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Central Positional Nystagmus

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Abstract

Purpose of review Central positional nystagmus (CPN) is attributed to disease affecting the central vestibulo-cerebellar pathways. It can be associated with prominent vertigo, oscillopsia, and dysautonomia. Its treatment highly depends on the etiology, and response is fairly heterogenous. This review presents a critical appraisal of CPN therapies.

Recent findings Anecdotal reports have stated efficacy of 3,4-diaminopyridine, 4-aminopyridine, and clonazepam in downbeating CPN secondary to structural lesions. In tumors, CPN may improve after tumoral resection and radiotherapy. In multiple sclerosis, intravenous steroids may abate CPN during a relapse. In paraneoplastic CPN, remission has been occasionally observed after tumoral excision, but relapses may follow. In autoimmune ataxia, intravenous immunoglobulin and oral baclofen have been shown to improve upbeating CPN. In genetic ataxia, acetazolamide seems to be more effective in resolving ictal episodes than non-ictal CPN and ataxia. In vestibular migraine, prophylactic treatment seems to provide long-term improvement of attacks manifesting with CPN. Non-invasive vagus nerve stimulation has abolished CPN in a vestibular migraine attack. CPN secondary to toxics not responding to drug discontinuation might need further treatment such as midazolam or clonazepam.

Summary Prospective randomized placebo-controlled treatment trials using objective baseline, short- and long-term assessments of CPN, and related symptoms are highly needed.

Introduction

Central positional nystagmus (CPN) is characterized by nystagmus triggered by changes in head position, and is caused by cerebellar and/or brainstem disorders involving the central vestibulo-cerebellar pathways, either in a permanent or transient fashion. These include structural lesions (e.g., tumors, stroke, multiple sclerosis), auto-immune (paraneoplastic and non-paraneoplastic), degenerative and genetic ataxias, vestibular migraine, and toxicity, among other [1•]. CPN can be paroxysmal or persistent (duration < 1 and > 1 min, respectively), and its direction is frequently vertical (e.g., downbeating or upbeating) in head hanging positions and horizontal (e.g., apogeotropic or geotropic) in lateral supine positions, often being multiplanar in the same individual. In contrast to its peripheral counterpart, i.e., benign paroxysmal positional vertigo (BPPV), CPN is frequently associated with additional central ocular motor and neurological signs, and does not respond to liberatory maneuvers [1•]. CPN is believed to reflect an abnormal integration of semicircular canal–related signals by the cerebellar nodulus, uvula, and/or tonsil, ultimately providing an erroneous estimation of head tilt and/or eye position coordinates [2–5]. CPN can be associated with intense vertigo, oscillopsia, and dysautonomia, particularly the paroxysmal form, and therefore, treatment might be needed [2, 3, 6, 7]. The latter is usually directed primarily towards the underlying disorder whenever possible, with the additional goal of alleviating clinical symptoms. Despite CPN being highly prevalent in several CNS disorders (e.g., 15% of patients with diffuse cerebellar disease [8], 90% of patients during an attack of vestibular migraine [9], 50% of patients with isolated cerebellar stroke [10], and up to 80% of patients with infratentorial tumors [11]), objective and standardized assessment of CPN before and after treatment has been scarcely reported in the literature. We provide a critical appraisal of current therapeutic strategies for CPN.

Methods

A PubMed search until 15 April 2022 using the key words "Central Positional Nystagmus", "Central Positional Nystagmus Treatment", "Positional Nystagmus" OR "Positioning Nystagmus" OR "Positional Vertigo" OR "Positioning Vertigo" AND "Central" AND "Treatment" was performed. Pertinent articles were assessed, and their references used to identify further publications of interest.

Treatment

We will discuss CPN treatment based on common etiologies and representative cases. See Table 1 for suggested recommendations on CPN treatment and Table 2 for a detailed list of CPN patients reported in the literature who underwent a specific treatment for CPN, and had information on CPN phenotype and outcome of CPN and/or related symptoms available.

Table 1 Treatment of central positional nystagmus — suggested recommendations

Etiology	Treatment[a]
Tumor	Tumor-directed therapy (surgical removal[b], radiotherapy, chemotherapy, etc.)
	Clonazepam, baclofen
	3,4-diaminopyridine, 4-aminopyridine
	Vestibular suppressants and antiemetics
Stroke	*Acutely:*
	Vestibular suppressants and antiemetics
	If CPN persists after stroke:
	Clonazepam, baclofen
	3,4-diaminopyridine, 4-aminopyridine
Multiple sclerosis	*Acutely, during a relapse:*
	Intravenous methylprednisolone
	Vestibular suppressants and antiemetics
	If CPN persists after a relapse or presents chronically:
	Clonazepam, baclofen
	3,4-diaminopyridine, 4-aminopyridine
	Carbamazepine, phenytoin, lamotrigine, lacosamide, levetiracetam, acetazolamide
Autoimmune cerebellar ataxia	Tumor-directed therapy (surgical removal, chemotherapy, radiotherapy, etc.)
	Intravenous methylprednisolone, dexamethasone
	Plasmapheresis
	Intravenous immunoglobulin
	Mycophenolate, cyclosporin, cyclophosphamide
	Rituximab
	Clonazepam, baclofen
	3,4-diaminopyridine, 4-aminopyridine
	Vestibular suppressants and antiemetics
Degenerative and genetic ataxia	Acetazolamide[c]
	4-aminopyridine, 3,4-diaminopyridine[c]
	Levetiracetam[c]
	Clonazepam, baclofen
	Vestibular suppressants and antiemetics
Vestibular migraine	*Acutely, during an attack:*
	Vestibular suppressants and antiemetics
	Zolmitriptan, sumatriptan, eletriptan
	If prophylaxis is needed to control CPN attacks' intensity and/or frequency:
	Propranolol, bisoprolol, metoprolol, verapamil, amlodipine, flunarizine, cinnarizine, lomerizine, valproic acid, topiramate, lamotrigine, acetazolamide, amitriptyline, nortriptyline, venlafaxine, paroxetine, duloxetine, escitalopram, di-hydroergotamine

Table 1 (continued)

Etiology	Treatment[a]
Toxicity	Offending drug discontinuation
	Midazolam, clonazepam
	Vestibular suppressants and antiemetics

Vestibular suppressants (e.g., meclizine, dimenhydrinate, scopolamine, diazepam, lorazepam, clonazepam, flunarizine, cinnarizine, betahistine, haloperidol, promethazine) and antiemetics (e.g., ondansetron, domperidone, metoclopramide) should only be used for short periods of time, being potentially helpful in short-lived CPN episodes (e.g., vestibular migraine attack). These can be used in isolation or as an additional measure to help relieve symptoms when other treatment/intervention has been initiated (e.g., inciting drug discontinuation in intoxication, intravenous methylprednisolone in a multiple sclerosis relapse)

CPN Central positional nystagmus

[a]Treatment is suggested if CPN is associated with vertigo, oscillopsia, and/or dysautonomia

[b]After surgery, new ocular motor and vestibular deficits (including CPN) attributable to the procedure might develop

[c]Acetazolamide, aminopyridines, and levetiracetam use has mostly been described in patients with familial hemiplegic migraine type 1, spinocerebellar ataxia type 6, and episodic ataxia type 2

Structural Lesions

Strategic lesions causing CPN commonly involve the cerebellar nodulus, uvula, tonsil, and/or areas containing fibers connecting the latter structures with the vestibular nuclei (e.g., cerebellar peduncles, lateral medulla, and dorsolateral region of the 4th ventricle) [1•].

Tumor

In patients with CPN associated with infratentorial (mostly cerebellar) tumors, both positional nystagmus, vertigo, and/or posturally evoked vomiting may be fully or partially improved after tumoral resection [12, 13] and post-operative radiation [14–16], albeit patients might be left with new ocular motor and vestibular deficits attributable to the surgical procedure [14, 16]. The above treatments might improve CPN by alleviating the compression of critical structures and/or pathways within the central vestibulo-cerebellar network, known to participate in CPN's generation, when dysfunctional. Baloh and colleagues provided electronystagmographic assessment in two representative cases. The first patient, an 18-year-old female, had paroxysmal downbeating CPN, vertigo, and nausea in head hanging position due to a cerebellar astrocytoma. Six months after resection and radiation, there was no positional vertigo. The second patient, a 16-year-old female, had paroxysmal upbeating CPN, vertigo, and nausea in supine position due to a midline cerebellar astrocytoma. Five months after sub-total lesion resection and radiation, positional symptoms and CPN subsided [16]. Tumor resection, however, does not always grant symptoms and/or CPN resolution. Lea et al. described a 65-year-old male with paroxysmal downbeating CPN and vertigo on lateral head hanging associated with a hemangioblastoma involving the left cerebellar peduncle and extending

Table 2 Treatment of central positional nystagmus — detailed cases

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Gregorius et al. Surg Neurol. [16]	18, F	Cerebellar astrocytoma	CPN: paroxysmal down and left beating nystagmus in head hanging position; downbeat nystagmus when seating up; left beating nystagmus in lateral positions Remaining exam: GEN; impaired smooth pursuit and OKN bilaterally; right upper extremity dysmetria; gait ataxia Symptoms: 3-month-positional vertigo, nausea and vomiting, intermittent diplopia	Tumor resection and radiotherapy	No positional vertigo, assessed 6 months after treatment Mild difficulty on tandem walking Skew deviation, after surgery, partially improved	Not detailed
	16, F	Cerebellar astrocytoma	CPN: paroxysmal upbeat nystagmus in supine position Remaining exam: normal Symptoms: 1-year-positional vertigo nausea and vomiting, and headaches	Tumor resection and radiotherapy	No further vertigo, assessed 5 months after treatment Spontaneous nystagmus and 6NP after surgery, fully improved	Not detailed
Watson et al. Can J Neurol Sci. [20]	20, F	Cerebellar vermis medulloblastoma	CPN: persistent horizontal geotropic nystagmus in lateral positions Remaining exam: normal Symptoms: 1-month-positional vertigo, nausea and vomiting, and headache	Tumor resection	Functioning normal, assessed 2 years after treatment	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
	28, F	Fourth ventricle subependymoma	CPN: paroxysmal right torsional nystagmus in right head hanging Remaining exam: normal Symptoms: 2-year-positional vertigo, nausea and vomiting	Tumor resection	Having trouble adjusting to disability, assessed 9 months after treatment GEN and 6NP, after surgery	Not detailed
	50, M	Intracranial hypertension	CPN: paroxysmal geotropic nystagmus in right head hanging Remaining exam: drowsiness; papilledema; bilateral hyperreflexia; upgoing toes Symptoms: positional vertigo, nausea, headache and stupor	Ventriculo peritoneal shunt	Remained well, assessed 1 year after treatment	Not detailed
Sakata et al. Acta Otolaryngol Suppl. [22]	63, M	Posterior fossa arachnoid cyst	CPN: paroxysmal right torsional nystagmus in head hanging; left torsional nystagmus on sitting up Remaining exam: VOR suppression impaired Symptoms: positional vertigo and headache, for years	Cyst removal	Symptom free, after treatment	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Barber. Otolaryngol Neck Surg. [14]	57, M	Renal cell carcinoma cerebellar metastasis	CPN: paroxysmal downbeating nystagmus on Hallpike's maneuver Remaining exam: gait ataxia Symptoms: 6-month-positional vertigo	Metastasis removal, primary tumor resection and radiotherapy	No postural vertigo and better balance, but very faint downbeat positioning nystagmus, assessed 5 months after treatment Ataxic on tandem gait Ocular motor and vestibular defects remained, after surgery	Not detailed
Chan et al. J Clin Neuroophthalmol. [13]	27, M	Cerebellar vermis arachnoid cyst	CPN: paroxysmal downbeating nystagmus after oblique head and neck extension laterally Remaining exam: normal Symptoms: 20-month-positional vertigo, vertical oscillopsia, headache and unsteadiness	Cyst removal	Complete resolution of symptoms and positional downbeat nystagmus, after treatment Skew deviation after surgery, corrected with prisms	Not detailed
Lea et al. Otol Neurotol. [17]	65, M	Cerebellar hemangioblastoma	CPN: paroxysmal downbeating nystagmus on Dix Hallpike test with either ear down Remaining exam: normal Symptoms: 3-year-history positional vertigo	Tumor resection	Paroxysmal positional downbeat nystagmus was unchanged, assessed 6 months after treatment	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Helmchen et al. J Neurol. [18]	43, M	Surgical removal of cerebellar nodulus and uvula multi-nodular dysembryoplastic neuroepithelial tumor	CPN: paroxysmal downbeating nystagmus in head hanging position Remaining exam: impaired downward smooth pursuit; perverted HSN; prolonged post-rotatory nystagmus, not suppressed by head tilt; gait ataxia Symptoms: positional vertigo and vertical oscillopsia, after surgery	3,4 -diaminopyridine 20 mg	Improvement of positional downbeating nystagmus and smooth pursuit, assessed 90 min after treatment	3,4 -diaminopyridine-related modulation of brainstem velocity storage or its inputs from the vertical VOR signals, by restoring deficient uvulo-nodular inhibition
Kremmyda et al. J Neurol. [19]	45, F	Cerebellar vermis hemangioblastoma	CPN: paroxysmal downbeating nystagmus in backward head movements or supine body position Remaining exam: macro-square wave jerks Symptoms: positional vertigo	Tumor resection 4-amynopiridine 5 mg t.i.d	Positional vertigo did not change, after surgery Symptoms disappeared, assessed 3 days after 4-amynopiridine	4-amynopiridine-related modulation of overactive otolith-ocular reflexes, by restoring deficient uvulo-nodular inhibition

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Oh et al. J Neurol. [24]	58, M	Intraventricular hemorrhage	CPN: paroxysmal downbeating nystagmus in straight head hanging and Dix-Hallpike; paroxysmal upbeat nystagmus when up righting; apogeotropic nystagmus during the supine head roll test Remaining exam: apparently normal Symptoms: positional vertigo and loss of consciousness	Baclofen 2 0 mg/day for 1 week Clonazepam, 1 mg/day	Baclofen failed due to drug intolerance Resolution of the paroxysmal downbeat and apogeotropic nystagmus, assessed 2 months after clonazepam	Clonazepam-related enhancement of inhibitory GABAergic synaptic transmission between the vestibulocerebellum and vestibular nuclei, and stabilization of the exaggerated postacceleratory secondary response during positioning
Anagnostou et al. J Neurol Sci. [27]	55, F	Demyelinating plaque in the inner part of the left superior cerebellar peduncle	CPN: persistent right torsional nystagmus in right Dix–Hallpike maneuver Remaining exam: skew deviation; spontaneous upbeat nystagmus Symptoms: 1 day-positional vertigo and vomiting, preceded by 2-day-vertical diplopia and nausea	Intravenous methylprednisolone, 500 mg/day for 5 days	Clinical manifestations virtually disappeared, assessed 5 days after treatment	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Anagnostou et al. J Neurol Neurosurg Psychiatry. [28]	60, F	Demyelinating plaque in the right superior cerebellar peduncle	CPN: persistent downbeating nystagmus in off-vertical head positions and straight supine, accompanied by an apogeotropic component in right ear down position Remaining exam: GEN; gait ataxia; hyperactive deep tendon reflexes; left extensor response Symptoms: 10 day-positional vertigo and vomiting	Intravenous methylprednisolone 1000 mg and clonazepam 2 mg/day	Gradual improvement of the symptoms, after treatment	Not detailed
Eggers et al. Neurology. [36]	25, M	Paraneoplastic cerebellar degeneration and Hodgkin lymphoma	CPN: paroxysmal downbeating nystagmus, followed by upbeating nystagmus, alternating between each other, while supine or with head-hanging; paroxysmal downbeating nystagmus in prone head positioning Remaining exam: GEN, exophoria Symptoms: 1 year-positional vertigo	Chemotherapy (2 cycles of ABVD [adriamycin, bleomycin, vinblastine, and dacarbazine]) and 20 Gy radiotherapy	Positional nystagmus did not change, after treatment	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Kearsley et al. Arch Neurol. [35]	63, M	Paraneoplastic cerebellar degeneration and chondrosarcoma	CPN: paroxysmal right torsional nystagmus in supine positioning with the right ear down Remaining exam: GEN; ocular flutter; impaired smooth pursuit and VOR suppression; right sensorineural hearing loss; gait ataxia Symptoms: vertigo, nausea, and unsteadiness	Dexamethasone, 16 mg/day Tumor resection Chemotherapy, plasmapheresis (six sessions) and baclofen, 10 mg four times daily	Symptoms deteriorated under dexamethasone Free of symptoms, assessed 4 weeks after surgery A relapse, 6 weeks later, did not respond to chemotherapy, plasmapheresis and baclofen	Not detailed
	58, F	Paraneoplastic cerebellar degeneration and fallopian tube carcinoma	CPN: persistent downbeating nystagmus in sitting and supine positions; on relapse, 18 months later: persistent downbeating nystagmus in supine and prone positions; persistent apogeotropic horizontal nystagmus in lateral positions Remaining exam: ocular flutter; upper limb ataxia; gait ataxia; on relapse, 18 months later: GEN, dysarthria, gait ataxia Symptoms: 1-week-vertigo, nausea and unsteadiness; on relapse, 18 months later: dysarthria and imbalance	Tumor resection and chemotherapy (chlorambucil 12 mg/day) Chemotherapy (cisplatin, two 100 mg doses)	Free of neurologic signs, assessed 12 days after surgery A relapse, 18 months after surgery, did not respond to chemotherapy	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Tafur et al. Mayo Clin Proc. [37]	28, M	Paraneoplastic cerebellar degeneration and testicular seminoma	CPN: paroxysmal torsional nystagmus in right Dix-Hallpike position and downbeating and left torsional nystagmus after sitting up Remaining exam: GEN; limb and gait ataxia Symptoms: 1 month-recurrent vertigo	Bilateral orchiectomy and radiotherapy (2250 cGy) Intravenous methylprednisolone (5 days) Oral cyclophosphamide	Fewer episodes of vertigo, resolution of ataxia, and improvement of GEN, assessed 4 months after treatment	Suppression of the autoimmune effectors that cause neuronal injury
Martins et al. J Neuroophthalmol. [39]	68, F	Anti-glutamic acid decarboxylase antibody ataxia	CPN: paroxysmal upbeating nystagmus in supine and head hanging position; paroxysmal geotropic nystagmus Remaining exam: spontaneous downbeat nystagmus; square wave oscillations; GEN; hypermetric horizontal saccades; hyperactive head impulses; alternating skew deviation; upper limb ataxia Symptoms: 2 year-positional vertigo and nausea	Baclofen 2,5 mg t.i.d Intravenous immunoglobulin 30 g, for 5 days followed by monthly administration	Positional upbeating nystagmus (but not spontaneous downbeating nystagmus) was transiently abated, after baclofen (for~2 weeks, then stopped due to gastric intolerance) Positional upbeating nystagmus and spontaneous downbeat nystagmus resolved, assessed 5 days after immunoglobulin Head impulse responses improved, while skew deviation, square wave jerks, saccade hypermetria, and upper limb ataxia remained unchanged	Baclofen-related restoring of inhibition of the velocity-storage mechanism, shortening the VOR time constant Immunoglobulin-related restoring of nodulus/uvula and flocculus/paraflocculus GABAergic inhibitory output over the vestibular nuclei

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Suzuki et al. J Neurol Sci. [47]	47, M	Familial hemiplegic migraine type 1	CPN: downbeat nystagmus from a sitting to a supine position Remaining exam: GEN; vertical saccadic pursuit; bilateral dysmetria Symptoms: 27-year-positional vertigo, oscillopsia and recurrent headache with aura and left-sided weakness and sensory disturbance	Acetazolamide 500 mg twice a day	Positional downbeat nystagmus resolved, assessed 14 months after treatment Imbalance and headaches improved	Acetazolamide-related modulation of pH could aid in stabilizing abnormal ion channel function
Yabe et al. J Neurol [48]	46, M	Familial hemiplegic migraine type 1	CPN: downbeating nystagmus Remaining exam: GEN; dysmetria; limb and gait ataxia Symptoms: 26-year-positional vertigo and oscillopsia and recurrent headache with left-sided weakness and sensory disturbance	Acetazolamide 500 mg twice a day	Positional downbeating nystagmus and ataxia did not improve Headaches were abolished	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Jen et al. J Neurol Neurosurg Psychiatry. [46]	42, F	Spinocerebellar ataxia type 6	CPN: downbeating nystagmus Remaining exam: gait ataxia Symptoms: 1-year positional vertigo, imbalance, and recurrent dizziness and imbalance	Acetazolamide 250 mg twice a day	Positional downbeating nystagmus and ataxia did not improve, assessed 3 years after treatment Recurrent dizziness markedly improved	Acetazolamide-related increase of the extracellular concentration of free protons in the cerebellum, likely stabilizing the transient dysfunction of mutant calcium channels by acidification
	56, M	Spinocerebellar ataxia type 6	CPN: downbeating nystagmus Remaining exam: spontaneous downbeat nystagmus; gait ataxia Symptoms: 5-year-positional vertigo, and recurrent dizziness and imbalance	Acetazolamide 750 mg/day	Positional downbeating nystagmus and ataxia did not improve Only infrequent episodes of recurrent dizziness	Acetazolamide-related increase of the extracellular concentration of free protons in the cerebellum, likely stabilizing the transient dysfunction of mutant calcium channels by acidification
	65, M	Spinocerebellar ataxia type 6	CPN: downbeating nystagmus Remaining exam: GEN; gait ataxia; hyperreflexia Symptoms:~40-year-positional vertigo, and imbalance	Acetazolamide	No benefit, assessed after 1 month	Acetazolamide-related increase of the extracellular concentration of free protons in the cerebellum, likely stabilizing the transient dysfunction of mutant calcium channels by acidification

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
El-Badry et al. Acta Otolaryngol. [64]	13 patients (10 F, 3 M)	Vestibular migraine	CPN: upbeating nystagmus (8); downbeating nystagmus (5) Inclusion criteria: patients with vestibular migraine only experiencing episodic positional vertigo with no spontaneous vertiginous attacks, and presence of positional vertical nystagmus	Cinnarizine Topiramate	Positional vertical nystagmus and vertigo disappeared in 12 patients, assessed 4 weeks after treatment, and did not recur after 6 months Headache attacks frequency and severity also improved	Cinnarizine-related L-type calcium channel blocker activity and weak anti-histaminic action (anti-H1), directly inhibiting vestibular hair cells stimulation Topiramate-related inhibition of sodium ion channels and activity of L-type, enhancement of neurotransmission mediated by c-aminobutyric acid, leading to suppression of the neuronal pain pathways in the trigeminal nucleus
Lechner et al. J Neurol. [61]	13 patients	Vestibular migraine	CPN: persistent geotropic nystagmus in lateral supine (5); persistent symmetrical apogeotropic nystagmus in lateral supine (8) Inclusion Criteria: Patients with symptomatic positional vertigo and horizontal positional nystagmus	Migraine prophylactic drugs	All patients experienced symptom resolution, after treatment	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Dieterich, Brandt. J Neurol. [58]	90 patients*	Vestibular migraine	CPN: Vertical nystagmus (3) Inclusion criteria: Patients with episodic vertigo related to migraine in whom medical migraine prophylaxis abolished the attacks	Ergotamines Metoprolol Flunarizine	In all patients, acute attacks were suppressed by ergotamines and/or the frequency of the attacks was significantly reduced by metoprolol and/or flunarizine	Not detailed
Mahrous. Acta Otolaryngol. [65]	52, M	Vestibular migraine	CPN: Persistent upbeating, torsional and geotropic nystagmus in right head hanging Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 100 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed
	60, F	Vestibular migraine	CPN: persistent upbeating, torsional and geotropic nystagmus in right head hanging Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 100 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed
	35, F	Vestibular migraine	CPN: apogeotropic nystagmus in lateral supine Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 50 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
	54, F	Vestibular migraine	CPN: persistent upbeating, torsional and geotropic nystagmus in right head hanging Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 100 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed
	50, F	Vestibular migraine	CPN: persistent upbeating, torsional and geotropic nystagmus in left head hanging Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 100 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed
	55, M	Vestibular migraine	CPN: persistent upbeating, torsional and geotropic nystagmus in right head hanging Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 100 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed
	38, M	Vestibular migraine	CPN: geotropic nystagmus in lateral supine Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 50 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
	47, F	Vestibular migraine	CPN: geotropic nystagmus in lateral supine Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 50 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed
	31, F	Vestibular migraine	CPN: persistent upbeating, torsional and geotropic nystagmus in right head hanging Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 50 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed
	44, F	Vestibular migraine	CPN: Paroxysmal upbeating, torsional and geotropic nystagmus in right head hanging Remaining exam: not detailed Symptoms: episodic vertigo attack lasting > 3 months	Topiramate 50 mg/day	Positional nystagmus disappeared and vertigo improved, assessed 6 months after treatment	Not detailed
Beh. Headache. [59]	41, F	Vestibular migraine	CPN: persistent geotropic nystagmus in lateral supine and head hanging Remaining exam: spontaneous left beating nystagmus Symptoms: 2-year-positional vertigo, nausea, occasional vomiting, oscillopsia, and headache	Topiramate 200 mg twice daily Eletriptan	Attack-free, assessed 31 months after treatment Attacks every 5 months were aborted with eletriptan	Not detailed

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Beh. Otol Neurotol. [71•]	58, F	Vestibular migraine	CPN: persistent right beating nystagmus in the left Dix Hallpike and supine head left positions Remaining exam: not detailed Symptoms: episodic positional vertigo, nausea, vomiting, headache, photophobia, phonophobia, and binaural pressure	Noninvasive Vagus Nerve Stimulation (bilateral 120-s stimulations, to the right and left side of the neck) Lamotrigine 100 mg twice daily	Positional nystagmus, vertigo and headache resolved, assessed 15 min after treatment	Noninvasive vagus nerve stimulation of cervical vagal A-fibers travelling to brainstem loci that host trigemino-vestibulovagal connections, predominantly located in the nucleus tractus solitarius and dorsal motor vagus nucleus, ultimately modulating abnormal neuronal activity in the vestibular nuclei, and vestibulocerebellum
Choi et al. J Neurol Sci. [73]	70, F	Pregabalin intoxication	CPN: paroxysmal downbeating nystagmus in straight head hanging position Remaining exam: impaired pursuit and saccades; perverted HSN; gait ataxia Symptoms: vertigo and imbalance while on pregabalin 150 mg twice a day	Drug discontinuation	Positional downbeating nystagmus, vertigo, ataxia, and perverted HSN disappeared, assessed 5 days after drug discontinuation	Removal of pregabalin-related decrease in excitatory neurotransmitter secretion through attachment to the alpha-2-delta subunit of the voltage-dependent calcium channels

Table 2 (continued)

Reference	Age (years), gender (M, male; F, female)	Etiology	Clinical phenotype	Treatment	Outcome	Proposed treatment mechanism
Oh et al. J Clin Neurol. [74]	31, F	Lamotrigine intoxication	CPN: persistent downbeating nystagmus on straight head hanging and on Dix-Hallpike maneuver Remaining exam: spontaneous downbeat nystagmus; Impaired downward pursuit; GEN; perverted HSN; limb and gait ataxia Symptoms: dizziness, oscillopsia, vomiting, imbalance while on lamotrigine 600 mg/day	Drug dosage decrease	Signs and symptoms resolved, assess 6 months after drug dosage decrease	Attenuation of lamotrigine-related transient dysfunction of the vestibulocerebellum
Arbusow et al. Neurology. [75]	70, M	Amiodarone intoxication	CPN: downbeat nystagmus on head-trunk tilt from a sitting position or turning the head to the sides when supine Remaining exam: spontaneous downbeat nystagmus; limb and gait ataxia Symptoms: 7-week positional vertigo and vomiting while on amiodarone 600 mg/day	Drug discontinuation Ondansetron, dimenhydrinate, and triflupromazine Midazolam and clonazepam	No improvement, assessed 2 weeks after drug discontinuation Vomiting was not suppressed with antiemetics Positional vertigo and vomiting were relieved with benzodiazepines, but downbeat nystagmus and limb ataxia were not affected	Removal of amiodarone-related disinhibition of archiocerebello-vestibular efferents to the ocular motor circuitry of the vestibulo-ocular reflex and to the postremal area and lateral reticular formation

CPN Central positional nystagmus, *GEN* gaze-evoked nystagmus, *OKN* optokinetic nystagmus, *6NP* Sixth nerve palsy, *VOR* vestibulo-ocular reflex, *HSN* head shaking nystagmus, *GABA* gamma-aminobutyric acid

*14 patients had positional vertigo during their attacks, and 3 out of 8 patients examined during their vertigo attacks showed CPN

into and deforming the midbrain and pons. Six months after resection of the lesion, CPN and vertigo were still present [17]. Still, in the above context, surgery and chemotherapy/radiotherapy constitute mainstay therapies which can be life-saving and might significantly increase life expectancy and, therefore, are performed regardless of CPN outcome.

Pharmacological treatment directed to the putative underlying mechanism of CPN, constitutes another line of therapy for tumor-related CPN, particularly in patients where CPN appeared or was not improved after surgery. Aminopyridines, i.e., 3,4-diaminopyridine (DAP) [18] and 4-aminopyridine (4AP) [19], have been used anecdotally, showing some benefit. DAP was used in 43-year-old male with intense paroxysmal downbeating CPN, vertigo, and vertical oscillopsia in straight head hanging, caused by surgical removal of a cerebellar nodulus and uvula multi-nodular dysembryoplastic neuroepithelial tumor. Ninety minutes after ingestion of DAP 20 mg, there was a modest (21%) reduction of CPN slow phase mean velocity (72 to 56°/s) [18]. Data on patient's symptoms after DAP was not provided. Possible interference of nystagmus fatigability in the results, a phenomenon which might be seen in CPN, was not discussed either [20]. Strupp and colleagues used 4AP in a 45-year-old female with paroxysmal downbeating CPN and vertigo on backward head movements and supine position, associated with a cerebellar vermis hemangioblastoma, after showing no improvement with surgery. After 3 days of 4-AP 5 mg t.i.d., symptoms and CPN disappeared, having reappeared 2 days after 4-AP treatment was stopped [19]. Paroxysmal downbeating CPN in the above cases was ascribed to a deficient uvulo-nodular inhibition of the brainstem velocity storage, vertical angular vestibulo-ocular reflex and/or otolith-ocular reflex during rapid head tilts. Aminopyridines, possibly by blocking potassium channels and increasing of Purkinje cells excitability [21], may have partially restored the uvulo-nodular deficit, this way reducing the asymmetric charge of the velocity storage [18] or decreasing the overactive vertical reflexes [19]. Further increase in regional cerebral glucose metabolism in the nodulus in one of the patients during 4AP treatment supports the above mechanism [19]. Unfortunately, none of the reports provided data on the long-term efficacy of DAP or 4AP in CPN and related symptoms.

Stroke

Strategic infratentorial vascular lesions may cause CPN [10, 22, 23]. While CPN and positional vertigo might go unnoticed during the acute phase unless detailed video-oculographic assessment is performed, CPN may persist over time and be associated with disabling positional vertigo, particularly in patients with downbeating (but not upbeating, apparently) CPN [23]. Also here, pharmacological treatment may significantly relieve symptoms and CPN, although reports on the efficacy of treatment of stroke-related CPN are scarce. Recently, a 58-year-old male with paroxysmal downbeating CPN and vertigo in head hanging positions after intraventricular hemorrhage was described. Mild paroxysmal upbeating CPN when uprighting, and apogeotropic CPN during the supine head roll were also present. An initial trial

with baclofen at 20 mg/day for 1 week failed due to intolerance to the drug. Subsequent treatment with clonazepam 1 mg/day, improved positional vertigo, and maximal slow phase velocity of downbeat CPN decreased from 32 to 6°/s. At the 2-month follow-up there was complete resolution of CPN and vertigo. Symptoms and CPN reappeared after clonazepam cessation, and were again abated once clonazepam was resumed [24]. Clonazepam enhances the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). In this case, clonazepam might have abated CPN by enhancing the inhibitory GABAergic synaptic transmission from the cerebellar nodulus and uvula to the vestibular nuclei, this way stabilizing a presumed exaggerated postacceleratory secondary response due to disinhibited irregular vestibular afferents [3, 24]. In another patient with paroxysmal downbeating CPN in head hanging positions after a lateral medullary stroke, CPN and/or symptoms did not improve with the introduction, 20 months after the onset of symptoms, of baclofen 10 mg bid for 2 months, followed by 4AP 10 mg bid for 2 months (mean slow phase velocity, pre- [16.4°/s] and 2 months post-treatment [14.4°/s]) (patient 18 from reference [23]).

Multiple Sclerosis

CPN is relatively rare in multiple sclerosis (MS) (~6%) [25], and BPPV [26] and vestibular migraine probably account for the majority of MS patients with recurrent positional vertigo. Similarly to stroke-related CPN, CPN and related symptoms in MS can present only acutely during a relapse, or persist afterwards and become chronic [23, 27, 28]. Anagnostou et al. reported a 55-year-old female with persistent torsional CPN in right head hanging position, possibly associated with a gadolinium enhancing demyelinating plaque in the inner part of the left superior cerebellar peduncle. The patient was started on 500 mg/day intravenous methylprednisolone for 5 days, leading to the disappearance of CPN and symptoms 5 days later [27]. The same group had previously reported a 60-year-old female with persistent downbeating CPN, vertigo, and vomiting in lateral supine, convincingly associated with a gadolinium enhancing demyelinating plaque in the right superior cerebellar peduncle. As in the former case, administration of intravenous methylprednisolone (1000 mg/d for five days), in this case combined with 2 mg/day clonazepam, "brought about gradual improvement of the symptoms" [28]. In the above cases, a strategic lesion in the superior cerebellar peduncle might have disrupted central otolithic connections between deep cerebellar structures and the vestibular nuclei [27]. Such disruption is believed to create a mismatch between eye position estimated by the burst generator and the neural integrator, hypothetically due to altered otolith input to one of these systems [4]. Methylprednisolone might have improved CPN by exerting its anti-inflammatory effects at several levels, including the inhibition of the inflammatory edema and the restoration of the blood–brain barrier disruption (which has been described to occur shortly after administration) [29], and modulation of cytokine and chemokine production, adhesion-molecule expression, and inflammatory-cell accumulation [30].

All of the above mechanisms may have helped to restore the otolithic connections between the cerebellum and the vestibular nuclei. In MS, two additional mechanisms should be taken into account for explaining paroxysmal events such as CPN, namely transversely spreading ephaptic activation of axons [31] and ion channel dysfunction [32] in partially demyelinated lesions. This is relevant, because paroxysmal events in MS can dramatically respond to antiepileptics (e.g., carbamazepine, phenytoin, lamotrigine, lacosamide, levetiracetam) and acetazolamide [31–33]. In another patient with paroxysmal downbeating CPN in head hanging positions after right pontomedullary demyelination, CPN and vertigo did not improve with the introduction, 16 months after the onset of symptoms, of 4AP 10 mg (mean slow phase velocity, pre- [8.8°/s] and 90-min post-treatment [10°/s]). She nevertheless subjectively improved positional vertigo (without a relevant change in CPN) after the introduction, 2 years after the onset of symptoms, of phenytoin 50 mg/day (patient 21 from reference [23]).

Autoimmune Ataxia

Immune-mediated cerebellar ataxias (IMCAs) constitute a group of ataxias that might respond well to induction and maintenance immunotherapy (e.g., steroids, immunoglobulins, immunosuppressants such as mycophenolate, plasmapheresis and/or rituximab), in addition to a gluten-free diet or tumor-directed therapy, when applicable. These include paraneoplastic cerebellar degeneration (PCD) and antiglutamic acid decarboxylase antibody (GAD) ataxia, among other [34]. Rarely, PCD may present with predominant positional vertigo and CPN, apart from subacute cerebellar ataxia and other cerebellar signs. CPN response to treatment in these cases is heterogenous, may or may not follow tumor response, may fail over time, and prognosis is largely dependent on the overall survival dictated by the primary tumor type and stage [35–37]. Since PCD often constitutes an immunological response against neuronal antigens expressed both by an underlying tumor and the cerebellum, tumor-directed therapy (e.g., resection, chemotherapy, radiotherapy, other) and immunotherapies (e.g., steroids, immunoglobulin, plasmapheresis, cyclophosphamide, rituximab) might theoretically improve CPN [38]. In a 28-year-old male with a seminoma and paraneoplastic paroxysmal torsional nystagmus during right head hanging and downbeating after sitting up, spontaneous and positional vertigo, gaze evoked nystagmus, and gait and limb ataxia, bilateral orchiectomy, radiotherapy, intravenous methylprednisolone, and oral cyclophosphamide were associated with substantial improvement of vertigo and ataxia [37]. While remission of PCD/CPN is possible after excision of the primary tumor, relapses may follow as exemplified in a 63-year-old male with a chondrosarcoma and paraneoplastic paroxysmal torsional CPN during right supine, spontaneous horizontal nystagmus, ocular flutter, and ataxia. Four weeks after tumor resection, PCD/CPN disappeared. However, 6 weeks later, symptoms returned and progressed inexorably, showing no response to chemotherapy, plasmapheresis, or to baclofen (10 mg four times

daily) [35]. Additionally, CPN and tumor-related responses may be disparate. In another patient, a 25-year-old male with Hodgkin lymphoma and paraneoplastic paroxysmal downbeating CPN and vertigo in supine, prone, and head-hanging positions, CPN did not respond to chemotherapy (2 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine) or radiotherapy (20 Gy radiation), while the tumor itself fully remitted [36].

Non-paraneoplastic IMCAs can also manifest with symptomatic CPN, including anti-GAD Ab- and anti-GQ1b Ab-related ataxias. In one representative case, a 68-year-old diabetic female presented with intense paroxysmal upbeating CPN, vertigo, and nausea in supine and head hanging positions and mild asymptomatic geotropic CPN in lateral supine. High titters of anti-GAD65 Ab were identified (239.07 U/mL). Interestingly, an initial trial with baclofen 2.5 mg 3 times daily fully abated CPN. However, the effect waned after 2 weeks, and the dosage could not be increased because of gastric intolerance. Subsequently, the patient was given intravenous immunoglobulin, 30 g/day over 5 days, followed by 30 g monthly administration, showing complete and sustained resolution of CPN and vertigo. Six months later, anti-GAD65 Ab levels had fallen to 40.88 U/mL [39]. In anti-GAD ataxia, an anti-GAD Ab–mediated autoimmune attack on the cerebellum and/or brainstem, causing a selective deficiency in gamma-aminobutyric acid (GABA) neurotransmission, has been hypothesized. Baclofen is a GABA agonist known to affect the vestibular and oculomotor systems. $GABA_B$ receptors are widely distributed in the cerebellum, and GABA is the major transmitter of the Purkinje cell output that ends in the vestibular nuclei [40]. In the above case, baclofen might have helped to restore nodulus/uvula GABAergic inhibitory output over the vestibular nuclei, this way abating CPN [39]. On the other hand, immunoglobulin use might have indirectly restored the same inhibitory output by exerting an immunomodulatory and anti-inflammatory effect [30, 39].

Recently, high titers of anti-GQ1b Ab have been associated with acute CPN, including persistent apogeotropic and geotropic CPN during lateral supine, and downbeating and upbeating CPN in head hanging positions [41, 42•]. Remission of anti-GQ1b Ab–related CPN, in cases where the outcome was detailed, was spontaneous over 3 to 12 months, without requiring specific treatment [41]. Intravenous immunoglobulin, plasmapheresis, and intravenous steroids have been reported as successful therapeutics in acute vestibular syndrome related with anti-GQ1b Ab. However, their use in CPN anti-GQ1b Ab–related CPN has not been detailed [42•]. Of note, plasmapheresis has a broad application in IMCAs. It probably acts by removing pathologic antibodies, immune complexes, and cytokines and may also have an immunomodulatory effect [43].

Degenerative and Genetic Ataxia

Patients with degenerative and genetic ataxia associated with CPN seem to demonstrate more frequently positional vertigo and nausea, and therefore, specific treatment might be needed [8]. Mutations in the brain-specific P/Q type Ca2 + channel alpha1 subunit gene, CACNA1A, have been identified

in three clinically distinct disorders, namely spinocerebellar ataxia type 6 (SCA6), familial hemiplegic migraine type 1 (FHM1), and episodic ataxia type 2 (EA2) [44]. SCA6 usually manifests as pure cerebellar ataxia with a late onset. Around 80% of SCA6 patients show CPN (mostly downbeating) and positional vertigo, often preceding the development of ataxia [45]. SCA6 patients may also have ictal episodes of ataxia lasting hours to days, often precipitated by physical exertion or emotional stress [46]. In 3 SCA6 patients with inter-ictal positional vertigo/downbeating CPN and truncal ataxia, and ictal episodes of ataxia (present in two of the patients), the use of acetazolamide 500 to 750 mg/day markedly decreased ictal episodes of ataxia, while showing no benefit on CPN and/or positional vertigo [46]. FHM1 on the other hand is mainly characterized by episodes of recurrent hemiplegia during the aura phase of a migraine headache, but progressive cerebellar ataxia is present in ~ 50% of patients, usually occurring independently of the migraine attacks [44, 47]. Thus, CPN may also be a feature in these patients. Suzuki et al. reported a 47-year-old patient with FMH1 and downbeating CPN, vertigo, and oscillopsia in supine position, in whom CPN slowly but completely resolved after 14 months of treatment with acetazolamide 500 mg, twice daily. Headaches were equally abolished [47]. In a similar FHM1 patient however, only headaches improved, while downbeating CPN remained unchanged after the same dosage of acetazolamide [48]. Finally, EA2 is characterized by paroxysmal attacks of ataxia triggered by stress and exercise. While downbeating CPN has been described in EA2, and both acetazolamide 750 mg/day and 4AP 20 mg/day have been shown to reduce EA2 attacks up to 60%, there are no reports evaluating CPN response to treatment [49, 50••]. Levetiracetam might reduce the attacks in EA2 patients in whom the former drugs are contraindicated, non-efficient or associated with intolerable adverse effects [51]. CPN in the above genetic ataxias probably represents an early manifestation of cerebellar atrophy (and neuronal loss), sometimes associated with cerebellar vermian atrophy in MRI [47]. The associated paroxysmal/ictal episodes (e.g., ataxia, headache), on the other hand, are believed to reflect a transient calcium channel dysfunction [52]. Acetazolamide, a carbonic anhydrase inhibitor, probably exerted its effect in the above cases by aiding in stabilizing transient abnormal ion channel function, through its modulation of pH (i.e., acidification) [53]. This might explain why acetazolamide was more effective in resolving paroxysmal/ictal episodes than permanent CPN and ataxia [46, 48]. In one FHM1 case, however, CPN was slowly abated after acetazolamide. Here, CPN might have represented an ictal phenomenon precipitated by abrupt head movements and not a permanent dysfunction of the vertical vestibulo-ocular reflex cancellation due to cerebellar neuronal loss [47]. Importantly, reports showing positive therapeutic responses of CPN in CACNA1A mutation–related diseases should be cautiously interpreted, since spontaneous resolution (i.e., without treatment) of vertigo has been observed in 4/13 SCA6 patients, before the onset of the ataxia [52].

In multiple system atrophy (MSA), a neurodegenerative disorder characterized by varying severity of parkinsonian, autonomic, and cerebellar features, the presence of CPN (mostly downbeating) constitutes an important

diagnostic clue for MSA in a patient presenting with a parkinsonian disorder [54]. Unfortunately, also here, there are no reports concerning CPN treatment and/or progression over time.

Vestibular Migraine

Vestibular migraine (VM) is one of the most common causes of recurrent vertigo. During VM attacks, 64% of patients refer positional vertigo, and CPN, usually mild, persistent and with variable direction, is observed in ~ 90% of cases [9]. Since there is no strong evidence that any treatment is effective for improving VM in the long-term, patients are usually treated with drugs commonly used in the preventive treatment of migraine (e.g., beta-blockers, antidepressants, antiepileptics, calcium channel blockers, etc.). In recent systematic reviews and meta-analyses, it was shown that propranolol and venlafaxine seem to show slightly more benefit than other drugs in the short-term follow-up (< 12 weeks), and venlafaxine may be superior to other drugs in improving depressive symptoms. Still, several other drugs also demonstrated improvement in dizziness handicap inventory (DHI) score and vertigo attacks' frequency and severity [55•, 56•]. Unfortunately, the only double-blind randomized placebo-controlled trial investigating the effectiveness of preventive treatment with metoprolol was inconclusive, due to poor patient accrual [57]. Studies specifically addressing CPN and positional vertigo response to preventive treatment in VM are rare. In a landmark paper by Marianne Dieterich and Thomas Brandt, among 90 VM patients, 3 had attacks consisting of severe positional vertical CPN (not habituating). As in all other patients in this series, in these three, migraine prophylaxis abolished the attacks [58]. Following this paper, several other small studies consistently showed that VM patients with predominant positional vertigo and CPN also responded to migraine preventive treatment, by improving their attacks' frequency and/or severity. For instance, VM attacks consisting of geotropic or apogeotropic CPN during lateral supine (and head hanging positions in one of the patients) were completely abolished with the use of topiramate 25 mg twice daily in one patient and 200 mg twice daily in another [59, 60]. In another series, all VM patients ($n = 13$) with a positional vertigo attack associated with apogeotropic or geotropic persistent CPN in lateral supine positions, experienced symptom resolution after initiation of preventive treatment [61]. However, CPN data after treatment was not provided. Importantly, in VM, ictal CPN seems to spontaneously resolve, improve, or change its direction over time [62, 63]. Yet, it is not clear if preventive treatment can influence/fasten this process (i.e., CPN progression during an attack). El-Badry et al. for instance showed that vertical persistent CPN (both upbeating and downbeating) and positional vertigo completely subsided in 12 out of 13 VM patients, after initiating cinnarizine, 37.5 mg twice daily, or topiramate, 50 mg once daily at night [64]. However, in this study, it was not completely clear whether CPN was observed during (i.e., ictal CPN) or between VM attacks (i.e., interictal CPN). In another VM series, 10 patients with acute persistent vertical

and horizontal CPN and vertigo in lateral head hanging and supine positions, showed complete resolution of CPN and vertigo after topiramate with gradual increasing dose from 25 up to 100 mg [65]. According to the authors, after 6 months of complete improvement, any trial of gradual stopping of topiramate from the patient's effective dose would make CPN and vertigo return [65]. It must be noted that in the above retrospective studies, in the absence of a placebo arm and a prospective design, it is difficult to appreciate the potential short-term effects of migraine preventive therapy on ictal CPN. Even conclusions about the long-term effects of these drugs should be carefully weighted, taking into account the natural course of VM, which can spontaneously vary over time [66, 67]. Additionally, in some VM treatment studies, one additional potential confounder in the results is the inclusion of patients taking additional vestibular suppressants in the acute phase, which can theoretically influence CPN intensity/phenotype [64]. Prophylactic drugs in VM may act on one or more of the following putative pathomechanisms: spreading depression, vasoconstriction, ion channel defect, sterile inflammation, release of neuropeptides, reduced threshold for trigeminovascular stimulation, and/or locus coeruleus and dorsal raphe nucleus hypersensitization, all ultimately affecting the cerebellar nodulus, uvula and tonsil, and/or the vestibular nuclei [63, 68, 69, 70].

On the other hand, abortive treatment in a VM attack could eventually dampen ictal CPN and positional vertigo more quickly. In one study addressing the effectiveness of zolmitriptan in VM attacks, results were inconclusive, due to limited study power [67]. In a recent work however, the use of non-invasive vagus nerve stimulation (NVNS) in a 58-year-old female patient with a VM attack, dramatically abolished persistent right beating CPN and vertigo during left head hanging and supine positions, 15 min after stimulation [71•]. As VM attacks can last as little as 5 min, further studies are needed to accurately assess the role of NVNS in VM-related CPN. NVNS seems to stimulate vagal fibers which travel to brainstem loci that host trigemino-vestibulovagal connections and further modulate the neuronal activity in the vestibular nuclei, vestibulocerebellum and their connections [71, 72]. Alternative mechanisms of NVNS include the inhibition of neurogenic inflammation, trigeminal nucleus caudalis activity, and the firing rate of trigeminocervical neurons [72].

Toxicity

Drugs with primary action in the central nervous system, putatively involving the cerebellar nodulus, uvula, and/or tonsil, may cause CPN [73–75]. The few reports available on CPN due to toxicity, which further provided CPN outcome and/or related symptoms after intervention, include the following: a 70-year-old female with paroxysmal downbeating CPN, vertigo, and dysautonomia during head hanging while on pregabalin 150 mg twice a day [73]; a 31-year-old female with downbeating CPN, vertigo, and dysautonomia during head hanging positions while on lamotrigine 600 mg/day [74];

a 70-year-old male with downbeating CPN, mild vertigo, and intense vomiting during off-axis head-trunk tilt and lateral supine, while on amiodarone 600 mg/day [75]. Discontinuation (pregabalin) or decreased dosing of the offending drug (lamotrigine), and/or the use of specific therapies including midazolam and clonazepam (amiodarone), all led to resolution or relief of positional vertigo and dysautonomia. CPN resolved 5 days, within 6 months, and possibly 5 weeks after intervention, respectively [73–75].

Vestibular suppressants (e.g., dimenhydrinate, flunarizine, cinnarizine, promethazine) and antiemetics (e.g., ondansetron, domperidone, metoclopramide) may temporarily improve CPN-related symptoms [12], but should be otherwise used judiciously only for short periods of time, taking into account their side effects and possible negative influence on vestibular adaptation [76].

Conclusions

Currently, CPN treatment options are based on anecdotal data. Moreover, in the few reports where objective assessment of CPN before and after treatment is available, rigorous assessment of the impact of related symptoms (vertigo, oscillopsia, dysautonomia, etc., by using, e.g., DHI) is usually lacking, as well as long-term evaluation of CPN and symptoms. Since CPN intensity and related symptoms may not always correlate or coincide in an individual patient, both objective and subjective assessments are needed to correctly interpret treatment responses. Moreover, since the natural progression of CPN and related symptoms is largely unknown in the majority of the conditions listed in the current paper, it becomes difficult to contextualize a single measurement in time showing CPN improvement after a specific therapeutic intervention. This issue becomes even more relevant when it is known that CPN intensity spontaneously fluctuates and is influenced by repeat positioning and velocity of the precipitant maneuver [49, 77]. Perhaps as an alternative to the use of single CPN measurements in the clinic, prone to several types of biases, continuous vestibular monitoring during daily activities could become a promising tool in CPN treatment trials, as it has the potential to provide a long-term, objective recording of eye movements under more natural conditions, data which could eventually better correlate with patients' symptoms [78]. In sum, prospective randomized multicentric treatment trials including different CPN etiologies are highly needed to better support treatment strategies in CPN.

Author Contribution

All authors contributed actively to the current manuscript.

Compliance with Ethical Standards

Conflict of Interest
The authors declare no competing interests.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.• Lemos J, Strupp M. Central positional nystagmus: an update. J Neurol. 2021. https://doi.org/10.1007/S00415-021-10852-8.
An updated review on central positional nystagmus.
2. Choi J-Y, Glasauer S, Kim JH, Zee DS, Kim J-S. Characteristics and mechanism of apogeotropic central positional nystagmus. Brain. 2018;141:762–75.
3. Choi J-Y, Kim JH, Kim HJ, Glasauer S, Kim J-S. Central paroxysmal positional nystagmus: characteristics and possible mechanisms. Neurology. 2015;84:2238–46.
4. Glasauer S, Dieterich M, Brandt T. Central positional nystagmus simulated by a mathematical ocular motor model of otolith-dependent modification of Listing's plane. J Neurophysiol. 2001;86:1546–54.
5. Choi SY, Jang JY, Oh EH, Choi JH, Park JY, Lee SH, Choi KD. Persistent geotropic positional nystagmus in unilateral cerebellar lesions. Neurology. 2018;91:e1053–7.
6. Büttner U, Helmchen C, Brandt T. Diagnostic criteria for central versus peripheral positioning nystagmus and vertigo: a review. Acta Otolaryngol. 1999;119:1–5.
7. Choi JY, Kim JS. Central positional nystagmus: characteristics and model-based explanations. Prog Brain Res. 2019;249:211–25.
8. Feil K, Strobl R, Schindler A, Krafczyk S, Goldschagg N, Frenzel C, Glaser M, Schöberl F, Zwergal A, Strupp M. What is behind cerebellar vertigo and dizziness? Cerebellum. 2019;18:320–32.
9. Young AS, Nham B, Bradshaw AP, Calic Z, Pogson JM, D'Souza M, Halmagyi GM, Welgampola MS. Clinical, oculographic, and vestibular test characteristics of vestibular migraine. Cephalalgia. 2021;033310242110060.
10. Lee SU, Choi JY, Kim HJ, Park JJ, Zee DS, Kim JS. Impaired tilt suppression of post-rotatory nystagmus and cross-coupled head-shaking nystagmus in cerebellar lesions: image mapping study. Cerebellum. 2017;16:95–102.
11. Nylen C. Statistical analysis of oto-neurological symptomatology in supra- and subtentorial tumours. Acta Otolaryngol. 1939;27:24–31.
12. Drachman DA, Diamond ER, Hart CW. Posturally - evoked vomiting; Association with posterior fossa lesions. Ann Otol Rhinol Laryngol. 1977;86:97–101.
13. Chan T, Logan P, Eustace P. Intermittent downbeat nystagmus secondary to vermian arachnoid cyst with associated obstructive hydrocephalus. J Clin Neuroophthalmol. 1991;11:293–6.
14. Barber HO. Positional nystagmus Otolaryngol Neck Surg. 1984;92:649–55.
15. Shoman N, Longridge N. Cerebellar vermis lesions and tumours of the fourth ventricle in patients with positional and positioning vertigo and nystagmus. J Laryngol Otol. 2007;121:166–9.
16. Gregorius FK, Crandall PH, Baloh RW. Positional vertigo with cerebellar astrocytoma. Surg Neurol. 1976;6:283–6.
17. Lea J, Lechner C, Halmagyi GM, Welgampola MS. Not so benign positional vertigo: paroxysmal downbeat nystagmus from a superior cerebellar peduncle neoplasm. Otol Neurotol. 2014. https://doi.org/10.1097/MAO.0000000000000245.
18. Helmchen C, Gottschalk S, Sander T, Trillenberg P, Rambold H, Sprenger A. Beneficial effects of 3,4-diaminopyridine on positioning downbeat nystagmus in a circumscribed uvulo-nodular lesion. J Neurol. 2007;254:1126–8.
19. Kremmyda O, Zwergal A, La Fougère C, Brandt T, Jahn K, Strupp M. 4-Aminopyridine suppresses positional nystagmus caused by cerebellar vermis lesion. J Neurol. 2013;260:321–3.
20. Watson P, Barber HO, Deck J, Terbrugge K. Positional vertigo and nystagmus of central origin. Can J Neurol Sci / J Can des Sci Neurol. 1981;8:133–7.
21. Etzion Y. Grossman Y (2001) Highly 4-aminopyridine sensitive delayed rectifier current modulates the excitability of guinea pig cerebellar Purkinje cells. Exp Brain Res. 2001;1394(139):419–25.

22. Sakata E, Ohtsu K, Itoh Y. Positional nystagmus of benign paroxysmal type (BPPN) due to cerebellar vermis lesions. Pseudo-BPPN Acta Otolaryngol Suppl. 1991;481:254–7.
23. Lemos J, Martins AI, Duque C, Pimentel S, Nunes C, Gonçalves AF. Positional testing in acute vestibular syndrome: a transversal and longitudinal study. Otol Neurotol. 2018. https://doi.org/10.1097/MAO.0000000000002067.
24. Oh EH, Kim H, Choi SY, Choi KD, Choi JH. Paroxysmal central positional nystagmus responsive to clonazepam. J Neurol. 2022;269:1028–31.
25. Thomsen J, Zilstorff K, Johnsen NJ. Positional nystagmus of the persistent type. ORL. 1978;40:86–91.
26. Frohman EM, Kramer PD, Dewey RB, Kramer L, Frohman TC. Benign paroxysmal positioning vertigo in multiple sclerosis: diagnosis, pathophysiology and therapeutic techniques. Mult Scler. 2003;9:250–5.
27. Anagnostou E, Varaki K, Anastasopoulos D. A minute demyelinating lesion causing acute positional vertigo. J Neurol Sci. 2008;266:187–9.
28. Anagnostou E, Mandellos D, Limbitaki G, Papadimitriou A, Anastasopoulos D. Positional nystagmus and vertigo due to a solitary brachium conjunctivum plaque. J Neurol Neurosurg Psychiatry. 2006;77:790–2.
29. Meier CA. Mechanisms of immunosuppression by glucocorticoids. Eur J Endocrinol. 1996;134:50.
30. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. N Engl J Med. 2012;367:2015–25.
31. Ostermann PO, Westerberg CE. Paroxysmal attacks in multiple sclerosis. Brain. 1975;98:189–202.
32. Espir ML, Millac P. Treatment of paroxysmal disorders in multiple sclerosis with carbamazepine (Tegretol). J Neurol Neurosurg Psychiatry. 1970;33:528.
33. Ciampi E, Uribe-San-Martín R, Godoy-Santín J, Cruz JP, Cárcamo-Rodríguez C, Juri C. Secondary paroxysmal dyskinesia in multiple sclerosis: clinical-radiological features and treatment. Case report of seven patients. Mult Scler. 2017;23:1791–5.
34. Mitoma H, Manto M, Hadjivassiliou M. Immune-mediated cerebellar ataxias: clinical diagnosis and treatment based on immunological and physiological mechanisms. J Mov Disord. 2021;14:10–28.
35. Kearsley JH, Johnson P, Halmagyi GM. Paraneoplastic cerebellar disease: remission with excision of the primary tumor. Arch Neurol. 1985;42:1208–10.
36. Eggers SDZ, Pittock SJ, Shepard NT, Habermann TM, Neff BA, Klebig RR. Positional periodic alternating vertical nystagmus with PCA-Tr antibodies in Hodgkin lymphoma. Neurology. 2012;78:1800–2.
37. Tafur AJ, Baumann Kreuzinger LM, Quevedo F. 28-Year-old man with severe vertigo. Mayo Clin Proc. 2008;83:1070–3.
38. Wray SH, Dalmau J, Chen A, King S, Leigh RJ. Paraneoplastic disorders of eye movements. Ann N Y Acad Sci. 2011;1233:279–84.
39. Martins AI, Carvalho JN, Amorim AM, Geraldo A, Eggenberger E, Lemos J. Disabling central paroxysmal positioning upbeat nystagmus and vertigo associated with the presence of anti–glutamic acid decarboxylase antibodies. J Neuro-Ophthalmology. 2017;38:1.
40. Cohen B, Helwig D, Raphan T. Baclofen and velocity storage: a model of the effects of the drug on the vestibulo-ocular reflex in the rhesus monkey. J Physiol. 1987;393:703–25.
41. Jeong S-H, Nam J, Kwon MJ, Kim JK, Kim JS. Nystagmus and ataxia associated with antiganglioside antibodies. J Neuro-Ophthalmology. 2011;31:326–30.
42.• Lee SU, Kim HJ, Choi JY, Kim JK, Kim JS. Acute vestibular syndrome associated with anti-GQ1b antibody. Neurology. 2019;93:e1085–e1092.
An important series including patients with acute vestibular syndrome associated with anti-GQ1b antibody, further providing data on the occurrence of central positional nystagmus and treatment outcomes.
43. Winters JL. Plasma exchange: concepts, mechanisms, and an overview of the American Society for Apheresis guidelines. Hematology. 2012;2012:7–12.
44. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell. 1996;87:543–52.
45. Yabe I, Sasaki H, Takeichi N, Takei A, Hamada T, Fukushima K, Tashiro K. Positional vertigo and macroscopic downbeat positioning nystagmus in spinocerebellar ataxia type 6 (SCA6). J Neurol. 2003;250:440–3.
46. Jen JC, Yue Q, Karrim J, Nelson SF, Baloh RW. Spinocerebellar ataxia type 6 with positional vertigo and acetazolamide responsive episodic ataxia. J Neurol Neurosurg Psychiatry. 1998;65:565–8.
47. Suzuki M, Fujiwara K, Tsubuku T, Yabe I, Sasaki H, Fukuda S. Time course of downbeat positioning nystagmus in familial hemiplegic migraine type 1 treated with acetazolamide. J Neurol Sci. 2016;368:206–8.
48. Yabe I, Kitagawa M, Suzuki Y, et al. Downbeat positioning nystagmus is a common clinical feature despite variable phenotypes in an FHM1 family. J Neurol. 2008;255:1541–4.
49. Ling X, Kim HJ, Lee JH, Choi JY, Yang X, Kim JS. Positioning velocity matters in central paroxysmal positional vertigo: implication for the mechanism. Front Neurol. 2020;11: 591602.
50.•• Muth C, Teufel J, Schöls L, Synofzik M, Franke C, Timmann D, Mansmann U, Strupp M. Fampridine and acetazolamide in EA2 and related familial EA. Neurol Clin Pract. 2021;11:e438–e446.

A recent randomized placebo-controlled trial showing that both fampridine and acetazolamide significantly reduce the number of attacks in patients with episodic ataxia type 2.

51. Na S, Kim T. Efficacy of levetiracetam in patients with episodic ataxia type 2 caused by CACNA1A mutation: three case reports. Neurol Sci. 2021. https://doi.org/10.1007/s10072-021-05368-y.
52. Yu-Wai-Man P, Gorman G, Bateman DE, Leigh RJ, Chinnery PF. Vertigo and vestibular abnormalities in spinocerebellar ataxia type 6. J Neurol. 2009;256:78–82.
53. Strupp M, Zwergal A, Brandt T. Episodic ataxia type 2. Neurotherapeutics. 2007;4:267–73.
54. Lee JY, Lee WW, Kim JS, Kim HY, Kim JK, Jeon BS. Perverted head-shaking and positional downbeat nystagmus in patients with multiple system atrophy. Mov Disord. 2009;24:1290–1295.
55.• Byun YJ, Levy DA, Nguyen SA, Brennan E, Rizk HG. Treatment of vestibular migraine: a systematic review and meta-analysis. Laryngoscope. 2021;131:186–194.

An important systematic review and meta-analysis showing that several classes of migraine prophylactic drugs are effective in vestibular migraine patients.

56.• Wang F, Wang J, Cao Y, Xu Z. Serotonin-norepinephrine reuptake inhibitors for the prevention of migraine and vestibular migraine: a systematic review and meta-analysis. Reg Anesth Pain Med. 2020;45:323–30.

An important systematic review and meta-analysis showing that serotonin-norepinephrine reuptake inhibitors are clinically safe and effective for vestibular migraine prophylaxis.

57. Bayer O, Adrion C, Al Tawil A, et al. Results and lessons learnt from a randomized controlled trial: prophylactic treatment of vestibular migraine with metoprolol (PROVEMIG). Trials. 2019. https://doi.org/10.1186/s13063-019-3903-5.
58. Dieterich M, Brandt T. Episodic vertigo related to migraine (90 cases): Vestibular migraine? J Neurol. 1999;246:883–92.
59. Beh SC. Horizontal direction-changing positional nystagmus and vertigo: a case of vestibular migraine masquerading as horizontal canal BPPV. Headache. 2018. https://doi.org/10.1111/head.13356.
60. Roberts RA, Gans RE, Kastner AH. Differentiation of migrainous positional vertigo (MPV) from horizontal canal benign paroxysmal positional vertigo (HC-BPPV). Int J Audiol. 2006. https://doi.org/10.1080/14992020500429658.
61. Lechner C, Taylor RL, Todd C, MacDougall H, Yavor R, Halmagyi GM, Welgampola MS. Causes and characteristics of horizontal positional nystagmus. J Neurol. 2014;261:1009–17.
62. Bertholon P, Tringali S, Faye MB, Antoine JC, Martin C. Prospective study of positional nystagmus in 100 consecutive patients. Ann Otol Rhinol Laryngol. 2006;115:587–94.
63. von Brevern M, Zeise D, Neuhauser H, Clarke AH, Lempert T. Acute migrainous vertigo: clinical and oculographic findings. Brain. 2004;128:365–74.
64. El-Badry MM, Samy H, Kabel AM, Rafat FM, Sanyelbhaa H. Clinical criteria of positional vertical nystagmus in vestibular migraine. Acta Otolaryngol. 2017;137:720–2.
65. Mahrous MM. Vestibular migraine and benign paroxysmal positional vertigo, close presentation dilemma. Acta Otolaryngol. 2020. https://doi.org/10.1080/00016489.2020.1770857.
66. Cutrer FM, Baloh RW. Migraine-associated dizziness. Headache J Head Face Pain. 1992. https://doi.org/10.1111/j.1526-4610.1992.hed3206300.x.
67. Neuhauser H, Radtke A, Von Brevern M, Lempert T. Zolmitriptan for treatment of migrainous vertigo: a pilot randomized placebo-controlled trial. Neurology. 2003;60:882–3.
68. Young AS, Lechner C, Bradshaw AP, MacDougall HG, Black DA, Michael Halmagyi G, Welgampola MS. Capturing acute vertigo: a vestibular event monitor. Neurology. 2019;92:E2743–53.
69. Von Brevern M, Radtke A, Clarke AH, Lempert T. Migrainous vertigo presenting as episodic positional vertigo. Neurology. 2004;62:469–72.
70. King S, Priesol AJ, Davidi SE, Merfeld D, Lewis R. Self-motion perception is sensitized in vestibular migraine: pathophysiologic and clinical implications. Sci Rep. 2019. https://doi.org/10.1038/s41598-019-50803-y.
71.• Beh SC. Nystagmus and vertigo in acute vestibular migraine attacks: response to non-invasive vagus nerve stimulation. Otol Neurotol. 2021;42:e233–6.

A recent small series showing promising results with the use non-invasive vagus nerve stimulation in vestibular migraine attacks, including in one patient manifesting with central positional nystagmus.

72. Henssen DJHA, Derks B, van Doorn M, Verhoogt N, Cappellen V, van Walsum AM, Staats P, Vissers K. Vagus nerve stimulation for primary headache disorders: an anatomical review to explain a clinical phenomenon. Cephalalgia. 2019. https://doi.org/10.1177/0333102419833076.
73. Choi JY, Park YM, Woo YS, Kim SU, Jung JM, Kwon DY. Perverted head-shaking and positional downbeat nystagmus in pregabalin intoxication. J Neurol Sci. 2014;337:243–4.
74. Oh S-Y, Kim JS, Lee YH, Lee AY, Kim J, Kim JM. Downbeat, positional, and perverted head-shaking nystagmus associated with lamotrigine toxicity. J Clin Neurol. 2006;2:283.
75. Arbusow V, Strupp M, Brandt T. Amiodarone-induced severe prolonged headpositional vertigo and vomiting. Neurology. 1998;51:917.
76. Scholtz AW, Steindl R, Burchardi N, Bognar-Steinberg I, Baumann W. Comparison of the therapeutic

efficacy of a fixed low-dose combination of cinnarizine and dimenhydrinate with betahistine in vestibular neuritis: a randomized, double-blind, non-inferiority study. Clin Drug Investig. 2012;32:387–99.
77. De Schutter E, Adham ZO, Kattah JC. Central positional vertigo: a clinical-imaging study. Prog Brain Res. 2019;249:345–60.
78. Phillips JS, Newman J, Cox S. Towards providing an automated approach to differentiating the nystagmus of ménière's disease, vestibular migraine, and benign paroxysmal positional vertigo. Otol Neurotol. 2021;42:890–6.

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