World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Familial migraine across three generations: A case series on genetic predisposition, vascular comorbidities, treatment challenges

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World Journal of Biology Pharmacy and Health Sciences, 2025, 21(03), 647-651

Publication history: Received on 17 February 2025; revised on 25 March 2025; accepted on 27 March 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.21.3.0320

Abstract

Background: Migraine is a highly prevalent neurological disease and has a significant genetic basis and shows co-occurrence in families across multiple generations. Familial migraine can differ in terms of onset, severity, triggers, and response to treatments, which can complicate management. In this case series, we share the clinical presentations, comorbidities, and treatment responses in three generations of female patients with migraine.

Methods: In this study, we identified a 67-year-old grandmother, a 48-year-old mother , and a 24-year-old young adult female with a history of migraine. Clinical data such as onset, duration, severity, associated symptoms, comorbidities and response to treatment were collected either through interviews with patients or from medical records. Drug treatments and responses were analyzed to recognize treatment response patterns across generations.

Results:

- The proband (24 years of age) has chronic, refractory migraine with pulsating headaches, photophobia, phonophobia, nausea, and loss of appetite lasting 2–3 days per episode. Despite the treatment with naproxen, sumatriptan her symptoms remain uncontrolled.
- The mother (48 years of age) developed migraine post-delivery and has a history of hypertension. She experiences moderate intensity attacks associated with photophobia and ophthalmic features, which are responsive to non-steroidal anti-inflammatory drugs and beta-blockers.
- The grandmother (67) suffers from episodic migraine with hypotension, triggered predominantly by stress and fatigue. Her symptoms are mild, and well-managed with analgesics and lifestyle modifications.

Keywords: Migraine; Photophobia; Hypertension; Hypotension; Genetic predisposition; Treatment resistance

1. Introduction

[1] Migraine is a genetically driven complicated neurological illness characterized by episodes of moderate-to-severe headaches that are usually unilateral and are accompanied by nausea and increased sensitivity to light and sound. The term "migraine" derives from the Greek word hemikrania, which was eventually translated into Latin as hemigranea. The phrase is translated as migraine in French. Migraine attacks are complicated and recurring neurological disturbances that can last for hours or days and have a substantial influence on people's everyday activities and quality of life. The most common kind of migraine, accounting for 75% of all instances, is migraine without aura.

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[2] A complicated and multifaceted illness, migraine is impacted by both environmental and hereditary factors. Efforts have been made to identify safe and effective prevention and treatment methods. The present drugs and non-pharmacological approaches, however, are still only partially helpful. As a result, migraine control is still difficult. To prevent and manage headaches, researchers have tried to create lifestyle modification techniques. Following the recognition of the significance of food triggers, nutrition therapy techniques for headaches, including migraines, have been developed.

2. Migraine Triggers and Prevention

2.1. [3] Primary Triggers

- Stress, auditory stimuli, fatigue, fasting, and menstruation.
- Women develop more migraine episodes than men.
- Menstruation is the most significant risk for migraines.
- Estrogen withdrawal is a leading cause of migraine onset during menstruation.
- Migraine episodes often occur before menstruation or on the first day.

2.2. Climate and Migraine

- High altitudes, humidity, and environmental pollution can cause migraines.
- Visual, acoustic, and olfactory stimuli can aggravate migraines.

2.3. Dietary Factors and Migraine

- Improper diet, alcohol, and obesity can promote migraine attacks.
- Obesity and migraine are associated with a high risk of activating inflammatory processes.

2.4. Dietary Strategies for Migraine Relief

- Ketogenic diet improves mitochondrial activity and energy metabolism.
- Low glycemic index diet may control headaches.
- Dietary weight-loss strategies can improve headaches/migraines.

2.5. Genetics in migraine

[4] Clinical experience suggests that migraine has a significant hereditary component and population-based family studies confirm this finding. According to these studies, the risk of migraine is significantly higher for immediate family members of migraineurs than for relatives of matched controls. It's interesting to note that the degree of handicap and aura presence affected the relative risk. First-degree relatives of migraine patients with aura had a four-fold higher relative risk of migraine, whereas relatives of migraine patients without aura only had a 1.9-fold higher risk. Twin studies that show a much greater pair wise concordance rate of migraine in monozygotic twins as opposed to dizygotic twins offer additional clues. Some specific biology has been uncovered that does inform our understanding of migraine aura, even if specific genetic abnormalities in typical kinds of migraine have not yet been described.

2.6. Role of heredity in migraine

[5] Migraines have a significant hereditary component, and a genetic predisposition is typically revealed by family history. 38 novel genomic loci, including the X chromosomes for migraines, have been found by genome-wide genetics investigations. Three of these genes control glutamergic neurotransmission, which could account for the migraine brain's neuronal hyperexcitability. These genes contribute to our understanding of the pathophysiology of migraine headaches by being expressed in vascular and skeletal muscle tissue. Additionally, Cortical Spreading Depression (CSD) has been found to have a genetic connection.

[6] Gene discovery and a deeper comprehension of the pathways and fundamental biology of migraine have been achieved through the use of genome-wide association study (GWAS) in case-control cohorts for the common polygenic form of migraine and family studies for the uncommon Mendelian forms of migraine. By mapping locations in family pedigrees and using genome sequencing to identify variations, the primary FHM genes for monogenic migraine, CACNA1A, ATP1A2, and SCN1A, were identified.

3. Treatment

3.1. Pharmacological treatments

[7] NSAIDs, triptans, and ditans are examples of over-the-counter analgesics that are used to treat acute migraines. There is no evidence to support the usage of triptans during the aura phase, however they are most effective when taken early in an attack. Other triptans may still be able to help even if one is ineffective. Sumatriptan used subcutaneously may be helpful if all other triptans are ineffective or if a patient's headache reaches its worst point. Patients may repeat treatment or mix it with fast-acting formulations in the event of a relapse. Alternatives such as ditans or gepants are available if triptans don't work or aren't recommended. The only ditan licensed for treating acute migraines is Lasmiditan; nonetheless, its usage is linked to transient impairment of driving. For nausea and vomiting, prokinetic antiemetics such as metoclopramide and domperidone can be helpful adjuncts.

3.2. Non-pharmacological treatments

If the use of pharmaceuticals is contraindicated, a variety of non-pharmacological preventive therapies can be employed in place of or as supplements to acute and preventative medications. A study of acupuncture revealed that it is not better than sham acupuncture, however there is some evidence to support the use of non-invasive neuromodulatory devices, biobehavioural therapy, and acupuncture. Contrary to common opinion, there is little to no data supporting nutritional treatments, spinal manipulation, or physical therapy. Since there is no data supporting the effectiveness of additional therapeutic options such melatonin, magnesium, and riboflavin, as well as little proof of their application in clinical practice, physicians do not advocate them.

4. Case Presentations

4.1. Case 1: First Generation, (Hypotension with Migraine)

A 65-year-old female with a long standing history of migraine and hypotension.

- **Clinical Features**: The migraine attack-identified as being mild, infrequent, bilateral, throbbing, and associated with sensitivity to light and nausea. Patient is Chronic hypotensive with readings under 90/60 mmHg for many years. Migraine attacks may be preceded by dizziness and fatigue, with symptoms triggered by fasting and dehydration.
- **Management:** Lifestyle Changes such as ensuring adequate hydration and diet control is primarily recommended for the patient.
- Analgesics like Acetaminophen-500mg or Naproxen-250mg; cover occasionally, given the lower intensity of the attacks.

4.2. Case 2: Second Generation, (Migraine with Hypertension)

A 48-year-old female with a past medical history of hypertension and migraine, which began following 2nd child birth and the migraine has persisted since then.

- **Clinical Features:** Migraine attacks are Recurrent, unilateral, pulsating, moderate headache. Often accompanied by photophobia and phonophobia. Patient is hypertensive with blood pressure, 140/90 mmHg on average. Migraine frequency is increased in the setting of poorly controlled hypertension typically triggered by stress, menstruation and dietary items (caffeine, processed foods)

4.2.1. Management

- The frequency of migraine episodes seems to be decreased by antihypertensive agents (Amlodipine 5mg once daily)
- Analgesics like Naproxen-250mg for symptomatic treatment, with overall better outcome than more severe case.

4.3. Case 3: Third Generation, (Migraine with Prominent Autonomic Symptoms and Treatment Resistance)

A 24-years-old woman with a history of migraine which began in childhood (at the age of 15) with no co-morbidities.

4.3.1. Clinical Features

The patient experiences common migraine attacks happening frequently, for instance 2–3 times per month with each episode lasting 2–3 days. Headaches are throbbing, pounding and pulsating; associated with intolerable photophobia and phonophobia and vomiting. Other general physical features are dizziness, sweating and tremors. Loss of appetite and interest in activities during attacks are pronounced. Sleep does not relieve the headache, and conventional painkillers do not help, or only help a little. In contrast to the other two cases, blood pressure varies through episodes and is not consistently hypertensive or hypotensive.

4.3.2. Management

- Management currently consists of symptomatic therapy and lifestyle modification; however, the patient is refractory to treatment (Triptans & mild analgesics).
- Given the severity and chronicity of the migraines, central sensitization or refractory migraine mechanisms may be at play.

5. Discussion

This familial case series demonstrates significant differences in migraine characteristics between three generations that may have a vascular and autonomic origin:

5.1. Fluctuation in the severity and frequency of migraines

- The maternal grandmother (first generation) and mother (second generation) have relatively infrequent and milder migraine attacks; the grandmother has low blood pressure, and the mother has high blood pressure.
- The daughter (third generation) has more frequent, severe, and resistant to conventional treatment of migraines, raising the possibility of the progression or variation of the underlying mechanism across generations.

5.2. Blood Pressure and Vascular Regulation

- The opposing blood pressure profiles—in the grandmother, hypotension; in the mother, hypertension—suggest how vascular status might impact migraine pathophysiology.
- The combination of extreme dysautonomia, with episodic surges in blood pressure and more traditionally seen reflex changes that can last for days to weeks, indicates that there may be an additional mechanism of dysregulation at play.

5.3. Autonomic Dysfunction

- The significant response of the autonomic (giddiness, sweating, tremors) symptoms in the third generation female underscored the potential for underlying autonomic nervous system involvement that could be responsible for increased severity and treatment resistance.
- The fact that these symptoms don't improve with sleep and pain relievers suggests that the driver of the patient's migraine attacks may be more complex than even these typical neurovascular cascade.

5.4. Takeaways for Management

- These differences indicate that individualized treatment strategies may be warranted. For example, the mother and grandmother may find some of their symptoms respond to lifestyle changes and regular analgesics, but the daughter may need an approach that targets both segments integrating central sensitization and autonomic dysfunction.
- More studies are warranted to help understand the relationship between migraine, blood pressure regulation and autonomic dysfunction, which could lead to more effective treatments among familial cases of migraine.

6. Conclusion

This familial case series illustrates the diversity of migraine presentation and severity that can exist between three generations of the same family, and potential influences of genetics and individual physiology. The young adult (daughter) suffers from constant, debilitating, and refractory migraines with neurological symptoms (giddiness, sweating, tremors), while their mother and grandmother present with milder episodes, with less frequency. The dissimilar comorbidities—hypertension in the mother and hypotension in the grandmother—strengthen the

association with vascular dysregulation and migraine pathophysiology. Such patterns, along with associated use conditions, highlight the importance of patient-tailored approaches to managing migraine. Further investigations need to be undertaken for genetic and vascular connections in migraine to refine prevention and treatment approaches.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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