Transient side shift of cluster headache attacks after unilateral greater occipital nerve injection

Brandt, R.B.; Naber, W.C.; Ouwehand, R.L.H.; Haan, J.; Ferrari, M.D.; Fronczek, R.

Received: 31 March 2023 | Accepted: 5 May 2023

DOI: 10.1111/head.14587

BRIEF COMMUNICATION

Transient side shift of cluster headache attacks after unilateral greater occipital nerve injection

Roemer B. Brandt MD[1] | Willemijn C. Naber MD[1] | Rosa-Lin H. Ouwehand BSc[1] | Joost Haan MD, PhD[1,2] | Michel D. Ferrari MD, PhD[1] | Rolf Fronczek MD, PhD[1]

[1]Department of Neurology, Leiden University Medical Centre (LUMC), Leiden, the Netherlands

[2]Alrijne Hospital Leiderdorp, Leiderdorp, the Netherlands

Correspondence
Rolf Fronczek, Department of Neurology, Leiden University Medical Centre (LUMC), Albinusdreef 2, Room Number: K-05-113, 2333 ZA, Leiden, the Netherlands.
Email: r.fronczek@lumc.nl

Abstract

Attacks of cluster headache (CH) are usually side-locked in most, but not all, patients. In a few patients, the side may alternate between or, rarely, within cluster episodes. We observed seven cases in whom the side of CH attacks temporarily shifted immediately or shortly after unilateral injection of the greater occipital nerve (GON) with corticosteroids. In five patients with previously side-locked CH attacks and in two patients with previously side-alternating CH attacks, a side shift for several weeks occurred immediately ($N = 6$) or shortly ($N = 1$) after GON injection. We concluded that unilateral GON injections might cause a transient side shift of CH attacks through inhibition of the ipsilateral hypothalamic attack generator causing relative overactivity of the contralateral side. The potential benefit of bilateral GON injection in patients who experienced a side shift after unilateral injection should be formally investigated.

KEYWORDS
case series, cluster headache, greater occipital nerve injection, side switch

INTRODUCTION

Cluster headache (CH) is a severe headache disorder, primarily characterized by attacks of excruciating unilateral pain in the orbital, supraorbital, or temporal regions accompanied by ipsilateral facial autonomic features. Attacks may last 15–180 min and may occur up to eight times a day, often also at night. In episodic CH, attacks typically occur in bouts (cluster episodes) lasting weeks or months, separated by periods of remission of at least 3 months. In patients with chronic CH, such remission periods are absent or are less than 3 months.[1] The exact pathophysiology of CH is unknown, but activation of the trigeminocervical complex and involvement of the hypothalamus have been implicated.[2]

In most (84%–91%) patients, CH attacks are clinically side-locked.[3] Hypothalamic activation ipsilateral to the headache was observed in a positron emission tomography–computed tomography study.[4] In some patients, however, spontaneous side shift of the attacks may occur between and rarely within cluster episodes.[3,5] In patients with chronic CH, unilateral electrical occipital nerve stimulation caused (transient) side shift of the attacks in some patients, which prompted the use of pre-emptive bilateral stimulation.[6,7]

Abbreviations: CH, cluster headache; GON, greater occipital nerve; LUMC, Leiden University Medical Center.

Roemer B. Brandt and Willemijn C. Naber contributed equally to this paper.

Unilateral corticosteroid injections that target the greater occipital nerve (GON) have been used since 1985 for prevention of CH attacks.[8] We observed several patients who reported a transient side shift of the attacks immediately or shortly after unilateral GON injection. These side shifts have been described after unilateral occipital nerve stimulation, but no previous reports regarding side shifts after GON injection were found. Here, we report seven of these cases and hypothesize about the underlying mechanism.

METHODS

Between December 2020 and December 2021, seven patients reported a side shift of CH attacks after GON injection during regular consultations. All consultations were performed by the authors (R.B.B. or R.F.) in the outpatient headache clinic of the LUMC. In total, 87 GON injections were performed during this period. All GON injections were performed as standard clinical care. In line with previous studies, a 3 mL mixture of 2% lidocaine and 80 mg methylprednisolone was injected at one third of the distance between the occipital protuberance and the mastoid process ipsilateral to the headache, directly below the superior nuchal line.[9] Written informed consent for the publication of the information was obtained from all patients. Data were retrospectively collected from participants' files. Telephone interviews were carried out to gather any missing information. The study was approved by the local ethics committee of the Leiden University Medical Center (LUMC) and all patients provided informed consent (METC LDD; protocol number G21.055).

RESULTS

For a summary of the cases, see Table 1.

Case 1

This 46-year-old man has experienced left-sided CH since 2016, initially episodic and then chronic from 2021. In 2020, immediately after a left GON injection, he had right-sided attacks for 4 weeks and then alternated right- and left-sided attacks for 2 weeks. After this, his normal pattern of left-sided attacks returned. The right- and left-sided attacks were clinically identical.

Case 2

A 49-year-old man had right-sided episodic CH since 2003. Immediately after a right GON injection in 2016, he had clinically identical left-sided attacks for several weeks. Immediately after a left GON injection, the side of the attacks changed back to the right.

TABLE 1 Patient and side shift characteristics.

				Attack side		Onset side-shift (after GON)	Duration side-shift	Autonomic symptoms		Attack frequency		Location		Duration attack		Intensity (NRS)	
Case #	Age	Sex	CH type	Before (%)	During (%)			Before	During	Before	During	Before	During	Before	During	Before	During
1	46	M	Episodic	L(100)	R(100)	Immediate	6 weeks	Present	=	1–2/day	?	M, O	=	180–240 min	+	10	− (9)
2	49	M	Episodic	R(100)	R(100)	Immediate	3 weeks[a]	Present	=	3/day	=	O,T	=	180–240 min	=	10	− (9)
3	40	M	Chronic	R(100)	L(90), RL(10)	Immediate	Ongoing	Present	=	6–7/day	2-3/day	O, T	Unknown	60–150 min	=	10	Unknown
4	45	M	Episodic	L(100)	R(100)	Immediate	1 week	Present	Absent	3–12/day	3/day	O	T	90–180 min	+	10	− (7, 8)
5	50	M	Chronic	L(100)	R(100)	Week 3	1 week	Present	=	2/day	?	M, O, T	T, O	240 min	=	4–10	− (7)
6	30	F	Chronic	R(80, L(20)	L(100)	Immediate	Ongoing	Present	=	3–4/day	0–2/day	O	=	180–240 min	=	10	+ (10)
7	21	F	Chronic	L(90), RL (10)	L(25), R(50), RL(25)	Immediate	4 weeks	Present	=	3–4/day	Initial 7, then 2/day	O, T	=	90–180 min	=	10	+ (10)

Note: Attack characteristics are compared between the usual CH attacks "before" and the CH attacks "during" the side shift. +, increase; −, decrease; =, equal.

Abbreviations: CH, cluster headache; F, female; GON, greater occipital nerve; L, left; M, male; M, maxillar; NRS, numeric rating scale; O, orbital; R, right; RL, bilateral; T, temporal.

[a]Shift back after contralateral GON injection.

Case 3

This 40-year-old man had had right-sided episodic CH since 2003. In 2014, immediately after a right GON injection, the side of the attacks shifted to predominantly left-sided attacks (90% left, 10% right). The left- and right-sided attacks were clinically similar. From 2017, the CH evolved into left-sided chronic CH.

Case 4

A 45-year-old man had left-sided episodic CH since 2001. In 2019, immediately after a left GON injection, he had right-sided attacks for 1 week, after which the attack side returned to the left. The right-sided attacks were less painful and lacked accompanying autonomic symptoms. After a second left-sided GON injection, no side shift occurred, but immediately after a third left-sided injection in 2021, he experienced a similar side shift as before.

Case 5

A 50-year-old man had chronic CH since 2009 and only left-sided attacks. He was successfully treated twice with GON injections without any change of the attack side; however, 3 weeks after the third injection he started having right-sided attacks, which were slightly less severe than the left-sided ones, but otherwise clinically identical. After a week, the attacks shifted back to the (usual) left side. A fourth injection, sometime later, had no effect on attack laterality. After a fifth injection, however, a similar phenomenon occurred as after the third.

Case 6

This 30-year-old woman had had predominantly right-sided chronic CH; occasional attacks occurred on the left side. In 2016, immediately after a right-sided GON injection, she had only left-sided attacks. For a fortnight, these were more intense than before, but with a lower frequency (twice daily). Thereafter the attack frequency returned to her usual 3–4 attacks per day. A few weeks later, the right-sided attacks returned, but now in an equal left–right ratio.

Case 7

A 21-year-old woman had had predominantly (90%) left-sided chronic CH since 2020; in 10% of the attacks, the side of the pain and autonomic symptoms shifted from left to right within the attack. Immediately after a left-sided GON injection, the attacks shifted predominantly to the right (50%). The remaining attacks were either left (25%) or side shifting within the attack (25%). Four weeks later, the attacks returned to predominantly left (50%) or side shifting within the attack (50%). Of note, during the side shift, the attacks were more severe.

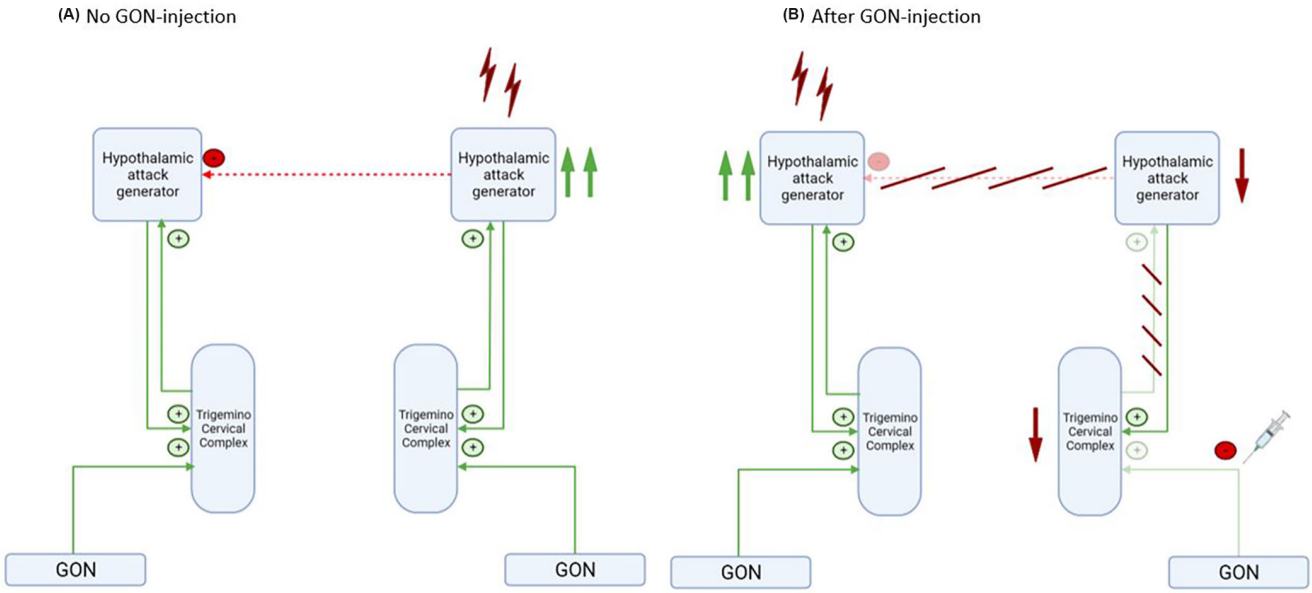

FIGURE 1 Proposed mechanism of side shifts after GON injection. (A) Usual situation during cluster headache episodes: the hypothalamic attack generator ipsilateral to the clinical side of cluster headache attacks suppresses the contralateral hypothalamic attack generator. (B) Unilateral injection of the GON with methylprednisolone causes attenuation of the excitatory effect of the ipsilateral GON and consequently a reduction of the activity of the ipsilateral trigeminal system, reducing the activity of the ipsilateral hypothalamic attack generator. In turn, this will result in (relative) overactivation of the "initially weaker" contralateral hypothalamic attack generator, causing a side shift. GON, greater occipital nerve; '+', excitatory; '−', inhibitory. [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

We report seven patients in whom the side of CH attacks temporarily changed immediately or shortly after a unilateral GON injection. Five of these patients never experienced attacks on the other side and two patients noticed a significant change in attack side distribution. Two patients even had such a side shift twice after a GON injection. Side shifts sometimes occur spontaneously between cluster episodes,[3] but almost never within a cluster episode.[10] Although a coincidental relationship cannot be ruled out, the close temporal relationship between the GON injection and the transient side shift was striking, especially since the duration of the side shift coincided with the duration of the presumed pharmacodynamic effect of the locally injected steroids. The mechanism by which GON injections with methylprednisolone can prevent CH attacks is unknown. It has been argued that the trigeminal circuits are overactivated during CH attacks.[11] Under normal conditions the GON has an excitatory effect on the trigeminal circuits.[11,12] We postulate that injection of the GON with methylprednisolone could reduce the excitatory effect of the GON and thereby inhibit trigeminal circuits via (i) a structural connection in the C2 spinal segments, where afferent nerve fibers of the GON and the trigeminal nerve converge and (ii) a more centrally located functional connectivity between these nerves[13,14] (Figure 1).

Why CH attacks are usually unilateral and side locked remains unclear. It has been postulated that both sides of the hypothalamus can act as an attack generator; however, during a CH episode, one side is more active than the other and suppresses the contralateral hypothalamus causing clinical features on the ipsilateral side (Figure 1A).[15] When the more active side of the hypothalamus cannot suppress the other side sufficiently, a side shift may occur. This hypothesis is supported by the observation that even outside a cluster episode the hypothalamic side ipsilateral to the attacks is hyperexcitable to external pain stimuli compared to the contralateral side supports.[16] Unilateral injection of the GON with methylprednisolone reduces the normally present excitatory effect of the GON on the trigeminal system ipsilaterally, resulting in reduced activity of the ipsilateral hypothalamic attack generator (Figure 1B). In turn, this will result in (relative) overactivation of the "initially weaker" contralateral hypothalamic attack generator, causing a side shift. Similarly, unilateral electrical neurostimulation of the GON can also cause a disturbance of this balance and consequently a side shift.[6,7] A spontaneous disturbance of the hypothalamic activity balance could explain spontaneous side shifts.

Due to the small numbers, no predictive factors could be identified; however, in two cases we observed a recurrence of a side switch after a new GON injection, suggesting that a previous side switch could be a predictive factor.

In conclusion, unilateral GON injection with methylprednisolone may sometimes cause a transient side shift of CH attacks, presumably through temporary attenuation of the excitatory effect of the GON on the ipsilateral trigeminal circuits. This, in turn, may shift the preexisting activity balance between the hypothalamic attack generator to the contralateral side. The potential benefit of bilateral, rather than unilateral, injections of the GON with methylprednisolone, should be formally investigated, especially in patients who experienced a side shift after unilateral injection.

AUTHOR CONTRIBUTIONS

Study concept and design: Roemer B. Brandt, Rolf Fronczek. *Acquisition of data*: Roemer B. Brandt, Willemijn C. Naber, Rosa-Lin H. Ouwehand, Joost Haan. *Analysis and interpretation of data*: Roemer B. Brandt, Willemijn C. Naber, Rosa-Lin H. Ouwehand, Joost Haan, Michel D. Ferrari, Rolf Fronczek. *Drafting of the manuscript*: Roemer B. Brandt, Willemijn C. Naber, Rosa-Lin H. Ouwehand. *Revising it for intellectual content*: Roemer B. Brandt, Willemijn C. Naber, Rosa-Lin H. Ouwehand, Joost Haan, Michel D. Ferrari, Rolf Fronczek. *Final approval of the completed manuscript*: Roemer B. Brandt, Willemijn C. Naber, Rosa-Lin H. Ouwehand, Joost Haan, Michel D. Ferrari, Rolf Fronczek.

CONFLICT OF INTEREST STATEMENT

Roemer B. Brandt, **Willemijn C. Naber**, **Rosa-Lin H. Ouwehand**, **Joost Haan**, **Michel D. Ferrari**, and **Rolf Fronczek** declare no conflicts of interest.

ORCID

Roemer B. Brandt https://orcid.org/0000-0002-2932-4872

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
2. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol*. 2018;17:75-83.
3. Meyer EL, Laurell K, Artto V, et al. Lateralization in cluster headache: a Nordic multicenter study. *J Headache Pain*. 2009;10:259-263.
4. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. *Lancet*. 1998;352:275-278.
5. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. *Neurology*. 2002;58:354-361.
6. Magis D, Gerardy PY, Remacle JM, Schoenen J. Sustained effectiveness of occipital nerve stimulation in drug-resistant chronic cluster headache. *Headache*. 2011;51:1191-1201.
7. Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J. Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. *Lancet Neurol*. 2007;6:314-321.
8. Ornello R, Lambru G, Caponnetto V, et al. Efficacy and safety of greater occipital nerve block for the treatment of cluster headache: a systematic review and meta-analysis. *Expert Rev Neurother*. 2020;20:1157-1167.
9. Brandt RB, Doesborg PGG, Meilof R, et al. Repeated greater occipital nerve injections with corticosteroids in medically intractable chronic cluster headache: a retrospective study. *Neurol Sci*. 2021;43:1267-1272.
10. Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G. Cluster headache—clinical findings in 180 patients. *Cephalalgia*. 1983;3:21-30.
11. Busch V, Jakob W, Juergens T, Schulte-Mattler W, Kaube H, May A. Occipital nerve blockade in chronic cluster headache patients and functional connectivity between trigeminal and occipital nerves. *Cephalalgia*. 2007;27:1206-1214.
12. Busch V, Jakob W, Juergens T, Schulte-Mattler W, Kaube H, May A. Functional connectivity between trigeminal and occipital nerves

revealed by occipital nerve blockade and nociceptive blink reflexes. *Cephalalgia*. 2006;26:50-55.
13. Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. *Brain*. 2002;125:1496-1509.
14. Gaul C, Roguski J, Dresler T, et al. Efficacy and safety of a single occipital nerve blockade in episodic and chronic cluster headache: a prospective observational study. *Cephalalgia*. 2017;37:873-880.
15. Young WB, Rozen TD. Bilateral cluster headache: case report and a theory of (failed) contralateral suppression. *Cephalalgia*. 1999;19:188-190.
16. Schulte LH, Haji AA, May A. Phase dependent hypothalamic activation following trigeminal input in cluster headache. *J Headache Pain*. 2020;21:30.

How to cite this article: Brandt RB, Naber WC, Ouwehand R-L, Haan J, Ferrari MD, Fronczek R. Transient side shift of cluster headache attacks after unilateral greater occipital nerve injection. *Headache*. 2023;63:1193-1197. doi:10.1111/head.14587