

Assessment and Management of Infantile Nystagmus Syndrome

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Abstract

This article is a review of infantile nystagmus syndrome, presenting with an overview of the physiological nystagmus and the etiology, symptoms, clinical evaluation and treatment options.

Keywords: Nystagmus syndrome; Physiologic nystagmus

Introduction

Nystagmus is a rhythmic, involuntary oscillation of one or both eyes. There are various classifications of nystagmus according to the age of onset, etiology, waveform and other characteristics. When the nystagmus is classified according to the onset of symptoms; the nystagmus that is noticed at birth or in the first months of life is classified as infantile nystagmus (previously congenital) and the nystagmus that is seen after 6 months of age, is classified as acquired nystagmus. Infantile nystagmus syndrome (INS) is an ocular motor disorder of unknown etiology that presents at birth or early infancy and is clinically characterized by involuntary oscillations of the eye [1,2]. Infantile nystagmus can be isolated or idiopathic without any associated ocular or systemic pathology and in these cases visual acuity is good, on the other hand in cases with associated ocular or systemic pathologies such as albinism, dyschromatopsia visual acuity is poor. Nystagmus can be physiologic or pathologic according to etiology. Physiologic nystagmus is the type of nystagmus that can be induced under laboratory conditions (vestibular system stimulation) or normal daily circumstances (watching the surroundings from a vehicle). Optokinetic nystagmus and end-point nystagmus are the best examples for this and these are normal responses of the visual system and the aim is to maintain clear and stable vision. The optokinetic system and smooth pursuit system are closely related to each other and optokinetic system is needed for maintenance of a steady image on the fovea when the image is moving. Physiological nystagmus can be categorized as;

End-point nystagmus: When the eyes are moved towards extreme gazes, about 10-20 seconds later, medium frequency, jerky nystagmus can be seen due to exhausted muscle tone.

Optokinetic nystagmus: When a subject views a series of moving objects, such as watching the view from a moving car or stripes on an optokinetic drum, rotating in front of the patient, the eyes tend to fixate on a stripe and follow the stripe for a time with a compensatory movement and then a saccade in the opposite direction (anticompensatory movement). This pattern of alternating slow and fast components is called optokinetic nystagmus (OKN). In human, this reflex is attention dependent. Looking at the stimulus results in large amplitude excursions with infrequent fast phases; staring at the stimulus results in smaller amplitude excursions with frequent fast

phases; active following of the stimulus results in poor correspondence between eye position and stimulus position. At higher velocity targets (greater than 100 deg/sec) optokinetic nystagmus can no longer be evoked. Unlike simple foveal smooth pursuit, OKN appears to have both foveal and peripheral retinal components [3]. Slow phase of the nystagmus is for following the target and the fast phase is for refixation saccade.

Vestibular nystagmus: Vestibular nystagmus is a jerky nystagmus that is induced by the stimulation from vestibular nuclei to the horizontal gaze centers. Vestibulo-ocular reflex functions to maintain steady gaze during head rotation and rotational acceleration of the head results in significant attempts by the oculomotor system to stabilize vision. Slow and quick phases of these eye movements constitute vestibular nystagmus, the slow phase of the induced nystagmus originates from the vestibular apparatus and the fast phase is a corrective movement that is not generated by the vestibular system, but by the brain stem and the frontomesencephalic pathways. The deviation of the eyes corresponds to the slow phase of vestibular nystagmus and is always in the direction opposite the change in rate of motion. This serves to stabilize the visual image. Vestibular reactions are reflexes and are not under voluntary control. The vestibular system is inhibited by the fixation maintenance mechanism. Optic fixation tends to inhibit vestibular nystagmus and optokinetic stimuli can completely dominate this system. Vestibular nystagmus is exaggerated in the dark, when the eyes are closed and by the use of high plus lenses [3]. Caloric stimulation of the semicircular canals will induce nystagmus and in cold water stimulation jerky nystagmus will be towards the opposite side and in case of warm water stimulation, nystagmus will be towards the same side. This is abbreviated with a mnemonic "COWS" (cold-opposite, warm-same). Rotatory nystagmus is seen mostly due to pathologies related to vestibular system.

Pathological nystagmus: This type of nystagmus disturbs the normal fixation reflex and consequently visual functions are affected. On the other hand, physiologic nystagmus is for stabilization of image on the retina. Physiologic nystagmus is conjugate, however, pathologic nystagmus can be dissociated and disconjugate.

Incidence

Estimations of incidence of INS vary from 0.03% to 0.0005% and the generally accepted figure is 0.015%. Estimates of incidence range

from 1 in 350 to 1 in 6550 and infantile strabismic patients have associated nystagmus up to 50% of the cases [2,4].

Etiology

The etiology of infantile nystagmus syndrome is not fully understood. Three major supranuclear inputs to the oculomotor system are important in stabilizing eye movements and their dysfunction may lead to nystagmus. These inputs are the pursuit system, the vestibular system and the neural integrator. Most forms of acquired nystagmus are caused by disease of vestibular system (centrally or peripherally) [2]. For infantile nystagmus, Brodsky and Dell'Osso suggested delay in maturation of cortical pathways and Tychsen suggested a failure in binocular cortical connections [5,6]. The pathophysiology of latent nystagmus and manifest/latent nystagmus (also named as fusion maldevelopment nystagmus syndrome) is different from and less well understood than INS. Because it is commonly associated with the infantile strabismus syndrome, its cause may be related to the documented persistence of nasotemporal motion processing asymmetry that is also characteristic for the syndrome. The etiology may be multifactorial, with the final common pathway being interference with ocular motor calibration during a period of sensitivity, at which time an insult results in irreversible changes [2].

Eye muscle studies with electron microscopy revealed variable anomalous enthesial nerve endings as well as anomalous vascular endothelial cells in INS patients and this was reported to be related to immaturity of postnatal development of neurovascular complexes specific to the ocular motor disorders [7].

Infantile nystagmus syndrome can be isolated and named as idiopathic, and may be associated with achromatopsia, albinism, aniridia, foveal hypoplasia, congenital stationary night blindness, optic nerve hypoplasia and all pathologies that disturb visual development at the early period such as congenital cataracts, congenital glaucoma, congenital corneal opacities will cause nystagmus. Any pathology that cause vision loss or low vision during infancy is usually associated with nystagmus and when a vision loss is associated with nystagmus we may assume that the underlying pathology has been present since infancy.

Symptoms

The patients with infantile nystagmus syndrome are usually asymptomatic and the parents' main complaint is usually about wiggling eyes. If low vision is associated with nystagmus, this can be another reason for seeking medical help.

Oscillopsia is an illusory movement of the environment and it is usually seen with acquired nystagmus and patients with infantile nystagmus, typically do not have complaint of oscillopsia. However, absence of oscillopsia is usually not helpful in distinguishing congenital and acquired nystagmus in children because even with acquired nystagmus, small children rarely have this complaint [2].

Infants with achromatopsia and congenital stationary night blindness (CSNB) present with nystagmus and unusual visual behaviour and inattention. In early phases, in achromatopsia nystagmus is a bit chaotic and feature vertical components. Photophobia becomes a main feature as the child grows and ambulates independently. The fundi are considered normal although some may have diminished foveal reflexes. Ophthalmic and ERG features do not necessarily distinguish pediatric patient with achromatopsia from those early cone-rod degenerations. Follow-up of patients with

achromatopsia is recommended. In early infancy the acuity measured by preferential looking may not be measurable or may be near the lower limits for normal age. A discrepancy between acuity measured in normal room light and that in dim room light is often observed with the better acuity being obtained in dim room light. Once the child reaches the age at which acuity can be measured, moderate to marked reductions about 20/200 with correction are typically found [8].

In Leber Congenital Amaurosis (LCA) or congenital retinal blindness, the infants presents with roving eye movements, sluggish papillary responses and visual inattention. Almost all of the infants have high hyperopia and ophthalmoscopic findings can be minimal [8]. If there is associated albinism, this can be obvious if the skin is involved or it is not so obvious if the skin is pale to blonde but not significant as in oculo-cutaneous albinism. In these cases, biomicroscopical examination of the iris will reveal transillumination defects and, also there is associated high hyperopia and astigmatic refractive errors.

Clinical Evaluation

The first goal of the history-taking and physical examination is to determine whether the nystagmus has been present since birth (the first few months of life) or acquired (after 4-6 months of age) [1]. Distinguishing acquired from the benign neonatal/infantile forms of nystagmus is important because of the implication for underlying neurological disease in acquired nystagmus [9]. Information regarding a family history of neonatal eye disease, the pregnancy, labor, delivery and growth and development since birth should be asked [1]. Other complaints such as convulsions, growth retardation, paralysis or paresis of the extremities, presence of convulsions, use of medication, history of surgery and other complaints are needed to be asked in detail. Any pattern of nystagmus with onset in the first months of life could be considered congenital and neurologically benign. However, the term "congenital nystagmus" has become synonymous with the most common form of neonatal nystagmus characterized by an accelerating slow phase on electronystagmography. The term "Infantile Nystagmus Syndrome (INS)" replaced the previous term congenital nystagmus [1,2,9-12]. Previously congenital nystagmus was accepted as "congenital motor nystagmus" if there was no associated ocular or systemic diseases and "congenital sensory nystagmus" if there was associated ocular or systemic diseases (such as albinism, dyschromatopsia). These terms replaced by "Infantile Nystagmus Syndrome" with "Classification of Eye Movement Abnormalities and Strabismus" (CEMAS) working group [12]. Infantile nystagmus syndrome is an ocular-motor disorder of unknown etiology that presents at birth or early infancy and clinically characterized by involuntary oscillations of the eyes.

Ocular Examination

Visual acuity: Measurement technique depends on the age, cooperation and mental status of the patient. In nonverbal or uncooperative patients, fixation behaviour, preferential looking, matching the symbols or letters with LEA symbols or HOTV optotypes can be used. In older, verbal children and cooperative patients Snellen or ETDRS charts can be used, however, ETDRS chart is more reliable as LogMar equivalents provide more accurate measurement especially acuities between 20/400 and 20/100. Binocular visual acuity should be measured prior to monocular visual acuity measurement as latent component of nystagmus may cause a decrease in visual acuity if one eye is covered with an opaque occluder. If the patient has an abnormal

head posture (AHP) during binocular measurement this must be allowed for optimum visual acuity and also for detection of abnormal head posture. While measuring monocularly, instead of an opaque occluder high plus lens (>4.0 D) or fogging techniques can be used. During visual acuity examination in patients with AHP, it is imperative to observe the direction of the posture during 5-7 minutes period as up to 17% of patients with nystagmus have a periodicity to the direction of their fast phase. This periodicity manifests clinically as a changing head posture in the direction of the fast phase [1,2]. It is important to keep in mind that binocular acuity is the "person's" acuity and monocular acuity is the "eye's" acuity and these are often very different in patients with nystagmus [1]. Binocular near acuity measurement is usually better than the distance as convergence at near results in better control of nystagmus.

Color vision: Color vision can be measured with different tests and can indicate association with hereditary cone dystrophies, achromatopsia.

Sensory status, binocular vision and stereopsis: in idiopathic INS cases binocular vision is good with fusion and stereopsis parallel to better visual acuity however, in cases with poor visual acuity and strabismus, suppression and resulting amblyopia cause poor binocular functions.

Anterior segment: Transillumination defects in the iris can be the only sign for albinism. In some cases anterior segment anomalies or pathologies such as corneal opacities dystrophies, iris and pupil anomalies can be detected with biomicroscopy. Also biomicroscopy can provide magnification and better understanding of nystagmus amplitude and frequency.

Motility: Eye movements usually have a slow and fast phase and the slow phase is accelerating characteristically in INS. There may be a vertical or torsional component also. With fixation, convergence and excitement intensity may increase and with sleep and inattention intensity may decrease. With different gaze positions and head posture, intensity may decrease and this can result in null zone and abnormal head posture. Head oscillations can also be detected with INS.

In an infant with INS, ocular motility can be helpful for evaluation of visual status. Analysis of monocular and binocular differences in waveforms and foveation periods reflect development of the afferent visual system. Pure pendular or jerk forms without foveation periods are associated with poorer vision whereas waveforms of either type with extended periods of foveation are indicators of good vision [2]. Also nystagmus changes with gaze (null or neutral zones) can be detected with eye movement evaluation.

During motility examination the nystagmus can be observed while moving the patient's head and associated motility systems (such as strabismus, pursuit, saccades and vestibulo-ocular reflex) can be evaluated. Prism cover and alternate prism cover tests at near and distance can give information for associated strabismus and also change with convergence. Nystagmus that is asymmetrical in two eyes, especially in the primary position of gaze, frequently suggests anterior visual pathway disease [2]. For ocular motility evaluation recordings can be performed and there are different techniques such as electronystagmography (ENMG), electrooculography (EOG), sclera contact coils. These are for documentation, follow-up or mostly for research purposes, not necessarily needed for treatment decision.

Fundus examination: Optic nerve hypoplasia (isolated or associated with other midline defects and endocrine abnormalities), foveal

hypoplasia (isolated or associated with albinism, aniridia) or optic atrophy (associated with intracranial lesions, hydrocephalus, intraventricular hemorrhage) are the main pathologies that can be seen with nystagmus. Also retinal degenerations can be seen with fundus evaluation. Fundus examination can be helpful also to understand the eye oscillations through the vessels of the posterior pole.

Refraction: In infants and young children, cycloplegic refraction is important for detection of refractive errors that can be associated with nystagmus. High hyperopia is usually detected with Leber Congenital Amaurosis, high hypermetropic astigmatism with albinism. In older children and adults subjective refraction can be tried as well as objective refraction.

Other Diagnostic Modalities

In infantile nystagmus syndrome, if the baby is healthy otherwise with no developmental delay and systemic problems, neuroradiological tests are not needed. In cases that have onset after 6 months of age and the cases that have associated neurological or developmental problems neuro-imaging should be considered.

For associated retinal and optic nerve pathologies, ERG, VEP and EOG may be helpful. Relatively new imaging techniques such as optic coherence tomography (OCT), multifocal ERG and sweep VEP can also be considered if available. Electronystagmography (ENMG) can be useful for waveform evaluation, differential diagnosis and documentation however, it is not necessary for treatment decision. OCT can be used for optic nerve head or foveal evaluation and can be helpful in detection and documentation of foveal hypoplasia however, fixation difficulty due to nystagmus may decrease image quality. There are also other methods to quantify foveation characteristics [13-15]. The accuracy and duration of foveation have been directly linked to visual acuity, especially in patients in whom no other sensory system disease can be found [13].

Genetic

Infantile nystagmus syndrome can be inherited as dominant, recessive or X-linked pattern and X-linked inheritance is probably the most common [2]. Different chromosomal abnormalities have been reported (eg; NYSI-5, X q26 etc). Mutations in FRMD7 (a gene that is accepted as associated with eye movement control) have been reported less than 10% in idiopathic, sporadic cases [16]. Mutations in the genes for cone transducin and the cone cyclic nucleotide gated cation channel have been identified in individuals with achromatopsia [8]. Several genes have been associated with uncomplicated Leber Congenital Amaurosis (LCA). Uncomplicated LCA means disease limited to the eyes without metabolic or independent systemic abnormalities [8].

Treatment

As there is no definitive cure for infantile nystagmus, the main aim of the treatment is to correct the refractive errors and strabismus if present and to achieve optimal development of visual system in the sensitive period [4]. Correction of refractive errors helps to get a clearer image on fovea diminishing the adverse effects of blurred image [4,17]. The correction of strabismus improves the binocular vision and this helps to keep the eyes aligned so that the intensity of nystagmus decreases. Correction of significant refractive errors in children with

nystagmus is the single most powerful and important therapeutic intervention for improving vision and visual function. Refractive etiologies of decreased vision include either one or a combination of conditions (eg., myopia, hyperopia, astigmatism or anisometropia). These refractive conditions can contribute significantly to already impaired vision in patients with other organic etiologies of decreased vision. Also for correction of associated deviations, refractive errors must be corrected prior to surgical treatment [2,9]. The correction of strabismus improves the binocular vision and this helps to keep the eyes aligned so that the intensity of nystagmus decreases.

Surgery: Surgery is usually performed to reduce the intensity of the nystagmus in order to increase foveation time or to shift the gaze position with the lowest nystagmus frequency (null zone) to the primary position and to decrease or eliminate the AHP. The presence of strabismus and abnormal head posture are indications for surgery. The patients with good binocular function and alignment in primary position are not accepted as candidates for surgery generally. The main outcome of surgery is to have decrease in nystagmus frequency and intensity, and improvement in head posture and visual acuity secondarily. The etiology of AHP includes; a gaze null due to INS or acquired nystagmus, or convergence dampening due to INS (nystagmus blockage) and a periodically changing head posture due to periodic alternating nystagmus [9]. There are various surgical techniques such as; Kestenbaum-Anderson, Anderson, four muscle recession, tenotomy of the rectus muscles. Kestenbaum-Anderson (recession and resection of horizontal rectus muscles) and augmented form of this surgery have been known for a long time for correction of AHP. The aim is to shift the null point that is provided by the head posture to the primary position so that visual acuity will improve with a decrease in nystagmus amplitude, frequency and intensity. In modified Anderson procedure, just the recessions of the yoke muscles without resection had a similar success rate for improvement of visual acuity [18]. Symmetric recession of all horizontal rectus muscles (retro-equatorial recession) were also reported to be successful with improvement in visual acuity and head turn without limitation in ocular motility [4,8,19-21]. Another surgical procedure is tenotomy to improve visual acuity and foveation time. The tenotomy and reattachment procedure was first described by Dell'Osso et al. on achiasmatic canines [22,23]. The mechanism of action was suggested as related to interruption of the afferent proprioceptive loop, producing a damped peripheral, ocular-motor response to the nystagmus signal [22,24,25]. The positive effect of four horizontal rectus muscle recession surgery may be related to the tenotomy performed, but it is hard to comment on whether this surgery would be effective without recession. The recession procedure decreases the arc of muscle on the globe and in addition to tenotomy this may have beneficial effect on decreasing nystagmus frequency [4,21]. It was also suggested that INS patients may be particularly prone to the placebo effect as they are highly motivated and may improve with repeated measurements due to decreased stress and even surgical intervention can have placebo effects [9]. Complications after surgery can be seen and ocular misalignment, new abnormal head posture with a new null point, fading effect of surgery with an increase in nystagmus amplitude and intensity.

Hertle reviewed the studies that have been published and almost all of the studies were uncontrolled case series [9]. Surgery was mostly done to improve head posture. Most of the authors concluded that nystagmus decreased and visual acuity improved after surgical intervention. The effect of surgery on vision of a patient is related to a number of unpredictable variables, such as patient age, underlying

visual sensory system diseases, associated strabismus, associated amblyopia, uncorrected refractive errors and associated central nervous system pathologies.

Apart from surgical treatment there are also medical and other options such as contact lenses and prisms. Pharmacological treatment is usually considered for acquired cases in order to decrease the complaints related to oscillopsia [26]. In INS, orally given baclofen, gabapentine and memantine have been reported to have beneficial effects as improvements in visual acuity and nystagmus amplitude [27-29]. Recently Hertle et al used topical use of topical carbonic anhydrase inhibitor (brinzolamide-Azopt) in a double-masked trial with placebo in INS patients and improvements in visual acuity and nystagmus waveform characteristics with objective measurements were reported [30]. Botulinum toxin injection to the extraocular muscles was suggested for decreasing nystagmus intensity however, need for repeated injections and unwanted effects like ptosis limit use of Botulinum toxin. Also retrobulbar injection especially in acquired cases may help to decrease nystagmus intensity and increase in visual acuity.

Contact lenses can be prescribed for the correction of refractive errors however, the nystagmus may cause difficulty in manipulation of the contact lenses as well as technical difficulties in wearing and taking off and/or in the presence of extreme position of gaze so the use of contact lenses are limited. On the other hand, clear image provided by the contact lenses may increase foveation time and decrease nystagmus intensity [31]. In a recent report, no differences were found in decreasing nystagmus intensity when soft contact lenses, rigid gas-permeable lenses and spectacles were compared [32]. Therefore the definitive solution for obtaining the best optical correction and visual performance seems to be refractive surgery, and in particular photorefractive keratectomy [33].

Prisms can be given for head posture, and in this case the base of the prism should be given towards the preferred gaze direction (in a case with a right head turn and null point at left gaze, the base of the prism should be at the left for both eyes and apex should be towards right in order to carry the image towards primary position). Another use of prisms is for convergence stimulation (base out prism in front of both eyes) so that the decreased nystagmus intensity with induced convergence may increase foveation and visual acuity.

Differential Diagnosis

The main difference between physiological nystagmus and the pathological nystagmus is the vision and visual acuity. In physiological nystagmus, the aim is to restore fixation and vision and the visual acuity is preserved. On the other hand, in pathological nystagmus visual system is affected, visual acuity is decreased and there is illusion of motion-oscillopsia. However, in infantile nystagmus there is no oscillopsia.

The difference between the nystagmus and the saccadic eye movements is the slow phase of the nystagmus. In saccadic, involuntary eye movements, there are involuntary to-and-fro eye movements of the eyes resulting in loss of fixation and there will be no slow phase as in nystagmus. Involuntary ocular oscillations containing only fast phases are referred to as "saccadic oscillations and intrusions" not nystagmus but differentiating true nystagmus from saccadic oscillations and intrusions is sometimes impossible clinically [1,2].

Prognosis: Prognosis of all nystagmus and ocular oscillations depends on type of underlying ocular and systemic disease. Generally in infantile nystagmus, waveforms decrease in amplitude and frequency with time till 6-8 years of age and remain stable afterwards unless they are associated with a degenerative, progressive ocular or systemic disease. Acquired forms are more disabling due to associated visual disturbance (oscillopsia) and the underlying degenerative or neurological disease [1,2].

Conclusion

Infantile nystagmus syndrome (INS) is an ocular motor disorder of unknown etiology that presents at birth or early infancy and is clinically characterized by involuntary oscillations of the eye. The Classification of Eye Movement Abnormalities and Strabismus (CEMAS) working group suggested that the disorders previously referred to as congenital nystagmus, infantile nystagmus and idiopathic motor and sensory nystagmus be referred to as infantile nystagmus syndrome which refers to a range of neonatal nystagmus types including those with identifiable causes. It is accepted as neurologically benign, however, in cases with associated systemic and neurological problems and in cases that is diagnosed after 6 months neuroradiological evaluation and systemic workup are required. The main goal of treatment for nystagmus is usually to reduce the intensity of the nystagmus in order to increase foveation time or to shift the gaze position with the lowest nystagmus frequency (null zone) to the primary position and to decrease or eliminate associated abnormal head posture. Before surgical decision, refractive errors must be corrected for optimal visual acuity and strabismus should be considered in the surgical plan. Also abnormal head posture must be reviewed in different visits for exclusion of alternating head posture or changing in the posture with time.

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