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REVIEW

Deafness and Vestibulopathy in Cerebellar Diseases: a Practical Approach

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Abstract

Cerebellar ataxias are a clinically heterogeneous group of neurological disorders. Besides the cerebellum, several forms of hereditary ataxias or non-genetic ataxias also affect other areas of the brain. Some forms of cerebellar ataxias may have cochlear and vestibular involvement and may present with deafness and symptoms or signs of vestibulopathy (dizziness, nystagmus and diplopia). Recognizing otoneurological symptoms in patients with cerebellar ataxias is mandatory, since these signs may guide a specific diagnosis, and clinicians may provide a suitable therapeutic approach. In this review, we describe and discuss the most common forms of cerebellar ataxias associated with deafness and vestibulopathy.

Keywords Cerebellar ataxia · Hereditary ataxia · Deafness · Hearing loss · Vestibulopathy

Introduction

Cerebellar ataxias are a clinically heterogeneous group of neurological disorders that manifest with gait imbalance, dysarthria, dizziness, or dysphagia, due to dysfunction either of the cerebellum/brainstem or its afferent or efferent pathways [1]. The cerebellar ataxias are subdivided into six major groups: autosomal dominant spinocerebellar ataxias (SCAs), autosomal recessive ataxias, congenital ataxias, mitochondrial ataxias, X-linked cerebellar ataxias, and sporadic or acquired ataxias [2].

Besides the cerebellum, several forms of hereditary ataxias or non-genetic ataxias also affect other areas of the brain. A wide range of neurological symptoms may be observed in patients with cerebellar ataxias, such as dysarthria, oculomotor disturbances, extra-pyramidal signs, and also retinopathy, optic atrophy, peripheral neuropathy, dysautonomia, cognitive impairment, and epilepsy [3]. Pathophysiological mechanisms are heterogeneous and depend on the underlying etiology. Pathological studies in different forms of cerebellar ataxias have demonstrated involvement of extracerebellar regions, such as brainstem, basal ganglia, cranial nerve, thalamus, cerebral cortex, spinal cord, and peripheral nerves [4].

Some forms of cerebellar ataxias may have cochlear and vestibular involvement and may present with deafness and symptoms or signs of vestibulopathy (dizziness, nystagmus, and diplopia). Recognizing otoneurological symptoms in patients with cerebellar ataxias is mandatory, since these signs may guide a specific diagnosis, and clinicians may provide a suitable therapeutic approach [5]. In this review, we describe and discuss the most common forms of cerebellar ataxias associated with deafness and vestibulopathy. Some acquired cerebellar ataxias related to structural damage, such as stroke, tumors, or demyelinating diseases were not included in this review. The search terms in PubMed library included "ataxia and deafness", "ataxia and hearing loss", and "ataxia and vestibulopathy".

Ataxia and Deafness

Cerebellar ataxia and deafness may occur in several neurological diseases. Pathophysiological mechanisms may involve

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the cochlea and the vestibulocochlear nerve [5]. Table 1 shows the main causes of cerebellar ataxias associated with deafness.

Mitochondrial Disorders

Mitochondrial disorders (MD) are a group of heterogeneous diseases, usually with central nervous system (CNS) and multisystem involvement. Ataxia may be the dominant manifestation of MD, which includes pure cerebellar, sensory, or spinocerebellar ataxia, but sensorineural deafness is a usual additional feature. Differential diagnosis of MD with association of ataxia and deafness includes Kearns-Sayre syndrome, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes syndrome (MELAS), and POLG mutations [6].

Kearns-Sayre Syndrome

Kearns-Sayre syndrome is characterized by retinitis pigmentosa, progressive external ophthalmoplegia, cardiac conduction block, dilated cardiomyopathy, onset before the age 20, and cerebellar ataxia. Many patients also show progressive deafness, intellectual decline, epilepsy, and dystonia. This disease is due to large-scale deletions of the mtDNA [7].

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a rare mitochondrial disorder with onset in childhood. Other features associated with this syndrome are diabetes mellitus, short stature, cognitive impairment, and sensorineural hearing loss. There are descriptions of patients with an overlap syndrome with features of both Kearns-Sayre syndrome and MELAS [8].

Table 1 Main causes of cerebellar ataxias associated with deafness

Mitochondrial disorders
Kearns-Sayre syndrome
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
POLG-related disorders
Cerebellar ataxia due to coenzyme Q10 deficiency
Spinocerebellar ataxias (SCAs)
SCA31
SCA36
DNMT1 gene mutations (autosomal dominant cerebellar ataxia, deafness and narcolepsy)
Other hereditary ataxias associated with deafness
Refsum disease
Perrault syndrome
Wolfram syndrome
KCNJ10 gene mutations
Lichtenstein-Knorr syndrome
Sporadic ataxias associated with deafness
Superficial siderosis

Cerebellar Ataxia Due to Coenzyme Q10 Deficiency

Cerebellar ataxia due to coenzyme Q10 deficiency are a heterogeneous group of conditions with primary or secondary deficiencies related to genes encoding CoQ10 biosynthesis enzymes. Respiratory chain defects and apoptosis contribute to the pathogenesis of CoQ10 deficiencies. Clinical manifestations, including primary or secondary forms, are encephalopathy, myopathy, epilepsy, nephropathy, cerebellar ataxia, and deafness. In patients with ataxia and CoQ10 deficiency, treatment with CoQ10 may improve some of the symptoms and its prescription should be considered [9].

POLG-Related Disorders

Polymerase gama-1 is an enzyme involved with replication and maintenance of the mtDNA. Mutation in POLG can cause late-onset syndromes from mtDNA deletions. *POLG*-related disorders comprise many different phenotypes, including Alpers-Huttenlocher syndrome, childhood myocerebrohepatopathy spectrum, mitochondrial recessive ataxia syndrome (MIRAS), sensory neuropathy dysarthria and ophthalmoplegia (SANDO), and autosomal dominant or autosomal recessive progressive external ophthalmoplegia (PEO). PEO phenotypic manifestations include myopathy, sensorimotor polyneuropathy, hypogonadism, parkinsonism, cataracts, and sensorineural hearing loss [10].

Spinocerebellar Ataxias

Spinocerebellar ataxias (SCAs) is a group of heterogeneous neurodegenerative disorders with autosomal dominant inheritance that involve the cerebellum and its connections. Different types of SCAs have peculiar clinical features other than ataxia symptoms, including deafness. Particularly in SCA 31, 36, and *DNMT1* mutations, deafness is highly associated with cerebellar findings. SCA31 (pure cerebellar ataxia and deafness) and SCA 36 (deafness, face and tongue fasciculations) are very rare subtypes of SCAs [11, 12].

DNMT1 gene mutations cause autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN). This disease usually presents with moderate to severe early sensorineural hearing loss beginning in the teens or early 20s. De novo *DNMT1* pathogenic variants may occur, and family history may be unremarkable [13].

Other Hereditary Ataxias Associated with Deafness

Refsum disease is a rare autosomal recessive disorder of fatty acid metabolism and it is secondary to mutation of peroxisomal enzyme phytanoyl-CoA hydroxylase gene. The major clinical manifestations are ataxia, polyneuropathy, retinitis pigmentosa, and high cerebral spinal fluid protein. Other findings include ichthyosis, anosmia, cardiomyopathy, and deafness. Histological studies have located the site of hearing impairment in the inner ear. The serum biomarkers of Refsum disease are elevated levels of phytanic acid [14].

Perrault syndrome is characterized by sensorineural hearing loss and ovarian dysfunction in females. Some patients with PS may have learning difficulties, peripheral neuropathy, and cerebellar ataxia. The diagnosis is confirmed by the presence of mutations in one of the six different genes (*HARS2*, *CLPP*, *ERAL1*, *HSD17B4*, *LARS2*, and *TWNK*) [15].

Wolfram syndrome is a rare autosomal recessive disorder characterized by the combination of diabetes mellitus, diabetes insipidus, optic atrophy, and deafness. Some patients with WS may have other symptoms like neuropsychiatric manifestations, ataxia, and urinary disorders. Brain MRI in WS may depict brain stem and cerebellar atrophy [16].

KCNJ10 mutation is a non-progressive congenital ataxia characterized by ataxia, epilepsy, sensorineural deafness, and tubulopathy. Usually, brain MRI is normal. (8) *NEUROD1* mutation is also a non-progressive congenital ataxia presenting neonatal diabetes, deafness, ataxia, and myopia. Brain MRI is characterized by cerebellar hypoplasia [17].

Lichtenstein-Knorr syndrome is a rare autosomal recessive disease caused by SLC9A1 gene mutations that causes progressive sensorineural hearing loss and cerebellar ataxia [18].

Cerebellar ataxia, areflexia, *pes cavus*, optic atrophy, and sensorineural hearing loss (CAPOS) are autosomal dominant diseases caused by *ATP1A3* gene mutations. Deafness is usually part of the clinical features in patients with *ATP1A3* gene mutations presenting as CAPOS syndrome, although other phenotypes, such as alternating hemiparesis or dystonia, are more common [19].

Other ataxias that may rarely present with deafness include Friedreich ataxia (patients may present with auditory neuropathy), Creutzfeldt-Jakob disease, and Wernicke's encephalopathy [20–22].

Sporadic Ataxias Associated with Deafness

Superficial siderosis of the central nervous system is characterized by deposition of hemosiderin in the leptomeninges, usually caused by chronic bleeding in subarachnoid space. The most vulnerable regions for deposition of hemosiderin are cochlear nerve and cerebellar cortex. The most common causes of chronic bleeding in superficial siderosis include aneurysms, cervical trauma, post-surgery, tumors, and arteriovenous malformations. Neurological symptoms and signs are characterized by deafness, progressive ataxia, and pyramidal signs. Variable degrees of cognitive impairment, anosmia, and anisocoria may occur. Brain MRI, particularly T2W*, shows hypointense rim in the leptomeninges around the cerebellum, brainstem, cranial nerves, cerebral hemispheres, and spinal cord. Cerebrospinal fluid commonly reveals hemorrhage and xanthochromia (Fig. 1) [23].

Figure 2 is an algorithm that may guide the clinical approach for patients that present with ataxia associated with deafness.

Vestibulopathy and Ataxias

Involvement of the vestibulo-cerebellar or cerebellar ocular motor systems may cause dizziness, vertigo, and oculomotor abnormalities in patients with cerebellar ataxias [5, 24]. In this section, we will summarize the main cerebellar ataxias associated with vestibulopathy.

Cerebellar Ataxia with Neuropathy and Bilateral Vestibular Areflexia Syndrome

Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS) is a novel ataxic disorder that

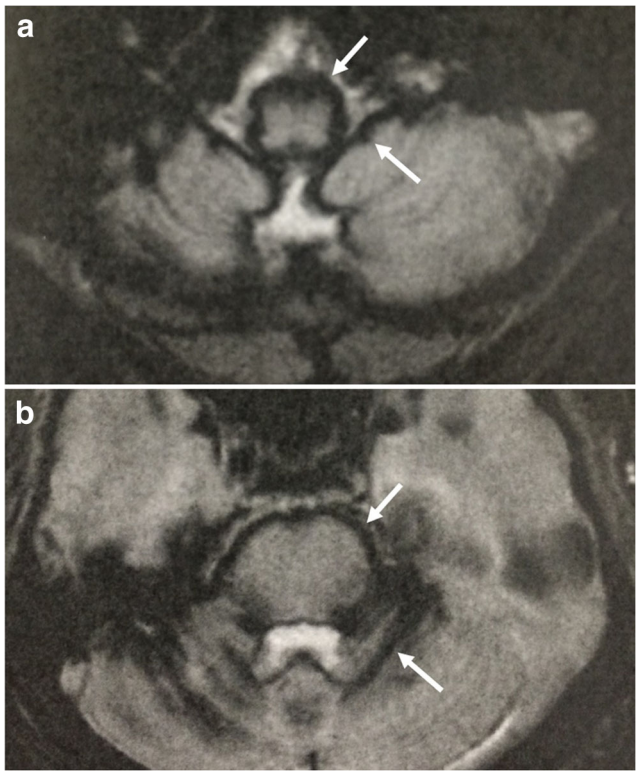

Fig. 1 Axial T2W*-weighted brain MRI of a patient with superficial siderosis shows hypointense rim in the leptomeninges around the cerebellum and brainstem, characterizing hemosiderin deposition

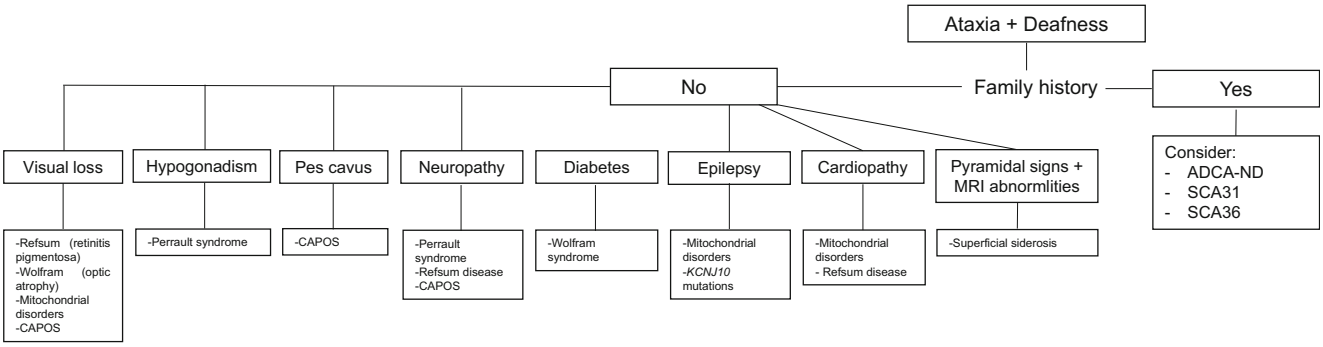

Fig. 2 Algorithm for clinical approach for patients that present with ataxia associated with deafness

consists of the triad of cerebellar impairment, bilateral vestibular hypofunction, and somatosensory deficit [25, 26]. Clinical symptoms are gait imbalance (worse in the dark), lower limb dysesthesia, oscillopsia, dizziness, and intrinsic falls [25, 26]. The mean age of symptom onset is 60 years and no sex difference exists [27]. The onset of the final component of the triad may take more than 10 years in patients with two components, such as cerebellar ataxia and bilateral vestibulopathy [28].

Most cases can be clinically diagnosed, and the characteristic clinical sign is the impaired visually enhanced vestibulo-ocular reflex (VVOR), which represents the combined impairment of the three compensatory eye movement reflexes: vestibulo-ocular reflex (VOR), smooth pursuit, and optokinetic reflex [29]. Nystagmus is also one of the clinical features, such as downbeat nystagmus, horizontal gaze-evoked nystagmus, and vertical gaze-evoked nystagmus [25, 26]. Bilateral vestibulopathy can be identified by caloric stimulation and video head impulse test (vHIT). Caloric responses are absent or severely reduced in patients with CANVAS [30]. CANVAS patients have a non-length-dependent, multi-modality sensory deficit. Nerve conduction studies show widespread reduction of sensory nerve action potential amplitudes in these patients, while motor nerve conduction is almost completely preserved. Such pattern suggests that sensory deficits in CANVAS are due to posterior neuronopathy (ganglionopathy) [27]. MRI reveals anterior and dorsal vermian atrophy (vermal lobules VI, VIIa, and VIIb) and lateral hemispheric atrophy predominantly affecting crus I (which corresponds to vermal lobule VII) but no pontine atrophy [25, 26].

Regarding genetics and histopathology features, the existence of affected sibling pairs suggests that CANVAS is a late-onset recessive disorder [25]. Recently, British investigators found homozygous intronic pentanucleotide repeat expansions to underlie most cases of CANVAS [31]. Post-mortem histopathological studies showed marked loss of Purkinje cells (predominantly in the vermis and lateral cerebellum) and of Scarpa's, trigeminal, and facial ganglion cells but not of spiral ganglion cells. The auditory nerve, vestibular end organs (cristae and maculae), and brainstem were unaffected. These findings indicated that vestibular areflexia is due to ganglionopathy [32]. Treatment is supportive with combination of neurological and vestibular rehabilitation [28].

Spinocerebellar Ataxias and Friedreich's Ataxia

Vestibular dysfunction has been also reported in other more prevalent inherited ataxias, either autosomal dominant (spinocerebellar ataxias (SCAs)) or recessive (ARCA) [33]. SCAs are a genetically heterogeneous group characterized by slowly progressive ataxia, usually accompanied by extracerebellar features. The most frequent subtype is SCA3 or Machado–Joseph disease, followed by SCA2, SCA1, and SCA6 [34]. Friedreich's ataxia is the most frequent autosomal recessive ataxia and typically characterized by early onset [35].

In a recent Brazilian study, Zeigelboim et al. found abnormal findings in the vestibular evaluation in both types of hereditary ataxias (SCAs and Friedreich's ataxia) [36]. Vestibular hyporeflexia and saccadic dysmetria were more prevalent in SCAs when compared with ARCAs (namely Friedreich's ataxia)—73.2% vs 47.3% and 62.5% vs 15.7%, respectively. In addition, multiple semi-spontaneous nystagmus and asymmetrical optokinetic nystagmus were found in 50% and 29% of the patients with SCAs, respectively, while only 36.8% of the subjects with ARCA presented each of these abnormalities [37]. These results indicate that central vestibular dysfunction takes place in both groups of ataxias. Lately, some authors provided evidence using vestibular myogenic evoked potentials that peripheral pathways emerging from the otoliths are also damaged in SCA3. These authors found abnormal results in 93% of patients tested [38, 39].

Degeneration of central vestibular nuclei and connections probably underlie central vestibular dysfunction in these patients. Neuroimaging studies in SCAs indeed found atrophy of infratentorial structures, especially pons, medulla, and spinal cord to be a conspicuous feature [37, 39]. In addition, anatomopathological studies revealed that the vestibular complex and its association fibers were targets of neurodegeneration in patients with SCA [40]. Similarly, Friedreich's ataxia is

associated with gliosis of vestibular and auditory systems, especially at the level of the medial vestibular, cochlear, and superior olivary nuclei [41]. Thus, the neuropathological damage may explain part of the postural instability with imbalance, oculomotor deficits, and the presence of the pathological vestibulo-ocular reflex in these patients.

Conclusions

Otoneurological findings—deafness and vestibular dysfunction—are often found in inherited cerebellar disorders. For some specific subtypes of ataxias, such as CANVAS, recognition of these manifestations is of utmost importance for proper diagnosis. Despite that, few systematic studies on the frequency, clinical relevance, and mechanisms underlying these manifestations are very scarce. Multidisciplinary studies combining neurologists and otorhinolaringologists should be implemented to address these unanswered questions. Such efforts will lead to better understanding of these diseases and possibly to more effective therapies.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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