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OTOLOGY

Electrophysiological and inner ear MRI findings in patients with bilateral vestibulopathy

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Abstract

Purpose Bilateral vestibulopathy (BV) is an uncommon disorder and the etiology remained idiopathic in most cases. Delayed 3D-FLAIR sequences have provided new insights into various inner ear diseases, allowing the evaluation of the endolymphatic space and the permeability of the blood–labyrinthine barrier (BLB). The aim of this study was to assess both the morphology of the endolymphatic space and the permeability of the BLB in patients with BV as evaluated by delayed 3D-FLAIR sequences.

Methods In this retrospective study, we performed 3D-FLAIR sequences 4 h after administering contrast media to 42 patients with BV. Two radiologists independently evaluated the morphology of the endolymphatic space (either vestibular atelectasis or endolymphatic hydrops) and the permeability of the BLB.

Results Morphologic anomalies of the endolymphatic space and vestibular blood–labyrinthine barrier impairment were observed in 59.6% of patients with BV. Bilateral vestibular atelectasis (VA) was found in 21 patients (50%), involving only the utricle and all three ampullas while the saccule was always observed with no sign of collapse: idiopathic BV ($n=19$), aminoglycoside administration ($n=1$) and few days following abdominal surgery ($n=1$). One patient had bilateral vestibular malformation. BLB impairment was observed in five patients (11.9%): paraneoplastic ($n=1$), lymphoma ($n=1$), autoimmune ($n=1$), and vestibular "neuritis" ($n=2$). Seventeen patients (40.4%) had normal MRI with no endolymphatic space anomaly or BLB impairment.

Conclusion Patients with BV presented with morphologic anomalies of the endolymphatic space or BLB impairment in 59.6% of patients.

Keywords MRI · Vestibular atelectasis · Vestibular neuritis · Bilateral vestibulopathy · Inner ear

Introduction

In 1941, Dandy described oscillopsia and postural instability exacerbated by visual deprivation in patients with Menière's disease who underwent bilateral vestibular neurectomy [1]. Later, the term Dandy's syndrome was used to describe patients with idiopathic bilateral vestibulopathy and without hearing loss [2, 3].

BV is an uncommon disorder and the prevalence has been estimated to be 28/100,000 [4]. It has been reported that BV causes a high decrease in quality of life [5]. Bilateral impairment of the peripheral vestibular organ leads to deficits in the vestibulo-spinal reflex causing imbalance during standing and locomotion. Moreover, it also leads to the vestibulo-ocular reflexes (VOR) deficit which causes oscillopsia during head movement due to the reduced gain of the VOR.

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The origin of BV remains controversial and the most commonly identifiable causes of BV are toxic (ototoxic drugs, vitamin deficiency), bilateral Menière's disease, paraneoplasic, cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), autoimmune, and meningitis [6, 7]. However, it has been shown that in 20–51% of cases, the etiology remained idiopathic [8].

3D-FLAIR sequences performed 4 h after an intravenous administration of gadolinium have provided new insights into various vestibular diseases. It allows the distinction between the utricle and the saccule on delayed 3D-FLAIR sequences, which is crucial for the diagnosis of endolymphatic hydrops that relies mostly on saccular dilatation [9–12]. Recently, Eliezer et al. have reported four patients with unilateral vestibular atelectasis (VA) in patients with atypical unilateral vestibular loss function [13]. Delayed 3D-FLAIR sequences also evaluate the permeability of the blood–labyrinthine barrier, which could be impaired in several diseases, such as otosclerosis, Menière's disease, and acute vestibular syndrome [14–16].

The aim of this study was to assess both the morphology of the endolymphatic space and the permeability of the blood–labyrinthine barrier in patients with BV, as evaluated by delayed 3D-FLAIR sequences.

Methods

Patients

This was a single-center retrospective imaging study (Commission Nationale de l'Informatique et des Libertés, CNIL 2215065) conducted between January 2017 and January 2019. Patients with BV were included based on the latest diagnostic criteria of the Barany Society [3]: (1) chronic vestibular syndrome when walking or standing and worsening in darkness and/or uneven ground; (2) no symptoms while sitting or lying down under static conditions; (3) bilaterally pathological horizontal vestibulo-ocular reflex (VOR) gain < 0.6 measure by VHIT and/or reduced caloric response.

The etiology for the BV was evaluated based on subjects' medical history, clinical examination, and laboratory test: history of exposure to ototoxins (e.g., antibiotics), otologic disorder (e.g., Menière's disease, vestibular "neuritis") and other neurologic (e.g., migraine), autoimmune and neoplastic disorders. All subjects underwent complete clinical examination, including ocular examination performed with three-dimensional infrared video-oculography and evaluation for spontaneous nystagmus, gaze-evoked nystagmus, head-shaking nystagmus, sound and/or pressure-induced nystagmus.

Video head impulse test (VHIT)

The VHIT was recorded using a lightweight portable VHIT device (Hardware: ICS Impulse, GN Otometrics, Taastrup, Denmark, Software: Otosuite® vestibular software). At least five head impulses were performed in the axis of each semicircular canal.

Cervical vestibular evoked myogenic potentials (cVEMPs)

During the test recordings, all subjects were asked to rotate their head away from the stimulated side. Surface electromyogram (EMG) activity was recorded with superficial electrodes. Tone bursts (90 dB nHL, 500 Hz) were presented through headphones. The amplitude of the first positive–negative peak (P13–N23) was recorded. Absence of a meaningful waveform with p13 and n23 was defined as 'No response'.

Ocular vestibular evoked myogenic potentials (oVEMPs)

During the test recordings, all subjects were asked to look straight up at a small fixed target above them. The active electrodes were placed on the face, below the center of the lower eyelid. The reference electrode was placed about 1 cm below the active electrode on the cheek, and the ground electrode was placed on the forehead. Tone bursts (95 dB nHL, 500 Hz) were presented through headphones. The initial negative–positive biphasic waveform comprised peaks N1 and P1. An absence of a meaningful waveform with N1 and P1 was defined as 'No response'.

Imaging

MRI examinations were carried out on a 3 T scanner (3 T Siemens Skyra®) with a 64-channel head–neck–spine coil. All patients underwent an MRI scan 4 h after a single intravenous dose of gadobutrol (Gd-DO3A-butrol, Gadovist® 0.1 mmol/kg, 1 mmol/mL) that provided a high contrast in the labyrinth [17]. We performed the 3D-FLAIR with the following parameters: FOV 140 × 140 mm, TR 10,000 ms, TE 641 ms, TI 2600 ms, 276 × 256, flip angle 140°, nex 2, GRAPPA 2 and scan time of 7 min 50 s. We also performed a 3D-T2 SPACE sequence with the following parameters: FOV: 160 × 160 mm, TR: 1470 ms, TE: 310 ms, 384 × 345, flip angle: 120°, nex: 2, GRAPPA: 2 and scan time of 5 min 56 s.

Imaging analysis

Images for each subject were evaluated independently with Osirix MD® by two readers who were blinded to the clinical data (ME and AA senior radiologists with certificates of added qualification in head and neck imaging).

The presence of the following structures was verified on the 3D-FLAIR sequence (Fig. 1):

- The saccule: the saccule appears as an area of low signal. It is located on the medial and anterior wall of the vestibule underneath the level of the lateral semicircular canal [18, 19].
- The utricle: the utricle appears as an elliptical zone of low signal at the level of the lateral semicircular canal. It occupies the superior part of the vestibule [18, 19].
- The membranous ampulla of each canal.

Based on the imaging study of Eliezer et al., we considered vestibular atelectasis of the pars superior on MRI when the utricle and at least two ampullas were not visible or barely visible [13]. By contrast, we considered the pars inferior as collapsed on MRI when the saccule was not visible [9].

We graded saccular hydrops using the SURI technique defined as the ratio between the area of the saccule and the area of the utricle, as evaluated in axial and sagittal slice on one reference image [9–12].

The presence of cochlear and vestibular blood–labyrinthine barrier (BLB) impairment was also evaluated and was defined as a marked enhancement in the perilymph of the basal turn of the cochlea, the vestibule and/or the semicircular canals as previously reported [14–16]. We also performed a visual assessment based on the presence of a low signal of the labyrinthine structures on 3D-T2 SPACE sequences since it has been suggested that patients with unilateral vestibular syndrome could present intralabyrinthine fibrosis [14].

Statistical analysis

Data were analyzed using R software v3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria).

The inter-reader agreement in detecting VA, saccular hydrops, and asymmetrical enhancement of the labyrinthine structures from the 3D-FLAIR sequence was estimated using Cohen's kappa coefficient (k). We considered a k value greater than 0.80 to indicate a very good agreement and less than 0.2 as a very poor agreement [20]. Continuous data are presented as the mean with a standard deviation.

Results

Population

All patients' characteristics are listed in Table 1.

Forty-two patients with BV (15 men) with a mean age of 60 ± 17 years were included in this study. The mean duration of symptoms was 4.3 ± 4.9 years ranging from 10 days to 10 years.

The definitive etiology of BV was determined in only 12 out of 42 patients (28.5%): leptomeningeal carcinomatosis ($n=1$), paraneoplastic ($n=1$), autoimmune ($n=1$), aminoglycoside toxicity ($n=2$), immediate post-operative period ($n=3$), inner ear malformation ($n=1$), and bilateral sequential vestibular "neuritis" ($n=3$). The etiology remained idiopathic in 30 patients (71.4%). Eight patients (18.6%) met the International Headache Society criteria for migraine and all of them had the diagnosis of idiopathic BV. Only three patients with idiopathic BV had a history of loud sound-induced nystagmus (Tullio) and no patients had pressure-induced nystagmus.

Vestibular tests

The mean VOR gains for the superior, lateral, and posterior semicircular canals were 0.58 ± 0.19, 0.50 ± 0.21, and 0.32 ± 0.25, respectively, on the right side and 0.48 ± 0.33, 0.49 ± 0.11, and 0.26 ± 0.25 on the left side. Twenty-seven out of 43 patients (62.8%) had bilateral impairment of all three semicircular canals.

Twelve patients had normal anterior VOR gain (nine right-sided, three left-sided, two bilateral), two had normal posterior VOR gain (one right-sided, one left-sided): idiopathic BV ($n=9$), bilateral sequential vestibular neuritis ($n=2$), and inner ear malformation ($n=1$).

Thirty-seven patients had oVEMP impairment: 34 patients had bilateral while three patients had unilateral oVEMP impairment (2 right-sided and 1 left-sided).

Sixteen patients had cVEMP impairment: 11 patients had bilateral while 5 patients had unilateral cVEMP impairment (1 right-sided and 4 left-sided).

MRI data (Table 1)

Seventeen patients had normal MRI with no endolymphatic space anomaly or BLB impairment: fifteen patients had idiopathic BV, two patients developed BV 2 weeks after orthopedic surgery, one patient had a history of aminoglycoside administration, and one patient had sequential bilateral vestibular neuritis. Eight of these patients had a complete semicircular canals hypofunction. Eleven of these patients had oVEMP dysfunctions: ten patients had bilateral

Table 1 Clinical and radiological characteristics in patients with BV

Patient	Age	Sex	Delay (years)	Familial History	Tullio	Migraine	VOR (gain)						oVEMP		cVEMP		FLAIR		T2-w Fibrosis	Etiology
							Right			Left							VA	BLB impairment		
							S	L	P	S	L	P	R	L	R	L				
1	49	F	2	0	0	1	0.27	0.13	0.54	0.5	0.24	0.23	A	A	A	A	0	0	0	I
2	56	M	0.03	0	0	0	0.12	0.04	0.16	0.08	0.23	0.16	A	A	A	A	1	0	0	I
3	65	M	0.16	0	0	0	0.2	0.1	0.2	0.2	0.15	0.3	A	A	A	A	0	1	0	Paraneoplastic
4	57	F	0.03	0	0	0	0.22	0.18	0.2	0.37	0.13	0.34	A	A	A	A	0	1	0	Autoimmune
5	71	F	0.25	0	0	0	0.59	0.57	0.27	0.46	0.41	0.54	A	A	N	N	0	0	0	Surgery
6	41	F	5	1	0	0	0.38	0.15	0.23	0.11	0.10	0.3	A	A	N	N	1	0	0	I
7	55	M	0.25	0	1	0	0.51	0,57	0.55	0.54	0.47	0.47	A	A	N	N	1	0	0	I
8	33	F	3	0	0	0	0.72	0.44	0.44	0.6	0.53	0.49	A	A	N	N	1	0	0	I
9	56	M	0.58	0	0	0	0.1	0.1	0.1	0.1	0.1	0.1	A	A	A	A	1	0	0	Surgery
10	63	M	7	0	0	0	0.51	0.24	0.34	0.34	0.37	0.22	A	A	N	N	1	0	0	I
11	48	M	2	0	0	1	0.1	0.4	0.1	0.1	0.5	0.5	N	A	N	A	1	0	0	I
12	71	M	7	0	0	0	0.16	0.32	0.26	0.12	0.5	0.33	A	A	A	A	1	0	0	I
13	29	F	2	0	0	1	0.74	0.6	0.63	0.5	0.6	0.58	A	A	N	N	1	0	0	I
14	62	M	2	0	0	0	0.38	0.26	0.33	0.59	0.49	0.18	A	N	N	A	0	0	0	I
15	62	F	4	0	0	0	0.46	0.49	0.12	0.49	0.39	0	A	N	N	N	1	0	0	I
16	64	F	15	0	0	0	0.49	0.33	0	0.43	0.34	0.07	A	A	N	N	1	0	0	I
17	73	F	2	0	0	0	0.52	0.15	0.39	0.23	0.26	0.36	A	A	N	N	0	0	0	I
18	82	F	10	0	0	0	0.24	0.12	0.31	0.13	0.07	0.18	N	N	N	N	0	0	0	I
19	62	F	2	0	0	0	0.1	0.5	0.2	0	0.4	0.4	A	A	A	N	0	0	0	I
20	79	F	15	0	0	0	0.64	0.19	0.14	0	0.32	0.44	A	A	N	N	1	0	0	Aminoglycoside
21	71	M	2	0	0	0	0.31	0.5	0.3	0.4	0.5	0.3	A	A	N	N	0	1	1	"neuritis"
22	45	M	0.5	0	0	0	0.69	0.6	0.24	0.53	0.57	0.51	N	N	N	N	0	0	0	Waardenburg
23	44	M	1	0	0	1	0.65	0.56	0.37	0.32	0.27	0.6	A	A	N	N	1	0	0	I
24	47	F	0.5	0	0	0	0.93	0.6	0.57	0.58	0.56	0.62	N	N	N	N	1	0	0	I
25	66	M	0.16	0	0	0	0.52	0.48	0,67	0,47	0.59	0.17	A	A	A	A	0	1	1	"neuritis"
26	50	F	8	0	0	0	0.4	0.49	0.37	0.75	0.6	0.6	A	A	N	N	1	0	0	I
27	70	F	0.4	0	0	0	0.17	0.23	0.06	0.18	0.14	0.25	A	A	A	A	0	1	0	Lymphoma
28	70	F	2	0	0	1	0.63	0.9	0.3	0.36	0.34	0.56	A	A	A	A	0	0	0	I
29	60	M	8	1	0	0	0.98	1	0.61	0.66	0.52	0.52	N	N	N	N	0	0	0	I
30	84	F	3	0	0	0	0.4	0.23	0.26	0.41	0.39	0.51	A	A	N	N	0	0	0	Surgery
31	71	M	6	0	1	1	0.42	0.48	0.59	1	0.9	0.55	A	N	N	N	1	0	0	I
32	43	F	2	0	0	0	0.48	0.18	0.15	0.24	0.09	0.5	A	A	N	N	1	0	0	I
33	78	F	7	0	0	0	0.34	0.32	0.1	0.34	0.17	0.23	A	A	N	A	0	0	0	I
34	57	F	4	0	0	0	0.81	0.57	0.2	0.14	0.49	0.82	A	A	N	N	0	0	0	"neuritis"
35	67	F	3	0	0	0	0.73	0.59	0.32	0.52	0.53	0.49	A	A	A	A	0	0	0	I

Table 1 (continued)

Patient	Age	Sex	Delay	Familial	Tullio	Migraine	VOR (gain)						oVEMP		cVEMP		FLAIR			T2-w	Etiology
							Right			Left							VA	BLB		Fibrosis	
			(years)	History			S	L	P	S	L	P	R	L	R	L		impairment			
36	63	F	0.1	0	0	1	0.8	0.48	0.47	0.55	0.42	0.9	A	A	N	N	0	0		0	I
37	65	M	3	0	0	0	0.3	0.41	0.46	0.01	0.46	0.43	A	A	N	N	1	0		0	I
38	45	M	2	0	1	0	0.47	0.91	0.39	0.54	0.6	0.48	N	N	N	N	1	0		0	I
39	85	F	20	0	0	0	0.39	0.36	0.39	0.56	0.28	0	A	A	N	N	0	0		0	I
40	51	M	18	0	0	0	0.54	0.88	0.36	0.43	0.74	0.45	A	A	N	N	1	0		0	I
41	66	F	6	0	0	0	0.53	0.36	0.47	0.5	0.31	0.44	A	A	A	N	0	0		0	Aminoglycoside
42	30	F	2	0	0	1	0.38	0.34	0.24	0.8	0.59	0.79	A	A	N	A	1	0		0	I

M male, *F* female, *Y* years, *R* right, *L* left, *S* superior, *L* lateral, *P* Posterior, *L* lateral, *N* normal, *A* abnormal, *I* idiopathic

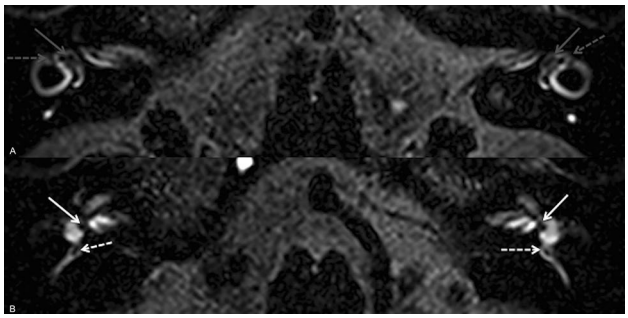

Fig. 1 **a** Axial 3D-FLAIR at the level of the utricle (gray arrow) and the lateral ampulla (gray dotted arrow) showed normal endolymphatic structures and no BLB impairment. **b** Axial 3D-FLAIR at the level of the saccule (white arrow) and the posterior ampulla (white dotted arrow) demonstrated normal endolymphatic structures and no BLB impairment

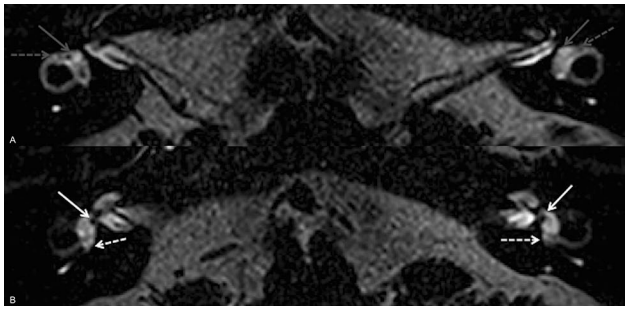

Fig. 2 **a** Axial 3D-FLAIR showing bilateral collapsed utricle (gray arrow) involving also the lateral ampulla (gray dotted arrow). The right utricle is barely visible while the left utricle is absolutely not visible. **b** Axial 3D-FLAIR at the level of the saccule (white arrow) and the posterior ampulla (white dotted arrow) showed a bilateral collapsed posterior ampulla while the saccule appeared normal on both sides

while one patient had unilateral oVEMP impairment (right-sided). Seven of these 16 patients had cVEMP impairment: 3 patients had bilateral while 4 patients had unilateral oVEMP impairment (2 right-sided, 2 left-sided).

Endolymphatic space morphology

Bilateral VA involving the utricle and all three ampullas was found in 21 out 42 patients (Fig. 2): 19 patients with idiopathic BV, 1 patient who had aminoglycoside administration and 1 who was diagnosed 10 days after abdominal surgery. The saccule was always observed with no sign of collapse. Nineteen patients with bilateral VA, had oVEMP dysfunction: 16 patients had bilateral oVEMP impairment while 3 patients had unilateral oVEMP impairment (2 right-sided, 1 left-sided). Two patients with idiopathic VA had bilateral VA and no oVEMP impairment. cVEMP impairment was

found in only 5 of these 21 patients: 2 patients had bilateral and 2 patients had unilateral saccular dysfunction.

Normal unilateral anterior VOR gain was only found in patients with bilateral VA.

One patient had bilateral superior and posterior semicircular canals, partial agenesis, and lateral semicircular dysplasia with a left enlarged space filled with endolymph. He had no utricular response on both sides, yet both saccular responses remained normal. Based on imaging findings, this patient was suspected of Waardenburg syndrome (Fig. 3).

None of these patients with endolymphatic space anomalies had endolymphatic hydrops or BLB impairment.

The inter-reader agreement was 0.86 for VA evaluation.

Blood–labyrinthine barrier assessment

BLB impairment was observed in five patients with no sign of endolymphatic hydrops or VA. Both bilateral cochlear and vestibular BLB impairment was observed in three patients (Fig. 4). There was a bilateral marked enhancement of the cochlea, the vestibule, and all three semicircular canals. One of these three patients had a gastric tumor, one patient had a lymphoma and another patient was treated by immunotherapy for lung cancer in remission since 3 years. These three patients had bilateral saccular and utricular impairment on cVEMP and oVEMP, respectively.

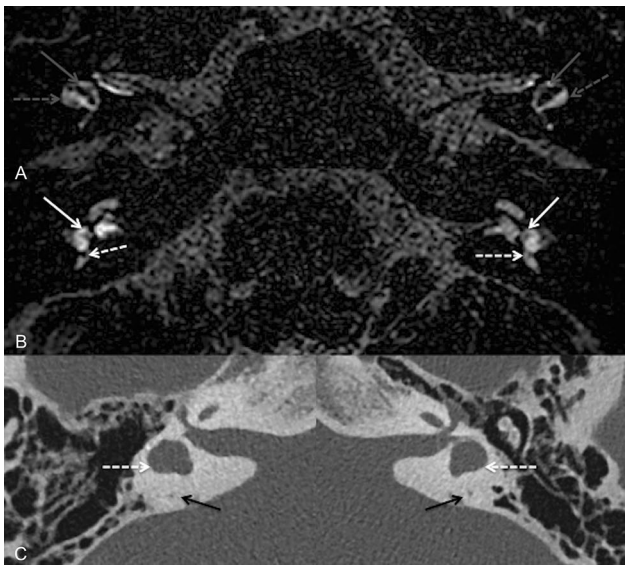

Fig. 3 **a** Axial 3D-FLAIR at the level of the utricle (gray arrow) showed bilateral lateral semicircular dysplasia (gray dotted arrow) with malformation of the utricle on the left side (gray arrow). **b** Axial 3D-FLAIR at the level of the saccule (white arrow) and the posterior ampulla (white dotted arrow) demonstrated normal endolymphatic structures and no BLB impairment. **c** Axial temporal bone CT showed bilateral lateral semicircular canal dysplasia (white dotted arrow) and hypoplastic posterior semicircular canals (black arrow)

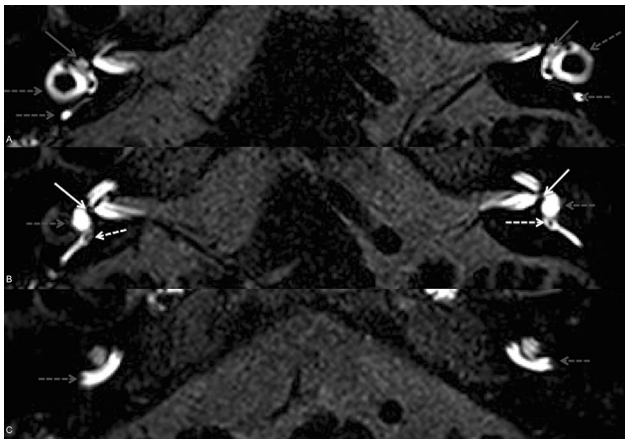

Fig. 4 **a** Axial 3D-FLAIR at the level of the utricle (gray arrow) showed vestibular BLB impairment with a marked enhancement of the lateral (white arrow) and the posterior (gray dotted arrow) semicircular canals. **b** Axial 3D-FLAIR at the level of the saccule (white arrow) and posterior ampulla (white dotted arrow) demonstrated BLB impairment with a marked enhancement of the vestibule (gray dotted arrow). **c** Axial 3D-FLAIR at the level of the basal turn of the cochlea (gray dotted arrow) showed bilateral BLB impairment

Unilateral vestibular BLB impairment was found in one patient who presented a marked enhancement of the right superior and lateral semicircular canals (Fig. 5) on the 3D-FLAIR sequence. On the contralateral side, a low signal involving the left superior semicircular canal was found on 3D-T2 SPACE sequence. This patient had a history of a left vestibular deficit 20 years ago and recently presented with a right acute vestibular syndrome. Since then, he has a complete bilateral vestibular loss with semicircular canals, and utricular and saccular dysfunction.

We observed bilateral fibrosis of the superior semicircular canals on 3D-T2 SPACE in one other patient who also presented typical symptoms of bilateral sequential peripheral vestibulopathy, with a history of a left acute vestibular syndrome 2 years ago and a right acute vestibular syndrome one year ago. Since then, he presented bilateral semicircular canals and oVEMP impairment while both saccular responses were normal on cVEMP.

Discussion

We demonstrated that 59.6% of patients with BV presented either morphologic anomalies of the endolymphatic space or vestibular blood–labyrinthine barrier impairment. Moreover, most of our patients with idiopathic BV showed evidence of MRI anomaly and for all of them, it was a bilateral vestibular atelectasis that was the primary event responsible for the vestibular symptoms.

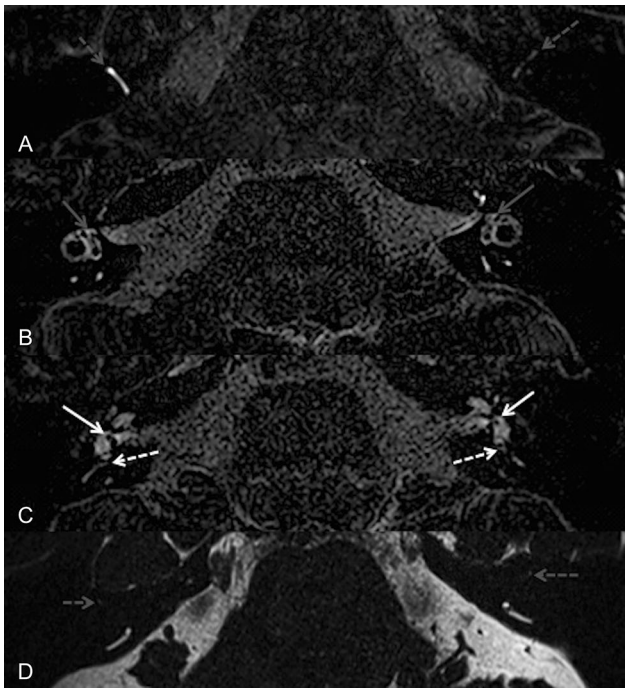

Fig. 5 **a** Axial 3D-FLAIR at the level of the superior semicircular canals (gray dotted arrow) showed an increased enhancement of the right superior semicircular canal. **b** Axial 3D-FLAIR at the level of the utricle (gray arrow) demonstrated no sign of VA or BLB impairment. **c** Axial 3D-FLAIR at the level of the saccule (white arrow) and the posterior ampulla (white dotted arrow) showed anomalies of the endolymphatic space and/or BLB impairment. **d** Axial T2-weighted sequence at the level of the superior semicircular canals demonstrated canal fibrosis in both canals (gray dotted arrow)

The etiology remained idiopathic in 30 patients (71.4%). In these patients, eight met the International Headache Society criteria for migraine. It has been suggested that the recurrent vasospasm related to migraine might lead to bilateral vestibular loss [21].

Endolymphatic space morphology

Delayed 3D-FLAIR sequences of the endolymphatic space evaluation showed bilateral VA in 59% of patients, involving only the utricle and all three ampullas while the saccule was always observed with no sign of collapse. Most VA patients (90.4%) had bilateral utricular involvement both on MRI and oVEMP while only 23.8% of patients had cVEMP impairment; yet we could not exclude the possibility that a slight collapse of the saccule was too subtle to be diagnosed. We believe that VA occurs before hair cell degeneration since three patients with bilateral VA had unilateral utricular dysfunction on oVEMP.

Most of these patients had a diagnosis of idiopathic BV. Bilateral VA has been already suggested in patients with idiopathic BV and recently, a radiological study described unilateral VA in patients with atypical unilateral vestibular loss [22–27]. In 1988, Merchant and Schuknecht described unilateral collapse of the walls of the ampullas and utricle, which they termed vestibular atelectasis. That was thought to be the primary pathologic event responsible for vertigo in these cases [28]. We raised the hypothesis that the absence of saccular atelectasis in BV patients is related to the lack of dark cells in the saccule but are found in the utricle and the ampullas (art Kimura). Dark cells present histochemical similarities with the cochlear stria vascularis and also express KCNQ1/KCNE1. Mutations of KCNQ1/KCNE1 cause collapse of the vestibular endolymphatic space and balance disorder [29].

Three patients developed BV after surgery. To date, we do not know the exact physiopathological mechanism causing BV in these patients. However, this association has already been described in a patient that developed BV after receiving a 10-day course of penicillin for a urologic surgery infection and non-steroidal anti-inflammatory drug for postoperatively pain [30].

We should mention that all of our patients with normal unilateral anterior VOR gain had bilateral VA and that one patient, who had aminoglycoside administration, presented bilateral VA on MRI. Nevertheless, it has been reported that the administration of aminoglycosides could cause collapse of the ampullas and the sensory epithelium with reductions in the hair cells in the utricle, as observed in our study [31].

Recently, Wenzel et al. have described four patients with BV associated with Tullio phenomenon and pressure-induced nystagmus [24]. They suspected VA and have speculated that the collapsed membranous labyrinth might come in contact with the stapes, causing abnormal vestibular stimulation with loud sound and/or pressure. We should note that only one of our patients with bilateral VA had loud sound-induced vertigo at the beginning of their disease, but MRI did not show any evidence of contact between the membranous labyrinth and the stapes. Yet, we could not exclude the possibility that this contact was too subtle to be detected by MRI.

Congenital disorders are one of the rare causes of BV, yet have been reported in various pathologies such as Alport and Waardenburg's syndromes [32]. Here, we found a patient with BV that presented typical imaging findings of Waardenburg's syndrome with large vestibular cavity, thick arch of a small diameter of the lateral canal, partial agenesis of the superior and posterior semicircular canals while their ampullas remained normal. We also found an enlargement of the left utricle as has been previously described in a histopathological study and, lately in a radiological study that has reported patients with isolated lateral semicircular canal dysplasia, sometimes with an enlargement of the endolymphatic space [33, 34]. Sensorineural hearing loss in patients with Waardenburg syndrome is caused by endolymphatic collapse

of the saccule and the organ of Corti, which is called cochleosaccular degeneration [35]. We should mention that our patient had both clinical and radiological normal saccules on both sides and normal hearing thresholds.

Blood–labyrinthine barrier permeability

The second anomaly that delayed 3D-FLAIR sequences can explore is linked to the pathology that leads to an impairment of the permeability of the blood–labyrinthine barrier. Lately, a study has demonstrated endothelial dysfunction in patients with BV [36]. BLB impairment was observed in 15% of our patients with BV. In our study, we observed four patients who presented vestibular BLB impairment as evaluated by MRI. Two patients presented bilateral vestibular BLB impairment with a marked enhancement of both labyrinths: the first of these patients presented a bilateral vestibulopathy 1 month before a gastric tumor was diagnosed. The second patient presented vestibular symptoms a few weeks after beginning immunotherapy treatment for lung cancer. For both patients, lumbar puncture eliminated leptomeningeal carcinomatosis. Therefore, we have speculated that the underlying mechanism was autoimmune: a paraneoplastic syndrome for the first patient and an autoimmune adverse effect of the immunotherapy treatment for the second patient, as has been previously reported [37, 38].

Two additional patients presented typical sequential acute vestibular syndrome (also known as vestibular "neuritis") with active BLB impairment and semicircular canal fibrosis suggesting BLB impairment sequelae. MRI revealed marked enhancement of the superior semicircular canal on the recently affected side, which, as a result of the vestibular BLB impairment, was associated with semicircular canal fibrosis on both sides [14]. Hence, it is conceivable to detect canal fibrosis in these patients who have not recovered their semicircular canal function. In addition, it is well known that there is a significant correlation between semicircular canal fibrosis and canal function loss since the accumulation of fibrous tissue might decrease the flow of endolymph [39].

Potential therapeutic implications

Routine inner ear MRI is usually performed in BV patients to exclude various disorders such as superficial siderosis, CANVAS syndrome, and bilateral internal auditory canal tumors [40, 41]. By evaluating the endolymphatic space compartment and the permeability of the blood–labyrinthine barrier, delayed 3D-FLAIR sequences might enable better management of these patients and highlight new disorders. On the one hand, the combination of utricular and ampullar dysfunction with conserved saccular function and MRI findings is highly evocative of VA as the cause of the vestibular deficit lesion. On the other hand, the presence of BLB impairment should alert the clinician to consider neoplastic or autoimmune disorders as one of the causes of bilateral dysfunction.

To date, we do not know the mechanism causing VA, which is the most common anomaly found in patients with "idiopathic" BV. However, we could expect that a local treatment using intra-tympanic administration could be adapted to target this intralabyrinthine disease, as has been reported in unilateral acute vestibular syndrome [42]. Here, we confirmed what Eliezer et al. have speculated, VA is one of the mechanisms of bilateral vestibular deficit [43]. MRI can provide knowledge on VA in patients with bilateral vestibular hypofunction, who could be eligible for a vestibular implant, because the lesions affect the labyrinthine sensory receptors and not the vestibular nerve [44]. In these cases, we can imagine that direct vestibular afferent nerve stimulation could bypass the collapsed vestibular sensory structures.

The main problem we encountered was the impossibility of confirming the volume of the vestibular endolymphatic space with pathological analysis in vivo. While these results are encouraging in a small number of patients, further multicenter studies are needed in a larger population to assess these patients.

Furthermore, bilateral VA could be caused by long-lasting disease with secondary atelectasis due to the vestibular deafferentation. However, as Merchant and Schuknecht have speculated, we believe that VA could be the primary pathologic event responsible for vertigo, because one patient underwent MRI 10 days after the onset and presented bilateral VA. By contrast, some patients with long-lasting disease (up to 10 years) had no VA on MRI.

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Compliance with ethical standards

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

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