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OMS - OCULAR MOTOR SCORE

A CLINICAL METHOD FOR EVALUATION AND FOLLOW-UP OF OCULAR MOTOR PROBLEMS IN CHILDREN

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ABSTRACT

Background: Eye movements can be a source of valuable information to clinicians. Different classes of eye movements, i.e. saccades, smooth pursuit (SP) and vestibular eye movements can be distinguished on the basis of how they aid vision. They are usually triggered by different well defined anatomical localisations in the brain and brain stem. The Ocular Motor Score (OMS) is a clinical test protocol which comprises 15 subtests regarding ocular motor functions that are important and relevant in clinical practice. The protocol was developed with the aim to create a quantitative measure of a series of combined mostly qualitative assessments today used in the orthoptic clinic in every day practice. In addition, the results of the different subtests will give a specific profile for each child who displays problems in the static or dynamic section of the test.

Aim: The aims of the current studies were to create a reference material for the OMS test protocol, to evaluate OMS according to intrarater and inter-rater agreement and to evaluate the OMS test protocol outcome in children with specific neuropaediatric disorders.

Methods: The OMS test protocol consists of 15 different subtests and are grouped into a static and dynamic section. Since the tests are scored, the overall score from the 15 subtests will give a total OMS (tOMS) score which then can be used as a comparison in the following up of a child. A low tOMS score will indicate a normal ocular motor performance, whereas a high score will indicate a serious ocular motor problem.

Subjects: Study I included a total of 233 neurological healthy children and young adults referred to the department of paediatric ophthalmology, who were divided into four age groups: 0.5-3, 4-6, 7-10 and 11-19. In study II, another 40 children aged 4-10 with and without ocular motor deficiencies were examined. The examinations of the subjects were videotaped to simplify the intrarater agreement procedure and to provide similar conditions for the three raters in the inter-rater agreement study. Study III involved 13 patients with a mitochondrial disease, Complex I deficiency and study IV 26 patients with congenital cytomegalovirus infection (cCMV). Both groups were included when they came for their ophthalmological examination that formed part of a wider multidisciplinary study.

Results: The findings from study I demonstrated that ocular motor functions tested in the OMS test protocol develop with age. Study II dealt with correlation and showed a high degree of agreement among the raters. However, there was less agreement in the saccades, smooth pursuit (SP) and fusion subtests, especially in the subnormal test results. Study III showed differences in ocular motor performance of children with Complex I deficiency. They showed dysfunctions of the saccades, dysmetric SP and pathological optokinetic nystagmus (OKN). In study IV children with cochlear implants due to cCMV more frequently had pathological Vestibular Ocular Reflex (VOR), which fits in with the balance disturbances reported in the same group.

Conclusion: The OMS test protocol can be of clinical value as a clinical tool in identifying ocular motor problems in children with subtle neuropaediatric disorders and can be used to follow up children with progressive neuropaediatric disorders.

Key words: Ocular Motor Score (OMS), children, normative material, agreement, neuropaediatric disorders, ocular motor function, eye movements, strabismus

DEDICATION

To my family with love
To my colleagues and students with respect

LIST OF PUBLICATIONS

I. **Olsson M**, Teär Fahnehjelm K, Rydberg A, Ygge J
Ocular Motor Score (OMS) a novel clinical approach to evaluating ocular motor function in children. Acta Ophthalmologica 2013 91:564-570

II. **Olsson M**, Teär Fahnehjelm K, Rydberg A, Ygge J
Ocular Motor Score (OMS): a clinical tool to evaluating ocular motor functions in children. Intrarater and inter-rater agreement. Acta Ophthalmologica 03/2015DOI:10.1111/aos.12704

III. Teär Fahnehjelm K, **Olsson M,** Naess K, Wiberg M, Ygge J, Martin L, von Döbeln U. Visual function, ocular motility and ocular characteristics in patients with mitochondrial complex I deficiency, Acta Ophthalmologica 2012: 90:32-43

IV. Teär Fahnehjelm K, **Olsson M**, Fahnehjelm C, Lewensohn-Fuchs I, Karltorp E
Chorioretinal scars and visual deprivation are common in children with cochlear implants after congenital cytomegalovirus infection. Acta Paediatrica 03/2015 DOI:10.1111/apa.12988

CONTENTS

LIST OF ABBREVIATIONS

ATP	Adenosine Tri Phosphate
BSV	Binocular single vision
CNS	Central Nervous System
cCMV	Congenital Cytomegalovirus
CT	Computed Tomography
CVI	Cerebral Visual Impairment
CVOR	Cancellation of Vestibulo Ocular Reflex
Cx26	Connexin 26
DNA	Deoxiribonukleinsyra
EOMs	Extra Ocular Muscles
FEF	Frontal Eye Field
HI	Hearing Impairment
LGN	Lateral Geniculate Nucleus
MRI	Magnetic Resonance Tomography
MLF	Medial Longitudinal Fasciculus
MST	Medial Superior Temporal Visual Area
MT	Middle Temporal Visual Area
mt DNA	Mitochondrial DNA
OA	Optic Atrophy
OKN	Optokinetic Nystagmus
OMS	Ocular Motor Score
PEF	Parietal Eye Field
PPRF	Paramedian Pontine Reticular Formation
PP	Primary Position
RP	Retinitis Pigmentosa
riMLF	rostral interstitial nucleus of the Medial Longitudinal Fasciculus
SC	Superior Colliculus
SEF	Supplementary Eye Field
SP	Smooth Pursuit
tOMS	Total Ocular Motor Score
TBI	Traumatic Brain Injury
VI	Visual Impairment
VOR	Vestibulo Ocular Reflex
VOG	Video Oculography

DEFINITIONS

Amblyopia a unilateral or bilateral condition of decreased visual function which is not a result of any clinically pathological anomaly of the eye or the visual pathways.

Anisometropia, difference in refractive error between the two eyes.

Abnormal retinal correspondence a binocular condition where there is a change in visual projection such that the fovea of the fixing eye has a common visual direction with an area other than the fovea of the deviating eye.

Cerebral Visual Impairment (CVI) a damage to the posterior visual pathway and occipital cortex that impairs visual fields and visual acuity, damage to the higher centers serving vision interferes with visual processing. These visual manifestations may occur either in isolation or in combination.

Eye movements - refer to the different classes of eye movements, which correlates to the neural supra nuclear level including gaze centers and cortical areas.

Ocular motility/Ocular motor - refers to the twelve extra ocular muscles (EOMs) and the innervation to the EOMs via the cranial nerves from the brain stem, which correlates to the neural infra nuclear level.

Oculomotor - refers to the third cranial nerve, oculomotor nerve III

Ocular motor functions /dysfunction, relating to a person's ocular motor performance normal or abnormal.

Suppression is the mental inhibition of visual sensations on one eye in favor of the other eye, when both eyes are open. This may occur in manifest strabismus to avoid diplopia.

Visual cognition, cognition involves the processing of information for conscious awareness and decision –making and to prepare for action, visual cognition builds on visual perception.

Visual impairment (VI), any loss or abnormality of visual function. Visual impairment is defined by the World Health Organization WHO: Visual acuity below 0.3 with the best optical correction. You can be visually impaired, even with higher visual acuity than 0.3, if the visual field is very limited.

Visual perception is the cognition process of visual information.

Proprioception is the conscious or unconscious awareness of joint position and muscle tension.

1 INTRODUCTION

1.1 BACKGROUND

The central area of the retina, the macula is the area for the highest visual acuity (Figure 1). Through evolution and natural selections the human eye has developed with a fovea, the centermost part of the macula responsible for our sharpest and most detailed vision. To be able to use the fovea humans had to develop head and eye movements to position the object of interest. The purpose of the eye movements is to direct the fovea to object of interest (saccades) and to maintain the high spatial resolution and clear vision the object of interest must be held in the center of the macula the fovea, a process called "foveation" (Purves et al 2008). Another category of eye movements which stabilizes the visual field on the retina when the head is moving is the VOR or when the surrounding is moving the OKN.

There are two types of photoreceptors in the retina: the cones and the rods. The cones are localized in the fovea to give a high spatial resolution, and a healthy fovea is the key for reading and other activities that require the ability to see details. The cones in the fovea are sensitive to color and form through the parvocellular pathway i.e. the ventral stream in the brain. The photoreceptors mainly the rods are less tightly packed in the periphery of the retina and give a much lower spatial resolution. They are important for detection of objects in the peripheral visual field and trigger the brain to initiate eye movements. The rods are sensitive to motion, low contrast and low luminance and projects through the magnocellular pathway i.e. the dorsal stream in the brain (Mercuri et al 2007).

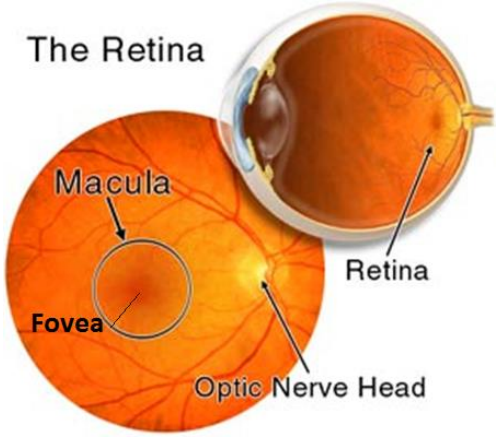

Figure 1. *Normal retina with the macula (5.5 mm in diameter) the fovea (1.5 mm) and the foveal pit (0.35mm) which is the centermost part of the macula. This tiny area is responsible for our central, sharpest vision. (Picture from www.stlukeseye.com/images/img-retina.jpg printed with permission)*

Patients with ocular motor problems such as strabismus, nystagmus and ocular nerve paralysis are evaluated in their everyday clinical practice by neurologists, ophthalmologists, optometrists and orthoptists. It is well known that different eye movements arise from different parts of the

brain and that an abnormal eye movement can give us a clue about the pathology behind the abnormality (Leigh & Zee 2006). Eye movements can also be a source of valuable information in the follow-up process of a disease affecting the central or peripheral nervous systems. Studying eye movements has been of interest since the middle of the 1800s. Already in 1738 Jurin referred to the "trembling of the eye" and in 1860 Helmholtz proposed that the "wandering of the gaze" served to prevent retinal fatigue. About 1899 Huey was one of the first to record this wavering of fixation by objective methods (Ratliff & Riggs 1950, Martinez – Conde et al 2004).

Today there are several advanced technical methods for recording eye movements, for example the videooculography (VOG) technique in which eye movements are recorded by two miniaturized video cameras mounted in a head mounted mask (Figure 2). Most of these methods demand the co-operation of the patient and are therefore not always suitable for use in children, especially children with attention difficulties and/or neurological deficiencies. Moreover, in everyday clinical practice at a department of paediatric ophthalmology or general ophthalmology there is no access to the advanced and expensive technology found in research laboratories and the testing can also be time consuming. The OMS test protocol was developed by Professor Jan Ygge at Marianne Bernadotte Centrum, St. Erik Eye Hospital in Stockholm, Sweden with the aim of creating a combined score of a series of mostly qualitative common orthoptic investigations. These commonly used orthoptic investigations provide accurate and detailed information about the patient´s ocular motor performance. Evaluating ocular motor functions according to OMS test protocol could offer a complement to traditional orthoptic examinations.

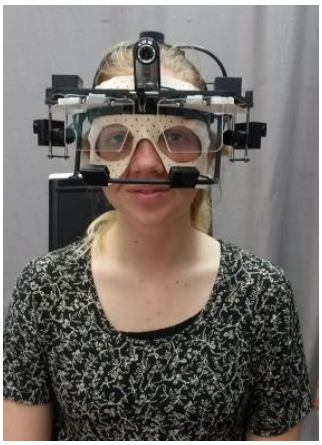

Figure 2. *Video oculography (VOG). Chronos Eye Tracking Device (C-EDT).*

1.1.1 Functions of different classes of eye movements

Based on the requirement to serve vision, eye movements can be divided into two main types: gaze shifting and gaze stabilization eye movements (Leigh & Zee 2006). In the newborn child the ocular motor system is very immature. Newborn children not infrequently display unconjugated eye movements and strabismus. The ocular motor system improves with maturation of the fovea.The cone photoreceptores are also immature, and the ganglion cells

have not yet migrated laterally so that the photoreceptors could form the foveal pit.The fovea reaches full maturity at around 4 years of age (Brodsky 2010) indicating that the ocular motor system could not fully mature before this date since the system is dependent on the foveal function.

1.1.1.1 Gaze shifting eye movements

When something appears in the periphery of the visual field the eye movement system triggers to direct the fovea and identify the object. The saccadic system brings the image of the object rapidly onto the fovea; the vergence system moves the eyes in opposite directions so that images of a single object are placed simultaneously on the two foveas (Leigh & Zee 2006).

1.1.1.2 Gaze stabilization eye movements

When the object of interest is identified it must be held steady on the fovea to be seen clearly, the fixation system retains the image of a stationary object when the head is immobile. During brief head movements the object is hold on the fovea by the VOR and when the head movements become sustained the optokinetic system OKN is activated as a supplement. The smooth pursuit (SP) system keeps the small moving object on the fovea (Wong 2008).

Basic knowledge of the properties of each of the six functional classes of eye movements will guide the examination. Awareness of basic anatomical facts about each functional class will aid with topological diagnosis and prognosis (Downey & Leigh 1998).

1.1.2 The clinical value of the OMS test protocol

The OMS test protocol is used as a tool to identify ocular motor problems and follow up in children and young adults with neuropaediatric disorders. The protocol can be of value to give accurate and detailed information about the child's ocular motor functions and indicate possible sources of aetiology. In addition, the results of the different subtests will give a specific profile in each child demonstrating problems in or a combination of the static and the dynamic section of the test. Neuropaediatric disorders may have different aetiologies such as prematurity, traumatic brain injury (TBI), congenital infections and metabolic disorders such as mitochondrial disease (Dutton & Bax 2011).These patients who more often present with posterior visual pathways pathology that can cause cerebral visual impairment (CVI). CVI comprises visual malfunctions due to retro-chiasmal visual and visual association pathway pathology (Philip & Dutton 2014). In this thesis the studies performed incorporates both healthy children and children with subnormal psychomotor development, a group of children with the metabolic disorder complex I deficiency, a mitochondrial disorder, and children with congenital cytomegalovirus infection (cCMV).

1.1.2.1 Mitochondrial diseases

The mitochondria are small organelles in the cell known as the "cellular power plants", the energy manufacturing structures in all cells responsible for production of the ATP (adenosine tri phosphate) needed for all muscular activity in our body (Esteitie et al 2005). A mitochondrial disorder is caused by an inadequate respiratory chain function (i.e. deficiency of one or several of the five enzyme complexes). The respiratory chain subunits are encoded by both nuclear DNA (deoxiribonukleinsyra) and mitochondrial DNA (mt DNA) genes. The mt DNA is strictly maternally inherited (Graff et al 2002) while the nuclear DNA will be inherited according to classic pattern as autosomal dominant/recessive or X-linked (Phillips & Newman 1997). The number of mitochondria in a cell varies widely by organism and tissue type. Mitochondrial diseases as Complex I deficiency often affect energy demanding organs such as central nervous system (CNS), heart, eyes, ears and muscles (Esteitie et al 2005). Many of the mitochondrial diseases can lead to visual impairment and problems with ocular motor functions. There is also a risk of posterior visual pathway damage. A mitochondrial disorder should be suspected in any child with optic nerve atrophy, progressive ocular motility deficits, pigmentary retinopathy or acute focal neurological deficits (Phillips & Newman 1997).

1.1.2.2 Congenital cytomegalovirus infection

Congenital cytomegalovirus infection is the most common congenital infection and occurs in 0.5% of children born live in Sweden (Ahlfors et al 1999). Cytomegalovirus (CMV) is a ubiquitous double-stranded DNA virus and the largest member of the herpes virus family (Coats et al 2000), with the capacity to establish life-long latency in the host (Malm & Engman 2007). The fetus and infant can either be infected via viral transmission through the placenta, during delivery via cervical secretion and blood, or from the mother via breast milk. The risk for transmission of the virus to the fetus is higher in primary infected mothers than in mothers with reactivated disease (Malm & Engman 2007). Approximately 90% of the congenital infected children are asymptomatic at birth (Coats et al 2000, Karltorp et al 2012). About 10-20% of these infants are at risk of developing sequelae later (Engman et al 2008). Hearing impairments (HI), neurological deficiencies and ophthalmological problems including chororetinal scars are common (Figure 3; Coats et al 2000). There is also a risk of posterior visual pathway damage.

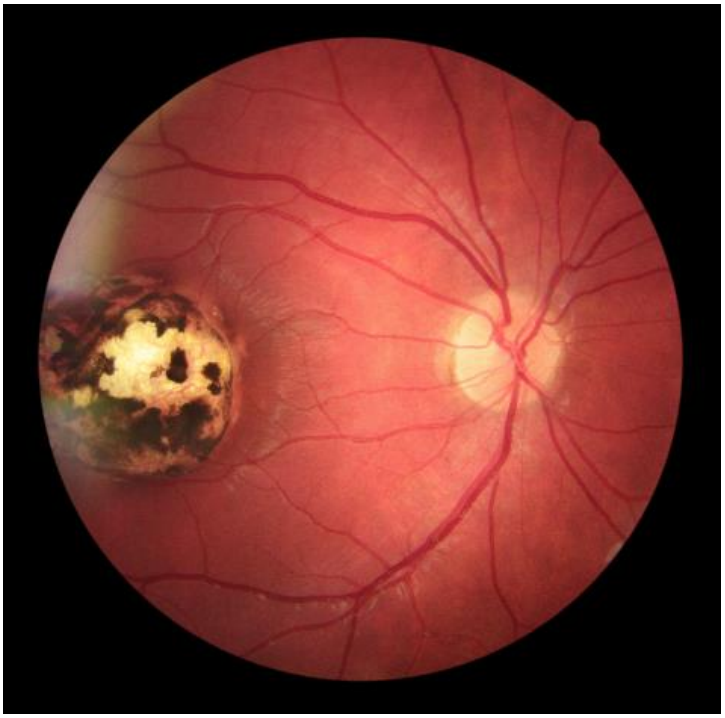

Figure 3. *Fundus photography from the right eye in a patient with congenital cytomegalovirus infection showing a large central chororetinal scar.*

This thesis is a description of the evaluation of the OMS test protocol. To help the reader to form an opinion about and get an understanding of why the OMS test protocol may be of clinical value, a brief introduction of the neuroanatomy behind vison, and ocular motor functions scored in the OMS test protocol seems appropriate.

1.2 ANATOMY OF THE OCULAR AND VISUAL SYSTEM

To initiate ocular motor functions by vision, stimulation of the retina is required. The visual system is divided into the anterior and the posterior visual pathways (Figure 4).

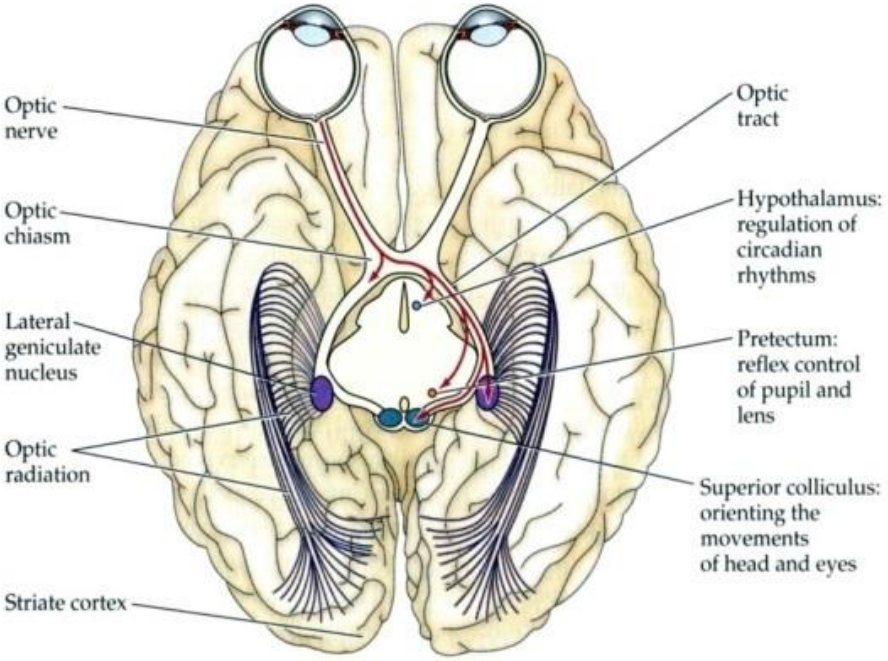

Figure 4. *The visual pathways, The anterior pathway from the retina to the lateral geniculate nucleus and the posterior pathway thereafter to the striate cortex (primary visual cortex) seen from below. (Picture from Purves et. Al. Neuroscience, Fourth Edition. Printed with permission)*

1.2.1 The anterior visual pathway

The anterior visual pathway refers to the structures anterior to the lateral geniculate nucleus (LGN). The first step in the process of seeing involves refraction of light by optics of the eye, the transduction of light energy into electrical signals by the photoreceptors, the cones and the rods (Figure 5). The cones and the rods in turn activate the bipolar, amacrine and horizontal cells, which in turn influence the ganglion cells. Most retinal ganglions cells receive input from several photoreceptors. In the peripheral retina many photoreceptors mainly rods connect to each ganglion cell. This part of the retina forms the beginning of the magnocellular pathway mostly sensitive to contrast and movement. In the central retina i.e. the macula and the fovea each ganglion cell receives input from only a limited number of photoreceptor mainly cones which are, mostly sensitive to form and colour and constitutes the start of the parvocellular pathway. The axons from the ganglion cells form the optic nerve. The two optic nerves join in the chiasma where the nerve fibers from the nasal retina cross over to the contralateral side while the axons from the temporal retina remain uncrossed. Thus, the partial crossing of the optic nerves in the chiasm brings together the corresponding inputs from each eye. The axons then continue in the optic tract towards the LGN. Part of the axons diverge from the optic tract and terminate in the hypothalamus. This retinohypothalamic pathway is known to be involved in the day/night cycle ant to influence visceral functions according to variation in light levels. Some axons also terminate in the pretectum which is a coordinating center for the pupillary light reflex i.e. the reduction of the pupil diameter when light falls on the retina (Purves et al 2008).

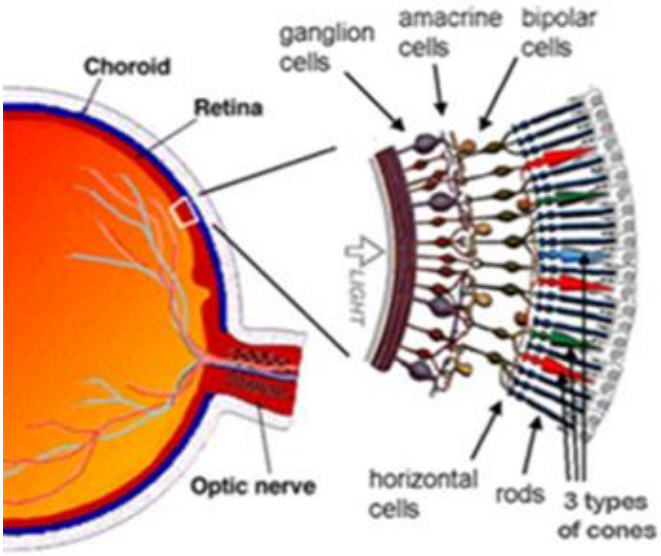

Figure 5. *A section of the posterior part of the human eye with an enlargement of a sector of the retina.* *(Picture from http://webvision.med.utah.edu/ printed with permission)*

In addition the superior colliculus (SC) receives input from the optic tract and is involved in parts of the visual reflexes and coordination of head and eye movements to visual as well as other targets (Purves et al 2008, Snell 2010).

1.2.2 The posterior visual pathways

The posterior visual pathway refers to structures behind the LGN which sends it output axons towards the occipital lobe through the optic radiation. The axons enter the primary visual cortex in the ipsilateral occipital lobe.

1.2.3 The primary visual cortex

The primary visual cortex is also called the striate cortex, area V1 or Brodman's areal 17 (Figure 4 & 6).The primary visual cortex has a retinotopic organization where the macula is represented by a large area (about one third) because of the large number of ganglion cells represented in the central retina (Purves et al 2008, Snell 2010). Signals from the right eye and the left eye are combined in the primary visual cortex (V1) area. Area V1 is organized in six superficial layers of neurons with different functions i.e. some neurons are eye specific and some neurons have binocular responses (Purves et al 2008).

1.2.4 Binocular single vision

Binocular single vision (BSV) is the ability to use both eyes simultaneously so that each eye contributes to a common single perception. Normal BSV occurs with bifoveal fixation and abnormal BSV in monofoveal fixation. BSV can be classified into three stages:
i) Simultaneous perception is the ability to perceive simultaneously two images, one formed on each retina, although there is a small disparity between the both images. The disparity of the

retinal images causes fusional movements.
ii) Fusion may be of sensory or motor origin. Sensory fusion is the ability to perceive two similar images; one from each retina, and interpret them as one image. Motor fusion is the ability to maintain sensory fusion through a range of vergences. At the end of fusional movements, not all disparity is annulled, a small disparity remains which acts as an error signal. The residual fixation disparity may control the direction and strength of the innervation that maintains the new binocular position. When the visual objects is fused by being imaged on disparate points, stereopsis results**.**
iii) Stereoscopic vision is the perception of the relative depth of objects on the basis of binocular horizontal disparity (Rowe 2012).The larger horizontal disparity, the greater the perceived depth effect. A vertical disparity produces no stereopsis. When the motor and the sensory fusion become impossible the disparity results in motor misalignment and causes diplopia. To avoid diplopia the visual system has at its disposal two mechanisms suppression and anomalous correspondence (von Noorden & Campos 2002).

1.2.5 Cortical organization of different visual functions.

As the visual information exits the occipital lobe and the primary visual cortex, it projects to the secondary visual cortex (i.e. V2, V3, V4, V5, and V6) by two main streams: The ventral stream also known as the "what" pathway plays a major role in the perceptual identification of objects. The ventral stream gets its main input from the fovea and the parafoveal areas in the retina. The parvocellular layers of the LGN projects to the V3 and V4, sensible for form and color discrimination. The second stream is the dorsal stream also known as the "where" pathway which mediates the required sensorimotor transformations for visually guided actions directed at such objects (Figure 6) (Mercuri et al 2007, Goodale & Milner 1992). The dorsal stream gets its input from the peripheral part of the retina through the magnocellular layers of the LGN, and projects to the area V5 and V6 which are responsible for movement and position in the visual field respectively. Both of these streams will often be activated simultaneously (with different visual information), thereby providing visual experience during skilled action (Goodale & Milner 1992, Kandel et al 2000). Knowledge about these streams is important in the examination and understanding of a child with suspected posterior visual pathway damage that can cause CVI which is common in children with neuropaediatric disorders (Dutton & Bax 2010).

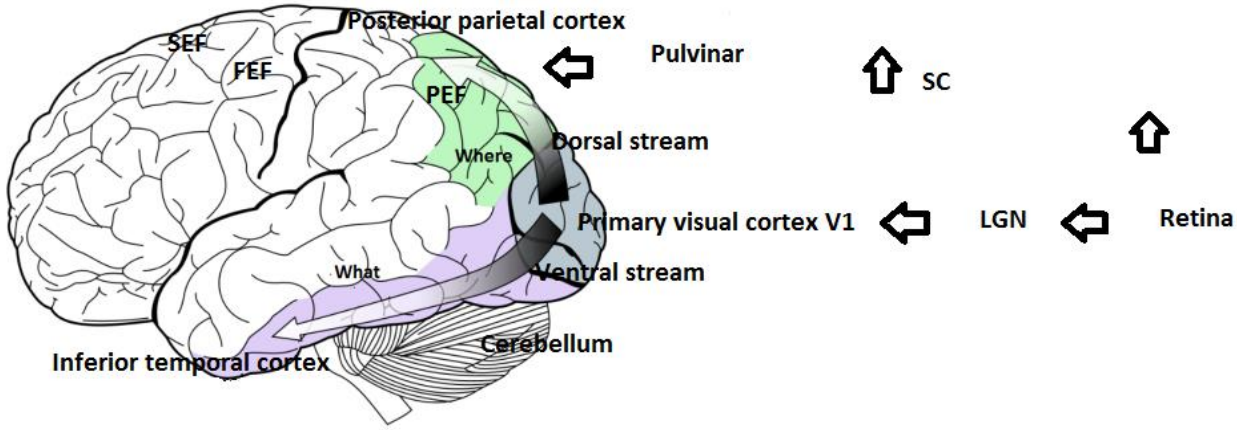

Figure 6. *Schematic picture of visual processing in cerebral cortex. The retina sends information to the lateral geniculate nucleus (LGN), which projects to primary visual cortex (V1). The ventral stream (purple) projects to the inferior temporal cortex. The dorsal stream (green) projects to the posterior parietal cortex, which also receive visual input from the superior colliculus (SC) via the pulvinar.*
(Picture from Wikipedia http://en.wikipedia.org/wiki/Human_brain)

1.3 BRAIN STRUCTURES INVOLVED IN OCULAR MOTOR CONTROL

Eye movements made in response to visual or other sensory stimuli are initiated in parts of the cerebral cortex. The cerebral cortex chooses significant objects in the environment on which to target eye movements. Cortical signals (the command to generate an eye movement) are relayed to motor circuits in the brain stem by the basal ganglia and the superior colliculus. The cortical and collicular signals do not specify the contribution of each muscle to the movement. Instead, the motor programming for horizontal eye movements is performed in the brainstem gaze centers: the paramedian pontine reticular formation (PPRF) and for the vertical eye movements in the midbrain in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). This two gaze centers translates the command from higher centers into appropriate muscle innervations for each muscle (Kandel et al 2000).

1.3.1 Cortical areas important in the control of eye movements

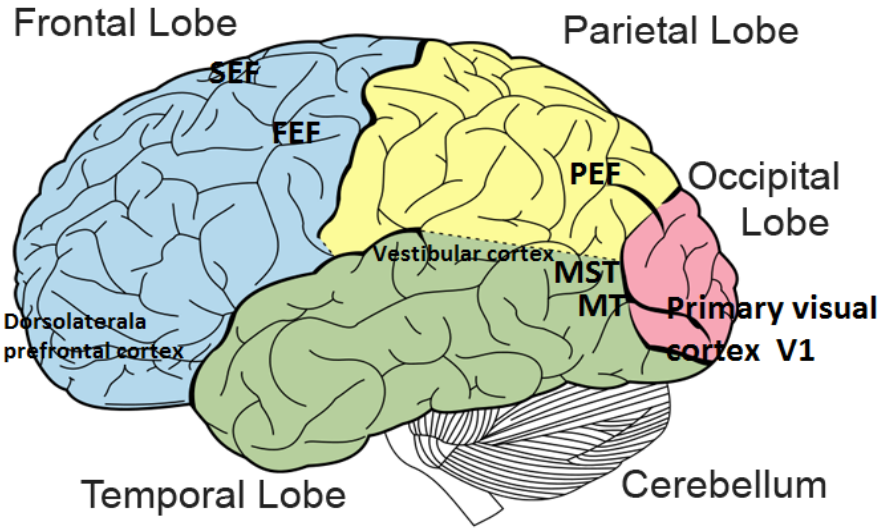

Figure 7. *Summary of cortical areas important in the control of eye movements. Visual input from the primary visual cortex (V1) projects to the Middle temporal (MT) and the medial superior temporal (MST) visual areas, where information about the speed and direction of moving targets is extracted. The parietal lobe is important for shifting of visual attention and contains the parietal eye fields (PEF). The frontal lobe contains the frontal eye fields (FEF) which control voluntary saccades. The supplementary eye fields (SEF), which are important when a sequence of saccades is made as part of a learned task, and the dorsolateral prefrontal cortex, which guides the saccades when they are made to remembered target locations. (Downey & Leigh 1998).* *(Picture from Wikipedia http://en.wikipedia.org/wiki/Human_brain)*

Middle temporal visual area (MT) receives input from the primary visual cortex (V1) through the dorsal stream; MT is involved in SP initiation and projects to the medial superior temporal visual area (MST) together with the frontal eye field (FEF) important for SP maintenance (Pierrot-Deseilligny 2008, Krauzlis 2004).
The MST also receives vestibular signals. Together the MT and MST project to the other cortical areas concerned with visual motion (Wong 2008). FEF is also involved with volitional, visually guides, purposive saccades (Rowe 2012). FEF will be activated when we with systematical effort examine our surroundings (intentional saccades).When watching to the right the left FEF is activated and vice versa. Parietal eye field (PEF) controls visual attention and is activated with more or less unconscious gaze adjustments to areas of the visual field, for example sudden movements in the edges of the visual field (reflexive saccades). Although FEF and PEF have strong interconnection when initiate SP and saccades, FEF are more involved in commando saccades and PEF more involved in SP and saccades needing visual stimuli (Rowe 2012). Supplementary eye field (SEF) is involved in the more cognitive aspect of the saccade (Rowe 2012). Descending pathways pass via the basal ganglia and superior colliculus to nuclei

in the pons and midbrain before they contact ocular motor neurons that lie in the nuclei of the cranial nerves III, IV and VI (Downey & Leigh1998).

1.3.2 Subcortical areas important in the control of eye movements

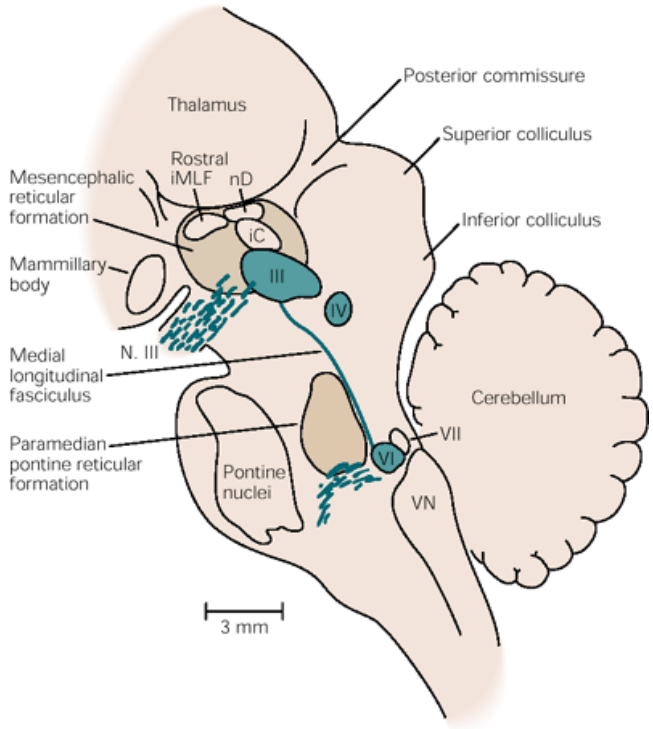

Figure 8. *A schematic parasagittal section of the brain stem showing the locations of structure important in the control of gaze. The oculomotor nucleus (cranial nerve III) is in the midbrain at the level of the mesencephalic reticular formation (MRF). The trochlear nucleus (nerve IV) is slightly caudal, and the abducens nucleus (nerve VI) lies in the pons at the level of the paramedian pontine reticular formation (PPRF), adjacent to the fasciculus of the facial nerve (VII), interstitial nucleus of Cajal (iC), interstitial nucleus of the medial longitudinal fasciculus (riMLF), nucleus of Darkshevich (nD) and the vestibular nuclei (VN).*
(Picture from Principles of neural science http://www.ib.cnea.gov.ar printed with permission)

The PPRF is the horizontal gaze center in the pons generating horizontal eye movements. The riMLF is the vertical and torsional gaze center in the mesencephalon generating vertical and torsional eye movements. Both gaze centers are linked directly to the motor neurons in the oculomotor nucleus III, trochlear nucleus IV and the abducent nucleus VI. The neural signal sent to each muscle has two distinct components related to eye – velocity (pulse) and the other to eye position (step). The neural pulse –step command are generated by the neural integrator that is responsible for inducing an appropriate pulse to induce an correct saccade velocity followed by an appropriate tonus level by the step to maintain the eye in the reached position. A defective pulse leads to slowing of the saccades whereas a defective step leads to gaze induced nystagmus since the eye are forced back towards the primary positon by the elastic restraining

forces of the eye muscles. The pulse- step command converges on the motor neurons that induce the innervation on the muscles via the cranial nerves (Leight & Zee 2006).

The medial longitudinal fasciculus (MLF) connects the abducent nerve nuclei (VI) with the oculomotor nerve (III). The MLF is of great importance for simultaneous onset of the abduction and adduction during conjugate horizontal eye movements. Any pathology to the MLF will induce disconjugate horizontal eye movements with usually a preserved abduction but a defective adduction. Interestingly, bilateral adduction (convergence) is usually preserved since it is controlled by the mesencephalon not involving in MLF pathway (Leight & Zee 2006).

1.3.3 Neural intergrator

Once the eye has been brought to a new position this eye position has to be maintained through an increased innervation. That is called the gaze holding mechanism. An increased innervation holds the eye in its new position against orbital elastic recoiling forces. For horizontal eye movements the gaze holding mechanism consists of the medial vestibular nucleus and adjacent nucleus prepositus hypoglossi in the medulla. For vertical and torsional eye movements, the gaze holding mechanism is in the interstitial nucleus of Cajal (iC) in the midbrain. A defect or leaky gaze holding mechanism makes the eye drift back to the central position resulting in gaze-evoked nystagmus (Wong 2008).

1.3.4 Cerebellum

Cerebellum can be divided in three parts: Spinocerebellum is responsible for balance and control of the trunk and extremity movements. This part receives proprioceptive inputs. The cerebrocerebellum is responsible for the initiation, planning and the "timing" of movements. The vestibulocerebellum regulates balance, head and eye movements. It receives vestibular input from the semicircular canals as well as the vestibular nuclei to which it return information. It also receives visual inputs from the SC and the visual cortex. The cerebellum acts like the repair kit of the brain and coordinates eye movement so that they are smooth and conjugated, mostly with inhibitory action. The cerebellum plays a special role in the saccade adaption (Schubert & Zee 2010). Cerebellar lesions impair the amplitude of saccades (i.e.dysmetria) and reduce the velocity of smooth pursuit (Pierrot-Desceilligny 2008). Damages to the cerebellum can cause ataxia, a neurological sign consisting of lack of voluntary coordination of muscle movements (Purves et al 2008) also seen in the eye movements for example in children with ataxia –telangiectasia (Baloh et al 1978, Riise et al 2007).

1.4 OCULAR MOTILITY AND THE EXTRAOCULAR MUSCLES

The term ocular motility refers to the twelve extra ocular muscles (EOMs) and their impact on eye movement (i.e. to stabilize and move the eyes). Each eye has six muscles, four recti (i.e. medial, lateral, superior and inferior) and two oblique (i.e. superior and inferior), which, when functioning properly, allow the eyes to work together and rotate the eye bulb in a wide range of gazes: adduction (the eye directing toward the nose), abduction (the eye directed laterally),

elevation (the eye directed up), depression (the eye directed down), intorsion (the top of the eye moving toward the nose) and extorsion (the top of the eye moving away from the nose). During the eye movements all six eye muscles work in together, some muscles increase their activity while others decrease it.That enables smooth eye movements. The EOMs compared to the skeletal muscles are faster and non-fatigue. The lack of fatigue in eye movements is partly due to the different types of muscles fibers in the EOMs; the fast twitch-fibers enable an all-or-nothing response and the non-twitch fibers a graded response. The EOMs muscles are divided into two layers; the outer orbital layer and the inner global layer (Hoogenraad el al 1979, Porter et al 1995, Rowe 2012). Each EOMs passes through an encircling ring or sleeves of collagen (pulley), located near the globe equator in Tenons´s fascia. The pulleys consist of contractile elements that are important for the dynamic and kinematics of the EOMs (Demer et al 2000).The EOMs is also more innervated than skeletal muscles and their cells contain more mitochondria. In addition to the structural and the physiological differences of the ocular muscles and the skeletal muscles, they have different immunological properties with the eye muscles being more sensitive to infections and skeletal muscles of dystrophies (Porter et al 1995, Wong 2008).

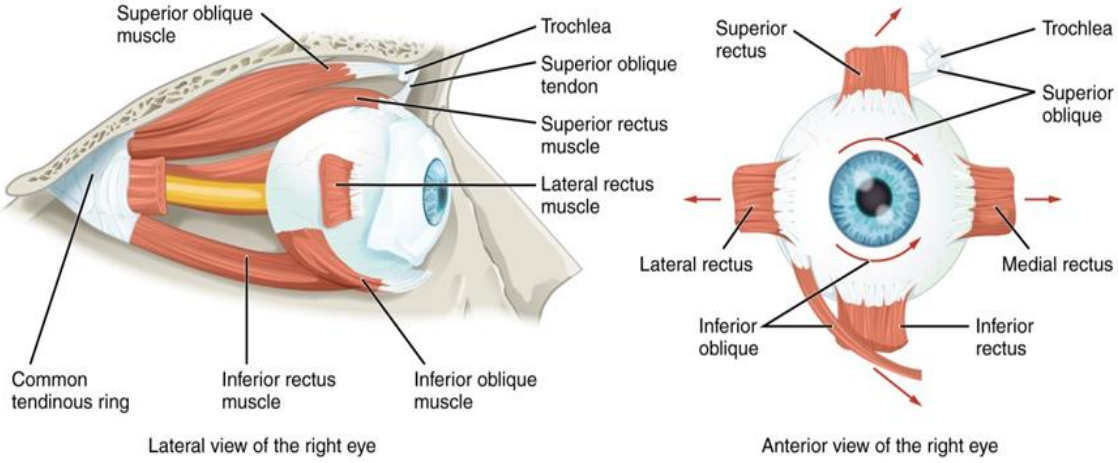

Figure 9. *The extraocular muscles move the eye within the orbit.*
(http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@6.12:92/Anatomy_&_Physiology) Download for free at (http://cnx.org/content/col11496/latest/).

1.4.1 Actions and innervations of extraocular muscles

The four recti muscles all origin from the annulus of Zinn at the apex of the orbit. Medial rectus and the lateral rectus act on the same horizontal plane, their contractions produces horizontal eye movements with the medial rectus adducting and the lateral rectus abducting it. The medial rectus is innervated by the third cranial nerve, oculomotor nerve III and the lateral rectus is innervated by the sixth cranial nerve, abducent nerve VI. The superior rectus acts above and enables elevation of the eye. Inferior rectus act below and enables depression of the eye. Both

superior rectus and inferior rectus are innervated by the third cranial nerve, oculomotor nerve III and have secondary and tertiary actions (Figure 9, Table 1).
The two oblique muscles superior oblique and the inferior oblique. The superior oblique also originates from the annulus of Zinn while the inferior oblique originates from anterior medial orbital floor. The superior oblique passes the trochlea an acts on the superior posterotemporal quadrant of the globe to enable incyclotorsion. The inferior oblique acts on the inferior posterotemporal quadrant of the globe to enable excyclotorsion. The muscles superior oblique is innervated by the fourth cranial nerve, trochlear nerve IV and inferior oblique by the third cranial nerve , oculomotor nerve III. They both have secondary and tertiary actions (Figure 9, Table 1).

Table1. Actions and innervations of the extraocular muscles

Extra ocular muscles	**Primary action**	**Secondary action**	**Tertiary action**	**Cranial nerve**
Lateral rectus	Abduction	None	None	N. VI
Medial rectus	Adduction	None	None	N. III
Superior rectus	Elevation	Incyclotorsion	Adduction	N. III
Inferior rectus	Depression	Excyclotorsion	Adduction	N. III
Superior oblique	Incyclotorsion	Depression	Abduction	N. IV
Inferior oblique	Excyclotorsion	Elevation	Abduction	N. III

1.4.2 Laws of ocular motor control

All eye movements involve more than one eye muscle and cranial nerve, to obtain single vision the muscles have to work together precisely. Eye muscles are working in pairs as synergists when they move an eye in the same direction, the primary moving muscle is called an agonist and a movement in the opposite direction is caused by its antagonist To enable this and ensure that the eye focuses in same direction and to keep the eyes aligned there are laws that help the brain.

Sherrington´s law of reciprocal innervation

Whenever an agonist receives an impulse to contract an equivalent inhibitory impulse is sent to its antagonist which relaxes and actually lengthens. This reciprocal innervation is mainly due to central connections in the brainstem (Wong 2008).

Hering´s law of equal innervation

When a nervous impulse is sent to an ocular muscle to contract, an equal impulse is sent to its contralateral synergist to contract as well (Rowe 2012).

2 THE OCULAR MOTOR SCORE (OMS) TEST PROTOCOL

The OMS test protocol (Appendix) consists of 15 different subtests which are grouped into a static and dynamic section. The tests are easy to perform and evaluate and are well tolerated by children at any age. The equipment required to perform the testing consists of a minimum of items (Figure 10). All subtests have a detailed description of how they should be scored to eliminate differences in examiners scoring. The overall score from the 15 subtests yields a total OMS (tOMS) score, which then can be used as a comparison in the following up a child. All subtests are given a score between 0 and 1, where 0 is considered normal and 1 is the maximum disability in that certain subtest. When assessing children the state of their ocular motor development must be taken in account, an OMS investigation of a healthy young infant will result in moderate tOMS whereas a healthy teenager will show a tOMS close to or zero (Olsson et al 2013). The results of the different subtests will give a specific profile in each child demonstrating problems in or a combination of the static or dynamic section of the test.

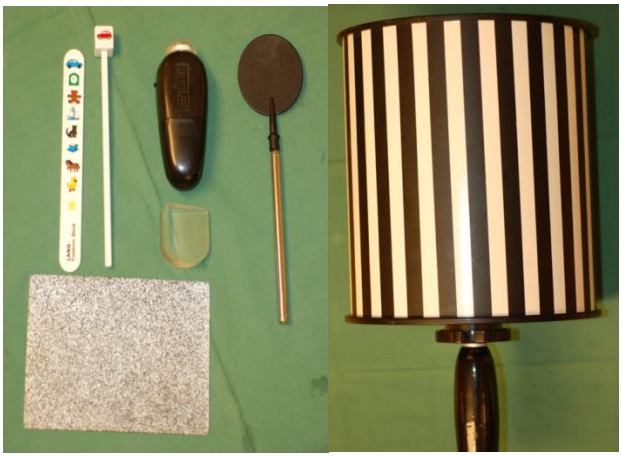

Figure 10. *The equipment required is Lang stereo test, torch, optokinetic drum, a prism, objects to fixate and a cover.*

2.1 THE STATIC SECTION OF THE OMS TEST PROTOCOL

The static section involves the afferent visual system where the visual information received by the eye and the signal is relayed by the retina, optic nerve, chiasm, tracts, lateral geniculate nucleus, and optic radiations to the primary visual cortex for final processing.

2.1.1 Head posture

Children with neuro –ophthalmological disorders often develop anomalous head posture (Brodsky 2010).The ophthalmological head posture can take the form of head tilt, face turn, and chin up, chin down or combination of them, depending on the specific etiology. However, there are many variations and the type of the head posture cannot reliably predict the underlying cause (Nucci el al 2014). An abnormal head posture may serve to restore single binocular vision, improve visual acuity or centralize a partial visual field with respect to the

body (Brodsky 2010). Anomalous Head posture is commonly seen in patient with nystagmus and strabismus.

2.1.2 Eyelid position

Congenital ptosis (Figure 11) can be the presenting sign of several neuro-ophthalmologic disorders. Specific attention has to be paid to ocular motility and pupillary examination as coexisting neurological signs, such as in oculomotor palsy or Horner`s syndrome (Brodsky 2010) Acquired ptosis in young children has many etiologies, including trauma, neurologic or a systemic disease such as mitochondrial disease like complex I deficiency and Leigh syndrome (Fahnehjelm et al 2012, Han et al 2014) or autoimmune disease as juvenile myasthenia gravis (Gadient et al 2009).

Figure 11. *Congenital ptos on the left side. Printed with permission from the parents*

2.1.3 Stereo acuity

Stereopsis is defined as the relative ordering of visual objects in depth, i.e. in the third dimension (von Noorden & Campos 2002). To obtain stereopsis the most exclusive type of binocularity must be used the sensory fusion, "the ability to perceive two similar images, one formed on each retina, and interpret them as one" (Rowe 2012). Stereopsis is measured in stereo acuity the angular measurement of the minimal resolvable binocular disparity which is necessary for the appreciation of stereopsis (Rowe 2012). Stereopsis requires good visual acuity in both eyes and a normal cortical development (Miller et al 2008). Stereo acuity develops with age and can be measured in a child from six month of age (Mercuri et al 2007). Defective stereopsis can be seen in children with heterotropia, amblyopia or ansiometropia.

2.1.4 Pupil response

The pupil response or reflex provides an important diagnostic tool that allows the examiner to determine neurological function, i.e. the integrity of the visual sensory apparatus, the motor outflow to the pupillary muscles (the dilator and the sphincter muscles of the iris) and the central pathways that mediate the reflex to the Edinger-Westphal nucleus and the oculomotor nerve III (Purves et al 2008). The pupil size, shape and reaction are altered by pathological processes. The changes that arising depend on the lesion location and its extend. For example, the afferent pupil defect in which response to direct light is absent and the indirect response are

maintained can result from damages to the retina and the optic nerve. The efferent pupil defect seen in damages to the oculomotor nerve III or the Edinger –Westphal nucleus in the brainstem where both the direct and the indirect response failure to elicit. Anisocoria, unilateral miosis can be seen in Horner´s syndrome and unilateral mydriasis can result from a congenital third cranial paresis (Isenberg 1989).

2.1.5 Strabismus

Strabismus, also known as heterotropia, is the manifest part of strabismus a condition in which the eyes are not properly aligned with each other. Strabismus which may be inwards esotropia, outwards exotropia, upwards hypertropia, downwards hypotropia, or rotated cyclotropia, is present while the patient views a target binocularly. Strabismus is present in about 3-3.5 % of otherwise healthy children in a population aged 4-15 (Kvarnström et al 2001, Aring et al 2005, Larsson et al 2014). Children with neuropaediatric disorders that affect the brain such as cerebral palsy, Down syndrome, hydrocephalus and brain tumor are more likely to develop strabismus. For example Strabismus has been reported in children with hydrocephalus was present in 69%; esotropia in 35%, exotropia in 28% and a combination of both types were seen in 5.4% of the children (Aring et al 2007a). Children with strabismus have an increased risk of amblyopia. Intermittent exotropia that increases during near fixation is a weak indication of neuropediatric disorder (Phillips et al 2005).

2.2 THE DYNAMIC SECTION OF THE OMS TEST PROTOCOL

The dynamic section refers to the efferent visual system. The visual system is considered as efferent when it is carrying innervation from the Central Nervous System (CNS) the cortex, brainstem and the cerebellum.

2.2.1 Ocular motility, ductions and versions

As mentioned earlier, ocular motility refers to the examining of the twelve EOMs. Ocular motility is the orthoptist`s area of expertise. We assess the EOM**s** according to function as normal, overacting or underacting in both ductions and versions. Pathological ocular motility is seen for example in palsies of the oculomotor III, trochlear IV, abducen nerve VI, and in mechanical disorders as Duanes retraction syndrom, Brown´s syndrom and thyroid eye disease.

2.2.2 Fixation

An active fixation system holds the image of a stationary object on the fovea by minimizing ocular drift (Leigh & Zee 2006). Normal visual fixation is an active process that maintains foveation by small miniature eye movements that are not detectable by the eye: micro saccades, micro drift and micro tremor (Wong 2008). The OMS test protocol includes examining the capacity to maintain a constant view of a visual target in PP and in eight gazes. Steady fixation requires sustained attention to the object of viewed (Downey & Leigh 1998). Visual fixation in is not developed in new born children, but acquired during the first 6 month (von Noorden &

Campos 2002). Fixation behavior changes over time between 4 and 15 years of age in healthy children (Aring et al 2007b). Fixation disturbances are also called nystagmus. Disturbance of fixation as nystagmus is commonly seen in children with neuropaediatric disorders (Brodsky 2010). Some patients with fixation system disorders, for example those with congenital nystagmus, do not have poor vision because their eyes are abnormal but because they cannot hold their eyes still enough for the visual system to work accurately. Others have poor vision because of abnormalities of the eyes that in their turn give rise to nystagmus. Pathological nystagmus may be spontaneous, present in the PP, positional, induced by a change in head position or gaze –evoked, induce by a change in eye position (Lang & McConn Walsh 2010). Nystagmoid fixation should always be investigated by an ophthalmological department and if no cause is found in the eyes, a neurological examination should be carried out.

2.2.3 Saccades

Saccades are rapid eye movements that shifts gaze to direct the fovea at a target of visual interest. They must be precise because of the small size of the fovea and fast and brief to prevent disruption of vision (Leigh & Zee 2006). Saccadic eye movements are used to explore the visual environment. Accurate saccades can be made in response not only to visual stimuli but also to sounds, tactile stimuli, memories of locations in space, and even verbal commands (Kandel et al 2000). A pulse-step mechanism is the process that generates a saccadic eye movement and this mechanism is composed of burst and pause cells (Rowe 2012). A small child's saccades are characterized by long latencies and hypometrics and in healthy children saccades are fully developed by the age of 12 (Bucci & Seassau 2012).There are strong links between FEF and PEF, where the FEF is involved with volitional, visually guided purposive saccades and PEF is involved when attention shifts to new targets that appear in the visual field (Rowe 2012). Slow saccades can indicate brainstem lesions, and dysmetric cerebellar or cerebellar peduncle lesions (Lang & McConn Walsh 2010). Although the cerebral cortex is involved in executive control, damage in cortical areas usually results in abnormal volitional saccades. The brainstem provides the immediate premotor signals for saccades, and damage to the brainstem affects both reflexive and volitional saccades. Damage in the cerebellum causes saccades to overshoot or undershoot the target (Wong 2008).

2.2.4 Smooth pursuit (SP) system

The SP system consists of conjugated slow eye movements that allow both eye to track a moving target smoothly in order to focus the visual imagine on the fovea (Rowe 2012). This is in order to stabilize moving objects on the retina thereby enabling perception of an object in detail (Rütsche et al 2006). The major stimulus for the generation of SP is a fixated target that moves across the fovea and the perifoveal retina (Rowe 2012). The system requires a moving stimulus in order to calculate the proper eye velocity. The SP cannot be generated voluntary without a suitable object, thus a verbal command or an imagined stimulus cannot produce SP. Though the SP system involves many brain structures, pursuit deficits do not usually have any

localizing value, other neurological and eye movement abnormalities are needed to pinpoint the location of the lesion (Wong 2008). The regulation of SP eye movements involves cortico-ponto- cerebellar circuits (Suzuki et al 1999). In young children SP movements are premature and very dependent on the maturity of the fovea so they have difficulties in following a slow moving target i.e. low gain. SP movements change with age according to attention time and gain for stimulus velocity and reach adult values at an age at 6 (Rütsche et al 2006). Maintenance of accurate SP requires continuous attention (Krauzlis 2004). Inadequate SP should always be considered an indicator that requires follow- up.

2.2.5 Convergence

Vergence movements move the eyes in opposite directions in a disjunctive eye movement so that the image is positioned on both foveae. The most common is the convergence (i.e. the both eyes rotate inward towards the nose) (Figure 12). There are two primary stimuli to disjunctive eye movements: disparity between the location of image on the two retinas, which produce diplopia and leads to fusional vergence movements, and retinal blur (defocused image), which leads to loss of sharpness and an accommodative linked vergence eye movement (Leigh & Zee 2006). Convergence triggered by accommodation is dependent on a well-developed fovea function. Convergence insufficiency is the most prevalent dysfunction of the binocular system and can both be of primary and secondary origin (Rowe 2012).

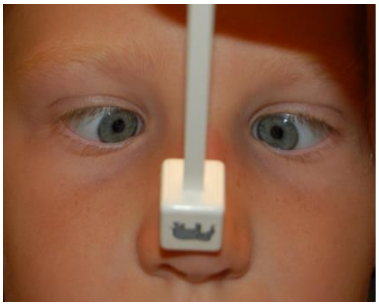

Figure 12. *Normal convergence in an eight year old child.*

2.2.6 Fusion

Sensory fusion is the ability to perceive simultaneously two images, one formed on each retina, and to interpret them as one (i.e. binocular single vision). This requires both eyes to work together and causes that can make this impossible are heterotropia, amblyopia or anisometropia. Motor fusion is the ability to maintain sensory fusion through a range of vergence movements (Rowe 2012). Pathological fusion is common in heterotropia. It can also give raise to diplopia.

2.2.7 Vestibular Ocular Reflex (VOR)

The VOR reflex is a short-latency reflex system trigged by head movement to generate compensatory eye movements to hold images still on the retina and is driven by signals from the vestibular system. Sensory signals from the labyrinthine composed of the 3 semicircular

canals that detect rotation (angular acceleration) of the head (i.e. horizontal, vertical and torsional) (Figure13). The otoliths organs, which consist of the utricle and the saccule, detect translation (linear acceleration) of the head (i.e. side to side, up and down, fore and aft (Wong 2008). This reflex in seen in the new born child i.e. Doll's head reflex and is considerate to be the first developed ocular motor function. The vestibular horizontal system is well developed at birth, while the vertical develops slightly later (Leigh & Zee 2006). The system is very important for a child´s development of the balance (Charpiot et al 2010) and dysfunctions can result in delayed postural control and lead to delayed walking onset. Patients with peripheral vestibular deficits show impaired gaze stabilization and consequently their visual acuity degrades during head movement. Patient with vestibular hypofunction adopt compensatory saccades as a strategy to assist gaze stabilization (Schubert & Zee 2010). Pathological VOR, balance dysfunctions and delayed walking onset has been reported in children with HI due to cCMV (Karltorp et al 2014, Fahnehjelm et al 2015). Similar condition can be found in children with HI due to Usher´s syndrome type I and III, the most frequent cause of combined HI and retinitis pigmentosa (RP) a progressive degeneration of the retinal photoreceptors (Liu et al 2007, Yan & Liu 2010).

Figure 13. *Example of rotation where the semicircular channels are active.*

2.2.8 Cancellation of VOR (CVOR)

A test of the CVOR is in fact an examination of the SP because SP cancels the VOR. To test CVOR, you can spin the patient in a swivel chair while the patient holds and fixates on a fixation object. The normal response is that the eyes should be able to maintain steady fixation. With inadequate CVOR, the eyes are taken off target by VOR slow phases, which results in corrective saccades. CVOR is managed by the vestibulocerebellum (Wong 2008).

2.2.9 Optokinetic Nystagmus (OKN)

OKN is the visually driven supplement to the VOR response to continue the eye movements while the VOR system has reduced its signals. Both systems are combined as the visual vestibulo-ocular reflex (Rowe 2012). Normal OKN requires intact development of smooth pursuit function (i.e. the slow phase in the direction of drum rotation), and saccadic function (i.e. the quick phase in the opposite direction) to be smoothly executed (Wong 2008). Neuro-ophthalmological disorders often produce pathological optokinetic responses.

3 AIMS OF THE STUDY

The aims of this study were to evaluate the OMS test protocol according to reference group, agreement and regarding analyses and characterisation of ocular motility disturbances in different neurological diseases.
The aims of each study are specified below.

3.1 PAPER I

To create a normative and age- related material for the OMS test protocol among neurologically healthy children, and to describe and set instructions for the examination procedure for the OMS test protocol.

3.2 PAPER II

To investigate the OMS test protocol according to intrarater agreement and between three independent raters in the inter-rater agreement as well as to present and discuss the outcomes.

3.3 PAPER III

To investigate ocular function and ocular characteristics in a group of children and young adults with the mitochondrial disease complex I deficiency and with the help of the OMS test protocol identify their ocular motor outcomes.

3.4 PAPER IV

To compare ocular function and ocular characteristic in a group of children with cochlear implants due to severe HI caused by cCMV infection with a control group of children with cochlear implants due to severe HI caused by Cx26, and by using the OMS test protocol, identify and compare the ocular motor outcomes in the both groups.

4 MATERIAL AND METHODS

All the patients included in the studies I and II were asked to participate when they came for a planned visit to the department of paediatric ophthalmology at Karolinska University Hospital, Huddinge. In studies III and IV the patients were included in other multidiscipline studies and were referred to the department of paediatric ophthalmology at Karolinska University Hospital, Huddinge for their ophthalmological examination.

4.1 PAPER I

Two hundred and thirty three (233) children and young adults103 males (M) and 130 females (F) were assessed according to the OMS test protocol at a median age of 6.6 years (range 0.5-19).The 233 subjects were divided into four age groups: 0.5-3, 4-6, 7-10 and 11-19. Subjects identified as healthy and with normal psychomotor development were enrolled in this study. Strabismus and refraction errors were not exclusion criteria, their ocular motor functions were scored according to the OMS test protocol. The total median OMS score for the 4 age groups were determinate and statistically analyzed.

4.2 PAPER II

Forty children aged 4-10 years, 23 girls with the median age of 6.5 (range 4.3-9.3) and 17 boys with the median age of 5.8 (range 4.1-9.8) whose ocular motor functions were scored using the OMS test protocol. The examinations were videotaped by the examiner. In the intrarater agreement, the examiner who had videotape the examinations studied and scored the subjects twice, first at the clinic and then after 14 days by watching the videotapes. In the inter-rater agreement study the videotapes were watched by three independent raters who scored each child´s ocular motor functions according the OMS test protocol. The children included were both children with and without strabismus and ocular motor deficiencies. There were no criteria of healthiness and normal psychomotor development, but the children had to be able to cooperate in all 15 subtests and understand the instructions.

4.3 PAPER III

Thirteen children and young adults with complex I deficiency median age of 12.8 years (range 3.1-23.4) who were diagnosed during 1995-2007 and assessed at our university clinic during 1997-2009 were included in a prospective study with longitudinal follow-up. Their latest results were chosen and their ocular motor functions were scored according the OMS test protocol. Twelve of those 13 patients underwent a complete OMS examination. The OMS outcome was compared with a group of 150 healthy children with the median age 7.5. This was the first study including the OMS test protocol and at that time it comprised 14 subtests, fusion 15/20 base out prism test was added later.

4.4 PAPER IV

This included 26 children with a median age 8.3 (range 1.4-16.7) with cCMV diagnose and 13 children with a median age of 5.6 (range 1.7-12.5) with Cx26 a genetic cause of hearing impairment, used as controls. Each child was examined by the multidisciplinary team: a paediatrician, a neuropaediatrican, a speech and language pathologist, a physiotherapist and an otolaryngist. There ophthalmological assessments were performed by the same ophthalmologist and orthoptist.The ocular motor functions were scored according the OMS test protocol and analysed according to the tOMS.

5 RESULTS

5.1 PAPER I

The median tOMS outcome for the entire reference group was 0.3 (range 0- 4.8). The youngest group of twenty five children (M14/ F11) aged 0.5-3 years, were given a median tOMS score of 0.9 (range 0.3-4.8) and 94 children (M 40/ F54) aged 4-6 years a lower median tOMS score of 0.3 (range 0-3.4), while 77 children (M 37/ F 40) aged 7-10 were given the same median tOMS score of 0.3 (range 0-2.3) and 37 young adults (M 12/ F25) in the group aged 11-19 a median tOMS score of 0 (range 0- 3.5) respectively. The youngest group of children, ages 0.5-3 years showed a significantly higher median tOMS compared to the other age groups ($p < 0.001$).

5.2 PAPER II

There was high overall observed intrarater (88%) and overall observed inter-rater (80%) agreement for the OMS test protocol. It was more difficult to obtain agreement in some of the subtests, such as saccades, SP and fusion, especially when it concerned a subnormal result for the subtests, normal and pathological results was easier to get agreement in. A cut-off for substantial observed agreement at 65% and almost perfect observed agreement at 85% for the OMS test protocol are proposed.

5.3 PAPER III

We were able to identify ocular pathology as optic atrophy (OA), retinal pigmentation and a pathological ocular motor performance in the group with complex I.
The median tOMS outcome in the healthy group was 0.3 (range 0-2.3) and in the Complex I group 1.9 (range 0-8.5). Nine patients in the complex I group had different degrees of ocular motor problems, mainly with saccades, SP, vergences, VOR and OKN. The main difference was seen in the dynamic section of the OMS test protocol. Ocular motor problems of this type indicate the involvement of EOMs, brainstem, basal ganglia and cerebellum, which was confirmed with MRI pathology in mainly these areas.

5.4 PAPER IV

Ocular motor problems were more common in the group of children with cCMV. In the comparison of the group of children with cCMV to the control group in the study five of the 26 cCMV children (19%) displayed unilateral chororetinal macular scars causing reduced best corrected visual acuity ≤ 0.3. None of the children with Cx26 had chorioretinal scars ($p=0.15$). Although ocular motor problems were more common among children with cCMV they more often scored subnormal for the subtests fixation in 8 gazes, saccades and SP but the difference was not significant ($p=0.20$). A single test, the VOR, was more often pathological in children with cCMV and significant at ($p= 0.011$). It correlated well with the balance disturbances reported in the group with cCMV (Karltorp el al. 2014)

6 DISCUSSION

In our everyday clinical practice we meet children and young adults with various types of visual deprivation or other ophthalmic disorders. Many have different types of refractive errors which can be treated with spectacles to obtain normal vison and binocularity. Other children have strabismus where the risk factors can be of both afferent origin i.e. deprivation of the visual information received by the retina to the primary visual cortex or efferent origin i.e. deprivation of the visual system carrying innervation from the CNS. Strabismus may be the first sign of both ocular pathology and neurological diseases (von Norden & Campos 2002).

The number of children with CVI is increasing since more children are born prematurely and children with other neuro-ophthalmological disorders risk developing posterior visual pathway damage. In clinical practice we usually test the different ocular motor functions in these groups of patients but if we do this testing in a structured way what conclusions can we draw from our findings and how can we use the information collected to optimize examinations and interventions?

The hypothesis of the present studies was that the OMS test protocol would be useful in the examination of ocular motor and some visual functions and could provide a more complete information of both the afferent and the efferent visual system that is so important in a neuro-ophthalmological examination of children. The studies were also intended to evaluate further the possibility of using the OMS test protocol to follow-up of abnormal ocular motor functions in children and in children with neuropaediatric disorders.

The OMS test protocol is a novel clinical approach for evaluating ocular motor functions in children where knowledge about the ocular motor functions is needed. In our first **study I**, normative data were established for the OMS test protocol on the basis of four age groups: 0.5-3, 4-6, 7-10 and 11-19 years. The youngest group 0.5-3 years demonstrated significantly higher tOMS ($p < 0.001$) compared to the other age groups. That correlates well with other studies on describing the development of different ocular motor functions in children. The development of the ocular motor functions is known to be dependent on the maturation of the fovea as well as attention and cortical motion processing (Jacobs et al 1992, Mezzalira et al 2005). Another factor to take into consideration for the high tOMS in the youngest age group is that these youngest children are not always the most cooperative patient and this can of course also affect the result. One example is in the subtests which should be performed both monocular and binocular. As young children often refuse to wear an eye-patch these tests could only be carried binocularly.

There was a high prevalence of strabismus in this study as 10 % of all the 233 children scored for strabismus, compared with 3-3.5% in other studies (Kvarnström et al 2001, Aring et al 2005 and Larsson et al 2014). This was the result of inclusion of subjects when they came to the department of paediatric ophthalmology usually because of suspect strabismus or visual

problems. The age group 11-19 was subjects often recruited when they came for follow-up of their manifest or intermittent strabismus. Children with simple refractive errors do not normally attend a department of paediatric ophthalmology for follow-up examinations.

Which score should be considered as normal or pathological?
To illustrate this two examples are given below:
Example I:A healthy 7-year-old child scoring for manifest strabismus (esotropia) will also score for the binocularity tests as stereo visual acuity and fusion and will end up with tOMS score at 2.5 (static 1.5, dynamic 1) compared to another healthy 7-year-old child without manifest strabismus, whose tOMS will be 0.
Example II: A 5-year-old child with the diagnosis of Arnold Chiari I, a malformation characterized by protrusion of the cerebellar tonsils down into the foramen magnum thereby inducing compression on the brainstem (Brodsky 2010). This child scored for head posture, stereo visual acuity, strabismus, eye motility, fixation in PP, fixation in 8 gaze directions, saccades, SP, fusion, VOR and OKN and ended up with a tOMS at 8.3 (static 2, dynamic 6.3).

Example II correlates with earlier studies that state the fact that children with neuropaediatric disorders more often have problems in performing or initiating specific eye movements. Children with CVI, for example can present with nystagmus, inaccurate saccades and low gain SP (Jacobson & Dutton, Philip & Dutton 2014). To determine the difference between healthy subjects and subjects with neuropaediatric disorders, 53 children and young adults with different well-defined neuropediatric disorder were divided into four age groups 0.5-3, 4-6, 7-10 and 11-19 years and were compared with the reference group of 233 children. The two groups were compared according to age, tOMS static and dynamic median tOMS. The median tOMS was 0.3 (0-4.8) among the healthy children and 2,6 (0-10.8) in the group of children with neuropaediatric disorder. The largest difference was seen in the age group 11-19, and in the dynamic elements of the OMS test protocol (Olsson et al 2012).

The assessment of normal, subnormal and pathological is, as in any clinical test, subjective and varies according to the examiner´s experience. To help in examinations the OMS test protocol has described specific criteria for scoring single subtest (Appendix).

Study II The 40 children included were randomly selected when there was a suitable time for video recording. Only children who were able to understand the instructions, cooperated in all the 15 subtests and participate in the video recording were included so there were no children with severe neuropaediatric disorder in the study. Nevertheless it is well known that children with severe neuropaediatric disorder more often present with pathological ocular motor functions (Shinmei et al 2007, Philip and Dutton 2014). The decision to video record the examination was taken by the examiner (MO) who was familiar with the use of video recording in clinical assessment. It was decided to use video recording in this study in order to provide similar conditions for the raters and avoid bias as children may get tired if examined

four times. There were also, socioeconomic aspects as the parent did not have to take time off work to return to the clinic with their child for repeated visits. Intrarater agreement was high (87%) when the examiner (MO) first scored the patient at the clinic during the video recording taping and then 14 days later while watching the videotape ones more. The overall agreement observed between inter-rater was 80%, when 3 raters scored the subtests according the OMS test protocol independently on the basis of the subtitled videos. It turned out to be difficult to obtain good quality in the videos of some of the subtests as pupil response were some of the patients were light sensitive and preferred to close their eyes and fusion were reflections from the prism and the child`s spectacles made those subtests difficult to score for the raters both in intrarater and inter-rater agreement. The agreement among the raters was generally high although some of the subtests were subtests with more disagreement. These were head posture, fixation in 8 gazes, saccades and SP. The differences arose in distinguishing between normal or subnormal while it was seldom difficult to agree on a pathological result. Some of the subtests in the OMS test protocol are ones that are not used so often during the standard in the traditional examinations today, for example the testing of VOR, CVOR and OKN tests. Providing more training and discussion on the use of these valuable clinical tools will enable orthoptists to acquire more in the information about children with suspect neuropaediatric disorders. The use of video technology in research is described both in qualitative and quantitative studies and the technique can be of great help in clinical situation both for discussion among clinicians and for educational purpose. Clinical experience allows each orthoptist to build up frames of reference of what is normal, but the OMS test protocol would help to quantify the differences.

In **study III** 12 children and young adults with the metabolic disorder complex I deficiency were investigated according to visual function, ocular characteristics and ocular motor functions according the OMS test protocol. Isolated complex I deficiency is the most common mitochondrial defect, though there is a wide range of clinical signs in the patients (Esteitie et al 2005). The group in this study had also different degrees of somatic symptoms such as muscle weakness, HI, cardiac involvement and subnormal mental development, findings that are well described in Fahnehjelm and co-workers (2012).Ocular motility disorders are reported in other syndromic mitochondrial disorder such as encephalopathy with lactic acid and stroke- like episodes (MELAS) were, for instance, the subjects had problems in initiatinge saccades and showed dysmetric saccades and low gain smooth pursuit (Shinmei et al 2007). In Leigh syndrome, strabismus and nystagmus are more common among the patients and ptosis has been seen as a possible initial sign (Han et al 2014). Our group of complex I deficiency patient presented a wide range of ocular motor problems such as dysmetric mostly hypometric saccades, asymmetrical SP, instability of in the fixation, defect VOR and OKN. Seven of the 12 patients had brain imagining pathology diagnosed most commonly in the pons and cerebellum (Fahnehjelm et al 2012). That correlates with other reports showing that damage to the pons commonly causes abnormal horizontal eye movements, and lesions in the midbrain cause disturbances in vertical eye movements and that damage to the cerebellum

impair the SP in all directions, the VOR adaption and the CVOR (Wong 2008). The tOMS also increased with age in the complex I group while the reference group showed decreased tOMS score with age, totally in line with Olsson and co-workers (2013). It could mean that the possibility of a follow-up progression of the disease would be possible. Long term follow up in these patients is planned.

In **study IV** the group of children with HI due to cCMV more often had balance disturbances and late onset of walking compared with the Cx 26 group (Karltorp et al 2014). That correlated with the outcomes in the VOR test using the OMS test protocol. Twelve of 23 (52%) children showed inadequate VOR response such as corrective saccades or asymmetries, and the vision was reduced by at least two lines for vison at distance (Fahnehjelm et al 2015). The balance disturbances stem from the fact that the CMV virus not only affects the cochlear part of the inner ear, but also the vestibular part of the inner ear (Teissier 2011). Balance control is an active sensorimotor process that maintains the body´s center of gravity over the base of support. Proprioceptive, visual and vestibular inputs are involved in this process (Charpiot et al 2010). Patient with vestibular hypofunction adopt compensatory saccades as a strategy to assist gaze stabilization whether or not patients can be trained to use them is unknown (Schubert & Zee 2010). In general visual defects are common in deaf individuals, such as refractive errors and binocular vision anomalies (Hollingsworth et al 2014). An examination of a child with HI should include examination of the VOR. Defective VOR adaption, balance disturbances, late walking onset and an unknown or known hearing deficit can indicate cCMV virus but also Usher syndrome type I and III. Thus, examination of ocular motor functions according to OMS test protocol can add information investigating children with HI.

7 CONCLUSION

This study confirms the findings of previous studies that that examination of ocular motor functions can give the examiner valuable information about the possible neurological underlying cause of the patient's difficulties.

Based on the results of this thesis we can draw the following conclusions:

- It is important to understand the ocular motor development of healthy children and on the basis of that knowledge be able to find subnormal or pathological conditions associated with abnormal ocular motor performance.

- The OMS test protocol can provide a useful complement in screening interventions as in healthy children as well as in children with suspected neuropaediatric disorders.

- Using the OMS test protocol regularly will increase the examiners experience of normal ocular motor status.

- Subnormal or pathological results in primarily the dynamic part of the OMS test protocol, can be a soft sign of neurological disease.

- It is important with an extended ocular motor examination of patients with ocular motor dysfunction or suspected neuropaediatric disorders as a follow–up.

8 FUTURE PERSPECTIVES

The visual system enable us to identify, categorize, and memorize visual objects. This function together with an intricate system of ocular motor activity enable us to act according to ambient events.

At the department of paediatric ophthalmology the orthoptists are skilled at identifying children with different ocular problems as refractive errors, amblyopia and strabismus. In the future we should become better at identifying children with ocular motor problems as these may indicate subtle neuropediatric disorders. These children may also have posterior visual pathway damage which can give rise to CVI.

Clinical guidelines

To implement the OMS test protocol as part of our orthopthic examination should add information about the child's ocular motor performance. It is well-known that it is more common with strabismus, nystagmus, and difficulties to make accurate saccades and normal smooth pursuits in children with different neuropaediatric disorder (Shinmei et al 2007, Philip & Dutton 2014).

Educational

In the orthoptist education more emphasis should be put on clinical examining of gaze – stabilization and gaze–shifting ocular motor functions and discussion of the underlying pathology.

Further studies

We have started studies to compare the OMS test protocol outcomes with quantitative ocular motor analysis after, recording eye movements using the Chronos Eye Tracking Device like, fixation stability in different gazes positions, OKN and CVOR and of saccades and SP using the eye tracker Tobii (T120).These studies will provide more information about the sensitivity of the OMS.

9 REFERENCES

Ahlfors K, Ivarsson SA, Harris S (1999): Report on a long-term study of maternal and congenital cytomegalovirus in Sweden. Review of prospective studies available in the literature. Scand J Infect Dis.204:1003-7.

Aring E, Andersson Grönlund M, Andersson S, Hård AL (2005): Strabismus and binocular functions in a sample of Swedish children aged 4-15 years.Strabismus 13:1-7.

Aring E, Andersson S, Hård AL, Persson EK, Uvebrant P, Ygge J, Hellström A (2007a): Strabismus, binocular functions and ocular motility in a population- based group of children with early surgically treated hydrocephalus. Strabismus. Apr-Jun; 15(2):79-88.

Aring E, Andersson Grönlund M, Hellström A, Ygge J (2007 b): Visual fixation development in children. Graefes Arch Clin Exp Ophthalmol. 245(11):1659-65.

Baloh R W, Yee R D, Boder E (1978): Eye movements in ataxia-telangiectasia. Neurology. 28(11):1099.

Brodsky M, (2010): Pediatric Neuro-ophthalmology 2nd edn.
New York: Springer-Verlag.

Bucci M P & Seassau M (2012): Saccadic eye movements in children: a developmental study. Exp. Brain Res 222:21-30.

Buchman CA, Joy J, Hodges A, Telischi FF, Balkany TJ (2004): Vestibular effects of cochlear implantation. Laryngoscope 114: October.

Charpiot A, Tringali S, Ionescu E, Vital-Durand F, Ferber-Viart C (2010): Vestibulo-ocular reflex and balance maturation in healthy children aged from six to twelve years. Audiol Neurotol 15:203-201.

Coats DK, Demmler GJ, Paysse EA, Du LT, Libby C (2000): Ophthalmologic findings in children with congenital cytomegalovirus infection. Journal of AAPOS volume 4 number 2 April 2000.

Demer JL, Oh SY, Poukens V (2000): Evidence for active control of rectus extraocular muscle pulleys. Investigative Ophthalmology & Visual Sciency, Vol.41, No. 6.

Downey DL & Leigh RJ (1998): Eye movements: pathophysiology, examination and clinical importance. J Neurosci Nurs 30 (1):15-22.

Dutton GN & Bax M (2010): Visual impairment in children due to damage to the brain. Mac Keith Press, London.

Engman ML, Malm G, Engström L, Petersson K, Karltorp E, Teär Fahnehjelm K, Uhlén I, Guthemberg C, Lewensohn Fuchs I (2008): Congenital CMV infection: Prevalence in newborn and the impact on hearing deficit. Scandinavian Journal of Infectious Diseases 40:935-942.

Esteitie N, Hinttala R, Wibom R, Nilsson H, Hance N, Naess K, Teär –Fahnehjelm K, von Döbeln U, Majamaa K, Larsson NG (2005): Secondary metabolic effects in complex I deficiency.Ann Neurol 58: 544–552.

Fahnehjelm KT, Olsson M, Naess K , Wiberg M, Ygge J, Martin L, Von Döbeln U (2012): Visual function, ocular motility and ocular characteristics in patients with mitochondrial complex I deficiency. Acta Ophthalmol.Scand 90: 32–42.

Fahnehjelm KT, Olsson M, Karltorp E, Fahnehjelm C, I Lewensohn-Fuchs (2015): Chorioretinal scars and visual deprivation are common in children with cochlear implants after congenital cytomegalovirus infection Acta Paediatrica 03/2015 DOI:10.1111/apa.12988.

Gadient P, Bolton J, Puri V (2009): Juvenil myasthenia gravis: Three case reports and literature review, J Child Neurol. 24:584-509.

Goodale M A & Milner D A (1992): Separate visual pathways for perception and action. TINS, Vol. 15, No. 1.

Graff C, The-Hung B, Larsson NG (2002): Mitochondrial diseases. Best Practice & Research Clinical Obstetrics and Gynaecology Vol 16, No.5 715-728.

Han J, Lee Y-M, Kim S M, Han S Y, Lee J B, Han S-H (2014): Ophthalmological manifestations in patients with Leigh syndrome.Br J Ophthalmol, published on line, doi: 10.1136/bjophthalmol-2014-305704.

Hollingsworth R, Ludlow A K, Wilkins A, Calver R, Allen P M (2014): Visual performance and ocular abnormalities in deaf children and young adults a literature review, Acta ophthalmol 92:305-310.

Hoogenraad TU, Jennekens FGI, Tan KEWP (1979): Histochemical fibres types in human extraocular muscles, an investigation of inferior oblique muscle. Acta Neuropathol. 45, 73-78.

Isenberg SJ (1989): The pupils of term and preterm infants. American Journal of Ophthalmology 108:75-79.

Jacobs M, Harris C, Shawkat F, Taylor D (1992): The objective assessment of abnormal eye movements in infants and young children. Australian and New Zealand Journal of Ophthalmology 20: 185-195.

Jacobson L K & Dutton G N (2000): Periventricular Leukomalacia:An important cause of visual and ocular motility dysfunction in children, Survey of ophthalmology volume 45:1.

Kandel ER, Schwarts JH, Jessell TM (2000): Principles of neural science 4edn, McGrawe –Hill Companies , USA. (Chapter 28, 39, 40).

Karltorp E, Hellström S, Lewensohn-Fuchs I, Carlsson-Hansén E, Carlsson P-I, Engman M-L (2012): Congenital cytomegalovirus infection- a common cause of hearing loss of unknown aetiology, Acta paediatrica101:357-362.

Karltorp E, Löfkvist U, Lewensohn-Fuchs I, Lindström K, Westblad ME, Teär Fahnehjelm K, Verrecchia L, Engman M-L (2014): Impaired balance and neurodevelopmental disabilities among children with congenital cytomegalovirus infection, Acta paediatrica DOI:10.1111/apa.12745.

Krauzlis R J (2004): Recasting the smooth pursuit eye movement system, J Neurophysiol 91: 591-603.

Kvarnström G, Jakobsson P, Lennerstrand G (2001): Visual screening of Swedish children : An ophthalmological evaluation, Acta Opthalmologica 79:240-244.

Lang E.E & Mc Conn Walsh R (2010): Vestibular function testing, Ir J Med Sci 179:173-178.

Larsson E, Holmström G, Rydberg A (2014): Ophthalmological findings in 10-year-old full-term children – a population-based study, Acta Ophthalmolog Scand. doi: 10.1111/aos.12476.

Leigh RJ & Zee DS (2006): The neurology of eye movements 4th edn
Oxford University press, New York.

Liu X, Bulgakov O V, Darrow K N, Pawlyk B, Adamian M, Liberman M C, Li T (2007): Usherin is required for maintenance of retinal photoreceptors and normal development of cochlear hair cells.

Malm G & Engman M-L (2007): Congenital cytomegalovirus infections, Seminars in fetal & neonatal medicine 12, 154-159.

Martinez-Conde S, Macknik S L, Hubel D (2004): The role of fixational eye movements in visual perception, Nature Volume 5 March.

Mercuri E, Baranello G, Romeo D.M.M, Cesarini L, Rocci D (2007): The development of vision, Early Human Development 83, 795-800.

Mezzalira R, Coelbo Neves L, Queiros Maudonnet O A, do Carmo Bilécki M M, Gobbi de Ávila F (2005): Oculomotricity in childhood: is the normal range the same as in adults?, Bras Otorrinolaringol. V 71, n5, 680-5.

Miller NR, Newman NJ, Biousse V, Kerrison JB (2008): Walsh and Hoyt´s clinical neuro-ophthalmology:The essentials, 2nd edn. Wolters Kluwer Philadelphia.

Nucci P, Curiel B, Lembo A, Serafino M (2014): anomalous head posture related to visual problems. In.t ophthalmol, Published online 10 April, doi: 10.1007/s10792-014-9943-7.

Olsson M, Fahnehjelm KT, Rydberg A, Ygge J (2012): Ocular Motor Score in children: A possible tool for identification and follow-up of neuoropeadiatric disorders. Transaction XII International Orthoptic Congress, Toronto, Canada.

Olsson M, Fahnehjelm KT, Rydberg A, Ygge J (2013): Ocular motor score a novel clinical approach to evaluating ocular motor function in children.
Acta Ophthalmologica Scand 91: 564-570.

Philip SS & Dutton GN (2014): Identifying and characterizing cerebral visual impairment in children: a review, Clin Exp Optom 97:196-208

Phillips PH, Fray KJ, Brodsky MC (2005): Intermittent exotropia increasing with near fixation a "soft" sign of neurological disease, Br J Ophthalmol : 89, 1120-1122.

Phillips PH & Newman NJ (1997): Mitochondrial diseases in pediatric ophthalmology. Journal of AAPOS vol 1 number 2 June.

Pierrot-Desceilligny C (2008): Cerebral control of eye movements. Pediatric Ophthalmology, Neuro-Opthalmology, Genetics Essentials in Ophthalmology: 253-266.

Porter JD, Baker RS, Ragusa RJ, Brueckner JK (1995): Extraocular muscles: Basic and clinical aspects of structure and function. Survey of ophthalmology Vol.39, number 6, May-June.

Purves D, Augustine GJ, Fitzpatric D, Hall WC, LaMantia A S, McNamara JO, Whote LE (2008): Neuroscience, 4 th edn. Sinauer Associates, Inc. Sunderland USA.

Ratliff F & Riggs L.A (1950): Involuntary motion of the eye during monocular fixation. J Exp. Psychol. 40, 687-701.

Riise R, Ygge J, Lindman C, Stray-Pedersen A, Bek T, Rodiningen OK, Heiberg A (2007) Ocular findings in Norwegian patients with ataxia-telangiectasia: a 5 year prospective cohort study. Acta Ophthalmologica Scand 85: 557-562.

Rowe Fiona (2012): Clinical Orthoptics, 3rd edn.Wiley-Blackwell, UK.

Rütsche A, Baumann A, Jiang X, Mojon D S (2006) Development of visual pursuit in the first 6 years of life. Graefes Arch Clin Exp 244 1406/1411.

Schubert M.C & Zee D.S (2010): Saccades and vestibular ocular motor adaption. Restorative Neurology and Neuroscience 28 (2010) 5-14.

Shinmei Y, Kase M, Suzuki Y et al. (2007): Ocular motor disorder in mitochondrial encephalopathy with Lactic acid and stroke-like episodes with the 3271 (T-C) point mutation in mitochondrial DNA. J Neuro-ophthalmol, vol.27, No1.

Snell R S (2010): Clinical Neuroanatomy, 7th edn., Lippincott Williams & Wilkins, China.

Suzuki D.A, Yamanda T, Hodemam R, YEE R.D (1999): Smooth-pursuit eye movements deficits with chemical lesons in Macaque nucleus reticularis tegmenti pontis. J Neurophysiol 82: 1178-1186.

Teissier N (2011): Inner ear lesions in congenital cytomegalovirus infection of human fetuses.Acta Neuropathol 122:763-774.

von Noorden G & Campos E (2002): Binocular vision and ocular motility:theory and management of strabismus, 6th edn. Moseby, St. Louis.

Wong A (2008): Eye movement disorders, 1st edn. Oxford university press, New York.

Yan D & Liu XZ (2010): Genetics and pathological mechanisms of Usher syndrom, Journal of Human Genetics 55, 327-335.

10 APPENDIX

Ocular motor score – OMS

Name: .....
Personal ID number: ……
Diagnosis: ……
Date of investigation: ……
Investigator: ……..

Static section

1. Head tilt / turn / thrusts / tremor

Head straight and none of the above	0	
Small tilt / turn (< 10 degs) or small thrusts / tremor	0.5	
Large tilt / turn (> 10 degs) or large thrusts / tremor	1	

2. Lids

Normal lid position	0	
Ptosis, retraction, lid nystagmus	0.5	
Total ptosis, pupil covering	1	

3. Stereo visual acuity

Points to and identifies Lang figures (small children)	0	
Hesitant in the Lang test, may eventually identify one figure	0.5	
No response to Lang test	1	

4. Pupil response

Normal light reflex, direct and indirect	0	
Anisocoria, slow light reflex or asymmetry	0.5	
No light reflex or inverse reflex	1	

5.Strabismus

No strabismus detected in near and distance viewing	0	
Esotropia detected	0.5	
Exotropia /vertical tropia detected	1	

Dynamic section

6. Motility / Ductions / Versions

No restrictions in 8 gaze directions	0	
Some form of motility restriction, over or under actions	0.5	
Advanced motility restriction / apraxia	1	

7. Fixation in primary position

Stabile fixation in primary position, no change in fixation with occlusion of one eye. Fixation stable at both distance/near	0	
Saccadic Intrusions, detectable drifts. Differences at distance/close fixation	0.3	
Nystagmus observed. Latent nystagmus /roving eye movements	1	

8. Fixation in 8 gaze directions

Stable fixation in 8 gaze directions, no signs of gaze induced nystagmus. Able to maintain fixation in extreme gaze position for several seconds	0	
Gaze induced nystagmus observed in one direction	0.3	
Gaze induced nystagmus observed in several directions	1	

9. Saccades

Adequate saccades on command. Normal latency, precision, conjugacy and no obvious hypo or hyper metria	0	
Long latency saccades, dysmetria and head movements	0.3	
Advanced dysmetria, long latency saccades poor conjugacy, head movement	1	

10. SP – smooth pursuit

Adequate SP, no intruding saccades, no head movement	0	
3-4 intruding saccades head movement,	0.3	
>5 intruding saccades, large head movement	1	

11. Convergence

Adequate response to vergence stimuli – convergence to < 10cm	0	
Drop one eye early > 10cm	0.5	
No convergence observed	1	

12. Fusion 15/20 base out prism test

Adequate response	0	
Inadequate response/ absence of response	1	

13. VOR – vestibulo-ocular reflex

Adequate response to head movement, no visual acuity loss with head movement	0	
Inadequate VOR-response as corrective saccades or asymmetries	0.5	
No VOR-reflex observed	1	

14. Cancellation of VOR

Adequate response to head movement, no saccades	0	
Frequent saccades during head movement	1	

15. OKN – optokinetic nystagmus

Adequate OKN response in all directions, no asymmetry	0	
Poor OKN-response / horizontal/ vertical asymmetry	0.5	
Large asymmetry / no OKN response observed	1	
Total score		

11 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

För att kunna se det vi vill titta på enkelt, stabilt och skarpt måste vi rikta ögonen mot objektet och fixera det med den del av näthinnan som är uppbyggd för att ge oss det bästa seendet. Denna del kallas för fovea. Till vår hjälp har vi olika huvud- och ögon-rörelser. Ögonrörelserna kan delas upp i blickförflyttande och blickstabiliserande. De blickförflyttande ögonrörelserna är sackaderna, de snabba ögonrörelserna som vi tar till då vi snabbt flyttar blicken från en punkt till en annan. Sackader använder vi vid t.ex. läsning för att flytta blicken framåt i texten. Vergenser är de ögonrörelser som vi använder för att hålla fixationen på ett objekt då vi gör blickförflyttningar i djupled t.ex. tittar på vår egen nästipp. De blickstabiliserande ögonrörelserna sammarbetar med balanssystemet och ser till att vi ska kunna se skarpt samtidigt som vi är i rörelse. Fixationsögonrörelserna håller ögonen stabilt fixerade på ett objekt. Det optokinetiska systemet (OKN) korrigerar seendet i relation till omgivningens rörelse t.ex. när vi tittar ut genom ett tågfönster, Vestibulär-okulära reflexen (VOR) använder vi för att stabilisera synen i samband med kropps- och huvudröreler. Följerörelser är långsamma ögonrörelser som håller en stabil fixation på ett rörligt objekt som t.ex. då vi tittar på en fågel som flyger.

Varje öga har sex muskler som i par med det andra ögat strävar efter att rikta ögonen mot och fixera blicken på det vi tittar på. Signalerna hur ögonmusklerna ska aktiveras kommer från hjärnan och hjärnstammen där olika typer av ögonrörelser utlöses från olika anatomiska områden. Därför kan onormala ögonrörelser signalera en specifik sjukdomsorsak och/eller anatomisk lokalisation av en sjukdomsprocess.

Patienter med ögonrörelseproblematik som skelning, ögondarr och ögonmuskelförlamningar undersöks dagligen på olika kliniker av ögonläkare, neurologer, optiker och ortoptister. Ortoptister är specialutbildade och vidareutbildade ögonsjuksköterskor som specifikt undersöker patienters ögonrörlighet. Resultaten av en klinisk ögonrörelsebedömning kan vara till hjälp vid diagnos och uppföljning av olika neurologiska sjukdomstillstånd och frågeställningar. Idag finns många kvantitativa metoder för registrering och utvärdering av ögonrörlighet. Många är dock tekniskt komplicerade, kräver god medverkan och går inte alltid att använda på barn. Speciellt barn med uppmärksamhetsstörningar och neurologiska funktionshinder kan vara svårundersökta med en sådan metodik

Ocular Motor Score (OMS) är ett protokoll sammansatt av professor Jan Ygge på Marianne Bernadotte Centrum, Karolinska Institutet, Sankt Eriks Ögonsjukhus. Syftet med protokollet (bilaga) är att kunna kvantifiera våra kvalitativa undersökningar av olika typer av ögonrörelser. OMS bygger på 15 kliniska deltester som alla är viktiga delar av en ortoptisk undersökning. OMS protokollet är uppdelad i en statisk och en dynamisk del. I den statiska delen bedöms patientens huvudlutning, ögonlocksposition, stereoseende, pupillreaktion och skelning och i den dynamiska delen bedöms ögonmotilitet, fixation, sackader, följerörleser, konvergens, fusion, VOR, cancellering av VOR samt OKN. Testerna är enkla att genomföra och att tolka och ger ett

specifikt svar på om det föreligger en avvikelse. Varje deltest poängsätts (score) från 0 poäng (normal) till 1 poäng (patologisk) och summan av de 15 deltesterna utgör den totala OMS (tOMS). Ålder och mognad hos en patient spelar stor roll vid dessa tester. Ett friskt spädbarn får ofta ett högre tOMS på grund av omognad i ögonrörelsesystemet medan en frisk tonåring i normala fall bör få en tOMS på 0.

Syftet med studierna har varit att utvärdera OMS testprotokollet genom att skapa ett normalmaterial för OMS genom att undersöka ett antal friska barn (n=233) uppdelade i fyra åldersgrupper (se artikel I). De yngre åldersgrupperna fick ett högre tOMS jämfört med de övriga grupperna. Detta är i linje med annan forskning där man sett att främst de dynamiska okulomotor funktionerna förbättras med åldern vilket grundar sig på näthinnans och foveas utveckling och mognaden av det centrala nervsystemet.
Ett vidare syfte har varit att utvärdera överensstämmelsen (agreement) mellan olika undersökares bedömning av samma patients enligt OMS protokollets deltester. Fyrtio barn mellan 4 och 10 år med som utan ögonrörelse problematik och utan krav på normal psykomotorisk utveckling, undersöktes och bedömdes enligt OMS protokollet samtidigt som denna undersökning videofilmades. Tre undersökare som alla är väl insatta i ögonmotorikundersökningar fick sedan oberoende av varandra, utan tidigare kontakt med patienten titta på videofilmerna och bedöma barnets ögonmotorik utifrån OMS protokollet (se artikel II). Det var allmänt god överenstämmelse av bedömningarna mellan undersökarna. Vissa deltester som sackader, följerörelser och fusion uppvisade dock sämre överensstämmelse speciellt vid mindre avvikelser.
Ett ytterligare syfte var att med hjälp av OMS se ifall det var möjligt att kunna identifiera och utvärdera avvikande ögonrörlighet hos barn och ungdomar med olika neuropediatriska sjukdomar, i denna studie bland barn och ungdomar med ämnesomsättningssjukdomen complex I defekt, en mitokondrie sjukdom och barn med medfödd cytomegalovirus (cCMV) infektion.

I complex I studien uppvisade tolv av 13 patienter nedsatt syn och ögonpatologi i form av synnervsförtvining (optikusatrofi), katarakt och näthinnepigmenteringar. Av gruppens 13 patienter kunde ögonmotoriken utvärderas enligt OMS protokollet hos 12 patienter. Nio av dessa patienter visade ögonmotorikpåverkan med huvudsaklig påverkan av sackader, följerörelser och fixation. Detta skulle kunna indikera påverkan av ögonmuskler, hjärnstam, basala ganglie eller lillhjärna (cerebellum). Gruppen visade också tecken på ett ökat tOMS med åldern (se artikel III).
I den sista studien studerade vi ögonkaraktäristika hos barn med kongenital cytomegalovirus infektion (cCMV) och som kontrollgrupp användes en grupp barn med genetiskt orsakad hörselnedsättning, Connexin 26 defekt (Cx26). Tjugosex barn med cCMV inkluderades tillsammans med 13 barn med Cx26. Fem av barnen i cCMV gruppen hade ensidiga chorioretinala ärr som gav upphov till en mycket reducerad syn på detta öga. Ögonmotorikproblem förekom oftare i cCMV gruppen. Den största skillnaden sågs vid undersökning av den vestibulo-okulära reflexen (VOR) som oftare var avvikande hos barn med cCMV. Detta korrelerade bra med de balansrubbningar och den sena gångdebuten som barn med cCMV uppvisar. Sammanfattningsvis är det viktigt med rutinögonundersökning av barn

med hörselnedsättning och undersökningen bör innefatta en utökad ögonmotorikkontroll (se artikel IV).

Idag på barnögonmottagningen är vi bra på att identifiera barn med olika oftalmologiska frågeställningar. I framtiden bör vi bli bättre på att identifiera barn med neuropediatriska störningar där skelning och ögonrörelse störningar kan vara det första tecknet. OMS testprotokoll som en del av undersökningen av barnet ger information om barnets ögonmotorikfunktioner, då det är väl känt att det är vanligare med skelning, nystagmus, svårigheter att göra adekvata sackader och följerörelser hos barn med olika neuropediatriska sjukdomar. Denna studie bekräftar att undersökning av ögonmotorikfunktioner kan ge undersökaren värdefull information om den möjliga neurologiska bakomliggande orsaken till barnets svårigheter.

Våra förhoppningar är att OMS protokollet som ett kliniskt verktyg ska kunna vara till hjälp vid diagnostik, utvärdering och uppföljning av avvikande ögonmotorik hos barn och ungdomar med neuropediatrisk sjukdom eller frågeställning. Det är viktigt att komma igång med adekvat behandling inklusive synbefrämjande åtgärder, då synen utgör en central del av ett barns psykomotoriska utveckling.

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