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Clinical Report

Instability Due to Drug-Induced Vestibulotoxicity

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OBJECTIVE: The therapeutic use of ototoxic drugs is relatively common, particularly in patients with severe diseases. It is likely that disturbances of balance in these patients are underestimated by clinicians.

MATERIALS and METHODS: The purpose of this study was to identify drugs involved in the vestibulotoxic origin of instability in a group of 18 patients.

RESULTS: Six patients showed both cochlear and vestibular damage, while 12 were affected only by posterior labyrinthine damage. Four groups of drugs were identified: antibiotics (nine patients), cytostatics (four), anti-tuberculosis medicinal products (three), and other drugs (two). Cytostatics were involved in many cases studied, a fact scarcely reported before.

CONCLUSION: It is important to ensure an early diagnosis to prevent ototoxic effects induced by drugs. We propose that patients receiving potential ototoxic drugs undergo cochlear and vestibular assessments. Further, we recommend that patients with instability undergo vestibular rehabilitation.

KEYWORDS: Ototoxicity, vestibulotoxicity, ototoxic drugs, dizziness, cytostatic drugs

INTRODUCTION

Labyrinthine injuries are some of the most frequent causes of vertigo and alterations of balance. An acute damage of the posterior labyrinth usually causes rotational vertigo, although sometimes, the absence of compensation may cause a persistent instability. When both labyrinths are simultaneously damaged, the predominant symptom from the beginning is instability, which may become severe and impair the ability of patients to perform their daily activities [1].

Causes of bilateral vestibulopathy are varied and not always easy to be identified and include Menière's disease, CANVAS syndrome (cerebellar ataxia with neuropathy and vestibular areflexia syndrome), meningitis, and ototoxicity. It is well known that ototoxicity is caused by aminoglycoside antibiotics [2, 3]. However, ototoxic effects induced by other drugs, such as salicylates, some chemotherapeutic agents, other non-aminoglycoside antibiotics, or sildenafil, have also been reported. Thus far, most studies on drug-induced ototoxicity focus on the cochleotoxic effect, while reports on the vestibulotoxic effect are relatively rare [4-10]. This fact may be due to several reasons. Cochlear damage can be evaluated (by audiometric tests) easier than vestibular damage (clinical examination and measurement of vestibular function make use of instruments not available in all hospitals). Cochlear damage usually is permanent with an irreversible hearing loss, while, in many patients with vestibulotoxicity, imbalance can remain inadvertent. Patients may accept vestibular symptoms as part of their disease and impairment of their general status. Compensatory mechanisms provided by other afferent signals (visual and proprioceptive) can contribute to ameliorate the clinical perception of vestibular symptoms.

It is likely that vestibulotoxicity is underestimated by clinicians. Drug-induced ototoxic damage on the posterior labyrinth frequently causes an important imbalance with an impairment in the quality of life. Thus, it becomes relevant to recognize, evaluate, and quantify an imbalance secondary to vestibulotoxicity. A high index of suspicion is required to avoid that the diagnosis of vestibulotoxicity will be overlooked and to ensure an adequate treatment (such as vestibular rehabilitation) to improve patient equilibrium.

The objective of this study is to report different causes of vestibulotoxicity in patients with instability.

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MATERIALS and METHODS

A prospective study in patients diagnosed with chronic imbalance due to drug-induced vestibulotoxicity was performed. Patients who were diagnosed in a Neurotology Unit of a tertiary hospital (Complexo Hospitalario Universitario de Santiago de Compostela, Spain) over 16 years (from 1999 to 2014) were included. The study was approved by the local Independent Ethics Committee, and all patients granted their informed consent to participate in it. All patients underwent the following protocol:

- A complete history (it is necessary to exclude other possible causes of symptoms and signs observed).
- Clinical examination of vestibular function, particularly tests that allow suspecting vestibular labyrinthine damage (spontaneous nystagmus with and without fixation of gaze, Halmagyi test, head-shaking test, Romberg test, and Unterberger test).
- Pure tone audiometry: Determination of auditory thresholds for pure tones at 125, 250, 500, 1000, 2000, 3000, 4000, and 8000 Hz. For this purpose, an audiometer (AUDIOTEST model 340, Interacoustic, Italy), with its own earphones, was used.
- Sensory organization test (SOT) of computerized dynamic posturography (CDP) performed using Neurocom Smart Equitest® and Neurocom Smart Balance Master® (Clackamas; Oregon, USA): Recording and measuring of changes in the patient's distribution of weight were obtained under six different sensory conditions (condition 1: immobile surface, immobile visual surround, eyes open; condition 2: immobile surface, eyes closed; condition 3: immobile surface, mobile visual surround, eyes open; condition 4: mobile surface, immobile visual surround, eyes open; condition 5: mobile surface, eyes closed; and condition 6: mobile surface, mobile visual surround, eyes open). This test allows measuring the total balance of patients and analyzing the contribution of each of the three sensory systems (somatosensory, visual, and vestibular) involved.
- Recording of spontaneous nystagmus and caloric-induced nystagmus. The recording and measuring of nystagmus were performed by electronystagmography (Nystar plus electronystagmograph) or videonystagmography (two videonystagmographs were used: VIDEONYSTAGMOGRAPHIE VEONYS IMV Biodigital model and HIS model, France). Patients underwent caloric stimulation with hot (44°C) and cold (30°C) water by applying the following sequence: Hot water in the right ear, hot water in the left ear, cold water in the right ear, and cold water in the left ear. Unilateral vestibular hypofunction was considered when the two ears showed an asymmetrical response (obtained by applying Jongkees formula at the maximal slow-phase velocity of the nystagmic response) of at least 25%. Bilateral vestibular hypofunction was considered when the addition of the maximal slow-phase velocity of the nystagmic response from the four stimuli was lower than 20°/s.

The inclusion criteria were as follows:

- Absence of a history of balance disorders before starting ototoxic drug administration.
- Acute onset of dizziness or imbalance during or just after ototoxic drug administration.
- Persistent symptoms for at least three months.
- Disequilibrium confirmed by abnormal dynamic posturographic results (SOT): A value of the average balance score of less than 68 and a deficit of at least the vestibular information input.
- Labyrinthine lesion demonstrated by one of the following data:
  - Presence of spontaneous or postheadshake nystagmus
  - Uni-or bilateral saccades as a response to the Halmagyi test
  - Uni-or bilateral hypofunction observed by the nystagmographic recording of caloric tests

The following exclusion criteria were considered:

- Presence of any other disease that would justify the symptoms
- Spontaneous disappearance of symptoms in less than three months
- Patients unable to undergo dynamic posturography because of their inability to remain in the standing position without support
- Patients unable to undergo caloric tests in good conditions (e.g., some diseases affecting middle and/or outer ear may contraindicate a stimulation with water, or, in some ophthalmologic diseases, a normal nystagmographic recording is not possible).
- Refusal of the patient to perform any of the above mentioned tests

Variables obtained from each patient were as follows:

- Sex
- Age when diagnosis was established
- Type of affectation (cochleovestibular or exclusively vestibular)
- Drug involved
- Previous pathology treated with a vestibulotoxic drug
- Symptoms reported by patients
- Pure tone audiometry
- SOT of CDP: Average balance score and evaluation of the contribution of sensory inputs
- Caloric tests: Normal, unilateral, or bilateral hypofunction, absent response uni- or bilaterally
- Treatment
- Evolution of symptoms

Data from patients were entered into a database created for this purpose.

RESULTS

There were 18 patients (11 women and 7 men). The mean age was 60.2 years (standard deviation: 16.41; range: 21–78 years). Six of them showed both cochlear and vestibular damage, while 12 were affected only by posterior labyrinthine damage.

With regard to the drug involved in toxicity, four groups can be identified:

- Antibiotics (nine patients). Eight patients received systemic gentamicin alone (two patients) or associated to vancomycin (five) or to metronidazole (one patient). The remaining patient

Table 1. Clinical data of patients with instability due to antibiotics

Case	Sex	Age	Cochlear damage	Main disease	Antibiotics	Symptoms	Pure tone audiometry	Spontaneous nystagmus or saccades in the Halmagyi test	Videonystagmography (caloric tests)	Sensory organization test (dynamic posturography)	Treatment of instability	Clinical course
1	M	78	Absent	Pneumonia	Amoxicillin/ clavulanic acid and azithromycin	Instability when walking	Moderate sensorineural hearing loss at high frequencies	Absent	Bilateral hyporeflexia	Average: 62 Pattern: vestibular deficit	No treatment	Return to the normal status
2	M	70	Absent	Endocarditis	Gentamicin and vancomycin	Instability when walking and oscillopsia	Moderate sensorineural hearing loss at high frequencies	Absent	Bilateral hyporeflexia	Average: 63 Pattern: vestibular deficit	Vestibular rehabilitation: dynamic posturography	Remarkable improvement
3	F	62	Absent	Peritonitis	Gentamicin and vancomycin	Continuous instability	Moderate sensorineural hearing loss at high frequencies	Absent	Bilateral hyporeflexia	Average: 66 Pattern: vestibular deficit	Walking	Return to the normal status
4	M	62	Present	Defibrillator infection	Gentamicin and vancomycin	Instability when walking	Severe sensorineural hearing loss at high frequencies	Absent	Bilateral hyporeflexia	Average: 64 Pattern: vestibular and visual deficits	Vestibular rehabilitation: dynamic posturography	Return to the normal status
5	F	76	Present	Infected elbow fracture	Gentamicin	Instability when walking and worsening of hearing loss	Moderate sensorineural pantonal bilateral hearing loss	Absent	Bilateral areflexia	Average: 49 Pattern: vestibular and visual deficits	Walking	Mild improvement
6	M	58	Absent	Endocarditis	Gentamicin and vancomycin	Instability when walking	Normal	Absent	Bilateral areflexia	Average: 52 Pattern: vestibular and visual deficits	Vestibular rehabilitation: dynamic posturography	Remarkable improvement
7	F	78	Absent	Peritonitis	Gentamicin and metronidazole	Continuous instability	Moderate sensorineural hearing loss at high frequencies	Absent	Bilateral areflexia	Average: 29 Pattern: vestibular and visual deficits	Vestibular: rehabilitation: dynamic posturography	Mild improvement
8	M	62	Absent	Defibrillator infection	Gentamicin	Continuous instability	Moderate sensorineural hearing loss at high frequencies	Absent	Bilateral hyporeflexia	Average: 29 Pattern: somatosensory, vestibular, and visual deficits	Vestibular rehabilitation: dynamic posturography	Remarkable improvement
9	F	78	Present	Dialysis catheter infection	Gentamicin and vancomycin	Continuous instability and worsening of hearing loss	Profound bilateral hearing loss	Absent	Bilateral hyporeflexia	Average: 28 Pattern: vestibular and visual deficits	No treatment (exitus)	

M: male; F: female

received amoxicillin/clavulanic acid and azithromycin. Clinical data are shown in Table 1.

- Cytostatics (four patients): The drugs administered to and clinical data of these patients are shown in Table 2.
- Anti-tuberculosis medicinal products (three patients): Ethambutol, plus either pyrazinamide and isoniazid, or rifampicin.
- Other drugs: One patient received tamoxifen (for the treatment of breast cancer) and another received melphalan (therapy for amyloidosis).

The clinical data for these last two groups of patients are shown in Table 3.

The symptom reported by all studied patients was instability, which showed different patterns:

- In six patients, the instability perception was continuous.
- Eleven patients complained of instability when they were on foot and walking.

Table 2. Clinical data of patients with instability due to cytostatics

Case	Sex	Age	Cochlear damage	Main disease	Drug(s)	Symptoms	Pure tone audiometry	Spontaneous nystagmus or saccades in the Halmagyi test	Videonystagmography (caloric tests)	Sensory organization test (dynamic posturography)	Treatment of instability	Clinical course
10	M	34	Absent	Hodgkin's disease	Vinblastine, adriamycin, DTIC, and bleomycin	Instability when walking	Normal	Absent	Bilateral hyporeflexia	Average: 66 Pattern: vestibular deficit	Walking	Return to the normal status
11	F	58	Absent	Breast carcinoma	Docetaxel and cyclophosphamide	Continuous instability	Normal	Absent	Bilateral hyporeflexia	Average: 62 Pattern: vestibular deficit	Walking	Mild improvement
12	F	50	Present	Lung carcinoma	CDDP+VNB	Continuous instability, oscillopsia, and tinnitus	Moderate sensorineural hearing loss at high frequencies	Absent	Bilateral areflexia	Average: 26 Pattern: somatosensory, vestibular, and visual deficits	Vestibular rehabilitation: dynamic posturography	Remarkable improvement
13	F	67	Present	Carcinoid tumor	111In-DTPA-octreotide	Instability when walking	Severe sensorineural hearing loss at high frequencies	Absent	Bilateral hyporeflexia	Average: 52 Pattern: vestibular and visual deficits	Walking	Remarkable improvement

M: male; F: female; DTIC: dacarbazine; CDDP: cisplatin; VNB: vinorelbine; DTPA: diethylenetriaminepentaacetic acid

Table 3. Clinical data of patients with instability due to anti-tuberculosis drugs, tamoxifen, and melphalan

Case	Sex	Age	Cochlear damage	Main disease	Drug(s)	Symptoms	Pure tone audiometry	Spontaneous nystagmus or saccades in the Halmagyi test	Videonystagmography (caloric tests)	Sensory organization test (dynamic posturography)	Treatment of instability	Clinical course
14	M	71	Absent	Disseminated tuberculosis	Ethambutol, pyrazinamide, and isoniazid	Instability when walking	Moderate sensorineural hearing loss at high frequencies	Absent	Bilateral areflexia	Average: 57 Pattern: vestibular deficit	Walking	Remarkable improvement
15	F	21	Absent	Disseminated tuberculosis	Ethambutol, streptomycin, and rifampicin	Instability when walking	Normal	Absent	Bilateral hyporeflexia	Average: 53 Pattern: vestibular and visual deficits	No treatment	Return to the normal status
16	F	40	Absent	Pulmonary tuberculosis	Ethambutol, pyrazinamide, and isoniazid	Instability when walking	Normal	Absent	Bilateral hyporeflexia	Average: 63 Pattern: vestibular and visual deficits	No treatment	Remarkable improvement
17	F	46	Absent	Breast carcinoma	Tamoxifen	Discontinuous instability (more intense in the morning)	Normal	Absent	Bilateral hyporeflexia	Average: 51 Pattern: vestibular and visual deficits	No treatment	Return to the normal status
18	F	76	Present	Amyloidosis	Melphalan	Instability when walking and tinnitus	Severe sensorineural hearing loss at high frequencies	Absent	Bilateral hyporeflexia	Average: 60 Pattern: vestibular and visual deficits	Walking	Remarkable improvement

M: male; F: female

- In the remaining patient, instability was discontinuous, being more intense in the morning.

In 13 patients, instability was the only symptom reported. The remaining five patients complained of other concomitant symptoms such as oscillopsia (two), bilateral tinnitus (two), and hearing loss (or exacerbation of a previous hearing loss) (two).

Six patients had normal pure tone audiometry results, while 12 had sensorineural hearing loss:

- A high-frequency hearing loss in 10 patients

- A profound bilateral hearing loss in one patient
- A mild hearing loss in all frequencies in the remaining patient.

All patients had an abnormal SOT on CDP. The SOT average balance score was 52.33 (SD: 14.88). With regard to the posturographic pattern, six patients showed a pure vestibular-deficient type, 10 showed a somatosensory-dependent pattern (with visual and vestibular deficits), and the remaining two had all inputs affected (somatosensory, visual, and vestibular).

None of the patients had spontaneous nystagmus or saccades with the oculocephalic maneuver (Halmagyi test). Caloric tests were bilaterally affected in all patients. Reduced (13 patients) or absent (five) caloric responses were demonstrated.

With regard to treatment, five patients did not receive treatment (four of them experienced a spontaneous improvement in their symptoms and one died as consequence of a previous illness). The remaining 13 patients underwent therapeutic vestibular rehabilitation:

- Seven patients: Walking and performing home vestibular retraining exercises
- Six patients: Undergoing instrumental vestibular rehabilitation by dynamic posturography

In the majority of patients, the clinical course was good. Only three patients complained of persistent problems of instability with handicapping effects. In the remaining patients, symptoms markedly improved because of vestibular rehabilitation exercises.

DISCUSSION

The use of ototoxic drugs is relatively common, particularly in patients with severe potentially life-threatening diseases (including malignant tumors and severe infections). In such cases, it is assumed that the risk of not using these drugs is greater than the risk of their potential ototoxic effects. Due to an impaired general clinical status of many of these patients, the disturbances of balance consistent with posterior labyrinthine toxic damage can remain inadvertent or be attributed to other causes. Thus far, most studies on drug-induced ototoxicity are limited to the cochleotoxic effect, while reports on the vestibulotoxic effect are relatively rare.

In many cases, pharmacological treatment includes some drugs, so it becomes difficult to elucidate which of these compounds is the cause of ototoxicity. The mechanisms of action of some of them are known. Aminoglycosides are capable of stimulating the formation of reactive oxygen species that play an important role in inner ear damage. This damage is ameliorated by the presence of free radical scavengers [11]. The presence of nitric oxide synthase was demonstrated in the vestibular epithelium. Nitric oxide may contribute to the induction of apoptosis in vestibular hair cells due to aminoglycosides [12].

Labyrinthine damage induced by other drugs has also been reported [4-10, 13]. This is the case for cisplatin, a chemotherapeutic agent that causes vestibular dysfunction. In animal models, cisplatin induces vestibulotoxicity by altering ATPase activities (cisplatin inhibits ATPase activities) and increasing oxidative stress in labyrinths [13]. It is well known that glutathione and glutathione-related enzymes protect against oxidative cell injury caused by free radicals. Specific changes in glutathione levels and enzymes in glutathione metabolism have been found with cisplatin treatment [14]. These findings are in agreement with the proposed mechanism of action based on oxidative stress.

We focused our attention on the fact that the vestibulotoxic potential of cytostatics has scarcely been studied. Their cochleotoxic potential has been reported in some studies, not so the vestibular damage [5, 10, 13, 15-17]. It is remarkable that vestibulotoxicity and cochleotoxicity do not always simultaneously occur. In our series of 18 patients, only one-third of them experienced symptoms consistent with cochlear affectation. This absence of auditory damage in many patients might also explain that vestibular damage remains undetected as patients and physicians ascribe imbalance to other causes. The finding of a normal auditory function does not imply that vestibular function is also unimpaired [3].

However, we consider important to detect this type of damage. Nowadays, neurotology provides us with a battery of diagnostic methods that allow us to confirm balance disorders (e.g., dynamic posturography) and assess the labyrinthine damage (e.g., Halmagyi test, videonystagmographic record of spontaneous nystagmus, and caloric tests). Once damage occurred, many patients experienced a spontaneous improvement of symptoms, explained by the contribution of other body systems (visual and proprioceptive) to the maintenance of balance. These inputs are usually able to compensate the affected vestibular function. In cases where this compensation is not achieved, therapeutic strategies (such as vestibular rehabilitation) can be applied to stimulate and increase this compensation. Vestibular rehabilitation is particularly useful in elderly people because in these patients, compensation mechanisms are weakened and less effective [18].

We propose that patients with instability undergo vestibular rehabilitation to reduce the clinical effects of vestibulotoxicity. In addition, it is important to ensure an early diagnosis and prevent this ototoxicity. Suspicion by clinicians is key to recognize the symptoms and signs of posterior labyrinthine damage. In these cases, the immediate discontinuance of vestibulotoxic drug administration and its replacement by other non-vestibulotoxic drugs are the best chance to avoid damage to the inner ear. However, there are patients with severe diseases where the cessation of drug administration is not possible. Different studies have suggested that the co-administration of substances with protective effects against drug-induced vestibulotoxicity in such patients reduces the adverse effects of treatment [19-21].

Ethics Committee Approval: Ethics committee approval was received for this study from the of Independent Ethics Committee of Galicia.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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