International Journal of Neurology and Neurosurgery
Volume 11 Number 1, January - March 2019
DOI: http://dx.doi.org/10.21088/ijnns.0975.0223.11119.6

Original Research Article

Study of Rare Migraine Variants Not Defined in ICHD-3

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Abstract

Migraine variants are atypical presentations of migraine in form of associated clinical features with or without headache in episodic pattern. These disorders are difficult to diagnose and require out of the box thinking and high index of suspicion. None of the cases described in this article are classified in ICHD-3 (international classification of headache disorders 3) and, in that way, are unique migraine variant cases. First two clinical cases are unexplained vertigo; the third case is of undetermined neurocardiogenic syncope and fourth case is dual variant of Alice in Wonderland Syndrome with abdominal migraine. All four cases are not associated with headache and suspected due to past or family history of migraine. Fifth case is of migrainous headache in which headache and the upper motor neuron facial palsy occur on the same side. This is a unique brainstem aura migraine variant. None of the cases described in this article are classified in ICHD-3 (international classification of headache disorders 3) and, in that way, are unique migraine variant cases. Migraine variant should be suspected in episodic neurological disorder of unexplained aetiology with normal neurological examination and undetermined investigations.

Keywords: Migraine Variants; Atypical Migraine; Vertigo; Syncope; ICHD-3

How to cite this article:

Jayanti Gurumukhani, Dhruvkumar M. Patel, Lachhmi J. Gurumukhani et al. Study of Rare Migraine Variants Not Defined in ICHD-3. Int J Neurol Neurosurg. 2019;11(1):36-43.

Background

Migraine is a complex disorder with multi factorial pathophysiology, genetic predisposition and various cephalic and multi system manifestations. Its diagnosis is mostly clinical [1,2]. Headache is a prominent symptom in migraine of both the varieties, with and without aura; in a few rare cases, headache may even be absent. Migraine variant (MV) is an episodic focal neurological syndrome not associated with classical headache. International classification of headache disorders 3 (ICHD-3) guideline has defined some forms of episodic syndromes like Migraine with brainstem aura, Abdominal migraine, Cyclic vomiting syndrome, Benign paroxysmal vertigo, Benign paroxysmal torticollis, Migraine aura triggered seizures, Retinal migraine and Typical aura without headache as MV [3]. However, there are reported cases of MV such as Visual snow, Ophthalmoplegic migraine, Acute confusional migraine, Infantile colic, Vestibular migraine and Alternating hemiplegia of childhood [4,5]. Recent research data suggests that 1-3 % of people suffer from a MV and 50% of such patients are at present undiagnosed or untreated [6]. MVs are notoriously difficult to diagnose as there are

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Received on 25.12.2018, **Accepted on** 02.02.2019

no special investigations to confirm whether or not the symptoms are due to the migraine or some other disease. These type of migraine cases mimic many neurological, ophthalmic, autoimmune and psychiatric disorders and require high index of suspicion for the diagnosis [7]. Here, we are presenting a case series of unique migraine variants, which are not described by ICHD-3 guidelines.

Case 1

A 30-year-old Asian female, working as a manager, presented with complaints of recurrent spontaneous vertigo lasting for about 30 minutes at DHC neurology clinic, Ahmedabad, India. It was preceded by severe fatigue and photophobia for about 5 to 10 minutes. While at work, 12 such episodes of vertigo occurred in last 3 months. These episodes occurred when she ate fermented food products or had inadequate sleep. None of the vertigo episodes were associated with headache during, before or after the attack. No history of hearing loss, tinnitus, dysarthria, weakness of face or limbs were noticed. She denied any past history of headache or significant medical illness. Her mother described history of episodic abdominal pain and vomiting from age 6 to 10. Her sister and mother had history of migraine with aura. Her vital signs, otoneurologic examination, cardiorespiratory system and CNS examinations were clinically normal. Her MRI brain diffusion study with MR angiography, done one-month back, was reported as normal. Her laboratory investigations and pure tone audiometry didn't add to the diagnosis. As clinical features and investigations were not suggestive of any vertigo aetiology, clinical diagnosis of migraine associated vertigo variant was made. As her vertigo episodes were disturbing her office work, prophylactic migraine treatment was planned. She was prescribed tablet topiramate 25 mg at bedtime for 7 days initially and then increased to 50 mg daily after 7 days. After three-months of taking topiramate, she significantly improved and stopped treatment without consultation. Within 15 days of discontinuation of the treatment, she started having episodes of vertigo. She was again put on previous treatment plan and she is on regular follow up since last 6 months and no such vertigo episode was reported.

Case 2

A 28-year-old Indian origin female, working as a computer operator, consulted to outdoor department of DHC neurology clinic, Ahmedabad, India with complaints of true vertigo lasting for 5 to 6 hours associated with nausea and heaviness of head but not classical headache. These episodes were not associated with tinnitus, hearing loss or imbalance or focal neurological deficit. She experienced 6-8 such episodes a month for a few months. She was having past history of headache which started at the age of 18 years and was diagnosed with migraine without aura as per IHS migraine criteria. Her migraine headache frequency was once a week and was triggered by menstruation or by consumption of oral contraceptive pills. Her migraine lasted up to the 23 years of her age and after that she was almost headache free. Her vital signs, cardiorespiratory system, otoneurologic examination, and CNS examination were normal. Her lab investigations, audiometry, MRI brain with contrast, diffusion weighted images and MR Angiogram were also normal. Her vertigo was not suggestive of any aetiology and considering her past history of migraine, she was clinically diagnosed as a case of migraine variant. Her vertigo episodes were frequent and responsible for many work leaves. After explaining the provisional diagnosis and treatment options, she was prescribed tablet topiramate 25 mg daily and up titrated to 50 mg daily after 7 days with which she was symptom free. After 2 months, when dose of topiramate was reduced to 25 mg daily, she again experienced vertigo episodes; dose of topiramate was increased to previous level and the patient was vertigo free again. She was advised regular follow up every month and has not experienced any such vertigo episodes since last 18 months.

Case 3

A 32-year-old Bangladeshi Asian female working as a housewife presented at Jay Neurocare and Physiotherapy Clinic, Bhavnagar, India, with history of recurrent syncope of total 8 episodes in last three months. All episodes occurred on the day of fasting. She had no history of prolonged standing or dehydration during any episodes. Headache did not occur before or after the syncope. On examination, she had no orthostatic hypotension. Her neurological examination and cardiorespiratory examination were normal. She was subjected for evaluation of syncope aetiology. Her electrocardiogram, 2D echocardiogram, tilt table examination, hemogram and routine biochemical tests were within normal range. Her MRI brain with angiography and EEG were normal as well. She had past history of headache suggestive of migraine without aura as per IHS criteria at the

age of 20 years which lasted for three years. All syncope episodes occurred during fasting state and no definite cause of the syncope was identified. She was diagnosed as a migraine variant syncope because of past history of migraine and no alternate diagnosis of the syncope was established in spite of extensive diagnostic work up. She was prescribed migraine prophylactic treatment in the form of propranolol 40 mg daily and the dose was augmented up to 80 mg daily. Her syncope episodes were reduced in one month but did not completely disappeared. Topiramate was added as a second prophylactic drug and she became symptom free in 3 weeks. Both drugs were stopped after 3 months for the challenge of the diagnosis. She again had same syncope episodes and needed reintroduction of the drugs.

Case 4

A 24-year Indian origin American female working as a physiotherapist assistant presented to neurology OPD of Spandan Hospital, Ahmedabad, India in May 2017 with recurrent episodes of strange visual symptoms lasting for 20 minutes followed by diffuse heaviness of head, photophobia and vomiting. After each episode, she had central abdominal colicky pain lasting for about 3 to 4 hours relieved with antispasmodic medicine. The average frequency of such episodes was thrice a month for the last 10 months.

She complained of visual symptoms of false perception of her height and horizontal dimensions. She perceived that she has become so tall that her head was touching the ceiling and right or left half of her body had become disproportionately wide. She felt as if she was walking on air and not able to cross any distance despite stepping forward. She noticed objects being distorted in size and shape and being either near or far away. She also noticed people looking shorter than her index finger. She had past history of migraine with visual aura which started when she was 14 years old but has been migraine free for the last 4 years. Her mother also had history of migraine with visual aura. Her vital signs, general examinations, cardiorespiratory system and per abdominal examination was normal. Her neurological and complete ophthalmological evaluation was normal. Her hemogram, metabolic profile including porphyria related investigations, EEG, VEP and MRI brain with contrast study, abdominal ultrasound and contrast enhanced CT abdomen were within normal limit. Her episodic visual symptoms were suggestive of Alice in Wonderland Syndrome (AIWS) with abdominal migraine. Considering her past and family history of migraine with aura, clinical diagnosis of migraine variant was suspected. She was prescribed propranolol tablet and the dose was titrated up to full therapeutic dose along with flunarizine 10 mg at evening time. She was symptom free after 4 weeks of starting treatment. She remained symptom free for 6 month and after that she was lost from the follow up.

Case 5

A 30-year-old Indian male, working as an executive in a company was admitted at DHC hospital, Ahmedabad, India with sudden onset drooping of left side of face for 10 to 15 minutes. After admission to the hospital, facial weakness recovered in 20 minutes, but he complained of severe left sided throbbing headache which accentuated over next 20 minutes and was associated with vomiting. Headache was relieved in 20 minutes after treatment with diclofenac and metoclopramide by parenteral route. On examination: his vital signs, cardiorespiratory system examination, and general examination were normal. His neurological examination during the episode revealed only positive finding of upper motor neuron type left facial nerve palsy. His routine laboratory investigations, MRI brain, MR angiography of head and neck were within normal range. He had history of similar episodes of one sided facial weakness followed by ipsilateral headache which was relieved with one or two episodes of vomiting or by consuming analgesic tablet. He reported 4-5 such episodes per month for last 6 months which were not associated with abnormal eye movements, hearing loss, headache, tinnitus, falls or focal neurological weakness. His mother and sister had history of migraine without aura, but it was not associated with facial weakness. He was not suffering from hypertension, diabetes or coronary artery disease. His neurological and systemic examination in between the episodes was completely normal. Provisional diagnosis of MV (migraine with brainstem aura) was considered and therapeutic trial of prophylactic topiramate drug was planned. He was started on topiramate 25 mg tablet once daily and built up to 50 mg daily after 7 days. He was symptom free within three weeks of starting the therapy which was continued for additional three months. After 2 weeks of stopping topiramate, he again started having same episodes. Topiramate was reintroduced and he became symptom free within few weeks.

Discussion

The first four cases are "sine headache migraine" means headache was not associated before, during or after migraine attack and very rare such types of cases have been reported. If the index of suspicion for migraine variant would not have been high, they all would have been missed. It was the paroxysmal nature of symptoms, past history of migraine, normal neurological examination in between the attacks, family history of migraine and response to treatment after ruling out secondary causes that clinched to the diagnosis of migraine variants. The association of migraine and vertigo has long been described with variety of terms like migraine associated vertigo, migraine related vestibulopathy and migrainous vertigo. For the first time, the ICHD 3 appendix described it as vestibular migraine. Our patients of case 1 & 2 had recurrent vertigo without headache. Whereas case 1 had history of Abdominal Migraine, case 2 had migraine without aura in the past. Case 1 also had family history of migraine with triggers like fermented food and inadequate sleep, which raised the suspicion of migrainous nature of the vertigo. Both patients had normal neurological examination in between episodes. After ruling out alternate causes of vertigo by necessary investigations including MRI brain and excellent response to topiramate, diagnosis of vestibular migraine was established. Also, when topiramate was stopped or dose was reduced, our patients had recurrence of vertigo emphasising effectiveness of this drug in preventing recurrent episodes. After reintroduction of topiramate both patients were symptom free up to last follow up at 6 and 18 months respectively. Vestibular Migraine is common in general population with lifetime prevalence of 7.4%. About 9% of patients of migraine has vestibular migraine and it is second most common cause of recurrent vertigo in children after benign paroxysmal vertigo. It occurs at any age with average age of onset being 30-40 years. The diagnostic criteria require at least 5 episodes of moderate to severe intensity vertigo lasting for 5 minutes to 72 hours in patient with current or past history of migraine with or without aura and at least half of the episodes have migrainous features [9]. Vertigo symptoms include spontaneous vertigo, positional vertigo, visually induced vertigo, head motion inched vertigo and head motion induced dizziness with nausea. The pathophysiology is believed to be both peripheral and central vestibular dysfunction [9,10].

Syncope and migraine are common in general population and both conditions occur together more than chance would predict. In case 3, patient had history of recurrent syncope and had no headache preceding or following syncope. A thorough evaluation of syncope was unrevealing. However, on basis of past history of migraine and syncope episode occurring on day of fasting, a suspicion of migraine variant syncope was made and trial of prophylactic drug propranolol and later topiramate revealed significant improvement, emphasising to consider the syncope as migraine equivalent.

In case 4, the patient had recurrent episodes of strange visual symptoms with photophobia and vomiting with diffuse heaviness in head followed by unexplained colicky abdominal pain lasting for 3 to 4 hours. In view of past and family history of Migraine with visual aura, normal investigations and significant improvement with migraine prophylaxis treatment, a diagnosis of rare migraine variant combination of AIWS with abdominal migraine was made. We think this is the first combo sine headache migraine variant of AIWS and abdominal migraine presented at this age. AIWS is a rare perceptual disorder which was first described in 1955 by British psychiatrist John Todd and the name refers to Lewis Carroll's well-known book "Alice's Adventures in Wonderland". In this condition, patient experiences alteration in body images especially head and hand which appear disproportionately small or large. Also, patient has false perception of the size of various objects. He also loses sense of time- which passes either too slowly or too rapidly. Patients often have insight of their symptoms which differentiates this condition from psychosis in which insight is impaired. There are various causes of this syndrome with migraine being most common in adults with others being ADEM, Viral Encephalitis, brain tumour and temporal lobe epilepsy [11-15]. Abdominal migraineis a poorly understood disorder seen mainly in children characterised by bouts of moderate to severe midline abdominal pain, pallor, nausea and vomiting with complete recovery between the episodes. It is the diagnosis of exclusion. It requires history of recurrent, stereotypical episodes, thorough evaluation to exclude organic cause with supportive family history of Migraine before considering abdominal Migraine. It is the most common paediatric migraine variants with prevalence of 1.7-4.1% between age 1-21 yrs. The pathophysiology is thought to be autonomic instability, altered hypothalamic- pituitary- adrenal axis and alters gut motility as both gut and nervous system are derived from same embryologic tissue [16,17].

Dorsal rostral part of pons is known as migraine generator and it is activated during migraine attacks. Functional connectivity of brainstem (migraine generator area), hypothalamus and spinal trigeminal nuclei is altered during and 24 hours prior the migraine episodes. Central autonomic connections of hypothalamus like locus coeruleus, caudate nucleus, cerebellum, hippocampal gyrus and the temporal lobe shows increased signals during migraine attacks [18,19]. Syncope as a result of autonomic dysfunction due to imbalance between the central sympathetic and parasympathetic system have been reported as syncope variant migraine patients [20]. Perisylvian grey area of midbrain and hypothalamus are responsible for higher parasympathetic and reduced sympathetic activity in genetically predisposed syncope migraine is one of the hypotheses for syncope [21-22]. Pathophysiology of sine headache migraine is altered functional connection between brainstem migraine generator area and hypothalamus in first two cases; and between perisylvian grey area and hypothalamus in third case. This may explain the migraine associated symptoms without headache. (Fig. 1-A)

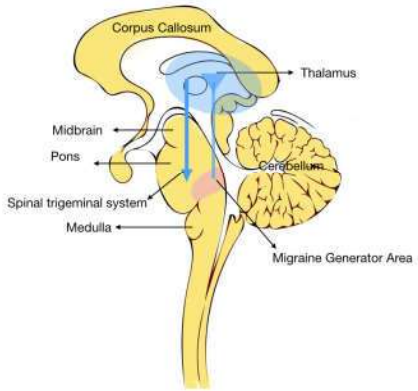

Fig. 1A: Neural Circuite for Migraine Variants

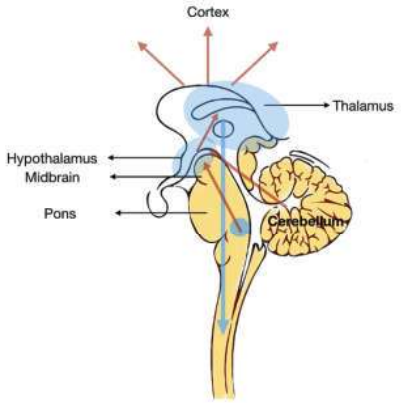

Fig. 1B: Neural circuits for migraine variants

Ponto-hypothalamus-cortical depolarisation suppression leads to alterations at temporo-parietal-occipital carefour region [15] and this theory is speculated for symptoms of AIWS in case-4 (Fig. 1-B). Autonomic instability same as in syncope variant is likely pathophysiology in abdominal migraine.

In case 5, patient had recurrent upper motor neuron facial weakness with ipsilateral headache with migrainous features. His neurological examination in between the episodes was normal and he had family history of migraine. He had no vascular risk factors and his MRI brain with angiography was normal. Although facial weakness is known in hemiplegic Migraine, but they always have limb weakness which was not present in our case. Similarly, facial weakness, when present in basilar migraine, is usually with other vertebrobasilar symptoms which were absent in our patient. Recurrent Bell's palsy with migraine like headache lasting weeks to months has also been described but our patient had upper motor neuron facial weakness for less than 1 hour. Hence a novel migraine variant facial paretic migraine was thought with only single case report in literature so far [23]. Structural and functional alterations of dorsal lower pons carrying corticobulbar fibres of facial nerve nucleus may occur in genetically susceptible migraine patients is hypothesis of migraine pathophysiology in this patient.

Followings are the other Migrant Variants that are described in the literature:

Migraine aura without headache: Aura is symptom complex which precedes, follows or continues during headache phase in patients with migraine with aura. It comprises of fully reversible visual, sensory, speech, motor, brainstem and retinal symptoms occurring gradually over 5 minutes and lasting up to 60 minutes. Sometimes, patients' typical aura does not have headache accompanying or following aura within 60 minutes. This is known as Migraine aura without Headache. It mimics serious conditions like TIA which needs to be ruled out by appropriate investigations especially in patients over age 40, when symptoms are negative, abnormally long or short [6,7].

Persistent aura without infarction: It is extremely rare but well documented in patients of Migraine with aura, one or more aura symptom that may persist for more than one week. It is usually bilateral lasting from weeks to months and sometimes years. It requires neuroimaging to exclude infarction [4,6].

Migraine infarction: It is diagnosed in patients

with Migraine with aura, if otherwise typical aura persists beyond 1 hour and neuroimaging confirms ischemic infarction. It mostly occurs in posterior circulation and in younger women. Most studies have shown a lack of association between Migraine without aura and ischemic stroke [24,25].

Cyclic vomiting syndrome: It is self-limiting condition seen mostly in children characterised by recurrent episodes of intense nausea, vomiting and lethargy separated by symptom free intervals. Symptoms most commonly occur in morning with multiple episodes of emesis per hour lasting 6-48 hours although they may be longer (5-45 days). The age of onset is 4-7 years while the mean age of diagnosis is 8.2-9.5 years because it may not be diagnosed until adulthood. Although episodes may occur infrequently in some children, they are very disabling: requiring emergency room visits and hospitalisation. Approximately 75% of affected children develop Migraine later on [26-27]

Benign paroxysmal Vertigo of childhood: It is characterised by recurrent, brief attacks of vertigo that occur without warning and resolve spontaneously without any warning in otherwise healthy children. It requires good clinical history, detailed neurological and neuro-otological evaluation for confirm diagnosis. Mean age of onset is 2-4 years and 7-11 years with frequency of 2-10 episodes/month. Since episodes are brief lasting seconds to minute, no acute pharmacological treatment is required. Since recurrence is so unpredictable, that prophylaxis is seldom needed. One must exclude posterior fossa tumours, seizures and other vestibular disorders by appropriate investigations [27-28].

Benign Paroxysmal Torticollis: It is benign disorder in infants characterised by episodes of head tilt with head rotation associated with pallor, agitation, irritability and vomiting. Majority of attacks occur in morning with no specific triggers and last for about 4.5 to 6 days. Neurological examination is normal between episodes and there is no developmental delay. Treatment is largely assurance to parents, not only of good prognosis of this disorder but high probability of relapses as well. Attacks usually disappear by 3 or 4 years of age [6,27].

Infantile Colic: It is characterized by bouts of prolonged inconsolable crying especially in evening for at least 3 hours per day for at least 3 days per week in preceding 3 weeks in otherwise healthy and well-fed baby. It has a prevalence of 5-19% among babies with peak at 6-8 weeks with strong family history of migraine in a first degree relative. Non-pharmacologic treatment includes modifying parent's response using motion and sound to calm baby. Instead provide dark quiet room, establish routine and regulated room temperature. No pharmacological treatment is recommended at this point. It usually resolves by 3-5 months of age. These infants have higher likelihood of developing migraine in later life [27,28].

Acute confusional migraine (ACM): It is a rare highly disabling migraine variant, often presents with confusion, agitation, altered mental status, speech and memory problems. It lasts from minutes to hours and there may or may not be recollection of the event and headache symptoms. It is most often seen in children and adolescents, although cases in adults are described as well. About 0.45 to 7.8% of the Paediatric migraine population experience ACM but the disorder may be underdiagnosed. It is often triggered by mild trauma. ACM is diagnosis of exclusion and a range of potential other cases need to be excluded including neoplastic, inflammatory, vascular, metabolic disorders and transient global amnesia. Hence diagnostic work up should include MRI Brain with contrast, MRA, lumbar puncture, EEG, inflammatory work up, metabolic work up and urine drug screen. About half the patients experience headaches proximally to the ACM event and few experience aura as well. Cortical spreading depression is currently hypothesized as the pivotal pathophysiological mechanism [27,28].

Retinal migraine: It is a rare disorder characterised by at least 2 attacks of monocular visual disturbance associated with or without Migraine headache. Recurrent monocular disturbances are strictly unilateral, although some experience side alternating attacks. Visual disturbances may include scintillating, scotoma, or blindness (blurring, grey outs and blackouts) that affects one eye and accompanied or followed within one hour of Migraine headache which is usually ipsilateral to visual loss. The duration of transient monocular visual loss varies widely between and within individual patients lasting few seconds to one hour, but sometimes prolonged fully reversible monocular visual loss can rarely occur (days to weeks) [29].

Visual Snow: It consists of black and white dots in the entire visual field persisting for at least 3 months which can persist for years. Additional visual phenomenon includes palinopsia (trailing and after-images), entoptic phenomena (floaters, spontaneous photopsia, blue field entoptic phenomenon, self-light of the eye), photophobia and nyctalopia (impaired night vision). It has major impact on patient's quality of life with

poor response to treatment. Diagnosis requires normal ophthalmology evaluation and no intake of psychotropic drugs [6,12,15].

Ophthalmoplegic Migraine: It is a rare disorder characterised by recurrent headaches and palsy of 3rd, 4th and 6th cranial nerves, with the 3rd cranial nerve being most commonly affected. Although ICHD-1 had classified OM as a variant of Migraine, in the ICHD 2 it has been reclassified as cranial neuralgias since MRI frequently showed enhancement and thickening of the affected nerve. Recently, it was proposed that uncontrolled Migraine may be the primary cause of ophthalmoplegic Migraine [30-32].

Alternating Hemiplegia Of Childhood (Ahc): It is a rare heterogenous paroxysmal disorder with onset before 18 months, characterised by episodes of hemiplegia involving alternately each side and historically been thought to be a Migraine variant, unusual form of epilepsy or a movement disorder. Clinical phenotype in AHC is associated with de novo mutation of gene ATP1A3. Treatment with variety of Migraine agents and anticonvulsants is largely unsuccessful. Long term outcome is poor due to developmental delay, recurrent seizures and progressive encephalopathy [33,34].

Migraine Aura-Triggered Seizures: Both Migraine and Epilepsy are paroxysmal disorders which unusually can occur together. In patients of migraine with aura, if seizure occurs during or within one hour after a migraine aura, it is defined as Migraine aura- triggered seizures. This rare phenomenon sometimes refers as migralepsy has no association in migraine without aura. EEG is usually normal or shows mild slowing interictally. MRI shows reversible brain abnormalities in view of focal supratentorial oedema. Treatment of choice is antiepileptic drugs like Topiramate or Valproate in view of its efficacy in treating both migraine and epilepsy [35].

Conclusion

Migraine variants are important to recognise and should be investigated thoroughly to differentiate from other mimics. If diagnosed correctly, treatment is gratifying. Any episodic neurological disorder with normal neurological examination in between the attacks and other potential differentials are ruled out by extensive investigations, is most likely migraine variant. Hence one should not be hesitant to give trial of migraine prevention treatment in this challenging disorder.

Conflict of Interest and funding: Nil

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