

Dr. Ian Carroll  
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## Research Updates in Spinal CSF Leaks

Thank you for the warm introduction. And the feeling is of course mutual. I've learned a ton from Andy [Callen].

I also think it's worth reflecting on what he was saying that when I started doing this, and some of the data I'm going to show you [is] from 2016 to 2018, offering patches to people whose imaging was negative was controversial. Doing it at Stanford had people at UCSF talking about like, What is this guy doing?

And I've heard my colleagues joke about patching people who aren't leaking, and I am sure that I have patched some people who aren't leaking as a considered approach, and what do you do when someone has symptoms suggestive of a leak, the devastating consequences of those symptoms on quality of life, and the imaging doesn't show a leak?

Sometimes that's because they're not leaking, and sometimes that's because of a deficit in our imaging sensitivity. And it's frankly hard to know when you can tell someone, we have definitively ruled out a leak. So, in that setting, in the setting of ambiguity, you have to decide what is a rational risk-benefit, reward based approach to people whose imaging doesn't show a leak. And I'm going to show you some of the data that we've collected on our results doing exactly that.

When you do something like that, it's never a solo project that always involves other people and indispensable help came from the people here, from the Neurology Headache Department, the Neuroradiology Department at Stanford, the Neurology Headache Clinic, and people like Dr. Callen and Dr. Schievink.

So, in 2016 my chair said to me, Listen, Ian, if you're going to be patching people who it's controversial, you might want to track outcomes because it's really important. Over time, you don't want to be patching people you shouldn't be, and you want to be identifying the people you're helping the most. And you want to show the impact that you're having. And so we decided to use this platform called Qualtrics to deploy a number of questionnaires that would investigate progress on the common symptoms of CSF leak.

And so we decided to use a PROMIS metric of global health. PROMIS is this suite of questionnaires developed by the NIH to measure symptoms, and it's a nice set of instruments because they're all normalized so that a score of 50 is the U.S. norm. So a PROMIS global health physical score of 50 would mean you're at the average U.S. norm for global health. And 10 points is a full standard deviation. So it

becomes kind of easy to interpret the scores. So we used that promised global health metric. We used the HIT-6 to measure head pain. We gave something called the Neck Disability Index to measure neck pain. The Rhodes Index of Nausea and Vomiting. Tinnitus Handicap Inventory. We did some things that people really hadn't done before. We started measuring actual neurocognitive deficits in people with CSF leak. Nothing. Nothing like that had been reported before, except for people with behavioral variant frontal temporal dementia. We used metrics of fatigue, validated metrics of fatigue, again, not reported before.

And between August of 2016 and November of 2018, which are really the first couple of years I was doing this, we considered 243 patients for possible patching and they completed those health measures. Of those 243, 32 completed the measures, but were never patched. Of the remaining 211, 89 wound up getting a patch before they ever completed the measures. So we can't really follow pre post what happened to them because they were patched before they ever completed the measures. But then we have 122 patients who completed at least one survey before their first patch. And of those, 85 completed a second measure after their patch. So we have 122 patients of which we've got 85 who completed measures before their first patch and another set of measures, at least one other set of measures after their patch.

The people in that cohort are like the people in this room. Average age was 42; 78 percent were women. The way they differ from some of the data you'll see at conferences and that was proposed here or shown here earlier, the average symptom duration of the people I'm seeing is eight years, eight years. In the meta analysis that was in JAMA that was talked about earlier from D'Antona, the average duration of symptoms when they looked at all of the published literature on SIH, all the published literature, the average duration was 32 days. All right, so most of the literature that's published is on people whose symptoms are on average 32 days.

Go ahead and raise your hand if you've been having symptoms for 32 days or less, right? That's not who we're dealing with. That's not the people who are suffering long term. That's not the people who are getting online. It is important to know how to treat someone with an acute leak. which is what that published data reflects. That wasn't what I was seeing and not what I was trying to help. I was interested in people with long term symptoms, and I think that they do present differently.

You can see that 98 percent reported head pain, 82 percent neck pain, 63 percent had tinnitus. Cognitive impairment was common, reported by 91 percent of patients, and fatigue was reported by 96 percent of patients. All right. Of those people who reported head pain, 84 percent said that it was orthostatic. And there's a wide range of what orthostatic means to people. So the upright time before head pain starts could be anywhere between the first quartile of 0 to 5 minutes, versus the fourth quartile from 108 minutes to 841 minutes.

This is their PROMIS global health physical score, this is their overall physical global health. Was 32, which means that it's 18 points below the mean. Remember,

standard deviation in the U.S. population is 10 points and the mean global health for the U.S. population is 50. So these people are 2 standard deviations on average below the U.S. mean. They're in the 4th percentile of global health. 4th percentile. These people, the people who we are trying to treat, the people who are in this room who are really affected, and our friends who can't come and are contributing online, have quality of lives that are similar to patients dying with cancer, suffering with HIV, severe rheumatologic diseases, as sick as it comes.

And motivating for reasons to try something that can be done prudently and safely to help them, even when it's not proven they have a leak. Okay. Their headache impact test 67, which is in the severe range of headache. And their fatigue scores, again, that mean fatigue for the U.S. population would be 50, they're almost two standard deviations above the mean.

They're having fatigue that is in the 95th percentile of the U.S. population. Of those 85 people, despite having had symptoms for eight years, 16 had positive imaging or a low opening pressure and met ICHD-3 criteria for low pressure headache. So by definition, they had been on average misdiagnosed for eight years.

But as I was referring to earlier, when you prospectively enroll people with orthostatic headache and other symptoms of a CSF leak, chronically, not acutely, but chronically, only about 1 in 5 is going to meet the criteria, the diagnostic criteria. The other 4/5ths don't. And in previous cohorts that have been published, those other four fifths are told, you're not leaking, we're not going to patch you, there is no treatment indicated other than to go to a headache clinic and be treated as if you have chronic migraine, or POTS, or chronic fatigue syndrome, or something else.

And we felt that actually, the sensitivity of imaging and opening pressure was not well enough established to tell these patients with confidence, you don't have a leak. We thought maybe some of them should be offered a patch. So, this is their ICHD-3 status. We've got the 16 who had positive imaging or a low opening pressure, and the 69 who did not.

After an average of 3.6 patches, on average the cohort got 3.6 patches, this is the data that we saw. I'm showing you the durable outcomes from pre-patch to the last assessment, which is a mean of 521 days after their first patch. Or 377 days from their last patch over a year out. And what you see here is that PROMIS physical health moderately improves statistically significantly, P less than 0.001. And in fact, across a broad range of measures of general health and symptom specific measures, we have statistically significant improvement. But are those modest improvements clinically meaningful? Well, it turns out that previous investigators have published just how much does your PROMIS global health physical have to change for it to be something that patients consider clinically meaningful.

So that was published in this paper, and when we look at the response rate where now we're looking at clinically meaningful change, what you see is in the among the group that were ICHD-3 positive, the ones that had positive imaging or a low

opening pressure, even though they have a defect that's been open for eight years, when you patch them, 13 out of the 16 will report that they had a clinically meaningful improvement.

I don't understand why, if they have some hole in their ventral dura that's been there for eight years, why putting blood over it transiently results in long term, durable, clinically meaningful improvement at this rate. There is something that these patches are doing that is different than simply sealing the leak.

So, what you see is, is that's a little data on a small subset that's, in fact, patching long-term leakers who have been long misdiagnosed will, in fact, benefit from patching. But what about the 81 percent of patients who did not conform to the ICHD-3 criteria? What about those 69 patients who were imaging negative and had normal opening pressure?

So if we break those out, 37 of the 69 had a clinically meaningful response. So the response rate among those who met ICHD-3 criteria is higher. It's like 81%. All right. Versus 54 percent if you didn't meet criteria. So if your goal is to have the highest patch response rate, only patch those people who are imaging positive.

But if in fact you want to help the most people that you can, recognize that three-quarters of the patients who had a clinically meaningful response came from the group that had negative imaging and a normal opening pressure. So if your job, if your mission is to help the most people that you can, you need to have more inclusive patch criteria.

If your job is to put some paper into the literature showing that your patch rate success rate is higher, patch much fewer people, but you're gonna be turning away a lot of people who you could have helped. Who you had a duty to help.

What can help us identify patients most likely to have a clinically meaningful response among those patients who are ICHD-3 negative, having negative imaging and negative opening pressure. So we looked at some baseline variables. This is before their last assessment. These are variables that were measured 500 days or more before the final assessment.

So what you see here is, simply having orthostatic head pain did not predict whether you were going to be better a year or two years later. The time upright before head pain starts has no predictive value in are you going to get better from a patch and stay better and have a clinically meaningful, durable response?

And similarly, having migraineous features is not a negative predictor. If you had photophobia or phonophobia or nausea, those didn't predict a higher likelihood of not responding to patching. In contrast what you see here is that before you were ever patched, the extent to which your head pain went away after staying flat for an

hour strongly predicted the likelihood you were going to have a durable, clinically meaningful response.

That lasted over a year after your last patch. Why is this important? This is important because the skeptics in the room and in the CSF leak treatment community would say, Ian, all you measured by measuring these pre post changes was the placebo effect. You delivered a very powerful placebo when you delivered these patches, and patients were better when you measured them later, but it was all placebo.

But in the setting of a placebo response, it's hard to understand why how much better someone's head pain got before they were ever patched predicts results over a year later.

Let's look at the raw data. So what do we have here? We've got a lot of data points. Let me walk you through it. So on the bottom, on the y axis, we have pre-patch headache severity after laying flat for an hour. So if you're on the left side of this curve, your pain mostly went away after staying flat for an hour.

If you're on the right side of this curve, your head pain was still pretty strong after having stayed flat for an hour. On the y axis, we have the improvement in this global validated measure of physical health. Okay? Remember that here we are at zero. That's no change. That's no change in your global physical health.

All right. So we first thing is, is to accommodate some of the people who got a lot better. I have to show you this graph asymmetrically, right? I'm not showing you it going down to negative 30 because nobody got worse by three standard deviations, but some people did get better by three standard deviations.

Okay. Anybody who's above this line, not only did they have a clinically meaningful response, they improved more than a full standard deviation in global physical health in a long-term way. Anyone below that line got worse by the same amount. And what you see, if we go back, is the ratio of people who improved more than a full standard deviation in global physical health by a whole US population standard deviation. The ratio of those people to the people who diminish by the same amount is 13 to 1.

And if we look at the people on the left side of the curve, people who, when they stayed flat, their head pain went down to a 0, or went down to a 1, almost all of them, 76%, had clinically meaningful improvement, and about half of those improved, not just to a clinically meaningful extent, but almost a full standard deviation of the U.S. population global health. So, in conclusion, it is hard to explain the statistically significant relationship between relief when flat, we kind of glossed over it, two measures, how much better your head pain gets when you're flat for an hour, and how much better your head pain gets when you stay flat overnight.

It's hard to explain that relationship between those findings and subsequent clinically meaningful improvement. Among people who are ICHD-3 negative, negative for imaging, negative for opening pressure, how do you explain that with a placebo response, or regression to the mean, or something called the Hawthorne effect? It implies a specific treatment effect.

Among patients with chronic disabling symptoms suggesting CSF leak in whom imaging does not conform a leak, 54 percent of patients showed a clinically meaningful improvement at long term follow up after an average of 3.6 epidural patches. Two factors associated with CSF leak, more complete head pain resolution upon reclining for an hour or overnight, predicted that likelihood of being a clinically meaningful responder.

Most of the patients who experienced a meaningful clinical improvement following epidural patching came not from those who had positive imaging, but from those whose imaging was negative. By a ratio of 3 to 1. Nonetheless, a higher rate of response is seen among the ICHD-3 positive patients. And so what does that mean?

That means if I'm a treater, and I've just been trained on how to patch people, and I'm working at Mayo, or I'm working at another institution, when I patch those people who are imaging positive, they're getting better at a high rate. I'm getting lots of positive feedback for that. They're calling me, they're always happy.

But when I patch someone who's imaging negative, I'm getting less positive feedback. I may be helping more people by doing it, but my hit rate's lower, and so I'm getting less frequent positive feedback. So as a treater, if I'm looking at the wrong metric, I'm getting the wrong feedback. So think about your goals.

If a high rate of response is your goal, then only treat the people who are imaging positive. You're going to have a very satisfying career. If that's not going to be satisfying to you, if it's going to be dissatisfying to you knowing that you're turning away people you could have helped who are imaging negative, then you should think about your goals and treat people who are imaging negative as well, if you can do so safely. That's what'd I have to say about that.