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<b>Abstract:</b>	<p><b>Introduction :</b> Gentamicin has a well-known potential for damaging the peripheral vestibular organs. However, it is considered to be innocuous to the CNS as it crosses the blood-brain barrier poorly. Here, we describe central neuro-otological abnormalities developed by a patient after deployment of gentamicin into his spinal space.</p> <p><b>Case summary :</b> A 61-year-old male unintentionally received gentamicin during spinal locoregional anesthesia for a urological procedure. During the first 48 hours the patient presented upper extremity dysmetria, dysarthria, and bilateral abducens nerve paralysis from which he recovered completely. He remained asymptomatic from day 3 to 10 after the incident. On day 11 he presented an acute vestibular syndrome. Severe bilateral vestibulopathy was confirmed by means of video head impulse testing. From day 14 onwards, he presented a persistent horizontal left-beating nystagmus, showing no variation or signs of compensation after 14 months, not responding to intensive vestibular rehabilitation or vestibular suppressant drugs. During follow-up, intercurrent gaze-evoked/direction-changing nystagmus has been recorded in various opportunities</p> <p><b>Discussion :</b> We interpreted these findings as signs of both severe peripheral bilateral vestibulopathy and cerebellar and/or midbrain late-onset neurotoxicity, which can be explained by the intrinsic neurotoxic capability of high doses of gentamicin in the CNS.</p>
<b>Response to Reviewers:</b>	

## **Central nystagmus and alterations in vestibular tests due to an inadvertent gentamicin administration into spinal space: A CARE case report**

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**Abstract:**

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**Key words:** Ototoxicity, Neurotoxicity, Gentamicin, Central vertigo, Adverse effects

## **Introduction**

Gentamicin selective toxic effect on peripheral vestibular organs is well known[1]. Far less is understood about the potential its effect on the central nervous system (CNS), and it has traditionally been considered as a “centrally-safe” drug, as it poorly crosses the blood brain barrier[2]. Here, we describe a late-onset impairment not only in peripheral vestibular organ but also in CNS, causing persistent vertigo and instability, after unintentional spinal administration of gentamicin. We report 20 months of follow-up, including abnormalities in physical examination, videonystagmography recordings and video Head Impulse test results.

## **Case Report**

A 61-year-old male (who gave his written informed consent to share his experience in this report), with no previous history of neuro-otological disorders, was submitted for a urological procedure, for which spinal locoregional anesthesia was selected. In this context, 60 mg of gentamicin (instead of bupivacaine) was unintentionally administered into the spinal space. Initially, no adverse reactions were observed, and the mistake was first adverted when no sensitive or motor blockage was obtained after 10 minutes. General anesthesia was then administered, and the programmed procedure was completed without surgical complications. The patient awoke asymptomatic. Seven hours later, the following symptoms installed themselves gradually: mild disorientation, bilateral lower extremity paresis and hypoesthesia, upper extremity dysmetria, abducens nerve paresis (with no nystagmus at this point) and dysarthria. Brain and medullar magnetic resonance imaging were normal. These symptoms lasted for 48-72 hours and then subsided completely. On the fourth day after the procedure, the patient was discharged asymptotically.

On the 11th day post-procedure vestibular symptoms appeared, including severe rotatory vertigo, instability, and a horizontal left-beating nystagmus, reaching 3.5 °/s of slow phase velocity with visual fixation removed under videonystagmography (VNG, see Figure 1a).

This nystagmus has persisted 20 months after onset of symptoms. The latest registry, one year after the incident, was almost identical to his first examination (Figure 1c). At some visits, the patient exhibited right-beating nystagmus when holding his gaze rightwards, which has been interpreted as intercurrent gaze-evoked nystagmus. Figure 1b shows a recording of this phenomenon at the 6<sup>th</sup> month post-incident. Additionally, a severe bilateral loss of vestibular function was appreciated in all semicircular canals (Figure 2). While gain was identically low in all canals, there was an asymmetrical organization of saccades between left and right-sided impulses. On left-sided impulses, saccades were triggered quite early (before 200 ms after the impulse) and were tightly grouped. On right-sided impulses, saccades appeared more disorganized and with a much larger triggering time, ranging up to 500 ms. We also want to highlight an almost complete absence of corrective saccades on vertical head impulses.

On vestibular evoked myogenic potentials (VEMP.), no response was obtained either on ocular or cervical VEMPs.

Analysis of voluntary saccades, smooth pursuit, and optokinetic nystagmus during VNG were all normal (not shown). Head-shaking nystagmus only exacerbated the left-beating nystagmus. No signs of deconjugation or gaze paresis were observed (particularly, no signs of abducens abnormality were seen). No cerebellar signs were present on physical examination. Again, there were no pathological findings on a second set of brain magnetic resonance imaging performed 4 months after the spinal injection. Also, there was no

increased cochlear aqueduct volume, or other anatomical abnormalities that would suggest increased risk of penetration to the inner ear from the spinal space[3].

The patient did not complain of hearing loss at any point, and hearing tests were normal (not shown).

The patient underwent extensive vestibular rehabilitation therapy (including visual stability, dynamic visual acuity, posture training, and gait rehabilitation using dual and multiple task, multimodal strategies, and including general fall-avoiding strategies), for over 8 months, which improved his static and dynamic stability. Nevertheless, he persists in exhibiting spontaneous nystagmus as previously described. No changes or benefits (clinically or in video-oculography) were observed after gabapentin (up to 600 mg per a month) or baclofen (up to 30 mg for three weeks) treatment attempts.

At the time of his last visit, the patient continued to present moderate to severe dizziness when in motion, persistent instability and a slightly ataxic gait (he can walk without assistance but suffers from falls occasionally). These symptoms are reported to have moderate to high impact in his quality of life, interfering with every-day activities and his field work as construction consultant.

## **Discussion**

Inadvertent epidural or spinal administration of unintended drugs is more frequent than might be expected[4]. Moreover, spinal injection of gentamicin has been reported previously but typically results in only mild back pain as a side effect with no further neurological complications[5]. We believe that in our case, our findings show severe gentamicin-induced vestibulotoxicity (GIV) as well as neurotoxicity in the CNS.

Peripheral GIV depends on the duration of exposure, cumulative dose, renal function, and patient age but also substantially on the patient's personal susceptibility, to the point that severe ototoxicity has been reported after a single dose[1,6,7]. In our patient, we believe that 60 mg of gentamicin delivered to the spinal compartment, reached the inner ear at a concentration high enough to produce severe bilateral vestibulopathy. It is also worth pointing out the delayed vestibulo-toxic effect after administration, a phenomenon well known in GIV from management of Ménière's diseases[8].

But beyond bilateral vestibulopathy our patient presented two sets of CNS impairments. First, shortly after the administration of gentamicin he presented a wide range of different neurological deficits. Fortunately, these symptoms were transient and disappeared completely after a few days. Whether these initial and transient neurological phenomena were specifically gentamicin-induced or were a product of chemical irritation of the CNS, can only be speculated.

However, almost two weeks after injection, persistent signs of central vestibular impairment appeared, namely: i) intercurrent gaze-evoked nystagmus; ii) persistent left-beating spontaneous nystagmus one year after the onset of symptoms (evidencing a severe deficit of central compensation); iii) asymmetrical corrective saccade abnormalities in head impulse testing.

These central impairments appear to share the delayed timing of peripheral damage, leading to the idea that gentamicin-induced ototoxicity and neurotoxicity share some of their mechanisms and dynamics[9]. In animal models, direct injection of aminoglycosides into the striatum in the brain has demonstrated not only severe dose-dependent neurotoxicity[10], but also that N-methyl-D-aspartate (NMDA) receptor hyperactivation and excitotoxicity to be the most likely mechanism for this phenomenon.

The actual site within the CNS of damage in our patient is more elusive. No abnormalities were found on repeated magnetic imaging studies. However, the neurological signs that we observed suggest probable implication of regions in the vestibular cerebellum (lack of corrective saccades in vertical head impulses, intercurrent gaze-evoked nystagmus, and principally, the lack of central compensation of spontaneous nystagmus).

These signs help explaining the persistence of symptomatology in our patient even after thorough and extensive vestibular rehabilitation. These therapies attempt to contribute to central compensation of peripheral vestibular damage, where the right and left vestibular nuclei adjust their passive firing rate (in absence of movement) to be equal with each other. If the central plasticity mechanisms involved in rearranging the brainstem vestibular network are impaired (which depend not only on the vestibular nuclei themselves, but strongly on the cerebellum), asymmetry in firing rate persists between the nuclei, and therefore persistent nystagmus is expected (slow phase velocity of nystagmus can be understood in many cases as a proportional to the amount of this asymmetry). Moreover, overall dynamic response to movement is also expected to be inaccurate, given this baseline asymmetry.

Usually, after peripheral vestibular damage onset, at least passive firing rate symmetry is achieved within days of weeks, particularly and faster, when vestibular rehabilitation is conducted. Persistence of spontaneous nystagmus evidence lack of central compensation, which explains the continuous dizziness our patient reports in his every-day life, as well as his persistent instability with inaccurate and inappropriate responses to movement.

## **Conclusions**

Altogether, this case raises concerns about the wider range of possible effects that gentamicin can have in the CNS, beyond peripheral vestibular structures. While used rarely in high doses in CNS[11], to understand this neurotoxicity potential may help patients presenting unexpected central vestibular symptoms.

**Conflicts of interest : none**

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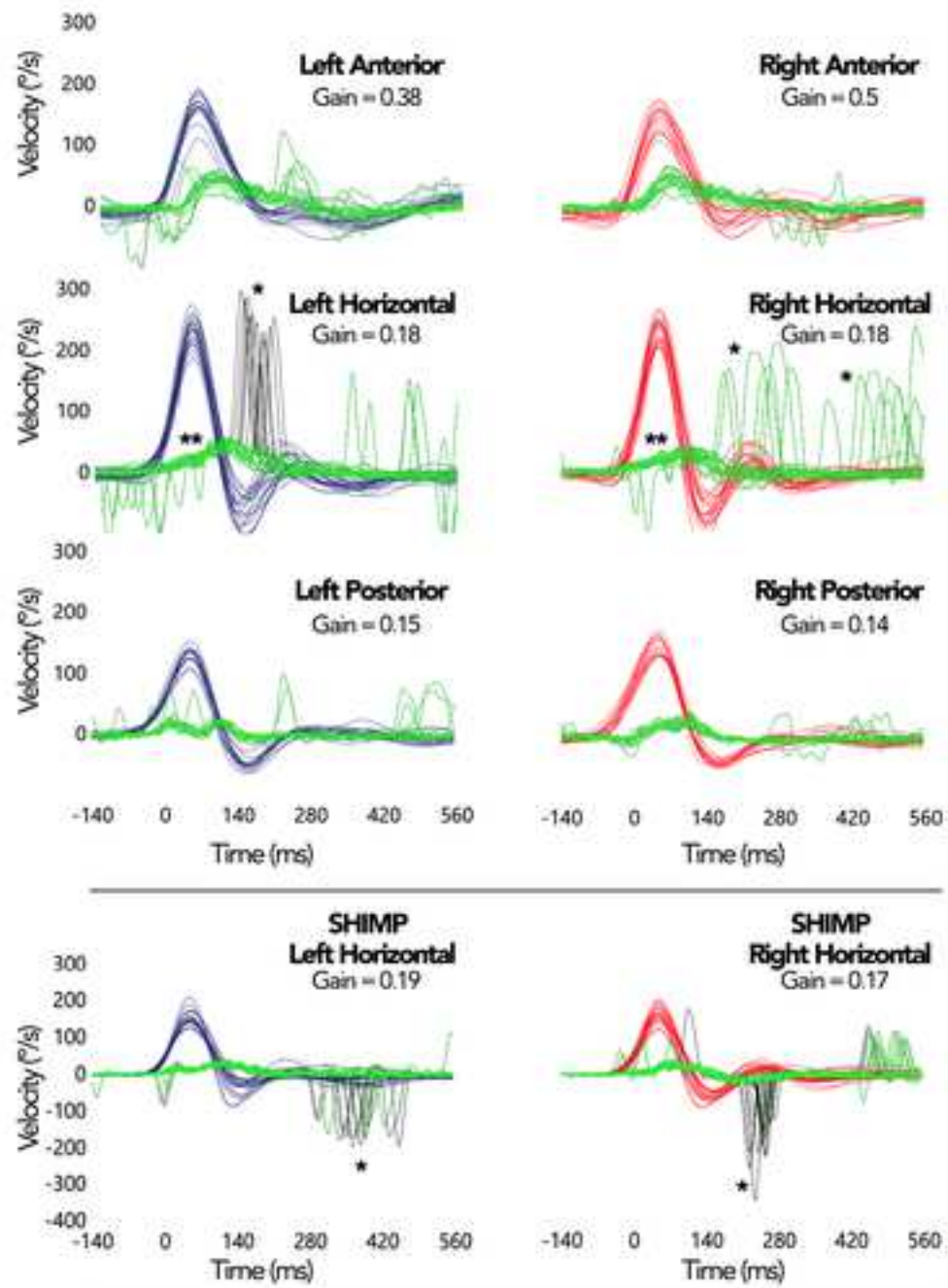
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Figure 1. Videonystagmography recordings are shown (only left eye traces) for central, leftward and rightward gazes. a) Initial recording by the authors, 8 weeks after onset of symptoms. b) Example of gaze-evoked nystagmus found at some visits. This example was taken 6 months after onset. c) Follow-up 12 months after onset of symptoms, exhibiting an almost identical nystagmus as that obtained a year earlier

Figure 2. Video head impulse test at month three after the gentamicin injection. The upper 6 panels show recordings from all six canals under the HIMP (Head impulse) paradigm: the patients head is quickly rotated while asking him to direct his gaze towards a stable-unmoving point in the surroundings. With a normal vestibular-ocular reflex, the patient should be able to hold his gaze to that point with negligible delay and no corrective saccades. In this case the presence of corrective saccades suggests an impairment in the vestibular-ocular reflex. The lower two panels show recordings for the horizontal canals under the SHIMP (Supression head impulse) paradigm: the patient head is quickly rotated while asking him to direct his gaze towards the projection of a laser beam being casted by the head impulse device (mounted on the patients head, with the effect of a red dot moving in his surroundings in perfect synchrony with the movement of the head). If no vestibular-ocular reflex is present at all, the patient's eyes will not move at all during head rotation, his gaze fixed on the moving red dot, and no corrective saccades are present). In this case there *are* corrective saccades present, evidencing some residual vestibular ocular reflex still active, that move the patients gaze away from the moving red dot during head rotation (as in attempting to maintain gaze towards a stable-unmoving point in the surrounding), and thus needing the later corrective saccades to move the eyes back to the red dot. Altogether both paradigms show a severe, but not complete, loss of the oculo-vestibular reflex.





# Central nystagmus and alterations in vestibular tests due to an inadvertent gentamicin administration into spinal space: A CARE case report

Running title: **Gentamicin induces central nystagmus**

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The publication of this case report has been approved by the Clinical and Research Ethics Committee at Clínica Alemana de Santiago, Santiago de Chile. Written informed consent was obtained from the patient following current guidelines from the mentioned Wthics Committee at Clínica Alemana de Santiag.

We declare no conflict of interest.

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Keywords: Gentamicin, bilateral vestibulopathy, central nystagmus

May 20<sup>th</sup>, 2021

Dear Dr. Laccourreye,

Editor in Chief

European Annals of Otorhinolaryngology, Head and Neck diseases

Ms. Ref. No.: ANORL-D-21-00179R1

As authors of the present revised version of our manuscript, we want to thank the reviewers for their new thorough and helpful revision. All their new comments have been considered, and corresponding changes have been made to the manuscript. Also, we have added specific comments in **BLUE** in this letter to answer specifically to each comment of both reviewers.

Thank you again for your time and the work you have given to this manuscript.

a) Modify the title in : Central nystagmus and alterations in vestibular tests due to an inadvertent gentamicin administration into spinal space : A CARE case report.

Done.

b) Delete Case report manuscript" from the title page.

Done.

c) After the conclusion add the following sentence : The patient agreed to have their data published"

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d) References in the text must be in brackets in the same format as the text such as [1] for instance

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Best Regards,

Hayo Breinbauer

