1   **Manuscript title: Supranuclear eye movements and Nystagmus in children: A review of the**

2   **literature and guide to clinical examination, interpretation of findings and**

3   **age appropriate norms.**

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Abstract

Abnormal eye movements in children present a significant challenge to Ophthalmologists and other healthcare professionals. Similarly, examination of supra-nuclear eye movements in children and interpretation of any resulting clinical signs can seem very complex. A structured assessment is often lacking although in many cases, simple clinical observations, combined with a basic understanding of the underlying neurology, can hold the key to clinical diagnosis. As the range of underlying diagnoses for children with abnormal eye movements is broad, recognising clinical patterns and understanding their neurological basis is also imperative for ongoing management. Here we present a review and best practice guide for a structured, methodical clinical examination of supranuclear eye movements in children, a guide to clinical interpretation and age-appropriate norms. We also detail the more common specific clinical findings and how they should be interpreted and used to guide further management. In summary, this review will encourage clinicians to combine a structured assessment and a logical interpretation of the resulting clinical signs, in order to recognise patterns of presentation and avoid unnecessary investigations and protracted delays in diagnosis and clinical care.

Introduction

The function of eye movements is to bring visual stimuli to the fovea and hold them there, during head movements or movement of the stimuli themselves. Examination of these eye movements in children, in an outpatient setting, can present a clinical challenge. However, the information gained from an effective examination can help the clinician discern benign from pathological disease, localise neuropathology and non-invasively monitor a variety of neurological disorders. Hereafter, we outline methods of eye movement examination, the most important findings and their clinical implications for clinicians without access to a dedicated eye movement laboratory.

49   Human supranuclear eye movement pathways can be conceptualised as providing solutions to the

50   following visual demands: to compensate for large head movements (the Vestibulo-Ocular Reflex,

51   VOR), to use visual information to fine-tune the VOR and to return the eyes to the central position

52   after full excursion (the Opto-Kinetic Reflex, OKR), to track a moving visual target without moving

53   the head (Smooth Pursuit, SP), to place a visual target onto the fovea (Saccades) to maintain

54   eccentric eye position (Gaze-Holding) and to allow binocular co-ordinated eye movements to

55   achieve and maintain binocular foveation (Vergence movements). Table 1 summarises the

56   supranuclear eye movement control systems of greatest clinical relevance in humans.

57   **Table 1**

History taking

58

59

60   As with all clinical assessments in children, a detailed history from the parent and child is important

61   and can direct the clinician to certain aspects of the subsequent examination. Table 2 details some

62   of the most useful questions to be included in a thorough history from a child with an eye movement

63   disorder.

64   **Table 2**

Clinical examination

65

66

67   When examining supranuclear eye movements in a child, it is important to assess each separate eye

68   movement control system in a systematic way, with an understanding of what to expect (3). 'Normal

69   findings' will vary with age. Table 3 summarises some of the normal clinical findings in infants and

70   children using more freely available clinical equipment (such as the OKR drum rather than a full-field

71   OKR stimulus). Subsequently, we describe clinical examination techniques for each system.

72   **Table 3**

Vestibulo-Ocular Reflex (VOR)

Underlying neuroanatomy

A 3-neuron arc, including the vestibular ganglion, vestibular nuclei and the oculomotor nuclei (Figure 1) (8) operate the VOR system, which holds the eye still in space during head movements. During head motion, movement of the semi-circular canals relative to endolymph creates an afferent signal, which passes via the vestibular nerve to the ipsilateral vestibular ganglion in the internal auditory meatus. These signals are relayed to the ipsilateral vestibular nuclei (Pons and Medulla), which then transmit excitatory inputs to the contralateral oculomotor nuclei, and inhibitory inputs to the ipsilateral oculomotor nuclei (Midbrain and Pons). The oculomotor nuclei pass motor signals to the yoked extra-ocular muscles via the IIIrd, IVth and VIth cranial nerves.

Figure 1

Figure 1 The Vestibulo-Ocular Reflex (VOR). LR=Lateral Rectus, MR=Medial Rectus, MLF=Medial Longitudinal Fasciculus, VI=sixth nerve nucleus, VIII=8th nerve (vestibular) nuclei, III=third nerve nucleus. This diagram represents a right face turn head movement with eye movement to the left.

Clinical assessment of the Vestibulo-Ocular Reflex (VOR)

A mismatch between the speed of head movement and the speed of the VOR movement (VOR gain) can be tested in older children by measuring visual acuity during slow head movements (which should not change). However, this test is rarely used in the clinic as it is not possible in preliterate children and isolated abnormalities of VOR gain are rare.

'Dolls Head Manoeuvre' (Oculocephalic Manoeuvre) or Spinning baby tests are the standard tests for VOR in the clinic.

Doll's head manoeuvre – The infant's head is held with both hands and rapidly, but gently, moved horizontally and vertically to test both VOR respectively. The eyes should stay fixed in position

102   despite the movements. The rotations can be small and should <u>not</u> be performed in children with

103   cervical spine problems or downbeat nystagmus (Figure 2).

104   **Figure 2**

105   **Figure 2** How to perform the doll's head manoeuvre on an infant in a clinical setting

106

107   **Spinning baby test** –The examiner stands and holds the infant at arm's length. In the case of a very

108   young infant the back of the head is supported as shown. The examiner rotates to the right with the

109   infant through 2-3 revolutions whilst observing the infant's eyes. This induces a per-rotatory

110   nystagmus (driven by VOR and OKR) in the infant with fast phases to the examiners left. The rotation

111   is then abruptly stopped inducing a post-rotatory vestibular nystagmus in the infant, with fast

112   phases beating to the examiners right. The procedure is repeated in the opposite direction and in

113   small infants can also be used to test vertical VOR by laying the infant flat in the examiners arms. In

114   older children this test can be modified by the child sitting on an examiners lap and facing them

115   while both rotate on a swivel chair. Older children can also be examined by sitting alone in a swivel

116   chair and spun. Normal findings include a large per-rotatory nystagmus (unless the child is fixing on

117   the examiners face) but importantly, only 2-3 post-rotatory nystagmus beats in the opposite

118   direction (Figure 3).

119   **Figure 3**

120   **Figure 3** Performing the spinning baby test in a clinical setting
121

122   Interpreting some common findings during VOR testing
123

124   • Loss of the fast phase of VOR, can be a normal finding in infants before 45 wks gestation or

125   reflect a saccade abnormality, for example Saccadic Initiation Failure (SIF). This can be seen

126   as 'Locking up' during spinning (i.e. both eyes fixed at the limit of gaze in the opposite

127   direction to spinning (9)).

128

129   • During doll's head testing, a catch-up saccade, when testing in one direction only, suggests a

130   specific semi-circular canal pathology.

131
132

133   • In the presence of acute vertigo in older children, abnormal VOR in one direction, lack of a

134   skew deviation and unidirectional nystagmus suggest a peripheral vestibular (e.g. vestibular

135   neuritis) rather than central cause (e.g. stroke).

136

137   • After spinning, post-rotational nystagmus lasting more than 2-3 beats is a sign that the VOR

138   is not being supressed by visually guided reflexes. This is either an indication of very poor

139   vision or a cerebellar disorder (e.g. ataxia-telangiectasia (10)).

140

141   • The VOR reflex may be decreased or absent in children with the CHARGE syndrome (a

142   disorder characterised by Coloboma, Heart defects, Atresia choanae, growth Retardation,

143   Genital abnormalities, and Ear abnormalities) (11), in Type 1 Ushers Syndrome(12) or forms

144   of inherited ataxia (e.g. spinocerebellar ataxia type 3, Friedreich's ataxia (10))

145

146 Optokinetic Reflex (OKR) (also called Optokinetic Nystagmus (OKN))
147

148 Underlying neuroanatomy
149

150 Some authors consider the pathway for OKR, tested with an OKR drum or tape in the clinic, as the

151 same as the smooth pursuit pathway, involving striate and extra-striate cortices with descending

152 connections via the internal capsule to the brainstem pontine nuclei, cerebellum (floccular region),

153   vestibular nuclei and the oculomotor nuclei (13). Most clinicians do not have access to testing

154   methods other than a hand-held tape or drum, therefore, the following information is directed

155   towards findings elicited by these tests.

156
157

158
159 ## Clinical assessment of the Optokinetic Reflex (OKR)
160

161   **OKR drum or tape** is held at 50cm from the child's face and rotated slowly in both horizontal and

162   vertical directions whilst observing the child's eye movements. It is performed both monocularly and

163   binocularly. The examiner would expect to see slow eye movements in the direction of the stimulus

164   with a fast movement seen in the opposite direction. (Figure 4).

165   **Figure 4**

166   **Figure 4** Using an OKR Drum in a clinical setting

167

168 ## Interpreting some common clinical findings during OKR testing
169

170   •   Lack of any OKR with drum or tape testing can be a sign of either extremely poor vision or

171   Delayed Visual Maturation (DVM) but may also be seen in drowsy infants. Interestingly, a full

172   field OKR can be elicited in some patients with DVM even where a small field OKR is absent.

173   It has been hypothesised that using a full field stimulus may elicit an OKR reflecting a more

174   primitive, subcortical OKR subtype called OKNd (14), however this test is not freely available.

175   •   Vertical OKR can be demonstrated in young infants with horizontal nystagmus as a

176   superimposed waveform if there is moderate vision. It can be used (prior to EDTs) to

177   reassure that there is unlikely a profound visual disorder. There has been debate about

178   whether horizontal OKR is lost, reversed or altered by shifting null zones in congenital

179   nystagmus. By clinical observation alone, it is rare to observe robust horizontal OKR in the

180   presence of horizontal nystagmus but where clearly demonstrable, possibly suggests that an

181   'idiopathic' or albinism related cause is less likely.

182   • Quick phases of the OKR are intermittently absent in Saccadic Initiation Failure (SIF) (see

183   disorders of saccades below). Similar to VOR testing, it can result in a lack of OKR or in

184   deviation of the eyes in the direction of the slow phases because of a mismatch between the

185   slow phase movement and the insufficient corrective saccade.

186   • Asymmetry in response to a right vs left moving OKR stimulus, when tested binocularly,

187   indicates a unilateral cortical or pontine lesion. Asymmetry of OKR when tested in this way

188   may occur in some patients with early onset poor vision in one eye.

189   • A vertical binocular OKR response which is worse than horizontal response indicates a

190   midbrain lesion.

191   # Saccades

192

193   ## Underlying neuroanatomy

194

195   Saccades are fast, voluntary or involuntary eye movements initiated in the visual cortex under the

196   control of frontal oculomotor areas for voluntary saccades and the parietal cortex for reflexive

197   saccades. The pathways then project through the internal capsule, divide into a dorsal limb which

198   projects to the superior colliculus and a ventral limb (oculomotor pathways) which projects to the

199   pons and midbrain nuclei. In the pons and midbrain, the neurons from the ventral limb input into a

200   local control system for saccadic firing. This comprises Excitatory Burst Neurons (EBNs), which fire to

201   generate saccades, Inhibitory Burst Neurons (IBNs), which are activated by EBNs and inhibit firing of

202   neurons to contralateral extraocular muscles and Pause Units. IBNs tonically fire to inhibit the EBNs

203   and therefore continuously inhibit spontaneous saccades. Horizontal saccades are mediated by the

204   ipsilateral pons and contralateral frontal eye field (FEF) and parietal eye field (PEF); vertical saccades

205 are generated in the midbrain. The EBNs project to the ipsilateral 6th nerve nucleus as well as

206 contralateral 3rd nerve nucleus via the medial longitudinal fasciculus (MLF) (Figure 5)

207 From a clinical stand point, it is important to remember that horizontal and vertical saccades are

208 localised separately in the ponto-medullary junction and the midbrain respectively and that the

209 cerebellum controls the metrics for both.

210 **Figure 5**

211 **Figure 5** Saccades. LR=Lateral Rectus MR=Medial Rectus MLF=Medial Longitudinal Fosiculus EBN=excitory burst neurons
212 IBN=Inhibitory burst neurons SC=superior colliculus PPRF=pontine paramedian reticular formations. This diagram shows
213 the pathway through the midbrain/pons of a saccade to the patient right

214
215

216
217 Clinical assessment of Saccades
218

219 Clinically, saccades can be tested in many ways according to age. The previously described **spinning**

220 **baby test** includes a saccadic component and can be the most informative assessment in younger

221 infants. In older children, a brightly coloured target is presented in front of the child at a large angle

222 (with or without a simultaneous sound in a neutral position) and eye movements are simply

223 observed for direction, accuracy and symmetry (test monocularly if cross-fixating). The examiner

224 should observe the presence of saccades to the right, left, up and down in both eyes. When looking

225 for asymmetry (between vertical vs horizontal saccades and between left vs right saccades) fixing on

226 the bridge of the nose can aid the examiner.

227 Interpreting some common clinical findings while testing saccades
228

229 • Saccadic latency in infants is up to 1 second for the primary saccade (200ms in adults) and

230 gross abnormalities are usually seen in Saccadic Initiation Failure (SIF).

231 • Saccadic Initiation failure (SIF) may be congenital with no recognisable pathology or

232 associated with many underlying disorders. It is usually horizontal only and intermittent; if

233   vertical it suggests a midbrain lesion or metabolic disorder such as Niemann-Pick disease

234   type C or Gauchers disease type 3(15).

235   • Isolated dysfunction of vertical saccades is due to a midbrain lesion such as

236   haemorrhage/Niemann-Pick disease type C. It is usually caused by lesions of the riMLF which

237   is the centre for vertical saccadic control. As upgaze movements are double innervated,

238   abnormalities of downward saccades are often observed first.

239   • Lesions of the interstitial nucleus of Cajal also cause dysfunction of vertical saccades but

240   usually in addition to a vertical Gaze Evoked Nystagmus (GEN).

241   • Lesions of the posterior commissure cause dysfunction of vertical saccades which may be

242   accompanied by convergence-retraction nystagmus and lid retraction in Parinaud Dorsal

243   Midbrain Syndrome. Pressure on the posterior commissure from raised intracranial pressure

244   is also thought to give rise to the 'setting-sun' sign (eye seemingly fixed in downgaze) which

245   is unique to infants and children(16).

246   • Lesions of the cerebellar oculomotor (dorsal) vermis or fastigial nucleus can cause saccadic

247   dysmetria. Hypermetric saccades are seen in lesions of the Fastigial nucleus (and Wallenberg

248   syndrome, lateral medullary syndrome) and hypometric saccades with lesions of the dorsal

249   vermis.

250   • Large visual field defects may also cause hypometric saccades into the area of loss and they

251   are also seen in resolving Delayed Visual Maturation (DVM) type 1.

252   • Isolated dysfunction (slowing +/- hypometria) of horizontal saccades is due to pontine lesion

253   of the PPRF e.g. bleeding/glioma/Gaucher disease type 3.

254   • Square-wave jerks are to one side of fixation only (<5 deg from fixation), last 200ms and are

255   most commonly seen in Spino-Cerebellar atrophies. They are an exaggeration of normal

256   microsaccadic fixation movements and are seen in 90% of infants at up to 3/minute and are

257   rarely of key clinical significance.

258 • Opsoclonus is characterised by intermittent, multidirectional, back-to-back saccades and is

259   best viewed after changing fixation or on lid closure. Ocular flutter describes the same

260   anomaly but confined to horizontal eye movements. They share a common aetiology which

261   is thought to be loss of cerebellar inhibition of spontaneous saccades. Opsoclonus-

262   Myoclonus Syndrome (OMS) describes the combination of opsoclonus, myoclonus and

263   ataxia and is most commonly associated with neuroblastoma, other para-neoplastic states

264   and CNS infections(17). Ocular flutter or hypermetric saccades can be seen as Opsoclonus

265   improves.

266 • Anti-saccades are voluntary saccades generated to the opposite direction of a target

267   introduced into the peripheral visual field. They represent a voluntary saccade overcoming a

268   reflexive saccade and may be misdirected (ie, implying a directional error) in children under

269   7, schizophrenia, ADHD and Tourette syndrome. They are rarely of clear diagnostic value in

270   young children.

271 • 'Voluntary nystagmus' is an infrequent but persistent cause for referral in children. It is

272   characterised clinically by back-to-back saccades (typically horizontal), usually induced by

273   convergence effort and often accompanied by mild lid closure. It is therefore **not nystagmus**

274   (as there are no slow phases). It can be simulated in many healthy subjects and clues to the

275   diagnosis include: miosis, lid flutter and an inability to sustain the movements for more than

276   30-45 seconds.

277 ## Gaze holding

278

279 ### Underlying neuroanatomy

280

281 Gaze holding is controlled by a group of neural structures which differ for vertical/torsional and

282 horizontal meridians. These distinct groups of structures are collectively termed the horizontal and

283 vertical 'neural integrators'. The horizontal neural integrator includes the nucleus prepositus

284 hypoglossi (Pons), vestibular nuclei (Pons and Medulla) and vestibulo-cerebellum (Cerebellum). The

285 vertical/torsional neural integrator is the Interstitial Nucleus of Cajal (Midbrain) although an intact

286 flocculus (Cerebellum) is also necessary. Both neural integrators have multiple neural connections

287 and their primary role is to coordinate tonic discharge to the extraocular muscles in order to

288 maintain eccentric gaze.

289 ## Clinical assessment of Gaze holding
290

291 Observe the eyes in primary gaze and in vertical and horizontal eccentric gaze either by turning the

292 patient's head, or by presenting a large stimulus in eccentric view. Abnormalities of gaze holding are

293 usually characterised by nystagmus, due to a slow drift towards primary position and a corrective

294 saccade into the attempted position of eccentric gaze (gaze-evoked nystagmus). Examination of

295 nystagmus is detailed below.

296 ## Interpreting some common clinical findings while examining Gaze holding
297

298 - Typical signs of damage to the neural integrator, whether vertical, torsional or horizontal,

299   include gaze evoked nystagmus (due to loss of eccentric gaze holding) and rebound

300   nystagmus (nystagmus beats seen in the opposite direction to the eccentric gaze when the

301   eye is returned to primary position). Abnormalities of VOR suppression (most commonly

302   seen as failure of dampening post-rotational vestibular nystagmus following the spinning

303   baby test) and OKR are also commonly seen together and reflect underlying cerebellar

304   pathology.

305 - Gaze evoked nystagmus (GEN) can also be seen with the use of anti-convulsants, sedatives

306   and other drug intoxications.

307 - Gaze evoked nystagmus in all directions implies a cerebellar lesion, particularly the flocculus

308   and has many causes.

309   •   Isolated horizontal GEN is often caused by an isolated pontine lesion. This is because

310   vestibulo-cerebellar disorders tend to yield additional oculomotor signs.

311   •   Purely vertical GEN is due to a lesion of the vertical/torsional neural integrator which is the

312   interstitial nucleus of Cajal (Midbrain).

313   •   The presence of rebound nystagmus may indicate chronic, rather than acute cerebellar

314   disease.

315

Vergence

316

317

Underlying neuroanatomy

318

319

320 The neuroanatomy underlying vergence eye movements is poorly understood. Neurons within the

321 Mesenchephalic Reticular Formation (Midbrain) and adjacent rostral Superior Colliculus have been

322 identified as being related to vergence movements. These include neurons whose discharge is

323 proportional to vergence angle (Near Response, NR neurons) and burst neurons. Subsets seem to

324 exist for convergence and divergence activity but detail is currently lacking.

325

Clinical assessment of Vergence

326

327

328 Vergence movements are binocular coordinated movements in opposite directions in order to move

329 the point of fixation towards, or away from the subject. Convergence movements can be observed in

330 infants using a large visual target, moved slowly towards the nose in primary gaze from

331 approximately two months of age. They are thought to be initially driven by accommodation but

332 after 4 months they are driven by retinal disparity which coincides with the development of fusion

333 and stereopsis (13). From around 6 months, tests for fusional vergence include the 20 prism-dioptre

334 base-out prism test and studies of fusional range. The examiner should note the range of vergence

335 movements from a near point to a distance target.

338 • Vergence abnormalities are rare in children unless associated with strabismus.

339 • Neuropathology associated with isolated anomalies of vergence is very rare.

340 • Numerous reports and case studies have suggested that **convergence spasm** can occur in

341 association with organic and non-organic disease. However, organic pathology is rarely

342 found in an otherwise well child with isolated convergence spasm(18, 19).

343 • **Convergence insufficiency** describes a remote near point of convergence, variable exophoria

344 for near and reduced fusional convergence at near. It is not associated with underlying

345 intracranial lesions and when occurring in isolation, usually in adolescents, may be treated

346 with orthoptic exercises and prisms.(20-22)

347 • **Convergence paralysis** is characterised by complete loss of convergence and crossed

348 diplopia. It is highly suggestive of intracranial pathology resulting from space occupying

349 lesions of the midbrain, infection, trauma, demyelination or toxins(23-25). It is therefore,

350 usually associated with significant additional neurological signs and rarely encountered as an

351 isolated phenomenon.

352 • **Divergence paralysis** is rare in both paediatric or adult practice. It is characterised by

353 complete loss of divergence, esotropia for distance and normal convergence. Bilateral sixth

354 nerve palsy should be excluded. Causes include intracranial infection and lesions of the

355 brainstem and periaqueductal grey matter(26-28).

356 • **Divergence insufficiency** is a more controversial entity and is characterised by an esotropia

357 for distance, normal convergence and variable or reduced fusional divergence(29). It has

358 been described as a continuum with divergence paralysis, in association with

359 neuropathology including raised intracranial pressure or as a mechanical rather than

360 neurological phenomenon(30-32). In the absence of an acute presentation, other

361   supranuclear eye movement anomalies or any neurological signs, underlying

362   neuropathology is rare.

363

Smooth Pursuit
364

365

Underlying neuroanatomy
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367

368 The neuroanatomical pathways underpinning smooth pursuit movements have been studied

369 extensively and many pathways and nuclei are known to play a part. The following is a simplification

370 of the core circuit. Visual information from V1 is conveyed to area V5 (middle temporal (MT) and

371 middle superior temporal (MST) areas) and then descends to the pontine nuclei. They are joined

372 here by additional inputs from descending fibres from the frontal eye field (Brodman area 8). Fibres

373 are relayed from the pontine nuclei to the flocculus and ventral paraflocculus of the cerebellum.

374 Floccular Purkinje cells then encode eye position, velocity and to a smaller extent, acceleration.

375 Projections then extend to the vestibular nuclei and on to the oculomotor nuclei within the

376 brainstem(13, 33, 34).

Clinical assessment of Smooth Pursuit
377

378

379 Testing should be performed both horizontally and vertically using a large, slow moving, brightly

380 coloured target or a slowly rotating mirror. The examiner should observe the character of the

381 smooth pursuit movements (jerky or smooth) and identify asymmetric smooth pursuit which can be

382 aided by focussing on the bridge of the patient's nose. An OKR drum or tape can be used if

383 examining an uncooperative infant. Suppression of VOR and smooth pursuit are closely related

384 oculomotor functions with similar underlying neurological substrates. Therefore, abnormalities in

385 both systems commonly occur together. VOR suppression can be assessed by:

386 •   Observing suppression of post-rotational nystagmus after the spinning baby test.

387 • Observing suppression of VOR while spinning baby and encouraging fixation on examiners face.

388 • Observing suppression of VOR using a target which moves with the head and encouraging

389   horizontal and vertical head movements. The target can be the patients finger held in front of

390   the face or a target on a tongue depressor held in the patient's mouth.

391

392 ## Interpreting some common findings while examining Smooth Pursuit
393

394 • Lesions of the flocculus or cerebellar pathways cause saccadic pursuit and loss of VOR

395   suppression by visual fixation in addition to down beat nystagmus (DBN).

396 • Reduced smooth pursuit in all directions indicates a 'general' cerebellar flocculus disorder

397   (drugs, alcohol, ataxias etc.).

398 • Asymmetrical loss of smooth pursuit (i.e. reduced binocularly to a left vs right moving target)

399   suggests a structural lesion of the ipsilateral cortex or cerebellum. It may also indicate early

400   onset poor vision in one eye.

401 # Nystagmus
402

403 Nystagmus is a disorder of eye movement which can be defined as "a repetitive, to-and-fro

404 movement of the eyes that is initiated by slow phases"(13). It is important to note that the

405 pathology is the initial slow movement. This is followed by either a 'corrective' fast movement (jerk

406 nystagmus) or a second slow movement (pendular nystagmus). It is relevant to many abnormalities

407 of eye movement in children. Therefore, in the following section, we discuss the key clinical features

408 to identify when nystagmus is found as part of the supranuclear eye movement examination

409 described above.

410 Classification of nystagmus has been inconsistent in the literature and in the following section, we

411 use the term Infantile Nystagmus Syndrome (INS) and Fusion Maldevelopment Nystagmus Syndrome

412   (manifest latent nystagmus or FMNS) according to the CEMAS classification of 2001(35). It is

413   important for the clinician to note that patients with INS or FMNS may have a variety of underlying

414   ocular/systemic conditions but these descriptions have some key eye movement signs which help to

415   exclude (often more concerning) differential diagnoses.

416   ## Clinical assessment of Nystagmus
417

418   • Observe the child at play to identify any consistent visual behaviours such as head positions

419   and head shaking (often, but not always, after 1 year of age), in addition to signs of systemic

420   neurological features such as ataxia.

421   • In addition to a routine, age appropriate history, orthoptic examination and refraction,

422   children's eye movements should be observed in 5 positions of gaze and note taken of the

423   direction of the fast phase of nystagmus (if jerk is seen), the amplitude of the nystagmus

424   (fine or coarse) and the effect of monocular viewing and removal of fixation.

425   • Where Manifest Latent Nystagmus / Fusional Maldevelopment Nystagmus Syndrome (MLN

426   or FMNS) is suspected, rotating the child to induce post-rotational nystagmus and then

427   occluding each eye separately can make identification easier. The induced post-rotational

428   nystagmus to the right or left will either add to the existing MLN or reduce it, depending on

429   which eye is covered, yielding a clear inter-ocular difference in nystagmus intensity.

430   • Abnormal eye movements should be observed for at least 5 minutes (ideally 10) to examine

431   for reversal of nystagmus direction and any alteration in head posture. Inconsistencies in

432   history/examination/previous clinical notes may suggest an alternating head posture often

433   due to periodic alternating nystagmus (PAN), which itself can be congenital or aquired.

434   • An examination of saccades/smooth pursuit/gaze holding/VOR/vergence should also be

435   performed as described above.

- An ocular examination should be performed with the best age dependant equipment available specifically looking for signs of photophobia, retinal dystrophy, retinal/choroidal hypopigmentation, iris transillumination and anterior segment anomaly e.g. cataract.

- Ocular Coherence Tomography (OCT) of the macular should be performed where possible to identify foveal hypoplasia and other abnormalities of retinal morphology that would give an indication of retinal origin for the nystagmus.

- Where possible, electrodiagnostic tests should be performed including: an electroretinogram (ERG) and a Visual Evoked Potential (VEP) to identify retinal and post-retinal pathology such as a retinal dystrophy, or abnormal decussation at the chiasm in albinism.

- Where possible, parents should be examined for the presence of subtle nystagmus, iris transillumination and foveal hypoplasia (seen in albinism phenotypes and *PAX6* gene disease) and retinal dystrophies (especially where equipment is not available to fully examine the young child and/or a family history is evident).

- Anomalous head postures are best viewed by asking the patient to view the smallest target they can resolve in the distance and giving them time to adopt a head posture if one is present.

- Videos of head postures and nystagmus can be extremely useful especially where only fleeting glimpses of the child are possible and to aid advice from other clinicians. In the authors' practice, videos taken by parents or referring clinicians can provide the most useful part of any referral or request for advice.

- Documenting nystagmus can be achieved in a variety of ways. The following diagrammatic representation is used in the authors' practice (Figure 6).

Figure 6

Figure 6 Recording nystagmus amplitude, frequency, direction and waveform in 9 positions of gaze

462

Interpreting some common clinical findings while examining Nystagmus

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464

465

Infantile Nystagmus Syndrome (INS)

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467

468 INS is characterised by horizontal nystagmus, staying horizontal in vertical gaze, associated with null

469 zones, dampening with convergence and made worse by visual attention and stress. It is rarely

470 associated with underlying neuropathology but can be seen due to congenital visual loss of any

471 cause.

472

Fusion Maldevelopment Nystagmus Syndrome (FMNS, previously MLN)

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474

475 FMNS is characterised by horizontal nystagmus which beats in the direction of the viewing eye,

476 worsening in abduction and improving in adduction of the viewing eye. It is commonly seen with

477 strabismus without neuropathology and is thought to be due to maldevelopment of fusion.

478

Periodic Alternating Nystagmus (PAN)

479
480

481 PAN may be congenital (isolated or commonly seen in albinism) or related to identifiable lesions of

482 the cerebellar nodulus/uvula. It alternates less regularly in congenital forms when it tends to be

483 more asymmetrical and less predictable (Asymmetrical Periodic Alternating Nystagmus (APAN)).

484

Vertical Nystagmus

485
486

487 • Down beat nystagmus (DBN) is often more pronounced in downgaze but also in horizontal gaze.

488   It can be accompanied by an alternating skew mimicking a superior oblique over-action. Some

489   children adopt a resulting chin down posture which can mimic tonic upgaze. DBN is typically

490 caused by lesions of the cerebellar flocculus bilaterally (such as in Arnold-Chiari malformations)

491 and can also be found less commonly in 'idiopathic' patients and those with retinal dystrophy.

492 • DBN may be responsive to treatment with aminopyridines and UBN and PAN also to Baclofen

493 treatment.

494 • Vertical and multidirectional nystagmus can be caused by intracranial lesions/metabolic disease

495 but also retinal dystrophies. We would advocate electro-diagnostic testing (where available

496 without significant delay) prior to neuroimaging for this reason in children with apparently

497 isolated vertical nystagmus.

498 • Up beat nystagmus (UBN) is usually due to lesions of the midbrain or medulla e.g. tumours or

499 Multiple Sclerosis (MS) in adults.

500 • See-saw nystagmus is characterized by a cyclic movement of both eyes. In one half of the cycle,

501 one eye will rise and intort and the other eye will fall and extort; then, in the next half cycle, the

502 vertical and torsional components are reversed. It is most commonly caused by parasellar

503 masses but has been described in many other conditions. It is rare in children.

504 • Vertical nystagmus may be seen as a side effect from systemic medications, commonly

505 antiepileptics, such as phenytoin.

506

507 ## Vestibular Nystagmus

508

509 Alexander's law states that nystagmus intensity increases when the eyes are moved in the direction

510 of the fast phase. Originally described for peripheral vestibular nystagmus it also holds true for

511 central vestibular nystagmus and possibly other forms. Torsional nystagmus is often vestibular and is

512 rare in primary position when it is usually medullary in origin (Syringobulbia or Wallenberg

513 syndrome).

514 # Some common clinical dilemmas

515

516   In this section, we discuss some of the more common clinical dilemmas faced by clinicians.

517   How to differentiate end-point from gaze-evoked nystagmus (GEN)
518

519   This is a common dilemma. The following features help the clinician to differentiate end-point

520   nystagmus from GEN. In the authors' experience, using the following criteria, these patients rarely

521   pose a significant diagnostic dilemma.

522

523   **Table 4**

524

525   How to differentiate Fusion Maldevelopment Nystagmus Syndrome (FMNS or MLN)
526   from Infantile Nystagmus Syndrome (INS) in a patient with early loss of fusion (such as
527   strabismus or cataract).
528

529   This is a frequent question for clinicians and many cases will have some features of FMNS and other

530   features suggesting INS. However, the most clinically relevant distinction to make is between those

531   cases with INS/FMNS and those with additional features suggesting a neurological cause, requiring

532   additional investigation and management.

533   • A full orthoptic examination looking for presence of early onset manifest strabismus (which

534   is often seen in FMNS) can provide a clue towards an FMNS diagnosis.

535   • A full examination of the anterior and posterior segments of the eye can identify monocular

536   cataract or optic nerve hypoplasia leading to FMNS. Bilateral pathology may cause INS,

537   FMNS or both.

538   • INS can include an FMNS component but is not always affected by monocular occlusion

539   unlike isolated FMNS in which the direction of the fast phase always changes towards the

540   viewing eye. INS with an FMNS component may result in an increase in frequency and

541   amplitude with monocular occlusion, without a change in the fast phase direction.

542   • Null positions and head postures are frequent in INS and much less common in FMNS unless

543   the child is cross-fixating. However, some children with very asymmetrical visual acuity and

544   FMNS may demonstrate a head posture to utilise adduction to dampen the FMNS in the

545   seeing eye.

546   • INS onset is often earlier (<6-12 months) than FMNS.

547

548   ## How to differentiate Opsoclonus/Flutter and Square Wave Jerks from other eye
549   movement conditions
550

551   Opsoclonus/flutter can occasionally be confused with nystagmus especially in younger children.

552   Making the distinction is important for clinical management and a few key differences exist:

553   • Opsoclonus/flutter have characteristic, seemingly random, fast eye movements with no slow

554   component (unlike nystagmus) and no inter-saccadic interval. When only horizontal they are

555   described as flutter.

556   • They are often intermittent (unlike nystagmus) and induced by changes in fixation or

557   blinking.

558   • Because opsoclonus/flutter is typically acquired and intermittent, children are often visibly

559   troubled during periods of abnormal eye movement (unlike early onset nystagmus).

560   • Onset of abnormal eye movements can be noted at any age in opsoclonus/flutter however

561   for most children with INS, the abnormal eye movements are noted between 3-6 months of

562   age and worsen before stabilising.

563   • Eye movement tics and voluntary nystagmus in older children has been confused with ocular

564   flutter. However, as stated above, opsoclonus and ocular flutter are more common with

565   changes in fixation or blinking and importantly, can be seen under closed eyelids which is

566   rarely seen with tics and voluntary nystagmus.

567   • Pathological square wave jerks are rarely seen in children but have been described in

568   association with various underlying pathologies and medications. The key distinction is that

569   they comprise of only fast (saccadic) movements rather than the anomalous slow movement

570   seen in nystagmus.

571

572 ## When to request neuro-imaging in a child with an apparent isolated supranuclear eye
573 ## movement abnormality?

574

575 For most clinicians, this is a major concern when faced with a child who has (often striking) abnormal

576 eye movements. Practice varies widely and is often governed by access to clinical tools, equipment,

577 necessity of general anaesthesia for brain imaging studies and varying opinion on risk of general

578 anaesthesia in young children. The following is a guide based on the authors own experience and

579 practice.

580   • In most tertiary referral practice, children with clinical features consistent with Infantile

581   Nystagmus Syndrome, INS (conjugate, clinically horizontal nystagmus, staying horizontal in

582   vertical gaze, +/- null zone, onset between 3-6 months of age, no other anomaly of

583   VOR/SP/Vergence/vertical OKR and accelerating exponential slow phases on eye movement

584   recordings if available), otherwise normal neurological development, normal posterior

585   segment examination and ERG/VEP would not undergo neuroimaging in the first instance.

586   Should subsequent examinations yield other eye movement findings, additional

587   developmental issues or new ophthalmic findings (such as subtle optic nerve hypoplasia)

588   neuro-imaging would be sought. A similar approach would be taken in a child with typical

589   FMNS (MLN) and early manifest strabismus or either INS or FMNS in a child with an

590   underlying condition known to be associated with nystagmus such as Down's syndrome.

591 • Where a clear underlying cause for the nystagmus is identified through clinical examination,

592 OCT and ERG/VEP, such as early onset retinal dystrophy or features of albinism,

593 neuroimaging would not be initially sought.

594 • Unilateral nystagmus (or significant inter-ocular asymmetry) or supranuclear eye movement

595 anomalies besides nystagmus would be joint managed with paediatric neurologists and

596 neuroimaging would form a part of a broader set of urgent investigations in all cases.

597 ## Summary
598

599 Isolated abnormalities of specific supranuclear eye movements in children are rare. For most, a

600 pattern will emerge from gaining some information about each of the systems described above, in

601 addition to an orthoptic workup, refraction, good history, electro-diagnostic tests (where available),

602 examination of the family and basic neurological examination. FMNS (MLN) is common, as is INS

603 related to albinism or an eventual 'idiopathic' diagnosis. Additional information can be gleaned from

604 eye movement recordings and hand-held OCT devices but in many cases the clinical diagnosis does

605 not rely solely on these scarce resources. Similarly, the role of genetic testing in these patients is

606 evolving but at present, hampered by the resources, financing and infrastructure required for

607 sequencing and variant interpretation. It is likely that in coming years these technologies will

608 become a part of routine clinical practice but even then, a methodical and detailed clinical

609 examination will remain paramount in assessing and managing this complex group of patients.

610

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691 **Table 1 – A summary of human supranuclear eye movements and their evolutionary prompts (1-3)**

	Evolutionary prompt	Type of eye movement	Function
┄┄→ Evolution ┄┄┄→	Balance organs (such as the semi-circular canals) evolve and mature. Maintaining retinal image stability during self-motion becomes an advantage	Vesibulo-Ocular movements (the slow component of the VOR reflex)	Maintain eye position during head movements regardless of fixation
	Visual advantage of fine tuning gross VOR movements and repositioning the eyes quickly after full excursion (to minimise retinal blur)	Opto-Kinetic Reflex (OKR)	To maintain eye position and fine tune VOR responses using visual proprioception during body movement or when viewing a moving visual scene
	Evolution of a retinal area of higher visual acuity (e.g. fovea)	Saccades	Fast movements to permit re-fixation of targets of interest onto the foveae (retinal areas of maximum acuity)
		Gaze holding	Tonic stimulation of extra-ocular muscles to keep the eyes in eccentric gaze
	Large visual fields become less of an advantage than stereovision. Eyes become frontal and retinal correspondence develops as a prerequisite for stereovision	Binocular Vergence movements	To coordinate convergence and divergence and permit foveation and stereovision
	Frontal eyes and fovea mean that binocular tracking of moving visual targets improves vision	Smooth pursuit (SP)	Binocular, coordinated smooth tracking of visual targets

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693

694 **Table 2 – Questions which can direct the clinician prior to examining a child with abnormal eye**

695 **movements.**

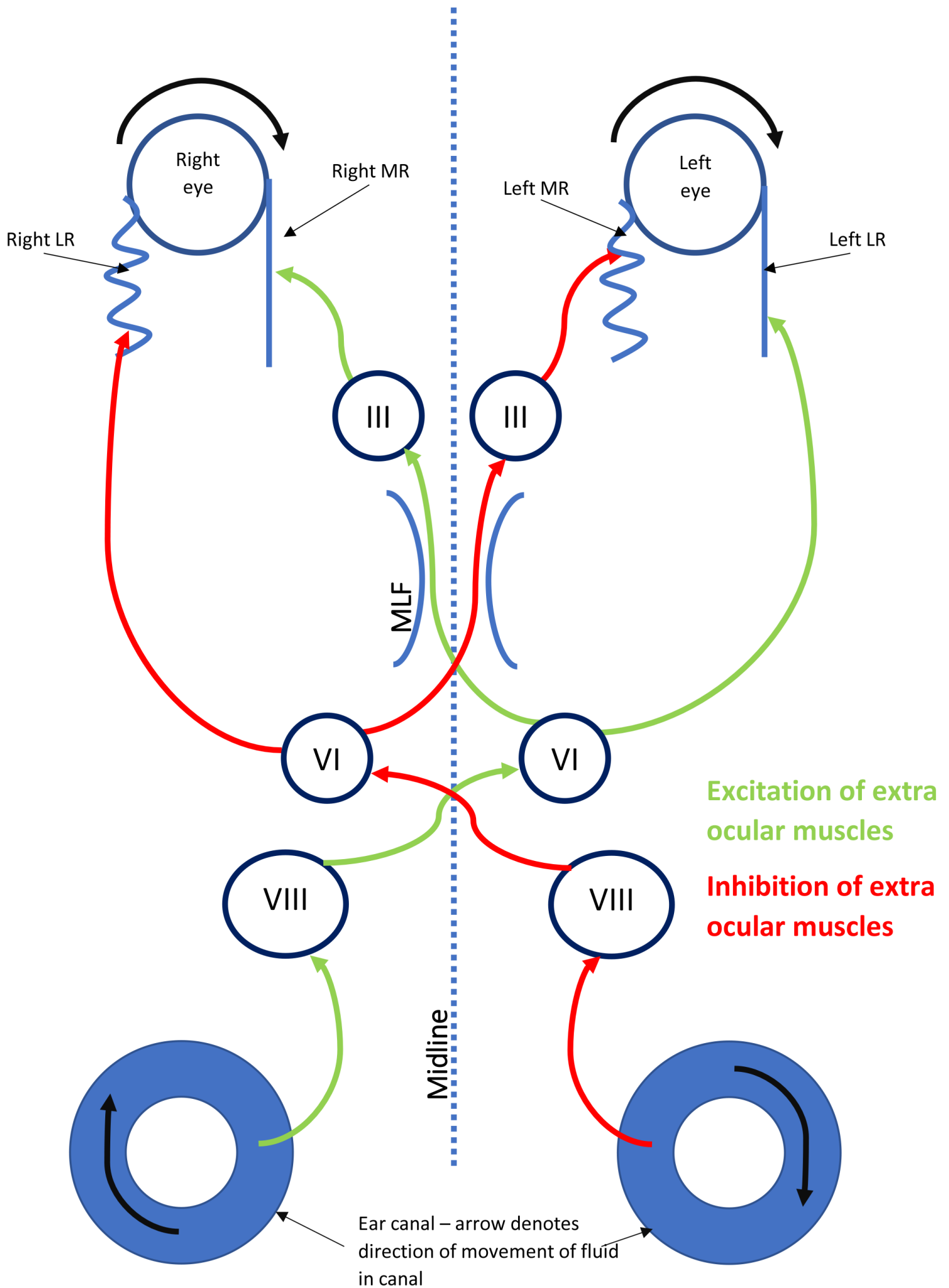| Question	Clinical relevance
Pregnancy, maternal medication/drug use and birth history	Maternal drug exposure and prematurity are associated with an array of eye movement abnormalities
Family history of eye/neurological disease/systemic disease	Many eye movement disorders have a hereditary component with different inheritance patterns indicating which genes may be involved. Neurological symptoms in relatives can also suggest an underlying aetiology (e.g. Spinocerebellar ataxias)(4)
Specific questions about visual behaviours – e.g. nyctalopia or photophobia	Photophobia and nystagmus are common findings in disorders of cone function and albinism. High frequency nystagmus with photophobia is more common in cone dysfunction. Nyctalopia is a common symptom in rod dysfunction
Does the child blink excessively or head thrust towards direction of intended gaze?	Can be seen in Saccadic Initiation failure (SIF)
Open questioning about other visual behaviours	Parents will often report a very detailed description of visual behaviours, which can direct clinical examination such as a child with chin depression and vertically 'wobbly eyes' (commonly seen in downbeat nystagmus), or pushing/rubbing eyes firmly for retinal stimulation in blind babies/children
Does the child experience oscillopsia?	Lack of oscillopsia in the presence of involuntary eye movements such as nystagmus, suggests early-onset; constant oscillopsia suggests an acquired disorder
If oscillopsia is reported, is it when stationary or when moving?	Oscillopsia which is only present during head movement implies a vestibular pathology (5)
Are there associated speech or swallowing problems?	Possible brainstem pathology or Myasthenia Gravis
Are there associated coordination problems?	Possible cerebellar pathology
Is there associated hearing loss or tinnitus?	Possible peripheral vestibular pathology
Is the patient on any medications?	Many medications can cause abnormalities of eye movement, most commonly anti-epileptic medication
Are there any concerns about any other aspect of the child's development or health besides their eyes?	Eye movement abnormalities form a part of many multisystem syndromes and can be the presenting feature

696

697

698   **Table 3 – A summary of normal clinical findings when examining supranuclear eye movements in children**

699   **(3, 6, 7)**

Age	Eye movement					
	VOR	**OKR (or OKN)**	**Saccades**	**Gaze holding**	**Vergence**	**Smooth pursuit**
Full term infant	Both slow and quick phases are present in most. 'Locking up' (eyes fixed in either left or right gaze) due to lack of the quick phase can be seen in some normal infants until 45 wks gestation	Binocular OKR is present. Monocular OKR is present to temporal-to-nasal but not nasal-to-temporal stimuli. Approximately 1-2 fast phases per second	Saccades are hypometric (fall short of target). Small secondary saccades can be seen especially after large saccades. Appear to have normal speed	Very eccentric gaze holding is rarely seen in healthy neonates. To moderate eccentricities, it appears normal (no back-drift)	Most are slightly divergent and no convergence movements are seen	Not usually present. Coarse, often jerky (saccadic) movements to large, slow targets develop in first few weeks
3 months	Clinically normal	Naso-temporal asymmetry (described above) disappears to moderate stimulus speed	Saccades become less hypometric and secondary saccades are smaller but may be seen	As above	Divergence has reduced or gone and coarse convergence movements can be seen	Usually seen to large slow moving targets. Become saccadic if target is moved more quickly
6 months	Clinically normal	As above	As above	Clinically normal	Divergence has usually gone and convergence movements are more established as fusion develops	Start to become saccadic only to fast target speeds
1 yr	Clinically normal	Clinically normal with fast phase frequency increasing to 2-4 per second	Clinically normal (still hypometric as in adults but secondary saccades rarely seen)	Clinically normal	Clinically normal	As above
5 yrs	Clinically normal	Clinically normal	Clinically normal	Clinically normal	Clinically normal	Clinically normal

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704

705   **Table 4** – Differentiating end-point from gaze-evoked nystagmus

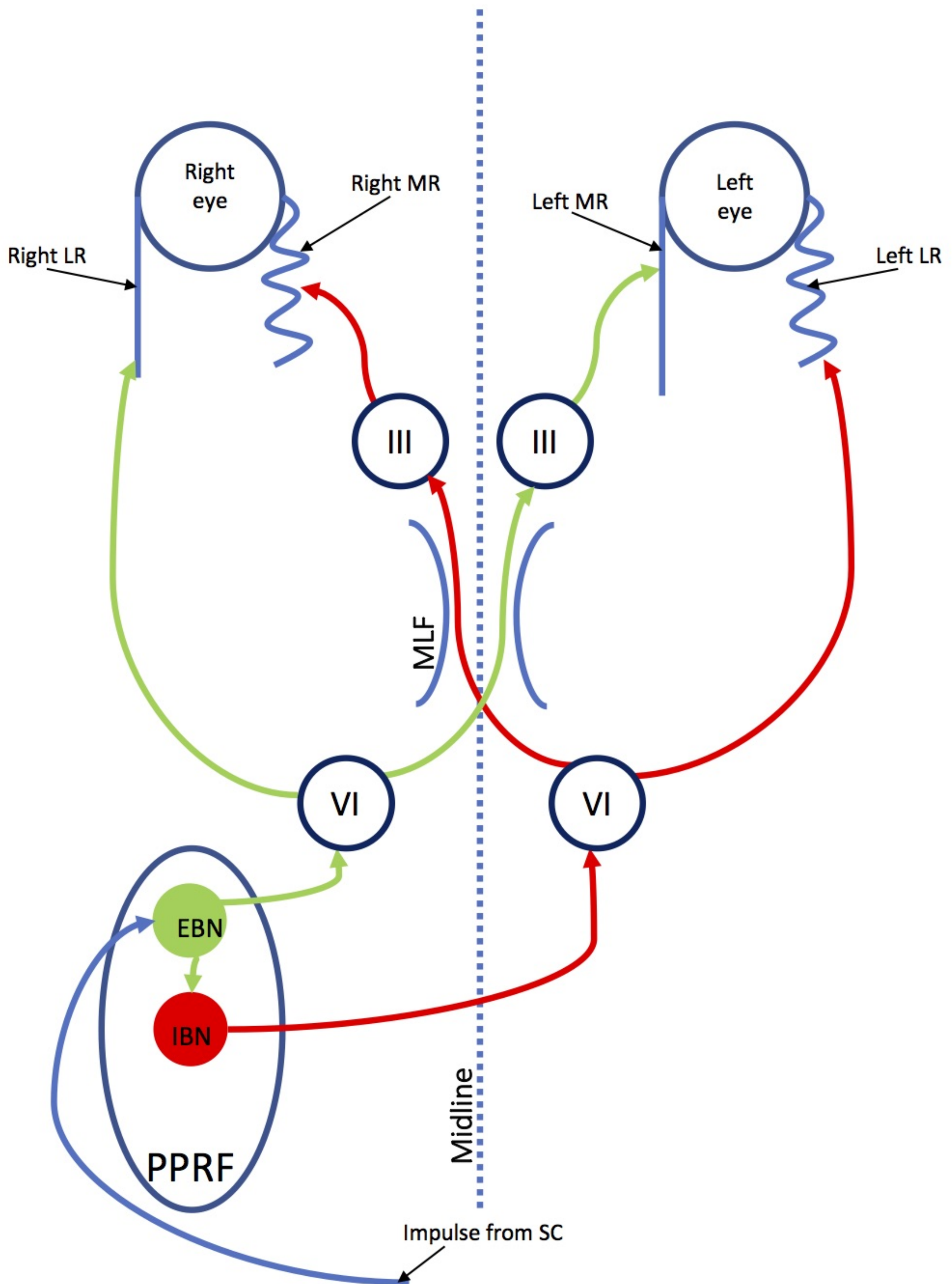| End-point nystagmus	Gaze-evoked nystagmus (GEN)
Unstained (dampens after a few beats)	Sustained. Continues after 20 seconds of eccentric fixation attempt
Delayed after the eccentric eye movement	Immediate on eccentric fixation
Usually only seen in extreme eccentric gaze	Often seen in only mildly eccentric gaze
Often low amplitude	Often high amplitude
Symmetrical	Often asymmetrical
No rebound nystagmus seen (nystagmus beating in the opposite direction once the eye has returned to its central position after 60 seconds eccentric gaze)	Rebound often seen
No other supranuclear eye movement abnormalities found.	Very rarely seen without co-existing smooth pursuit abnormalities
Typically horizontal nystagmus on side gazes only	May be horizontal and/or vertical

706

Right eye

Right MR

Right LR

Left MR

Left eye

Left LR

III III

MLF

VI VI

Excitation of extra ocular muscles

Inhibition of extra ocular muscles

VIII VIII

Midline

Ear canal – arrow denotes direction of movement of fluid in canal

Up Gaze

Small amplitude moderate frequency up beat nystagmus in up gaze

↑ ↑

Right gaze

Small amplitude high frequency right beat jerk nystagmus on right gaze

← ← ←

Large amplitude low frequency rotary nystagmus in primary position

↻

Large amplitude low frequency left beat jerk nystagmus on left gaze

→

Left gaze

Moderate amplitude moderate frequency pendular nystagmus in down gaze

↔ ↔

Down Gaze

Amplitude = length of arrow
Frequency = number of arrows
Direction = arrowhead
Waveform = shape of shaft

● ● ●   No nystagmus

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