Remission of Recurrent Cochlear Hydrops Associated With Bromocriptine Treatment for Macroprolactinoma

Košec, Andro; Kruljac, Ivan; Ajduk, Jakov

Source / Izvornik: **American Journal of Audiology, 2019, 28, 548 - 552**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1044/2019_AJA-18-0191

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:163210

Remission of Recurrent Cochlear Hydrops Associated With Bromocriptine Treatment For Macroprolactinoma

Running Head: Is Bromocriptine an Option in Cochlear Hydrops?

Andro Košec, MD, PhD, FEBORL-HNS[a], Ivan Kruljac, MD, PhD[b], Assistant Professor Jakov Ajduk, MD, PhD[a]

[a] Department of Otorhinolaryngology and Head and Neck Surgery, Zagreb School of Medicine, University Hospital Centre “Sestre milosrdnice”, Zagreb, Croatia

[b] Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Centre “Sestre milosrdnice”, Zagreb, Croatia

Word count: 1205 words

Conflict of Interest

The authors have no conflict of interest to report.

Declaration of Funding

No funding was obtained in the preparation of this manuscript.

Corresponding author:

Andro Košec, MD, PhD, FEBORL-HNS

Department of Otorhinolaryngology and Head and Neck Surgery, Zagreb School of Medicine, University Hospital Center "Sestre Milosrdnice", Vinogradska cesta 29, 10000, Zagreb, Croatia

E-mail: andro.kosec@yahoo.com, tel. +38513787111

Abstract

Objective: Current recommendations for cochlear hydrops treatment include systemic glucocorticoids and diuretics. Cochlear cells express dopamine receptors, although their role is unknown in the pathophysiology of cochlear hydrops.

Case description: We report the case of remission of recurrent right sided cochlear hydrops in a young male patient treated with bromocriptine due to pituitary macroprolactinoma. Transient improvement was observed after oral steroid and diuretic treatment, but cochlear hydrops recurred until the dose of bromocriptine was increased to 10 mg daily.

Conclusion: Bromocriptine may stimulate dopamine receptors in cochlear cells with potential therapeutic role in patients with cochlear hydrops. There are no widely accepted and effective treatments for endolymphatic hydrops and identifying potential new and efficacious therapeutics is of high relevance.

Key words: cochlear hydrops; bromocriptine; treatment; dopamine receptors

Introduction

Cochlear hydrops may be considered as a variant of endolymphatic hydrops and is considered a distinct entity from idiopathic sensorineural hearing loss, with progression to Meniere's disease in some patients. (Glasscock, 1977) It is characterized by acute low-frequency hearing loss, aural fullness without vertigo or nausea, and most likely associated with membranous labyrinth distension confined to the cochlea at the apical turn. (Thai-Van, 2001) Options for therapy range from a low-salt diet restriction and diuretics to oral steroid treatment. Despite ubiquitous use, treatment efficacy of both diuretics and oral steroids has not been definitely shown in published literature. (Crowson, 2016) The common theme in these treatment modalities is modulation of ion transport across the labyrinth membranes, with over half of patients responding to treatment with restoration of a normal hearing threshold within two weeks of treatment. (Kakigi, 1995) Possible pathophysiologic mechanisms include reduction of hydrops and reversal of ion gradient disturbances on the *stria vascularis* that affect auditory physiology. (Salt, 1989) This paper discusses possible effects of bromocriptine on cochlear hydrops identified in a patient treated for pituitary prolactinoma. Prolactinomas are the most common hormone-secreting pituitary tumors and treatment is indicated if mass effects from the tumor and/or significant effects from hyperprolactinemia are present. (Serri, 1994) Bromocriptine has been used in treatment of functional prolactinomas since 1982, with no specific effect on the cochlea reported to date. (Rivera, 1976) Ototoxicity is not a common side effect of treatment and was noted in only three patients in published literature to date, with daily doses exceeding 20 mg. (Archer, 1982, Lanthier, 1984)

Case Description

A 32-year old male patient presented with aural fullness and fluctuating sensorineural hearing loss in his right ear in December 2017. His pure tone audiogram showed a right sided hearing threshold of 55 dB on 125, 250 and 500 Hz, respectively (Fig. 1). Oral steroids and furosemide treatment were recommended (80 mg of methyl-prednisolone with a tapered dose up to 8 mg through 8 days and 20 mg of furosemide daily with a tapered dose down to 10 mg every other day through 6 days). The symptoms resolved within a week of therapy and a follow-up pure tone audiogram showed normal hearing of the right ear (Fig. 1). After weaning from oral steroid therapy, the patient returned to the audiology department in February 2018 as well, complaining of a worsening of symptoms, and the audiogram showed a borderline hearing threshold of 20-25 dB on 125, 250 and 500 Hz, 10 dB lower than his normal hearing threshold. This incident could not be classified as a clear recurrence, since it did not cross over into hearing loss. However, he presented with another recurrence of right sided cochlear hydrops in April 2018, with his pure tone audiogram showing a hearing threshold identical to the one during the initial visit. Low-frequency sensorineural hearing loss regressed after reintroducing oral steroid and diuretic treatment in May 2018. After complete remission of his symptoms, the patient underwent magnetic resonance imaging (MRI) of the brain in May 2018. MRI disclosed a pituitary macroadenoma measuring 18×15×12 mm with signs of necrosis and involvement of the right cavernous sinus (Fig. 2). Endocrinological evaluation showed profoundly increased serum prolactin levels (605 μg/L, normal <20 μg/L). The patient was diagnosed with macroprolactinoma and treatment with bromocriptine was initiated in May 2018. The starting dose of bromocriptine was 2.5 mg daily, which was planned to increase to 10 mg daily over the next three months. The patient did not experience any bromocriptine-related side effects and had tolerated treatment well. However, another recurrence of right sided cochlear hydrops occurred in June 2018, while taking 3.75 mg of bromocriptine daily. The symptoms resolved within a week

of therapy and a follow-up pure tone audiogram showed normal hearing of the right ear (Fig. 3). The dose of bromocriptine was increased to 10 mg daily. The patient did not have any further recurrence of the cochlear hydrops and his prolactin levels decreased to 68 µg/L. We performed regular follow-up exams every 2 months (July, September, October 2018) with audiograms showing a normal hearing threshold. The last audiogram was performed in March 2019, showing a normal hearing threshold on the right side. (Fig. 4)

Discussion

To the best of our knowledge, this is the first case reporting the association between remission of recurrent cochlear hydrops and bromocriptine treatment. Although the strength of evidence that bromocriptine may be associated with the remission of cochlear hydrops is rather low, our paper may serve as a benchmark for future clinical trials. Several previous investigations have implicated that dopamine may exert protective effects on hearing. The dopaminergic innervation of the cochlea arises from the lateral olivocochlear (LOC) efferent system (Mulders and Robertson, 2004), with major peripheral targets of all LOC neurons being the unmyelinated terminals of cochlear nerve fibers in the IHC area. (Liberman, 1980) Dopamine acts as a neurotransmitter and mediates neural transmission between the LOC efferent terminals and the dendrites of the afferent nerves in the cochlea. (Ruel, 2006) Despite this reported expression pattern, cochlear perfusion of dopamine agonists and antagonists in guinea pig also affects cochlear responses generated mainly by OHCs. (Maison, 2012) Evidence exists, that dopamine released from the LOC efferents, has a protective effect in minimizing glutamate excitotoxicity at the IHC/afferent synapse following acoustic overexposure. (Ruel, 2001) LOC input is known to be important in noise-induced trauma. After LOC removal, noise can induce larger and more

harmful effects in the cochlea compared to cases with functional LOC fibres (Mulders, 2004). Moreover, ischemia also stimulates dopamine secretion in LOC efferent terminals, which most likely exerts a protective effect (Maison, 2012). Since D2 receptors are expressed in LOC efferent terminals, we can hypothesize that dopamine agonists may increase dopamine secretion with potential beneficial effects in patients with cochlear pathology (Lendvai, 2011). However, clinical trials with dopamine agonists in this setting have not been conducted. There is currently no evidence to support alternative mechanisms to explain a therapeutic effect of bromocriptine; e.g., restoration of electrochemical balance in the endolymph and/or endolymphatic pressure. Interestingly, previous reports suggest that dopamine agonists may be associated with ototoxicity. Bromocriptine-induced ototoxicity has been previously reported in three patients with chronic hepatic encephalopathy. (Lanthier, 1984) After increasing the daily dose for chronic encephalopathy treatment >20 mg, an ototoxic effect was observed, with daily dose reduction to 10 mg followed by pure tone audiogram hearing threshold improvement in all three reported patients. They did not have cochlear hydrops previously, and the results suggest that bromocriptine may have a dose dependent effect on the cochlea, with possible ototoxicity occurring in doses over 20 mg per day. It is difficult to claim that reversible ototoxicity was caused exclusively by bromocriptine, since the patients had severe hepatic encephalopathy, with many other possible pathophysiologic pathways leading to neural toxicity symptoms. However, these three incidents were listed to attempt to establish a link between bromocriptine and hearing threshold shifts. (Lanthier, 1984)

The two most common dopamine agonists are bromocriptine and cabergoline. Bromocriptine stimulates all dopamine receptor subtypes and may have several side effects. Cabergoline is a newer agent that has selective affinity to D2 dopamine receptor subtype. Hence, cabergoline showed superior efficacy and fewer side effects in patients with prolactinomas (Melmed, 2011).

Both cabergoline and bromocriptine are safe, well-tolerated and associated with low treatment costs. On the other hand, there are no widely accepted treatment options for cochlear hydrops. Based on our case presentation and aforementioned discussion, we believe that there is a rationale to perform a randomized clinical trial to assess the efficacy of bromocriptine and cabergoline in the treatment of cochlear hydrops.

Finally, we need to address the limitations of our paper. The possibility of the remissions to be spontaneous also casts a shadow on the reproducibility of bromocriptine treatment as described in the case report. In contrast, a recent study describes attack frequencies of 1 to 4 attacks per month, even after more than 20 years (Havia, 2004); this is supported by the experience of many centers. (Brandt, 2010) This is in stark contrast to our patient's experience, where he had no objective or subjective signs of cochlear hydrops since raising the bromocriptine dose to 10 mg per day (9 months of recurrence-free follow-up).

Conclusions

The case report is the first instance proposing novel pharmacological effects of bromocriptine on the human cochlea. It may represent a possible treatment option if the hypothesis is confirmed.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Glasscock, M. E., Miller, G. W. (1977) Diagnosis and management of cochlear hydrops. *Laryngoscope,* 87, 198-206.
2. Thai-Van, H., Bounaix, M. J., Fraysse, B. (2001) Menière's disease: Pathophysiology and treatment. *Drugs,* 61, 1089–1102.
3. Crowson, M. G., Patki, A., Tucci, D. L. (2016) A systematic review of diuretics in the medical management of Meniere's Disease. *Otolaryngology–Head and Neck Surgery,* 154, 824-34.
4. Kakigi, A., Takeda, T., Saito, H., Kataoka, H. (1995) Effect of isosorbide on hearing loss due to endolymphatic hydrops. *Acta oto-laryngologica. Supplementum*, 519, 223-226.
5. Salt, A. N., Inamura, N., Thalmann, R., Vora, A. (1989) Calcium gradients in inner ear endolymph. *American Journal of Otolaryngology*, 10, 371-375.
6. Serri, O. (1994) Progress in the management of hyperprolactinemia. *N Engl J Med*, 331, 942-944.
7. Rivera, J.L., Lal, S., Ettigi, P., Hontela, S., Muller, H.F., Friesen, H.G. (1976) Effect of acute and chronic neuroleptic therapy on serum prolactin levels in men and women of different age groups. *Clin Endocrinol (Oxf),* 5, 273-282.

8. Archer, D. F., Lattanzi, D. R., Moore, E. E., Harger, J. H., Herbert, D. L. (1982) Bromocriptine treatment of women with suspected pituitary prolactin-secreting microadenomas. *American Journal of Obstetrics & Gynecology,* 143, 620-5.
9. Lanthier, P. L., Morgan, M. Y., Ballantyne, J. (1984) Bromocriptine-associated ototoxicity. *Journal of Laryngology & Otology*, 98, 399-404.
10. Maison, S. F., Liu, X., Eatock, R. A., Sibley, D. R., Grandy, D. K., Liberman, M. C. (2012) Dopaminergic signaling in the cochlea: receptor expression patterns and deletion phenotypes. *Journal of Neuroscience*, 32, 344–355.
11. Mulders, W. H., Robertson, D. (2004) Dopaminergic olivocochlear neurons originate in the high frequency region of the lateral superior olive of guinea pigs. *Hearing Research*, 187, 122–130.
12. Liberman, M, C. (1980) Efferent synapses in the inner hair cell area of the cat cochlea: An electron microscopic study of serial sections. *Hearing Research*, 3, 189–204.
13. Ruel, J., Nouvian, R., Gervais d'Aldin, C., Pujol, R., Eybalin, M., Puel, J. L. (2001) Dopamine inhibition of auditory nerve activity in the adult mammalian cochlea. *European Journal of Neuroscience*, 14, 977–86.
14. Lendvai, B., Halmos, G. B., Polony, G., Kapocsi, J., Horváth, T., Aller, M., Sylvester Vizi, E., Zelles, T. (2011) Chemical neuroprotection in the cochlea: the modulation of dopamine release from lateral olivocochlear efferents. *Neurochemistry International,* 59, 150-8.
15. Melmed, S., Casanueva, F. F., Hoffman, A. R., Kleinberg, D. L., Montori, V. M., Schlechte, J. A., Wass, J. A. (2011) Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, 96,273-288.

16. Havia, M., Kentala, E. (2004) Progression of symptoms of dizziness in Ménière's disease. *Archives of Otolaryngology–Head & Neck Surgery,* 130, 431-435.
17. Brandt, T., Huppert, T., Hüfner, K., Zingler, V. C., Dieterich, M., Strupp, M. (2010) Long-term course and relapses of vestibular and balance disorders. *Restorative Neurology and Neuroscience,* 28, 69-82.
18. Ruel, J., Wang, J., Dememes, D., Gobaille, S., Puel, J. L., Rebillard, G. (2006) Dopamine transporter is essential for the maintenance of spontaneous activity of auditory nerve neurones and their responsiveness to sound stimulation. *Journal of Neurochemistry*, 97, 190–200.

Figure Labels

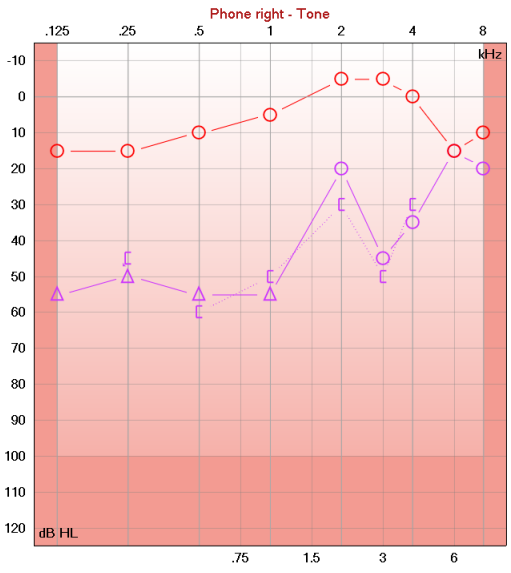
Fig. 1. Pure tone audiogram on initial presentation (purple color, December 2017) showing right sided low-frequency sensorineural hearing loss with a hearing threshold of 55 dB on 125, 250 and 500 Hz and hearing threshold after a week of oral steroid and diuretic therapy showing restitution of normal hearing on the right side (red color, January 2018).

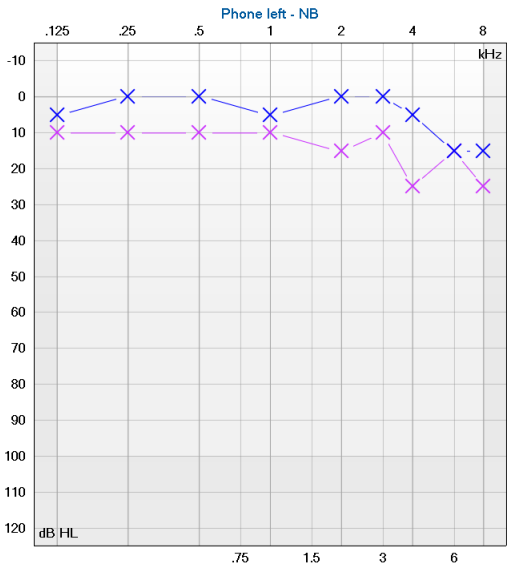
Fig. 2. Magnetic resonance imaging showing pituitary macroadenoma invading the right cavernous sinus shown on native T1-weighted coronal sequence (a) and signs of necrosis as shown on T2- weighted (b) and contrast-enhanced T1-weighted transversal sequence (c).

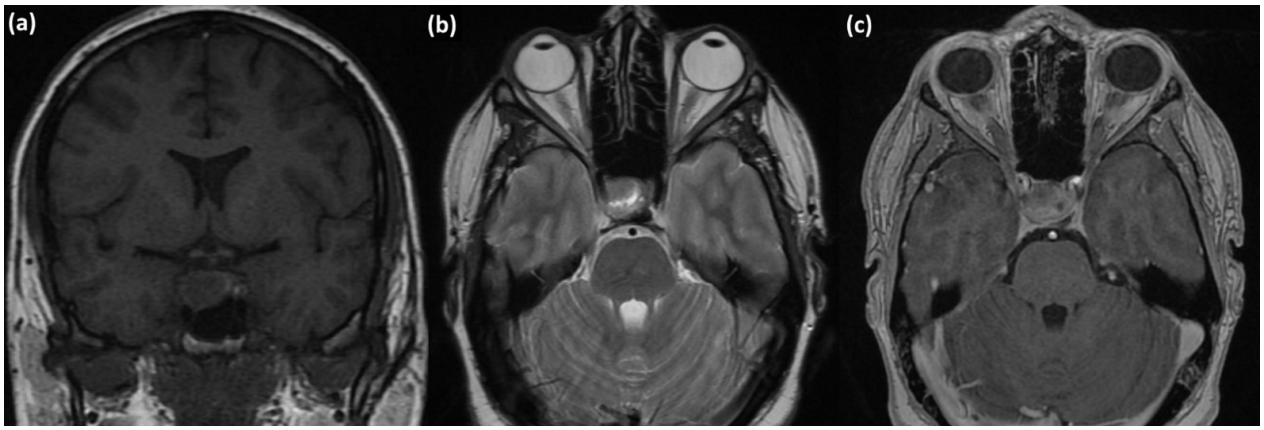
Fig. 3. Pure tone audiogram of a recurrence of right-sided low-frequency sensorineural hearing loss (red color, June 2018) corresponding to cochlear hydrops, showing low-frequency sensorineural hearing loss with a hearing threshold of 50 dB on 125, 250 and 500 Hz, and hearing

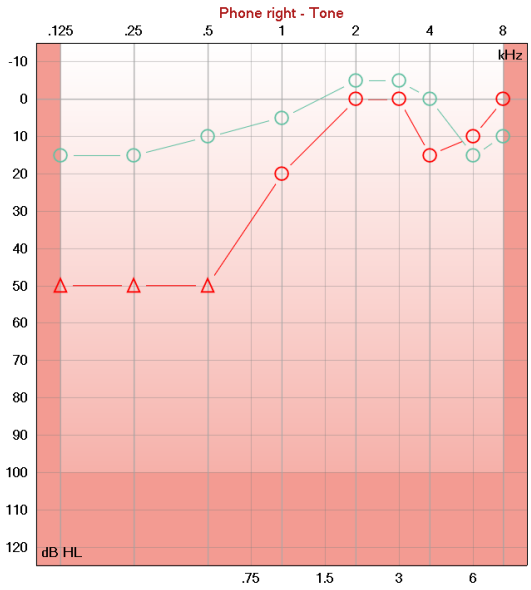
threshold after increasing the bromocriptine daily dose to 10 mg, showing restitution of normal hearing on the right side (green color, June 2018).

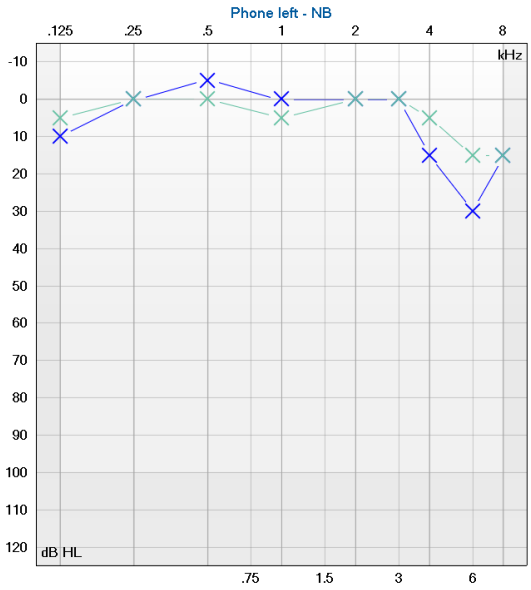
Fig. 4. Pure tone audiogram showing a normal hearing threshold after continued bromocriptine treatment (March 2019).

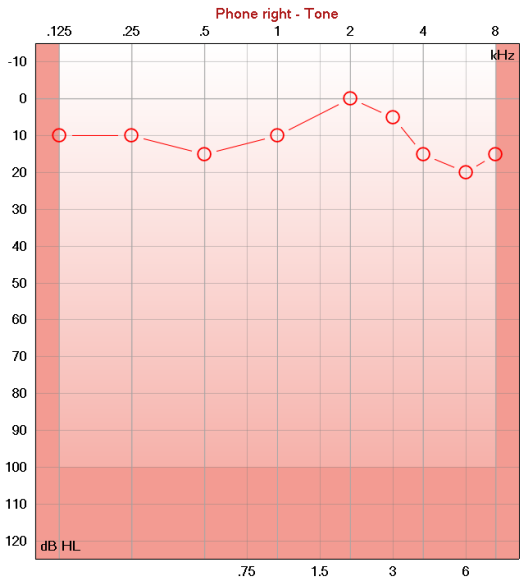

Phone right - Tone
.125
.25
.5
1
2
4
8
kHz
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
dB HL
.75
1.5
3
6

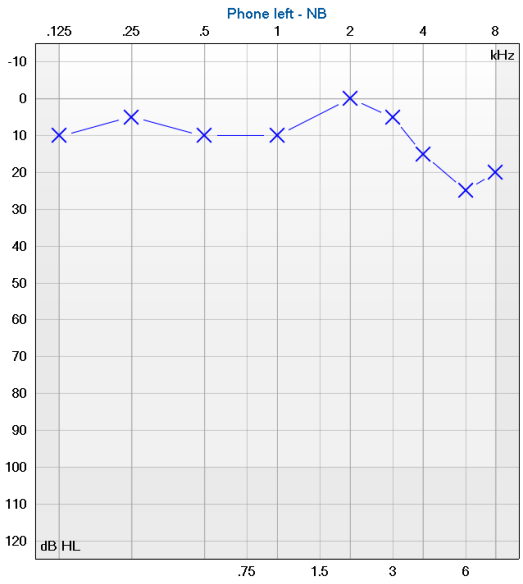

Phone left - NB
.125
.25
.5
1
2
4
8
kHz
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
dB HL
.75
1.5
3
6


(a)
(b)
(c)


Phone right - Tone
.125
.25
.5
1
2
4
8
kHz
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
dB HL
.75
1.5
3
6


Phone left - NB
.125
.25
.5
1
2
4
8
kHz
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
dB HL
.75
1.5
3
6


Phone right - Tone
.125
.25
.5
1
2
4
8
kHz
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
dB HL
.75
1.5
3
6


Phone left - NB
.125
.25
.5
1
2
4
8
kHz
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
dB HL
.75
1.5
3
6