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# Unilateral Vestibulotoxicity Due to Systemic Gentamicin Therapy

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Systemic gentamicin can cause acute bilateral, simultaneous, symmetrical loss of vestibular function manifested by symptoms and signs of chronic vestibular insufficiency (ataxia and oscillopsia). We report 6 patients presenting with ataxia and oscillopsia, but without a history of vertigo, who had severe unilateral loss of vestibular function on caloric testing. The absence of vertigo in these patients could be explained by two possible mechanisms: either, the unilateral loss of vestibular function was subacute, occurring over several days so that compensation could occur, or bilateral vestibular loss occurred which was then followed by asymmetrical recovery of vestibular function. The second hypothesis is supported by the observation that vestibular hair cells can regenerate after aminoglycoside damage. *Key words*: *ototoxicity*, *aminoglycosides*, *vestibular function*.

## INTRODUCTION

Some aminoglycosides, particularly gentamicin, are selectively vestibulotoxic in humans, particularly when given systemically. Caloric and rotational testing in patients with gentamicin vestibulotoxicity (GVT) reveals bilateral symmetrical or almost symmetrical, total or subtotal loss of lateral semicircular canal function, usually without loss of cochlear function (1). Patients with systemic GVT always present with symptoms of chronic vestibular insufficiency (CVI), i.e. ataxia and oscillopsia, but not vertigo. We suspect that in some previous papers dealing with GVT, the authors did not distinguish between an illusion of rotation (vertigo) and ataxia and motion-induced oscillopsia, which occurs in patients with CVI.

There are no previous reports of unilateral or of markedly asymmetrical loss of vestibular function due to systemic GVT. In fact, on theoretical grounds one could doubt if such a situation could occur. After all, why should a drug administered systemically cause loss of vestibular function in only one ear? Nonetheless, we have seen 6 patients with unilateral, or at least markedly asymmetrical, loss of vestibular function due to GVT. Each patient presented in the usual way for GVT, with CVI, and none recalled ever having experienced acute spontaneous vertigo either before, during or after the gentamicin therapy. These observations might have implications about the possible pathogenesis, prevention and management of GVT.

In order to elucidate the concepts being presented in this paper, it is important first to define what is meant by the terms ''acute spontaneous vertigo'' and ''chronic vestibular insufficiency'', and second, to review the acute and chronic pathophysiologic consequences of unilateral and bilateral vestibular deafferentation.

### *Acute unilateral vestibular deafferentation*

Acute destruction or deafferentation of one intact labyrinth invariably produces a stereotyped, temporary syndrome of profound motor and sensory abnormalities in animals and in humans (2). There is an ocular tilt reaction (OTR) and a spontaneous nystagmus, with the slow phases toward the side of the unilateral vestibular deafferentation (uVD), and vomiting. Humans (and perhaps animals) also sense an illusion of rotation (i.e. acute spontaneous vertigo) and experience nausea. In fact, it has hard to conceive that a human could undergo acute uVD without experiencing vertigo. Humans and animals invariably recover, more or less completely, from the acute uVD syndrome by the process of vestibular compensation (2, 3).

### *Chronic progressive unilateral vestibular deafferentation*

Chronic progressive uVD, such as would occur with a vestibular schwannoma, never produces the acute uVD syndrome of vertigo, vomiting, OTR and nystagmus. In fact, if a patient presents with signs of uVD, and categorically denies ever having experienced acute spontaneous vertigo, one can be (almost) sure that the uVD was not acute, and should therefore look for a progressive cause of uVD.

### *Bilateral vestibular deafferentation*

Acute or chronic progressive, simultaneous and symmetrical destruction or deafferentation of both labyrinths never produces the symptoms or signs of uVD, but rather the symptoms and signs of CVI. In particular, bilateral vestibular deafferentation (bVD) never produces an illusion of rotation (vertigo), but does invariably produce oscillopsia on head movement and imbalance of posture and gait, particularly

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on a soft support surface in the absence of visual fixation (i.e. vestibular ataxia). Bilateral, sequential, acute uVD produces two attacks of the acute uVD syndrome of vertigo, vomiting, nystagmus and OTR, followed by the CVI syndrome of ataxia and oscillopsia. The second uVD will be followed by a second acute uVD syndrome only if there has been adequate time for compensation from the first uVD to have occurred—about two days in a guinea-pig, and one week in a human. The development of a second acute uVD syndrome, if the second uVD is carried out after recovery from the first (in contrast to the failure to develop a second acute uVD syndrome after the second acute uVD is carried out soon after the first) is called the Bechterew effect (4).

*Stable permanent unilateral vestibular deafferentation*

Although the vestibulo-ocular reflex never recovers completely after uVD, most patients with one totally deafferented labyrinth become completely asymptomatic within a few weeks after acute uVD. While none of these patients will continue to experience vertigo or any of the other components of the uVD syndrome, after recovering from the acute uVD about 20% will develop symptoms and signs of CVI—i.e. oscillopsia and ataxia, even if there is no evidence of vestibular impairment in the sole functioning labyrinth. These patients' symptoms can be indistinguishable from those experienced by patients with bVD (5, 6).

In summary, it is important to appreciate that while acute uVD almost always produces acute spontaneous vertigo, bilateral simultaneous, symmetrical bVD never does, but in contrast always produces chronic vestibular insufficiency.

## METHODS

Caloric testing was performed using standard 30 and 44° water irrigation, and ice water for confirmation of a severe canal paresis. A significant canal paresis was defined as a greater than 25% difference between maximum slow phase velocity measurements for each ear when compared to the sum of slow phase velocities. A significant directional preponderance was defined as a greater than 30% difference between the sums of right beating and left beating nystagmus.

Rotational chair testing was performed in 5 of the 6 patients. Sinusoidal stimulation was performed at two or more frequencies between 0.08 and 0.33 Hz, maximum velocity 50°/s, and in response to velocity steps of 100°/s and 20°/s/s acceleration. Vestibulo-ocular reflex (VOR) gain, phase and asymmetry of slow phase velocity were calculated for sinusoidal rotation, and maximal slow phase velocity and time constant of nystagmus decay were calculated for velocity steps.

## RESULTS

Between the years 1993 and 1995 we saw 6 patients, each presenting with CVI which had developed soon after systemic gentamicin therapy, and who had either total or subtotal loss of caloric responses (Table I). Each had presented with ataxia; 3 patients had a history of oscillopsia, and 2 others had noted impaired visual acuity during head motion (7). None of the patients recalled ever having had an episode of acute spontaneous vertigo or an episode of prolonged unexplained vomiting. Five patients had received intravenous gentamicin; one had received intraperitoneal gentamicin for peritonitis complicating chronic ambulatory peritoneal dialysis. Each patient, except the one who received intraperitoneal gentamicin, had normal serum creatinine levels before and during the gentamicin therapy.

Only 3 patients had serum gentamicin levels performed, all of which were within the normal range for both trough and peak measurements. None of the 5 patients who received intravenous gentamicin had peak doses which were above the generally accepted safe dose of 50 mg/kg total, or 5 mg/kg/day for 10 days.

Each patient had a significant unilateral vestibular paresis on caloric testing ranging between 50 and 100% (Fig. 1). Two patients had a significant degree of contralateral directional preponderance on caloric testing, perhaps reflecting inadequate central compensation for the unilateral lesion.

Of the 5 patients who had rotational testing, all had asymmetry which corresponded to the side of the canal paresis. Total VOR gain was normal or mildly reduced, and time constants were usually symmetrically reduced.

Cases 1 and 2 had magnetic resonance scans of the brain, which did not show any cerebellar, brain stem or eight cranial nerve pathology.

Pure tone audiometry was performed in all patients. Apart from Case 1, who had a normal audiogram, all other cases had evidence of a significant bilateral sensory-neural hearing loss, much of which was probably pre-existing. No patient had noted any recent change in hearing, and there was no marked asymmetry in any case to suggest unilateral auditory toxicity.

## DISCUSSION

How can one explain a severe or total unilateral loss of vestibular function, producing CVI in the absence of any history of acute spontaneous vertigo, in patients with no reason to have a disorder of the vestibular system apart from having received systemic

Table I. *Clinical details of patients, results of caloric tests and gentamicin dosages*

| Case, sex, age | Time from gentamicin therapy to diagnosis | Indication | Caloric responses | | | | | | Rotation test results | Gentamicin dose | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Affected side | | Normal side | | | | | Peak daily dose (mg/kg/day) | Total dose (mg/kg) |
| | | | 30° | 44° | 30° | 44° | CP (%) | DP (%) | | | |
| 1. F 55 | 1 week | Pyrexia of unknown origin | 3 | 3 | 10 | 29 | 73 | 42 | Marked cDP | 4.1 | 16.3 |
| 2 M 59 | 2 months | Gram negative septicaemia | 3 | 0 | 18 | 34 | 88 | 35 | Mild reduction in gain, bilaterally-reduced Tc, cDP | 3.7 | 11.7 |
| 3 M 77 | 12 months | Endocarditis | 3 | 0 | 22 | 26 | 88 | 13 | Bilaterally-reduced Tc, cDP | 1.7 | 12.0 |
| 4 F 73 | 5 months | Gram negative septicaemia | 6 | 3 | 15 | 14 | 50 | 5 | Mild reduction in gain, bilaterally-reduced Tc, cDP | 3.7 | 44.0 |
| 5 M 73 | 40 months | Gram negative septicaemia | 0 | 0 | 34 | 60 | 100 | 27 | Not done | 2.9 | 24.4 |
| 6 F 73 | 12 months | Peritoneal dialysis; peritonitis | 0 | 0 | 12 | 15 | 100 | 11 | Bilaterally-reduced Tc | Intra-peritoneal | – |

CP = canal paresis ($n < 25\%$); DP = directional preponderance ($n < 30\%$); cDP = contralateral directional preponderance; Tc = time constant.

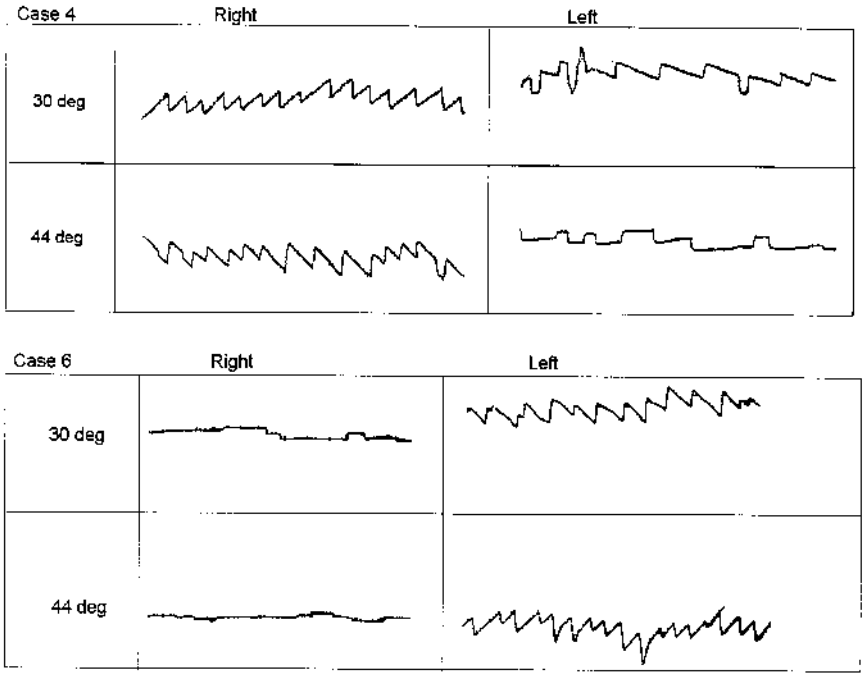


*Fig. 1.* Caloric data from cases 4 and 6.

gentamicin? We can suggest 3 potential explanations for these findings:

1. That the patients had pre-existing, asymptomatic, unilateral loss of vestibular function. While one cannot totally refute this explanation, it would be exceptional for acute uVD to occur without producing acute spontaneous vertigo or vomiting or both. While chronic progressive uVD can, in our experience, occur even in the absence of a slowly growing tumor such as a vestibular schwannoma, none of these patients had experienced symptoms of CVI before they were treated with systemic gentamicin.
2. That there was a subacute unilateral loss of vestibular function due to the gentamicin therapy. Presumably, in response to unilateral loss of vestibular function which occurs over several days, sufficient central compensation occurs so that vertigo is not produced. While this is a potential explanation, we are not aware of a precedent for this particular pattern of unilateral vestibular loss.
3. That these patients may in fact have suffered bilateral loss of vestibular function at the time of the gentamicin therapy, which was then followed by asymmetrical recovery of vestibular function. Some recovery of vestibular function following GVT can occur in humans (8); however, asymmetrical recovery has not previously been reported. This mechanism would explain the absence of vertigo in our patients. Although, in our view, asymmetrical recovery is a more likely mechanism than asymmetrical toxicity, there is in fact a precedent for asymmetric toxic effects from systemic drug therapy. Osteonecrosis of the femoral head following corticosteroid therapy is often unilateral (9).

In any case, these patients demonstrate that unilateral GVT, just like bilateral GVT, can occur in the absence of toxic serum gentamicin levels or renal insufficiency (1), and a high index of suspicion towards the development of ataxia or oscillopsia is required in patients receiving this drug. If in fact these cases do reflect asymmetrical recovery of vestibular function, this would be further evidence that recovery from GVT can occur, and would provide another reason for developing a means of preventing GVT. In our view, two simple steps could prevent or ameliorate GVT: *(i)* not giving the drug to any patient who is not ambulant; *(ii)* asking any patient receiving systemic gentamicin to perform a modified Romberg test before each dose of gentamicin is given. Any patient unable to stand on a foam mat with the eyes closed (10) should not be given any more gentamicin.

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