



Pathophysiology of Headache Progression

Moderated by **Peter Goadsby, MD¹**

Discussants: **Rami Burstein, MD²; Andrew Charles, MD³; Jean Schoenen, MD⁴**

DR. GOADSBY: I'm Peter Goadsby from the University of California San Francisco (UCSF), where I direct the headache program. I have with me in the discussion today Rami Burstein, Andrew Charles, and Jean Schoenen. I'll let them introduce themselves.

DR. BURSTEIN: I am Rami Burstein. I am the academic director of the Headache Center at Beth Israel Deaconess Medical Center; Vice Chairman of Research in the Department of Anesthesia and Critical Care; and Professor of Anesthesia and Neuroscience at Harvard Medical School.

order to so, we should define at the start what we mean by "headache progression" so we're all starting from the same point. Dr. Charles, when we talk about headache progression, what does it make you think about?

DR. CHARLES: I am Andrew Charles. I am a professor in the Department of Neurology at the UCLA School of Medicine and Director of the Headache Research and Treatment Program here.

DR. CHARLES: It makes me think about a patient who has episodic migraine that occurs infrequently, let's say once a month or once every other month, who at some point in the course of their life begins having headaches much more frequently, let's say 2 or 3 or 4 times per week. Accompanying that, there may be a change in the quality of the headache, where it becomes somewhat less classic for episodic migraine and has fewer of the typical features that we consider associated with migraines.

DR. SCHOENEN: I'm Jean Schoenen. I'm a neurologist and professor at the University of Liege in Belgium and Director of the Headache Research Unit at the University hospital.

DR. GOADSBY: We are talking about the pathophysiology of headache progression, and in

DR. GOADSBY: That's very helpful. What we're really talking about and what we're going to narrow

ABSTRACT

The discussion focused primarily on: 1) The definition of headache progression; 2) pathophysiology of migraine progression; 3) differences in migraine pathophysiology and migraine progression among migraine patients; 4) association between treatment and migraine progression; 5) nature of migraine progression in terms of frequency; 6) presence of brain lesions in migraine patients; 7) differences between migraines with and without auras; 8) findings of magnetic resonance imaging and functional magnetic resonance imaging; 9) relationship between analgesic use and migraine progression; 10) nature of chronic pain due to medication overuse; 11) frequency of sensitization with nonsteroidal anti-inflammatory drug and triptan use; and 12) use of aggressive preventative medicine to restrict headache progression. *Med Roundtable Gen Med Ed*, 2014;1(4):280-288.

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ourselves down to is talking about the pathophysiology of migraine progression because we wouldn't be able to cover all of the types of headaches. Dr. Schoenen, what is your comment on headache progression?

DR. SCHOENEN: I agree with what Dr. Charles said, although, clinically, I think that this disorder is quite heterogeneous between patients. Any migraineur has experienced, at some time in his life, progression of the disorder, where it becomes more frequent and then drops back again to its former frequency, but there seems to be a small population of patients in whom the disorder sometimes progress and then tips over into chronic migraine. That's

not the case for all migraineurs who progress, and many patients progress for some time and then do not progress up to what we call chronic migraines. So that may be something we have to consider from the pathophysiological point of view: What differs between those who progress to chronic migraine from those who do not?

DR. GOADSBY: Yes, you make a good point. Dr. Burstein?

DR. BURSTEIN: Maybe another aspect of the progression of headache is defined by treatment. When younger patients get a migraine, they go to sleep. When they wake up, their migraine is gone. They then progress to a point where they are unable to sleep off the migraine. They combine sleep with over-the-counter drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) in

order to abort the migraine. As the disease progresses, they need something stronger than sleep and NSAIDs. As the disease continues to progress and they develop symptoms such as depression, anxiety, and fatigue, they benefit less from sleep and NSAIDs and seek alternative therapies, such as triptans.

Eventually, some aspects of the progression make them more and more resistant to conventional treatment and clearly define a

"[There] is a group of migraineurs who have increased frequency and some change in quality. The treatment effects are perhaps important for them...Does analgesic use drive or follow the problem?"

Peter Goadsby

pathophysiological or pathological change that makes it more difficult for them to become pain-free or respond to medication.

DR. GOADSBY: I think the other aspect of this, which is not often stated but may be incredibly informative if we understood it, is the basis for the regression of this progression. It seems that the population estimates for chronic migraine are stable, and that there's clearly a group of people for whom the frequency of headaches can increase each year. There must be, clearly, a group of people in equal size who go from having more headache to less headache, and I wish I thought that was because we treated them properly, but I don't think that's the case on a population basis.

The resolution is almost as interesting as the induction.

When we talk about progression, we're talking about addition of burden, whether in terms of frequency, change in the type of headache, or, as Dr. Burstein just said, treatment. The other aspect of progression that's discussed is whether there's any progression of a consequent nature: Progression to acquisition of brain changes and, what have been, I think, erroneously been called brain lesions, progression in cognitive function. Dr. Schoenen, do you have a view about any of those things?

DR. SCHOENEN: I do not really believe that the majority of migraine patients accumulate brain lesions over their lifetime, even when they progress.

Most patients who progress and experience chronic migraines have migraines without aura, very few or no white-matter lesions, and very little or no increased risk for stroke.¹ Brain lesions on magnetic resonance imaging (MRI) were mainly reported in migraine-with-aura patients, and predominantly in females. The nature of these lesions is not known. In some studies, their prevalence was somewhat correlated with attack frequency, but the majority of subjects in the general population who suffer from migraine with aura experience low frequency of attacks. So, I do not believe that migraine without aura causes lesions in the brain, but I do believe that migraine without aura impairs, to some extent, cognitive performance, but that's not related to the frequency of attacks, but likely due to the abnormal information processing that can be recorded in the brain of migraineurs between attacks.

DR. GOADSBY: Yes, exactly. Dr. Charles?

DR. CHARLES: The other imaging modalities that have shown changes are morphometric studies with MRI and functional MRI scans that show chronic changes in brain structure and function, particularly in areas related to pain processing, in patients with migraine. That is, I believe, something that may be occurring in patients who have progression of migraine, that there's a plasticity of the brain that results in these structural and functional changes over time. I think that's an area of great interest in terms of trying to understand how to reverse that process of progression.

DR. SCHOENEN:

I agree completely with that. The problem is that many of these changes do not seem to be very specific to migraine. They are merely a consequence of the recurring head pain and also found in other pain disorders. Very few are specific to migraine. When patients develop chronic migraine, central sensitization occurs, and plastic changes appear in brain areas involved in pain processing and control. These areas are not specific to migraine. Taken together, I think brain changes seen in episodic migraine interictally are, for most cases, causally related to the disorder. In chronic migraine, these migraine-specific changes become overwhelmed by other brain modifications related to chronic pain, which have therapeutic implications.

DR. CHARLES: Yes, I agree.

DR. BURSTEIN: I think the biggest question that keeps coming up from all the imaging studies that show differences between migraine and non-migraine patients or migraine patients that progress and migraine patients that do not progress is what comes first: the changes that we see, which are responsible for the patient's symptoms in the migraine, or the progression of the headache, which is causing the brain changes. For this, at least now, we don't have

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a clear answer, although I think that most believe that progression of the migraine results in progressive changes and the beginning of brain malfunction. But the answer is not clear, and this belief somewhat conflicts with the concept of genetics, because if migraine patients do have genetic defects, you expect all changes to be there all along.

DR. GOADSBY: We currently have no clear data on what happens to migraineurs' brains over time. Various changes in structure have been reported, but we do not know what happens, for example, if the migraine is controlled, do the brain changes revert? First, we must consider whether brain changes over time are linked with anything

related to the headache. For example, if there's high headache frequency or severity and then resolution, did changes occur? There don't seem to be any long-term consequences of migraines. All the work done studying French people over the age of 70 on a population basis points to no untoward effect of a migraine on cognitive status,² as do the data from the Women's Health Study.³ Prospective examination of cognitive functions in that cohort identified absolutely no cognitive death attributable to migraine status. Whatever is happening in the brain can't be all bad, since it doesn't seem to have palpable consequences. I find that reassuring for patients.

DR. BURSTEIN:

I agree. I think that the fact that a neurologist who's blind to

whether a patient has ever had a headache cannot tell from the results of a cognitive test of that patient whether they ever had a migraine in their life always raises a big question about the functional consequences or further changes associated with migraine that we see structurally in the brain.

DR. GOADSBY: I find the cognitive facts very reassuring for patients. I also find it reassuring to be able to tell them, even those with small changes, that as long as they live to even 75, they won't have any particular problems.

I think we've probably come to the broad brush, that is, a group of migraineurs who have increased frequency and some change in quality.

The treatment effects are perhaps most important for them. Before we go into the details of the pathophysiology, we should get some comments about the role of analgesic use, or the use of it in, as it is sometimes described, the evolution of migraines. Does analgesic use drive or follow the problem? I'll start with Dr. Burstein.

DR. BURSTEIN: I belong to the group of people who believe that analgesics are overused, especially opiates and barbiturates, and contribute tremendously and significantly to the transition from acute to chronic pain, and from treatment that works to treatment that doesn't work. They contribute on a molecular basis to sensitization; increase hyperexcitability; and add to the molecular aspects of the pathophysiology of increased excitability along the pain pathways in general, and in this case along the active trigeminovascular pain pathway.

DR. GOADSBY: We probably all agree that opioids are a problem, however, it's how you look at it. Do you have in mind a particular site in the brain or particular pathways when you think about this process, or do you think "outside the brain" when you think about opioids and their role in this problem?

DR. BURSTEIN: I think that it will be in the first synapse between the peripheral and the central neuron.

I think that the opioid's ability to virtually bring to almost a complete stop the glutamate transporter and the inability of glutamate to clear itself out of the synapse contribute a lot to accessibility to susceptible pain neurons in the spinal cord, which is not where they eliminate pain. They eliminate pain in the brain stem, the rostral ventral inner medulla, the periaqueductal gray, and basal ganglia. When you eliminate the "off switch" by stopping medication, you're left with a hyperexcitable spinal cord that has spinal glia that has a significantly reduced ability to clear glutamate from the synapse in the spinal cord.

are a problem in the United States. Analgesics containing opioids are very rarely overused in Europe right now because there are stricter limitations in their availability. The only one that still exists on the market is codeine combined with paracetamol. The most frequently overused preparations are non-opioid analgesics or NSAIDs combined with caffeine or triptans. The underlying process may be different between these molecules. Do you agree that it is possible that the daily intake of analgesics or NSAIDs by fibromyalgia patients, for instance, may play a role in chronicizing their pain?

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DR. BURSTEIN: Yes, I do. I think that whenever we prescribe opioids we make a big mistake, especially in the field of headache.

DR. GOADSBY: I will say one thing about Europe, when I was practicing there, the single biggest problem with overuse was codeine

DR. SCHOENEN: You're right, but is that specific to migraine or not? Do you think that chronification due to medication overuse exists in other pain disorders?

DR. BURSTEIN: Yes, I think we have known that since 1988, when it first became clear in animal studies and then in human studies that opioids produced allodynia, hyperalgesia, and central sensitization.⁴

DR. SCHOENEN: I agree, but opioids are not a problem in Europe. Opioids

because codeine was available in the supermarkets. Medication overuse has regional and cultural dimensions, depending on what you have access to. Dr. Charles?

DR. CHARLES: I think with regard to the opioids, the other thing to keep in mind is that while they're commonly viewed as having depressant or inhibitory actions, they in fact are excitatory in many areas of the brain, as well as the spinal cord. For example, most of the commonly used opioids can in

fact cause seizures, and clearly have excitatory effects in the cortex. So it's quite possible that in an episodic disorder of brain excitability, like migraine, they're actually working not simply by changing pain, but also by changing some of the basic mechanisms until they reach a threshold that triggers migraine in the brain, even before the pain starts.

DR. GOADSBY: From that hypothesis, you might predict that patients with migraine with aura and opioid overuse would have more aura. You see where I'm headed with that?

DR. CHARLES: Sure. I wasn't necessarily specifically referring to the visual cortex, but, in general, making the point that opioids have excitatory effects in the brain and using seizures as an example of a phenomenon, but not necessarily saying that it's the cortex itself. Maybe it's the hypothalamus or the thalamus or some other area of the brain in which they're exerting excitatory effects.

DR. BURSTEIN: It can be the peripheral nervous system. Look, they produce itch, suggesting they are excitatory to certain classes of peripheral receptors.

DR. GOADSBY: Dr. Charles, do you agree that opioid-induced medication overuse problems precede as opposed to follow increased headache frequency, because there is this possibility that some medication overuse is simply because

headache gets worse and patients just do what they need to do? I'm not sure lumping everyone together and saying everyone who overuses actually produces headache with the overuse so much as there's more than one group.

DR. CHARLES: That's right. Broadening the discussion to other medications, I think that it's important to not lump all the acute medications for migraine into the same categories because they have such pharmacologically distinct properties that it isn't plausible that they could all have the same effects. I think, as Dr. Schoenen mentioned, the combination analgesics, particularly those with caffeine, are particularly problematic. Recently in the

the rheumatology clinic and the one that Becker did in the gastro clinic, clearly show that there are people who overuse opioids by any standard definition who don't have headache at all as a problem. So, there's an important interaction, I think, between a genetic predisposition and these medicines. It's something that would be wonderful to get at so we could be able to understand who are at risk and who aren't at risk. One day I hope that we'll be able to do that. Do you think that people who are at risk for one type of overuse are at risk for all? Let me ask Dr. Schoenen.

DR. SCHOENEN: I don't know. I can only say that I see patients in whom overuse recurs and with a different drug. There are patients with overuse of a combined analgesic who return to an episodic form of migraine after drug withdrawal, but come back to my office 6 months or 1 year later with daily headache and daily use of a simple NSAID or analgesic.

There may be a genetic predisposition to chronification by overuse of any anti-migraine drug, despite the fact that in practice simple NSAIDs are less likely to chronify the disorder.

Just to pick up what Andrew said, there is clearly a difference between the drugs and their effect on the brain. For example, looking at sensitivity in the somatosensory cortex with evoked potentials, there's clearly a difference between patients overusing triptans and

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 **Jean Schoenen**

United States, we've had a big uproar because of a shortage of one of the aspirin-and-caffeine-containing preparations. That, I think, is an example of how caffeine-containing preparations can be particularly problematic as a cause of medication-overuse headache.

DR. GOADSBY: Yes, I think the other component of this must be that there is some predisposition to it. The two studies that I'm aware of, the one that we were involved in in

those taking NSAIDs, although their clinical phenotype is the same.

DR. GOADSBY: While you're talking about your work, can you summarize for us the imaging study on medication overuse you did a few years ago?

DR. SCHOENEN: Oh, yes. Well that was a study where we looked at metabolic changes with fluorodeoxyglucose positron emission tomography in brain areas that belong to the so-called pain matrix, but also in areas that are known to be involved in substance abuse.⁵ What we found was that metabolism was clearly decreased in several areas that are thought to belong to the pain matrix, but these changes were reversible after withdrawal of the drug 3 weeks later. The only area where hypometabolism was not reversible after drug withdrawal was the orbitofrontal cortex. The orbitofrontal hypoactivity was even worse after withdrawal, and it was more pronounced in those patients who were overusing combined analgesics. The orbitofrontal cortex has been shown to play a crucial role in substance dependence. Its hypofunction could predispose patients to recurrence of medication-overuse headache. To prove this, we're completing a long-term follow-up study.

DR. GOADSBY: That is interesting because I think that's one of the important contributions to the pathophysiological understanding in humans.

DR. SCHOENEN: A Swiss group just published similar results measuring the amount of brain tissue with MRI.⁶ They found decreased tissue density in the orbitofrontal cortex, as well as in the dorsal pons, where abnormal activity is known to occur during migraine attacks.

DR. GOADSBY: You brought up nonsteroidals, a slightly more vexed issue. I'll start with Dr. Charles. Do you think nonsteroidals, and you don't have to lump them all together if you don't want to, have a role in medication overuse in terms of inducing headache?

DR. CHARLES: My own view is no. It's only the nonsteroidals in combination with caffeine that are the cause of medication overuse. I think that view is supported by the study by Bigal and Lipton,⁷ which basically suggests that, at a population level, frequent use of nonsteroidals is not associated with progression of headache. In fact, there's a slight trend in the opposite direction, which has led them to suggest that it may possibly be protective. So, no, I do not put nonsteroidal anti-inflammatory drugs in the same category as a cause, but I see them more as a consequence, or frequent use as a consequence of frequent headache rather than as a cause.

DR. GOADSBY: How do you see the difference in a mechanistic sense? I'll give everyone a chance to weigh in on this.

DR. CHARLES: This is something that may have to do with agonism versus antagonism of receptors and specific mechanisms of analgesia. I think the things that we think about that are the significant players in terms of causing medication overuse are ones that are working on neurotransmitter receptors, like γ -aminobutyric acid receptors and opioid receptors, and, in the case of caffeine, maybe adenosine receptors. I think the issue with the nonsteroidals is harder to understand, particularly how they might pharmacologically actually cause medication overuse. So, I think that mechanistically, those are the questions that are before us now.

STUDY DISCUSSED:

Women's Health Study

COMPOUNDS DISCUSSED:

analgesics, aspirin, barbiturates
caffeine, codeine, ibuprofen
nonsteroidal anti-inflammatory
drugs, opioids, paracetamol, triptans

DR. GOADSBY: Dr. Burstein, you published on nonsteroidals and triptans in the context of sensitization.⁸ What's your view about this, particularly at a mechanistic level?

DR. BURSTEIN: Mechanistically, the data suggest that triptans disrupt communication between peripheral and central trigeminovascular neurons and that NSAIDs inhibit both the peripheral and the central neurons.

Accordingly, it is reasonable to suggest that triptans do not reverse central sensitization because they do not inhibit central trigeminovascular neurons directly, not at the level of the spinal cord at least, and that NSAIDs reverse central sensitization indirectly, through their anti-inflammatory action in the spinal cord (mostly unknown mechanism).

I think, again, that in the context of the opioid treatment, it became apparent both in the animal data and in patient data that opioid treatment makes patients resistant to successful NSAID treatment. NSAIDs work much better in patients who do not have a history of favoring opioids. Once patients begin to use opioids, however, they see a noticeable decline in the potential benefit of NSAIDs or triptan treatments. Again, I think that the key to that is the spinal cord inability to clear glutamate from the synapse, although I don't think

that the NSAIDs target glutamate release in any way.

DR. SCHOENEN: I do partially agree with what has been said. I think clinically, we clearly see patients who with overuse of simple analgesics, like paracetamol or a single NSAID like ibuprofen, enter the vicious circle of chronification and reverse to episodic migraine after reducing intake of these drugs.

The second point is that in the electrophysiological studies of patients overusing simple NSAIDs, there is clearly indication of sensitization in sensory cortices. Thirdly, Dr. Charles was alluding to the Bigal et al. study showing that NSAIDs protect against migraine chronification contrary to triptans.⁶ In this study, however, the protective effect of NSAIDs was only seen with patients who had low frequency of headaches. In patients with high frequency of headaches at baseline, NSAIDs also had a deleterious effect.

DR. GOADSBY: In the last few minutes that we have, I'd like to get some views about whether you think that more aggressive treatment with preventives would be helpful in terms of restricting headache progression. When medical practitioners see people who experience 6 or 8 headaches a month, and a couple months later they have 10 or maybe 12 or 14, they want to help them get better before they get worse. So if we intervened earlier, do we think that we could do a better job? Is that mechanistically plausible? I'll start with you, Dr. Charles.

DR. CHARLES: I think it's an appealing concept, but unfortunately I think that in practice we don't see that concept being realized. Taking a cynical view, I think in many

cases, even with preventative therapy, migraine finds its way around them, and even patients on preventative therapy end up having progression. So I think until we better understand the process, we can't really say with confidence that early preventive therapy is something that is going to prevent the progression of the disorder.

DR. GOADSBY: Dr. Schoenen?

DR. SCHOENEN: I fundamentally agree with that. I think we are

very lousy in the prevention of migraine. Most of the drugs don't reach 50% efficacy. The patients who respond to these drugs may be those who have a peculiar pathophysiological, possibly genetic, profile, and do not progress. Those who do not respond are probably those who are most prone to chronification of migraine and at last fail on all available preventative drugs. So, in addition to much better preventative treatments, we also really need many more treatments.

Clinical Implications

- ▶ Analgesics are frequently overused by migraine patients, contributing to the development of chronic migraine.
- ▶ A proportion of migraine patients experience progression in a manner that makes them increasingly resistant to conventional treatment and clearly defines a pathophysiological or pathological change making it more difficult for them to become pain free or respond to medication.
- ▶ Imaging studies have shown differences between migraine and non-migraine patients and between migraine patients that progress and migraine patients that do not progress, but it is unclear what comes first: the changes that can be observed, which cause the headache symptoms, or the progression of headache, which causes the brain changes.
- ▶ Migraine patients who respond to drugs may have a peculiar pathophysiological, possibly genetic, profile, and do not experience progression, while patients who do not respond are prone to chronification and unlikely to respond to currently available preventative drugs.
- ▶ The development of much better, and many more, preventative drugs is required for migraine patients who do not respond to currently available drugs.

DR. GOADSBY: Yes. Dr. Burstein?

DR. BURSTEIN: Well, I want to take it in a slightly different direction. I am aware of the fact that there is no evidence for it because nobody has done the study, but the question that I would like to answer is whether migraine progression would look completely different in a group of patients whose migraine attacks were treated early from

the first migraine attack in their life (ie, they didn't let their migraine last more than a few hours). Comparing this "early-treatment" group to a group of patients who treat late (ie, they let themselves have a migraine for 8, 10, or 12 hours before it goes away by itself or before they treat it).

DR. GOADSBY: Well, that would be an interesting study, very expensive

as well. But as you say, one of the things we lack very much in longitudinal study is what's really a dreadful problem, because whatever we think about the pathophysiology of headache progression, we'd all agree it's bad to have more headache, it's bad to have worse headache, and it's bad to have headaches that don't respond to therapy. It's a subject which deserves study.

FACULTY DISCLOSURES:

Dr. Rami Burstein is on the advisory board of Allergan; has received fees for non-CME services directly from Merck; and has done contract research for Allergan, Merck, and GlaxoSmithKline. The CME content over which he has control contains information about healthcare products or services provided by Merck and GlaxoSmithKline.

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Dr. Jean Schoenen is an advisory board member of Allergan, CoLucid, GammaCore, Medtronic, St. Jude Medical, ATI, and STX-Med.

Dr. Andrew Charles is on the scientific advisory board of AGA Medical, Amgen, Bristol-Myers Squibb, MAP Pharmaceuticals, Merck, MonoSol Rx, and Neuralieve. He has received speaker honoraria from Merck. He is on the editorial board of Cephalgia (Associate Editor, 2010-Present) and provides research support to MAP Pharmaceuticals and the Department of Defense, DOD CDMRP PR100085, Co-PI, 2011–2014.

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