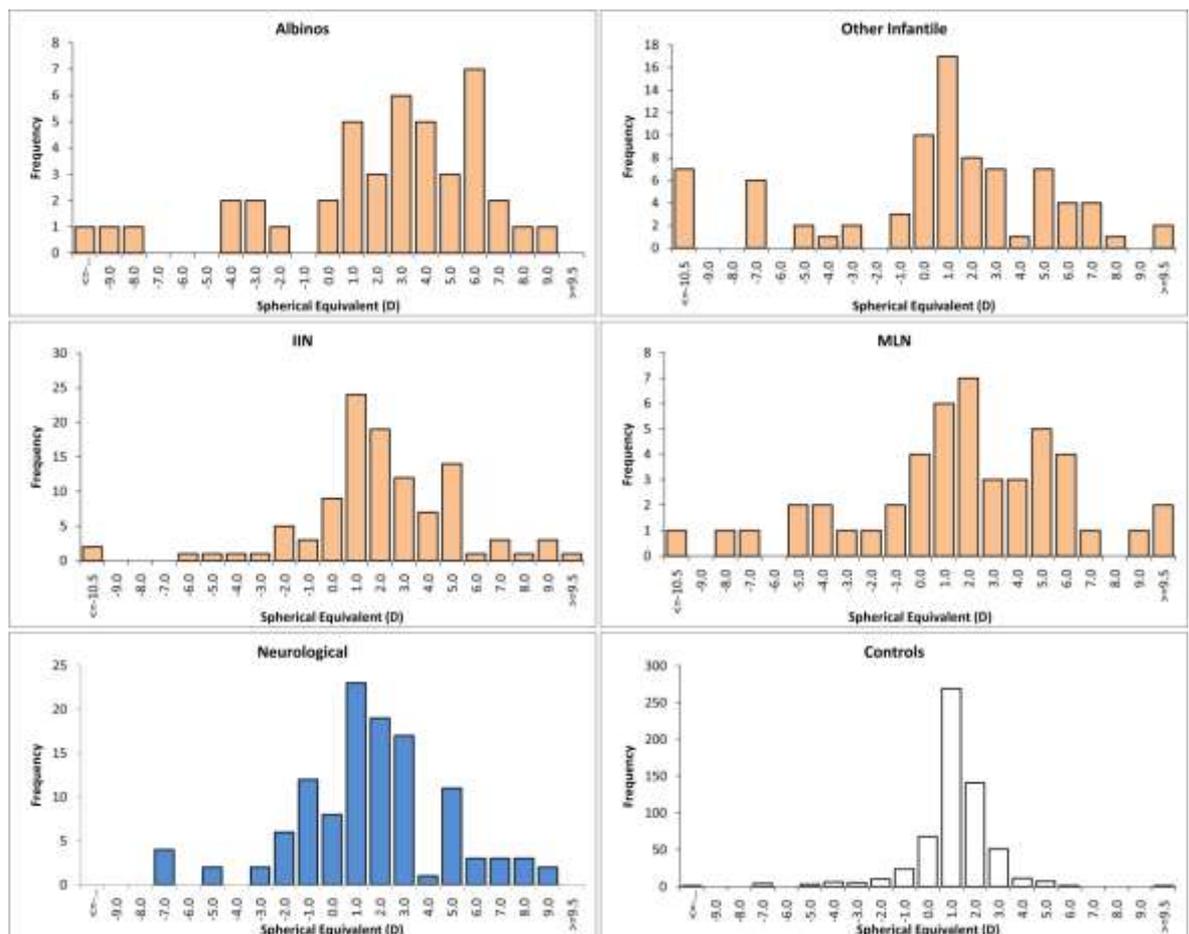
The data shows that the distribution of refractive errors amongst patients has higher numbers of patients with high hypermetropia and myopia in all infantile groups in comparison to normal controls. In the group of patients with albinism, there are more patients with hypermetropic refractive errors. There are less patients with hypermetropia and myopia greater than 6 dioptres in idiopathic infantile nystagmus compared to patients with albinism, manifest latent nystagmus and other infantile nystagmus.

4.3.2. Astigmatism

The amount of refractive astigmatism in patients with nystagmus is compared to normal controls in Figure 4.2.

Figure 4.2: Distribution of refractive astigmatism in patients with nystagmus and normal control group.
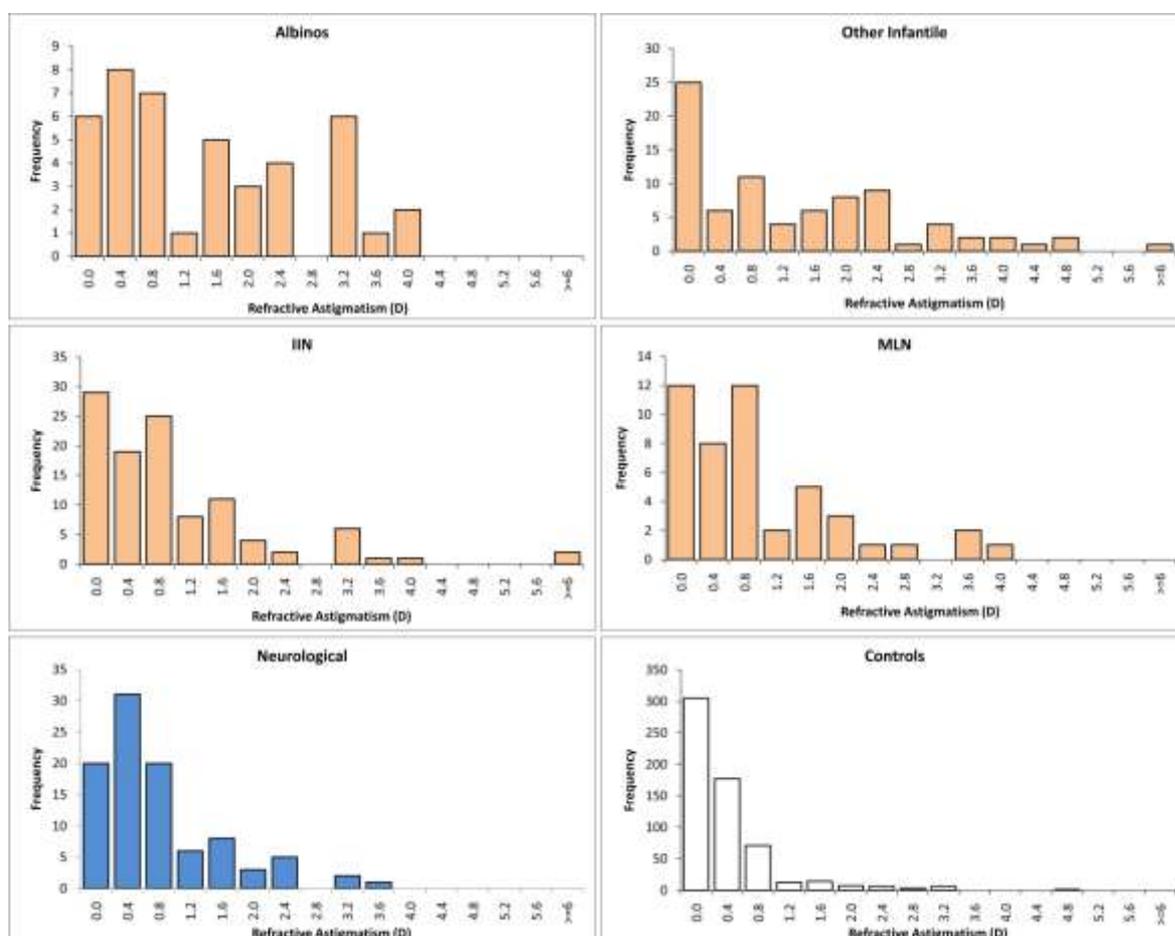
The proportion of individuals with astigmatism greater than 0.5 dioptres is high in all patients with nystagmus compared to the control group.

4.3.3 Statistical analysis

Analysis of the distribution of both spherical refractive error and astigmatism was carried out using the Pearson Chi Square test. The results are summarised below in Table 4.1. We used refractions from the control group to estimate the 95% confidence interval for the data by calculating the 2.5 percentile and 97.5 percentile. Using percentiles avoided any assumptions of the distribution of the data.

The numbers of patients both within and outside the 95% confidence intervals for both nystagmus and control groups were calculated and are shown in Table 4.1. Patients within the neurological group for nystagmus had a different control group of older age-matched patients compared to analysis carried out for the infantile nystagmus patients. The relative proportion of these numbers in each group was statistically compared using the Chi-square test.

The distribution of spherical errors in all infantile and neurological nystagmus patients were shown to be different from the normal control group. These differences were highly statistically significant ($p<0.001$). This arises due to the higher number of patients with both high myopia (below 2.5 percentile) and high hypermetropia (above 97.5 percentile) in all groups of patients with nystagmus.

The distribution of astigmatism for patients with nystagmus was compared to controls. With the exception of patients with neurological nsytagmus, the distribution of astigmatic refractive errors amongst patients with the other subgroups of nystagmus is different from controls and the result was statistically significant ($p<0.01$). Table 4.1 shows that the proportion of individuals with high amounts of

astigmatism (above the 97.5% confidence interval) for patients with albinism, manifest latent nystagmus, idiopathic infantile and other infantile forms of nystagmus was larger than for controls.

Table 4.1: *Summary of statistical analysis of difference in spherical and astigmatic refractive errors between patients with nystagmus and age-matched normal controls*

Spherical Equivalent

group	controls				patients				Pearson Chi-square	
	lower CI	upper CI	outside 95%CI	inside 95%CI	below 2.5%CI	above 97.5%CI	outside 95%CI	inside 95%CI	value	p
Albinism	-3.747	3.000	31	571	7	15	22	21	112.667	0.000
IIN	-3.747	3.000	31	571	6	27	33	75	72.068	0.000
MLN	-3.747	3.000	31	571	8	16	24	23	118.491	0.000
Other Infantile	-3.747	3.000	31	571	17	18	35	47	116.619	0.000
Neurological	-4.400	3.237	12	217	5	13	18	78	14.735	0.000

Astigmatism

group	controls				patients				Pearson Chi-square	
	lower CI	upper CI	outside 95%CI	inside 95%CI	below 2.5%CI	above 97.5%CI	outside 95%CI	inside 95%CI	value	p
Albinism	0.000	2.244	16	586	0	13	13	30	71.067	0.000
IIN	0.000	2.244	16	586	0	12	12	96	17.274	0.000
MLN	0.000	2.244	16	586	0	5	5	42	8.868	0.003
Other Infantile	0.000	2.244	16	586	0	22	22	60	80.363	0.000
Neurological	0.000	2.500	5	224	0	0	0	5	0.112	0.738

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A summary of the distribution of astigmatism amongst patients with infantile and neurological nystagmus in comparison to the control group without nystagmus is shown in the bubble plots in figures 4.4 and 4.5.

Figure 4.4: Bubble plots showing distribution of astigmatism in patients with infantile nystagmus compared to the control group. The shaded yellow areas (±15 degrees) of 90° and 180° are used to define of with-the-rule or against-the-rule astigmatism (Plots produced by Dr Frank Proudlock, University of Leicester).
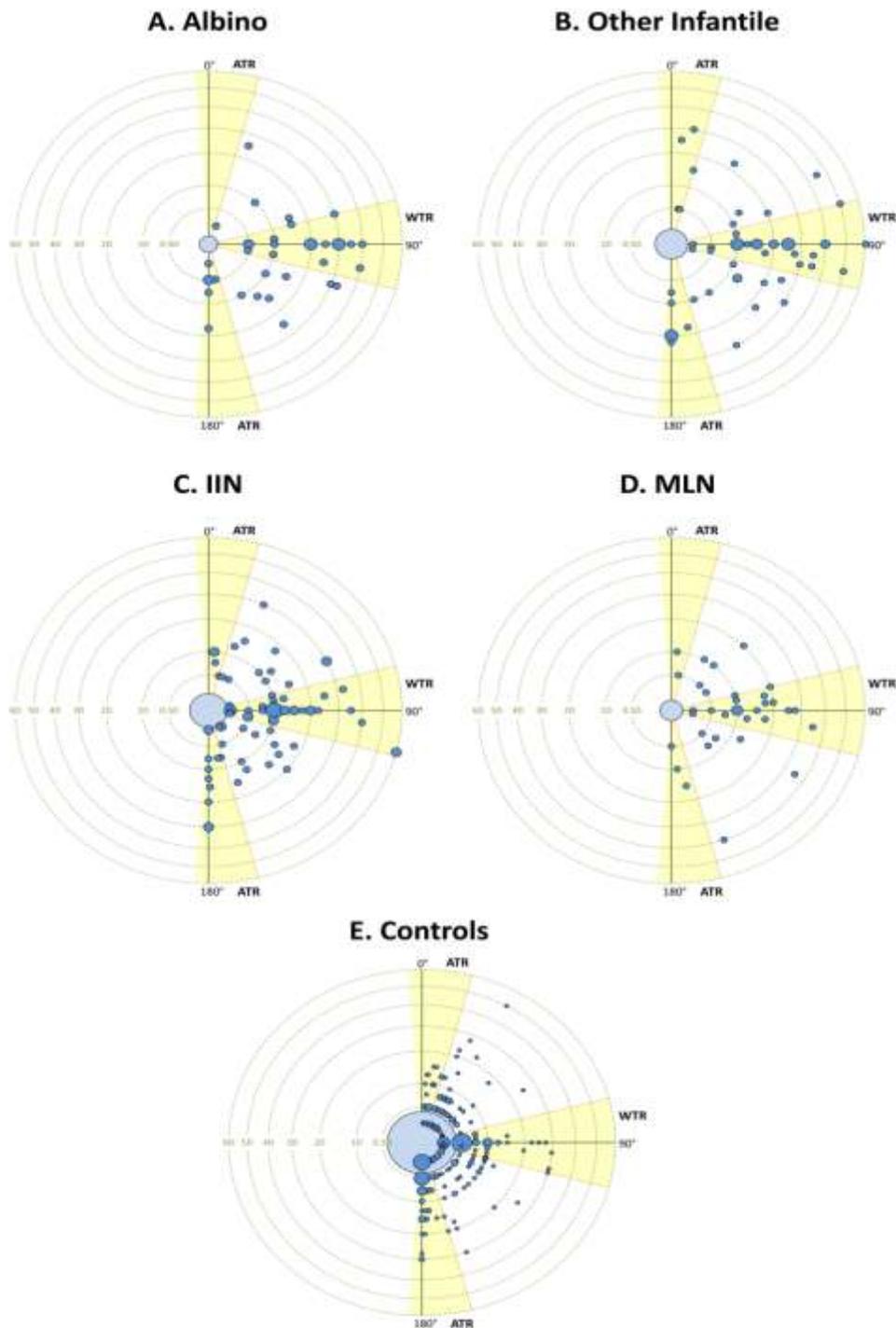
Figure 4.5: Bubble plots showing distribution and spread of refractive astigmatism amongst patients with neurological nystagmus compared to age-matched controls. The shaded yellow areas (±15 degrees) of 90° and 180° are used to define of with-the-rule or against-the-rule astigmatism (Plots produced by Dr Frank Proudlock, University of Leicester).
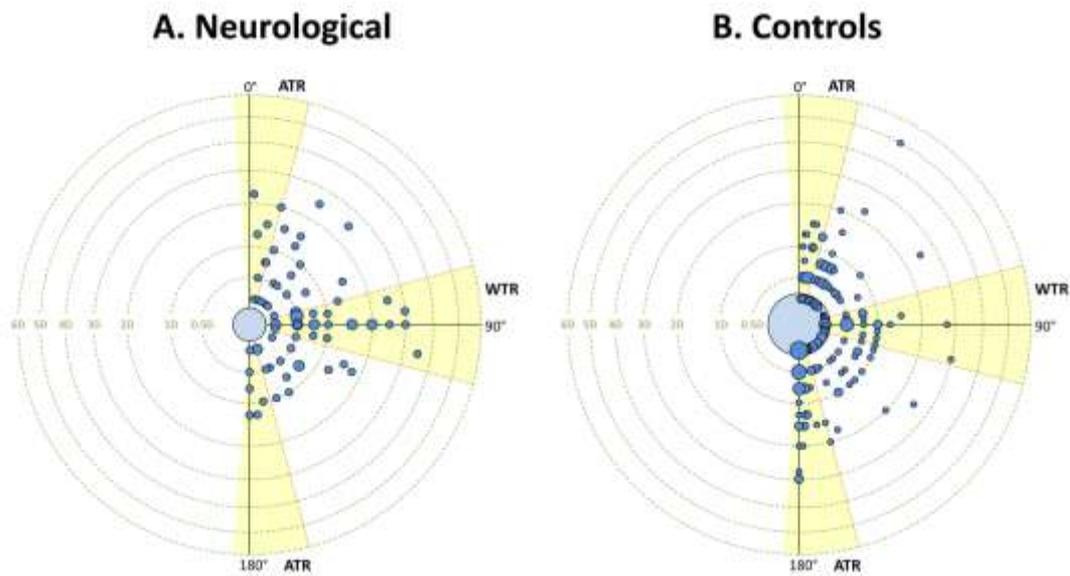

The data for the frequency of with-the-rule and against-the-rule astigmatism is summarized in Figure 4.5.

The relative proportions of with-the-rule astigmatism (WTR) and against-the-rule astigmatism (ATR) in infantile nystagmus (age 26.9, SD 21.6) were 34.3% and 13.9% for idiopathic infantile nystagmus, 44.2% and 14.0% for albinos, 40.4% and 10.6% for manifest latent nystagmus and 35.1% and 15.9% for other infantile forms of nystagmus. These results are summarised in Figure 4.5. The proportion of WTR to ATR astigmatism was significantly higher than controls (14.5% and 16.4% respectively; mean age 26.1, SD 24.7) for all groups ($p<=0.007$). The degree of astigmatism (mean cylinder ±SD) was 1.00±1.14D for idiopathic infantile nystagmus, 1.52±1.20D for albinos, 1.02±1.01D for manifest latent nystagmus and 1.42±1.43D for other infantile forms of nystagmus, in comparison to 0.37±0.60D for controls. Chi-Square statistical analysis reveals that the predominance of with-the-rule astigmatism is statistically significant in all groups of patients with nystagmus when compared to the control group ($p=0.006$ in albinos, $p=0.002$ in idiopathic infantile nystagmus, $p=0.002$ in manifest latent nystagmus, $p=0.007$ in other infantile nystagmus, $p= 0.031$ in neurological nystagmus).

Figure 4.5: Distribution of axis of astigmatism in patients with nystagmus compared with the control group. ATR = against-the-rule, WTR = with-the-rule astigmatism. Statistical analysis was carried out using Chi Square testing to compare the difference between against-the-rule astigmatism and with-the rule astigmatism in each group of patients.
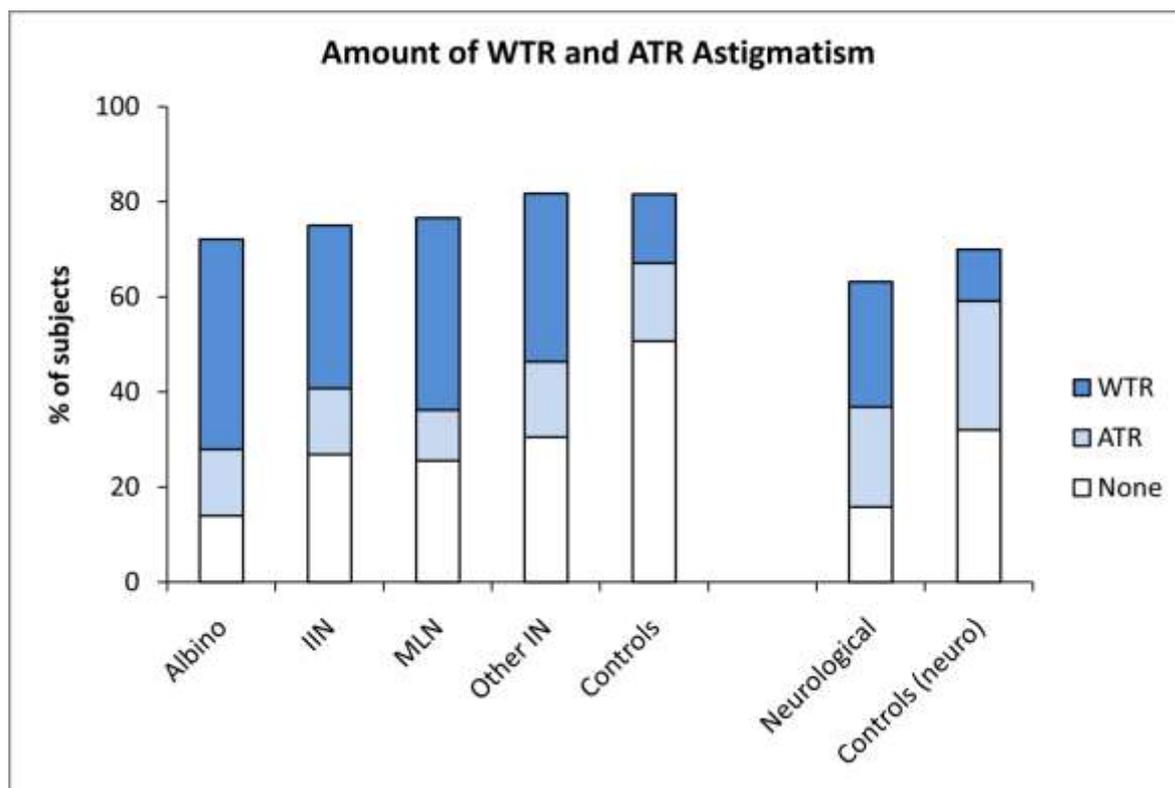
Proportion of WTR and ATR astigmatism in comparison to controls

Chi Squ

group	p-value
albinos	0.006
IIN	0.002
MLN	0.002
Other IN	0.007
Neurological	0.031

4.4. Discussion

The development of refractive error is influenced by ocular, genetic and environmental factors. Normal infant eyes undergo a process of emmetropization in which the cornea, axial length and lens growth occurs at a complimentary rate which results in a reduction in refractive error (Hung and Ciuffreda, 1999). Of all the ocular factors, axial length appears to be the main factor in determining refractive error as shown in studies on normal infants (Mutti et al., 2005) and in investigations in children with ocular diseases such as retinopathy of prematurity, congenital cataracts, retinal diseases and systemic diseases such as Down syndrome.

In retinopathy of prematurity, a seven to ten year follow up of 88 children being screened for retinopathy of prematurity found myopia in 25% of children with treated retinopathy of prematurity compared to myopia in 5% of children who did not have retinopathy of prematurity (Fledelius, 1996). A later study looked for possible factors involved in the development of refractive errors associated with prematurity and found that premature infants tended to have shorter axial lengths, shallower anterior chambers and highly curved corneas. They found that the latter two factors were significantly associated with an increased of myopia (Cook et al., 2003).

A further retrospective study of 123 children referred for investigation of low vision or nystagmus to Moorfields Eye Hospital found that there was a higher prevalence of refractive errors in children with abnormal electroretinography suggesting that the retina is also involved in the process of emmetropization (Flitcroft et al., 2005). Studies on changes in refraction in children undergoing surgery for congenital cataracts

provides further evidence for changes in rates of emmetropization in children where ocular pathology exists (Flitcroft et al., 1999). Removal of the cataract results in myopic shift with initial rapid increase in axial length over the first three to six months of life and a lesser myopic shift seen in developmental cataracts where surgery tended to be carried out at an older age.

Children with Down syndrome also show evidence of delayed emmetropization with a wide range of refractive errors, including higher astigmatism compared to their normal peers from a young age (Woodhouse et al., 1997). Interestingly, they continue to show changes in their refraction until adulthood with more initially emmetropic children developing refractive errors in teenage years compared to their normal age-matched counterparts (Cregg et al., 2003).

There are therefore both genetic and environmental influences in the process of emmetropisation. Visual deprivation from ocular diseases has a role to play in altering the rate of axial length growth, particularly during the 'sensitive' period of visual development which is thought to have three phases, each with different time courses – (i) a period of visually-driven normal development, (ii) a sensitive period for damage (i.e. interfering with normal ocular growth) and (iii) a sensitive period for recovery (i.e. ocular growth occurring after disease has recovered or been treated) (Lewis and Maurer, 2005, Olitsky et al., 2002).

Our study looked at patients with different clinical types of nystagmus to see if there were characteristic types of refractive errors or astigmatic refractive errors which could be attributed to each group enabling appropriate screening for this by local optometrists or health professionals. The affected individuals were compared to age-

matched controls. The right eye refraction was used in this study in all patients in order to compare our results to other published. However, this means that anisometropia or amblyopia could have affected the final results.

In terms of spherical equivalent refractive error, Figure 4.1 and subsequent analysis shows that most normal individuals have refractive errors close to emmetropia, whereas there is a much higher frequency of both high hypermetropic and high myopic refractive errors in individuals with both infantile and neurological nystagmus. Individuals with idiopathic infantile nystagmus have a spherical error distribution which more closely resembles the control group and this could be partly due to a near normal emmetropization process which occurs in these individuals who tend to have better visual acuities and stereopsis than other patients with infantile nystagmus.

A similar study to this (Sampath and Bedell, 2002) used kurtosis values to reflect the distribution of refractive errors in normal controls taken from a previous study carried out on army recruits (Sorsby et al., 1960) and their patients with idiopathic infantile nystagmus and albinism. The kurtosis ($\alpha4$) for our normal controls was calculated at 9.073 and in the latter study at 7.9. These high values suggest that the refractive errors in normal individuals tend to follow a leptokurtic distribution. The kurtosis values for their patients with idiopathic infantile nystagmus was 0.18 compared to 3.64 in our study and in albinism 0.67 compared to 3.273 in our study. The study by Sampath et al used much smaller numbers of patients (19 with albinism and 46 with idiopathic infantile nystagmus) compared to higher numbers of patients in our study, which could have resulted in less numbers of patients with high myopic or hypermetropic refractive errors. Our normal control population was also age matched

whilst the normal controls in their study was taken from male army recruits aged between 18 and 22 years.

Statistical analysis showed that there was a significant deviation of distribution of refractive errors from normal in all groups of patients with infantile nystagmus particularly in manifest latent nystagmus, nystagmus secondary to albinism and idiopathic infantile nystagmus. Many factors could account for this abnormal process of emmetropization in patients with nystagmus including abnormal or retarded axial length growth due to visual image blur secondary to foveal hypoplasia, optic disc changes, retinal dystrophy etc. Work carried out on emmetropisation in macaque monkeys (Repka and Tusa, 1995) showed that the primates who had occlusion within the first 25 days of birth developed hypermetropia whereas later occlusion after 25 days was associated with the development of myopia. There were more patients with hypermetropia in all infantile and neurological nystagmus groups suggesting that impaired visual development from birth may contribute to this. The authors suggested that impaired accommodation could also result in the persistence of hypermetropia and impaired emmetropisation.

Wildsoet et al(2000) also noted a wide spread of refractive errors in their subjects with albinism and attributed this to impaired emmetropization. This author felt that there was 'meridional emmetropization' occurring in nystagmus subjects when analysing horizontal and vertical refractive errors separately and speculated a link with horizontal nystagmus being much more prominent in nystagmus associated with albinism resulting in a dominance of vertical image blur. Additionally, work carried out on albino chicks (Rymer et al, 2007) suggests that the impaired retinal pigmentation

could cause abnormal signalling between the retina and emmetropisation process, resulting in both myopic and hypermetropic refractive errors.

In summary, the process of development of abnormal spherical refractive errors appears to have many contributing variables including retinal image blur, retinal pigmentation, impaired accommodation and dependency on meridian of nystagmus. Further work needs to be carried out on whether these abnormalities result in abnormalities present at birth or during ocular growth.

Astigmatism in all patients with nystagmus was mainly with the rule and this has been reported in other studies (Rymer et al., 2007, Sampath and Bedell, 2002, Dickinson and Abadi, 1984). Corneal topography in the latter study did not find any correlation with corneal diameter to explain this. Other theories have been corneal moulding by the eyelids in patients with nystagmus (Wildsoet et al., 2000, Mandel et al.) but this has not been formally tested. There appears to be a close link between high astigmatic refractive errors and abnormal spherical errors and abnormal emmetropization is therefore the common cause of both abnormalities (Sampath and Bedell, 2002) although a recent study has disputed this theory (Mandel et al., 2010). A longitudinal study looking at the development and progression of astigmatism in infants, where infants were refracted from the first year of birth for a period of 6-23 years showed that despite half of the infants having astigmatism under six months of age, the prevalence declined rapidly to approximately 5% of children aged 6 to 10 years (Gwiazda et al., 2000). The study found that the presence of astigmatism in infancy was associated with a statistically higher likelihood of development of myopia and astigmatism in later life. They postulate that this is due to either image blur resulting

in disruption of emmetropisation or structural flattening of the crystalline lens due to asymmetrical pull of the ciliary muscles resulting in mechanical changes to accommodation and altered eye growth. This structural process could be a factor in nystagmus where the mechanical eye movements and resulting 'pull and push' forces in the axis of the extraocular muscles could result in differential growth of the eyeball and resultant astigmatism. One study has shown that in individuals with infantile nystagmus and astigmatism of less than 1.5 dioptres, nystagmus intensity (amplitude x frequency) can be correlated to optotype acuity (Beddell et al., 1991).

Our study also showed that patients with neurological nystagmus appeared to have significant amounts of astigmatism compared to their normal counterparts which could imply that there may be an effect of the eye movements in nystagmus on the development of astigmatism in older individuals. Figure 4.2 shows that there is much more astigmatism in all groups of patients with nystagmus.

This study looked at both infantile and neurological forms of nystagmus and compared refractive errors to age-matched controls, which has not been carried out previously. We did not correlate our findings with visual acuity, presence of strabismus, axial lengths, corneal curvature, anterior chamber depth, lens thickness and nystagmus amplitude and frequency. We did not carry out a comparative study of refractive errors and nystagmus between the two eyes, which could provide further information into whether the emmetropization process is a central nervous system or more locally driven process within each eye.

4.5. Conclusion

This study shows that there is a high frequency of refractive errors in patients with infantile and neurological nystagmus and correction of this could result in visual improvement for these patients. Early and regular screening for refractive errors is indicated. There are many factors which could influence this abnormal process of emmetropization in individuals with nystagmus including ocular, genetic and environmental factors and further studies looking at each specific factor are indicated in order to see if this abnormal process could be halted at an early stage.

Chapter 5

General Overview and Conclusions

Chapter 5: General overview and conclusions

5.1. Overview

The work in this thesis has been a culmination of several years of study into the epidemiology, clinical features and refractive development in infants, children and a wide range of adults with nystagmus. Prior to this work, most of the publications into the pathophysiology of nystagmus were small studies or case series or nystagmus and was discussed as a small subsection of larger studies into patients with other ocular diseases. Nystagmus is a chronic disease for which there is no cure at present but the studies into genetics (Tarpey et al., 2006, Kerrison et al., 1999, Oetting, 2002, Kohl et al., 2002, Sundin et al., 2000, Bech-Hansen et al., 2000, Jalkanen et al., 2007) and treatment of both infantile and neurological nystagmus (Averbuch-Heller et al., 1997, Bandini et al., 2001, McLean et al., 2007) have been exciting areas of development in the last three decades. There continues to be many fundamental questions which remained unanswered, for example, the prevalence of the disease, the variation in clinical presentation of the disease and the influence of nystagmus on ocular development e.g. refractive error. Our work has attempted to answer some of these questions and the benefits and limitations of each investigation are discussed below with suggestions for further work into these areas of research.

5.2 Epidemiology of nystagmus

Prior to the nystagmus survey carried out in Leicestershire, research into this area had been primarily into infantile nystagmus (Hemmes, 1927, Norn, 1964, Forssman and Ringner, 1971, Stewart-Brown and Haslum, 1988) and there were biases towards individuals with poor vision. Our study was the first population-based study aimed at specifically determining the prevalence of nystagmus. We used detailed clinical assessment tools to ensure that patients attending the survey had accurate diagnoses made and we used publicity, public lectures and community allied medical professionals e.g. optometrists to recruit as many people as possible including those with good vision who may not have been attending hospital services. The use of three independent sources of information enabled us to carry out robust statistical analysis to determine the prevalence figures. This was the first time some estimate was made of the prevalence of neurological nystagmus, which we estimated to be 2.4 in 1000 and therefore higher than we previously thought.

There were limitations to our study in that the use of visual impairment registration forms dating back to the 1960s meant that there were patients whose diagnosis of the type of nystagmus may have been different if the patient had been seen in this decade with availability of standardised electrodiagnostic and electrooculography testing. Consequently, not all forms would have documented nystagmus as a primary cause of visual impairment.

This study in a population with a wide base of different ethnic groups, is of significance in that it provides a basis for further important work into the pathophysiology,

genetics and treatment of nystagmus. The data on prevalence of the different groups of nystagmus provides important information for health, social and education providers in terms of planning for resource allocation.

5.3 Clinical spectrum of nystagmus in a tertiary referral centre

Many clinicians in smaller hospital units may only be confronted with a patient with nystagmus once or twice a month. As a tertiary referral centre at the University of Leicester and University Hospitals of Leicester NHS trust, we have a large pool of patients with nystagmus of various aetiologies. Previous studies have attempted to assess what characteristics in a patient with nystagmus could help distinguish between for example nystagmus secondary to albinism from idiopathic infantile nystagmus using infrared oculography, clinical features and electrodiagnostic testing (Dell'Osso, 1985, Abadi and Bjerre, 2002, Barton and Cox, 1993a, Leigh et al., 2002). With further advancements in technology, we carried out a further analysis of patients with nystagmus including neurological forms of nystagmus to see if there were distinguishing features between different groups of nystagmus. For example we found idiopathic infantile nystagmus was significantly more common in males. Patients with neurological nystagmus did not tend to adopt an anomalous head posture and surprisingly over one third of patients with multiple sclerosis and one half of patients with cerebrovascular disease had clinically conjugate nystagmus.

Our study included patients of all ages and three hundred and ninety one patients agreed to participate which represents a larger series compared to previous studies.

This was a prospective study and enabled a thorough clinical assessment in order to accurately diagnose the aetiology of each patient's nystagmus. There were some other interesting findings including the discovery that there were a high proportion of patients with idiopathic infantile nystagmus and manifest latent nystagmus whose vision was within legal limits for driving and on the other end of the spectrum, patients with other infantile forms of nystagmus tended to have vision poor enough for registration as blind. These findings show that treatment of some individuals with idiopathic infantile nystagmus whose visual acuity is just outside the legal threshold for driving, may provide a significant improvement in their quality of life, whilst it is also important to provide early blind registration and input from education and social services for the other group of visually impaired patients with nystagmus.

We also described the first case of nystagmus occurring in Sphrintzen-Goldberg syndrome. However, our clinical study did not have a control population and statistical analysis was limited. We did not analyse the eye movement recordings in detail and correlate the findings with visual acuity, conjugacy and other clinical measurements.

5.4 Distribution of refractive errors in patients with infantile and neurological nystagmus

Infantile nystagmus develops before two months of age and it has therefore been hypothesised that this affects the process of visual development known as emmetropization which in turns influences the development of refractive errors in these individuals. Animal (Repka and Tusa, 1995, Rymer et al., 2007) and human studies (Cook et al., 2003, Hung and Ciuffreda, 1999, Sampath and Bedell, 2002) have shown that the process of emmetropization can be influenced by ocular, genetic and environmental factors. We carried out a prospective analysis of refractive errors in patients with infantile and neurological nystagmus to assess the distribution of refractive errors within this group of individuals compared to normal individuals. Compared to previous studies, our study provided a larger patient population and included neurological nystagmus. The patients with neurological nystagmus over 18 years, there was a higher frequency of myopic refractive errors compared to the normal control group. There were also a higher proportion of patients with with-the-rule astigmatism compared to normal controls.

We had a large age-matched control group for statistical comparison. However, we did not control for other possible ocular risk factors such as axial length and corneal diameter, environmental factors such as maternal smoking, maternal infection and did not separate out members within the same family with nystagmus. Our study did show a wide spectrum of refractive errors in patients with nystagmus particularly high hypermetropia and high myopia compared to the normal population. There were a significantly higher proportion of patients with hypermetropic refractive errors in

albinism, idiopathic infantile nystagmus and manifest latent nystagmus compared to the control group. There was a significant amount of with-the–rule astigmatism compared to the control group. The differences in both spherical refractive error and astigmatic refractive error seen in patients with nystagmus compared to age-matched normal individuals suggests that emmetropization is affected by the disease and this study provides a platform for further research into this process.

5.5 Proposed future work

The data from these studies can be extended further and correlated with eye movement recording data to see how much further information can be obtained in terms of characterisation of different types of nystagmus. The research work carried out in all the studies in this thesis involved accurate clinical characterisation of the patients with nystagmus and this, together with the eye movement recordings data could provide a basis for further future studies. Some of the volunteers in these studies have participated in placebo-controlled medical treatment studies into nystagmus in the University of Leicester (Shery et al., 2006, McLean et al., 2007).

Optical coherence tomography offers another exciting new tool in research and clinical practice and work to correlate findings from both anterior and posterior segment tomography with clinical findings will enable most clinicians who do have access to this instrumentation in their clinical practice, to investigate and diagnose different clinical forms of nystagmus better. This could also be used as a tool in monitoring visual development in children and may in the long term provide, in some

cases, an alternative diagnostic and therapeutic tool to current electrodiagnostic testing and eye movement recordings which can be cumbersome and technically difficult to perform in some individuals.

The research carried out at the University of Leicester has furthered our understanding of nystagmus. For example, the most common form of nystagmus is due to albinism and most patients with this condition have visual acuities ranging between 6/12 and 6/60, with many patients with high hypermetropic and myopic refractive errors and significant amount of with-the-rule astigmatism. We have furthered our understanding of which groups of patients with nystagmus will need early refractive screening and monitoring of refractive error and monocular deficit by community optometrists and orthoptists in order to prevent permanent visual loss in patients from lack of early treatment with both and/or occlusion treatments. The results of our research can provide health and social care services further information on how common nystagmus is, which groups of patients are more likely to need medical and social input and empower parents of patients or patients to seek suitable genetic screening or treatment with better understanding of the clinical features of their particular type of nystagmus.

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