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Retinitis Pigmentosa: Evaluation of the Vestibular System with Cervical and Ocular Vestibular Evoked Myogenic Potentials and the Video Head Impulse Test

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Objective: Retinitis pigmentosa (RP) represents a group of inherited disorders in which abnormalities of the photoreceptors lead to progressive visual loss. Night blindness, peripheral visual field loss, and eventual total blindness represent typical visual damage of such disease. No study has previously evaluated the presence of a ''latent'' vestibular deficit in patients with RP.
Study Design: Prospective study with caloric test, cervical vestibular evoked myogenic potentials (C-VEMPs), ocular vestibular evoked myogenic potentials (O-VEMPs), and video head impulse test (v-HIT).
Setting: Tertiary referral center.
Patients: 16 patients suffering from RP.
Intervention: Evaluation of vestibular dysfunction with caloric test, C-VEMPs, O-VEMPs, and the measurement of the vestibular-ocular reflex (VOR) using the v-HIT.
Results: Only five patients with RP showed normal values in all the vestibular tests performed. Three patients had an evident deficit at the caloric test, whereas eight (50%) of them had a normal caloric test but a pathological response in at least one of the other vestibular tests performed. No patient of the study showed a bilateral otolith or ampullary dysfunction.
Conclusion: Our patients with RP unexpectedly showed pathological responses in at least one of the vestibular tests performed. Nowadays, in patients affected by RP, a vestibular diagnostic protocol must include VEMPs and v-HIT to confirm the vestibular damage and to identify selective damage of the vestibular nerve. **Key Words:** Retinitis pigmentosa—Usher syndrome—VEMPs—v-HIT.

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Retinitis pigmentosa (RP) represents a group of inherited disorders in which abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium lead to progressive visual loss. Night blindness, peripheral visual field loss, and eventual total blindness represent the visual damage resulting from this disease. Mutations in more than 50 different genes or loci are known to cause RP (1,2).

All RP conditions are progressive, but the speed and the pattern of deterioration of sight varies among patients. In fact, the same gene mutation can cause variable symptoms depending on the environmental factors (1–4).

When progressive pigmentary retinopathy is associated with congenital hearing loss and vestibular disorders, an autosomal recessive disorder known as Usher's syndrome is described (5–7).

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Frey and Haivimerscheag (8) (1904) were the first to suggest that impairment of the vestibular function, which is rare in uncomplicated recessive deafness, occurs more frequently in Usher's syndrome patients. However, later on, Arnvig et al. (9) expressed the belief that vestibular involvement in subjects with recessive deafness may point to the presence of either manifest or ''latent'' RP.

Recently, at least nine genes encoding proteins of different classes and families, including motor and structural proteins, scaffold proteins, cell adhesion molecules, and transmembrane receptor localized to the photoreceptor, stereocilia, or to the common synaptic and periciliary areas of the ear and eye have been identified (5–7,10). Extensive information regarding mutations of these proteins such as Myosin VIIa or Cadherin 23 has emerged from molecular studies in mouse models that identified variations in both audio vestibular and/or visual function, thus confirming that these proteins are integrated into a protein network that regulates hair bundle morphogenesis in the inner ear (7,10,11).

Sterocilia dysfunction has been reported in patients with RP. Studies reported that there are generally approximately

50 to 80 stereocilia and one kinocilium per vestibular hair cell, arranged in a distinct geometrical alignment. Thus, their dysfunction could result in various types of vestibular disorders (7,10,12).

To our knowledge, no study has previously evaluated the presence of ''latent'' vestibular damage in patients with RP (5,13,14). Furthermore, no investigation has been reported regarding the study of otolith dysfunction with cervical vestibular evoked myogenic potentials (C-VEMPs) and with ocular vestibular evoked myogenic potentials (O-VEMPs) and the measurement of the vestibular-ocular reflex (VOR) using the video head impulse test (v-HIT).

The aim of this paper is, therefore, to investigate otolith and ampullary dysfunction in a group of patients affected by RP using a new diagnostic protocol employing C-VEMPs, O-VEMPs, and v-HIT to confirm the unknown vestibular damage and to identify possible selective damage of the vestibular nerve.

MATERIALS AND METHODS

Sixteen patients suffering from RP (mean age 52.1 years, range 26–77 years; 11 women and 9 men) were investigated between January 2011 and September 2013 at the Organi di Senso Department of Rome University ''Sapienza.''

None of the patients with RP had ever suffered from persistent vestibular disorders, although sporadic vertigo was reported in four patients.

All patients underwent audiometry, impedance test, Fitzgerald-Hallpike caloric vestibular testing, C-VEMPs, O-VEMPs, and v-HIT. Each of them or their tutors gave written informed consent for the aforementioned tests. Our prospective study was approved by the local ethics committee.

Each patient underwent Fitzgerald-Hallpike caloric vestibular test with cold (30°C) and warm stimulation (44°C) defining canal paresis of the horizontal semicircular canal (HSCC) as a difference greater than 15%.

In all patients, the C-VEMPs evoked through air-conducted sound were measured using an MK22 Amplaid with the patient lying supine on a bed. The reference electrodes were placed bilaterally on the sternocleidomastoid (SCM) muscles, with the exploring electrode placed over the middle of the clavicle; an additional electrode was placed on the forehead as a ground. During the recording sessions, patients were asked to lift their head and to bend onto the neck during the acoustic stimulus to obtain bilateral contraction of the SCM muscles. The electrode impedance was checked before each recording and did not exceed 5 kΩ. The signals were amplified and band-pass-filtered from 15 to 2,000 Hz. A 500-Hz logon of negative polarity was used for binaural acoustic stimulation. The intensity of the signal was fixed at 130 dB SPL at a rate of 4/s. In this study, we used a logon composed of negative semiwaves, corresponding to the rarefaction phase of an acoustic stimulus. Two hundred stimuli were administered in each test using TDH 49 earphones. A second recording was made to evaluate the reliability of the response. The average of the two runs was calculated for the first positive–negative peak of the VEMPs (15–19).

The criteria adopted for assessing abnormality of C-VEMPs comprised the absence of p1-n1, the so-called p13-n23 complex, or the increase of latency and the decrease of the amplitude of p1-n1 more than 2 standard deviations with reference to our age-related normative reference range (15,20) (p1 latency normal value, 16.25 ± 1.52 ms ; n1 latency normal value, 25.4 ± 2.8 ms; p1-n1 amplitude normal value, 39.75 ± 21.68 μV).

A handheld Mini-shaker (4810; Bruel and Kjaer, Naerum, Denmark) was used to measure O-VEMPs through bone-conducted vibration with the patient lying in the supine position and shown a target placed approximately 15 to 30 degrees backwards at a distance of 2 m. The two exploring electrodes were positioned below the center of the lower eyelids with the two reference electrodes placed 1 to 2 cm below the active ones and a ground electrode was positioned on the forehead. Recorded signals were amplified and band-pass-filtered from 20 to 500 Hz (15–19).

O-VEMPs were evaluated using the same criteria for the C-VEMPs: the absence of n10 wave or increase of latency and the decrease of the amplitude of the n10 wave more than 2 standard deviations with reference to our age-related normative range (15,20) (N10 wave latency normal value, 10.29 ± 0.6 ms; N10 wave amplitude normal value, 6.57 ± 2.01 μV).

The various parameters of the C-VEMPs were ipsilaterally analyzed, whereas O-VEMPS (as a result of their crossed vestibulo-ocular responses) were calculated in the ear opposite the one with the vestibular disorders (15,20).

Assessment of v-HIT was performed using a camera assembled on a tripod connected to a computer that filmed the patient's face from a distance of approximately 90 cm (developed by Ulmer and the company Synapsis, Marseille, France) (21,22). It measures the response of each of the six semicircular canals compared to its normal reactivity after a short fast passive head movement (22–24). The system software simultaneously analyzes the direction of the patient's gaze and the head acceleration measuring the vestibulo-ocular reflex deficit for each semicircular canal with a difference of 40% or greater considered to be abnormal (15,20,22). The normal functionality of each semicircular canal is graphically expressed as a green circle and the abnormal findings as red circles (22,23,25). Our reported values were based on an average of responses obtained from 10 repetitions for each side (15,20).

RESULTS

Table 1 gives an overview of the audiovestibular tests performed in the patients of our study.

None of the 16 patients with RP showed a profound hearing loss.

Three patients (18.7%) showed pathological values or lack of any response to bithermal caloric stimulation. Thirteen patients (81.3%) had a normal caloric test.

Four patients (25%) of the 16 showed absence of O-VEMPs, whereas only one (6.2%) showed absence of C-VEMPs.

A v-HIT pathological response of the superior semicircular canal (SSCC) was observed in eight patients (50%). The HSCC presented a dysfunction in two patients (12.5%), whereas the other two patients (12.5%) showed a deficit of the posterior semicircular canal. Note that only one of the two patients with v-HIT pathological response of the HSCC presented an altered caloric test.

Only five patients showed normal values in all the vestibular tests performed. The remaining patients showed pathological responses in at least one of the other vestibular tests performed. Abnormal values of C-VEMPS or O-VEMPS associated with a v-HIT alteration of one of the

TABLE 1. *Retinitis pigmentosa, vestibular tests*

Pts	Pathology	Age	Caloric test	Side	v-HIT SSC (%)	v-HIT HSC (%)	v-HIT PSC (%)	o-VEMPs latency n10 (ms)	o-VEMPs amplitude n10 (μV)	c-VEMPS latency p13-n23 (ms)	c-VEMPS amplitude p1-n1 (μV)
1	RP	47	N (5%)	LS	67	8	14	10.9	4.8	14.4–20.9	67.13
				RS	26	7	12	10.3	6.3	15.6–24	71.8
2	RP	60	N (2%)	LS	17	5	11	10.9	10.1	19.1–27.2	62.3
				RS	9	13	5	10.9	9.7	19–30	77
3	RP	45	N (8%)	LS	8	3	14	9.1	9.8	16–24	31.5
				RS	5	12	25	10.08	9.6	16–25.2	31.2
4	RP	77	N (10%)	LS	6	15	3	10	2.9	Absent	—
				RS	20	16	32	10.3	5.6	18.4–25.6	35.6
5	RP	65	P (71%)	LS	24	15	19	10	9.9	16.5–24.9	15.9
			right side	RS	50	16	16	10.3	8.6	14.8–22.6	18.1
6	RP	33	N (3%)	LS	19	12	15	Absent	—	17.2–26.8	42.5
				RS	81	52	16	10.9	7.2	18.8–26.4	46.8
7	RP	65	A (100%)	LS	65	81	64	10.9	2.56	17.2–24.3	28.1
			left side	RS	30	22	28	Absent	—	18.4–23	31.9
8	RP	58	N (12%)	LS	87	4	28	10.6	8.6	17.2–26.4	42.3
				RS	31	27	29	10.9	6.1	17.2–25.6	53.9
9	RP	68	N (3%)	LS	75	18	82	10.3	3.5	14.8–26.4	43.1
				RS	15	26	22	10.9	5	18–27.6	36.3
10	RP	45	N (5%)	LS	78	4	28	10.6	7.4	17–29.5	26.2
				RS	11	10	27	10.3	6.5	16–28.8	30.9
11	RP	44	N (8%)	LS	15	7	21	10.3	2.4	18.4–27.6	38.5
				RS	8	10	6	Absent	—	18–28	41.1
12	RP	57	N (4%)	LS	20	18	7	9.8	6.4	17.9–21	26.7
				RS	9	4	12	Absent	—	18.3–22.4	25
13	RP	40	N (2%)	LS	27	18	20	10.9	3.1	19.1–28.2	8.6
				RS	23	8	36	11.2	2.7	18–24.8	12.9
14	RP	44	P (81%)	LS	90	21	15	11.3	2.6	15.4–22.3	59.3
			left side	RS	36	1	20	11.2	3.5	16.8–23.4	61
15	RP	60	N (5%)	LS	30	12	13	10.3	3	14–23.9	77
				RS	15	6	10	9.8	2.9	17.3–24.5	74.4
16	RP	26	N (9%)	LS	37	5	35	10.2	8.3	15.2–24.9	62.2
				RS	25	3	17	9.1	6.4	18–28.8	76.6

Pts indicates patients; RP, retinitis pigmentosa; P, pathological; N, normal; A, arefexia; LS, left side; RS, right side.

semicircular canals were observed in two patients. However, if we consider each single vestibular end organ or nerve evaluated with VEMPs and VHIT, no patients showed a total vestibular deficit for each side examined. Besides, no patient of the study showed a bilateral otolith or ampullary dysfunction in any of the tests performed.

DISCUSSION

RP is a clinically and genetically heterogeneous group of hereditary retinal disorders in which abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium lead to progressive visual loss (1,2). No morphological alterations of the audiovestibular apparatus have been described in RP patients (10,26), and no study has previously assessed the presence of vestibular damage in patients with RP (5,13,14,27).

We conducted a study with a new diagnostic protocol including caloric test, VEMPs, and v-HIT in 16 with RP to evaluate selective damage of the vestibular nerve.

VEMPSs and v-HIT have had a revolutionary impact on the diagnosis of vestibular dysfunction introducing the possibility of studying otolithic function in both its saccular (C-VEMPS) and utricular (O-VEMPS) partition, as well as the distribution of semicircular involvement (v-HIT). Their advent has provided otologists and neurologists with diagnostic tools able to identify dysfunctions of each single vestibular end organ afferent to the vestibular nerve.

Unexpectedly, among 16 patients with RP, only five showed normal values in all the vestibular tests performed, whereas three patients showed a pathological response to the caloric test. It should be noted that eight patients with RP were found to have an otolith dysfunction evidenced by C-VEMPs and O-VEMPs or an ampullary pathological response using v-HIT despite a normal response to the caloric test, thus suggesting the presence of a partial damage of the vestibular structures.

VEMPs appeared to be pathological in five (31.25%) patients with RP, of whom four had utricular dysfunctions and one impairment of the saccular component. Regarding damage to the semicircular canals, v-HITs showed ampullary dysfunction in eight patients affected by RP with the superior semicircular canal being the site most involved. Note that five patients showed pathological SSCC v-HIT despite the fact that all the other tests performed were negative. Therefore, this test should always be accompanied VEMPs and the caloric test.

Finally, it emerged from our study that two of the five patients with the absence of VEMPs were 65 and 77 years

old, respectively. Although this finding could suggest that the abnormality of VEMPs in these patients was linked to the older age and not to RP, we cannot exclude that the ultrastructural abnormalities of the saccular and utricular neuroepithelium proceed similarly to the well-known damage of the retinal pigment epithelium (1–4).

Obviously, these data confirm a greater ''latent'' vestibular impairment than that previously reported in patients affected by RP. If we consider each single vestibular end organ or nerve evaluated using VEMPs and VHIT, no patient of the study showed a bilateral otolith or ampullary dysfunction in all tests performed; moreover, a total vestibular deficit for each side examined was not detected.

Our study showed the absence of a frank vertigo in these patients. The interpretation of this finding is a source of debate. As well known, an acute semicircular canal insult is enough to cause vertigo. The absence of vestibular disturbances in our RP patients could be explained taking into consideration a progressive and not particularly rapid development of vestibular sensory cell alterations. This phenomenon may favor vestibular compensation explaining the absence of continuous vertigo in our RP patients.

Despite the limited number of subjects in the sample examined, our findings indicate that a specific diagnostic protocol employing C-VEMPS, O-VEMPS, and v-HIT beyond the caloric test thus enables us to confirm or exclude vestibular damage in totally asymptomatic patients and allows a more precise definition of the vestibular site involved. Undoubtedly, assessment of larger series is advisable. In this context, another study with a long-term follow-up is underway to evaluate the possibility of bilateral development of vestibular damage in these patients and the onset of clinical symptoms.

CONCLUSION

In patients with retinitis pigmentosa, the presence of vestibular damage cannot be excluded even in the absence of vertigo. Although our study showed the absence of bilateral vestibular receptor involvement or concurrent deficit in both otolithic and ampullary structures, 13 of the 16 patients with RP unexpectedly showed pathological responses to at least one of the vestibular tests performed. Nowadays, in patients affected by RP, any vestibular diagnostic protocol has to include VEMPs and v-HIT to confirm the vestibular damage and to identify selective damage of the vestibular nerve.

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