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Navigating the waves of cluster headache: clinical aspects and GON modulation

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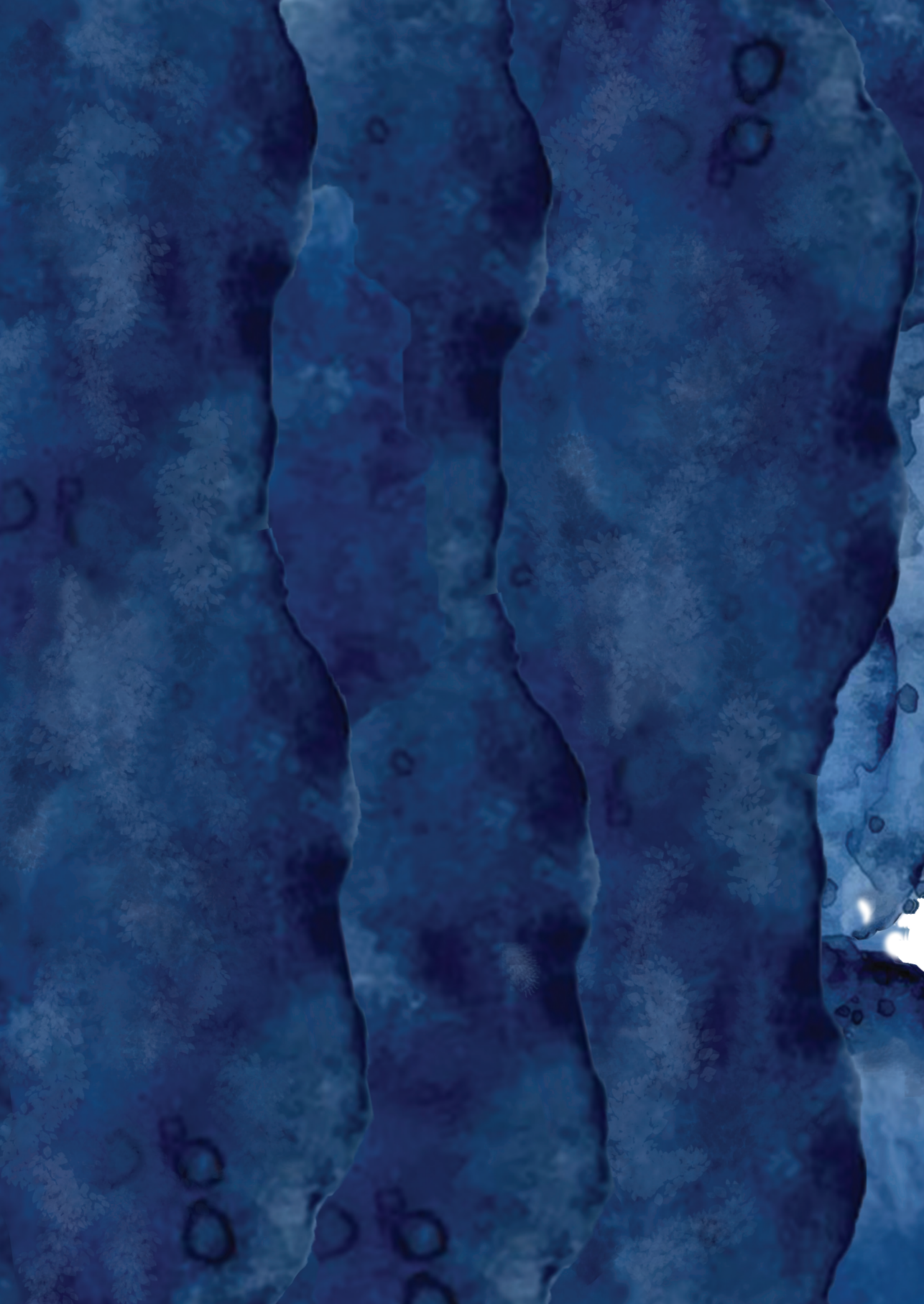
PART

II

BREAKING THE WAVES

GON MODULATION IN CLUSTER HEADACHE



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TRANSIENT SIDE-SHIFT AFTER UNILATERAL GREATER OCCIPITAL NERVE INFILTRATION

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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 7 cases in whom the side of CH attacks temporarily shifted immediately or shortly after unilateral injection of the greater occipital nerve (GON) with steroids. 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 conclude 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.

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 minutes 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 three months. In patients with chronic CH, such remission periods are absent or are less than three 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 PET-CT 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]
Unilateral corticosteroid injections that target the greater occipital nerve (GON) are 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 hypothesise on the underlying mechanism. The study was approved by the local ethics committee of the LUMC and all patients provided informed consent (*METC LDD; protocol number G21.055*).

METHODS

Between December 2020 and December 2021, seven patients reported a side-shift of cluster headache attacks after GON-injection during regular consultations. All consultations were performed by the authors (RBB or RF) in the outpatient headache clinic of the Leiden University Medical Center. 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.

Table 1. Patient and side shift characteristics.

Case #	Age	Sex	CH Type	Attack Side		Onset side-shift (after GON)	Duration side-shift	Autnomic 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*	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	?	60-150 min.	=	10	?
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)

Legend: Attack characteristics are compared between the usual cluster headache (CH) attacks "before" and the CH attacks "during" the side-shift. Legend: +:Increase, -:decrease, =: equal.*: shift back after contralateral Greater Occipital Nerve (GON)-injection. Numeric Rating Scale (NRS). Male (M) and female (F)
L=left; R=right; RL=bilateral. M=maxillar; O=orbital; T=temporal. ?=unkown

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 from 2021 chronic. 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 week. Immediately after a left GON-injection, the side of the attacks changed back to the right.

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 one 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 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 has 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, three 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 (usuall) 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 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 GON-injection, the attacks shifted predominantly to 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.

DISCUSSION

We report seven patients in whom the side of CH attacks temporarily changed immediately or shortly after an unilateral GON injection. Five of these patients never experienced attacks on the other side and two patients noticed a significant chance 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 fibres of the GON and the trigeminal nerve converge; and (ii) a more centrally located functional connectivity between these nerves (Figure 1). [13, 14]

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. How-

ever, 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).

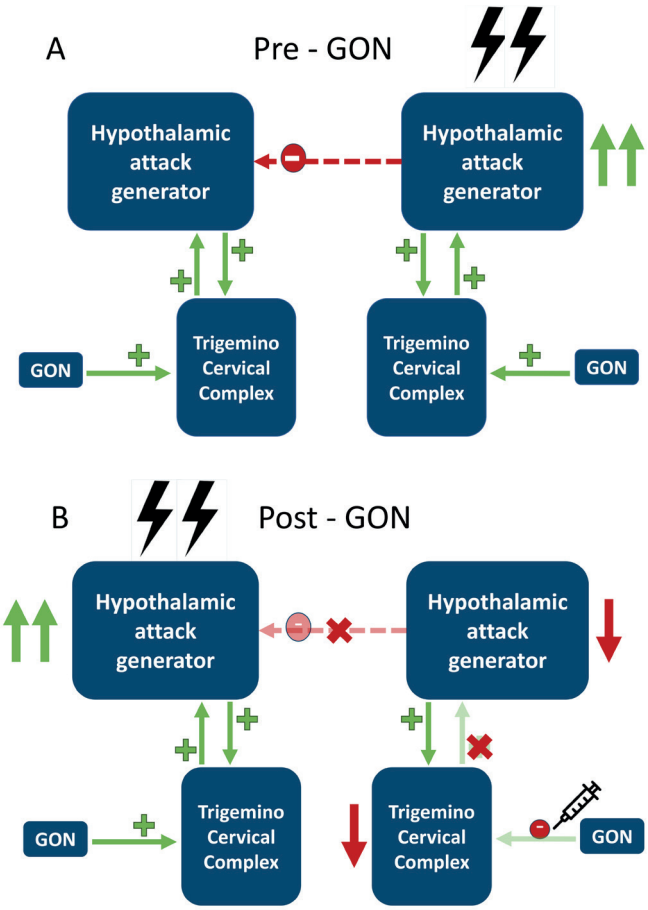

Figure 1. Proposed mechanism of side-shifts after GON injection.

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.

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.

ARTICLE HIGHLIGHTS

- Attacks of cluster headache are usually side-locked in most, but not all patients.
- Unilateral GON-injections might cause a transient side-shift of cluster headache 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.

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