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Are Genetics the Predicting Factor for the Success of Migraine Surgery? A Report on Identical Twins ☆

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ABSTRACT

Migraine affects more than 1 billion people globally, with distinct genetic variations influencing susceptibility. Thereby, genetic variations play a key role in the probability of developing migraine. However, personalized genetic analysis-based treatment options in migraine treatments are limited. Notably, surgical deactivation of extracranial trigger has shown efficacy in the treatment of migraine patients with identifiable trigger points in specific anatomical locations in the head and neck region.

We present the first case of monozygotic twin sisters, both experiencing occipital and temporal-triggered migraine headaches with identical history and characteristics and without response to conservative migraine treatments. After surgical intervention, targeting the greater and lesser occipital nerves as well as auriculotemporal nerves, both twin sisters exhibited an over 99% reduction in symptoms without postoperative complications. This case

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suggests a potential correlation between genetic background, irrespective of environmental factors, and the effectiveness of surgical deactivation of trigger points in migraine management.

Introduction

Migraine affects more than 1 billion people worldwide.[1] There is compelling evidence indicating that both specific monogenetic and polygenetic variations contribute to an individual's susceptibility to develop migraine.[2] The exploration of an extracranial, peripheral origin of migraine headache within a distinct subgroup of migraineurs has introduced a novel treatment approach involving the surgical deactivation of potential extracranial trigger points. The overarching objective of migraine headache surgery, like any other migraine treatment, is to optimize symptoms by reducing duration, frequency, and intensity of pain. Surgical intervention for migraines demonstrates success, defined as a symptom reduction exceeding 50%, in a range of 58.3% to 95.5% of patients.[3]

In this report, we present the first case of identical twin sisters suffering from occipital and temporal-triggered migraines, both experiencing significant relief through the deactivation of occipital and temporal trigger sites. This raises the question of whether genetic variations not only make individuals prone to a specific type of headache but also act as a factor influencing the success of migraine surgery.

Patients and Results

Twin Sister 1

A 36-year-old woman presented to our department with treatment-refractory chronic migraine with aura since childhood. Diagnosis of migraine was independently confirmed by two neurologists. Her primary migraine triggers included hormonal fluctuations and stress, with no history of trauma. Migraine-specific medications and other treatment modalities failed.

As illustrated in Figure 1a, her pain started bilaterally, 3 cm caudal and 1.5 cm lateral to the occipital protuberance, predominantly on the right side and radiated toward the forehead and to the back of both eyes. Concurrent symptoms included neck tightness, ear pain, and vertigo. A bilateral nerve block with local anesthetics targeting the greater (GON) and lesser occipital nerve (LON) during an active migraine episode led to a notable reduction in pain intensity from NRS 9.5/10 before injection to NRS 0/10 5 minutes after injection, with effects lasting for 5 hours.

Subsequent surgical intervention included decompression of both GON trigger points and neurectomy of both LONs. The GON nerve exhibited compression by muscle fascia and muscle, with a change in color and caliber predominantly observed at its exit point from the semispinalis capitis muscle (see Figure 2a). In addition, a prominent occipital artery was identified and clipped. Compression signs (as well as pain preoperatively) were more severe on the right side. The LONs were found in close proximity with a dominant vessel. Both nerves were avulsed, with vessels cauterized. The evaluation of pre- and postoperative symptoms including the calculation of the Migraine Headache Index (MHI), derived from the multiplication of migraine frequency, intensity, and duration, is consolidated in Table 1.

Preoperatively, Sister 1 exhibited an MHI of 136.5, which decreased to 6.0 at 2-year follow-up (95.6% pain reduction). Residual symptoms manifested on both temples with pulsating pain at the preauricular region. After a positive nerve block, both auriculotemporal nerves (ATNs) were surgically avulsed and the superficial temporal artery and vein clipped under local anesthesia, leading to a further decrease in MHI to 0.75 at 1-year follow-up, representing a 99.5% reduction in pain.

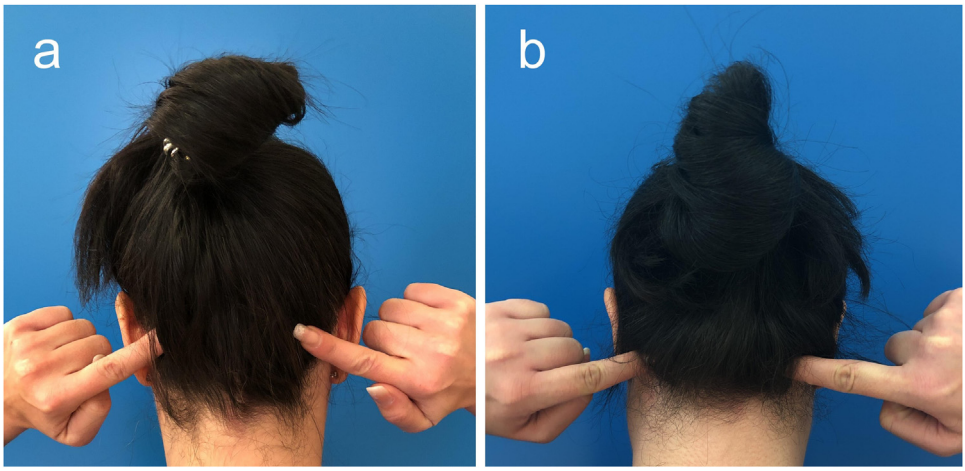

Figure 1. Preoperative photographs of Sister 1 (a) and Sister 2 (b) illustrating the typical greater occipital nerve (GON) trigger point, where the onset of migraine pain occurs: located 3 cm caudal and 1.5 cm lateral to the occipital protuberance.

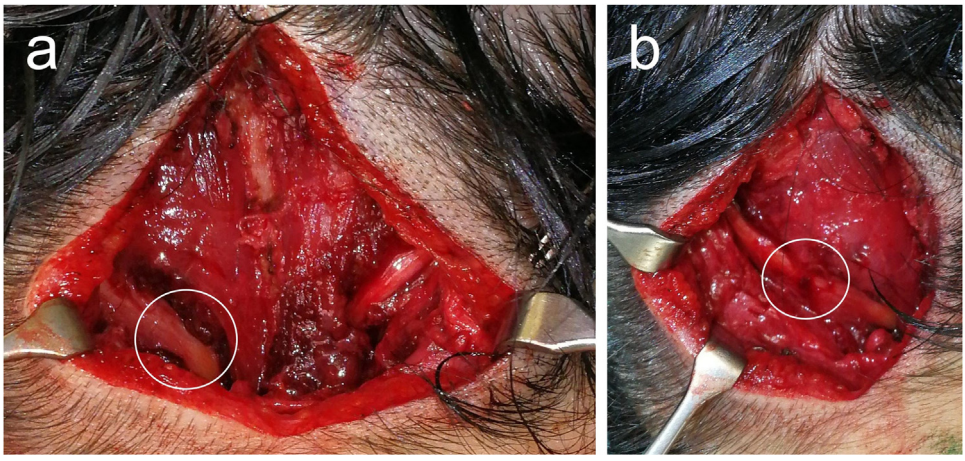

Figure 2. Intraoperative photographs of decompression of both GON trigger points in Sister 1 (a) and Sister 2 (b) with typical signs of compression at its exit point from the semispinalis capitis muscle.

Twin Sister 2

Sister 1's monozygotic twin also suffered from refractory chronic migraine with aura since childhood. Her pain and migraine triggers mirrored those of her sister, as outlined above (see Figure 1b). A nerve block using local anesthetics at the GON triggers during an active migraine attack with a pain intensity of NRS 7/10 resulted in a temporary complete elimination of symptoms. Subsequently, bilateral nerve decompression surgery of GON trigger points with ligation of an intertwining occipital artery was performed. Like Sister 1, the nerve displayed typical signs of compression at the exit point of the semispinalis capitis muscle, more pronounced on the right side compared with the left (see Figure 2b). Preoperatively, Sister 2 exhibited an MHI of 210.0, which decreased to 7.5 at 6-month follow-up (96.4% pain reduction). Residual symptoms emerged at both LON trigger sites, radiating to the ear, accompanied by vertigo, and at both temples with pulsating pain at the preauricular region, mirroring the symptoms observed in Sister 1. After a nerve block of the LON as well as ATN, providing

Table 1
Summary of pre- and postoperative symptoms of both sisters and calculation of Migraine Headache Index (MHI = frequency × intensity × duration as a fraction of 24 hours; MH = migraine headache; NRS = Numerical Rating Scale; FU = Follow-up) and Pain Reduction in percentage (%).

	Sister 1			Sister 2		
	preop	FU 2 years (after 1st surgery)	FU 1 year (after 2nd surgery)	preop	FU 6 months (after 1st surgery)	FU 1 year (after 2nd surgery)
Frequency (MH/month)	21.0	4.0	2.0	30.0	3.0	1.0
Intensity (NRS 0-10)	6.5	3.0	3.0	7.0	5.0	4.0
Duaration (hours/24hours)	24.0	12.0	3.0	24.0	12.0	12.0
MHI	**136.5**	**6.0**	**0.75**	**210.0**	**7.5**	**2.0**
Reduction (%)		**95.6%**	**99.5%**		**96.4%**	**99.1%**

Sister 1 exhibited a reduction in MH frequency from 21 days before surgery to two days at 1-year follow-up. The MHI of 136.5 decreased to 0.75 (99.5% pain reduction). Sister 2 exhibited a reduction in MH frequency from 30 days preoperatively to one day at 1-year follow-up. Her MHI of 210.0 decreased to 2.0 (99.1% pain reduction).

complete relief of symptoms, bilateral avulsion of both LONs and ATNs with ligation of vessels was performed. The MHI further decreased to 2.0, representing a 99.1% reduction in pain.

Discussion

Twin studies are considered a gold standard for investigating the genetic predisposition to a disorder. Monozygotic twins, with their identical genomes, provide a realistic model where shared genetic variations help untangle the interplay between genetics and environmental influences. A multinational twin study revealed a genetic contribution to migraine ranging from 34% to 57%.[4] Furthermore, familial aggregations of rare migraine subtypes, such as familial hemiplegic migraine, occipital neuralgias, and nervus intermedius neuralgias, have been documented in the literature.[5,6]

In addition, twin studies examining the heritability of peripheral compressive neuropathies, such as carpal tunnel syndrome (CTS), have shown a genetic susceptibility. Hakim et al. demonstrated a predominant genetic contribution to CTS in female-female twin pairs, with a heritability estimate of 46%, whereas environmental risk factors showed no significant association with CTS.[7] Moreover, recent findings indicate a correlation between upper extremity nerve entrapment neuropathies, including CTS, and headache disorders, suggesting a potential genetic influence. In particular, patients in need for multi-site peripheral nerve decompression carry the highest risk of concomitant migraine headache,[8,9] raising the question of a shared genetic basis in nerve compression syndromes, encompassing the prototypical CTS as well as migraine headaches triggered by compression of extracranial nerves. Studies have demonstrated that multi-site deactivation of trigger sites in migraine headaches yields superior results compared with single-site migraine surgery alone. Both patients had significant relief from GON decompression, further benefiting from addressing additional minor trigger points as LON and ATN.

Although it was evident from the beginning that Sister 1 would benefit from GON and LON deactivation surgery, Sister 2 initially did not receive LON treatment because of complete relief of symptoms after preoperative GON nerve block and the absence of typical LON symptoms such as vertigo and ear pain. However, improvement in symptoms was observed with single-site GON decompression, seaming to be the most relevant trigger deactivation in both patients. After addressing the ATN in Sister 1 and both the LON and ATN in Sister 2 during a second surgery to address minor residual symptoms, both individuals achieved (almost) complete relief from their symptoms. Currently, both sisters are free from pain in the occipital and temporal regions. The remaining headache is localized to the frontal area, likely attributed to compression of the supraorbital and supratrochlear nerves. Despite these minor symptoms, neither sister sought further treatment.

Our report underlines the efficacy of migraine deactivation surgery in a carefully selected patient cohort, resulting in a reduction of migraine symptoms exceeding 99%. The staged surgical treatment achieving the same outcome in a monozygotic twin pair emphasizes the homogeneity between both patients, independent of environmental factors. Moreover, it highlights the substantial impact of genetic background on treatment options and success. The observed symptoms and their simultaneous control support this hypothesis, suggesting that certain genetic background in individuals with migraines may in future be crucial predictors for the success of migraine surgery.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of AI and AI-assisted technologies in the writing process

AI and AI-assisted technologies have not been used in the writing process.

Declaration of Helsinki

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Informed consent

Informed consent was obtained from patients for publication.

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References

1. GBD 2016 Disease and Injury Incidence and Prevalence CollaboratorsGlobal, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1211–1259.
2. Khan J, Asoom LIA, Sunni AA, et al. Genetics, pathophysiology, diagnosis, treatment, management, and prevention of migraine. *Biomed Pharmacother*. 2021;139:111557.
3. Henriques S, Almeida A, Peres H, Costa-Ferreira A. Current evidence in migraine surgery: a systematic review. *Ann Plast Surg*. 2022;89(1):113–120.
4. Mulder EJ, Van Baal C, Gaist D, et al. Genetic and environmental influences on migraine: a twin study across six countries. *Twin Res*. 2003;6(5):422–431.
5. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med*. 2001;345(1):17–24.
6. Riederer F, Sandor PS, Linnebank M, Ettlin DA. Familial occipital and nervus intermedius neuralgia in a Swiss family. *J Headache Pain*. 2010;11(4):335–338.
7. Hakim AJ, Cherkas L, El Zayat S, MacGregor AJ, Spector TD. The genetic contribution to carpal tunnel syndrome in women: a twin study. *Arthritis Rheum*. 2002;47(3):275–279.
8. Gfrerer L, Lans J, Chartier C, et al. Migraine headaches in patients with upper extremity compressive neuropathy. *Plast Reconstr Surg*. 2022;150(6):1333–1339.
9. Law HZ, Amirlak B, Cheng J, Sammer DM. An association between carpal tunnel syndrome and migraine headaches-National Health Interview Survey, 2010. *Plast Reconstr Surg Glob Open*. 2015;3(3):e333.