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Combined Central and Peripheral Degenerative Vestibular Disorders: CANVAS, Idiopathic Cerebellar Ataxia with Bilateral Vestibulopathy (CABV) and Other Differential Diagnoses of the CABV Phenotype

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Abstract
Purpose of Review The traditional dichotomy of central versus peripheral causes of imbalance may be viewed as an obstacle, rather than an aid to diagnosis. This paper aims to review the clinical assessment of conditions with combined central and peripheral vestibular impairment and the more common conditions which may manifest this joint pathology.
Recent Findings Cerebellar ataxia with bilateral vestibulopathy (CABV) was initially believed to be a distinct syndrome but has more recently been recognised as a phenotype which may be found in a number of disorders including CANVAS, Friedreich's ataxia, spinocerebellar ataxia types 3 and 6 and multiple system atrophy. Oculomotor assessment provides a valuable means of identifying such patients and centres around the identification of an abnormal visually enhanced vestibulo-ocular reflex.
Summary Identification of the CABV phenotype limits the differential diagnoses and then provides a directed investigation pathway.

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Introduction

Imbalance is one of the most common medical presentations globally [1, 2] with an overall incidence of 5–10%, imbalance effects 40% of people older than 40 years and the incidence of falls is 25% in those aged 65 and over [3]. Diagnosis of balance disorders is often challenging, with no single cause accounting for more than 5–10% of cases [4]. Traditionally, the fundamental diagnostic question has been whether the underlying pathology involves the vestibular system *or* the brain (generally the cerebellum and its connections). However, more recently, there is an increasing recognition of *combined* cerebellar and vestibular pathology.

Accurate and appropriate eye movements enable acquisition and maintenance of a stable image of our visual world. This in turn allows us as humans—a visually dependent organism—to safely and effectively navigate our environment. The vestibulo-ocular reflex (VOR) and smooth pursuit (SP) are vital to this process. In the assessment of patients with imbalance, oculomotor abnormalities are amongst our most helpful diagnostic tools [5]. Recent developments in diagnostic technology have meant that objective, portable and non-invasive oculomotor measurement is readily accessible [6, 7].

The VOR is an exquisitely sensitive, bilaterally coupled inner ear system for detecting head motion and rapidly conveying this to various components of the oculomotor system. The VOR essentially converts this information into rapid corrective eye movements that drives the eyes an equal amount, but in the opposite direction, to any relatively quick head movement. In doing so, the eye movement cancels out the

head movement and thus prevents the degradation of vision that would otherwise result from motion of the head relative to the visual target. The vestibulocerebellum is that part of the cerebellum that responds to stimuli important for motion detection, such as movement of the head or a visual target of interest [8]. The vestibulocerebellum is required to modulate the VOR, a plastic or 'learning' reflex. This adaptation improves vision by reducing the retinal slip that would otherwise result from head motion [9].

Visual-Vestibular Interactions

The eyes move for two reasons: (1) to be able to 'look' at a moving visual target, i.e. to fixate and (2) to 'look' at a new target, i.e. to refixate. Maintaining stable vision during head movement requires compensatory eye movements. These eye movement systems normally interact. In the case of VOR, the addition of visual input, such as smooth (SP), results in the visually enhanced vestibulo-ocular reflex (VVOR). Hence, VVOR is the addition of VOR *and* vision (i.e. SP) and functions to stabilise the image of an earth-fixed target while the subject is moving. VOR suppression (VORS) is a cerebellar-mediated function and usually acts to suppress VOR, so that gaze can be changed during head movement, such as following a moving target with eyes and head. In this way, VORS involves subtraction of the contribution of the VOR from eye movement. The study of VOR in isolation is a useful research metric, but in day-to-day visually guided tasks; the VOR is constantly interacting with other oculomotor reflexes. The process by which the VOR is informed by visual information, which then directs compensatory eye movements, occurs principally in the vestibular nuclei [10].

The Clinical Relevance of an Abnormal VVOR

In 1979, Baloh et al. demonstrated that an abnormal VVOR was present in patients with a compound deficit of cerebellar impairment and bilateral vestibular hypofunction [11]. Subsequently, other researchers have exploited this combined central and peripheral vestibular pathology in their work on vestibular physiology [12, 13].

In 2004, cerebellar ataxia with bilateral vestibulopathy (CABV) was described as a distinct clinical syndrome with the VVOR as its characteristic oculomotor deficit [14••]. Subsequently, a somatosensory deficit was identified in a large subset of CABV patients, and we defined a new clinical syndrome: cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) [15]. In our work on the VVOR, we found many patients with cerebellar ataxia and a bilateral vestibulopathy, who had diagnoses other than CANVAS, and so altered the use of the term 'CABV' from a *syndrome* to a *phenotype*, which could be seen in a number of diseases including spinocerebellar ataxia (SCA) types 3 and 6 [16, 17], Friedreich's ataxia (FA) [18••], multiple system atrophy with predominant cerebellar ataxia (MSAc) [17], Wernicke syndrome [19••] and combined pathology of independent aetiologies (for example, a patient with cerebellar degeneration and superimposed gentamicin vestibulotoxicity) [7].

An abnormality of the VVOR reflects a compound deficit of cerebellar *and* vestibular oculomotor control [11], (i.e. the three key compensatory eye movement systems: the VOR [vestibular], the optokinetic reflex and SP [both cerebellar]). An impaired VVOR can be demonstrated clinically by turning a patient's head slowly (at approximately 0.5 Hz) from side-to-side, while the patient's gaze is directed at an earth-fixed target (e.g. a coloured dot on a wall) and observing that the compensatory eye movements are saccadic rather than smooth. The VVOR is a simple, brief and reproducible bedside test [14••].

The emergence of this compound phenotype, CABV, provides reason to question the traditional anatomical delineation between peripheral and central vestibular causes of imbalance. The vestibular nuclei are located in the medulla, i.e. located outside the cerebellum, are not named as cerebellar nuclei, but are generally considered to be the anatomical equivalent of the deep cerebellar nuclei of the vestibulocerebellum [20]. The cerebellar nuclei and the lateral vestibular nucleus constitute the efferent or output pathways of the cerebellum [21]. Furthermore, the lateral vestibular nucleus does not receive vestibular root fibres, but rather, receives cerebellar input in the form of the Purkinje cell axons and is therefore often considered to be a cerebellar, rather than a vestibular nucleus [22]. Given the intimate developmental association of the cerebellar and vestibular nuclei, some consider the differentiation of the two to be somewhat contrived, or believe the distinction to be of limited functional value. This provides further basis for questioning the traditional *central* versus *peripheral* dichotomy, and whether this may be a somewhat artificial delineation, particularly in the sphere of the more complex balance disorders.

Gait ataxia, that is, a broad-based and unsteady gait, may be due to an impairment in any of the following: cerebellar, vestibular and somatosensory function. Similarly, any patient who presents with a diagnosis of an isolated bilateral vestibulopathy, cerebellar ataxia or a peripheral neuropathy (or neuronopathy) should be assessed for the presence of one or two of the other deficits. It then follows that in any patient presenting with an ataxic gait, that all three of these systems are evaluated. Cerebellar dysfunction is clinically assessed by examining for the presence of cerebellar oculomotor abnormalities (e.g. saccadic visual pursuit, gaze-evoked or downbeat nystagmus), cerebellar dysarthria, limb ataxia and atrophy may be seen on MRI (but may be absent in the earlier stages of a cerebellar disorder) [7]. The presence of a bilateral vestibulopathy is most readily seen at the bedside

during the head impulse test [23••] and identified objectively using modalities such as the video head impulse test, bithermal caloric irrigation or the rotational chair. Somatosensory impairment may manifest as abnormal or absent perception of one or more of light touch, pin prick, vibration or joint position sense. This is best evaluated objectively with a nerve conduction study looking for reduced or absent sensory nerve action potentials (SNAPs), as the bedside assessment of sensation is far from reliable [24]. The combination of cerebellar ataxia and a bilateral vestibulopathy can be seen during the oculomotor examination as a broken-up (or saccadic) VVOR [14••, 25]. Early and subtle VVOR abnormalities are more easily visualised with infra-red video-oculography or quantitatively with rapid video-oculography [7]—we find the rotational chair to be a less sensitive modality.

Conditions That May Present with the Cerebellar Ataxia with Bilateral Vestibulopathy Phenotype

Cerebellar Ataxia with Neuronopathy and Vestibular Areflexia Syndrome

CANVAS is comprised of the triad of the following: (1) cerebellar impairment, (2) bilateral vestibular hypofunction and (3) a neuronopathy (ganglionopathy) [7]. The process of uncovering such cases began with identifying patients with combined central and peripheral vestibular pathology, i.e. the CABV phenotype [26•]. Once the CABV patients were identified, neurophysiological testing was used to select those who had a third component of pathology—a somatosensory impairment [24]. In addition to an abnormal VVOR [7, 14••, 25], patients with CANVAS have deficits in peripheral sensory perception, including that of light touch, vibration or proprioception [15, 26•]. Patients primarily present with slowly progressive gait ataxia and somatosensory impairment which generally begins in the 5th to 7th (but may present as early as the 3rd) decades of life. Whilst there is no published clinical examination data regarding the sensory dysfunction of the geniculate or trigeminal ganglia, electrophysiological evidence of these cranial ganglionopathies exists [24]. Our group has seen over 90 patients with CANVAS. In addition to the triad of cerebellar impairment, bilateral vestibulopathy and somatosensory deficits, we do not uncommonly find autonomic dysfunction (e.g. orthostatic hypotension) and chronic cough [26•]. Importantly, the hearing is unaffected by CANVAS, and any hearing abnormalities are unrelated, such as presbycusis or noise-induced hearing loss [23••].

Neuropathology and otopathology revealed the clinicopathological correlates in CANVAS. Post-mortem studies have revealed a consistent pattern of cerebellar atrophy that preferentially involves the anterior and dorsal vermis (lobules VI, VIIa and VIIb) and laterally, predominantly involves the crus I region [15, 27]. Temporal bone otopathology has demonstrated the presence of a severe vestibular (Scarpa's) neuronopathy (ganglionopathy) as the cause of the bilateral vestibulopathy seen clinically in CANVAS. Additionally, the geniculate (facial) and trigeminal ganglia, but not the spiral (cochlear) ganglion, are similarly affected [28•]. The somatosensory deficit seen in CANVAS patients correlates with the marked neuronal loss seen in the dorsal root ganglia (DRG) [27]. The DRG neuronal loss causes axonal degeneration which is clinically apparent as reduced perception of sensation and electrophysiologically identifiable as reduced or absent SNAPs [24].

The pedigrees of multiple families with several affected members suggest a genetic aetiology (in at least a subset of the cohort) and is consistent with either an autosomal recessive or an autosomal dominant pattern of inheritance with incomplete penetrance [23••, 26•]. Based on the differential diagnoses for a patient who presents with the CABV phenotype in combination with electrophysiological evidence of peripheral sensory impairment, a diagnostic protocol was constructed, (in part, to exclude other causes of gait ataxia which may manifest with the same clinical triad as CANVAS, including several of the autosomal dominant spinocerebellar ataxias and late onset Friedreich's Ataxia) (Table 1) [23••].

Readers are referred to the following paper for information regarding the management of CANVAS [26•].

Friedreich's Ataxia

FA is the most commonly occurring inherited ataxia [29••]. FA is generally caused by a mutation in the gene encoding frataxin, which is located on chromosome 9q 26, and its heritability is autosomal recessive [30, 31••]. Prevalence varies between 2 and 4.5 per 100,000 [32]. Symptom onset generally occurs between 8 and 19 years of age [33, 34]; however, late onset FA begins later in adult life, with symptom onset after the age of 40 years [35]. A pathological hallmark of FA is progressive atrophy of the dentate nucleus of the cerebellum and is due to neuronal loss [29••]. FA involves widespread

Table 1 Key differential diagnoses for the CABV phenotype

Inherited
Friedreich's ataxia
Spinocerebellar ataxia (particularly SCA3, SCA6)
Cerebellar ataxia with neuronopathy and vestibular areflexia (CANVAS)[a]
Acquired
Multiple system atrophy with predominant cerebellar ataxia (MSAc)
Idiopathic cerebellar ataxia with bilateral vestibulopathy (iCABV)
Wernicke encephalopathy
*Consider dual pathology

[a] The mode of inheritance in CANVAS is yet to be established

neurodegenerative sequelae, involving corticospinal, dorsal column and spinocerebellar tract degeneration, and sensorineural hearing loss in approximately 20% [29••]. Mild cerebellar atrophy, particularly affecting the vermis, may be seen in advanced cases [36]. Clarke's columns are characterised by neuronal loss, and a dorsal root ganglionopathy also exists [37], which may underlie, at least in part, the proprioceptive component of the ataxia.

Oculomotor disturbances are common, and stable gaze fixation is often compromised by saccadic intrusions, which are most commonly square-wave jerks, but occasionally ocular flutter. VOR gain tends to be reduced in most [18••]. Scarpa's (vestibular) ganglia cell loss with vestibular nerve atrophy has been described, whilst the vestibular end organ and the facial nerve were unaffected. There is marked loss of spiral ganglion cells with a near normal organ of Corti [38, 39]. A somatosensory deficit (neuropathy or neuronopathy) is a common accompaniment in FA [29••].

Spinocerebellar Ataxia Type 3 (Machado-Joseph Disease)

SCA3 or Machado-Joseph disease is the main cause of autosomal dominant ataxia worldwide, comprising 20 to 50% of SCAs. Disease age of onset varies from childhood to late adult life, but in the majority of cases, symptoms start between 20 and 45 years of age [40, 41].

The cerebellum appears to be a particular target of abnormal gene expression [42]. MRI tends to visualise a combination of fourth ventricle enlargement, cerebellar vermal, hemispheric, superior cerebellar peduncle and pontine atrophy [43]. Macroscopic examination reveals atrophy of the cerebellum, pons, and cranial nerves III to XII [44]. Oculomotor manifestations include gaze-evoked nystagmus, slowing of saccades, saccadic dysmetria, square-wave jerks and rebound nystagmus [44, 45]. Impairment of the VOR is a common feature in SCA3 [46, 47••].

Hearing abnormalities have been reported in one third of SCA 3 patients tested [48•], and although there do not appear to be any published reports of otopathology in SCA 3 patients, Hoche et al. found widespread pathological involvement of the auditory brainstem nuclei as a possible explanation for these auditory abnormalities [49]. In addition to cerebellar ataxia, SCA 3 patients may present with the combination of reduced VOR gain and a peripheral sensory neuropathy [50].

Spinocerebellar Ataxia Type 6

SCA6 is a late onset slowly progressive cerebellar ataxia [51]. The mutation responsible for SCA6 is a CAG repeat (polyglutamine) expansion in the CACNA1A gene coding for a voltage-dependent calcium channel [52]. Alternative mutations of this gene are associated with episodic ataxia type 2 and familial hemiplegic migraine [53]. Disease onset for most patients is after 50 years of age, and disease progresses is relatively slow [54]. The late onset of symptoms may explain why SCA6 is found in approximately 10% of patients with apparently idiopathic sporadic cerebellar ataxia [55]. MRI changes are generally limited to cerebellar atrophy [54]. Oculomotor abnormalities include saccadic pursuit, square-wave jerks, saccadic dysmetria and downbeat nystagmus [56••]. Vestibular function in SCA6 patients has traditionally been reconsidered to be *either* normal [44], hypoactive [56••, 57] or hyperactive [58]. More recently, Huh et al. reported that the VOR gain in response to high acceleration, high frequency stimulation is increased in mild disease, whilst VOR gain is decreased in more severe disease [16]. Episodic vertigo is often present [56••], whilst peripheral sensory impairment is a more variable feature [59]. A recent study found a somatosensory deficit in 22% of SCA6 patients [50].

Multiple System Atrophy with Predominant Cerebellar Ataxia

Multiple system atrophy (MSA) encompasses the former diagnostic entities of olivo-pontocerebellar atrophy, striatonigral degeneration and Shy-Drager syndrome [60]. MSA is principally a sporadic disorder, although familial cases have been identified [61]. It is a degenerative disease causing various degrees of extra-pyramidal, pyramidal, cerebellar and autonomic features [62]. The contemporary classification of MSA is based on the predominant motor features at the time of assessment [63••]. They are (i) MSA with predominant parkinsonism (MSAp) and (ii) MSA with predominant cerebellar ataxia (MSAc). It is important to note that whilst divided on the basis of clinical phenotype, the presenting features often form a considerable degree of overlap. Additionally, the predominant motor presentation can alter with time [64]. The annual incidence of MSA is approximately 3 per 100,000 [65] with an estimated prevalence between two and five cases per 100,000 population [66, 67]. The male-to-female ratios range from 1.1:1 to 1.5:1.85 with a mean age of onset of 52 (range from 31 to 78) years [66, 67]. MSAp occurs two to four times as commonly as MSAc [68, 69] except in Japan, where MSAc occurs approximately twice as often [70]. Brain MRI in patients with MSA may reveal atrophy of the putamen, pons and middle cerebellar peduncles [71, 72]. Degeneration of transverse pontocerebellar fibres may give rise to the characteristic 'hot cross bun sign'; however, this sign lacks specificity and has been seen in other neurodegenerative conditions [71].

The following oculomotor abnormalities have been noted in MSA patients: excessive square-wave jerks, mild vertical supranuclear gaze palsy, gaze-evoked nystagmus, positioning downbeat nystagmus, saccadic hypometria, impaired SP and abnormal VOR suppression [73]. There is limited reference in the literature to the effect of MSA on the VOR, but it does appear that disruption of the cerebellum's descending

inhibition on the vestibular apparatus may lead to abnormalities in the VOR gain [73, 74]. We have found that VOR gain may be reduced in a subset of MSAc patients [17]. Whilst there do not appear to be any accounts of otopathological examination in MSAc patients, one study was unable to find any hearing impairment in 32 MSAc patients when compared to age-matched controls [75].

Wernicke Encephalopathy

Wernicke encephalopathy (WE) is an acute life-threatening syndrome which may complicate thiamine (vitamin B1) deficiency [76] and is most often associated with chronic alcoholism [77, 78]. Autopsy studies indicate a higher incidence of WE in the general population than recognised clinically [79, 80]. Wernicke's patients present with a range of central oculomotor abnormalities and not uncommonly with a bilateral vestibulopathy [81]. Given the known cerebellar involvement in WE, these patients may present with the CABV phenotype. Kattah et al. [19••] describe a series of patients who were not encephalopathic, that is, suffered with Wernicke disease, who had a bilateral vestibulopathy and this further emphasises the importance of recognising the oculomotor abnormalities in this group of ataxic patients.

CABV Due to Dual Pathology

The CABV phenotype may be the combination of two separate pathologies. For instance, a patient who suffered a cerebellar haemorrhagic stroke and then received parenteral gentamicin for sepsis, which was subsequently complicated by vestibulotoxicity. Whilst this patient has the combination of cerebellar ataxia and a bilateral vestibulopathy, they are not

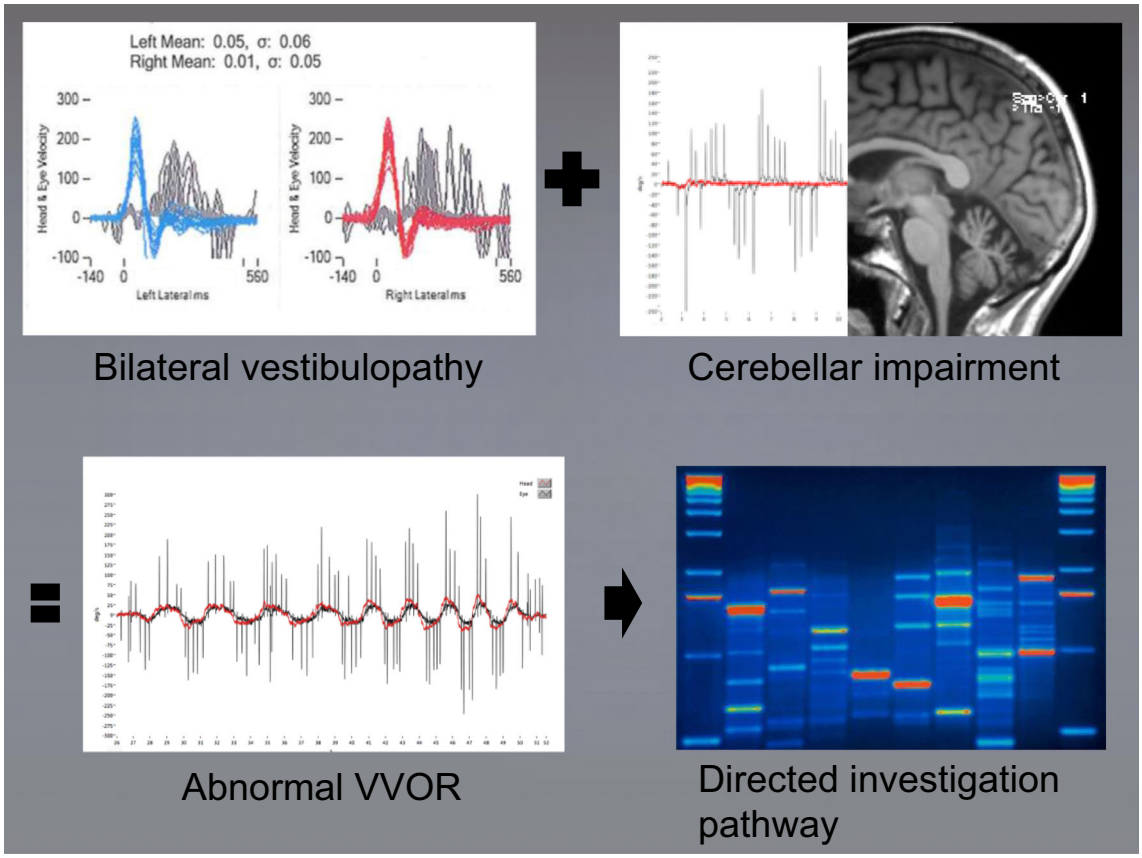

Fig. 1 The clinical utility of identifying the CABV phenotype. *Upper left panel*: bilateral vestibulopathy shown on horizontal impulsive testing recorded using an ICS impulse video-oculographic system (GN Otometrics, Taasstrup, Denmark). The head rotation stimulus is shown in *blue* and *red* (up to a peak angular velocity of 250°/sec and an angular acceleration of 2000°/sec^2); eye movement response is shown in *grey*. With horizontal impulses, the maximum gain of the VOR is less than 0.2 in each direction. There are overt catch-up saccades. *Upper right panel*: cerebellar impairment results in saccadic visual pursuit recorded using an ICS video-oculographic system (GN Otometrics, Denmark). There is no head rotation (*red*) as the eyes slowly pursue a slow moving target; salvos of corrective saccades are required (*black*). *Lower left panel*: impaired horizontal VVOR recorded using an ICS video-oculographic system (GN Otometrics, Denmark). The head rotation stimulus is shown in *red*, and the eye movement response is shown in *black*. The CABV patient makes salvos of catch-up saccades in response to a reduced VVOR gain. *Right lower panel*: identification of the CABV phenotype narrows the number of diagnostic possibilities, and hence, the investigation pathway, which includes genetic testing for certain spinocerebellar ataxias and Friedreich's ataxia

due to a shared aetiology. Other cases we have seen include haemorrhage into a cerebellar tumour complicated by superficial siderosis leading to bilateral vestibular hypofunction.

Idiopathic Cerebellar Ataxia with Bilateral Vestibulopathy

A not insignificant number of cases who have the CABV phenotype are unable to be diagnosed with a specific disorder or underlying aetiology. For these patients, we have coined the term 'Idiopathic Cerebellar Ataxia with Bilateral Vestibulopathy (iCABV)'. We have found that manifestation of the final component of the CANVAS diagnostic triad may take more than 10 years. We speculate that a proportion of CABV cases will go on to develop CANVAS, that is, *CANVAS in evolution* [26•]. It follows then, that an individual with the CABV phenotype should be reviewed at regular intervals to ascertain whether they go on to satisfy the diagnostic criteria for CANVAS (or indeed another disorder), i.e. develop a somatosensory deficit [23••]. It is possible that in time, other diagnostic entities which present with combined cerebellar and bilateral vestibular impairment will be recognised.

Conclusion

Once the CABV phenotype has been identified, it not only reduces the number of potential differential diagnoses but also outlines a diagnostic pathway as a means of obtaining a definitive diagnosis (Fig. 1). Combined cerebellar and peripheral vestibular dysfunction should be considered in any chronic, particularly progressive, gait ataxia. The presence of either a bilateral vestibulopathy or cerebellar ataxia should not preclude the investigation of the other, or indeed, a somatosensory deficit. The benefits of this approach include increased diagnostic accuracy, more targeted management and further elucidation of the interplay between these three systems in a range of balance disorders. The combination of developing more precise phenotypes and the expansion and increased availability of genetic testing, holds the promise of improved nosology, as a prelude to more definitive treatments.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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