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Clinical and Ocular Motor Characterisationof Infantile and Acquired Nystagmus Using Eye Movement Recordings

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Abstract

Title: Clinical and Ocular Motor Characterisation of Infantile and Acquired Nystagmus Using Eye Movement Recordings

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Our aim was to characterise the ocular motor abnormalities in infantile (IN) and acquired nystagmus (AN) using eye movement recordings in order to improve diagnosis and understanding of these diseases. The first aim was to compare a genetically homogenous idiopathic IN group (*FRMD7*-IN) with albinism associated IN. The second aim was to investigate acquired pendular nystagmus (APN) due to MS along with other ocular motor abnormalities, in relation to disease severity and MS subtype.

Eye movements were recorded in all IN and AN participants (n=117). Ocular motor characteristics of the nystagmus were analysed. Other clinical features were compared including strabismus, stereopsis and anomalous head posture (AHP) in IN and the disability score and MS subtype in MS.

FRMD7-IN contained higher proportions of pendular waveform compared with albinism. Nystagmus frequency was significantly lower in albinism compared with *FRMD7*-IN. Strabismus and AHP were more frequent in albinism, and stereopsis was worse compared with *FRMD7*-IN. In MS APN coexisted with various other ocular motor deficits including gaze-evoked nystagmus, internuclear ophthalmoplegia and square wave jerks although the occurrence of these was not related to MS severity or subtype. The APN was dysconjugate mainly due to a difference in amplitude between the two eyes rather than frequency. There was no clear change in APN parameters with MS severity or subtype.

We describe for the first time the differences in nystagmus characteristics associated with albinism and *FRMD7*- IN which may be useful information in the future elucidation of mechanisms underlying the nystagmus and also in diagnosis. In MS we confirm that APN is mainly dysconjugate due to amplitude and can co-exist with various ocular motor abnormalities. Eye movement recordings can assist in differentiating various ocular motor abnormalities in IN and AN that are difficult to characterise on clinical examination.

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Last but not least, I would like to thank my family: my parents Rathna and Suryanarayana, for blessing me, my wife Radha who has always been my pillar of strength, my joy and my guiding light.

I would like to dedicate this work to my son Karthik who has been the internal strength of my life to achieve this milestone, for me to leave a good legacy behind for him to continue as a torch bearer of the family.

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1.0 INTRODUCTION

1.1 Overview

The advancement in the knowledge of neural circuitry underlying ocular motor control has been closely related to the advancements in the technology for recording eye movements. The areas involved in the circuitry of eye movements are distributed across a number of regions including the afferent visual pathway, vestibular apparatus, and neuronal centres in midbrain, pons, medulla and cerebellum. Demonstration of normal eye movements hence reflects the integrity of these centres, on the contrary abnormalities in these areas causes detectable abnormalities in the ocular motor performance.

Clinical classification of nystagmus into either infantile (previously known as congenital) or acquired nystagmus is based on the history of onset of nystagmus and presence or absence of oscillopsia. However there are reports of incidence of infantile nystagmus occurring at a later date (Gresty *et al.*, 1991) and also the presence of oscillopsia in infantile nystagmus. This can make the clinical diagnosis difficult. Eye movement recordings help to diagnose infantile nystagmus by identifying the presence of accelerating slow phases and the presence of a null region. They also help in differentiating specific forms of infantile nystagmus such as manifest latent nystagmus and infantile periodic alternating nystagmus for which the management is entirely different. The presence of dysconjugate nystagmus on eye movement recording is highly suggestive of acquired nystagmus which warrants further investigation in the form of neuroimaging.

Although there have been attempts to classify infantile nystagmus into various subcategories based on the waveforms and other ocular motor abnormality seen on

eye movement recordings, there is no consensus on the exact mechanism causing these various sub-types of infantile nystagmus. This classification uses the term ‘infantile nystagmus’ to include both idiopathic nystagmus and nystagmus associated with other sensory abnormalities such as albinism and achromatopsia. Without understanding of the underlying mechanism the treatment of infantile nystagmus is mainly empirical.

Electrodiagnostics can help in differentiating the different subtypes of infantile nystagmus such as idiopathic nystagmus. However, it has its own limitations, for example in getting accurate VEP and ERG recordings in children who are more likely to be uncooperative. The differentiation is important in view of genetic counselling and management. The Nystagmus Survey performed in Leicestershire region found the commonest causes of infantile nystagmus to be idiopathic nystagmus and nystagmus associated with albinism (Sarvananthan *et al.*, 2009). Most often nystagmus due to albinism is misdiagnosed as idiopathic nystagmus, especially ocular albinism. The diagnosis of albinism is based on clinical signs such as iris transillumination defects, foveal hypoplasia and misrouting of optic nerve at the chiasm. These signs can be missed easily even by an astute clinician. A further complication is that these clinical signs can be also seen in various other conditions. Although the gold standard test to identify these conditions is by performing genetic analysis, it is not routinely performed. This has led us to seek for new diagnostic tools which could aid in the diagnosis of albinism. Optical coherence tomography has recently been used to detect foveal hypoplasia which has assisted in the diagnosis of infantile nystagmus in adults (Thomas and Gottlob, 2012, Mohammad et al., 2011) and also in children(Lee *et al.*, 2013)

Acquired nystagmus is mainly due to neurological disease of which the most important cause is multiple sclerosis (MS). The Nystagmus Survey performed in the

Leicestershire region found the incidence of nystagmus secondary to MS to be 1.9 per 1000 (Sarvananthan *et al.*, 2009). MS is an autoimmune demyelinating disease involving multiple areas of the brain including the centres of ocular motor control causing various ocular motor deficits to be seen in these patients. Clinical differentiation of these ocular motor deficits is difficult and often missed. The importance of identifying these ocular motor deficits may help the clinician to, not only monitor the progression of the disease, but also in the initiation of proper medical management. Eye movement recordings have improved the precise diagnosis these ocular motor deficits even when the clinical signs are subtle or difficult to diagnose.

This study consisted of two sections. In the first section we consider whether eye movement recording helps to differentiate between albinism and idiopathic infantile nystagmus (IIN). In the second section of the study we analyse and characterize the various eye movement abnormalities seen in patients with multiple sclerosis based on eye movement recordings. We also try to correlate the ocular motor characteristics to the subtype of multiple sclerosis and the disability score.

1.2 Basic mechanisms of ocular motor control

To maintain steady vision and high visual acuity images must be focussed on the retina steadily. Image motion of only a few degrees of second is enough to cause significant blurring of vision (Chung and Bedell, 1996). The image motion across the retina can be caused by either eye movement of the observer or the motion of the visual object of interest. To reduce image motion on the retina five distinct subsets of eye movements have evolved. These include the vestibulo-ocular reflex (VOR), optokinetic nystagmus (OKN), the saccadic system, and the smooth pursuit system and vergence eye movements. Understanding these five functionally and anatomically distinct subtypes of ocular motor control is critical for analysing and understanding pathological eye movements.

The VOR and OKN stabilize images on the retina during head rotation by rotating the eyes to the opposite direction to the head rotation. The VOR has a shorter latency than any other visual feedback systems of less than 10msec. Due to the mechanical properties of the semi-circular canal the VOR reflex decays during sustained contractions. Hence during sustained head rotation the compensatory eye movements gradually shift from VOR to OKN which is driven by visual cues.

Saccadic, smooth pursuit and vergence eye movements shift gaze to bring or keep an object of interest on the fovea. Saccadic eye movements are generally conjugate and are aimed at bringing an object of interest in the retinal periphery onto the fovea. Smooth pursuit eye movements help keep the object of interest on the fovea by using the visual feedback. Smooth pursuit can also lead to suppression of the VOR while tracking object with head movements. Vergence eye movements are horizontal dysconjugate eye movements which are generated through the disparity between the images or as a part of accommodation.

Motor neurons of the third, fourth and sixth cranial nerves are the final output for the control of eye movements. They encode all vestibular-optokinetic, saccadic and pursuit signals.

1.3 The neural integrator

To maintain clear vision of an object located in eccentric position, the eyes must be held steadily in this position in the orbit. This requires the tonic contraction of the extraocular muscles to overcome the elastic forces imposed by the orbital tissues, which would tend to bring the eyes to a central position. To achieve this tonic contraction the ocular motor system must be able to generate a signal proportional to the desired eye position. The premotor neurons encode the velocity signal from the vestibular-optokinetic, saccadic and smooth pursuit system. These velocity signals have to be converted to the position signal for the ocular motor neurons. This mathematical integration of converting the velocity command to the positional command must be performed by the neural integrator (Nakamagoe *et al.*, 2000). For the horizontal eye movements the neural integration depends on the Nucleus Prepositus Hypoglossi-Medial Vestibular Nucleus (NPH-MVN) region in the caudal Pons and medulla (Arnold *et al.*, 1999). For the vertical gaze holding the Nucleus of Cajal plays ananalogous role (Lee *et al.*, 2012). In addition the flocculus region in the cerebellum also contributes to both vertical and horizontal neural integrators.

1.4 Nystagmus

Nystagmus consists of repetitive to and fro movements of the eyes. The term nystagmus derives from the Greek word ‘νυσταγμός‘(*nystagmos*) which is used to describe the head movements of a person in a drowsy state; typically a slow downward drift followed by a corrective quick upward movement. Nystagmus with this appearance, i.e. slow phases followed by corrective quick phases, are called *jerk nystagmus*. Nystagmus is described as *pendular* when it consists of sinusoidal oscillations.

1.4.1 Classification

The two broad categories of classification of nystagmus are into either : (i) infantile (or congenital) nystagmus which is usually seen within a few weeks after birth or (ii) acquired nystagmus which is secondary to ocular or neurological pathology.

The CEMAS classification

A workshop sponsored by the National Eye Institute of the United States of America developed a classification for eye movement abnormalities and strabismus during 1998-1999. This workshop classified eye movement disorders and strabismus in a systematic manner for use in clinical research. In this classification, nystagmus is listed at Serial Number 8 along with other ocular motor oscillations. In the published document that emerged from the proceedings of the workshop, it was noted that until then interdisciplinary agreement on definitions, contents and classification of eye movement disorders did not exist. The workshop was the first attempt to reach a consensus in this respect. The following is the ***C***lassification of ***E***ye ***M***ovement

Abnormalities and ***S***trabismus, emerged at the workshop, more commonly known by the acronym ***CEMAS***.

NYSTAGMUS AND OTHER OCULAR MOTOR OSCILLATIONS

a. Physiological Fixational Movements

1. Microtremor
2. Slow Drifts
3. Microsaccades

b. Physiological Nystagmus

1. Vestibular Nystagmus
2. Optokinetic Nystagmus
3. Eccentric Gaze Nystagmus

c. Pathologic Nystagmus

1. Infantile Nystagmus Syndrome (INS)
2. Fusion Maldevelopment Nystagmus Syndrome (FMNS)
3. Spasmus Nutans Syndrome (SNS)
4. Vestibular Nystagmus
    a. Peripheral Vestibular Imbalance
    b. Central Vestibular Imbalance
    c. Central Vestibular Instability
5. Gaze-Holding Deficiency Nystagmus
    a. Eccentric Gaze Nystagmus
    b. Rebound Nystagmus
    c. Gaze-Instability Nystagmus (“Run-Away”)
6. Vision Loss Nystagmus
    a. Pre-chiasmal
    b. Chiasmal
    c. Post-chiasmal
7. Other Pendular Nystagmus and Nystagmus Associated with Disease of Central Myelin

a. Multiple sclerosis, Peliazaeus-Merzbacher disease, Cockayne's syndrome, peroxisomal disorders, Toluene abuse.

b. Pendular Nystagmus Associated with Tremor of the Palate.

c. Pendular Vergence Nystagmus Associated with Whipple's disease.

8. Ocular Bobbing (Typical and Atypical)
9. Lid Nystagmus

d. Saccadic Intrusions and Oscillations

1. Square-Wave Jerks and Oscillations
2. Square-Wave Pulses
3. Saccadic Pulses (Single and Double)
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

The *CEMAS* is comprehensive and it includes most of the forms of nystagmus; however, it does have drawbacks. It is based mainly on the waveform observed on eye movement recordings and is hence it is not possible to use the CEMAS in routine clinical practice. It pools together different types of infantile nystagmus such as idiopathic infantile nystagmus (IIN), nystagmus associated with albinism and achromatopsia since all these three types of IN show similarity in having accelerating slow phase on eye movement recording. This limits the use of the CEMAS for the clinician in clinical practice since, for example, IIN and achromatopsia or albinism are obviously distinct clinical conditions and have different implications for the patient.

1.5 Prevalance of nystagmus

Various studies have reported the prevalence of nystagmus in the general population to be 1/20000, 1/6500, 1/1500 and, 1/1000 (Stewart-Brown and Haslum, 1988, Forssman and Ringnér, 1971, Norn, 1964). These studies included only children and young adults and hence did not include acquired nystagmus. Sarvananthan et al. (Sarvananthan *et al.*, 2009) conducted a population based nystagmus survey to detect the incidence of both infantile and acquired nystagmus. They found the prevalence of nystagmus in the general population to be 24 per 10000 in Leicestershire, UK.

The Leicester group in 2006 found a novel gene which caused idiopathic infantile nystagmus- the *FRMD7* gene (Tarpey et al., 2006). The finding of the gene causing idiopathic infantile nystagmus gave us a unique opportunity to study the phenotypical characteristics of nystagmus in patients with the mutation in the *FRMD7* gene and those without mutation in the gene (Thomas et al., 2008). Phenotypical differences were found in the patients with and without *FRMD7* mutation, with both these group of patients clinically having normal ocular examination and electrodiagnostic tests including VEP (Visual evoked potential) and ERG (electroretinogram).

In 2009 the nystagmus survey conducted by the Leicester group found the most common type of infantile nystagmus to be nystagmus secondary to albinism, and amongst the acquired group to be secondary to multiple sclerosis.

Charles et al (Charles *et al.*, 1993) reported 20% of the affected male with nystagmus from UK pedigrees had been previously misdiagnosed as IIN. This led us to conduct the first part of research to find difference between nystagmus due to albinism, which was the commonest type seen in our survey and the genetically homogenous group of

patients with *FRMD7* mutation, both clinically and also using the eye movement recordings.

The Leicester centre is one of the largest referral centres in UK for patients with nystagmus. We get referrals from all over UK for diagnosing and management of ocular conditions due to various causes of acquired nystagmus which causes oscillopsia which can incapacitate patients. This study was conducted to see the common oculomotor abnormalities seen in patients with different subtypes of MS so that the treatment could be more a targeted approach rather than a empherical treatment and also to see if the EDSS score correlates with the oculomotor abnormality.

1.6 Use of eye movement recordings

Eye movement recording forms a basic part of the neuroscience research. The technique of examining the eye movements has evolved over the centuries with the earliest method based on observation of afterimages to describe the slow and fast phase of vestibular nystagmus. In the early 19th century, Huey (Huey, 1900), and Delabarre (Delabarre, 1898) used a device consisting of a lever attached to a plaster eyecup to record eye movements. The double Purkinje image (DPI) eye tracker which uses light reflection from the cornea and a lens to measure the orientation of the eyes was later developed.

Currently the common types of eye tracking equipment used are the electrooculogram (EOG), infrared oculography, the scleral search coil and video-oculography. EOG and infrared oculography can record eye movements in the horizontal and vertical planes; however these methods cannot measure the torsional eye movements. Scleral search coil and 3D video-oculography are capable of

measuring torsional eye movements in addition to vertical and horizontal eye movements. A description of the various types of equipment with advantages and limitations follows:

1.6.1 The electro-oculogram (EOG)

This method of recording eye movements is based on the feature that the human eye is an electrical dipole. Mowrer et al.(Mowrer et al., 1936) showed that EOG is primarily caused by electrical dipole between cornea and retina, which moves with the eye.

The voltage at the retina is more negative than at the cornea with a potential difference of about 6mV. Since the axis of this dipole is in the same axis as the optical axis the dipole rotates with the rotation of the eyes. Hence movement of the eye causes a small difference in the potential with reference to the skin electrodes that are placed on the temporal canthus and on the upper and lower eye lid. A movement to the right increases the surface potential at the temporal canthus of the right eye and decreases the surface potential at the temporal canthus in the left eye. A similar phenomenon occurs for the vertical eye movements. The main advantage of EOG is its ability to record eye movements with the eyes closed. The main disadvantage of EOG is the presence of noise due to other electrical activity in the body such as that cause by eye blinks.

1.6.2 The search coil method

The search coil system can measure eye movements in all the three different planes. It uses magnetic coils moulded onto the soft contact lens to measure the eye

movements. The disadvantages of the sclera coil are the noise of system and invasiveness of the method.

1.6.3 Video oculography

Advancement of the electronic data processing technology has made the video-oculography a popular tool for eye movement recording. Most systems record the eye movements in two planes but some systems can record all three planes (horizontal, vertical and torsional) of eye movements. These are useful for recording eye movements in subjects with conditions such as seesaw nystagmus and certain types of acquired nystagmus which has a torsional component. The 3D systems have the disadvantage of recording at a lower sampling rate and usually with more noise.

1.6.4 2D Video oculography (the EyeLink system)

EyeLink I is the pupil tracking 2D video recording system (SMI Research GmbH, Berlin, Germany) that was mainly used in this study to record and analyse the eye movements in patients with nystagmus. The measurements from EyeLink have very low noise level (<0.01 root mean square) compared to other methods of eye movement recording and the data can be calibrated on line or off line for further analysis. Both horizontal and vertical eye movement recording can be performed using this instrument.

1.7 Nystagmus waveforms

Classification of nystagmus is not possible with a simple clinical examination, which prevents an accurate diagnosis, but requires eye movement recording. Based on the data of eye movement recordings Dell'Osso and Daroff (Dell'Osso and Daroff, 1975) classified the waveforms of patients with infantile nystagmus into three main groups (**Figure-1.1**):

i. Pendular nystagmus
ii. Jerk nystagmus
iii. Dual jerk nystagmus

The jerk group is further divided into unidirectional and bidirectional jerk based on the direction of the quick phases present in each cycle. Based on the waveform characteristics Dell'Osso and Daroff proposed the following definition for both pendular and jerk nystagmus:

Pendular nystagmus: An ocular motor instability resulting in periodic motion of the eye such that the waveform is approximately sinusoidal. Sometimes small breaking saccades can be seen on the peaks which correspond to the target foveations.

Jerk nystagmus: An ocular motor instability resulting from a pathological slow eye movement defect which causes the eyes to drift away from the target and a corrective saccade in the opposite direction to overcome this.

Dual Jerk Nystagmus: It a simultaneous mixture of jerk and pendular nystagmus with the superimposition of a rapid small amplitude sinusoidal oscillation upon the larger amplitude jerk nystagmus.

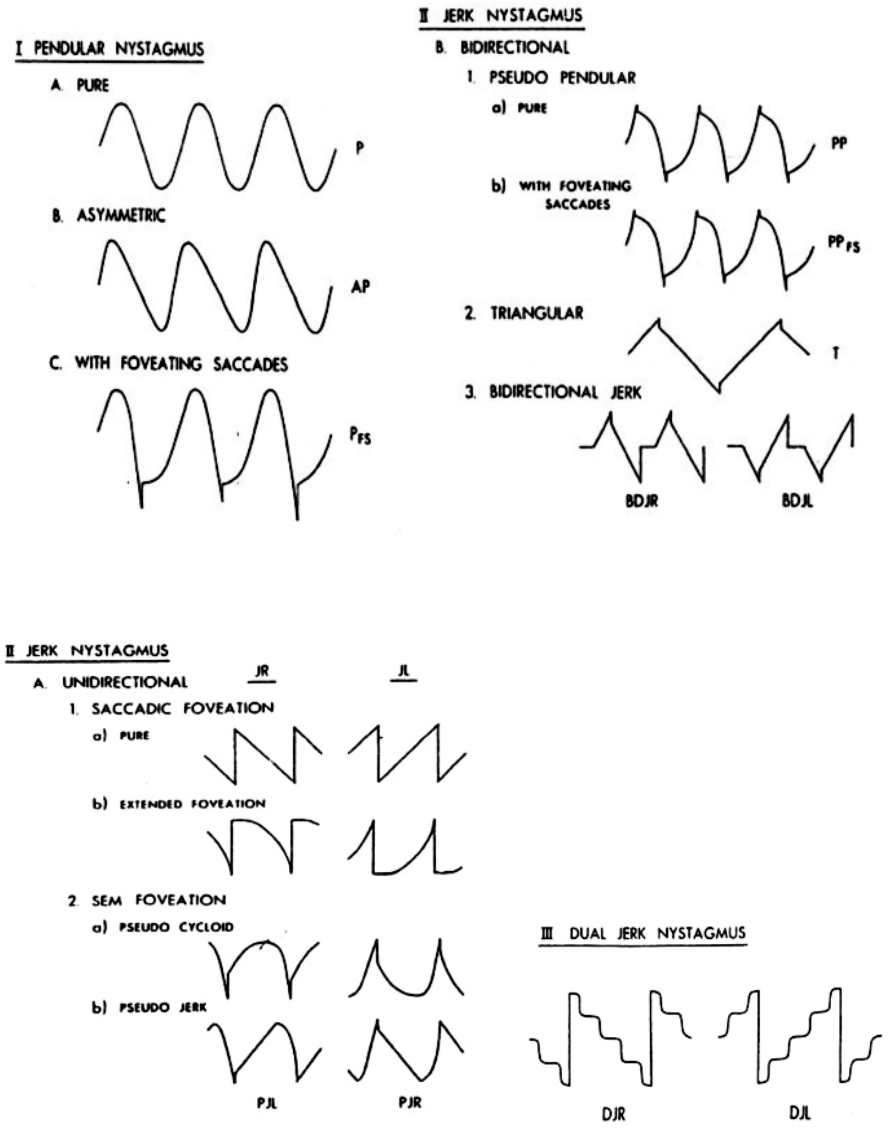


Figure-1.1 *An illustration of the various waveforms commonly seen in infantile nystagmus. Reproduced from Dell'Osso* & Daroff, 1975

Eye movement recordings are extremely helpful in diagnosing the various other forms of infantile nystagmus such as manifest latent nystagmus and infantile periodic alternating nystagmus. The differentiation of these forms of nystagmus from infantile nystagmus syndrome is very important as the treatment for these disorders are entirely different.

1.8 Manifest Latent Nystagmus (MLN)

Manifest latent nystagmus is most commonly associated with infantile or childhood onset esotropia as well as ambylopia. MLN is defined as jerk nystagmus that develops at an early age and increases with monocular viewing, triggered by occlusion of one eye. Previously latent nystagmus was distinguished from MLN where no nystagmus was detected when both eyes were open. However, it has been shown that in cases clinically diagnosed as “latent nystagmus”, nystagmus is seen on eye movement recordings even when both eyes are open (Dell'Osso *et al.*, 1979). Hence manifest latent nystagmus/latent nystagmus is considered as a single entity (MLN).

Characteristically, the amplitude of MLN decreases in adduction and increases in abduction, with the fast phase of the nystagmus beating towards the side of the fixating eye or open eye. MLN has a distinctive slow phase with an exponentially decreasing or linear velocity in all positions of gaze as shown in **Figure-1.2**. As nystagmus decreases in adduction patients with MLN frequently develop an anomalous head posture (AHP) towards the side of the fixating eye when the fellow eye is occluded. The AHP changes to the other side on alternating monocular occlusion which helps in the diagnosis of MLN. If patients with MLN have alternating fixation the head turn can change spontaneously, depending upon which eye is fixing.

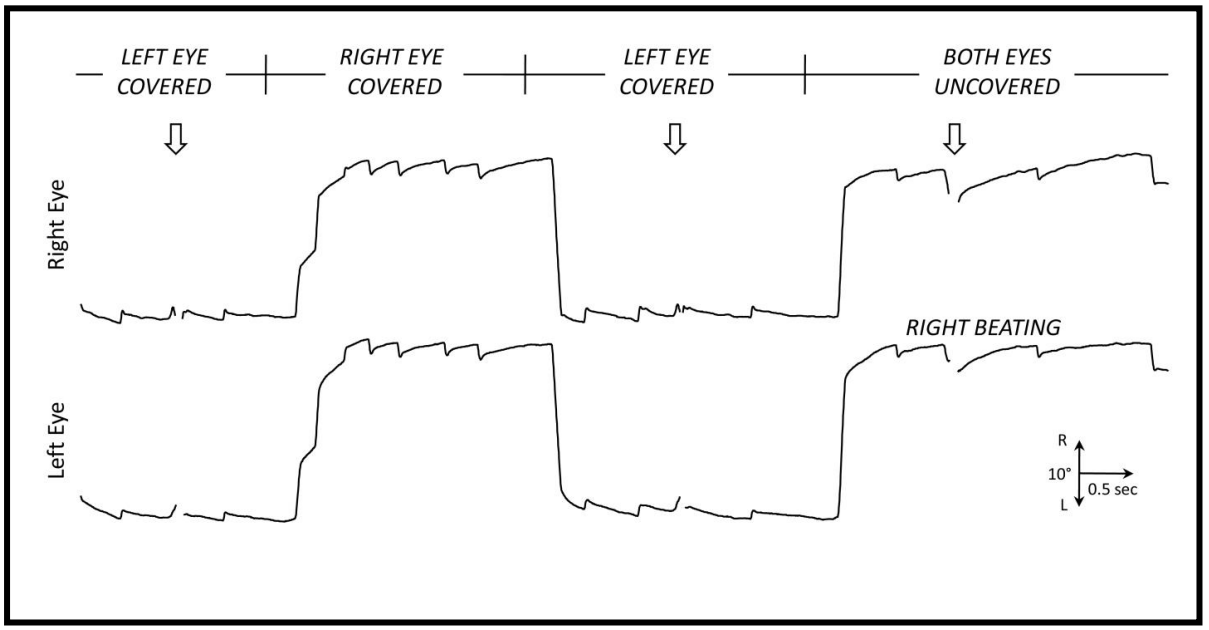


Figure-1.2 *Original horizontal eye movement recordings of both eyes of a patient with manifest latent nystagmus (MLN). Eye movements to the right are represented by an upward deflection, and eye movements to the left by a downward deflection. The fast phase is always beating towards the open eye (to the right with the left eye covered and to the left with the right eye covered). When both eyes are open the direction of the fast phase is towards the dominant left eye. The velocity of the slow phase is decelerating or linear. Arrows indicate blinks.*

1.9 Periodic Alternating Nystagmus

Infantile periodic alternating nystagmus (PAN) is classified as a variant of infantile nystagmus according to the CEMAS classification. Eye movement recording shows a characteristic active phase with right/left beating nystagmus followed by a quite transition phase and then an active left/right beating nystagmus (**Figure-1.3**). The frequency of infantile PAN is variably reported in the literature. Gradstein (Gradstein *et al.*, 1997) et al. in a retrospective analysis of approximately 200 infantile nystagmus patients with and without sensory deficits found 18 patients (9%) with a diagnosis of PAN. Five of these 18 patients had albinism. AHP was seen in 16 of the 18 patients. Shallo-Hoffman et al. (Shallo-Hoffmann and Riordan-Eva, 2001) in a prospective study involving 18 patients with infantile nystagmus without sensory deficits found that seven patients (39%) had PAN. Abadi and Pascal (Abadi and Pascal, 1994b) found 12

patients with PAN in 32 patients with oculocutaneous albinism (37.5%). These 12 patients did not exhibit AHP nor had dampening of nystagmus on convergence.

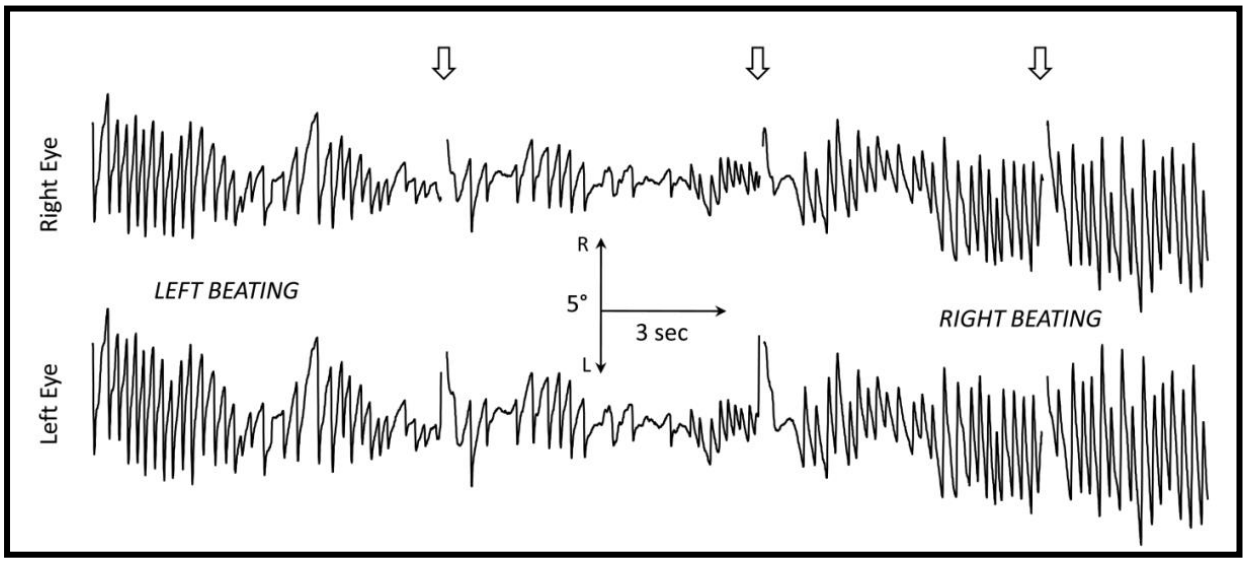


Figure-1.3 *Original eye movement recordings of a patient with idiopathic infantile periodic alternating nystagmus (PAN) of the right and left eye showing left beating nystagmus, a quiet phase and right beating nystagmus. Eye movements to the right are represented by an upward deflection, and eye movements to the left by a downward deflection. Arrows indicate blinks*

2.0 Diagnosis of idiopathic infantile nystagmus and ocular albinism: a clinical challenge

Nystagmus in childhood or infantile nystagmus poses a real challenge to the paediatric ophthalmologist, not only in terms of diagnosing the cause for the nystagmus but also in answering the long list of questions that follow from the anxious parents about the child's condition. The two most common types of nystagmus seen in childhood are idiopathic infantile nystagmus (IIN) and nystagmus associated with albinism. Although often the diagnosis of albinism can be apparent, it is not always so clear. As in case of ocular albinism, as the name suggests, the manifestations are mainly ocular which can be very subtle to detect clinically. The aim of this study was to investigate the difference in nystagmus in IIN and albinism using eye movement recordings with a view to improving diagnosis and also to understand the mechanism of nystagmus in these two different conditions.

2.1 Infantile nystagmus

Pathological infantile nystagmus consists of involuntary periodic to and fro oscillations of the eye. It usually presents within the first 3 months of life, however onset as late as 12 months to 10 years has been reported in a few cases (Abadi and Bjerre, 2002). Infantile nystagmus is often described in the literature as being a jerk nystagmus with an accelerating slow phase; however it may show different waveforms that usually vary with eccentricity. Frequently, infantile nystagmus consists of underlying pendular oscillations interrupted by regularly occurring foveating saccades (quick phases). Nystagmus intensity often changes with the direction of gaze with the region of lowest nystagmus intensity and longest foveations periods being known as

the ‘null region’. This is often the preferred region of fixation for optimal vision with the head position being used to maintain vision in the null region. Consequently, patients often exhibit an anomalous head posture (AHP) if the null region is eccentric.

Typically, the oscillation drifts towards the null region with the drift becoming accentuated further away from the null region. This result in the quick phases usually beating away from the null region with slow phases often accelerating towards the null region. The movements in infantile nystagmus are mainly in horizontal plane although there may be vertical or torsional components. In a nystagmus survey performed in the UK by Sarvananthan et al.(Sarvananthan *et al.*, 2009), two of the most common forms of infantile nystagmus were IIN and nystagmus associated with albinism. Both IIN and nystagmus associated with albinism are classified as infantile nystagmus syndrome in the CEMAS classification and share the same clinical characteristics as summarized in **Table-2.1**.

Clinical characteristics of infantile nystagmus

- Onset in early infancy
- Nystagmus is mainly horizontal and conjugate
- Eye movement recordings show either pendular or jerk waveforms
- Jerk nystagmus waveforms have a characteristic accelerating slow phase
- Presence of anomalous head posture, strabismus, refractive errors associated with nystagmus
- Decreased amplitude of nystagmus at the null region
- Dampening of nystagmus on convergence
- The intensity of nystagmus increases with fixation and decreases with sleep or inattention

Table 2.1 *Summary of clinical characteristics of infantile nystagmus*

2.2 Idiopathic Infantile Nystagmus (IIN)

IIN is one of the most common types of infantile nystagmus. The incidence of IIN in the Leicestershire nystagmus survey has been reported to be as 1.9 per 10000. IIN is a diagnosis of exclusion. A brief description of the genotype and phenotype of IIN is as below.

2.2.1 Genotypical characteristics of IIN

Idiopathic infantile nystagmus is a genetically heterogeneous disorder. The different modes of inheritance are either autosomal dominant (MIM 164100), autosomal recessive (MIM 257400) or X-linked inheritance patterns (MIM 31700). The most common form of inheritance is X-linked with incomplete penetrance (Kerrison *et al.*, 1999).

2.2.1.1 Autosomal dominant IIN

To date three different loci have been implicated to contain genes causing autosomal dominant inheritance. These include 6p12 (NYS2), 7p11 (NYS3) and 13q (NYS4). The pedigree shows a male to male transmission.

- The causative gene on loci 6p12 was mapped to an 18cM region between D6S271 and D6S455 by haplotype analysis (Kerrison *et al.*, 1999).

- The 7p11 locus causing IIN was found due to balanced translocation between chromosome 7 and 15 (7; 15) (p11.2;q11.2) (Patton *et al.*, 1993).

- Linkage analysis of another family with infantile nystagmus found the locus on chromosome 13 (13q31-q33). It is assigned NYS4. Familial vestibulo-cerebellar disorder was seen in this family (Ragge *et al.*, 2003).

2.2.1.2 Autosomal recessive IIN

A pedigree with autosomal recessive mode of inheritance (MIM257400) has been reported, however no definitive loci has been identified.

2.2.1.3 X-Linked IIN

The most common mode of inheritance seen in families with IIN is X-linked (NYS1). Irregularly dominant pattern of X-linked inheritance is common, although some pedigrees support X-linked recessive inheritance (Self et al., 2006, Guo et al., 2006) The penetrance is full in males and in obligate female carriers the penetrance can vary from 30% to 100% (Kerrison et al., 1999, Self et al., 2006, Cabot et al., 1999, Zhang et al., 2005). Two distinct loci, Xq26-q27 (Kerrison *et al.*, 1999) and Xp11.4 (Cabot *et al.*, 1999), have been reported for X-linked dominant IIN. The X-linked recessive IIN is also mapped on the Xq26-q27 region (Self et al., 2007, Zhang et al., 2005).

Tarpey *et al.* (Tarpey *et al.*, 2006) found 22 mutations in a novel gene called *FRMD7* (xq26.2)(NYS1) which is the major cause of X-linked IIN. Subsequently, various investigators have found many more mutations in the FERM domain (Schorderet et al., 2007, Self et al., 2007, Zhang et al., 2007). These mutations are clustered around the B41 and FERM-C domain. It is thus possible to genetically screen patients with X-linked pattern of inheritance by performing *FRMD7* gene screening. Sequence analysis of exons and splice sites are used to confirm mutations in *FRMD7* gene. The frequency of detection of mutation by this method is between 80-90%.

2.2.2 Phenotypical characteristics of IIN

The phenotypical characteristics of IIN patients with X-linked (Thomas *et al.*, 2008) and an autosomal dominant mode of inheritance (Kerrison *et al.*, 1998) have been studied. Thomas *et al.* compared the phenotypical characteristics of patients with and without mutation in the *FRMD7* gene causing X-linked IIN. They compared 90 patients

with mutations in the gene with 48 patients without mutations, and in addition investigated 58 female obligate carriers. Kerrison *et al.* also described the phenotypical characteristics in a single large family with autosomal dominant IIN linked to chromosome 6p12. The family consisted of 28 affected and 30 unaffected subjects. Fourteen patients underwent detail clinical examination.

Visual acuity, strabismus, AHP, stereopsis, refractive error, colour vision and predominant waveform on eye movement recording have also been studied in IIN by various groups:

i. **Visual acuity**: In patients with and without *FRMD7* mutations, visual acuity was similar with a median visual acuity of 6/9 (Thomas *et al.*, 2008). In patients with autosomal dominant IIN visual acuity ranged from 6/9 to 6/30. Forssman *et al.*(Forssman, 1971) reported normal or near normal visual acuity in more than one third of their subjects with IIN. Abadi *et al.* (Abadi and Pascal, 1991) found the visual acuity varied from 6/36 to 6/6 in a study involving 11 patients with IIN.

ii. **Strabismus:** The prevalence of strabismus found in patients with *FRMD7* mutations was 7.8% and in the non-*FRMD7* patients was 10% (Thomas *et al.*, 2008). Strabismus was seen in 36% of autosomal dominant IIN patients (Kerrison *et al.*, 1998). In contrast, Self et al. (Self *et al.*, 2007) reported prevalence of strabismus in patients with *FRMD7* mutation to be as high as 44%. Forssman *et al.*(Forssman, 1971), Brodsky *et al.* (Brodsky and Fray, 1997), Gelbart & Hoyt (Gelbart and Hoyt, 1988) and Hertle *et al.* (Hertle *et al.*, 2002) reported the prevalence of strabismus in patients with IIN to be 16%, 17%, 23% and 33%, respectively.

iii. **Anomolous head posture (AHP):** AHP was absent or less than 5° in 85% of patients in *FRMD7* group compared to 49% in the non-*FRMD7* group (Thomas *et*

al., 2008). Significant AHP of more than 15° was noted in 27% of the patient in non-*FRMD7* group compared to none in the *FRMD7* group (Thomas *et al.*, 2008). Hertle *et al.* (Hertle *et al.*, 2002) and Abadi *et al.* (Abadi and Whittle, 1991) in separate studies involving patients diagnosed as IIN found the incidence of AHP to be 19% and 53%, respectively.

iv. **Refractive Status:** The refraction in patients with autosomal dominant IIN was hyperopia in 50% of patients, myopia in 42%, and astigmatism in 67%. Hyperopia and myopia were less than 3 diopters, and astigmatism less than 2 diopters, with only 2 patients having astigmatism between 2 to 4 diopters. Natan *et al.* (Nathan *et al.*, 1985) and Dickinson and Abadi *et al.*(Dickinson and Abadi, 1984) found the mean spherical equivalent refractive error was more hyperopic in children with albinism than in those with IIN.

v. **Colour vision:** This was found to be normal in patients with IIN (Thomas *et al.*, 2008).

vi. **Predominant waveform:** Pendular nystagmus was commonly seen in *FRMD7* group, and the amplitude of nystagmus was gaze dependent and lower in the primary position compared to the non-*FRMD7* group. Hertle *et al.* (Hertle *et al.*, 2002) found jerk nystagmus to be commonly associated with IIN. Large intrafamilial variation in visual acuity, strabismus, and nystagmus waveform was noted in both X-linked and autosomal dominant inherited IIN.

Female Carriers

In female carriers of X-linked IIN associated with mutations in *FRMD7*, 50% were affected clinically (Thomas *et al.*, 2008). The median visual acuity was better in affected females than males. None of the female carriers had strabismus or anomalous

head posture. Eye movement recordings showed identical features as seen in affected male patients (Thomas *et al.*, 2008).

2.3 Albinism

Albinism is one of the most common conditions associated with infantile nystagmus. The incidence of albinism in the Leicestershire Nystagmus Survey has been reported to be 2.5 per 10,000. The diagnosis of albinism is based on the clinical findings and findings on visual evoked potential. A brief description of the genotype and phenotype of albinism follows.

2.3.1 Genotypical characteristics of albinism

Most cases of albinism have associated nystagmus. With advancements in molecular genetics the diagnosis of albinism is no longer just based on clinical observations. In the past the classification of albinism was based on the phenotypical characteristics into either oculocutaneous or ocular albinism. With molecular genetics it is possible to diagnose various subtypes of albinism on the basis of genetic defects. This has led to a reclassification of albinism into varies subcategories. However, unfortunately not many centres offer genetic testing in routine clinical settings.

2.3.1.1 Oculocutaneous albinism (OCA):

Oculocutaneous albinism (OCA) follows an autosomal recessive inheritance pattern. It is divided into syndromic and non-syndromic. Syndromic OCA usually involves other systems in addition to hypopigmentation of the skin and the hair. The common causes of syndromic OCA include Hermansky-Pudlack syndrome, Gricelli syndrome and Chediack-Higashi syndrome.

2.3.1.2 Ocular albinism:

The different modes of inheritance of ocular albinism are X-linked recessive (Nettleship-Falls type) (OMIM 300500) and autosomal recessive (OMIM 203310). X-linked ocular albinism is categorized as ocular albinism type 1 (OA1).

X-Linked ocular albinism

The locus for X-linked ocular albinism is situated on short arm of X chromosome (Xp22-3) (Bergen et al., 1990, Bergen et al., 1991, Schnur et al., 1991, Charles et al., 1992b, Charles et al., 1993). GPR143 (OA1) is the only gene known to be associated with ocular albinism. Carrier detection of X-linked OA is possible using linked DNA markers (Charles *et al.*, 1994).

Autosomal recessive ocular albinism (AROA)

AROA is genetically heterogeneous. Genetic analyses in patients with AROA have shown abnormalities in either the tyrosinase gene (chromosome 11) or on the P gene (chromosome 15) which are found in oculocutaneous albinism (OCA), and therefore AROA represents a form of OCA. Phenotypically they also have mild characteristics of both oculocutaneous albinism type 1 and type 2 (Fukai *et al.*, 1995). There may be other genes responsible for AROA which are yet to be identified (Fukai *et al.*, 1995).

Contiguous gene syndromes involving the Xp22.3 region

Kallmann syndrome (Bouloux *et al.*, 1993), X-linked Ichthyosis (Sunohara *et al.*, 1986), X-linked recessive chondroplasia punctata (Meindl *et al.*, 1993), X-linked ocular albinism with late onset deafness (OASD) (Winship *et al.*, 1993) have been linked to the OA1 gene.

Åland islands disease, an X-linked inherited disease was initially referred as OA2, but in this disease the routing of the optic nerves is normal compared to the excessive decussation seen in albinism. It is caused by mutation in the CACNA1F gene. X-Linked incomplete Congenital Stationary Night Blindness (CSNB2A) is also caused due to the mutation in the same gene. The common findings seen in patients with Åland islands disease are decreased visual acuity, nystagmus, high myopia, protan colour vision defect, fundal hypopigmentation and defective dark adaptation (FORSIUS and ERIKSSON, 1964) .

The various abnormalities and the chromosome location of these different types are listed in **table-2.2**.

Oculocutaneous albinism

Non Syndromic OCA

OCA1 (MIM 606933)	Tyrosinase gene (TYR)
OCA1A(MIM 203100)	
OCA1B(MIM 606952)	
OCA temperature sensitive	
OCA minimal pigment	
OCA2(MIM 203200)	P gene (P)
OCA3(MIM 203290)	Tyrosinase related protein-1gene (TYRP1)
OCA4(MIM 606574)	SLC45A2,MATP

Syndromic OCA

Hermansky pudlak syndrome (MIM 203300)

HPS1 (MIM 604982)	HPS1 gene
HPS2 (MIM 603401)	Adaptin ß-3A gene (ADTB3A)
HPS3(MIM 606118)	HPS3 gene
HPS4 (MIM 606682)	HPS4 gene
HPS5 (MIM 607521)	HPS5 gene
HPS6 (MIM 607522)	HPS6 gene
HPS7 (MIM 607145)	Dysbindin gene (DTNBP1)
HPS8 (MIM 609762)	BLOC1 subunit 3 gene (BLOC1S3)

Chediak-Higashi syndrome (MIM 214500) CHS1 gene (CHS1)

Griscelli syndrome

GS1 (MIM 214450)	Myosin 5A gene
GS2 (MIM 607624)	RAB27A gene
GS3 (MIM 609227)	Melanophilin/SLAC2A gene

Ocular Albinism

X-Linked ocular albinism	GPR143 (OA1)
Autosomal recessive ocular albinism (AROA)	no single gene found

Table-2.2 *List of different types of albinism and their chromosomal abnormalities.*

2.3.2 Phenotypical characteristics of albinism

In contrast to IIN, where nystagmus is the main visual phenotypical characteristics, albinism is associated with a variety of phenotypical characteristics that are found throughout the visual pathway as well as in pigmentation of the hair and skin. In albinism the phenotypical presentation depends on the type of albinism either oculocutaneous or ocular albinism. The visual acuity is between 6/36 and 6/60 (King and Summers, 1988). Other ocular abnormalities commonly seen in albinism are iris transillumination, foveal hypoplasia and abnormal optic nerve crossing at chiasma. The refractive errors in albinism are generally abnormal, with high with-the-rule astigmatism being frequently encountered (Spedick and Beauchamp, 1986, Stark, 1987, Dickinson and Abadi, 1984, Nathan et al., 1985).

The other anterior segment anomalies commonly seen in albinism are anterior segment dysgenesis (van Dorp et al., 1984, Hayakawa et al., 1986) in the form of posterior embryotoxon, Axenfeld's anomaly and megalocornea. The posterior segment findings seen in patients with albinism are optic disc hypoplasia/dysplasia, tilted disc and optic disc colobomas (Spedick and Beauchamp, 1986). The nystagmus in patients with albinism has been described as being similar to IIN with an exponential slow phase velocity seen on eye movement tracing. This was before recent developments in genetic determination of IIN subtypes. In albinism the incidence of periodic alternating nystagmus has also been described as being higher (Abadi and Bjerre, 2002).

In patients with ocular albinism normal pigmentation of the skin and the hair is seen. The ocular findings are identical to that seen in patients with OCA. However there is a considerable heterogeneity in the presentation of these findings. The female carriers have a fundus picture characterized by mosaic pattern of pigmentation and

depigmentation, classically termed as “mud splattered” appearance (Charles *et al.*, 1993). This pigmentary mosaicism in the fundus is a clinical manifestation of X-inactivation or Lyonization (Bassi et al., 1995). The skin and hair pigmentation is clinically normal in both patients and carriers.

The skin biopsy in affected subjects and carriers show characteristic macromelanosomes in patients with X-linked ocular albinism.

2.4 Diagnostic Challenges in differentiating between IIN and Albinism

Diagnosis of IIN is made after excluding the various other causes of infantile nystagmus. This is achieved by detail clinical examination and with the help of electrodiagnostic (ERG and VEP). It is possible even for an astute clinician to sometimes miss albinism and misdiagnose it as IIN due to the varied phenotypical presentation of albinism, especially so in those patients with good visual acuity, no iris transillumination and normal fundal pigmentation. Charles *et al.*(Charles *et al.*, 1993) reports 20% of the affected male with nystagmus from British pedigree had been previously misdiagnosed as IIN. According to Shioni *et al.*(Shiono *et al.*, 1995) 70% of patients with X-linked ocular albinism from Japanese ethnicity are misdiagnosed as having infantile nystagmus with or without macular hypoplasia.

As has been documented in various studies the most consistent findings in albinism when compared to IIN are iris transillumination defect, foveal hypoplasia, hypo pigmented fundus, optic nerve changes such as hypoplasia, dysplasia, tilted disc, disc pallor and the characteristic optic nerve misrouting at the chiasm evident on electrophysiological testing. In ocular albinism in addition the female carriers have a

characteristic “mud splattered” appearance of the fundus with varying degrees of iris transillumination.

Each of these clinical signs in itself does not amount to a clinical diagnosis of albinism. There are a number of other clinical conditions which have similar clinical signs. Iris transillumination is seen in Åland Island disease, and it can also be seen in normal individuals and with advancing age (Jay et al., 1976, Norn, 1971, Charles et al., 1992a). Iris transillumination defect is clinically not seen in most patients with ocular albinism in Afro-Caribbean and Japanese ethnicities. Foveal hypoplasia, an important clinical sign for the diagnosis of albinism and the only consistent ophthalmological finding in Afro-Caribbean’s with X-linked ocular albinism (O'Donnell *et al.*, 1978), it may also be associated with aniridia (Hittner *et al.*, 1980), Åland Island disease (O'Donnell *et al.*, 1980), or it may occur as an isolated anomaly when it is sporadically (Curran and Robb, 1976) or dominantly inherited (O'Donnell and Pappas, 1982). Foveal hypoplasia and chiasmal misrouting has also been reported in a case series of 3 patients who had nystagmus, no iris transillumination defect and normal fundal pigmentation (van Genderen *et al.*, 2006). One of the patients was diagnosed to have Kartagener’s syndrome. Ung *et al.*(Ung *et al.*, 2005) reported optic nerve misrouting recorded on pattern onset VEP recording in 15% of their patients diagnosed to have infantile stationary night blindness (CSNB). Tremblay *et al.* (Tremblay *et al.*, 1996) also reported crossed VEP asymmetry in 9 of 10 patients diagnosed with CSNB2.

The different mode of investigations to identify or diagnose the anatomical abnormalities most commonly seen in albinism and the drawbacks of these investigations are highlighted below.

2.4.1 Misrouting Of Optic Nerve

In normal subjects the nasal retina projects to the contralateral hemisphere, whereas the temporal retina projects ipsilaterally. The line of decussation that divides between the crossed and uncrossed fibers coincides normally with the vertical meridian running through fovea. In albinism a greater number of fibers from the temporal retina cross the midline at the optic chiasm, therefore the line of decussation is shifted to the temporal retina (Lund, 1965, Creel, 1971, Guillery et al., 1975).

The classical method of identifying the misrouting of optic nerve at the chiasma has been by either flash or pattern visual evoked potential. However, recently other methods such as magnetoencephalography, positron emission tomography and functional MRI have been emerged for detection of misrouting.

2.4.2 Visual evoked potential

Lund (Lund, 1965) was the first to report an abnormal decussation in albino rats in 1965. Creel *et al.* (Creel, 1971) showed for the first time abnormal visual projection in patients with albinism using VEP. The misrouting of the optic nerve can be detected by VEP examination in which monocular stimulation show a contralateral predominance in response (Creel et al., 1974, Coleman et al., 1979, Apkarian et al., 1983) **Figure-2.1**.

The stimulus used in recording VEP can be either flash or pattern-onset stimulation. Various studies have shown that flash stimulation is more reliable than pattern-onset stimulation in detecting asymmetry in infants and children (Kriss et al., 1990, Apkarian, 1992). Apakarian (Apkarian, 1992) advocates the use of flash stimulus for children less than 3 years of age and the use of both flash and pattern-onset stimulation for children between 3 and 6 years of age. Kriss et al (Kriss *et al.*, 1990) however found flash

stimulation better than pattern stimulation in the detection of asymmetry in children up to 11 years of age.

VEP recording can be analysed to detect asymmetry by various methods, both non-quantitative and quantitative. The sensitivity and specificity in detecting asymmetry varies in each of these methods. Apkarian (Apkarian, 1992, Apkarian and Shallo-Hoffmann, 1991) reported 100% detection rate when asymmetric index method was used to calculate from a 5-channel VEP recording.

Soong *et al.*(Soong *et al.*, 2000) compared the various techniques used to detect VEP asymmetry in albinism. They found a specificity of 86% and sensitivity of 71% using the asymmetric index method. According to Soong *et al.* (Soong *et al.*, 2000) using Pearson's correlation to compare the interhemispheric difference in potential between right and left eye was an efficient, practical and objective method to detect asymmetry in albinism. This technique was found to have a specificity of 81% and sensitivity of 86%. However, this method fails to discriminate between abnormal chiasmal decussation seen in albinism from anatomical defects in the chiasma such as achiasma or chiasmal hypoplasia.

Dorey *et al.* reported a study that correlated the clinical features of albinism with the electrophysiological abnormalities. VEP, with both flash and pattern onset stimulation, was performed on a wide spectrum of subjects with various severities of clinical features of albinism. They found no significant difference in pattern appearance, interhemispheric latency difference, or amplitude asymmetric index between patients with and without cutaneous signs of albinism. Subjects with more clinical features of albinism were likely to have significant VEP asymmetry. They also found inter hemispheric latency asymmetry measurement was more sensitive to detect albinism

than amplitude asymmetric index and more significantly correlated with the clinical features.

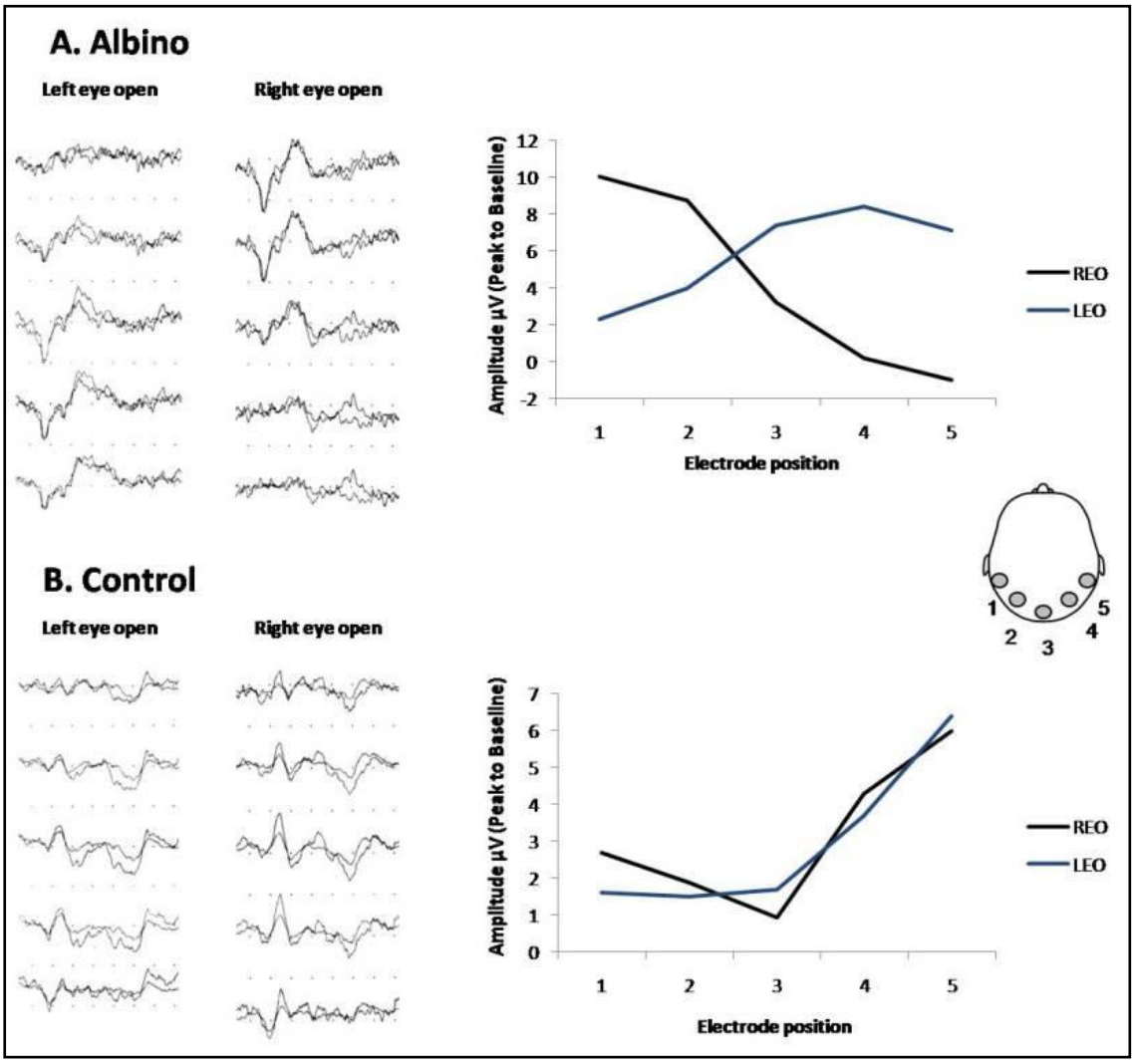


Figure-2.1 *VEP recordings in (A) a patient with albinism, and (B) a normal subject, in response to monocular left and right pattern- onset stimulation. Recordings for each electrode placed across the occiput are displayed in a diagram on the right. The electrode are placed starting from left hemisphere (electrode 1) to right hemisphere (electrode 5). The distribution of amplitude across horizontal row from left to right hemisphere is shown on right column for both groups*

2.4.3 Foveal Hypoplasia

Modelling of the fovea occurs during embryogenesis. The site of the future fovea can be identified at 22 weeks gestation by presence of rod free zone (Hendrickson and Yuodelis, 1984). The fovea is not fully developed until 15 to 45 months of age (Hendrickson and Yuodelis, 1984, Abramov et al., 1982). The stages of macular development has been divided into 5 stages by Isenberg (Isenberg, 1986).

Stage 1: an indistinct pigment area

Stages 2 and 3: the development of annular reflex

Stage 4: the appearance of the foveal pit

Stage 5: the development of the foveal light reflex.

In the nineteenth century, Elschnig described for the first time that the human albino lacked a fovea, and that the parafoveal and macular region was underdeveloped (Elschnig, 1913). Naumann *et al.* reported an absence of the foveal pit due to continuation of the 6-8 cell layers of ganglion cells as seen on histopathogical examination in a patient with albinism. Fulton *et al.*(Fulton *et al.*, 1978) performed light and electron microscopic examination of an eye from a patient with albinism and found an absence of both foveal differentiation and the rod free zone, and continuation of ganglion cell layer throughout the macula. Foveal hypoplasia can be detected clinically with the indirect ophthalmoscope or with the help of newer imaging tool such as optical coherence tomography (OCT) **(Figure-2.2).** Studies have also been performed to analyze the changes in the brain architecture in patients with foveal hypoplasia (Schmitz *et al.*, 2004).

Harvey *et al.* (Harvey et al., 2006) described a method to detect the foveal hypoplasia with indirect ophthalmoscopy. They devised a grading system to grade the

macular transparency in which grade 1 represents a transparent macula with easily visible choroidal vasculature and grade 3 represents an opaque macula through which choroidal vessels are not visible. As both luten and melanin can affect the macular transparency and albinism affects the melanin pigment only, a refined technique was found to detect the granular grey pigment, which is due to melanin pigment, at the macula with the indirect ophthalmoscope. Foveal hypoplasia was assessed by noting the presence or absence of the annular and foveolar light reflex. Harvey *et al.* (Harvey *et al.*, 2006) compared the detection rate of foveal hypoplasia by indirect ophthalmoscopy and optical coherence tomography (OCT) in patients with albinism. They found indirect ophthalmoscopy was more sensitive in detecting the foveal abnormalities than OCT.

Optical coherence tomography is a relatively new diagnostic tool that enables ultra-high resolution, non-invasive, in vivo imaging of the retinal architecture. It provides retinal images of high-resolution which can be compared to images seen on histopathology. OCT has been used in ophthalmology mainly in the diagnosis of macular diseases like AMD. With OCT, retinal images can be processed to identify and quantitatively measure intraretinal structures, which help in the early diagnosis and also in monitoring of the disease process.

OCT has been used by various groups to study foveal hypoplasia (Meyer et al., 2002, Meyer et al., 2003, Recchia et al., 2002, McGuire et al., 2003). Seo *et al.* (Seo *et al.*, 2007) in 2007 proposed a foveal grading system for using OCT in patients with albinism. He also tried to determine the correlations of visual acuity to iris transillumination, macular transparency and foveal hypoplasia grades in patients with albinism. They also found that grading foveal hypoplasia by OCT predicted the visual acuity much better than the iris transillumination or the macular transparency. Chong *et al.* used OCT to evaluate the spectrum of foveal architecture in patients with albinism.

They found the visual acuity correlating well with the degree of foveal hypoplasia as documented on OCT.

In the ophthalmology group, University of Leicester parallel studies to these ocular motor investigations were performed looking at the functional significance of foveal abnormalities in albinism measured using spectral-domain optical coherence tomography. Although not the main theme of this thesis, many of the participants in this ocular motor study were also included in these OCT investigations on which I was a key collaborator assisting in recruitment and clinical measurements and interpretation of findings (Thomas et al., 2011b, Thomas et al., 2013, Mohammad et al., 2011)). We analysed the OCT scans in forty seven patients with albinism and compared it with normal(Mohammad *et al.*, 2011). We found that the photoreceptor outer segment was the strongest predictor of best corrected visual acuity in patients with albinism. The visual acuity did not correlate to the retinal thickness at macula nor the foveal pit architecture. These results suggest that detailed SD OCT images of photoreceptor anatomic features provide a useful tool in assessing the visual potential in patients with albinism (Mohammad *et al.*, 2011).

We also performed a study to characterize and grade the spectrum of foveal hypoplasia based on different stages of arrested development of the fovea (Thomas et al., 2011b). Grading was performed using morphologic findings obtained by ultra-high-resolution spectral-domain optical coherence tomography. Best-corrected visual acuity (BCVA) was calculated for different grades of foveal hypoplasia. We found four grades of foveal hypoplasia: (i) Grade 1, shallow foveal pit, presence of ONL widening, presence of OS lengthening; (ii) grade 2, i.e. like grade 1 but with an absence of foveal pit; (iii) grade 3, like grade 2 but absence of OS lengthening; and (iv) grade 4, like grade 3 but with absence of ONL widening. There was significant difference in visual acuity (VA) associated with each grade (P<0.0001). Grade 1 was associated with the

best VA (median VA, 0.2), whereas grades 2, 3, and 4 were associated with progressively poorer VA with a median VA of 0.44, 0.60, and 0.78, respectively. The atypical features seen with foveal hypoplasia associated with achromatopsia were characterized by decreased retinal and ONL thickness and deeper foveal depth (Thomas *et al.*, 2011b).

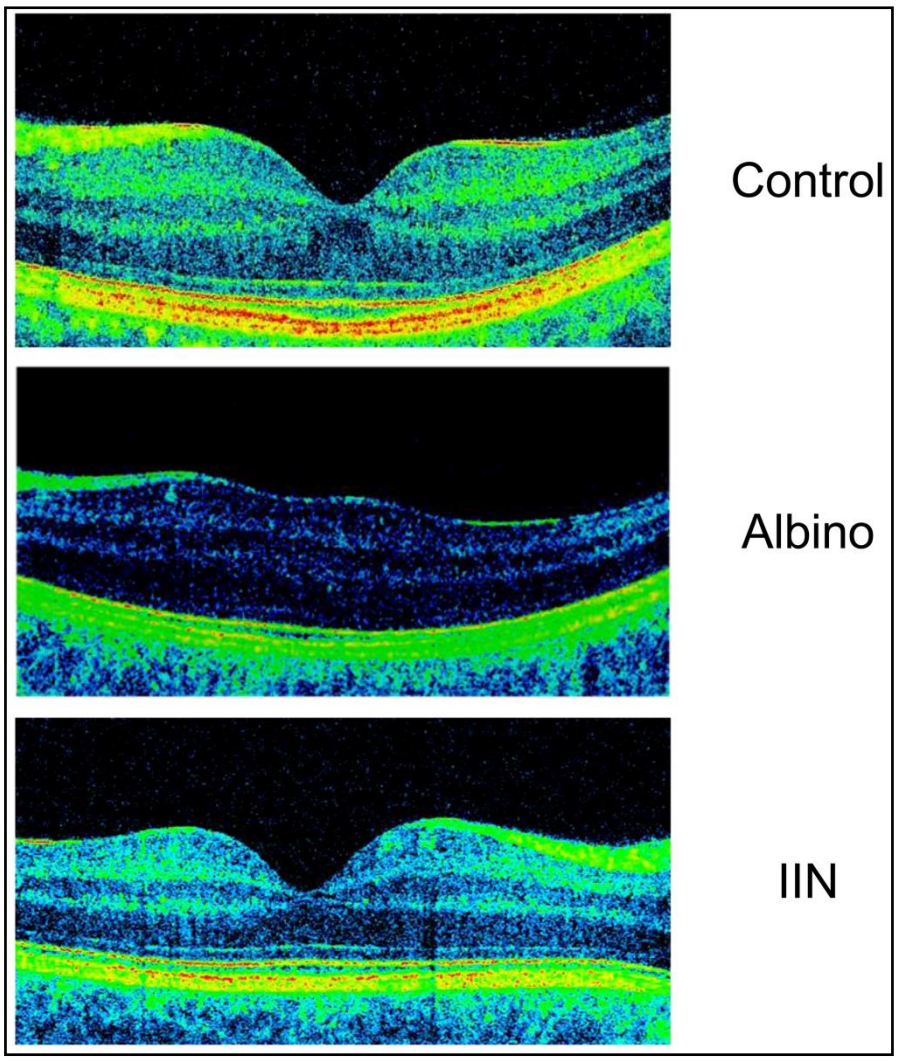


Figure-2.2 *Optical coherence tomography as seen in A) a normal subject, B) in a participant with albinism, C) and (C) in IIN. In the patient with albinism there was a diminished foveal pit and thickening of the inner retinal layers.*

2.5 Background and Aims

Nystagmus associated with albinism and IIN are grouped under a common category using the CEMAS classification as infantile nystagmus syndrome (INS). One argument for this classification is a proposed shared mechanism behind the nystagmus associated with groups in the INS category. However it is still unclear whether nystagmus associated with sensory abnormalities such as foveal hypoplasia and misrouting of the optic nerve at chiasma caused by albinism could be due to a different mechanism compared to nystagmus unassociated with clear sensory deficits. Albinism was previously grouped under the classification “sensory nystagmus” based on this supposition. In contrast IIN has little or no associated sensory abnormalities although a recent preliminary report from our Leicester Ophthalmology group suggest mild retinal deficits may exist even in patients with *FRMD7* mutation as detected by both immunohistochemistry studies and OCT findings (Thomas *et al.*, 2012). Similarly, the term used previously to describe IIN was “motor nystagmus”. However, the mechanism underlying the majority of infantile nystagmus forms is still unclear.

What was already known about IIN and albinism clinically?

Various reports in the literature have shown the clinical features of albinism and idiopathic nystagmus to be quite variable as shown in table below.

	IIN				ALBINISM			
STUDIES	VISUAL ACUITY	STRABISMUS	AHP	STEREOPSIS	VISUAL ACUITY	STRABISMUS	AHP	STEREOPSIS
Abadi et al.	+0.35 (SD 0.26)LogMAR	-	-	100%	+0.67 (SD 0.28)LogMAR	90.50%	-	4%
Brodsky et al.		17%			-	53%	-	-
Kerrison et al.	0.2-0.7 LogMAR (mode 0.4)	36%	-	-	-	-	-	-
Gradstein et al.	-	-	-	-	0.00-1.20 LogMAR	74%	62.96%	40%
Self et al.	0.1-0.5 LogMAR	44%	-	-	-	-	-	-
Thomas et al.	0.176 median LogMAR	7.80%	15%	93.40%	-	-	-	-

What we expected from the study?

The main aim of the first study is to see if the ocular motor characteristics of patients with albinism are different from that idiopathic infantile nystagmus due to mutations in the *FRMD7* gene. Although the mechanism behind the nystagmus in both groups is unclear, the genetic mutation behind both groups has been determined to some degree. This means that the nystagmus associated with all albinism patients shares a common mechanism and the nystagmus associated with *FRMD7* associated nystagmus shares a common mechanism. It is not clear, however, whether the nystagmus in the two groups is equivalent. Similar nystagmus characteristics would suggest that these two diverse groups (with and without obvious sensory abnormalities) share a common mechanism behind the nystagmus.

In addition another reason for investigating ocular motor characteristics in these two groups is to assist in the diagnosis of these conditions especially between IIN and OA where the pigmentation abnormalities may be more subtle. The diagnosis of albinism is very important in terms of genetic counselling and visual prognosis. A proper skin care can also be given to these patients to prevent skin complications due to sun exposure. Consequently, any assistance eye movement recordings could help with accurate diagnosis could have important clinical impact.

2.6 Patient and methods:

2.6.1 Patients

Fifty-two subjects with albinism (mean age 36 years, range 17-67 years) were recruited along with 83 subjects (mean age 36 years, range 3-88 years) who were clinically diagnosed with IIN and subsequently found to have mutations in the *FRMD7* gene (Tarpey *et al.*, 2006). The study fulfilled the tenets of the Declaration of Helsinki and was approved by the local ethical committee. Written informed consent was obtained from all subjects.

2.6.2 Diagnosis of Albinism and FRMD7 associated IIN

Detailed ophthalmological examination was performed on all subjects including slit lamp biomicroscopy in the dark to identify iris transillumination defects. Electrodiagnostics was performed on all the subjects according to the ISCEV standards, including both electroretinography (ERG) and visual evoked potential (VEP). ERG was performed to rule out any retinal pathology causing nystagmus and all subjects with ERG abnormalities were excluded from the study. Multi-channel VEP was performed in all the subjects, and asymmetry of hemispheric responses on monocular stimulation was used as to indicate chiasmal misrouting.

Albino volunteers exhibited a wide range of phenotypical characteristics, ranging from a physically normal appearance to obvious features such as hypopigmentation of skin and hair. Diagnosis of albinism was confirmed by the coexistence of three signs: (i) presence of asymmetric hemispheric VEP responses on monocular stimulation, (ii) macular hypoplasia

confirmed by either fundus examination or optical coherence tomography, and (iii) iris transillumination (Summers, 2009).IIN subjects had a normal ERG and no asymmetry was seen on VEP. All the subjects had an X-linked mode of inheritance with mutations in the *FRMD7* gene (Tarpey *et al.*, 2006).

The following clinical tests were performed in all the subjects:

2.6.2.1 History

A detail history was obtained from all the subjects as follows

- Onset of nystagmus
- Presence or absence of oscillopsia
- Family history of nystagmus to ascertain the mode of inheritance
- Birth history with particular attention to birth trauma
- Any associated systemic abnormalities

2.6.2.2 Vision

All subjects included in the study had best-corrected visual acuity (BCVA) measured using Snellen opotypes at 6 meters. Visual acuity was measured during monocular viewing for each eye and also with both eyes open. Snellen notations were converted to logMAR for subsequent analysis.

2.6.2.3 Stereopsis

Stereopsis was measured using either the Lang test, Frisby test or Bagolini test. In participants who were Lang positive, the degree of stereopsis was measured using Frisby charts. In subjects who were Lang negative, Bagolini test was performed to look for the presence of gross stereopsis.

2.6.2.4 Strabismus

Strabismus was detected with corneal light reflex testing and measured with alternating prism cover test (used for statistical analysis).

2.6.2.5 Anomalous Head Posture (AHP)

Anomalous head posture (AHP) was measured while volunteers read a distance visual acuity chart. The AHP was classified into three categories (minimal AHP, i.e. <5° of head turn; moderate AHP with 5-15° of head turn; and large AHP with >15° of head turn). AHP was measured using a Harms wall where a light mounted on the head projects a cross onto a wall marking out visual angles.

2.6.2.6 Slit-Lamp Examination

All subjects had a slit-lamp biomicroscopy examination. A detail examination of the anterior and posterior segment was performed. An anterior segment examination with particular attention to iris transillumination defects for diagnosing albinism was carried

out. Transillumination defects were graded using the Summers classification scheme (Summers, 2009). Posterior segment examination using a 78D lens was performed to investigate optic nerve and macular changes, and to assess the degree of retinal pigmentation. These examinations, particular grading of the transillumination defect using the Summers classification scheme, also contributed to a publication by the group on the relationship between iris abnormalities and other phenotypical features of albinism on which I was a collaborator (Sheth *et al.*, 2013).

2.6.2.7 Eye Movement Recording

The eye movement recordings were performed by either Ms.McLean or Dr. Proudlock.

Horizontal and vertical eye movement recordings were recorded at 250Hz using an Eye link I pupil tracker (Senso Motoric Instruments GmbH, Berlin, and Germany). Eye movements were recorded in all 52 volunteers in the albinism group and 51 volunteers in the *FRMD7*-IIN group. For the albino group targets were projected onto a rear projection screen (1.8m wide and 1.2m high) at 1.2m distance using a video projector (Epson EMP-1715). The primary analysis was performed on sections of data (minimum 3 seconds) when the volunteers were attempting to maintain fixation at primary position and targets at ±15° eccentricity, horizontally.

Computer control of EyeLink I

Two computers are used to control and record the EyeLink I system:

1. The first computer samples and processes the infrared camera data and this information is used to determine the pupil and head positions during each recordings. This software uses MS-DOS to allow accurate timing.

2. The second computer sends commands to the first computer to initiate and manage the eye movement recordings. This computer also controls the hardware for visual stimuli.

A third computer, called the VisLab system (Sensomotoric instruments GmbH, Berlin, Germany), produces the visual stimulus and triggers the system to start recording at the same time. The visual stimulus was projected onto the rear projection screen (1.8x1.2m, viewing distance 1.2m) using a video projector (Hitachi CP-X958).

The following visual tests were performed on each subject and the eye movements were recorded.

1) Measurement of nystagmus while maintaining steady fixation in primary position and at ±15° gaze (to the left and right). Each recording in these positions was for at least 20 seconds duration. Each of these recordings were done with both eyes open, and with either eye covered.

2) On the majority of patients a horizontal and vertical saccades task with targets presented in the following positions -20°, -10°, 0°, 10° and 20° visual angle was performed. Also a horizontal and vertical smooth pursuit task from -20° to 20° moving at a linear velocity of 20°/s was also performed. The data from these tasks was not used in subsequent analysis.

Data Analysis:

The eye movements were recorded as a binary file (*.edf file). This was converted to a *.smr file which can be analysed using custom written scripts in the neurophysiological software Spike2 (Cambridge Electronic Design, Cambridge, UK). Data from each eye was calibrated separately offline by selecting foveations periods when fixating targets at ±15° eccentricity, horizontally and vertically, and primary position (0°). Using a script

for Spike2 (customised by Dr.Proudlock for the experiment), eye movement recordings were analysed after it was recalibrated offline and appropriate smoothing of the data to derive at the fundamental frequency of nystagmus and filter the noise. The primary analysis was performed on sections of data (minimum 3 seconds) when the volunteers were attempting to maintain fixation at primary position and targets at ±15° eccentricity, horizontally. The amplitude and frequency of nystagmus were defined from peak to peak excursions of the fundamental oscillation (determined from adaptive smoothing of the data).

Waveforms were characterized based on the 12 waveforms described by Dell'Osso and Daroff (Dell'Osso and Daroff, 1975) . The predominant waveform seen in the recording was taken as a primary waveform. Extended nystagmus visual acuity (NAFX), which predicts the visual acuity based on the foveations seen on eye movement recordings, was calculated for both primary position and ±15° gaze positions using scripts developed by Jacobs and Dell'Osso (www.*omlab.org).* Since all nystagmus in both albinism and *FRMD7*-IIN was conjugate only the data for the right eye was used in the analysis. The vertical component of the nystagmus was estimated as the vertical amplitude / horizontal amplitude x 100%. Periodic alternating nystagmus (PAN) was identified from prolonged periods of recording (>7 mins) when the eyes were fixating a target at primary position (0°). Although difficult to characterize definitively due to the underlying nystagmus as well as possible PAN, manifest latent nystagmus (MLN) was identified from monocular occlusion of either eye. MLN was defined as that leading to a change in the beating direction of the nystagmus, with the beating direction always towards the open eye. Although not classified as MLN changes in nystagmus waveform cause by monocular occlusion were also noted.

2.6.2.8 Electrodiagnostics

Most of the electrodiagnostic testing was performed in the medical physics department at Leicester Royal Infirmary by Dr.Degg. Some of the electrodiagnostic testing, especially of subjects diagnosed as IIN due to *FRMD7* mutations, was performed at other hospitals from which they were referred initially.

All subjects had both ERG and VEP testing carried out. ERG was performed to rule out retinal pathologies (other than foveal hypoplasia associated with albinism) causing nystagmus. Any subjects with ERG abnormalities were excluded from the study.

Multi-channel VEP was performed in all subjects. All subjects diagnosed as albinism on clinical characteristics had abnormal crossing on monocular stimulation detected on VEP. Subjects with *FRMD7* mutation had a normal VEP.

2.7 Statistical analysis

The choice of the statistical test depended on the type of data (numerical/categorical), number of groups, related or unrelated samples and distribution of data (normal or not normal). The data collected for visual acuity, amplitude, frequency, NAFX are numeral data on continuous scale. The categorical data values collected are for stereopsis, strabismus, waveforms and anomalous head posture.

Normality of the data was tested using Shapiro-Wilk test. If the data was normally distributed parametric analysis can be applied. If the data was not consistent with a Gaussian distribution non-parametric analysis was applied (Sheskin, 2004). .

Visual acuities were compared using a Mann-Whitney test. Categorical variables were compared using the Pearson chi-square test (used for stereopsis, strabismus and waveform) and the gamma statistic (used for anomalous head posture).

Since the majority of the eye movement data was not normally distributed, amplitude, frequency, intensity and NAFX values were log transformed leading to a closer approximation to normality. This enabled use of linear mixed model allowing the inclusion of paired (i.e. eccentricity) and unpaired factors (albinotic vs *FRMD7* associated) in the model and exploration of interactions between terms. The reason for using Linear mixed model is because we have repeated measure data (data from the left and right eye from the same patient). The fixed factor is either the albinism or FRMD7-IIN.

All statistical analyses were performed using SPSS for Windows (version 16.0).

2.8 Results

The results are categorised under two headings, first the findings seen on clinical examination and second the findings found using eye movement recordings.

2.8.1 Clinical Measures:

2.8.1.1 Visual acuity

In the albinism group, visual acuity was tested in all 52 subjects, and in the *FRMD7* group visual acuity was tested in all 83 subjects.

The median logMAR visual acuity showed higher trend in the albinism (median = 0.50, quartiles = 0.46 to 0.73) compared to the *FRMD7*-IIN group (median = 0.176, quartiles = 0.097 to 0.301) (Mann Whitney, Z=-8.164, p<0.0001) (**Figure 2.3**).

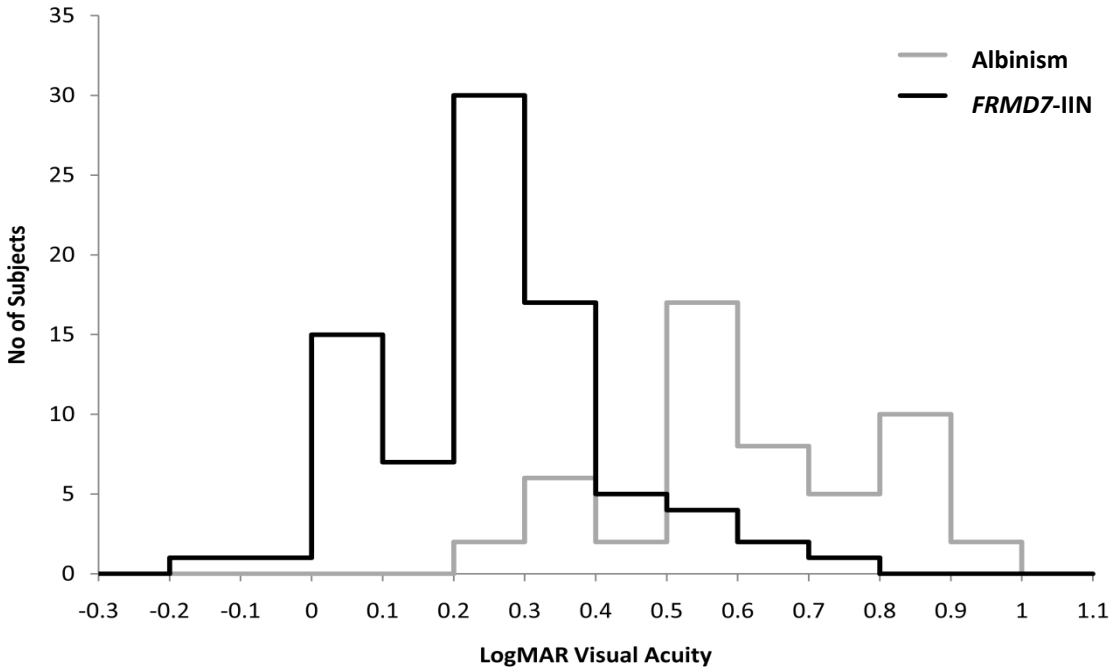


Figure-2.3 *Frequency distribution of the logMAR visual acuity of patients with albinism and FRMD7-IIN subjects showing a reduced visual acuity in patients with albinism.*

2.8.1.2 Stereopsis:

All the 52 subjects in the albinism group were tested for stereo acuity. 80% (n=42) of the subjects exhibited good stereopsis and were Lang negative. Twenty-two subjects who were Lang negative were positive on Bagolini test, and the other twenty did not have stereo vision. Of the ten subjects who were Lang positive, nine subjects had good stereopsis on Frisby test.

Amongst the IIN subjects with *FRMD7* mutation 76 out of the 83 subjects were tested for stereo acuity. 93.4% (n=71) of the subjects were Lang positive. All the subjects who were Lang positive had good stereo acuity on Frisby test. 6.5% (n=5) of subjects were Lang negative, out of which four were Bagolini positive and one subject was Bagolini negative. Pearson chi-squared test was used to compare the relative proportions of subjects who were Lang negative and showed a significantly higher trend in the albinism group ($p<0.0001$) (**Figure 2.4**).

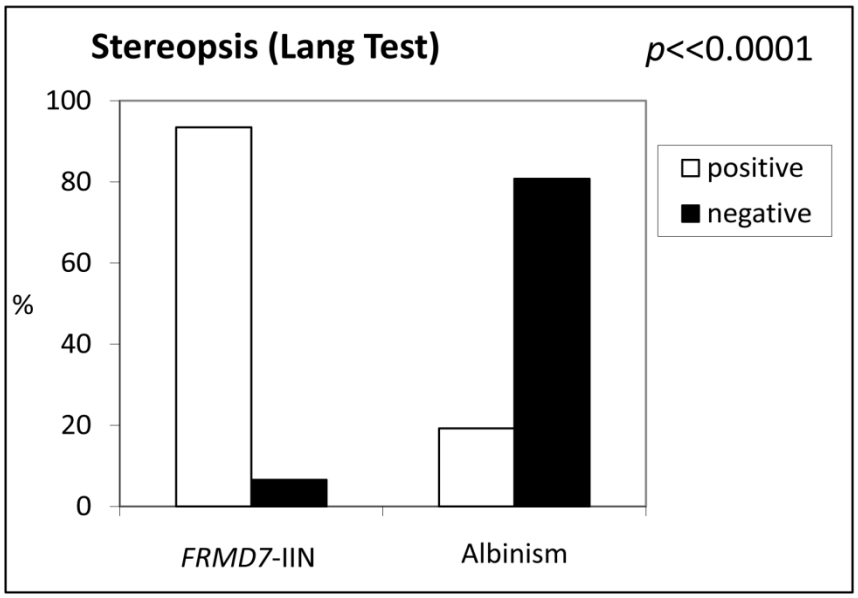


Figure-2.4 Comparison *of stereopsis between the two groups. 93% of subjects in the FRMD7 group had good stereopsis compared to 19.23% of subjects in the albinism group***.**

2.8.1.3 Strabismus

Strabismus was detected in 71.2% (n=37) of participants with albinism. Twenty seven subjects had esotropia and ten subjects had exotropia.

Strabismus was detected only in 7.8% (n=7) of the subjects in the IIN group. Out of the seven subjects in the *FRMD7* group three subjects had esotropia, three exotropia and one subject had hypertropia. Pearson Chi-squared test was used to compare the relative proportions of subjects with strabismus in each group and showed a significantly higher proportion in the albinism group ($p<0.0001$) (**Figure 2.5**).

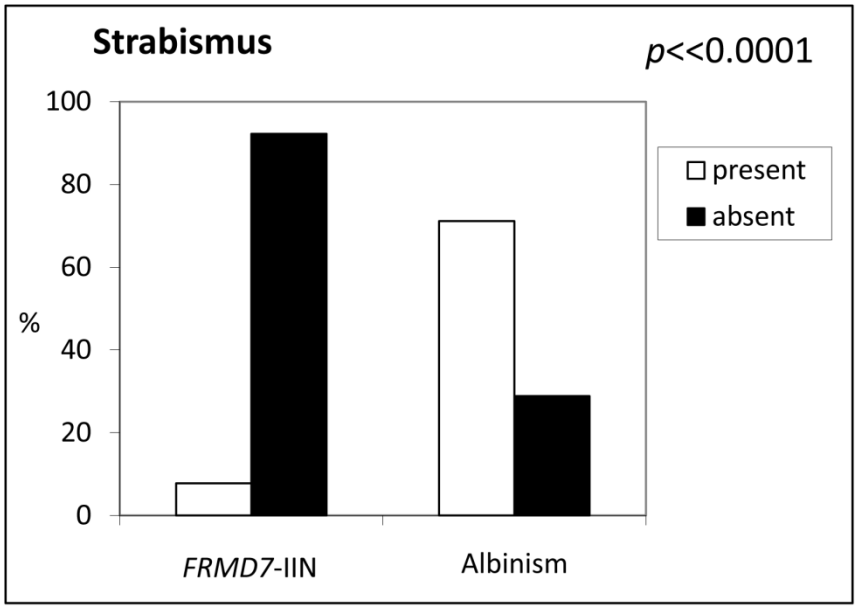


Figure-2.5 *Bar chart showing the comparison of percentage of strabismus between FRMD7-IIN and albinism.*

2.8.1.4 Anomalous Head Posture (AHP)

AHP was recorded in 47 subjects of the albinism group and 80 subjects in the *FRMD7*-IIN group. 85% (n=68) of subjects in the *FRMD7*-IIN group had <5° of AHP compared to 48.9% in albino group (n=23). Interestingly 14.9% (n=7) in the albinism group had AHP of >15° compared to none in the *FRMD7*-IIN group **Figure 2.6.**

Gamma statistics was used to compare the relative proportions between groups and found AHP to be significantly present in albinism group compared to the *FRMD7* group (p<0.0001).

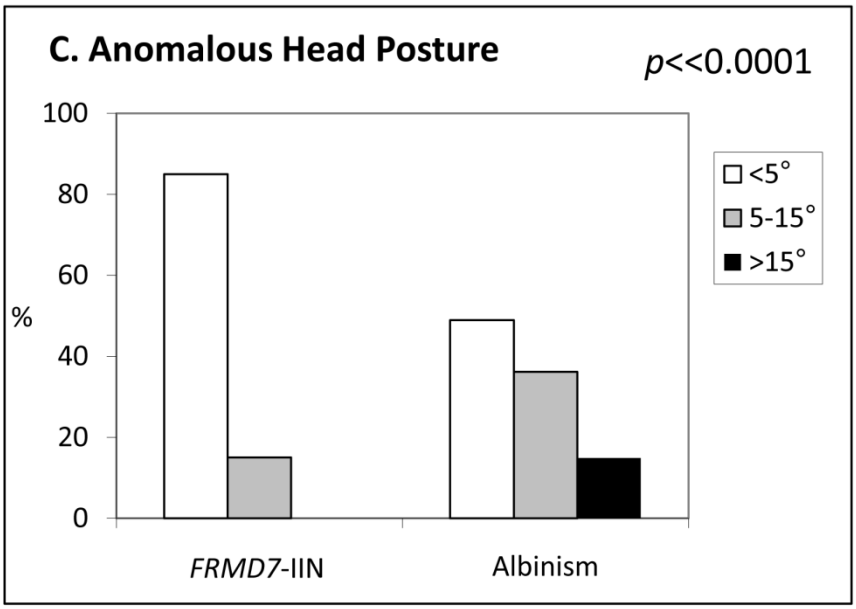


Figure-2.6 *Comparison of percentage of anomolous head posture between the FRMD7 and albinism group.*

2.8.2 Analysis of Nystagmus Waveforms

2.8.2.1 Plane of nystagmus and waveform

All volunteers in the albino and *FRMD7*-IIN group had conjugate nystagmus that was primarily horizontal in direction (**Figure 2.7**). A small vertical component to the nystagmus was present in both groups (albinism group: median=3.10%, interquartile range=4.53%; *FRMD7*-IINgroup: median=6.28%, interquartile range=4.88%) although the vertical component was significantly higher in the *FRMD7*-IINgroup (Mann-Whitney test, p=0.014).

Nystagmus waveforms were classified into the 12 categories of pendular, jerk and bidirectional waveforms described by Daroff and Dell'Osso (Dell'Osso and Daroff, 1975) (excluding PAN) and are represented in **Figure 2.8** banded according to visual acuity. The overall proportion of pendular, jerk and bidirectional nystagmus was 25.7%, 66.7% and 7.6% in the albinism group and 42.7%, 42.7% and 14.5% in the *FRMD7*-IINgroup **Figure2.9**. The *FRMD7*-IIN group contained a higher proportion of all three types of pendular waveform types compared to albinism group whereas higher proportions of all four types of jerk nystagmus were evident in the albinism group (Pearson chi-square test, p<0.0001). Pure jerk waveforms (J) were associated with poor visual acuity (≥0.7) in the albinism group. Although these had minimal foveation periods, unlike vestibular and optokinetic jerk waveforms, a brief acceleration in the slow phase immediately following the quick phase was evident.

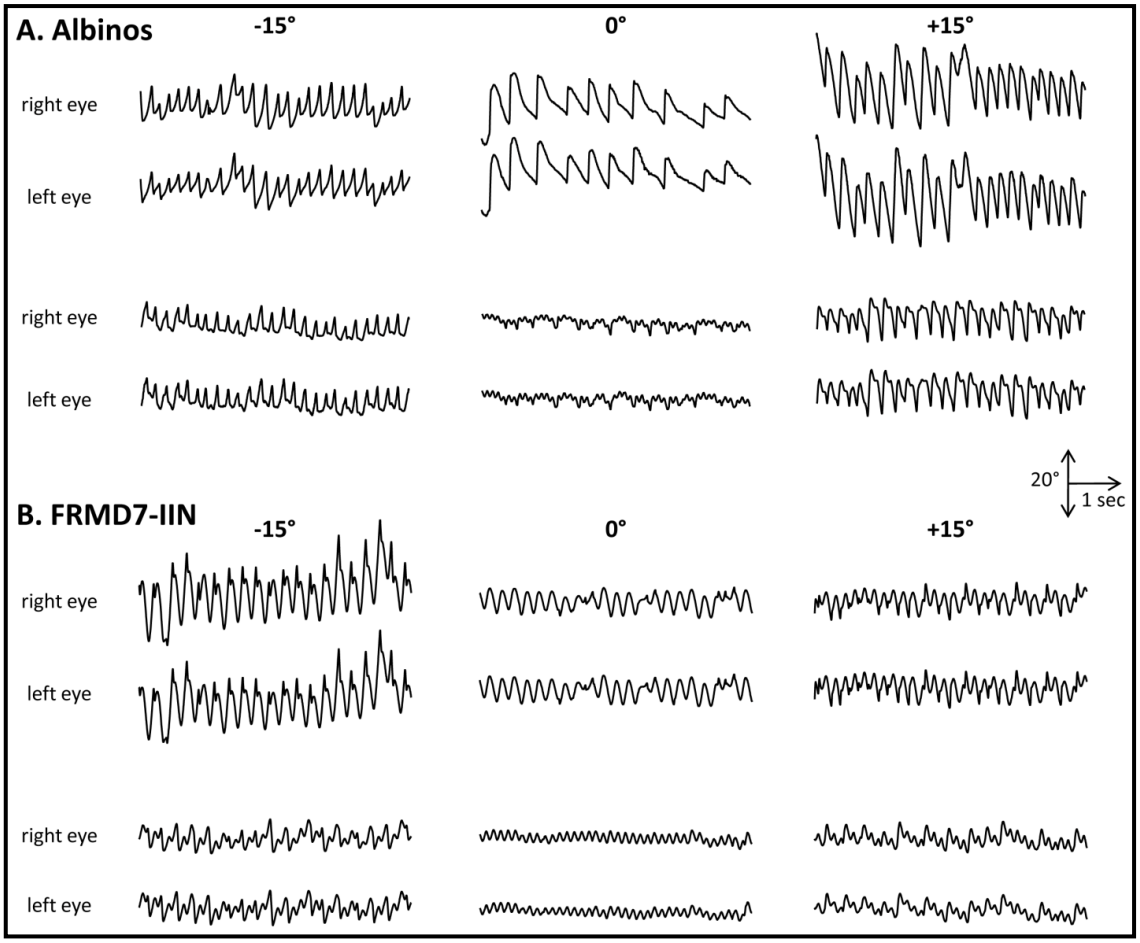


Figure-2.7 Original *eye movement data of two albinism and two FRMD7-IIN subjects. The data shows eye movements in primary position (0°) and 15° to right (+15°) and left (-15°) for both eyes.*

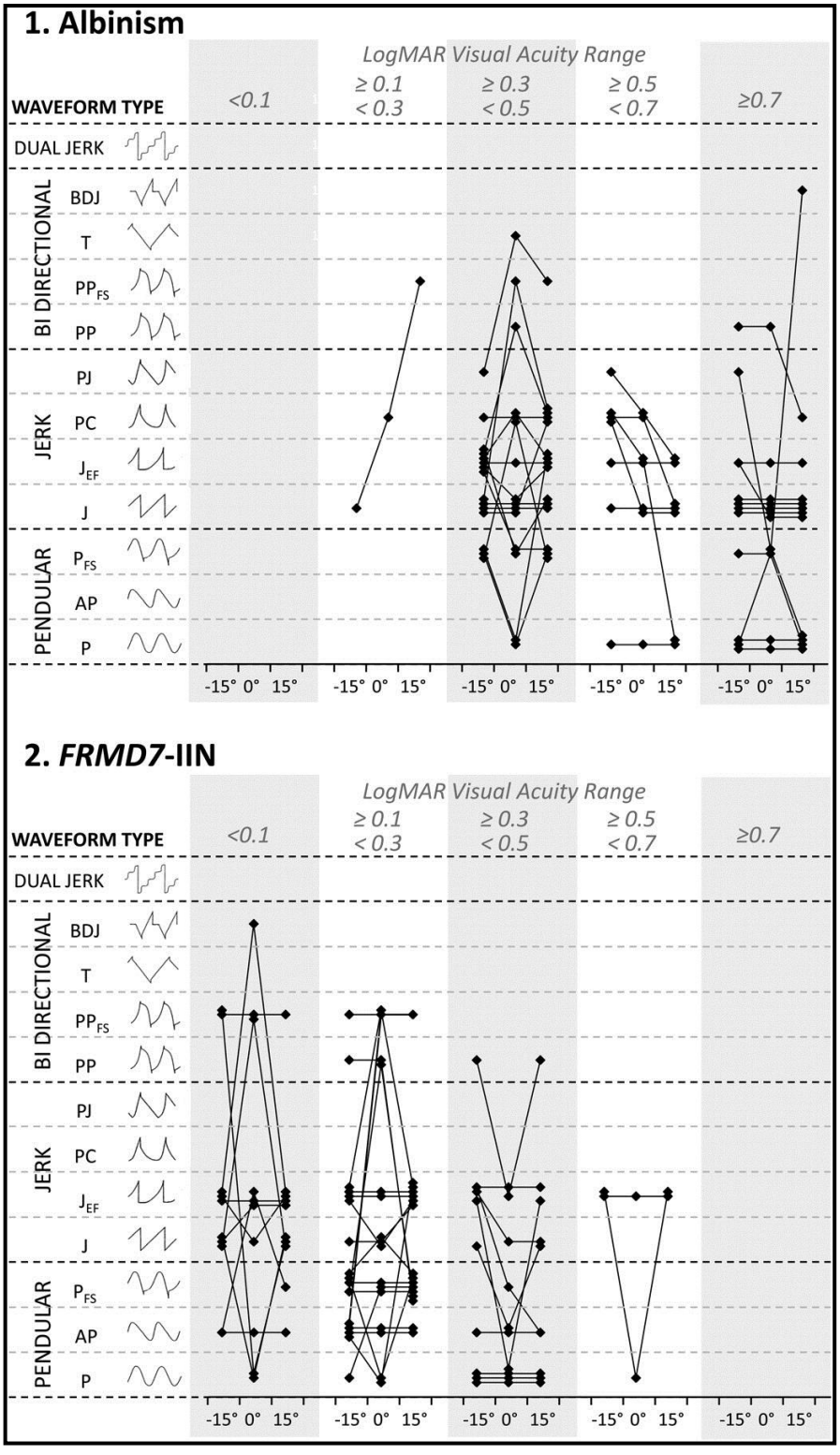


Figure-2.8 *The proportion of waveform types from the classification given by Dell'Osso and Daroff (Dell'Osso and Daroff, 1975) for the albinism and the FRMD7 group. The straight line connects three dots of individual patient at primary position (0˚) and eccentric gaze (*±15˚). The waveform seen a these three positions is depicted in figure. *The FRMD7-IIN group contained a higher proportion of all three types of pendular waveform types compared to albinism group whereas higher proportions of all four types of jerk nystagmus were evident in the albinism group. Pure jerk waveforms (J) were associated with poor visual acuity (≥0.7) in the albinism group.*.

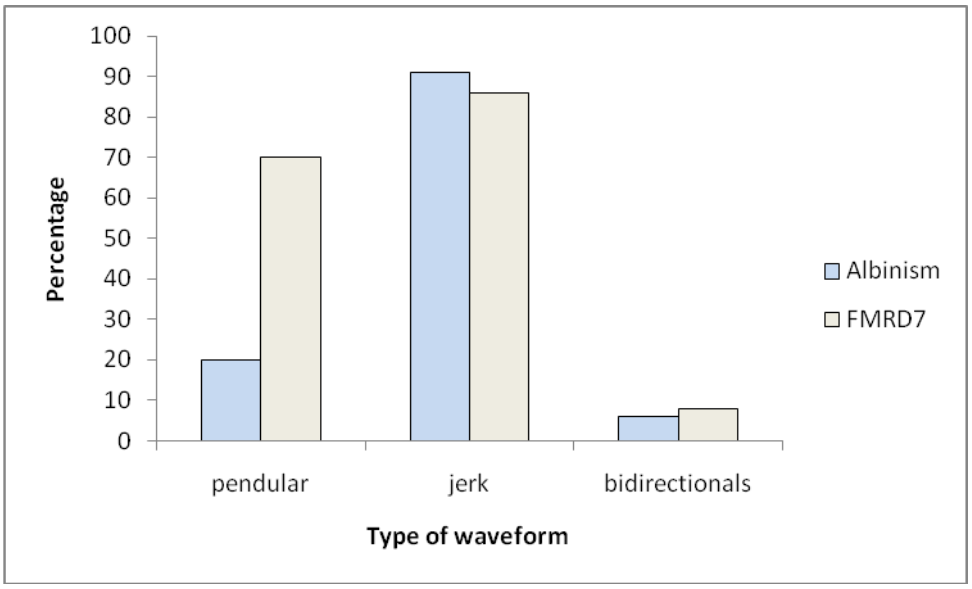


Figure-2.9 Comparison *of the percentage of different types of waveforms seen in the two groups*

2.8.2.2 Periodic Alternating Nystagmus

Periodic alternating nystagmus was observed in 29.4% of individuals in the albinism group and 23.5% of the *FRMD7*-IINgroup. Nystagmus waveforms associated with PAN for both groups were either jerk-related (80% in albinism and 75% in *FRMD7*-IIN; mainly jerk extended foveation or pseudocycloid) or dual jerk waveforms (20% in albinism and 25% in *FRMD7*-IIN) during active phases. During the quiet phase the most commonly encountered oculomotor patterns were no significant oscillation (66.7% in albinism and 50% in *FRMD7*-IIN), followed by pendular waveforms (33.3% in albinism and 41.7% in *FRMD7*-IIN).

2.8.2.3 Manifest latent nystagmus (MLN)

Manifest latent nystagmus, defined as that which led to a change in the beating direction of the nystagmus, with the beating direction always toward the open eye in combination with the presence of decreasing velocity or linear slow, was identified in 8 of the 52 albino volunteers (15.4%) and none of the 51 volunteers in the *FRMD7*-IIN group. 14 albino volunteers and 7 *FRMD7*-IIN volunteers also showed a change in nystagmus waveform, that is, a change in the quick phase beating direction, intensity, or slow-phase velocity characteristics with monocular occlusion of either eye. The presence of MLN without infantile nystagmus waveforms was detected in one individual with albinism where the nystagmus during binocular viewing (which was much smaller than during monocular viewing) had slow phases that were always decelerating.

2.8.2.4 Amplitude, frequency, intensity and foveation of nystagmus

The amplitude, frequency, intensity and foveation characteristics (measured using the extended nystagmus acuity function (NAFX)) of the nystagmus for patients without PAN in left gaze (-15°), primary position (0°) and right gaze (+15°) for subjects in both the groups is shown in **Figure2.10**.Linear mixed models were used to show that there was no significant effect of group (albino versus *FRMD7*-IIN, F=2.87, p=0.092) or eccentricity (F=2.03, p=0.13) on nystagmus amplitude. In contrast the difference in nystagmus frequency between albino and *FRMD7*-IIN groups was highly significant (F=42.2, p<0.0001) with a significant effect of eccentricity (F=3.18, p=0.044). The mean frequency was 3.20Hz (SD 0.99Hz) in

albinism and 4.18Hz (SD 1.29Hz) in the *FRMD7*-IIN group. For nystagmus intensity there was no significant effect for group (F=1.16, p=0.28) although there was for eccentricity (F=3.85, p=0.023). For NAFX there was a significant effect for both group (F=4.47, p=0.036) and eccentricity (F=5.06, p=0.007).

No significant differences (p=0.05) were observed between the *FRMD7*-IIN and albinism groups with respect to the null region location (medians: *FRMD7*-IIN, 3.0°; albinism, 3.0°) and eccentricity (medians: *FRMD7*-IIN, 3.0°; albinism, 6.0°), or amplitude (means: *FRMD7*-IIN, 1.6°; albinism, 2.7°), frequency (means: *FRMD7*-IIN, 3.0 Hz; albinism, 2.8 Hz), intensity (means: *FRMD7*-IIN, 6.5°/s; albinism, 8.4°/s) and NAFX (means: *FRMD7*-IIN, 0.41; albinism, 0.55 logMAR equiv.) at the null region. The waveform of the nystagmus at the null region was mostly pendular related in the *FRMD7*-IIN group (pendular with foveating saccades-3; pendular-1; jerk-1) and either jerk-related or with minimal nystagmus due to a very slow drift in the albinism group (jerk extended foveation- 2; bidirectional jerk- 4; very slow drift-7; pendular-4).

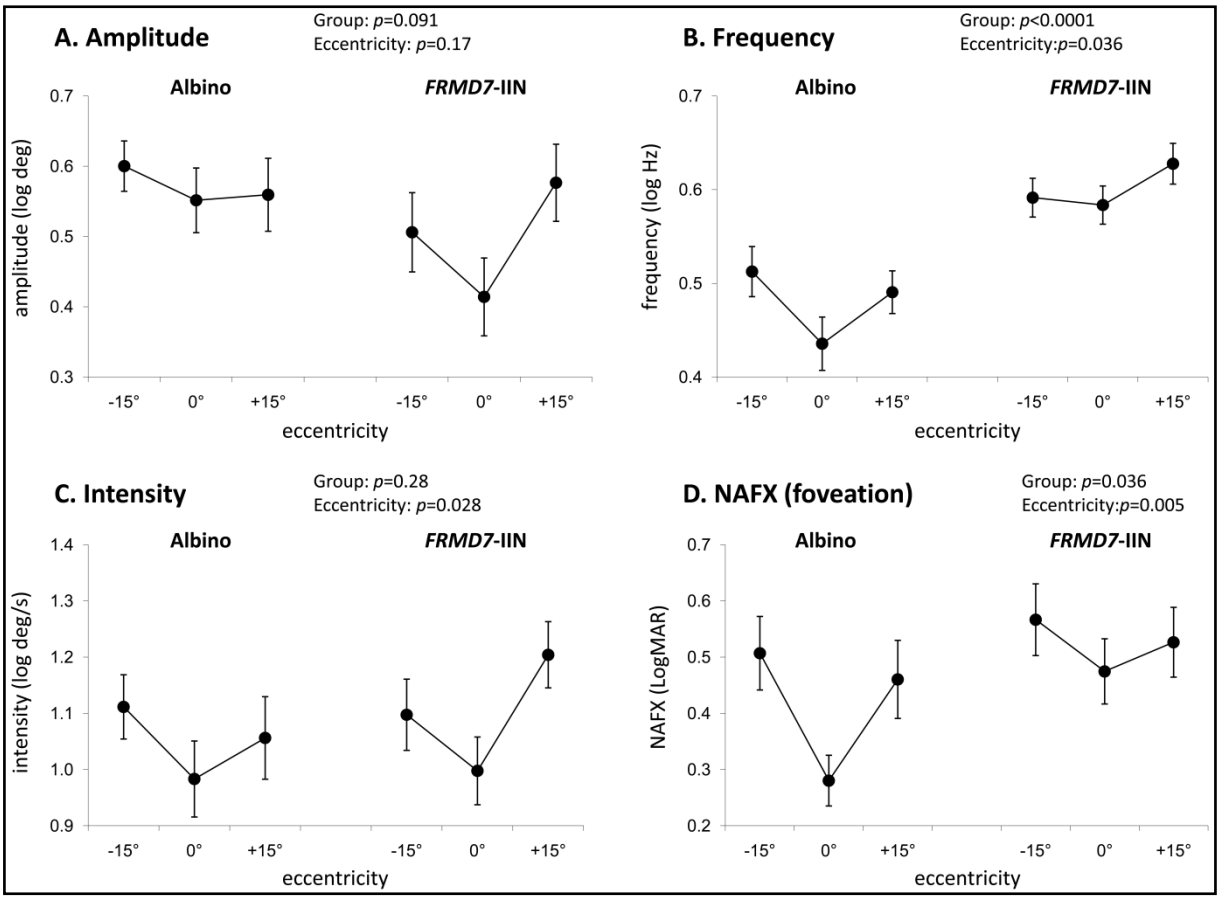


Figure-2.10 *Means (error bars represent SEM) of (A) amplitude (log values), (B) frequency (log values), (C) intensity (log values), and (D) extended nystagmus acuity function (NAFX in logMAR) are shown during attempts to hold left (−15°) central (0°) and right gaze (+15°) for albinos and FRMD7-IIN volunteers*

As the frequency of nystagmus in the albinism cohort was significantly less compared to the *FRMD7*-IIN cohort, we wanted to know the percentage of subjects in each group at different frequency levels which was arbitrarily selected. The probability of diagnosis of albinism was 89.3% when the frequency was <2Hz, whereas the probability of diagnosis of IIN was 92% when the frequency of nystagmus was >5Hz (**Figure 2.11**)**.**

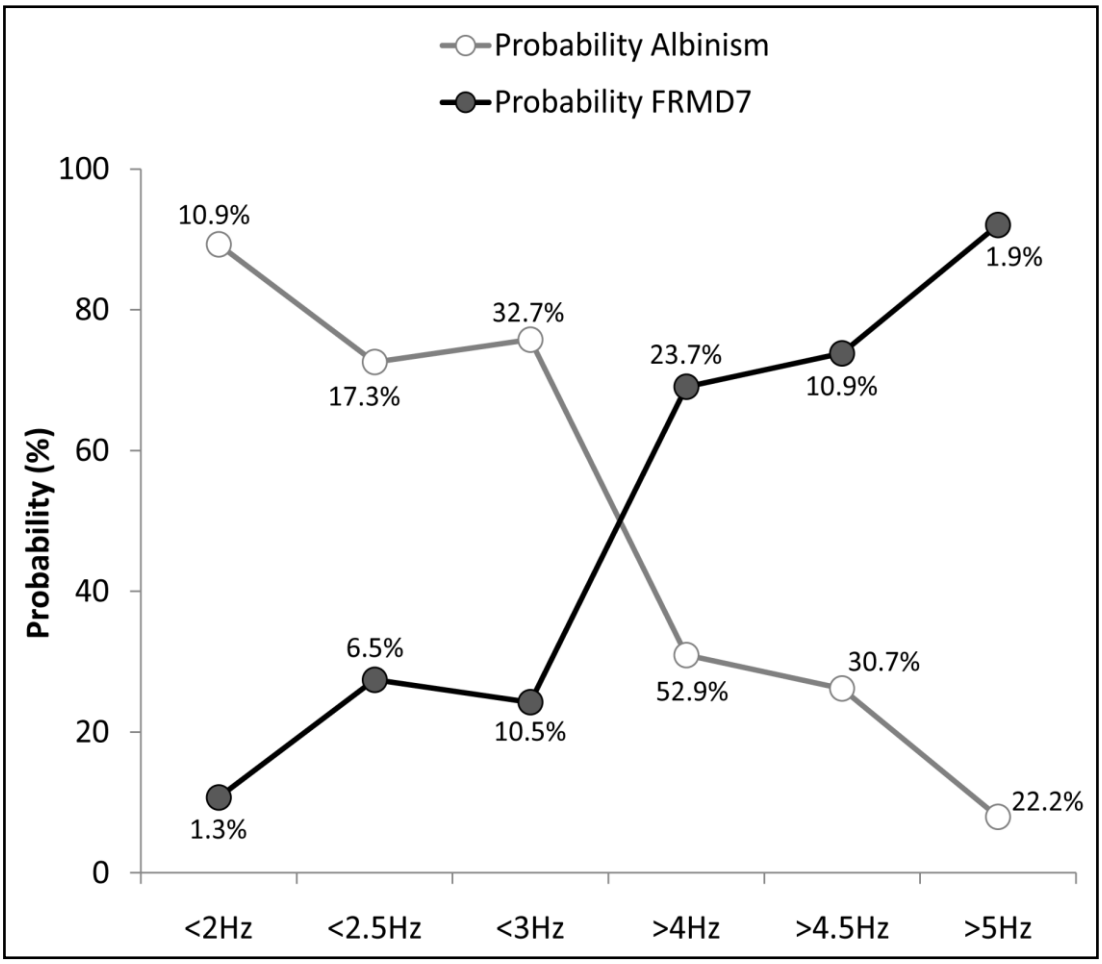


Figure-2.11 *The probability that given a certain frequency of nystagmus for an individual taken at random from the whole data set that the nystagmus will be associated with albinism or FRMD7-IIN. The numbers shown next to the symbols indicate the % of the whole group each point represents.*

2.9 Discussion and Conclusion

The mechanism(s) behind infantile nystagmus are poorly understood. Numerous models have been developed which generate common waveforms associated with infantile nystagmus most of which include abnormal circuitry of the slow eye movement and gaze holding systems(Abadi, 2002) Optican and Zee (Optican and Zee, 1984) modelled IN on an unstable neural integrator due to a reversal of the velocity feedback loop leading to accelerating (exponential) slow phases. Jacobs and Dell'Osso (Jacobs and Dell'Osso, 2004) suggest that, rather than abnormal neural integrator feedback loops, IN waveforms are caused by an abnormality in the feedback loop internal to the smooth pursuit subsystem leading to sinusoidal oscillations. These are shaped by the interposition of braking and foveating saccades. Based on time series analysis, Akman et al. (Akman et al., 2006, Akman et al., 2012) also suggest that the origin of jerk waveforms is in unstable circuitry that lies prior to the neural integrator. However, they suggest a model of the saccadic system based on nonlinear dynamics is able to produces all the jerk, bidirectional jerk and pendular nystagmus waveforms associated with IN. In contrast to models that introduce abnormalities in oculomotor circuitry, Harris and Berry have proposed that IN may be caused by plasticity in the normal oculomotor system during periods of early visual deprivation (Harris and Berry, 2006). They suggest that if the normal visual system is deprived of high-spatial frequency contrast stimulation during visual development, then oscillations develop to improve the contrast sensitivity to stimuli of lower spatial frequency. It is also possible that different mechanisms underlie jerk nystagmus, which is usually gaze-dependant, and pendular nystagmus which is less gaze-dependant although frequently these waveforms coexist in the same individual.

We describe, for the first time, differences in nystagmus characteristics between a group of patients with albinism and a group with IIN associated with FRMD7 mutations. We also confirm the existence of a number of other abnormalities, namely presence of strabismus leading to absent stereopsis, large anomalous head posture and reduced visual acuity.

Due to the phenotypical heterogeneity the diagnosis of albinism is not always straightforward. Charles et al (Charles *et al.*, 1993) reported 20% of the affected male with nystagmus from UK pedigrees had been previously misdiagnosed as IIN. According to Shiono et al. (Shiono *et al.*, 1995), 70% of patients with X-linked ocular albinism are misdiagnosed as having idiopathic infantile nystagmus (IIN) with or without macular hypoplasia. King et al. (King *et al.*, 1985) described the clinical characteristics of seven patients with oculocutaneous albinism who were previously diagnosed as having infantile nystagmus or disorders of retina other than albinism. Genetic testing helps in definitive diagnosis of these conditions, but it is not performed routinely and is negative in 15% or 20% of patients (Suzuki and Tomita, 2008). In this study we had the opportunity for the first time of using a genetically homogeneous group of patients with *FRMD7* mutations avoiding the possibility of patients with albinism being misdiagnosed with IIN.

Gelbart et al.(Gelbart and Hoyt, 1988) in a study involving 152 subjects with infantile nystagmus found sensory problems in 119 subjects while 13 had pure motor nystagmus. One of the main sensory problems was albinism both ocular and oculocutaneous. They proposed classification of nystagmus into sensory and motor nystagmus.

The diagnosis of albinism is made based on the clinical features of iris transillumination defect, macular hypoplasia detected both clinically and with the help of optical coherence tomography, and optic nerve misrouting at the chiasm detected by multichannel VEP.

Foveal hypoplasia and chiasmal misrouting has also been reported in a case series of 3 subjects who had nystagmus, no iris transillumination defect and normal fundal pigmentation (van Genderen *et al.*, 2006). One of the subjects was diagnosed to have Kartagener's syndrome. Ung *et al.* (Ung *et al.*, 2005) reported optic nerve misrouting recorded on pattern onset VEP recording in 15% of their subjects diagnosed to have infantile stationary night blindness (CSNB). Tremblay *et al.* (Tremblay *et al.*, 1996) also reported crossed VEP asymmetry in 9 of 10 subjects diagnosed with CSNB2. Dorey *et al.*(Dorey *et al.*, 2003) in their study showed VEP asymmetric measurement using amplitude asymmetry index method failed to identify 3 subjects as having albinism. False positive VEPs have also been reported by previous authors (Shallo-Hoffmann and Apkarian, 1993, Apkarian and Shallo-Hoffmann, 1991, Soong et al., 2000, Bouzas et al., 1994).

The visual acuity in albinism is reported to vary from 6/6 to 3/60 (Witkop et al., 1973, Summers et al., 1991, Edmunds, 1949, Taylor, 1978). The visual acuity is variedly reduced in albinism depending on the type of albinism and the amount of ocular melanin pigment present. Summer et al.(Summers *et al.*, 1991) reported variable expression of vision and ocular alignment in two siblings with albinism. One sibling had normal vision no nystagmus or strabismus, while the other sibling had nystagmus with reduced visual acuity and large angle esotropia. Comparable with the other studies we also found the

visual acuity to be significantly less in the albinism group compared to the IIN group.

Visual resolution in albinism is limited by factors other than the infantile nystagmus (Abadi and Pascal, 1991). However, Castronuovo et al. (Castronuovo *et al.*, 1991) demonstrated a strong correlation between the severity of nystagmus and visual acuity deficit. The reduction of vision in albinism is reported to be due to varies factors which include foveal hypoplasia, misrouting of optic nerve at the chiasma, nystagmus, high refractive errors with associated ambylopia. The adoption of different foveations strategies is said to influence the visual performance in albinism subjects(Abadi and Pascal, 1991).

Estimates of the prevalence of strabismus in subjects with infantile nystagmus vary widely. Norn et al. (Norn, 1964) and Forsmann et al.(Forssman, 1964), found the incidence of strabismus in infantile nystagmus subjects to be 54% and 16%, respectively. Dello'Osso (Dell'Osso, 1985) found 33% prevalence of strabismus in infantile nystagmus. Gelbart and Hoyt.(Gelbart and Hoyt, 1988) found the incidence of strabismus in 18.5% subjects with infantile nystagmus associated with visual sensory deficits, and 23% in subjects with idiopathic infantile nystagmus. Bordsky et al.(Brodsky and Fray, 1997) found the incidence of strabismus to be 53% in albinism subjects as compared to 17% of IIN subjects. Abadi et al.(Abadi and Bjerre, 2002) found strabismus in 26.7% of albinism subjects compared to 37.08% in subjects with infantile nystagmus due to various other causes including IIN. Gradstein et al. (Gradstein *et al.*, 2005) found strabismus in 74% of subjects with the Hermansky-Pudlack syndrome a form of oculocutaneous albinism. The prevalence of strabismus found in subjects with *FRMD7* mutations has been

reported as 7.8% (Thomas *et al.*, 2008) and 44% (Self *et al.*, 2007). Strabismus was seen in 36% of autosomal dominant IIN subjects.

In our study we found strabismus to be present in a high proportion of albinism subjects (71.2%) when compared to *FRMD7*-IIN subjects (7.8%). The prevalence of strabismus seen in these two groups is different compared to the previous reports. The high prevalence seen in the albinism group could be explained by the clear cohort sample. The high prevalence of strabismus seen in albinism subjects is attributed to the cortical, callosal and chiasmal misrouting seen in these subjects (Boylan and Harding, 1983).

In our study we found good stereopsis in 19.2% (n=10) of subjects in the albinism group. Other studies have also reported the presence of clinically detectable stereopsis in subjects with albinism (Guo et al., 1989, Apkarian and Reits, 1989, Castronuovo et al., 1991). The exact neural mechanism by which subjects with albinism demonstrate stereopsis is not known. Various studies suggest that the compensatory restructuring of corpus callosal projections could facilitate binocular disparate information in albinism subjects (Apkarian, 1996, Apkarian and Reits, 1989, Marzi et al., 1980). Another possible explanation is that in albinism subjects who demonstrate stereopsis probably has lesser proportion of misrouting at the chiasma than other albinism subjects. VEP which is performed to detect this misrouting is an “all or none” phenomenon and is not sensitive to detect the degree of misrouting among albino subjects. In the IIN group the majority of subjects had good stereopsis. The subjects with poor stereopsis had strabismus which could explain the probable association of fusional maldevelopment in these subjects.

AHP was seen in subjects with eccentric null region. In this head position the intensity of nystagmus is at the lowest to achieve optimal vision. It has been postulated that subjects with albinism may not benefit from using AHP because of their associated foveal hypoplasia (Shallo-Hoffmann *et al.*, 1999). Previous studies have also shown AHP to be less frequent in albinism subjects than other infantile nystagmus groups (Abadi and Pascal, 1994a, Gradstein et al., 1997). Hertle et al.(Hertle *et al.*, 2002) in a study on the clinical features of infantile nystagmus in first 6 months of life reported AHP of 19% (five of 27 subjects). Abadi et al.(Abadi and Whittle, 1991) found AHP in 53% (nine out of 16 subjects) subjects in a study which included both IIN and albinism subjects. The adoption of head posture was not linked to either albinism or IIN or ocular anomaly group in their study.

Hertle et al. (Stevens and Hertle, 2003), in a study carried out to determine whether a relation exists between visual acuity and AHP in subjects with infantile nystagmus, found that the presence of AHP correlated with good vision in infantile nystagmus.

Contrary to the previous studies we found AHP in higher proportion of subjects in albinism group than the IIN group, and the visual acuity being better in the IIN group inspite of no or minimal AHP. This suggests that subjects with albinism have an eccentric null and probably use the parafoveal area to fixate on the object.

All the twelve waveforms described by Dell'Osso and Daroff were seen in our subject population(Dell'Osso and Daroff, 1975). However, we found a higher proportion of pendular waveform types in the *FRMD7*-IIN group compared with more

jerk waveforms seen in the albino group. This stands in contrast to that observed by Abadi et al.(Abadi and Dickinson, 1986) who did not find any particular waveform specific to either IIN or albinism. Given that there are no obvious direct sensory deficits associated with the *FRMD7*-IIN accept those indirectly caused by the nystagmus itself, it is interesting that more pendular nystagmus is associated with nystagmus that is more likely to be motor in origin. This contradicts the commonly accepted notion that “motor” nystagmus is jerk and “sensory” nystagmus is pendular.

We noted that the frequency of nystagmus was significantly less in the albinism group (mean = 3.3 Hz), in all three positions of gaze, compared to the IIN group (mean =4.3 Hz), and the difference was highly significant (p<0.0001). We also observed slightly better foveation characteristics for the albino group in comparison to the *FRMD7*-IIN group. This implies that the major determinant of the reduced visual acuity observed in the albino group is due to sensory abnormalities although it is not clear as yet how foveal hypoplasia relates to visual acuity. This also suggests that foveation may still be useful even in the absence of a normal fovea. Abadi & Dickinson in a study of waveform characteristics in infantile nystagmus found that the waveform shape and precision of foveations to be better indices of visual acuity than intensity of nystagmus(Abadi and Dickinson, 1986). This has led to the development of the extended nystagmus acuity function which estimates visual acuity based on the foveation characteristics.

A number of oculomotor features were also similar between the two groups. These included the presence of a primarily horizontal nystagmus in all cases observed and a significant proportion of periodic alternating nystagmus (PAN) in both groups (29.4% of individuals in the albinism group and 23.5% in the

FRMD7-IIN group). The PAN observed in the two groups had similar characteristics. These were in accord with that previously described by Abadi and Pascal in albinism patients(Abadi and Pascal, 1994b). There were no significant differences in null region characteristics between the two groups. Manifest latent nystagmus was observed only in the albinism group and is associated with the higher prevalence of strabismus in this group. A number of Patients (14 albino and 7 *FRMD7*-IIN) did not demonstrate this specific combination but showed a change in nystagmus waveform (e.g., change in beating pattern, intensity, or the velocity characteristics of the slow phase) under monocular occlusion. It is possible that these patients were demonstrating a latent component of MLN that was interacting with the nystagmus waveform associated with infantile nystagmus syndrome. Manifest latent/latent nystagmus is likely to be a single entity since most patients with clinical latent nystagmus show a small spontaneous jerk nystagmus on eye movement recordings with both eyes viewing(Dell'Osso *et al.*, 1979). It is likely that there may also be a manifest component in these patients that is masked by the waveform associated with the infantile nystagmus syndrome.

Conclusion:

It is not clear at this point if the differences we observed in nystagmus waveforms are due to a common mechanism behind the nystagmus in the two groups being affected differentially by associated deficits in albinism, such as foveal hypoplasia and/or MLN. The similarities observed in the nystagmus in the two groups might suggest this. Alternatively, different mechanisms could

underlie nystagmus associated with albinism and that associated with *FRMD7*-IIN, although more evidence is required to substantiate this.

After the details of this study have been published in a Peer reviewed journal, no other relevant study has been published to further our knowledge regarding this subject.

3.0 Study of oculomotor abnormalities associated with multiple sclerosis

3.1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating neurological disease of young adults. It commonly affects women more than men with onset typically between 20-40 years of age. A definite clinical diagnosis of MS requires the occurrence of at least two neurological events consistent with demyelinating that are separated both anatomically in the CNS and time (Confavreux *et al.*, 1980).The prevalence of MS varies with ethnic origin and latitude. The prevalence of MS is greatest at extremes of latitude in both northern and southern hemisphere. United Kingdom has one of the highest prevalence of the disease, with an estimated prevalence of 74 to 112 MS cases per 100 000 in England and Wales (Ford et al., 1998, Roberts et al., 1991) and 145 to 193 per 100 000 in Scotland and its offshore islands (Forbes et al., 1999, Rothwell and Charlton, 1998). In recent study the prevalence of MS in UK was 203 per 100,000. The prevalence in England, Wales, Scotland and Northern Ireland were 199, 168, 255 and 213 per 100,000 respectively (Mackenzie et al.).

The disease progression can vary. Clinical symptoms may be episodic with occurrence of relapses or progressive or a combination of both. The symptoms can be mild or severe. The lesion could be disseminated throughout the CNS or primarily involve lesions affecting the optic nerve, brainstem or spinal cord. This

marked variability in the disease progression has led to classify the disease into various subgroups.

The advisory committee on clinical trials of new agents in MS of the National MS society (NMSS) undertook a survey to develop a consensus on the definitions and terminology used to describe the clinical outcomes and course patterns in subjects with MS. They surveyed 215 members of the international MS clinical research community, including the members of the NMSS medical advisory board (Lublin and Reingold, 1996). The consensus final definition of each of these different types of MS is as follow:

Relapsing Remitting Multiple sclerosis (RRMS): The initial diagnosis of MS is RRMS in 85% of patients. Clearly defined disease relapses with full recovery or with sequel and residual deficit upon recovery. The periods between relapses are characterized by a lack of disease progression.

Primary Progressive Multiple sclerosis (PPMS): Disease progression from onset with occasional plateau and minor fluctuations in progression but with no distinct relapses.

Secondary Progressive Multiple sclerosis (SPMS): The disease initially starts as the Relapsing Remitting disease which is followed by progression with or without occasional relapses, minor remissions and plateaus.

Progressive Relapsing Multiple sclerosis (PRMS): The disease is progressive from the onset with clear acute relapses, with or without full recovery. The periods between relapses are characterized by continuous progression.

3.2 Diagnostic criteria for MS

Diagnostic criteria's for MS has evolved over the past few decades. All the published diagnostic criteria emphasize the disease being disseminated in space and time, documented by either clinical, para-clinical, or laboratory criteria. They have also emphasized that alternative diagnosis for the clinical presentation should be thought of and excluded before the diagnosis of MS can be made (Poser et al., 1983, McDonald et al., 2001, Polman et al., 2005).

In 2001, the "International Panel on the Diagnosis of Multiple Sclerosis" proposed diagnostic criteria for MS, known as "McDonald Criteria" (McDonald *et al.*, 2001). The same committee met in 2005 and proposed revised criteria for the diagnosis of MS which is widely used today. The main requirement for diagnosis of MS requires the neurological events due to demyelination separated in space and time. This requires the classification of the presenting symptoms and signs as either monofocal (no dissemination in space, for which a single CNS lesion can explain signs and symptoms) or multifocal (dissemination in space, for which symptoms and signs can only be explained by at least two lesions in separate parts of the CNS). Classification also requires identifying whether the presenting symptoms and signs over time are monophasic (a single occurrence), multiphasic (relapsing), or progressive in nature.

The revised McDonald criteria gave importance to the MRI lesions and cerebrospinal fluid (CSF) results in the diagnosis of MS. The revised criteria is listed in the **table-3.1**

Clinical presentation	Additional data required for MS diagnosis
Two or More attacks;objective clinical evidence of two or more lesions	None
Two or more attcks; objective clinical evidence of one lesion	Dissemination in space demonstrated by; • MRI or • Two or more MRI-detected lesions consistent with MS plus positive CSF,or • Await further clinical attack,implicating a different site.
One attack; objective clinical evidence of two or more lesions	Dissemination in space demonstrated by; • MRI or • Second clinical attack
One attack, Objective clinical evidence of one lesion (monosymptomatic presentation; CIS)	Dissemination in space demonstrated by; • MRI, or • Two or more MRI-detected lesions consistent with MS plus positive CSF,and Dissemination in time demonstrated by; • MRI, or • Second clinical attack
Insidious neurological progression suggestive of MS	One year of disease progression (retrospectively or prospectively determined) and Two of the following: • Positive brain MRI (nine T2 lesions or four ot more T2 lesions with positive VEP) • Positive spinal cord MRI (two focal T2 lesions) . Positive CSF

3.3 Laboratory findings

The laboratory investigations that aid in the diagnosis of multiple sclerosis are CSF analysis, evoked potentials and neuroimaging of the brain and spinal cord.

3.3.1 Cerebrospinal Fluid (CSF)

CSF parameters are abnormal in majority of subjects during the course of MS. The CSF abnormalities include mildly elevated CSF white cell count (typically <50 lymphocytes) and elevated IgG in CSF compared to blood serum. Other protein indices that are abnormal in MS are IgG index (the ratio of IgG to albumin), the ratio of CSF IgG to serum IgG, IgG synthesis rate and the identification of two or more unique oligoclonal bands by CSF electrophoresis. Oligoclonal bands are characteristic of but not specific to MS. They can be seen in other conditions such as acute disseminated encephalomyelitis, sub-acute sclerosis panencephalitis, Behçet's disease, systemic lupus erythematosus and sarcoidosis (McLean *et al.*, 1995). Oligoclonal bands are seen in 90-95% of MS during the course of the disease, but not necessarily during the early course of the disease.

3.3.2 Evoked Potentials

An evoked potential is an electrical event in response to a nervous system stimulus. Evoked potentials measure the conduction along the afferent CNS pathways. Delayed conduction along the visual, somatosensory and brain stem auditory pathways can suggest a demyelination process. This could aid in the diagnosis of MS.

3.3.3 Neuroimaging

Magnetic resonance imaging (MRI) of the brain and spinal cord is the most sensitive investigative tool which helps in the diagnosis of MS (Fazekas *et al.*, 1999). The new criterion for the diagnosis of MS incorporates the MRI findings (Tintoré et al., 2003, Swanton et al., 2007, Montalban et al., 2010). Different MRI sequences can help detect various aspects of the disease process. T1 weighted MRI sequence can be with and without gadolinium administration. T2 weighted sequences include proton density (PD) and FLAIR (fluid attenuated inversion recovery). T1 weighted sequences without gadolinium can be used to identify the structural brain anatomy better with better visualization of the corpus callosal, cerebral, and spinal cord atrophy which occurs as the MS disease progresses. However, T1 weighted sequences without gadolinium do not demonstrate demyelinated lesions. With the administration of gadolinium the T1 scan shows enhancement of acute and actively demyelinating lesions. T2 PD and FLAIR sequences demonstrate demyelinating lesions as well, but they cannot differentiate active demyelinating lesions from chronic lesions. T2 sequences with PD are better for lesions of the posterior fossa. FLAIR

sequences are superior for identifying periventricular and juxtacortical lesions as it reduces the image artefact from the CSF signals.

Newer MRI imaging techniques such as diffusion tensor imaging, magnetic transfer imaging, and spectroscopy improves the detection of demyelination in the brain.

The diagnosis of MS should not be made on MRI findings alone. The neurological event that the patient experienced should be evaluated. The neurological event should be consistent with an inflammatory process as the cause for the event. All the alternate diagnosis of MS has been excluded before making a diagnosis of MS. It is important to establish that the lesion has developed at different times and are in different anatomical locations for the diagnosis of relapsing-remitting MS. Similarly it is important to establish progressive neurological deterioration over a year or more for the diagnosis of the Primary progressive MS.

3.4 Differential diagnosis

A clinical presentation similar to MS can occur in patients who have an infectious, neoplastic, metabolic, or vascular disease. It can also be seen in conditions such as neuromyelitis optica, acute disseminated encephalomyelitis which are grouped under non-MS idiopathic inflammatory demyelinating diseases. The pathophysiology, disease course and the management of these conditions other conditions differs to MS.

Differential Diagnosis of Multiple Sclerosis	
	Acute disseminated encephalomyelitis
Other demyelinating diseases	Neuromyelitis optica (Devic disease)
	Idiopathic transverse myelitis
Inherited disorders	Adrenoleucodystrophy
	metachromatic leucodystrophy
Systemic inflammatory disease	SLE
	Sarcoidosis
	The Behçet syndrome
	anticardiolipin syndromes
	Hashimoto's disease
	coeliac disease
Metabolic disorders	Adult-onset leukodystrophy
	Vitamin B12 deficiency
	Vitamin E deficiency
Infections	HIV
	Lyme disease
	syphilis
Vascular disorders	Dural arteriovenous fistula
	The Susac syndrome
	Migraine
Neoplasia	glioma
	lymphoma
	astrocytoma

Table 3.2: *Chart showing the differential diagnosis of Multiple sclerosis*

3.5 The neuro-ophthalmological manifestations of multiple sclerosis

As MS is caused by demyelinating lesions disseminated throughout the CNS, several distinct neuro-ophthalmic lesions involving both the optic nerve and the ocular motor system can be seen.

The neuro-ophthalmic problems associated with MS are listed below

- Optic neuritis
- Uveitis

- Nystagmus
- Saccadic intrusions and oscillations
- Internuclear ophthalmoplegia and related syndromes
- Skew deviation and vestibular abnormalities
- Cranial nerve palsies

3.5.1 Optic neuritis

Acute demyelinating optic neuritis is frequently the initial clinical manifestation of MS. It constitutes one of the clinically isolated syndromes. It typically occurs between 20-50 years of age and more common in women than men in the ratio of 3:1.

3.5.1.1 Clinical Characteristics

The patient typically experiences a decreased visual acuity over 7-10 days period, associated with pain on eye movements. There is associated reduced contrast sensitivity and colour vision. Some degree of visual recovery is expected within 30 days' time in the case of typical optic neuritis.

The pain associated with visual loss serves as a useful feature in the differential diagnosis of optic neuritis. In the "Optic Neuritis Treatment Trial" (ONTT) 92% of patients experienced pain on ocular movements associated with visual loss (Chan and Lam, 2004).

Patients with optic neuritis can present with a wide range of visual field defects. The field defects could be in the form of diffuse visual field loss, central or centrocaecal scotomas, altitudinal or nerve fiber bundle type defects. The visual field defect usually tends to resolve with time (Keltner *et al.*, 1993)

In addition to the optic nerves any other part of the visual pathway can be involved by the demyelinating process, including the optic chiasm, optic tracts, optic radiations, and striate cortex(Plant *et al.*, 1992) . The corresponding visual field defect can be produced based on the site of lesion. In the ONTT 13.2% of patients demonstrated evidence of chiasmal or retrochiasmal visual field defects of which 5.1% had bitemporal defects and 8.9% showed homonymous field defects (Plant *et al.*, 1992). 75.7% of patients who had these retrochiasmal defects had an abnormal baseline MRI scan compared to 46% without such defects.

Optic neuritis can recur either in the same eye or the fellow eye. According to the ONTT study 28% of patients had recurrence of optic neuritis within 5 years (Beck et al., 2004a, Group, 1997) and 35% within 10 years (1997, Beck et al., 2004b).

According to the revised McDonald diagnostic criteria, a monosymptomatic presentation as seen in some cases of Clinically Isolated Syndromes (CIS) would be considered as an episode but would not be sufficient to make a diagnosis of MS (Polman *et al.*, 2005). To make a diagnosis of MS there would need to be a second episode of optic neuritis and/or supported by further radiological and laboratory investigations. Para-clinical criteria becomes more stringent if the clinical presentation is less definite, as seen in patients with

single demyelinating events with CIS or in patients with insidious progressive disease.

3.5.2 Uveitis

Rucker in 1945 (Rucker, 1945) was the first to describe sheathing of retinal veins in patients with multiple sclerosis. The incidence of symptomatic uveitis in patients with MS ranges from 1.1% to 7% (Biousse *et al.*, 1999) compared to the general population of 0.13% (Gritz and Wong, 2004). However asymptomatic inflammation of the eyes, including perivascular sheathing has an incidence of 18% to 46% in patients with MS (Graham et al., 1989, Bregerbc and Leopold, 1966).

The uveitis in MS patients follows the same natural course of the disease. Granulomatous uveitis has been reported in MS patients (Zein *et al.*, 2004). The exact mechanism of the coexistence of MS and uveitis is not clear. It has been hypothesized that the uveitis seen in MS could be due to an immune response against a myelin protein present in the iris (Huhtala, 1976) and/or alpha beta crystalline protein in the lens. Similar reactions have been shown also in other autoimmune disease such as Vogt Koyanagi Harada syndrome.

3.5.3 Ocular motor defects in MS

Ocular motor defects in MS are mainly acquired pendular nystagmus, gaze evoked nystagmus, internuclear ophthalmoplegia and saccadic abnormalities.

Due to widespread changes in the brain any of these oculomotor defects can be seen.

3.5.3.1 Acquired pendular nystagmus (APN)

Multiple sclerosis is one of the commonest causes for acquired pendular nystagmus (APN). APN can also be seen in other acquired conditions such as Whipple disease (Schwartz *et al.*, 1986), Peliazaeus-Merzbacher disease (Trobe *et al.*, 1991), acute brain stem stroke (Keane, 1986), hypoxic encephalopathy (Averbuch-Heller *et al.*, 1997), spinocerebellar degeneration (Averbuch-Heller *et al.*, 1997) and toluene abuse (Hunnewell and Miller, 1998).

The trajectory of the APN can have horizontal, vertical and torsional components or a combination of these. The trajectories can be conjugate but are often dysconjugate. The amplitude of APN is the most common cause of disconjugacy between two eyes but the frequency of nystagmus is usually quite similar between two eyes at around 2-8 Hz (Lopez *et al.*, 1996). The difference in the amplitude can sometimes lead to monocular nystagmus as seen on clinical examination.

APN causes severe oscillopsia and reduced visual acuity. The site of lesion for APN has been suggested to be cerebellar nuclei as it is commonly associated with cerebellar signs (Aschoff *et al.*, 1974). Gresty et al.(Gresty *et al.*, 1982) proposed the site of lesion to be in the vicinity of the ocular motor nuclei due to the fact that APN is most often associated with internuclear

ophthalmoplegia and also the lesion at this site in the brainstem could explain the dysconjugacy. Lopez et al.(Lopez *et al.*, 1996) in a study using MRI to delineate the areas involved in causing APN showed the central tegmental tract, the medial vestibular nucleus, the red nucleus and the inferior olive as possible sites causing APN. The pathophysiology of APN is not known, but a cholinergic system abnormality has been suggested as some patients improve with anticholinergic drugs (Leigh et al., 2002, Starck et al., 1997). Also, APN usually develops after months to years of development of the disease, and this could be due to development of denervation hypersensitivity to acetylcholine receptors (Starck *et al.*, 1997).

3.5.3.2 Gaze evoked nystagmus

The ability of holding the eyes in eccentric position of gaze against the elastic restoring forces of the orbit requires a tonic contraction of the extraocular muscles which is achieved by a sustained rate of discharge of the ocular motor neurons. This tonic signal is generated by a neural integrator that also integrates all conjugate eye movement commands such as saccades, smooth pursuits, VOR, and which converts the velocity coded information into position coded signals. For horizontal eye movements the neural integrator is located in the nucleus prepositus hyperglossi (Cho *et al.*, 2008). Diseases affecting the neural integrator cause an inability of eyes to be held in an eccentric position in the orbit. A leaky or abnormal neural integrator causes the eyes to drift back to the central position, which in turn leads to a corrective saccade causing gaze evoked nystagmus. It is clinically very important to differentiate gaze evoked

nystagmus with the physiological end point nystagmus in which the nystagmus usually comes on immediately after turning the eyes to eccentric position and dampens after several seconds. Common causes of gaze evoked nystagmus are drugs such as anticonvulsants, sedatives, alcohol, tranquilizers, brain stem and cerebellar disorders, multiple sclerosis (Leigh RJ, 2006).

3.5.3.3 Saccadic intrusions and oscillations

Saccadic intrusions can be both physiological and pathological eye movements. In normal subjects the eyes are not perfectly stable during periods of fixation, but are frequently interrupted by slow drifts, and saccadic intrusions (Abadi and Gowen, 2004). Saccadic intrusions can be differentiated from nystagmus, in that there is no drift of the eyes from the desired position of gaze but the primary abnormality is intrusion of saccades during fixation. Saccadic intrusions should also be differentiated from saccadic dysmetria in which the main abnormality is the overshoot or undershoot of saccades before landing on the target.

Saccadic intrusions and oscillations could be classified into the following types:

i. Square wave jerks
ii. Macro square wave jerks
iii. Macro saccadic oscillations
iv. Ocular flutter
v. Opsoclonus

Square wave jerks

These are small, conjugate, horizontal saccades which take the eyes away from the fixation position by approximately 0.5° and a return back after a period of about 200 to 400ms. These are commonly seen in elderly individuals, and in subjects secondary to neurological disease such as cerebellar syndromes (Rabiah *et al.*, 1997), cerebral hemispheric disease (Sharpe *et al.*, 1982), and progressive supranuclear palsy (Troost and Daroff, 1977). They can also be called square wave oscillations as they may occur almost continuously. These oscillations can be clinically mistaken for nystagmus.

Macro square wave jerks

These oscillations have larger amplitude than square wave jerks of more than 5° and at a frequency of 2-3Hz. These saccades also take the eyes away for the target and return after a latency of 80ms. These oscillations occur in bursts and are reported in multiple sclerosis and multi-system atrophy (Klotz and Klockgether, 2005).

3.5.3.4 Internuclear ophthalmoplegia (INO)

INO is one of the classical signs seen in patients in MS. It is due to lesions in the medial longitudinal fasciculus (MLF). The MLF are a pair of white fibre tracts that extend through the brain stem. They are important tracts for transmitting information that is crucial for the control and coordination of eye movements. They contains fibres which interact with ocular motor circuitries

involved in coordination of horizontal, vertical and torsional eye movements (Frohman *et al.*, 2008). The MLF act as a final common pathway for all conjugate eye movements including saccades, smooth pursuits, and vestibulo-ocular reflex. The three cranial nuclei namely the 3rd, 4th and 6th cranial nuclei which are involved in the ocular motor control are interconnected via the MLF.

Internuclear ophthalmoplegia is one of the most localizing sign resulting from the lesion in the MLF in the dorsomedial brainstem tegmentum of either the pons or the midbrain (Frohman et al., 2008, SMITH and DAVID, 1964). INO is the most common saccadic abnormality affecting between 17% and 41% of patients with multiple sclerosis (Müri and Meienberg, 1985) . The increased incidence if INO seen in patients with MS could be due to the location of the ocular motor apparatus in the region of the brainstem periventricular zone an area which for some reason is highly susceptible to demyelination. The ocular motor abnormality seen in INO is characterized by ocular dysconjugacy during horizontal saccades. The adducting eye is slow with limitation of movements which may or maynot be accompanied by abducting nystagmus in other eye. Multiple sclerosis patients usually have bilateral INO.

INO is not always detected on clinical examination. In more subtle forms the range of adduction is normal however the velocity of adduction is reduced. In such cases this subtle form of INO can only be appreciated using eye movement recording.

3.6 Expanded Disability Status Scale (EDSS)

Measuring disease progression is an important both from treatment aspect aswell as for MS clinical trials. Clinical scales are used as primary and secondary outcome to record the disease progression in MS. The Kurtzke Expanded Disability Status Scale (EDSS) is used as a gold standard for measuring disability in MS despite its limitations (Kurtzke, 1983). The EDSS scale ranges from 0 to 10 in 0.5 unit increments where higher values represent higher levels of disability. The scoring system takes into account the walking distance of patient with MS, along with the involvement of the functional systems (FS) such as:

- Pyramidal functions
- Cerebellar functions
- Brainstem
- Sensory functions
- Bowel and Bladder function
- Visual Function
- Cerebral functions
- Others

0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid - cane, crutch, etc. to walk about 100m with or without resting
6.5	Requires two walking aids - pair of canes, crutches, etc. - to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

Table-3.3: The Kurtzke Expanded Disability Status Scale (EDSS) reproduced from **www.mstrust.org.uk**

3.7 Background and aims of the study

Ocular motor abnormalities are a common finding in patients with MS. Eye movement abnormalities offer reliable and valuable information of the proper functioning of the cerebellar and brain stem function. However, in a clinical setup the standard testing of the eye movement abnormalities is limited to examination of the range of ocular movements and detection of nystagmus(Serra *et al.*, 2003). It is difficult to characterize clinically the various ocular motor deficits of MS patients based on clinical examination alone. Eye movement recordings in these patients offer us an opportunity to detect the presence of various ocular motor abnormalities.

The indications of disease progression or improvement from clinical drug trial perspective are the findings seen on MRI (Grimaud *et al.*, 1999) and the EDSS scores (Kurtzke, 2008). There are only few studies describing the ocular motor abnormalities in MS and the correlation between the severity of the disease as indicated by the EDSS score and the extent of ocular motor abnormalities seen. There are also no previous studies to our knowledge investigating the relationship between primary progressive and the relapsing type of MS in relation to the extent of ocular motor abnormality. These two conditions form distinct subtypes of MS as far as the pathogenesis is concerned. With the advances in our understanding on the specific area in brain causing each of these oculomotor abnormalities and with some specific treatments available, the indentification of these oculomotor abnormalities may also become important.

The aims of the study were:

i. To detect the various oculomotor abnormalities seen in patients with multiple sclerosis (MS) using eye movement recordings.

ii. Analyse the extent of oculomotor abnormality in relation to disease severity (Expanded Disability Status Scale, EDSS score)

iii. To compare the differences in ocular motor abnormalities in the different subtypes of MS

iv. To analyse the pendular nystagmus observed in patients with MS

3.8 Patient and Methods

All patients included in this study were initially seen in the context of specialized neuro-ophthalmology clinic at Leicester Royal Infirmary. All the patients were referred by the neurologist for further management of nystagmus. The clinical subtype of multiple sclerosis and the EDSS score at the time of referral was noted by the referring neurologist. Hence the primary inclusion criterion was acquired oculomotor abnormality in patients diagnosed with MS.

The total cohort of the MS patients in our study was sixty five (n=65), of which the different subtypes of MS were 14 patients in the RRMS subtype, 21 patients in the SPMS subtype and 15 patients in the PPMS subtype. In 15 patients the neurologist had not specified the subtype of MS. The male to female ratio in our study was 1**:**1.6. The male to female ratio in the subtypes of

MS are RMMS 1**:**2,, SPMS 1**:**1.5 and PPMS 2**:**3.. The patients age ranged from 37 to 50 years with mean of 45.5 yrs.

3.8.1 Visual acuity

All subjects included in the study had best-corrected visual acuity (VA) measured using Snellen optotypes at 6 meters which was then converted to logMAR visual acuity for analysis. Visual acuity was measured for each eye and also with both eyes open. Visual acuity data was not available in 11 patients.

3.8.2 Eye Movement Recordings

This study had a similar setup to the previous study (see Chapter-2). All the eye movement recordings were analyzed by AK. The findings were confirmed by Dr Frank Proudlock in case of ambiguity in the characterization of the ocular motor abnormalities. The following ocular motor abnormalities were identified in all patients.

3.8.2.1 Pendular nystagmus

If the eye movement recording showed pendular nystagmus, we further characterized it into either conjugate or dysconjugate nystagmus. To do this the amplitude and frequency of the pendular nystagmus was further

analyzed using the script developed by Frank during of period of stable fixation (5 seconds) in primary position. Peaks and troughs in a smoothed waveform were used to identify maxima and minima in the original eye movement trace which were then used to calculate amplitude and frequency measures (intensity is the product of amplitude and frequency). The conjugacy of the amplitude and frequency of the pendular nystagmus was compared in both the eyes.

We also looked at whether the conjugacy/dysconjugacy of the pendular nystagmus were related to the optic nerve dysfunction reflected by the visual acuity in the two eyes.

3.8.2.2 Internuclear Ophthalmoplegia (INO)

INO was diagnosed by observing the eye movement recordings during a horizontal saccadic task. INO was positively detected mainly from hypometric saccade in the adducting eyes with hypermetric saccades in the abduction eye and also the presence of abducting nystagmus was observed in some participants. The INO could be unilateral or bilateral.

3.8.2.3 Gaze evoked Nystagmus (GEN)

Gaze evoked nystagmus was detected by comparing the pattern of eye movements in the primary position to that during gaze holding ±15° in leftward and rightward secondary positions. Patients with GEN had right or left beating nystagmus while looking at these respective gaze positions, i.e. left beating in left gaze position..

3.8.2.4 Saccadic Intrusions and Oscillations

Saccadic intrusions and oscillations were detected by observing the eye movement recordings of patient during a central fixation task. Any saccadic movement that takes the eye of the fixation and brings the eye back to the primary position with an intersaccadic interval was noted.

3.8.3 Statistics

A Chi-square test was performed to compare the proportions of the different forms of ocular motility abnormalities such as pendular nystagmus, gaze evoked nystagmus, internuclear ophthalmoplegia and vertical nystagmus, between the different subtypes of MS (RRMS,PPMS,SPMS) and the disease severity (EDSS score).

We compared the EDSS scores between the three different subtypes of MS using a Kruskal-Wallis test since the data was non-parametric. Similarly, an analysis of whether the severity of MS (EDSS score) was related to existence of the ocular motor deficit was made by comparing the median EDSS scores in patients in whom signs were present or absent (pendular, SWJ, INO, vertical and GEN). The two proportions were compared using a Mann Whitney U test due to the data being non-parametric.

Coefficient of variation (COV) was used to assess difference between amplitude and frequency of nystagmus between left and right eye. This would

provide information whether the dysconjugate nystagmus was due to variability in amplitude, frequency or both.

Regression analysis was performed to investigate the relationship between monocular logMAR visual acuity and the amplitude, frequency and intensity of nystagmus in each eye.

3.9 Results

3.9.1 Co-existence of Ocular Motor Abnormalities

More than one ocular motor abnormality was observed in all patients for all the subtypes of MS with the exception of patients 37, 38 and 39 who had only pendular nystagmus and patient 66 who had only GEN. The various ocular motor abnormalities seen in our cohort is shown below **Figure 3.1** where each row represents a single patient and the corresponding ocular motor signs. As can be seen there is a coexistence of more than one subtype of oculomotor abnormality in each of these patients.

One interesting aspect to note is that none of the patients in our cohort had overlap of all the five oculomotor abnormalities we analysed. Most patients showed a coexistence of a number of oculomotor deficits including pendular nystagmus, GEN, INO and SWJ although the occurrence of these was not related to MS severity or type ($p>0.05$). Pendular nystagmus was the most common type of nystagmus and was present in 60% of patients (n=39),

followed by INO (52%; n=34), saccadic abnormalities (41%; n=27), GEN (38%; n=25), and vertical nystagmus (34%; n=22).

Pendular	Saccadic Intrusions	INO related	Vertical Jerk	Horizontal Jerk
pendular	SWJ	INO	-	-
pendular	SWJ	INO	-	-
pendular	SWJ	-	upbeat	-
pendular	SWJ	-	downbeat	GEN
pendular	SWJ	-	downbeat	-
pendular	SWJ	-	-	GEN
pendular	SWJ	-	-	GEN
pendular	SWJ	-	-	-
pendular	SWJ	-	-	-
pendular	SWJ	-	-	-
pendular	-	INO	upbeat	GEN
pendular	-	INO	upbeat	-
pendular	-	INO	downbeat	-
pendular	-	INO	-	GEN
pendular	-	INO	-	GEN
pendular	-	INO	-	GEN
pendular	-	INO	-	GEN
pendular	-	INO	-	GEN
pendular	-	INO	-	-
pendular	-	INO	-	-
pendular	-	INO	-	-
pendular	-	INO	-	-
pendular	-	INO		GEN
pendular	-	-	upbeat	GEN
pendular	-	-	upbeat	GEN
pendular	-	-	upbeat	GEN
pendular	-	-	upbeat	-
pendular	-	-	upbeat	-
pendular	-	-	downbeat	GEN
pendular	-	-	downbeat	GEN
pendular	-	-	downbeat	GEN
pendular	-	-	downbeat	-
pendular	-	-	downbeat	-
pendular	-	-	downbeat	-
pendular	-	-	-	GEN
pendular	-	-	-	-
pendular	-	-	-	-
pendular	-	-	-	-
pendular		INO		
-	SWJ	INO	upbeat	-
-	SWJ	INO	downbeat	-
-	SWJ	INO	-	GEN
-	SWJ	INO	-	-
-	SWJ	INO	-	-
-	SWJ	INO	-	-
-	SWJ	INO	-	-
-	SWJ	INO	-	-
-	SWJ	INO	-	-
-	SWJ	-	upbeat	-
-	SWJ	-	upbeat	-
-	SWJ	-	-	GEN
-	SWJ	-	-	GEN
-	SWJ	-	-	-
-	SWJ	-	-	-
-	SWJ	-	-	-
-	-	INO	downbeat	GEN
-	-	INO	-	GEN
-	-	INO	-	GEN
-	-	INO	-	GEN
-	-	INO	-	-
-	-	INO	-	-
-	-	INO	-	-
-	-	INO	-	-
-	-	-	-	GEN

Figure-3.1 *Chart showing the coexistence of various ocular motor abnormalities in the patient cohort. Each row represents a single patient and each row is a single ocular motor abnormality.*

The coexistence of more than one oculomotor abnormalities were seen in 93% (n=61) of patients, and the remaining 7% (n=4) of patients had only one ocular motor abnormality detected. Amongst the patients with coexistence of more than one ocular motor abnormality only 4% (n=2) had four different ocular motor abnormalities detected on eye movement recordings, while 44% (n=24) had three ocular motor abnormality, and 52% (n=28) had two coexisting ocular motor abnormalities.

Although there was no one particular ocular motor abnormality that was consistently seen in the presence of more than one ocular motor abnormality detected, pendular nystagmus was a more common ocular motor abnormality than the rest.

3.9.2 Interesting eye movements showing the overlap of different ocular motor deficits in patients

There was an overlap of different oculomotor abnormalities seen in a single patient. A number of interesting examples of the co-existence of ocular motor abnormality are described here.

3.9.2.1 Pendular nystagmus with gaze-evoked nystagmus

Pendular with gaze evoked nystagmus was observed in 17 patients (43%). Eye movement recording of one of the patients is depicted in **Figure 3.2**.The horizontal eye movement recordings of both eyes in central gaze show a low

amplitude pendular nystagmus with few left beating jerk nystagmus waveforms (green arrow) in the primary position of gaze. On right gaze the recordings shows a right beat jerk nystagmus (blue arrow) with low amplitude pendular nystagmus and on left gaze a left beat jerk nystagmus (yellow arrow) with the amplitude of the pendular nystagmus increasing in the left gaze.

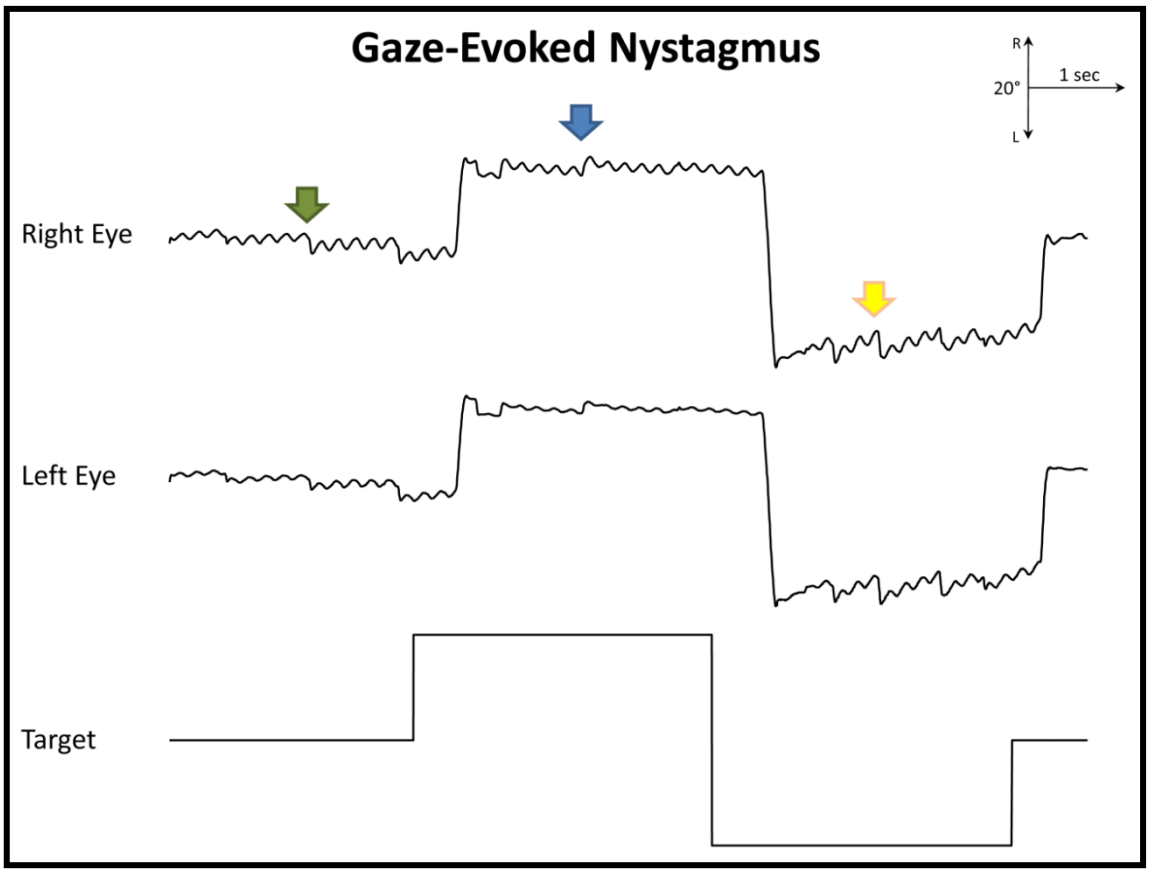


Figure-3.2 *Horizontal eye movement recordings of both eyes show a low amplitude pendular nystagmus with gaze evoked nystagmus. The lower scale shows the target at primary position, to the right by 20° (upwards on the figure) and to the left 20° (downwards on the figure). The corresponding right and left eye movements are shown.*

3.9.2.2 Square wave jerks with INO

Square wave jerks with INO was observed in 10 patients (25%). The eye movement recordings in one patient with bilateral internuclear ophthalmoplegia are depicted in **Figure 3.3**. The horizontal eye movement recordings of the right and left eyes show large amplitude macro square wave jerks with INO where abducting saccades are hypometric and adducting saccades are hypermetric. Consequently, left saccades in the right eye are hypometric and right saccades hypermetric. The converse pattern in observed in the left eye. A pendular nystagmus is also visible during phases where there was no SWJ. Pendular nystagmus with macro SWJ was seen in 2 patients (3%).

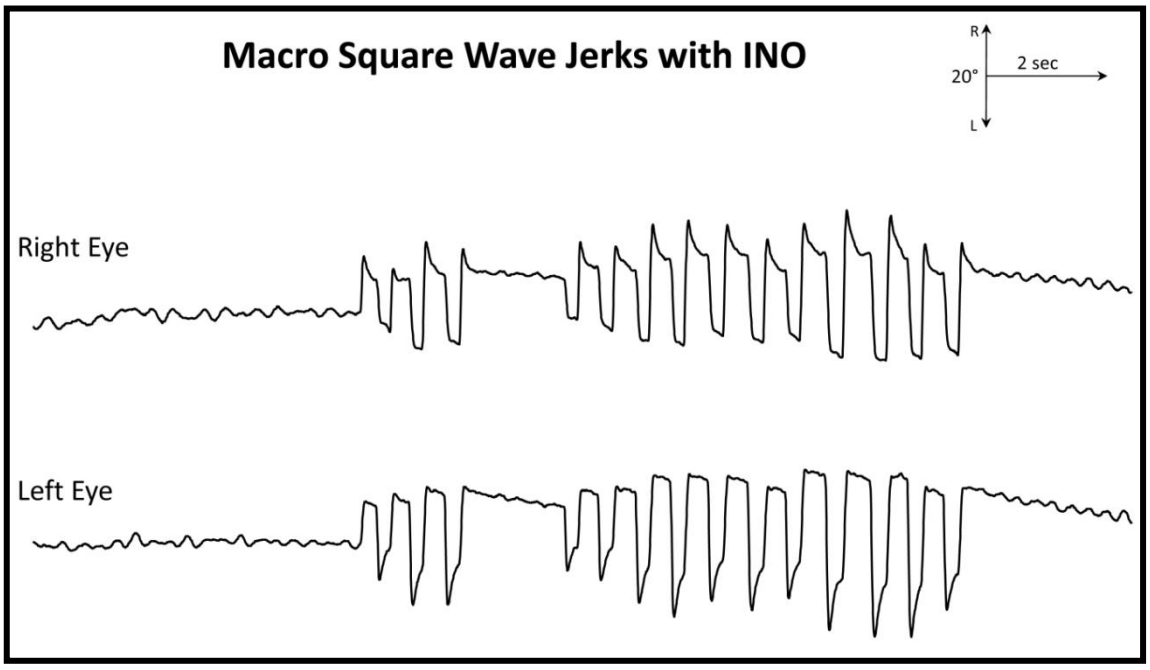


Figure-3.3 *The eye movement recordings show the right and left eyes in primary position. The initial phase show a low amplitude pendular nystagmus which is followed by bursts of saccadic eye movements, i.e. macro square wave jerks. The overshoot and drift centrally when the right eye saccades to the right and the left eye saccades to the left is caused by the INO.*

3.9.2.3 Pendular with upbeat nystagmus

Pendular nystagmus with upbeat vertical nystagmus was observed in 8 patients (12%). Eye movement recordings help in clearly delineating the subtle vertical upbeat nystagmus on top of the pendular nystagmus waveform (**Figure 3.4**)**.**

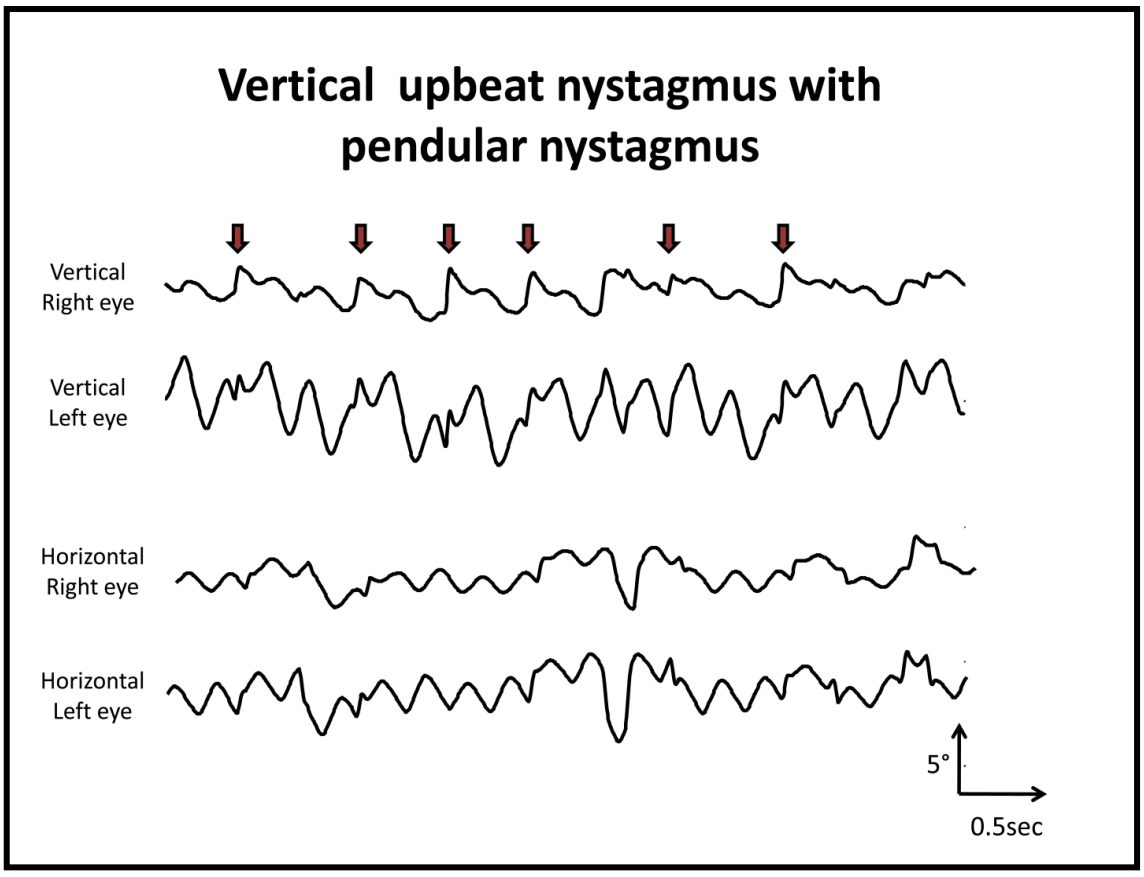


Figure-3.4 *Horizontal and vertical eye movement recording of right and left eye show the pendular nystagmus in both horizontal and vertical eye movement tracings of both eyes. The eyes are clearly dysconjugate on horizontal and vertical traces. A vertical jerk nystagmus is particularly evident in the right eye which is upbeat (quick phases indicated by arrows).*

3.9.2.4 Pendular with downbeat nystagmus

Pendular nystagmus with downbeat nystagmus was seen in 9 patients (14%) (**Figure3.5**).The eye movement recordings show pendular waveforms in horizontal and vertical traces of both eyes indicating elliptical waveforms. A vertical jerk nystagmus which is down beat is seen in the left eye.

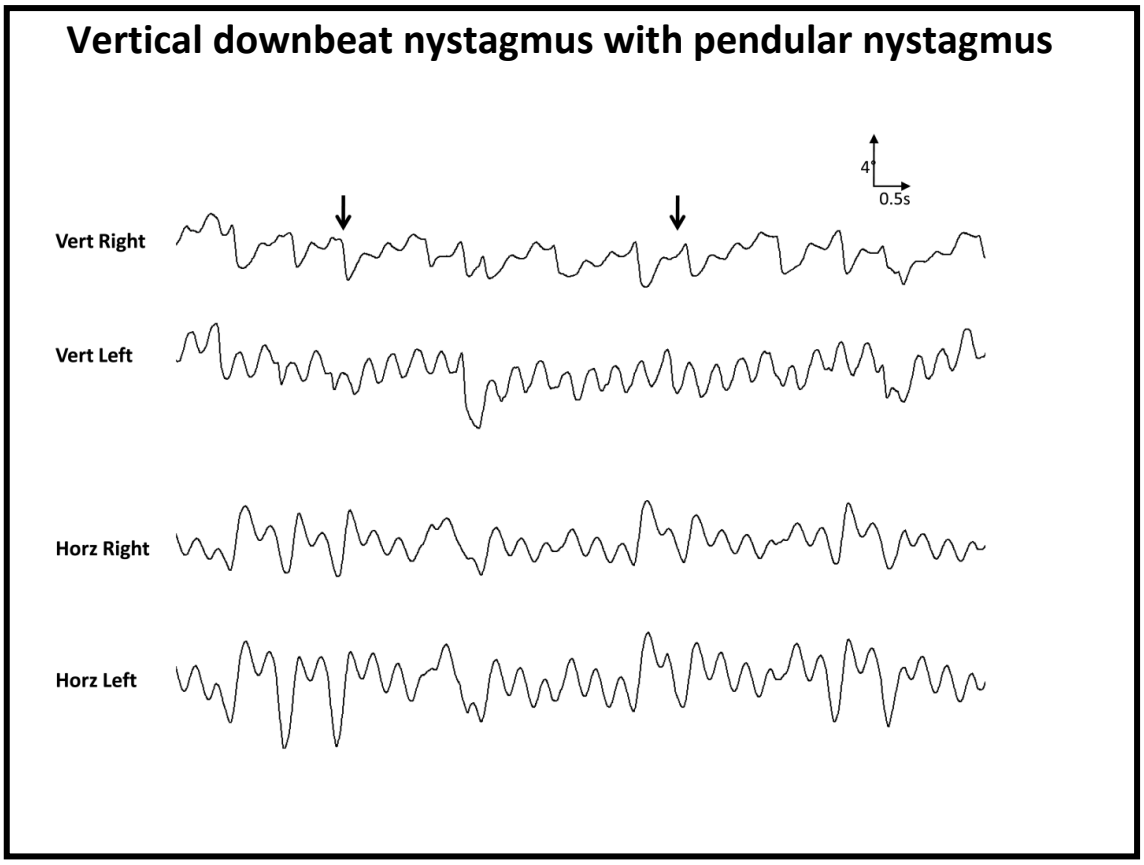


Figure-3.5 *Horizontal and vertical and eye movement recordings of right and left eye showing the pendular nystagmus in both horizontal and vertical eye movement tracing with jerk nystagmus which is downbeat and more visible in the right eye (indicated by arrow).*

3.9.3 Ocular Motor Abnormalities in Relation to MS Subtype

We calculated the proportion of ocular motor abnormality seen in each subtype of MS. A chi-square test was performed compare the proportions of the subtypes between the groups (**Figure 3.6**).

The proportion of pendular and GEN nystagmus in the SPMS (76% and 48%,respectively) and PPMS (73% and 40%,respectively) subtypes was higher compared to the RRMS subtype (36% and 21%, respectively). This was statistically significant (p=0.034 and p=0.289, respectively).

In contrast the proportion of SWJ and INO was higher in the RRMS subtype (57% and 64%, respectively) compared to SPMS (24% and 52%, respectively) and PPMS (53% for both) subtypes although this was not a significant difference (p= 0.084 and p=0.761).

Vertical nystagmus was seen in higher trends in the PPMS subtype (40%) compared to RRMS (21%) and SPMS (33%) subtypes although again this was not significant (p=0.555).

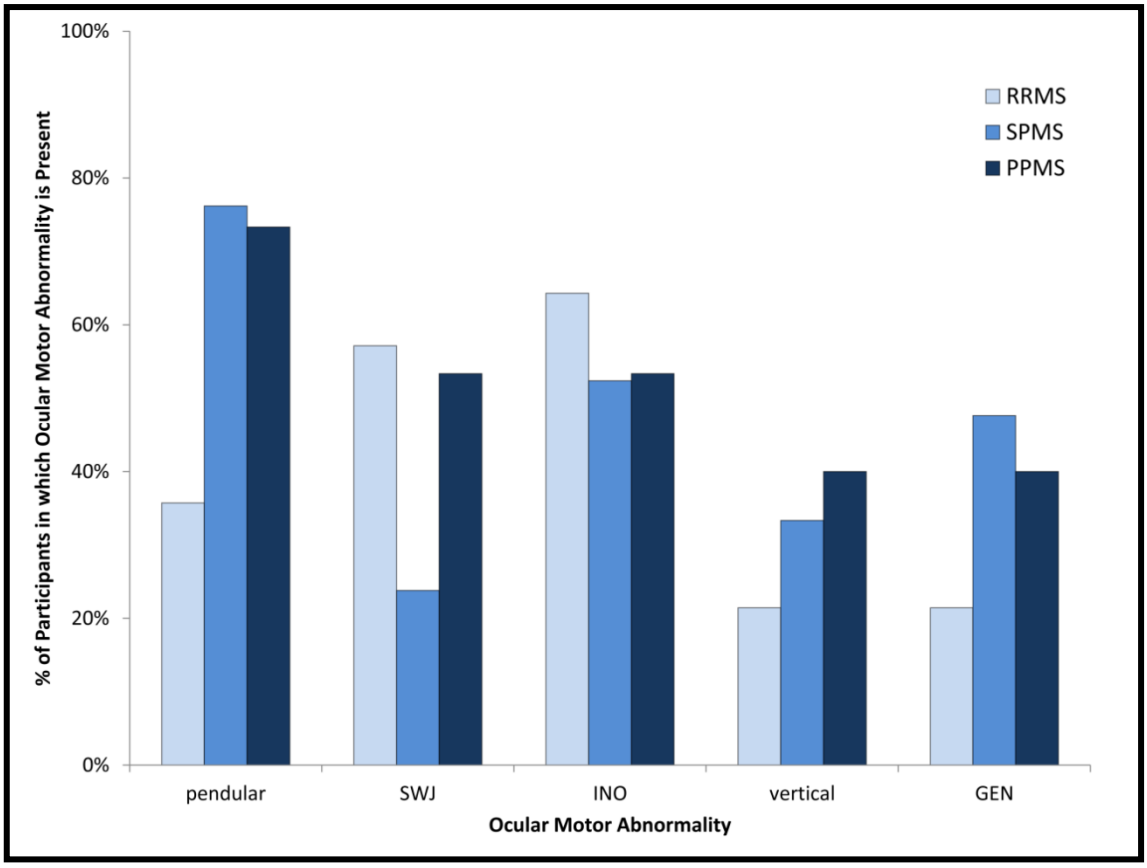


Figure-3.6 *A bar chart showing the percentage of each ocular motor abnormality in the three different subtypes of MS*

3.9.4 Ocular Motor Abnormalities in Relation to MS Severity (EDSS Score)

The Expanded Disability Status Scale (EDSS) score was recorded by the referring neurologist and the EDSS score on the first visit was noted. Two patients in the SPMS subtype of MS did not have a recorded EDSS score. The distribution of the EDSS score in the three MS subtypes is shown in **Figure 3.7**.

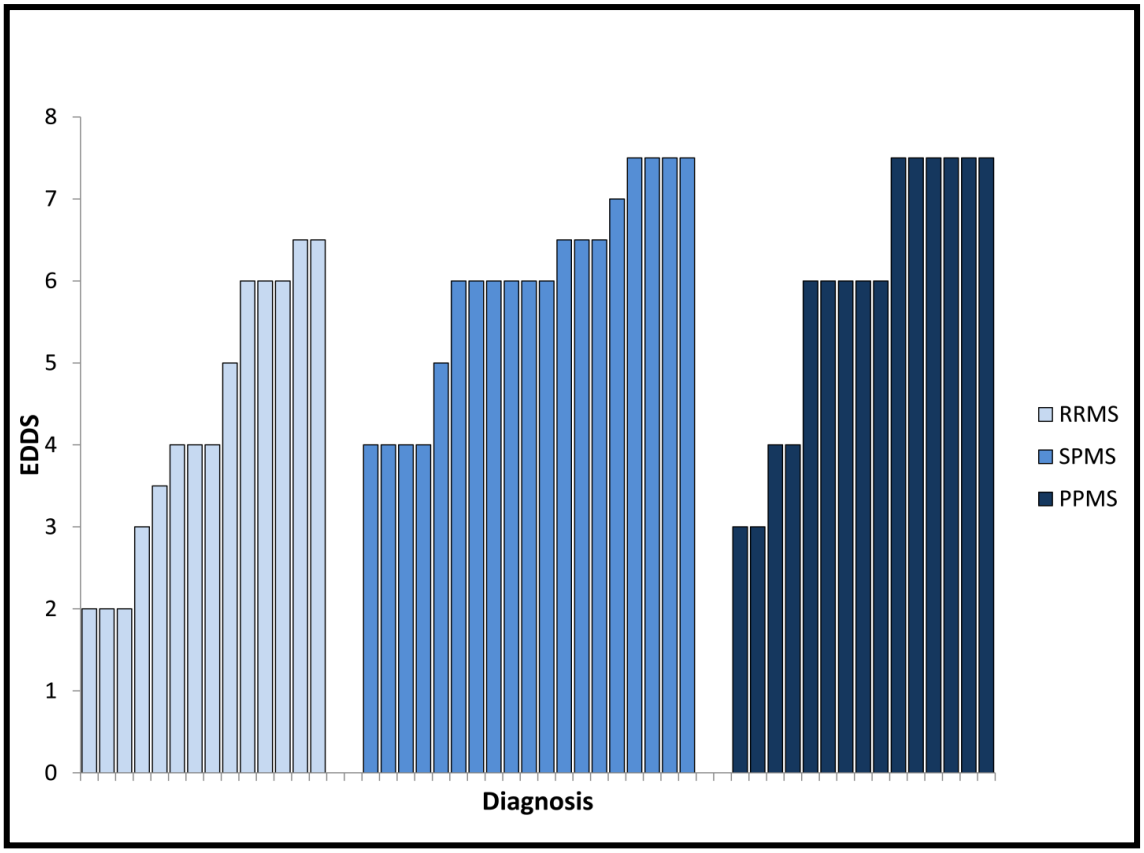


Figure-3.7 *EDSS score for the three different types of MS patients in our cohort*

The EDSS scores between the three MS groups was compared using a Kruskal-Wallis test as the data was non-parametric. A statistically significant difference was observed between the RRMS group (median EDSS score = 4.30) and the other two groups (median EDSS in the SPMS group = 5.97, PPMS group = 5.93; RRMS vs SPMS: p=0.006; RRMS vs PPMS: p=0.022). However, no statistical difference was noted between SPMS and PPMS (p=0.90).

The median EDSS scores in patients with the different types of oculomotor defcitis are shown in figure 3.8. GEN was the only sign that showed statistical significance with the EDSS score being significantly worse when the sign was present (p=0.027).

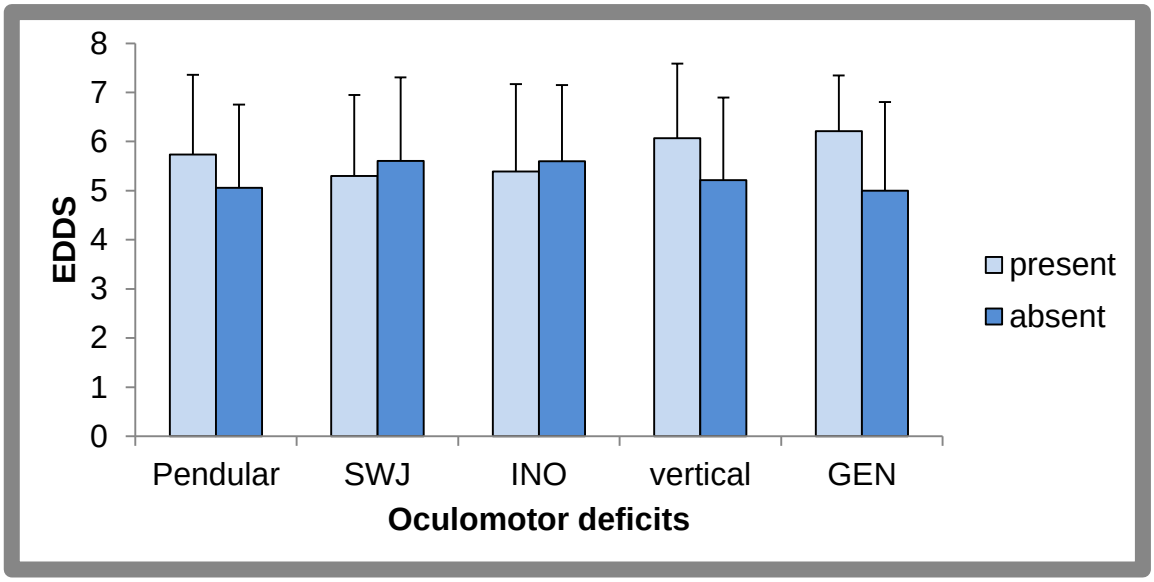


Figure-3.8 *Median EDSS scores (± quartiles) in patients where the ocular motor abnormality was present or absent.*

3.9.5 Analysis of Pendular Nystagmus

Pendular nystagmus was observed in 66.7% of patients with a mean amplitude (±SD) of 1.57° (±1.48°) and frequency of 4.06Hz (±1.14Hz). 94% of patients with pendular nystagmus were judged to have dysconjugate nystagmus on clinical observations of the eyes or by looking at eye movement traces visually without any formal analysis.

The amplitude, frequency and intensity of pendular nystagmus were calculated using a custom script written by Dr.Proudlock. The amplitude, frequency and intensity of the pendular nystagmus were compared between the two eyes in both the primary position and also at 15° in left and right gaze.

Analysis of horizontal and vertical eye movement recordings showed that the dysconjugacy was mainly due to difference in the amplitude rather than frequency between the two eyes at 0° (COV for amplitude = 45%; COV for frequency =3.5%), +15° (COV for amplitude = 44.1%; COV for frequency = 14.5%) and -15° (COV for amplitude = 57.2% and COV for frequency =6.0%) (**Figure 3.9**)**.**

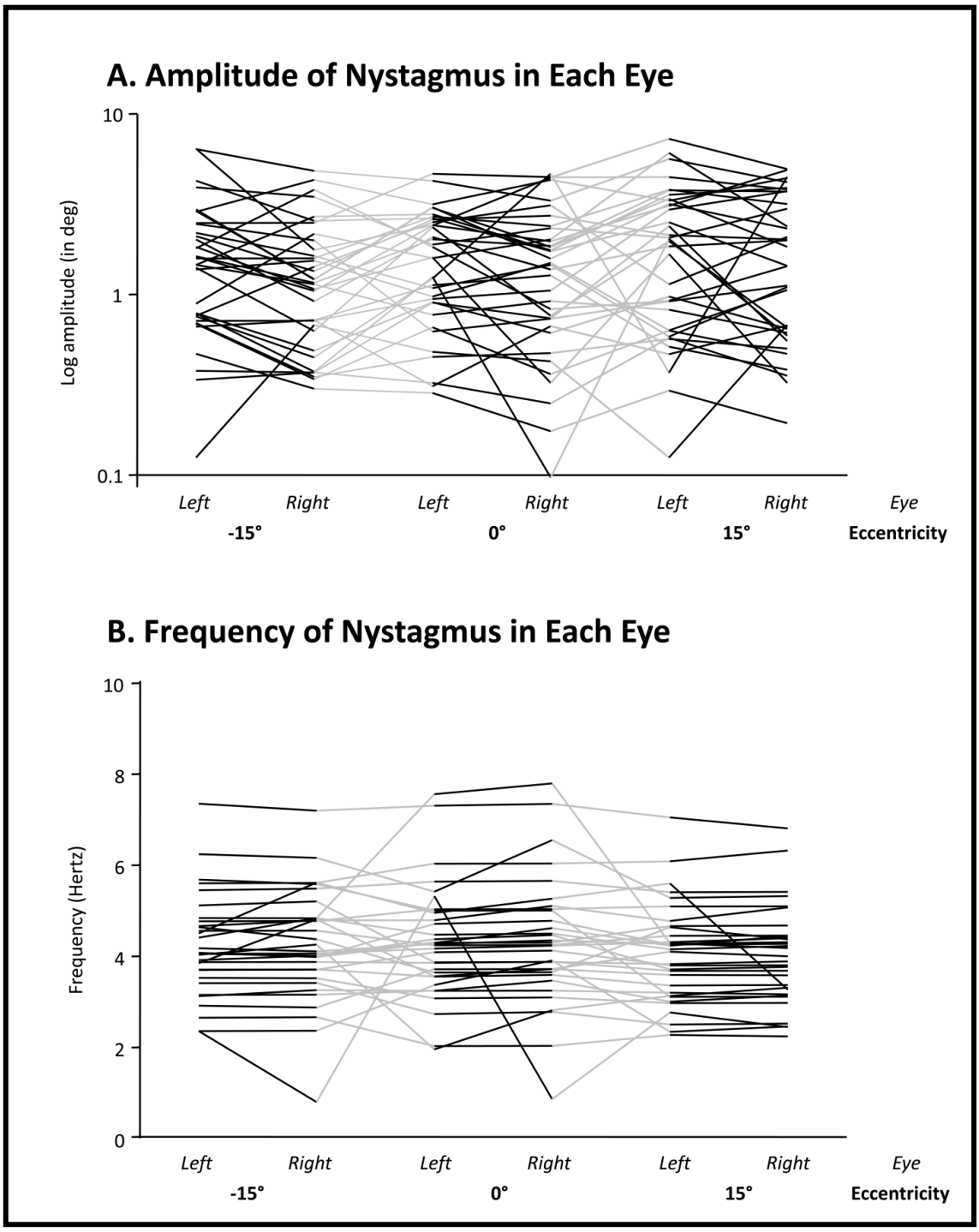
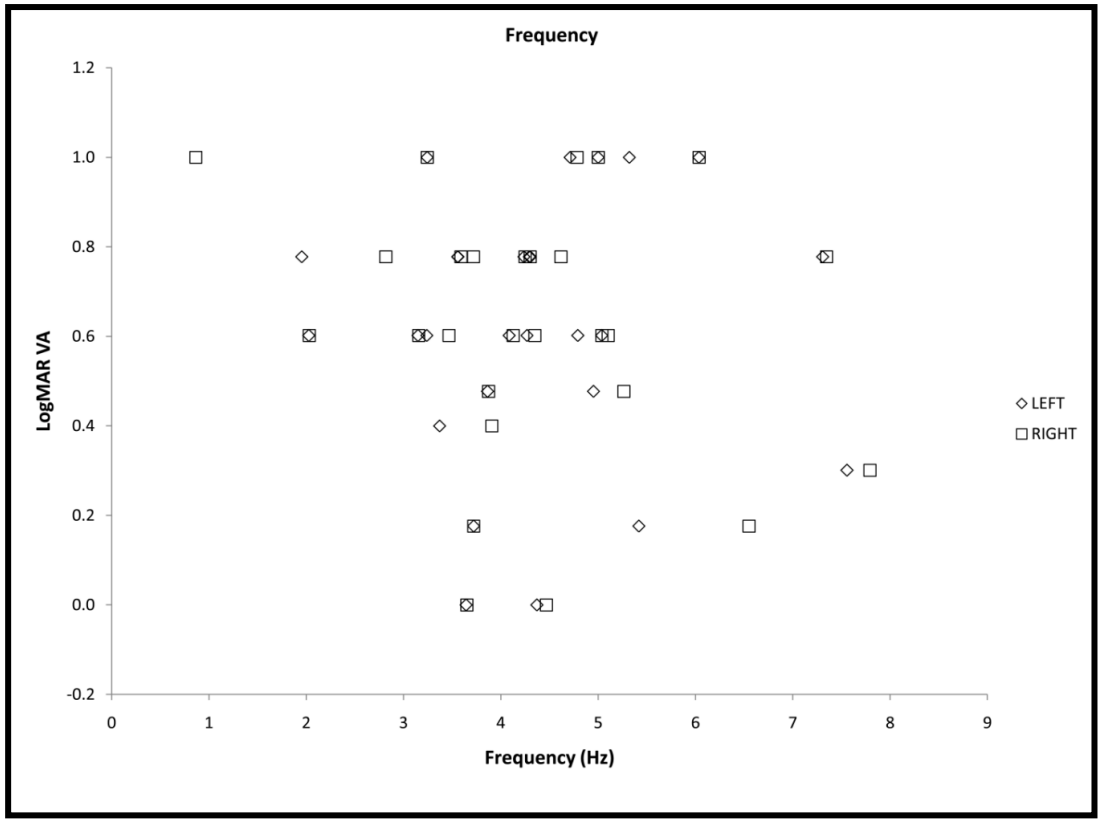
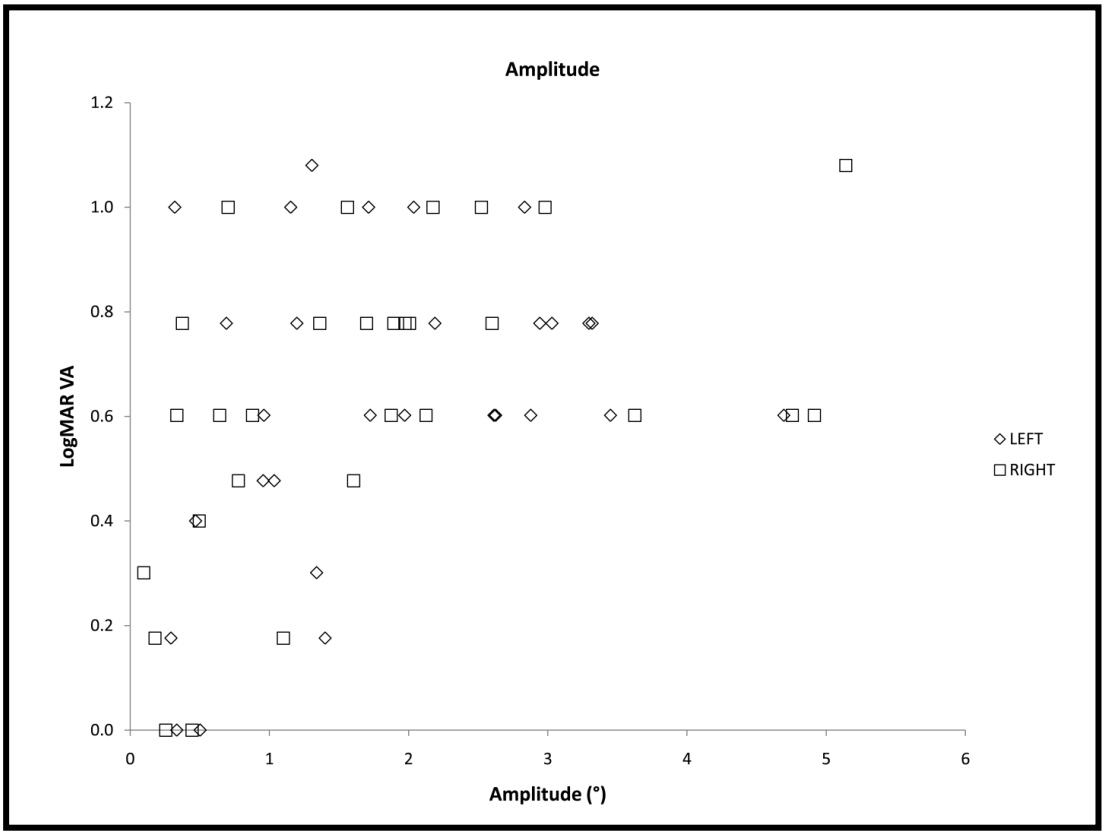


Figure-3.9 *Dysconjugacy of pendular nystagmus for A. Amplitude and B. Frequency in primary position (0°) left gaze (-15°) and right gaze (+15°). The dark line represent the position of the right and left eye in primary position and eccentricity, the faint line connects between these different positions for the same patient. As seen in the figure the main reason for the dysconjugacy was mainly due to the difference in the amplitude between the two eyes.*

3.9.5.1 Comparison of Visual Acuity to the Amplitude, Frequency and Intensity of Pendular Nystagmus

Regression analysis was performed to investigate the correlation between monocular logMAR visual acuity and the amplitude, frequency and intensity of nystagmus in each eye. Both the amplitude and intensity showed inverse correlation to the visual acuity (R^2=0.164 p=0.0016 and R^2=0.142, p=0.0034, respectively), while the frequency of pendular nystagmus did not correlate to the visual acuity (R^2=0.0067 p=0.55) (**Figure 3.10**).


Frequency
LogMAR VA
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
0
1
2
3
4
5
6
7
8
9
Frequency (Hz)
LEFT
RIGHT


Amplitude
LogMAR VA
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Amplitude (°)
LEFT
RIGHT

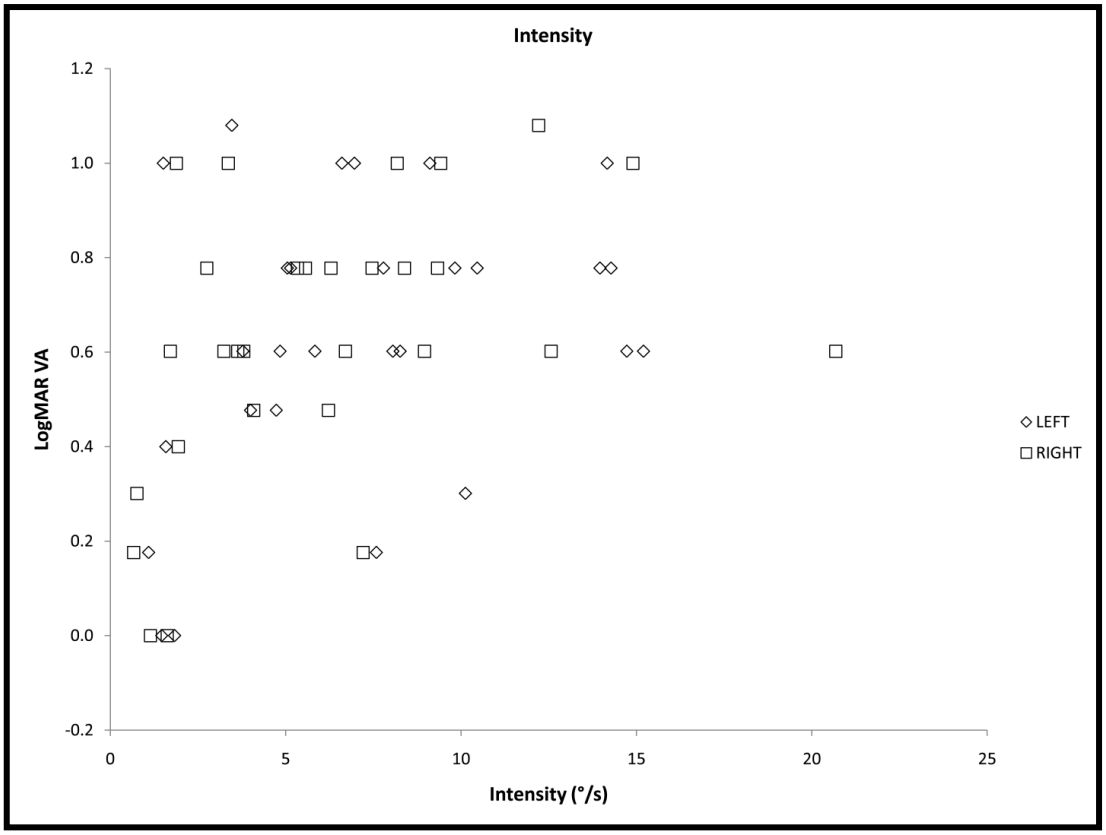


Figure-3.10 *Plots of monocular logMAR visual acuity against amplitude, frequency and intensity of pendular nystagmus in right and left eyes. Small square represent the visual acuity of the patients in right eye and the small diamond represents the visual acuity of the left eye. Both the amplitude and intensity showed inverse correlation to the visual acuity while the frequency of pendular nystagmus did not correlate to the visual acuity.*

3.10 Discussion

Eye movement disorders are important diagnostic signs of many diseases involving the central nervous system (Serra *et al.*, 2003). Multiple sclerosis, a demyelinating disease with a predilection to involve brainstem and cerebellum causes a broad range of eye movement abnormalities. Evaluation of a patient either suspected or diagnosed to have MS is not complete without a systematic evaluation of the eye movements and vision. The neuroophthalmic examination

not only helps in the diagnosis but also contribute to prognosis (Frohman *et al.*, 2005).

Clinical examination of patients with ocular motor defect in clinical settings is limited to testing the range of movements, sometimes testing saccadic and smooth pursuit responses, and detection of nystagmus (Serra *et al.*, 2003). Analysis of eye movement recordings help in the detection of various oculomotor abnormalities. Early detection of MS has become very important as initiation of treatment at an early stage may be beneficial to the patient. The affection of the anterior visual pathways such as optic neuritis is more often diagnosed without much difficulty than the ocular motor abnormalities due to lesions involving the brain stem and cerebellum. The detection of INO and saccadic abnormalities which are commonly seen in patients with MS can be quite challenging (Frohman *et al.*, 2003).

3.11 Frequency of occurrence of oculomotor abnormalities

In our study pendular nystagmus was the most common type of nystagmus (60%; n=39), followed by INO (52%; n=34), saccadic abnormalities (41%; n=27), gaze-evoked nystagmus (38%; n=25), and vertical nystagmus (34%; n=25). More than one oculomotor abnormality was noted in 83% of the patient cohort. There was no relation between the subtype of MS, severity of disability as shown by EDSS score and the number of oculomotor abnormalities seen ($p>0.05$).

Serra et al.(Serra *et al.*, 2003) in their study of eye movement recordings in 50 patients with MS found 20 patients with abnormal ocular movements of which INO (60%) and saccadic dysmetria (80%) were the most common abnormalities. However in their study they included patients even with normal eye movements. Downey et al.(Downey *et al.*, 2002) also found saccadic dysmetria to be the most common ocular abnormality (91%), followed by INO (68%), GEN (36%) with pendular nystagmus being the least (18%).

Tilikete et al.(Tilikete *et al.*, 2011) analyzed eye movements in 24 patients with MS and found INO most common (58%), followed by GEN (46%), saccadic dysmetria (25%) and pendular nystagmus (21%).

It is difficult to compare between two different studies on the incidence of oculomotor abnormalities as it depends on the type of subtype of MS, duration of disease and other factors in patient cohort which are difficult to compare.

All the patients in our cohort were referred from the neurologist due to visual disability experienced by patients often associated with nystagmus. Since the Leicester Ophthalmology Clinic is the only tertiary referral centre in UK to treat nystagmus, this could be the reason why we have more pendular nystagmus in our cohort.

As the demyelination process due to MS is widespread in the brain with no predilection for any particular site, there is no common oculomotor abnormality seen due to one particular subtype of MS.

3.12 Acquired Pendular Nystagmus

Acquired pendular nystagmus (APN) in MS was the most common oculomotor abnormality was observed. It is an important abnormality clinically as it leads to the distressing phenomenon of oscillopsia. It also causes decreased visual acuity due to retinal motion of images through continuous oscillations with the additional complication of optic nerve lesions which are a common associated finding in patients with APN (Straube *et al.*, 2004).The correct localisation of the lesions causing APN and success of treatment with drugs such as memantine and gabapentin has greatly helped patients with APN in MS (Starck et al., 1997, Leigh et al., 2002).

In our study pendular nystagmus was observed in 66.7% of patients with a mean amplitude (±SD) of 1.57° (±1.48°) and frequency of 4.06Hz (±1.14Hz). 94% of pendular nystagmus was dysconjugate. The dysconjugacy was mainly due to a difference in amplitude between the two eyes (coefficient of variation =45%) rather than frequency (coefficient of variation =3.5%). There was no clear change in pendular nystagmus amplitude, frequency or intensity with MS severity or type (p>0.05 for all).

Aschoff et al. (Aschoff *et al.*, 1974) analysed pendular nystagmus due to MS in 25 patients with eye movement recordings. They found the average frequency of pendular nystagmus to be 3.9Hz +/- 0.05Hz, and the amplitude of nystagmus to be less than 2°. They also found the frequency of the nystagmus to be the same in all positions of gaze, but marked variation in the amplitude.

Gresty et al.(Gresty *et al.*, 1982) analysed acquired pendular nystagmus in 52 patients due to various aetiologies including MS. 12 patients of the 52 patients had definite MS. The mean frequency of pendular nystagmus was 3.6Hz, with the mode between 2.6 and 3 Hz.

APN due to various diseases other than MS such as Whipple disease, Oculopalatalmyoclonus all have the frequency between 2-6Hz and the amplitude of the nystagmus can vary.

Most of the studies mentioned above including our study have found the frequency of nystagmus to be the same in the two eyes in a given patient, whereas the amplitude is often different. There are no studies to our knowledge that compares the severity of disability due to MS based on the EDSS score and the subtype of MS.

The lesion involving the afferent pathways to the olive nucleus are proposed to be the likely cause of pendular nystagmus (Gresty *et al.*, 1982). Inferior olivary neurons tend to fire at frequencies of 3-6Hz when they are actively depolarised (Llinás and Sasaki, 1989, Llinás and Yarom, 1986, Llinás and Yarom, 1981, Llinás and Volkind, 1973). Any lesion involving the tracts that project into the inferior olivary nucleus causes depolarisation of the neurons in the nucleus leading to ocular oscillations. This may explain why the frequency is similar across different studies including our own whereas the amplitude of the nystagmus varied.

One of the earlier theories proposed as the cause of APN in MS was that it is due to the delay in the visual processing due to demyelination of the anterior visual pathways (Barton and Cox, 1993). Averbuch- Heller et al. (Averbuch-

Heller et al., 1995) by manipulating the latency to onset of visual guided eye movements did not alter the oscillations of APN due to MS. This confirms that the APN is generated independently from the visual feedback mechanism.

In our study anterior visual pathway abnormalities in the form of optic atrophy were seen in 80% of patients. However, there was no correlation between the frequency of nystagmus and the visual acuity (R^2=0.0067 p=0.55).

3.13 EDSS score

EDSS score has become the accepted standard for clinical trials and many speciality MS clinics use the EDSS scores to follow up patients.

Downey et al. (Downey *et al.*, 2002) studied the correlation between the patients with normal and abnormal eye movements diagnosed with MS and their relation to the disability score. They found the patients with abnormal eye movements had more disability than patients with normal eye movements, with age and duration of the disease being identical. Derwenskus et al. (Derwenskus *et al.*, 2005) confirmed that similar findings in a follow-up prospective study of the same patients after 2 years.

In our study we found the EDSS score to be worse in patients with the progressive form of MS compared to the relapsing remitting type of MS which was clinically significant (RRMS vs SPMS: p=0.006; RRMS vs PPMS: p=0.022). This reflects the disease activity and agrees with the definition of the RRMS type in that there are episodes of neurological dysfunction followed by

substantial improvement, whereas the progressive form (SPMS, PPMS) show deterioration, with worsening of the EDSS score.

We found the EDSS score was worse in patients who had gaze-evoked nystagmus (GEN) (p=0.027). GEN is caused by lesions of the cerebellum and the brainstem which lead to deterioration of the neural integrators. The presence of GEN indicates a more generalised posterior fossa involvement. This is further substantiated by our finding that the proportion of GEN nystagmus in the progressive form of MS (PPMS, SPMS) is significantly higher compared to the RRMS subtype (p=0.289).

The involvement of a particular region of the brain may be common to all the three types of MS causing identical oculomotor abnormality.

3.14 Internuclear Ophthalmoplegia

Internuclear ophthalmoplegia (INO) is one of the most common oculomotor abnormalities seen in MS accounting for nearly one third of cases (Keane, 2005). INO is caused due to lesion involving the medial longitudinal fasciculus. Frohman et al. (Frohman *et al.*, 2003) performed a study to assess the accuracy of detection of INO by 279 physicians. The study involved playing videos of 18 subjects with unilateral, bilateral INO of varying degree or without INO. When the INO was subtle most of the physicians failed to recognise the condition. However it could be easily recognised by using eye movement recordings.

In our study we found INO to be commonly associated with pendular nystagmus (47%), followed by GEN (32%), saccadic dysmetria (29%) and vertical nystagmus(14%). The association between INO and pendular nystagmus has also been noticed in other studies (Lopez et al., 1996, Tilikete et al., 2011). Based on the observation of increased association of INO with pendular nystagmus and the localising value of INO Gresty et al.(Gresty *et al.*, 1982) proposed that the lesions responsible for pendular nystagmus are in the vicinity of oculomotor nuclei. The lesions of the afferent pathways to inferior olive nucleus situated in the brainstem are involved in the origin of pendular nystagmus. Similarly the association of the INO with GEN is due to brainstem lesion.

Tilikete et al. (Tilikete *et al.*, 2011) in their study found INO to be commonly seen in the PPMS group. In contrast we found INO to be more common in the RRMS and SPMS subtypes. This could be explained by the involvement of the different sites by MS.

4.0 Conclusion and Further studies

Eye movement analysis has moved beyond the confines of neuro-ophthalmologists and is now widely used by neuroscientists, visual scientists, and psychologists. Eye movement abnormalities have been used as a biological marker in the diagnosis of conditions such as schizophrenia (Clementz and Sweeney, 1990). The use of eye movements as experimental tool has become more popular because they can be conveniently and accurately measured and analysed. Our understanding of the neural control of eye movements have improved the interpretation of eye movements and applying them for better understanding of the mechanism underlying the disease process, diagnosis and treatment of both congenital and acquired.

Eye movement recording has been an important tool in our understanding of nystagmus, both congenital and acquired nystagmus.

In our first study we have shown how with the help of eye movement recordings one could differentiate the varies types of infantile nystagmus such as the latent nystagmus and periodic alternating nystagmus. We have also recorded the various wave forms seen in the infantile nystagmus and for the first time have shown that the albinism group has higher jerk related waveforms and the frequency of the waveform to be reduced. We have also shown that the pure jerk waveform was associated with poor visual acuity.

The reason why the frequency of nystagmus is reduced in albinism group is difficult to explain at this stage. Although one of the main differences that is known between albinism and IIN is the presence of foveal hypoplasia in the albinism patients and hence the differentiation of the nystagmus due to afferent

problem (due to foveal hypoplasia) or efferent problem (due to changes in the brain), the difference found in our study between the two groups cannot be solely explained by this structural abnormality seen in the albinism group. Interestingly Thomas et al. (Thomas et al., 2012, Thomas et al., 2011a) based on high resolution spatial and temporal in-situ hybridization studies in developing embryonic and foetal tissue found strong hybridization signals from the structures involved in setting up the vestibulo-ocular reflex and optokinetic reflex arc. This included the developing cerebellum, vestibular apparatus and developing neural retina. The study also showed retinal abnormalities in patients with *FRMD7* mutation using high-resolution OCT measurements. We have also seen clinically foveal hypoplasia in few patients who had *FRMD7* mutations.

Mclean et al. (McLean *et al.*, 2007) from the Leicester group carried out a randomised controlled trial to test pharmacological treatment of IN in both idiopathic IN and in IN associated with albinism, achromatopsia and other optic nerve problems. They found that both memantine and gabapentin improves the visual acuity in the idiopathic IN group but not in those with associated sensory deficits. The hypothesis put forward was that the latter group was a different subgroup with known structural abnormalities in retina, such as foveal hypoplasia in albinism and cone abnormalities in achromatopsia that limit visual acuity.

Further studies need to be performed to elucidate the mechanism underlying these different infantile nystagmus forms to effectively treat them based on the underlying pathology.

In the second part of the study we have demonstrated using eye movement recordings how the various different oculomotor abnormalities can be present in patients with MS. Clinically it will be difficult to differentiate these various oculomotor abnormalities. The importance of identifying these varous oculomotor abnormalities lie in the treatment of these conditions. The medical management of these oculomotor abnormalities are depicted in the **table 4.1**. To date the treatment of nystagmus due to MS is empirical. In a survey performed on the management of acquired nystagmus in UK by Choudhuri et al.(Choudhuri *et al.*, 2007) the most common cause of acquired nystagmus seen by both ophthalmologist and neurologist was secondary to multiple sclerosis and stroke. In the same survey the most common modes of pharmacological management of acquired nystagmus were found to be baclofen and gabapentin. Treatment failure with either baclofen or gabapentin can be explained by the presence of more than one oculomotor abnormality as shown in our study.

Table 4.1: The table showing the various oculomotor abnormalities and the medical management

PROBLEM	LESION LOCATION	TREATMENT	REFERENCE
Optic Neuritis	Optic Nerve	Steroids	Hickman et al.
Internuclear Ophthalmoplegia (INO)	Medial Longitudinal Fasciculus (MLF)	1. Steroid acutely 2. Botulinum Toxin 3. Strabismus Surgery	1. Adams et al. 2. Jenkins et al. 3. Murthy et al.
Gaze Evoked Nystagmus (GEN)	Cerebellum Central Vestibular Pathways	1. Steroid acutely 2.Gabapentin 3. Baclofen 4. Clonazepam 5. 3,4 Diaminopyridine	1. Frohman et al. 2. Mehta and Kennard (2012)
Pendular Nystagmus	1. Anterior Visual Pathway 2. Cerebellum	1. Gabapentin 2. Memantine	1. Frohman et al. 2. Jain et al.
Saccadic Intrusions	1. Cerebellum	Steroid acutely	Frohman et al.

Further studies need to be done to validate the incorporation of these oculomotor abnormalities into the disability scale which predicts the prognosis of the disease.

5.0 **Publications**

1. Thomas, S., Proudlock, F. A., Sarvananthan, N., Roberts, E. O., Awan, M., McLean, R., Surendran, M., **Kumar, A. S**., Farooq, S. J., Degg, C., Gale, R. P., Reinecke, R. D., Woodruff, G., Langmann, A., Lindner, S., Jain, S., Tarpey, P., Raymond, F. L. & Gottlob, I. (**2008**) Phenotypical characteristics of idiopathic infantile nystagmus with and without mutations in FRMD7. *Brain*, 131 (Pt 5): 1259-1267.

2. Diagnosis of idiopathic infantile nystagmus and ocular albinism: a clinical challenge: **Anil Kumar**; Irene Gottlob. (**2009**) *Expert Review of Ophthalmology,* August, Vol. 4, No. 4, Pages 395-412.

3. **Kumar, A**., Sarvananthan, N., Proudlock, F., Thomas, M., Roberts, E. & Gottlob, I. (**2009**) Asperger syndrome associated with idiopathic infantile nystagmus--a report of 2 cases. *Strabismus*, 17 (2): 63-65

4. **Kumar, A**., Thomas, S., McLean, R., Proudlock, F. A., Roberts, E., Boggild, M. & Gottlob, I.(**2009**) Treatment of acquired periodic alternating nystagmus with memantine: a case report. *ClinNeuropharmacol*, 32 (2): 109-110.

5. Analysis of Eye Movement Recordings in Multiple Sclerosis. **A. A. Kumar**, C. S. Constantinescu,F. A. Proudlock, M. G. Thomas, R. J. McLean, and I. Gottlob (**2010**) .*ARVO Meeting **Abstracts***April 11, 51:

6. **Kumar, A**., Gottlob, I., McLean, R. J., Thomas, S., Thomas, M. G. & Proudlock, F. A. (**2011**). Clinical and oculomotor characteristics of albinism compared to FRMD7 associated infantile nystagmus. *Invest Ophthalmol Vis Sci,* 52 (5): 2306-2313.

7. Thomas, M. G., Crosier, M., Lindsay, S., **Kumar, A**., Thomas, S., Araki, M., Talbot, C. J., McLean, R. J., Surendran, M., Taylor, K., Leroy, B. P., Moore, A. T., Hunter, D. G., Hertle, R. W., Tarpey, P., Langmann, A., Lindner, S., Brandner, M. & Gottlob, I. (**2011**) The clinical and molecular genetic features of idiopathic infantile periodic alternating nystagmus. *Brain*, 134 (Pt 3): 892-902

8. Sheth, V., Gottlob, I., Mohammad, S., McLean, R. J., Maconachie, G. D., **Kumar, A**., Degg, C. & Proudlock, F. A. (**2013**) Diagnostic Potential of Iris Cross-sectional Imaging in Albinism Using Optical Coherence Tomography. *Ophthalmology.*

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