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BRIEF COMMUNICATION

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

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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.

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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 80mg 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.

Case #	Age	Sex	CH type	Attack side		Onset side-shift (after GON)	Duration side-shift	Autonomic symptoms		Attack frequency		Location		Duration attack		Intensity (NRS)	
				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.

^aShift back after contralateral GON injection.

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.

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