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# Case Series of Vestibular Migraine in Fragile X Premutation Carriers

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## INTRODUCTION

Vestibular migraine (VM) presents with spontaneous or positional vertigo (usually with head motion, visually-induced dizziness, dizziness with nausea) and is associated with a history of migraines and migraine associated symptoms [1]. It is one of the most common causes of recurrent vertigo, with a 1% prevalence in the general population and 10-20% of individuals presenting to headache specialty centers [2]. The diagnostic criteria for VM can be seen in Table 1.

Table 1: Diagnostic criteria for vestibular migraine [3]

Vestibular migraine
1. At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting
5. minutes to 72 hours
1. Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD-3)
2. One or more migraine features with at least 50% of the vestibular episodes:
- Headache with at least 2 of the following characteristics: 1-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity
- Photophobia and phonophobia
- Visual aura
1. Not better accounted for by another vestibular or ICHD diagnosis

Probable vestibular migraine (not included in ICHD-3)
1. At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting
5. minutes to 72 hours
1. Only 1 of the criteria B and C for vestibular migraine is fulfilled (migraine history or migraine features during the episode)
1. Not better accounted for by another vestibular or ICHD diagnosis

The etiology of VM headaches is uncertain, but it is currently thought to be a crossover between genetic, neurochemical, and inflammatory causes [2,4-7]

Individuals who are carriers of the fragile X messenger ribonucleoprotein 1 gene (FMR1:55-200 CGG repeats) are relatively common in the general population. It affects approximately 1:130-250 females and 1:250-810 males [8-9]. While research has identified a high prevalence of vestibular deficits and migraines among fragile X premutation carriers, there has been no discussion about VM within this population [10-14].

## OBJECTIVE

This case series plus review seeks to describe the clinical characteristics and pathophysiology of VM among individuals with the fragile X premutation. We also seek to discuss treatment and future steps in addressing VM in this population.

## SUBJECTS

Three carriers of the FMR1 premutation (3 female) were evaluated. All subjects were seen as a part of a family study of probands diagnosed with fragile X syndrome (FXS) or part of an adult study of individuals who are premutation carriers with and without FXTAS. No subject was referred to our clinic for headache or vestibular related problems. All subjects were seen at the UC Davis Medical Center MIND Institute, Fragile X Treatment and Research Center. All subjects signed an informed consent. A standardized medical history and physical examination were performed by a physician (RJH). The medical history touched on specific questions regarding migraine history, development of vertigo symptoms, work-up for vestibular migraine and current presentation. All subjects underwent confirmatory FMR1 DNA testing either at our facility or an outside facility. FMR1 molecular measures included CGG repeat number.

## CASES

| Case # / Age Gender | CGG repeat # | Family History | History of Migraine | History of Vertigo | Treatments |
|---|---|---|---|---|---|
| 1 / 78F | 107 | Younger sister with premutation and migraine, younger brother and son with FXS | Migraine headaches with aura in 40-50's. | First severe episode of vertigo following ear wax removal in early 70's, vertigo episodes persisted and progressive balance issues with shuffling gait began in mid 70's. MRI head showed white matter disease and cerebral atrophy | Home exercises for vertigo (no improvement), verapamil hydrochloride SR 240mg qday (improvement), |
| 2 / 59F | 69 | Mother with premutation and migraine, two sons with FXS | Migraine headaches in 20's (1-2x/year), ocular migraine in 40's causing eye pain and vision changes | Vertigo episodes in 40's (lasted 1 day and 3-4x/year), worst vertigo episode at age 51 (lasted 3 days), resolution of symptoms following septoplasty and medications | Septoplasty for deviated septum (improvement), verapamil hydrochloride SR 200mg qday (mild improvement), Paleolithic diet (improvement) |
| 3 / 63F | 81 | Father with premutation and FXTAS, two sons with FXS | Migraine headaches in late 30's/early 40's (1-2x/month), possibly associated with menstrual cycle, occasional ocular migraine episodes | Vertigo episodes around age 50 (lasted few hours, 1-2x/year), progressive balance issues with mild tremor began in late 50's | No treatment interventions |

## RESULTS

All three patients reported in our case series are female, and migraine episodes manifested earlier in life with development of vestibular symptoms near menopause—which are common characteristics of individuals with VM [2]. Based on the diagnostic criteria for VM by Lempert et al [3] our patients would fall under the "probable VM" criteria, as they often presented to their ENT or primary doctor with a history of migraine headaches in the past and with a new onset of vertigo episodes.

Case 1's MRI findings of white matter disease and cerebral atrophy were consistent with findings of FXTAS. Both Case 1 and Case 3 developed VM first, which gradually progressed to more significant balance problems and symptoms of Fragile X-associated tremor/ataxia syndrome (FXTAS). Case 2 was not noted to have these progressive balance problems, however she is younger than the other two cases and will have to be further monitored for development of FXTAS symptoms. Cases 1 and 2 found improvement or resolution of their VM episodes with pharmacological and/or lifestyle interventions.

## CONCLUSIONS

VM has been determined to be most common cause of recurrent vertigo, and while its presentation was previously unclear, it was established with diagnostic criteria by the Barany Society and the International Headache Society (IHS) in 2012 [3]. The pathophysiology of VM remains uncertain but possibilities include mitochondrial abnormalities [15], cranial nerve VIII toxicity secondary to neurotoxic protein accumulation [14], and calcitonin gene-related peptide (CGRP) signaling dysfunction [2,8] due to altered levels of fragile X messenger ribonucleoprotein (FMRP). It is important to recognize VM among premutation carriers because beneficial treatments are available. It seems that a combination of both medications and lifestyle factors were the most effective for treatment for our patients with the premutation and VM. It is also possible that VM may be followed by FXTAS in some premutation carriers. Future studies are needed regarding the prevalence of VM and the relationship to subsequent FXTAS.

## REFERENCES

1. von Brevern M, Lempert T. Chapter 22 - Vestibular migraine. In: Furman JM, Lempert T (eds) Handbook of Clinical Neurology. Elsevier, pp. 301–316.
2. Lempert T, von Brevern M. Vestibular Migraine. Neurol Clin 2019; 37: 695–706.
3. Lempert T, Olesen J, Furman J, et al. Vestibular migraine: diagnostic criteria. J Vestib Res Equilib Orientat 2012; 22: 167–172.
4. Lee H, Jen JC, Wang H, et al. A genome-wide linkage scan of familial benign recurrent vertigo: linkage to 22q12 with evidence of heterogeneity. Hum Mol Genet 2006; 15: 251–258.
5. Bahmad F, DePalma SR, Merchant SN, et al. Locus for Familial Migrainous Vertigo Disease Maps to Chromosome 5q35. Ann Otol Rhinol Laryngol 2009; 118: 670–676.
6. Koo J-W, Balaban C. Serotonin-Induced Plasma Extravasation in the Murine Inner Ear: Possible Mechanism of Migraine-Associated Inner ear Dysfunction. Cephalalgia 2006; 26: 1310–1319.
7. Von Brevern M, Ta N, Shankar A, et al. Migrainous Vertigo: Mutation Analysis of the Candidate Genes CACNA1A, ATP1A2, SCN1A, and CACNB4. Headache J Head Face Pain 2006; 46: 1136–1141.
8. Paul R, Pessah IN, Gane L, et al. Early onset of neurological symptoms in fragile X premutation carriers exposed to neurotoxins. Neurotoxicology 2010; 31: 399–402.
9. Tassone F, Iong KP, Tong T-H, et al. FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. Genome Med 2012; 4: 100.
10. Au J, Akins RS, Berkowitz-Sutherland L, et al. Prevalence and Risk of Migraine Headaches in Adult Fragile X Premutation Carriers. Clin Genet 2013; 84: 546–551.
11. Chonchaiya W, Nguyen D, Au J, et al. Clinical involvement in daughters of men with fragile X-associated tremor ataxia syndrome. Clin Genet 2010; 78: 38–46.
12. Smith LE, Barker ET, Seltzer MM, et al. Behavioral Phenotype of Fragile X Syndrome in Adolescence and Adulthood. Am J Intellect Dev Disabil 2012; 117: 1–17.
13. Wheeler AC, Bailey Jr DB, Berry-Kravis E, et al. Associated features in females with an FMR1 premutation. J Neurodev Disord 2014; 6: 30.
14. Schneider A, Ballinger E, Chavez A, et al. Prepulse Inhibition in Patients with Fragile X-associated Tremor Ataxia Syndrome. Neurobiol Aging 2012; 33: 1045–1053.
15. Ross-Inta C, Omanska-Klusek A, Wong S, et al. Evidence of mitochondrial dysfunction in fragile X-associated tremor/ataxia syndrome. Biochem J 2010; 429: 545–552.

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