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Abstracts and Citations

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MIGRAINE PHYSIOLOGY

Schankin C, Maniyar F, Digre K, Goadsby P. "Visual snow" – a disorder distinct from persistent migraine aura. *Brain*. 2014;137:1419-1428. doi:10.1093/brain/awu050

Patients with "visual snow" report continuous tiny dots in the entire visual field similar to the noise of an analogue television. As they frequently have migraine as a comorbidity with ophthalmological, neurological, and radiological studies being normal, they are offered various diagnoses, including persistent migraine aura, post-hallucinogen flashback, or psychogenic disorder. Our aim was to study patients with "visual snow" to characterize the phenotype. A three-step approach was followed: (1) a chart review of patients referred to us identified 22 patients with "visual snow". Fifteen had additional visual symptoms, and 20 patients had comorbid migraine, five with aura; (2) to identify systematically additional visual symptoms, an internet survey ($n = 275$) of self-assessed "visual snow" subjects done by Eye On Vision Foundation was analysed. In two random samples from 235 complete data sets, the same eight additional visual symptoms were present in >33% of patients: palinopsia (trailing and after-images), entoptic phenomena (floaters, blue field entoptic phenomenon, spontaneous photopsia, self-light of the eye), photophobia, and nyctalopia (impaired night vision); (3) a prospective semi-structured telephone interview in a further 142 patients identified 78 (41 female) with confirmed "visual snow" and normal ophthalmological exams. Of these, 72 had at least three of the additional visual symptoms from step (ii). One quarter of patients had "visual snow" as long as they could remember, whereas for the others the mean age of onset was 21 ± 9 years. Thirty-two patients had constant visual symptoms, whereas the remainder experienced either progressive or stepwise worsening. Headache was the most frequent symptom associated with the beginning or a worsening of the visual disturbance (36%), whereas migraine aura (seven patients) and consumption of illicit drugs (five, no hallucinogens) were rare. Migraine (59%), migraine with aura (27%), anxiety and depression were common comorbidities over time. Eight patients had first-degree relatives with visual snow. Clinical investigations were not contributory. Only a few treatment trials have been successful in individual patients. Our data suggest that "visual snow" is a unique visual disturbance clinically distinct from migraine aura that can be disabling for patients. Migraine is a common concomitant, although standard migraine treatments are often unhelpful. "Visual snow" should be considered a distinct disorder and systematic studies of its clinical features, biology, and treatment responses need to be commenced to begin to understand what has been an almost completely ignored problem.

Comments: The syndrome of visual snow is a well-recognized phenomenon seen in the context of assorted conditions. It involves the perception of "static" or "television snow" in the visual fields of one or both eyes, often worse in the dark but seen in all lighting conditions and with the eyes closed. It may be symptomatic of disorders of the eye (glaucoma) or optic nerve (optic neuritis), or it may accompany or follow the use of hallucinogens such as LSD or ecstasy. As headache specialists we are asked to address this complaint, either diagnostically or therapeutically, as a variant of migraine aura. Migraine with persistent aura, particularly of a visual nature, is occasionally seen in our clinics and has been described extensively in the literature.[1-3] These authors tackled the important question of whether visual snow is indeed merely one form of migraine with persistent aura. The presence of visual snow often overlaps that of migraine, or perhaps that of migraine potential risk factors, and sometimes may be seen in the context of more typical aura. In my experience, many of the visual complaints listed in these visual snow patients are quite common to migraine – photophobia, photopsias, impaired night vision, floaters. Palinopsia has been less common and typically in those migraineurs with a dizzy or vertiginous element. Interestingly, I have often felt that visual snow was related to typical visual aura as constant migraine-related dizziness was to vertiginous aura – both are persistent, often difficult to manage, and frequently comorbid with anxiety disorders. Regardless, we have much more to learn about this specific visual complaint.

1. *Liu GT, Schatz NJ, Galetta SL, Volpe NJ, Skobieranda F, Komorsky GS. Persistent positive visual phenomena in migraine. Neurology. 1995;45:664-668.*
2. *Jager HR, Giffin NJ, Goadsby P. Diffusion- and perfusion-weighted MR imaging in persistent migrainous visual disturbances. Cephalalgia. 2005;25:323-332.*
3. *Wang YF, Fuh JL, Chen WT, Wang SJ. The visual aura rating scale as an outcome predictor for persistent visual aura without infarction. Cephalalgia. 2008; 28:1298-1304.*

—Robert G. Kaniecki, MD

Indeed we have much more to learn. I have often wondered whether patients or authors were even talking about the same condition when discussing visual snow (VS). Do we need a VS rating scale to characterize this condition further? What exactly would it actually do, standardize the population

or identify subgroups? While I have no real difficulties agreeing with the authors that VS is clinically distinct from migraine aura, I find that a particularly comfortable conclusion for neurological splitters. However, while my clinical experience is limited, as I suspect it is for nearly all of us, I often have found myself lumping VS with aura in those with migraine (likely both confirmation and selection biases). It seems to occur with extremely high association with migraine, although definitely not universally (although I have thought from my reading that this was dependent on who was asking the history) and sufferers report other migraine-like phenomena frequently, upon which both the authors and RGK comment. While not typical migraine aura, I fall on the side that migraine and VS genomics greatly overlap; we will know when we learn more about the genomes, and likely only then the accuracy of what is written now. Another recent VS article in English is provided should the reader want more.[1]

1. *Bessero AC, Plant GT. Should "visual snow" and persistence of after-images be recognised as a new visual syndrome? J Neurol Neurosurg Psychiatry. 2014 Mar 7. doi: 10.1136/jnnp-2013-306827. [Epub ahead of print].*

—Frederick R. Taylor, MD

In my humble opinion after reading this abstract and my coauthors' comments, visual snow may be migraine-induced or a distinct migraine-associated disorder. As always, the spectrum of migraine and the "neurological lumpers and splitters" are alive and well.

—Stephen H. Landy, MD

Hansen J, Baca S, VanValkenburg P, Charles A. Distinctive anatomical and physiological features of migraine aura revealed by 18 years of recording. *Brain*. 2013;136:3589-3595.

The mechanisms underlying the initiation and propagation of the migraine aura, and the visual percept that is produces, remain uncertain. The objective of this study was to characterize and quantify a large number of visual auras recorded by a single individual over nearly two decades to gain insight into basic aura mechanisms. An individual made detailed drawings of his visual percept of migraine aura in real time during more than 1000 attacks of migraine aura without headache over 18 years. Drawings were made in a consistent fashion documenting the shape and location of the aura wavefront or scotoma in the visual field at 1-minute intervals. These drawings were digitized and the spatial and temporal features of auras were quantified and analysed. Consistent patterns of aura initiation, propagation, and termination were observed in both right and left visual fields. Most aura attacks originated centrally (within 10° eccentricity), but there were also other distinct sites of initiation in the visual field. Auras beginning centrally preferentially propagated first through lower nasal field (69-77% of all auras) before travelling to upper and temporal fields, on both sides. Some auras propagated from peripheral to central regions of the visual field – these typically followed the reverse path of those travelling in the opposite direction. The mean velocity of the perceived visual phenomenon did not differ between attacks starting peripherally and centrally. The estimated speed of the underlying cortical event (2-3 mm/minute) was in the same range as has been previously reported by others. Some auras had limited propagation and spontaneously "aborted" after a few minutes, despite being initiated in similar locations to those that spread throughout the entire visual field. The visual percept of the aura changed corresponding with the presumed propagation from the V1 to the V2 region of the occipital cortex. In some cases the visual percept disappeared for several minutes before reappearing in a distant location, providing direct evidence that the aura can be clinically "silent." These results indicate that there can be multiple distinct sites of aura initiation in a given individual and suggest that the spatial pattern of propagation in the occipital cortex is non-concentric with a variable extent of propagation. The visual percept of migraine aura changes depending on the region of the occipital cortex that is involved.

Comments: Seminal publications in the 1940s laid the groundwork for linking the clinical phenomenon of migraine aura with the physiologic phenomenon of cortical spreading depression (CSD).[1,2] *Cerebral blood flow studies subsequently established concentric waves of spreading oligemia developing posteriorly in cerebral cortex and propagating anteriorly, potentially representing the vascular phase of the neuronal activity associated with CSD.*[3,4] *More recent papers have added further evidence and commentary to this speculated basis to migraine aura.*[5] *Animal models using CSD have been advocated as a means of assessing migraine-preventive medications, and since such medications are effective outside the presence of aura, "silent aura" occurrences have been proposed.*[6] *Here Hansen et al add another piece to the puzzle linking CSD with aura. Although taken from a single subject, the number of recordings (>1000 migraine attacks) documented meticulously over an extended period of time (18 years) provides not only an impressive data source, but one that is unique in that it provides recordings with precise spatial and temporal resolution captured in real time. Among the lessons learned: (1) propagation may be preferential rather than concentric, following anatomic lines of cerebral cortex; (2) the curvilinear appearance of aura may be due more to functional cortical anatomy rather than the shape of the propagating wave; (3) features of the transition from V1 to V2 visual cortex aura suggest CSD may be, at times, clinically "silent." This paper is a fascinating "old school" descriptive account of migraine aura that deserves reading.*

1. *Lashley K. Patterns of cerebral integration indicated by the scotomas of migraine. Arch Neurol Psychiatry. 1941;46:331-339.*
2. *Leão AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol. 1944;7:359-390.*
3. *Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol. 1981;9:344-352.*
4. *Woods RP, Iacoboni M, Mazziotta J. Brief report: Bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. N Engl J Med. 1994; 331:1689-1692.*

5. *Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A. 2001; 98:4687-4692.*
6. *Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz M. Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol. 2006;59:652-661.*

—Robert G. Kaniecki, MD

Clearly, RGK found his Brain, which has gone giddy over migraine lately. And great finds they are. Read this abstract, a true throwback to the Headache Journal-reading days of old and on to the next.

—Frederick R. Taylor, MD

This is "old school" for sure, RGK. This individual's migraine visual auras vary from attack to attack probably dependent on occipital lobe localization and progression. This case report confirms what we see clinically, that not only do migraine patients' triggers and headaches differ from attack to attack in the same individual but so do their auras.

—Stephen H. Landy, MD

Amin F, Hougaard A, Schytz H, Asghar M, Lundholm E, Parvaiz A, de Koning P, Anersen M, Larsson H, Fahrenkrug J, Ashina M. Investigation of the pathophysiological mechanisms of migraine attacks induced by pituitary adenylate cyclase-activating polypeptide-38. *Brain*. 2014;137:779-794.

Pituitary adenylate cyclase-activating polypeptide-38 (PACAP38) and vasoactive intestinal polypeptide are structurally and functionally closely related but show differences in migraine-inducing properties. Mechanisms responsible for the difference in migraine induction are unknown. Here, for the first time, we present a head-to-head comparison study of the immediate and long-lasting observations of the migraine-inducing, arterial, physiological and biochemical responses comparing PACAP38 and vasoactive intestinal polypeptide. In a double-blind crossover study 24 female migraine patients without aura were randomly allocated to intravenous infusion of PACAP38 (10 pmol/kg/minute) or vasoactive intestinal polypeptide (8 pmol/kg/minute) over 20 minutes. We recorded incidence of migraine during and after infusion (0-24 hours). Magnetic resonance angiography of selected extra- and intracranial arteries, blood samples (plasma PACAP38 and vasoactive intestinal polypeptide and serum tryptase), and vital signs (blood pressure, heart rate, respiratory frequency, and end-tidal pressure of CO_2) was recorded before and up to 5 hours after infusion. Twenty-two patients (mean age 24 years [range 19-36]) completed the study on both days. Sixteen patients (73%) reported migraine-like attacks after PACAP38 and four after vasoactive intestinal polypeptide (18%) infusion ($P = .002$). Three of four patients, who reported migraine-like attacks after vasoactive intestinal polypeptide, also reported attacks after PACAP38. Both peptides induced marked dilatation of the extracranial ($P < .05$), but not intracranial arteries ($P > .05$). PACAP38-induced vasodilatation was longer lasting (>2 hours), whereas vasoactive intestinal polypeptide-induced dilatation was normalized after 2 hours. We recorded elevated plasma PACAP38 at 1 hour after the start of PACAP38 infusion only in those patients who later reported migraine attacks. Blood levels of vasoactive intestinal polypeptide and tryptase were unchanged after PACAP38 infusion. In conclusion, PACAP38-induced migraine was associated with sustained dilatation of extracranial arteries and elevated plasma PACAP38 before onset of migraine-like attacks. PACAP38 has a much higher affinity for the PAC_1 receptor and we therefore suggest that migraine induction by PACAP38 may be because of activation of the PAC_1 receptor, which may be a future anti-migraine drug target.

Comments: Am I the only one confused by the possibly contradictory reports emanating from this Danish group? Among their numerous publications are many that delve into the issue of extracranial vasculature involvement in migraine headache. In 2010, they established dilation of the middle meningeal artery, but not the middle cerebral artery, following administration of calcitonin-gene-related peptide. This was reversed by sumatriptan.[1] *In 2011, they published a study using a novel high-resolution direct magnetic resonance (MR) angiography imaging technique which concluded, "These data show that migraine without aura is associated with dilatation of extra- and intracerebral arteries and that the headache location is associated with the location of the vasodilatation. Furthermore, contraction of extracerebral and not intracerebral arteries is associated with amelioration of headache."*[2] *In 2013, we have a third paper on this topic which concluded, "Sumatriptan constricts extracerebral arteries more than cerebral arteries. We suggest that sumatriptan may exert its anti-migraine action outside of the blood–brain barrier."*[3] *Last year in these pages we reviewed a fourth paper from this same group which generated a great deal of interest – and one wonderfully cited letter to the editor from Elliot Shevel we subsequently published in full. The authors again performed MR angiography on patients with migraine and found pain was not accompanied by extracranial arterial dilatation, but only by slight intracranial dilatation. They concluded "Future migraine research should focus on the peripheral and central pain pathways rather than simple arterial dilatation."*[4] *Now we have another article addressing migraine physiology, interestingly with a focus again on the extracranial vasculature. This component of migraine physiology again appears relevant? This group here compared the vascular and biochemical effects of 2 functionally and structurally related neuropeptides, PACAP38 and VIP. Both are known cerebral and dural vasodilating agents. In this study 73% of subjects developed migraine-like attacks following administration of PACAP38 vs only 18% following VIP infusion. The former also resulted in a more prolonged vasodilatory effect in extracranial, but not intracranial, vessels. So the vessels are important in migraine physiology. Am I the only one a bit confused here? Perhaps SHL or FRT can straighten me out.*

1. *Asghar MS, Hansen AE, Kapijimpanga T, et al. Dilation by CGRP of middle meningeal artery and reversal by sumatriptan in normal volunteers. Neurology. 2010;75:1520-1526.*
2. *Asghar MS, Hansen AE, Amin FM, et al. Evidence for a vascular factor in migraine. Ann Neurol. 2011;69:635-645.*

3. *Amin F, Asghar M, Ravneberg J, et al. The effect of sumatriptan on cephalic arteries: A 3T MR-angiography study in healthy volunteers. Cephalalgia. 2013;33:1009-1016.*
4. *Amin FM, Asghar MS, Hougaard A, et al. Magnetic resonance angiography of intracranial and extracranial arteries in patients with spontaneous migraine without aura: A cross-sectional study. Lancet Neurol. 2013; 12:454-461.*

—Robert G. Kaniecki, MD

Better than my comments would be the authors either generating a paper summarizing their data with conclusions or comments to these A&C coeditors. As I read RGK's yeoman's work summarizing this group's research, I am struck by how well it mirrors progress for the vast majority of science moving forward – that is with a preponderance of findings (extracranial middle meningeal artery dilation) and co-existent contradictory findings. I think RGK knows that rarely are we not confused along the way of scientific discovery. Now I may be confused about concerns over vasoconstriction as I understand PACAP38 is a vasodilating agent and a highly successful migraine inducer. So we hope that this leads to a future anti-migraine drug target? Through vasoconstriction, have we not been working to get away from that? Or as so often is true, another more important mechanism will be found for any anti-PACAP38 inhibitor with vasoconstriction an undesirable side-effect? SHL?

—Frederick R. Taylor, MD

I will attempt to simplify this discussion based on my understanding that VIP causes dilation of cranial arteries but does not trigger migraine attacks.[1] Previously migraine patients infused with PACAP38 experienced delayed migraine-like attacks indicating a possible neuronal rather than vascular mechanism.[2] Taken together this information suggests that a purely vascular mechanism of PACAP38 for migraine is unlikely.[3]

1. *Rahmann A, Wienecke T, Hansen JM, Fahrenkrug J, Olesen J, Ashina M. Vasoactive intestinal peptide causes marked cephalic vasodilation, but does not induce migraine. Cephalalgia. 2008;28:226-236.*
2. *Schytz HW, Birk S, Wienecke T, Kruuse C, Olesen J, Ashina M. PACAP38 induces migraine-like attacks in patients with migraine without aura. Brain. 2009; 132:16-25.*
3. *Goadsby PJ. The vascular theory of migraine – a great story wrecked by the facts. Brain. 2009;132:6-7.*

—Stephen H. Landy, MD

Maniyar F, Sprenger T, Monteith T, Schankin C, Goadsby P. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain*. 2014:137;232-241.

Our aim was identify brain areas involved in the premonitory phase of migraine using functional neuroimaging. To this end, we performed positron emission tomography scans with H2 15O to measure cerebral blood flow as a marker of neuronal activity. We conducted positron emission tomography scans at baseline, in the premonitory phase without pain and during migraine headache in eight patients. We used glyceryl trinitrate (nitroglycerin) to trigger premonitory symptoms and migraine headache in patients with episodic migraine without aura who habitually experienced premonitory symptoms during spontaneous attacks. The main outcome was comparing the first premonitory scans in all patients to baseline scans in all patients. We found activations in the posterolateral hypothalamus, midbrain tegmental area, periaqueductal grey, dorsal pons and various cortical areas, including occipital, temporal, and prefrontal cortex. Brain activations, in particular of the hypothalamus, seen in the premonitory phase of glyceryl trinitrate-triggered migraine attacks can explain many of the premonitory symptoms and may provide some insight into why migraine is commonly activated by a change in homeostasis.

Comments: Functional neuroimaging performed during the headache phase of acute migraine has consistently demonstrated activation of the dorsal pons.[1,2] The aura phase of migraine has also received much attention, but to date neither the prodrome nor postdrome of migraine have merited neuroimaging studies. Prodromal symptoms are often vague and constitutional, with fatigue, malaise, yawning, moodiness, nausea, and neck discomfort most commonly reported. Interestingly, administration of nitroglycerin to a migraine patient may not only trigger typical migraine headache pain, but also prodromal symptoms.[3] These authors took advantage of this finding and triggered prodromal symptoms in 11 subjects previously demonstrated to have such complaints triggered in this model. Each patient had positron emission tomography (PET) scans in 3 conditions: baseline, premonitory phase, and migraine headache. Eight patients were included in the final analysis. In the early premonitory phase, as compared with baseline, they found activations in the right posterior and lateral regions of the hypothalamus and the adjacent right midbrain ventral tegmentum – areas where activation could certainly become symptomatic through the common prodromal complaints reported above.[4,5] The discussion section of the paper highlights the potential neuroanatomical and neurochemical substrates for these symptoms. This is a quite interesting paper well worth the read, particularly for those interested in migraine pathophysiology.

1. *Afridi S, Giffin NJ, Kaube H, et al. A positron emission tomographic study in spontaneous migraine. Arch Neurol. 2005;62:1270-1275.*
2. *Afridi S, Matharu MS, Lee L, et al. A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Brain. 2005;128:932-939.*
3. *Afridi S, Kaube H, Goadsby PJ. Glyceryl trinitrate triggers premonitory symptoms in migraineurs. Pain. 2004;110:675-680.*
4. *Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. Headache. 2007;47:1418-1426.*
5. *Akerman S, Holland P, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci. 2011;12:570-584.*

—Robert G. Kaniecki, MD

As a migraine sufferer reading this paper who may suffer quite profound postdromal symptoms, a strange feeling came over me, perhaps a premonitory symptom warning me that I should attend to the human subjects of this paper. One hundred and forty-two hardy souls responded to media advertisements, not otherwise specified, were interviewed by phone, with 25 meeting inclusion criteria, most importantly requiring episodic migraine without aura and premonitory symptoms before headache. These 25 then allowed nitroglycerin infusion expecting a nitro headache that averaged about 30 minutes and potentially a migraine attack; treatment not listed as provided (a listing of individual customary treatments included). If in the baseline nitro infusion they were lucky enough to experience premonitory symptoms and delayed migraine headache (11 subjects), they consented to a prolonged imaging phase whereupon positron emission tomography (radiation included) was collected upon initial premonitory symptoms and later-onset migraine with scans about every 10 minutes. Eleven entered the imaging phase and 8 delivered data with 3 exclusions for migraine following nitro without a pain-free interval or the premonitory phase was too short to scan (if only they had done either of these in the baseline phase, they would probably have been spared another induced migraine). Much perhaps of more value can be discussed and perhaps SHL will further comment on the paper. For me I could not help marvel at these subjects and what they allowed and tolerated and for what – well the paper and supplement does not tell us the reward. Their suffering is our reward.

—Frederick R. Taylor, MD

It is commonly accepted that the hypothalamus is anatomically involved with the migraine prodrome.[1] This fascinating functional neuroimaging research and publication corroborates hypothalamic involvement and elucidates the neuroanatomical network responsible for this frequent migraine phase.[2,3]

1. *Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. Headache. 2007;47:1418-1426.*
2. *Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: An electronic diary study. Neurology. 2003;60:935-940.*
3. *Kelman L. The premonitory symptoms (prodrome): A tertiary care study of 893 migraineurs. Headache. 2004; 44:865-872.*

—Stephen H. Landy, MD

NOCICEPTION

Han L, Ma C, Liu Q, Weng HJ, Cui Y, Tang Z, Kim Y, Nie H, Qu L, Patel KN, Li Z, McNeil B, He S, Guan Y, Xiao B, Lamotte RH, Dong X. A subpopulation of nociceptors specifically linked to itch. *Nat Neurosci*. 2013;16:174-182.

Itch-specific neurons have been sought for decades. The existence of such neurons is in doubt recently due to the observation that itch-mediating neurons also respond to painful stimuli. Here, we genetically labeled and manipulated MrgprA3+ neurons in dorsal root ganglion (DRG) and found that they exclusively innervate the epidermis of the skin and respond to multiple pruritogens. Ablation of MrgprA3+ neurons led to significant reductions in scratching evoked by multiple pruritogens and occurring spontaneously under chronic itch conditions whereas pain sensitivity remained intact. Importantly, mice with TRPV1 exclusively expressed in MrgprA3+ neurons exhibited only itch- and not pain behavior in response to capsaicin. Although MrgprA3+ neurons are sensitive to noxious heat, activation of TRPV1 in these neurons by noxious heat did not alter pain behavior. These data suggest that MrgprA3 defines a specific subpopulation of DRG neurons mediating itch. Our study opens new avenues for studying itch and developing antipruritic therapies.

McCoy ES, Taylor-Blake B, Street SE, Pribisko AL, Zheng J, Zylka MJ. Peptidergic CGRPα primary sensory neurons encode heat and itch and tonically suppress sensitivity to cold. *Neuron*. 2013;78:138-151.

Calcitonin gene-related peptide (CGRP) is a classic molecular marker of peptidergic primary somatosensory neurons. Despite years of research, it is unknown whether these neurons are required to sense pain or other sensory stimuli. Here, we found that genetic ablation of CGRPα-expressing sensory neurons reduced sensitivity to noxious heat, capsaicin, and itch (histamine and chloroquine) and impaired thermoregulation but did not impair mechanosensation or β-alanine itch-stimuli associated with nonpeptidergic sensory neurons. Unexpectedly, ablation enhanced behavioral responses to cold stimuli and cold mimetics without altering peripheral nerve responses to cooling. Mechanistically, ablation reduced tonic and evoked activity in postsynaptic spinal neurons associated with TRPV1/heat, while profoundly increasing tonic and evoked activity in spinal neurons associated with TRPM8/cold. Our data reveal that CGRPα sensory neurons encode heat and itch and tonically cross-inhibit cold-responsive spinal neurons. Disruption of this crosstalk unmasks cold hypersensitivity, with mechanistic implications for neuropathic pain and temperature perception.

Comments: Occasionally we venture off the topic of migraine to review articles involving pain which might also be of interest to the readership. Traditionally linked to pain is the sensation of itch, which I learned years ago reflected merely lower-grade stimulation of traditional nociceptors. The truth appears to be different. For the first time researchers in 2013 identified a discrete population of itch receptors. It had been previously established that itch sensation is transmitted through a group of small-diameter sensory neurons in the trigeminal and dorsal root ganglia (DRG). The authors in the first paper identified a unique subset of unmyelinated sensory neurons that solely innervate skin and appear to specifically mediate itch. Han et al decided to study a group of G protein-coupled receptors known as Mrgprs (Mas-related G protein-coupled receptors) which are known to play an important role in sensing chemical stimuli and are specifically expressed by small-diameter DRG neurons in mice as well as in humans. They determined that MrgprA3+ neurons comprised a specific subpopulation of DRG neurons mediating itch. The second paper from McCoy et al revealed that CGRPα sensory neurons encode heat and itch

and tonically cross-inhibit cold-responsive spinal neurons. Since itch receptors may be found in dorsal root and trigeminal ganglia, and since CGRP-expressing neurons are involved, it seems reasonable to at least consider the possibility that such chemoreceptors are involved in dural irritation from CGRP, histamine, or other inflammatory mediators. I have included a couple of additional references for those whose taste buds have been whetted.[1,2]

1. *Wood JN, Eijkelkamp N. Noxious mechanosensation – molecules and circuits. Curr Opin Pharmacol. 2012;12:4-8.*
2. *McCoy ES, Taylor-Blake B, Zylka MJ. CGRPα-expressing sensory neurons respond to stimuli that evoke sensations of pain and itch. PLoS ONE. 2012;7:e36355*. [Epub 2012].

—Robert G. Kaniecki, MD

We have all experienced itch, obviously with wide variability, and it is "cool" to know some of its underpinning. I, for one, had no particular understanding of or particular problem with itch, although hives from iodinated contrast was clearly histaminic and itchy. RGK will have to give us follow up when another March and a long winter gives him the itch again.

—Frederick R. Taylor, MD

Zhang XY, Wen J, Yang W, Wang C, Gao L, Zheng LH, Wang T, Ran K, Li Y, Li X, Xu M, Luo J, Feng S, Ma X, Ma H, Chai Z, Zhou Z, Yao J, Zhang X, Liu JY. Gain-of-function mutations in SCN11A cause familial episodic pain. *Am J Hum Genet*. 2013;93:957-966.

Many ion channel genes have been associated with human genetic pain disorders. Here we report two large Chinese families with autosomal-dominant episodic pain. We performed a genome-wide linkage scan with microsatellite markers after excluding mutations in 3 known genes (SCN9A, SCN10A, and TRPA1) that cause similar pain syndrome to our findings, and we mapped the genetic locus to a 7.81-Mb region on chromosome 3p22.3-p21.32. By using whole-exome sequencing followed by conventional Sanger sequencing, we identified 2 missense mutations in the gene-encoding voltage-gated sodium channel Nav1.9 (SCN11A): c.673C > T (p.Arg225Cys) and c.2423C > G (p.Ala808Gly) (1 in each family). Each mutation showed a perfect cosegregation with the pain phenotype in the corresponding family, and neither of them was detected in 1021 normal individuals. Both missense mutations were predicted to change a highly conserved amino acid residue of the human Nav1.9 channel. We expressed the 2 SCN11A mutants in mouse dorsal root ganglion (DRG) neurons and showed that both mutations enhanced the channel's electrical activities and induced hyperexcitablity of DRG neurons. Taken together, our results suggest that gain-of-function mutations in SCN11A can be causative of an autosomal-dominant episodic pain disorder.

Leipold E, Liebmann L, Korenke GC, Heinrich T, Giesselmann S, Baets J, Ebbinghaus M, Goral RO, Stödberg T, Hennings JC, Bergmann M, Altmüller J, Thiele H, Wetzel A, Nürnberg P, Timmerman V, De Jonghe P, Blum R, Schaible HG, Weis J, Heinemann SH, Hübner CA, Kurth I. A de novo gain-of-function mutation in SCN11A causes loss of pain perception. *Nat Genet*. 2013;45:1399-1404.

The sensation of pain protects the body from serious injury. Using exome sequencing, we identified a specific de novo missense mutation in SCN11A in individuals with the congenital inability to experience pain who suffer from recurrent tissue damage and severe mutilations. Heterozygous knock-in mice carrying the orthologous mutation showed reduced sensitivity to pain and self-inflicted tissue lesions, recapitulating aspects of the human phenotype. SCN11A encodes Nav1.9, a voltage-gated sodium ion channel that is primarily expressed in nociceptors, which function as key relay stations for the electrical transmission of pain signals from the periphery to the central nervous system. Mutant Nav1.9 channels displayed excessive activity at resting voltages, causing sustained depolarization of nociceptors, impaired generation of action potentials, and aberrant synaptic transmission. The gain-of-function mechanism that underlies this channelopathy suggests an alternative way to modulate pain perception.

Liang J, Liu X, Zheng J, Yu S. Effect of amitriptyline on tetrodotoxin-resistant Nav1.9 currents in nociceptive trigeminal neurons. *Mol Pain*. 2013 Jun 22;9:31. doi: 10.1186/1744-8069-9-31

Background: Amitriptyline (AMI) is tricyclic antidepressant that has been widely used to manage various chronic pains such as migraines. Its efficacy is attributed to its blockade of voltage-gated sodium channels (VGSCs). However, the effects of AMI on the tetrodotoxin-resistant (TTX-r) sodium channel Nav1.9 currents have been unclear to present.

Results: Using a whole-cell patch clamp technique, this study showed that AMI efficiently inhibited Nav1.9 currents in a concentration-dependent manner and had an IC50 of 15.16 μM in acute isolated trigeminal ganglion (TG) neurons of the rats. 10 μM AMI significantly shifted the steady-state inactivation of Nav1.9 channels in the hyperpolarizing direction without affecting voltage-dependent activation. Surprisingly, neither 10 nor 50 μM AMI caused a use-dependent blockade of Nav1.9 currents elicited by 60 pulses at 1 Hz.

Conclusion: These data suggest that AMI is a state-selective blocker of Nav1.9 channels in rat nociceptive trigeminal neurons, which likely contributes to the efficacy of AMI in treating various pains, including migraines.

Comments: Research into inherited pain disorders has shed significant light on the mechanisms underlying pain transmission. The first 2 papers document different mutations in SCN11A, a gene identified to code for the alpha subunit of voltage-sensitive sodium channels. Voltage-gated sodium channels (VGSCs) are essential for the generation of action potentials, with the alpha subunit composing the core protein of the channel and auxiliary beta subunits modifying the channel function. VGSCs Nav1.1-Nav1.9 play critical roles in electrical signaling through action potential generation and propagation in the nervous system; some specific channel subtypes have been implicated in a number of

chronic pain conditions. According to their relative sensitivity to tetrodotoxin (TTX), VGSCs are classified as TTX-sensitive channels (Nav1.1-Nav1.4, Nav1.6 and Nav1.7) and TTX-resistant channels (Nav1.5, Nav1.8 and Nav1.9).[1] Nav1.7 has been among the best studied, with loss-of-function mutations associated with insensitivity to pain and gain-of-function mutations associated with paroxysmal pain disorder. Nav1.9 has also captured some recent attention as a potential key player in neuopathic pain.[2,3] Expression in damage-sensing neurons located in the peripheral nervous system has been shown to be upregulated by inflammatory mediators.[4] The first 2 groups abstracted here have identified mutations in SCN11A leading to 2 different gain-of-function phenotypes in the protein Nav1.9. Interestingly, one resulted in a familial pain disorder, while the other insensitivity to pain. The third abstract enhances the clinical relevance of channel manipulation for those of us treating headache or neuropathic pain. Liang et al, using a rat model, established that amitriptyline efficiently inhibited Nav1.9 currents in a concentration-dependent manner in isolated trigeminal ganglion neurons. These 3 studies are examples of an ever increasing body of work that provide optimism that manipulating Nav1.9 could provide a new pathway for treatment of pain.

1. *Catterall WA, Goldin AL, Waxman SG. International Union of Pharmacology. XLVII. Nomenclature and structure–function relationships of voltage-gated sodium channels. Pharmacol Rev. 2005;9:397-409.*
2. *Dib-Hajj S, Black JA, Cummins TR, Waxman SG. NaN/Nav1.9: A sodium channel with unique properties. Trends Neurosci. 2002;25:253-259.*
3. *Priest BT, Murphy BA, Lindia JA, et al. Contribution of the tetrodotoxin-resistant voltage-gated sodium channel NaV1.9 to sensory transmission and nociceptive behavior. Proc Natl Acad Sci U S A. 2005;9:9382-9387.*
4. *Lolignier S, Amsalem M, Maingret F, et al. Nav1.9 channel contributes to mechanical and heat pain hypersensitivity induced by subacute and chronic inflammation. PLoS ONE. 2011;6:e23083.* [Epub 2011 Aug 12].

—Robert G. Kaniecki, MD

My comments reveal that I am no expert on this subject. Perhaps like you, our reader, selected topics commonly lead me to search the literature further for my understanding and sometimes even yours. I uncovered 2 articles which discussed a chemotherapeutic agent that induces pain but through effects on selective voltaged-gated sodium channels. In the Minett et al paper,[1] the agent oxaliplatin failed to induce pain through Nav1.7 tetrodotoxin (TTX)-sensitive channels or Nav1.8 TTX-resistant channels, both important pain-producing channels. Perhaps the Deuis et al reference[2] may eventually lead to an understanding of allodynia in migraine and other pain disorders as it associates the TTX-sensitive Nav1.6 channel to induced cold allodynia. A necessary conclusion is that similar pain phenotypes arise through distinct cellular and molecular mechanisms. The first reference further concludes that rational analgesic drug therapy requires patient stratification in terms of mechanisms and not just phenotype. We have much to learn about this pain arena which RGK has eloquently introduced. If you were pain-resistant to this topic, an editorial which accompanies RGK's Leopold et al abstract on loss of pain sensitivity and is referenced.[3]

1. *Minett MS, Falk S, Santana-Varela S, et al. Pain without nociceptors? Nav1.7-independent pain mechanisms. Cell Rep. 2014;6:301-312.*
2. *Deuis JR, Zimmermann K, Romanovsky AA, et al. An animal model of oxaliplatin-induced cold allodynia reveals a crucial role for Nav1.6 in peripheral pain pathways. Pain. 2013;154:1749-1757.*
3. *Cox JJ, Wood JN. No pain, more gain. Nat Genet. 2013;45:1271-1272.*

—Frederick Taylor, MD

Üçeyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, Casanova-Molla J, Reiners K, Sommer C. Small fibre pathology in patients with fibromyalgia syndrome. *Brain*. 2013;136:1857-1867.

Fibromyalgia syndrome is a clinically well-characterized chronic pain condition of high socio-economic impact. Although the pathophysiology is still unclear, there is increasing evidence for nervous system dysfunction in patients with fibromyalgia syndrome. In this case-control study we investigated function and morphology of small nerve fibres in 25 patients with fibromyalgia syndrome. Patients underwent comprehensive neurological and neurophysiological assessment. We examined small fibre function by quantitative sensory testing and pain-related evoked potentials, and quantified intraepidermal nerve fibre density and regenerating intraepidermal nerve fibres in skin punch biopsies of the lower leg and upper thigh. The results were compared with data from 10 patients with monopolar depression without pain and with healthy control subjects matched for age and gender. Neurological and standard neurophysiological examination was normal in all patients, excluding large fibre polyneuropathy. Patients with fibromyalgia syndrome had increased scores in neuropathic pain questionnaires compared with patients with depression and with control subjects ($P < .001$ each). Compared with control subjects, patients with fibromyalgia syndrome but not patients with depression had impaired small fibre function with increased cold and warm detection thresholds in quantitative sensory testing ($P < .001$). Investigation of pain-related evoked potentials revealed increased N1 latencies upon stimulation at the feet ($P < .001$) and reduced amplitudes of pain-related evoked potentials upon stimulation of face, hands and feet ($P < .001$) in patients with fibromyalgia syndrome compared to patients with depression and to control subjects, indicating abnormalities of small fibres or their central afferents. In skin biopsies total ($P < .001$) and regenerating intraepidermal nerve fibres ($P < .01$) at the lower leg and upper thigh were reduced in patients with fibromyalgia syndrome compared with control subjects. Accordingly, a reduction in dermal unmyelinated nerve fibre bundles was found in skin samples of patients with fibromyalgia syndrome compared with patients with depression and with healthy control subjects, whereas myelinated nerve fibres were spared. All 3 methods used support the concept of impaired small fibre function in patients with

fibromyalgia syndrome, pointing towards a neuropathic nature of pain in fibromyalgia syndrome.

Oaklander AL, Herzog ZD, Downs HM, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain*. 2013;154:2310-2316.

Fibromyalgia is a common, disabling syndrome that includes chronic widespread pain plus diverse additional symptoms. No specific objective abnormalities have been identified, which precludes definitive testing, disease-modifying treatments, and identification of causes. In contrast, small-fiber polyneuropathy (SFPN), despite causing similar symptoms, is definitionally a disease caused by the dysfunction and degeneration of peripheral small-fiber neurons. SFPN has established causes, some diagnosable and definitively treatable, e.g., diabetes. To evaluate the hypothesis that some patients labeled as having fibromyalgia have unrecognized SFPN that is causing their illness symptoms, we analyzed SFPN-associated symptoms, neurological examinations, and pathological and physiological markers in 27 patients with fibromyalgia and in 30 matched normal controls. Patients with fibromyalgia had to satisfy the 2010 American College of Rheumatology criteria plus present evidence of a physician's actual diagnosis of fibromyalgia. The study's instruments comprised the Michigan Neuropathy Screening Instrument (MNSI), the Utah Early Neuropathy Scale (UENS), distal-leg neurodiagnostic skin biopsies, plus autonomic-function testing (AFT). We found that 41% of skin biopsies from subjects with fibromyalgia vs 3% of biopsies from control subjects were diagnostic for SFPN, and MNSI and UENS scores were higher in patients with fibromyalgia than in control subjects (all $P < .001$). Abnormal AFTs were equally prevalent, suggesting that fibromyalgia-associated SFPN is primarily somatic. Blood tests from subjects with fibromyalgia and SFPN-diagnostic skin biopsies provided insights into causes. All glucose tolerance tests were normal, but 8 subjects had dysimmune markers, 2 had hepatitis C serologies, and 1 family had apparent genetic causality. These findings suggest that some patients with chronic pain labeled as fibromyalgia have unrecognized SFPN, a distinct disease that can be tested for objectively and sometimes treated definitively.

Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev*. 2014 Jan 3;1:CD007115. doi: 10.1002/14651858.CD007115.pub3

Background: Duloxetine is a balanced serotonin and noradrenaline reuptake inhibitor licensed for the treatment of major depressive disorders, urinary stress incontinence and the management of neuropathic pain associated with diabetic peripheral neuropathy. A number of trials have been conducted to investigate the use of duloxetine in neuropathic and nociceptive painful conditions. This is the first update of a review first published in 2010.

Objectives: To assess the benefits and harms of duloxetine for treating painful neuropathy and different types of chronic pain.

Methods: On 19th November 2013, we searched The Cochrane Neuromuscular Group Specialized Register, CENTRAL, DARE, HTA, NHSEED, MEDLINE, and EMBASE. We searched ClinicalTrials.gov for ongoing trials in April 2013. We also searched the reference lists of identified publications for trials of duloxetine for the treatment of painful peripheral neuropathy or chronic pain.

Selection criteria: We selected all randomised or quasi-randomised trials of any formulation of duloxetine, used for the treatment of painful peripheral neuropathy or chronic pain in adults.

Data: We used standard methodological procedures expected by The Cochrane Collaboration.

Main results: We identified 18 trials, which included 6407 participants. We found 12 of these studies in the literature search for this update. Eight studies included a total of 2728 participants with painful diabetic neuropathy and 6 studies involved 2249 participants with fibromyalgia. Three studies included participants with depression and painful physical symptoms and 1 included participants with central neuropathic pain. Studies were mostly at low risk of bias, although significant drop outs, imputation methods and almost every study being performed or sponsored by the drug manufacturer add to the risk of bias in some domains. Duloxetine at 60 mg daily is effective in treating painful diabetic peripheral neuropathy in the short term, with a risk ratio (RR) for ≥50% pain reduction at 12 weeks of 1.73 (95% CI 1.44 to 2.08). The related NNTB is 5 (95% CI 4 to 7). Duloxetine at 60 mg daily is also effective for fibromyalgia over 12 weeks (RR for ≥50% reduction in pain 1.57, 95% CI 1.20 to 2.06; NNTB 8, 95% CI 4 to 21) and over 28 weeks (RR 1.58, 95% CI 1.10 to 2.27) as well as for painful physical symptoms in depression (RR 1.37, 95% CI 1.19 to 1.59; NNTB 8, 95% CI 5 to 14). There was no effect on central neuropathic pain in a single, small, high-quality trial. In all conditions, adverse events were common in both treatment and placebo arms but more common in the treatment arm, with a dose-dependent effect. Most adverse effects were minor, but 16% of participants stopped the drug due to adverse effects. Serious adverse events were rare.

Conclusions: There is adequate amounts of moderate quality evidence from 8 studies performed by the manufacturers of duloxetine that doses of 60 mg and 120 mg daily are efficacious for treating pain in diabetic peripheral neuropathy but lower daily doses are not. Further trials are not required. In fibromyalgia, there is lower quality evidence that duloxetine is effective at similar doses to those used in diabetic peripheral neuropathy and with a similar magnitude of effect. The effect in fibromyalgia may be achieved through a greater improvement in mental symptoms than in somatic physical pain. There is low to moderate quality evidence that pain relief is also achieved in pain associated with depressive symptoms, but the NNTB of 8 in fibromyalgia and depression is not an indication of substantial efficacy. More trials (preferably independent investigator-led studies) in these indications are required to reach an optimal information size to make convincing determinations of efficacy. Minor side effects are common and more common with duloxetine 60 mg and particularly with 120 mg daily, than 20 mg daily, but serious side effects

are rare. Improved direct comparisons of duloxetine with other antidepressants and with other drugs, such as pregabalin, that have already been shown to be efficacious in neuropathic pain would be appropriate. Unbiased economic comparisons would further help decision making, but no high quality study includes economic data.

Comments: The term fibromyalgia is likely to represent a number of conditions, at least some possessing an organic basis. The first 2 papers provide evidence that at least in some, the pathology may be found in small peripheral nerve fibers. The questions now to be raised: Exactly which patient subset should be subjected to such investigation, and how will such findings, if present, effect management? From a perspective of management, a recent Cochrane database review is included.

—Robert G. Kaniecki, MD

These fibromyalgia articles were just calling out for connection to the prior 3 pain articles on gene-encoded voltage-gated sodium channels. I have listed 3 references[1-3] should you wish to explore this connection further.

1. *Vargas-Alarcon G, Alvarez-Leon E, Fragoso JM, et al. A SCN9A gene-encoded dorsal root ganglia sodium channel polymorphism associated with severe fibromyalgia. BMC Musculoskelet Disord. 2012;13:23.*
2. *Martinez-Lavin M, Solano C. Dorsal root ganglia, sodium channels, and fibromyalgia sympathetic pain. Med Hypotheses. 2009;72:64-66.*
3. *Wang SY, Calderon J, Kuo Wang G. Block of neuronal Na+ channels by antidepressant duloxetine in a state-dependent manner. Anesthesiology. 2010;113:655-665.*

—Frederick R. Taylor, MD

After reading the last 3 abstracts, "I hurt all over" for fibromyalgia patients. It is good to know that some may have small-fiber polyneuropathy, a somewhat more objective and quantifiable disorder that may be more responsive to duloxetine.[1]

1. *Hovaguimian A, Gibbons CH. Diagnosis and treatment of pain in small fiber neuropathy. Curr Pain Headache Rep. 2011;15:193-200.*

—Stephen H. Landy, MD