II. ANSWERS

SESSION 1
CASE 1 (CT). THE NEGATIVE CONSEQUENCES OF BEING FIT

Superior Oblique Myokymia
The right eye showed irregular bursts of torsional and vertical movement, suggestive of superior oblique myokymia. The bursts increased with hyperventilation. MRI specifically looking for an abnormality of trochlear nerve or orbit was normal.

Superior oblique myokymia should be suspected in patients complaining of brief, recurrent episodes of monocular oscillopsia or blurred vision. Less often, patients complain of paroxysmal vertical or torsional diplopia. The abnormal eye movements are often difficult to appreciate but spasms of torsional-vertical rotation were seen easily in this patient. This case is not typical because the attacks usually last less than 10 sec. MRI shows no lesion in most cases, although neurovascular compression at the root entry zone has been reported.1

Superior oblique myokymia corresponds to desynchronized contraction of muscle fibers caused by trochlear nerve hyperactivity. The hyperactivity may be related to regeneration following mild damage of the trochlear nerve such as that caused by neurovascular compression at the root entry zone.

Several drugs have been used effectively for superior oblique myokymia.2 In this patient, we tried carbamazepine, gabapentin and clonazepam without success. Finally, oral beta blockers prescribed for hypertension improved the symptoms coincidentally.

REFERENCES

CASE 2 (CT) DON’T MAKE ME MAD

Hyperventilation-Induced Nystagmus with Vestibular Schwannoma
MRI disclosed a left vestibular schwannoma. In this patient, the absence of spontaneous nystagmus is explained by the gradual nature of vestibular loss, which allowed central rebalancing of resting vestibular activity. Right-beating nystagmus after head-shaking resulted from decreased left vestibular input to the velocity storage mechanism. Hyperventilation-induced left-beating nystagmus resulted from hyperexcitability of the damaged left vestibular nerve. The pathological increase in left vestibular input caused slow phases directed away from the side of the lesion.
Hyperventilation causes a respiratory alkalosis, which increases the concentration of free calcium. Increased calcium levels cause hyperexcitability of demyelinated fibers and may increase the level of tonic discharge and induce vertigo and nystagmus. These cases are mainly observed with vestibular schwannoma, but other compressive lesions of the vestibular nerve such as tumors and vascular malformations have been described.

REFERENCES


CASE 3 (WF) WHAT GOES UP COMES DOWN TOO

Ocular Neuromyotonia with Occult Thyroid Orbitopathy

The video shows neuromyotonia of the right superior rectus muscle induced by upgaze, and right lid lag with downgaze. Review of the orbital CT showed subtle but definite enlargement of all eye muscles except the lateral recti. Anti-acetylcholine receptor antibody assay was negative and thyroid function was normal. Over the next 20 months, serial orthoptic testing showed stable findings and the diplopia was relieved by stronger prisms.

The term “ocular neuromyotonia”, coined in 1970 by Ricker and Mertens, denotes episodic eye deviation lasting seconds to minutes due to tonic contraction of one or more eye muscles. It may occur spontaneously or be triggered by sustained gaze in the pulling direction of the affected muscle(s).

By 2012, 66 cases of neuromyotonia had been reported in 48 publications. About 60% of cases were associated with previous radiotherapy of sellar or parasellar tumors. Less common causes include various neoplasms, vascular compression (including aneurysms), demyelination and stroke. There have been at least five case reports of neuromyotonia associated with thyroid eye disease but four of the five cases had manifest thyroid eye disease before the onset of neuromyotonia. This case shows that, in the absence of orbital signs, occult thyroid eye disease should be considered as a possible cause of neuromyotonia.

REFERENCES


CASE 4 (WF) FALLING DOWN BUT NOT LOOKING DOWN

Adult-onset Niemann-Pick type C

Examination showed marked slowing and hypometria of downward saccades, mild slowing of upward saccades and absent quick phases of vertical vestibular and optokinetic nystagmus. Vertical smooth pursuit and vestibular and optokinetic slow phases were relatively preserved. Horizontal eye movements were normal, including saccades and quick phases. A diagnosis of Niemann-Pick type-C was confirmed by serum oxysterol analysis and molecular genetic testing.

Niemann-Pick type-C is a rare autosomal recessive disorder of intracellular cholesterol/lipid transport, which affects several organs and areas of brain. Mutations in a large gene on chromosome 18, termed NPC1, account for > 95% of cases. The classic juvenile and later infantile phenotypes comprise variable combinations of hepatosplenomegaly, ataxia, dystartria, dysphagia, cataplexy, dystonia, seizures and cognitive decline. There is considerable heterogeneity but deficits typically progress and cause death within a decade of diagnosis. A vertical supranuclear saccadic gaze palsy is very common, particularly affecting downward saccades, resulting from selective loss of neurons in the rostral interstitial nucleus of the MLF.

The adult form of Niemann-Pick type C (onset ≥ 15-years old) is likely under-recognized. Since the advent of new biochemical and genetic testing, adult-onset cases have been identified more frequently and now account for 17% - 27% of Niemann-Pick type-C diagnoses. Ataxia, dystartria and VSGP each affect 80% of adult cases and dystonia, cognitive decline and psychiatric disturbances affect over 50%. Hepatosplenomegaly is often absent. The prognosis in the adult form is better than in juveniles, and slower progression of disease generally correlates with older age of onset. A few patients have had no symptoms until the sixth decade and have remained undiagnosed for several years.

Miglustat, a glucosylceramide synthase inhibitor, has recently been reported to stabilize or improve symptoms in Niemann-Pick type-C, providing added impetus to considering Niemann-Pick type-C in the diagnosis of vertical supranuclear saccadic gaze palsy in adults. A validated Niemann-Pick type-C “suspicion index” is available on the web at http://www.npc-si.com.

REFERENCES


CASE 5 (DZ) WHAT SHIFTED IN HIS OVERHEAD BIN?

Infantile (Congenital) Nystagmus: Forme Fruste

Eye movement recordings showed a nystagmus during attempted smooth pursuit to the left with the slow phases directed in the opposite direction (a reversed pursuit pattern as seen in congenital nystagmus):

This patient and a second identical patient (both with nystagmus induced by tracking to the left) were reported by Kelly et al in 1989. The mechanism is unclear though “shifting of the null”, reversed visual afferent projections (as Albinos) and miswiring in motor circuits have been invoked. The pattern of nystagmus also argues for a fixation system that is independent of pursuit (“tracking of a zero-velocity target”) with the instability emerging when fixation is turned off.

The key clinical point is to recognize the peculiar symptom of unidirectional-induced oscillopsia and the potential for a congenital nystagmus like pattern to emerge when the fixation system is in abeyance.

REFERENCES

CASE 6 (DZ) LIFE OF THE (NEURO-OPHTHALMOLOGY) PARTY

Voluntary Infantile (Congenital) Nystagmus

This patient could voluntarily turn on and off a left beating jerk nystagmus in the light or with fixation removed (Frenzel lenses). The only eye movement abnormality was a gaze-evoked nystagmus on left gaze under Frenzel lenses. This is an example of voluntary control over a fixation system that normally prevents a congenital nystagmus like instability from manifesting itself.

Much like the previous case of pursuit induced “congenital” nystagmus, this case—and others reported by Tusa et al in 1989—expands our concept of variable degrees of instability in congenital nystagmus. Presumably in these patients the instability underlying the nystagmus can be suppressed under certain fixation conditions, and the fixation mechanism is under some degree of voluntary control. Even in the dark, without other visual cues, fixation mechanisms presumably recreate internal signals that can mimic an actual fixation target and suppress nystagmus. This capability is under voluntary control. We note a similar phenomenon with latent nystagmus.

Finally note this phenomenon differs from the usual “voluntary nystagmus” which actually is a saccadic oscillation akin to flutter with back to back saccades released by removal of pause cell inhibition upon an inherently unstable saccadic burst neuron network.

REFERENCES

CASE 7 (MB) A DIVERGENT POINT OF VIEW

Congenital Fibrosis Syndrome, Type 1

Congenital fibrosis syndrome is associated with esotropia or exotropia, fixed downgaze, and bilateral ptosis. In this hereditary condition, affected extraocular muscles are hypoplastic and normal muscle is replaced by fibrotic tissue. Congenital fibrosis syndrome is often associated with a constellation of ocular motor synkinesis including synergistic divergence (simultaneous abduction of the eyes), Marcus-Gunn jaw winking, and convergence during attempted upgaze.1,2

The coexistence of ocular motor synkinesis provided the first clinical clue that the congenital fibrosis syndrome must result from a primary failure of normal neuronal connections to be established at their target sites, with ocular motor misdirection and extraocular muscle fibrosis occurring as secondary effects.1,2 This hypothesis has since been confirmed with neuroimaging and neuropathology.1 This form of congenital fibrosis syndrome usually results from a mutation in kinesin KIF21A gene, which encodes for an anterograde microtubule-based motor protein.3
REFERENCES:


CASE 8 (JB) TILTING AT WINDMILLS
Paroxysmal Ocular Tilt Reaction
The patient had irregular episodes of counter-clockwise torsion of both eyes with a right hypertropia, in contrast to her baseline of right head tilt with inconstant left hypertropic skew. The findings were consistent with a partial ocular tilt reaction to the right, and paroxysmal episodes of left ocular tilt reaction. This suggested a left mesencephalic lesion in the region of the interstitial nucleus of Cajal. MRI showed a left thalamic cavernous angioma.

Two cases of paroxysmal ocular tilt reaction have been reported, one with probable multiple sclerosis and the other with an abscess in the zona incerta, near the inC. Paroxysms lasted seconds to minutes and occurred frequently throughout the day. One responded to carbamazepine, the other to baclofen. Attacks of 20 to 80 seconds of torsional nystagmus, skew and frontalis contraction, occurring 10 to 50 times a day, were reported in a case that also responded to carbamazepine, and was attributed to vascular compression. There is one report of paroxysmal skew with a brainstem glioma.

REFERENCES


CASE 9 (JB) THE DISTRACTING DINNER DATE
Orbital Varix
CT imaging was repeated with and without his teeth clenched. This showed a small homogenous lesion in the lateral orbit that ballooned in size when he clenched his teeth, consistent with an orbital varix.

An orbital varix is an enlarged thin-walled venous channel(s) with direct communication to orbital or extra-orbital veins. Primary orbital varices are idiopathic congenital lesions, confined to the orbit, and are rare. Secondary varices are due to increased blood flow from intracranial arteriovenous malformations, carotid-cavernous fistulas or dural arteriovenous fistulas.

A primary orbital varix typically does not become symptomatic until 10 – 30 years of age. Orbital varices present with intermittent diplopia or proptosis, sometimes precipitated by straining or stooping. There may be slight enophthalmos between episodes. Varices may cause intraorbital haemorrhage, or thrombose, with acute retro-orbital pain, proptosis and decreased visual acuity from optic nerve compression.

As in our case, diagnosis with orbital ultrasound, CT or MRI is facilitated by a provocative maneuver, most often a Valsalva maneuver or prone position. Thrombosis is evident as heterogeneous high signal within the mass on T1 or T2 weighted images.

Treatment is not necessary if symptoms are minimal. Electrothrombosis, stereotactic gamma knife radiosurgery, sclerotherapy, surgical resection, and glue embolization are options.

REFERENCES


SESSION 2

CASE 10 (MB): LOOK THIS WAY, NO, THAT WAY
Periodic Alternating Gaze Deviation with Congenital Ocular Motor Apraxia
The combination of periodic alternating gaze deviation and congenital ocular motor apraxia are almost always associated with Joubert syndrome, which is now diagnosed by the classic “molar tooth” sign seen on MR imaging. His MRI did not show this sign but did reveal mild vermis hypoplasia: the cerebellar hemispheres were apposed inferiorly and malrotated, with abnormal foliation and lateralization of the
dentate nuclei. Genetic testing with a ciliopathy panel did not reveal a pathogenic mutation, but showed variants of uncertain significance in DNAAF3, TTC21B, and ZNF423.

In this patient diffusion tensor imaging showed absence of the normal decussation of the pyramidal tracts within the medulla and the superior cerebellar peduncles within the midbrain. These findings suggest that brainstem non-decussation (which is usually diagnosed in the setting of Joubert syndrome) may provide the neurological substrate for both periodic alternating gaze deviation and congenital ocular motor apraxia.

REFERENCES

CASE 11 (MB) BOUNCING BABIES

Transient Positional Vertical Opsoclonus

In these twins, the clinical course differed from the normal presentation of transient neonatal opsoclonus in that 1) the oscillations began at three months of age; 2) they were evoked by supine positioning; and 3) they appeared to be limited to the vertical plane. Opsoclonus confined to the vertical plane is exceptional.\(^1\)

In an infant, opsoclonus must raise concern about an underlying neuroblastoma. It usually occurs between the ages of 6 months and 4 years of age. There are 9 known reports of monzygotic twins being concordant for neuroblastoma.\(^2\)\(^6\) In some it is thought to be on the basis of placental twin-to-twin metastasis, while in others it may represent simultaneous onset of primary tumours.

Although its pathophysiology remains unclear, the spontaneous resolution and lack of associated systemic and neurological findings in both twins suggests that this familial disorder may represent a variant of transient benign neonatal opsoclonus.\(^7\)\(^9\)

This has been noted in healthy full-term infants within a few days of delivery, with gradual resolution over 1-3 months.\(^2\)\(^8\) It has also been observed in pre-term infants at about 1 month, again with gradual resolution by 3-6 months of age. These children do not have any other neurological or visual signs; long-term outcome is not known.

Along with consideration of neuroblastoma, neurological examination and follow-up is required. Infantile opsoclonus can also be associated with ataxia, developmental delay, seizures, and visual loss: in such cases, opsoclonus is persistent.\(^10\)

REFERENCES:

CASE 12 (DZ) THE BACK-ROW KID

Familial Saccadic Oscillations

The child also mentioned that her mother may have had the same problem when the mother was a child. The mother was examined and showed the same abnormality, brief small amplitude horizontal saccadic oscillations, especially during pursuit. During ophthalmoscopy a continuous, high-frequency shimmer of the optic disc was noted. Eye movement recordings showed a low-amplitude, high-frequency saccadic oscillations (Figure).

Both the mother and child had a mild hand tremor similar to that seen in familial (essential) tremor. The mother was given a beta-blocker for hypertension and coincidentally both her hand and eye tremor diminished.

We developed a model of this problem assuming it was an ion-channel mutation making the saccadic system inherently unstable.\(^1\) A possible glycine inhibitory defect was hypothesized and the response to a beta-blocker suggests an effect in the HCN channel (If current) which would decrease burst neuron excitability (Figure).

Normal subjects who can generate voluntary “nystagmus” (actually back to back flutter-like saccadic oscillations) may have a similar borderline saccadic instability. Patients with microsaccadic flutter, often seen in migraine patients, present with brief periods of oscillopsia in which the world appears to vibrate at a high-frequency, and such patients may have the same inherent propensity to burst neuron instability.\(^2\)
healthy subject

Patient

Saccades

Eye position (°)

D 0

20

10

0

-10

400 ms

200 ms

Normal fixation

B

Eye position (°)

Normal arm posture

C

Normal fixation

Horizontal Vertical Torso
tal

Cupula

Micro-saccadic oscillations

E

Limb tremors

F

250 ms

250 ms

Accelerations (units)

100

0

-100

-200

400 ms

T-type Ca channel (P)

Non-NMDA Glu Current (EPSP)

MCh channel (R)

Stiffness-sensitive Gly channel (IPSP)

Na channel (Q)

Cl

Cao^2+

Ca^2+

NMDA channel 

[Glutamatergic excitation]

Passo

neuron

GENIC ALLESTHESIA

CASE 13 (DZ) IS THIS ON THE CONSENT FORM?

MRI-induced Nystagmus from Labyrinthine Excitation

This subject has a nystagmus due to labyrinthine stimulation from the magnetic field itself. The nystagmus does not relate to any image-taking. The mechanism relates to a basic principle of physics. Fluids in which there is an ionic current, when subject to a magnetic field, develop a pressure (force) in the fluid itself, the Lorentz force. In the case of the labyrinth, the pressure is developed in the endolymph from ionic currents that maintain hair cell firing rate in the utricle, which is located just near the opening to the lateral semicircular canal. The pressure is directed into the lateral semicircular canal and pushes on the cupula, just as if the head were rotating at a constant acceleration.

In this case the endolymph, a potassium-rich fluid that fills the vestibular labyrinth serves a dual purpose. It transmits ionic current into hair cells in the utricle to sustain their resting discharge, and it transmits force, as pressure onto the cupula (the ear’s rotational sensor) within the semicircular canal, producing a sustained nystagmus.

Note that the nystagmus induced in an MRI machine could influence functional imaging studies and can also be used to study labyrinthine function and its central projections, as well as the adaptive mechanisms that try to rid the body of an unwanted spontaneous nystagmus. Note also that the most common cause of disabling vertigo after an MRI is activation of benign paroxysmal positional vertigo.

REFERENCES


CASE 14 (CT) DRIVING WITH THE TOP DOWN

Bilateral Superior Semi-circular Canal Dehiscence

Lithium toxicity was suspected initially but a serum lithium level was normal and the pulse-synchronous eye oscillations and the nystagmus evoked by the Valsalva manoeuvre were not typical of lithium toxicity. These findings suggested that the pulse pressure was being transmitted to structures involved in eye movement control. CT of the temporal bones disclosed bilateral dehiscence of the bony roof of the superior semi-circular canals.

The superior canal dehiscence syndrome comprises vertigo, oscillopsia, nystagmus and/or disequilibrium evoked by sound (Tullio phenomenon) or a change in middle ear pressure (Hennebert sign) or Valsalva maneuver. Patients may have pulsatile oscillopsia or tinnitus, and sensitivity to external vibration. A variety of auditory symptoms also have been described.

The dehiscence of bone overlying the superior canal creates a third mobile window that makes the canal responsive to changes in pressure in the middle ear or intracranial compartment. In this case, the normal pulse-synchronous oscillation of intracranial pressure likely caused pulsatile alternation of endolymph pressure and cupular deflection, leading to pulse-synchronous pendular nystagmus at rest. The nystagmus was aligned with the plane between both superior semi-circular canals, compatible with bilateral simultaneous stimulation. The sustained increase in intracranial pressure accompanying the Valsalva manoeuvre likely caused prolonged cupular deflection in one canal, leading to the torsional-upbeating nystagmus typical of unilateral superior canal dehiscence.

REFERENCES


Monocular Pulse-synchronous Vertical Nystagmus Due to Sphenoid Wing Dysplasia from Neurofibromatosis Type 1

Palpation of the patient’s pulse revealed that it was synchronous with the nystagmus. CT showed a large bony defect of the right sphenoid wing contiguous with the superior orbital fissure. There was no herniation of dura or temporal lobe into the orbit, and no exophthalmos. MRI also showed no orbital abnormalities apart from a slightly larger right globe. There was also mild widening of the right foramen rotundum and foramen ovale. The extracranial right mandibular nerve was expanded and the right masseter and lateral pterygoid were atrophic.

Sphenoid wing dysplasia affects 4% - 11% of patients with neurofibromatosis type 1. It is unclear whether the absence of bone results from abnormal mesodermal development or from dissolution of bone in early childhood related to mechanical or metabolic processes. Plexiform neurofibromas and dural ectasia are frequently found adjacent to the bony defect and may contribute to its formation. In some children, serial imaging has shown slowly progressive enlargement of the defect.

Pulsatile exophthalmos may develop due to herniation of the temporal lobe into the posterior orbit. The present case shows slowly progressive enlargement of the defect.

REFERENCES

CASE 16 (WF) FRONT AND CENTER

Frontotemporal Tauopathy Due to MAPT G389R Mutation

Voluntary saccades to command, both horizontal and vertical, were either delayed and hypometric or not initiated at all. Reflexive saccades to novel targets were intact. When asked not to make saccades to novel targets, he had difficulty restraining them. When asked to steadily fixate a central target, he made several spontaneous saccades away from the target. A similar impairment of gaze was seen after saccades to peripheral targets. Clinical examination showed no abnormalities of saccadic velocity, smooth pursuit, OKN, VOR cancellation or convergence. Antisaccades were delayed but directed correctly.

Repeat MRI one year after the first scan showed marked progression of frontal lobe atrophy. Targeted gene sequencing showed the presence of a heterozygous mutation (c.1165G>A; p.G389R) in the microtubule associated protein tau (MAPT) gene. Over the next 2 years, his neurological status steadily deteriorated and he died 3 years after onset of symptoms. At autopsy, the brain showed severe atrophy of the frontal lobes, greatest on the right and in superior frontal gyri. Histology revealed marked neuronal loss and status spongiosis in layers 3 and 5 of frontal cortex and positive staining for phosphorylated tau in layer 2 and in white matter threads. A few Pick bodies were present but no Pick cells.

Mutations in the MAPT gene, located on chromosome 17q21, may cause an autosomal dominant tauopathy associated with frontotemporal dementia, often together with Parkinsonism (FTDP-17 MAPT). The disease may present with psychiatric symptoms or mimic Alzheimer disease, primary progressive aphasia, PSP or corticobasal degeneration. The average age of symptom onset is 49 years but onset in the late teens or early twenties has been reported in at least three other cases. In each case, the G389R mutation was present.

The clinical features of this case, including abnormal control of saccades, likely were caused by severe bilateral dysfunction of frontal cortex. Frontal cortex contains at least 4 distinct areas important for voluntary control of saccades: the frontal eye field, supplementary eye field, dorsolateral prefrontal cortex and anterior cingulate eye field. The frontal eye field, at the posterior end of the middle frontal sulcus, anterior to the precentral sulcus (Brodmann area 6), is involved in dispatching voluntary saccades and suppressing saccades to visual targets in the contralateral field. The supplementary eye field in dorsomedial frontal lobe helps to program learned or complex saccades. The dorsolateral prefrontal cortex (junction of areas 9 and 46) helps generate antisaccades and saccades to remembered targets. The cingulate eye field (junction of areas 23 and 24) may contribute to antisaccades, memory-guided saccades and self-paced saccades.

Acute bilateral frontal lobe lesions may cause acquired ocular motor apraxia, characterized by loss of all voluntary eye movements with preserved reflex eye movements. Voluntary saccades usually recover, likely due to preserved parietal eye fields. Enduring saccadic deficits may include impairments of reaction times, ability to disengage fixation, accuracy (hypometria), suppression of inappropriate saccades to novel targets, and antisaccades or more complex saccades such as memory-guided or pre-planned sequential saccades. A limited oculographic study of 3 patients with FTDP-17 showed slowed, mildly hypometric prosaccades with normal latencies, and abnormal performance of antisaccades.

REFERENCES
CASE 17 (JB) THE WHEELS ON THE BUS

Joubert Syndrome
He had horizontal pendular nystagmus, with large “wheel rolling” tonic alternating cyclodeviations. Attempted horizontal gaze shifts showed substitution of head thrusts for saccades at times (ocular motor apraxia). These are features of Joubert syndrome, in particular, the wheel-rolling deviations. The deviation shares similarities with paroxysmal ocular tilt reaction and cyclic skew deviation, and may reflect a central otolithic anomaly. Other ocular motor abnormalities include horizontal strabismus, see-saw nystagmus, pendular nystagmus, elevation of the abducting eye or lid in lateral gaze, congenital ocular motor apraxia, and periodic alternating gaze deviation. The presence of seesaw nystagmus and asymmetric visual evoked potentials suggest an abnormality of decussation at the optic chiasm.

Joubert syndrome presents in early childhood with hypotonia, episodic tachypnea or apnea, ataxia, abnormal eye movements, pigmentary retinopathy, and intellectual disability. There are at least 21 identified DNA mutations, which affect proteins of the primary cilium or its basal body, with sporadic, autosomal recessive or X-linked inheritance patterns.

A characteristic radiologic sign is the molar tooth sign, consisting of “an abnormally deep cleft in the isthmus of the brain stem, thickened and reoriented superior cerebellar peduncles, and vermian hypoplasia.” These were evident on this patient’s CT scan.

REFERENCES