



Children can struggle to explain their symptoms with words, so Carl Stafstrom at Johns Hopkins Medicine asks them to draw their migraines.

Think of the children

Researchers' understanding of migraine in young people is shifting, offering hope for better long-term management of the condition. **By Emily Sohn**

It was 2010, and paediatric psychologist Scott Powers was growing frustrated by the lack of research into migraine in children. Medications commonly prescribed to young people had been studied mainly in adults. As a result, paediatricians were in the dark about which treatments would be safest for their young patients, or how long children should wait for improvement on one drug before moving on to another.

Powers wanted to offer evidence-based guidance, so he and his colleagues at Cincinnati Children's Hospital Medical Center in Ohio designed a trial. They would evaluate two of the most common preventive medications in children with chronic migraines and compare them against a placebo.

The Childhood and Adolescent Migraine Prevention (CHAMP) trial began in 2012,

recruiting 328 children, aged 8 to 17, at more than 30 centres across the United States. The researchers randomized the children into three groups that received a placebo, the antidepressant amitriptyline or the anti-epileptic medication topiramate. On the basis of previous research, the team suspected that the placebo would show substantial benefits. But in surveys before the trial began, physicians said they would still prescribe a medication if it worked even 10–15% better than placebo.

The researchers planned to drop the placebo arm of the study if early results showed clear benefits of the drugs. But the decision was taken out of their hands: the trial was stopped suddenly after independent statisticians conducted an interim analysis in November 2015. Nearly a year later, Powers

learned why: the placebo did just as well as medications at preventing migraines. In all three groups, more than half of the children reported a 50% reduction in headaches after six months¹. Reviewers determined that it was futile to continue giving drugs to the treatment group if they were no more effective than placebo.

When the team presented the results at a paediatric neurology meeting in Vancouver, Canada, in 2016, Powers says there was an audible gasp in the audience, which was full of doctors who had been prescribing the drugs to young people. It was the first major, multi-centre trial to investigate the effect of placebo on migraines in children.

The CHAMP findings, and accumulated evidence since, have revealed key differences between migraine in children and adults.

This information has led to more interest in non-pharmaceutical treatments, while suggesting a need to focus on the 40% or more of children whose migraines do not improve with drugs or placebo. One hope is that better management early in life could bring long-term benefits, influencing brain development and interrupting the progression to chronic migraines in adulthood.

Funding remains limited, but the work is helping to shift how researchers think about migraines in young people. “We’re finding a big warning sign that says kids aren’t little adults,” Powers says. “Our data are starting to say, if you want to know about kids you have to study kids.”

Picture perfect

Migraine is a neurological disorder that occurs in up to 10% of young people and becomes more common as they age; in the United States, it is estimated to affect up to 3% of 3–7-year-olds and up to 23% of 15-year-olds. And most children with migraines continue to have headaches as adults, although here the rate splits by sex, with about 19% of women and 10% of men experiencing migraines (see page S16).

Despite their prevalence, migraines often go undiagnosed and have been understudied by researchers – particularly in children. One reason for this is that there is no way to identify the condition with a laboratory test. Instead, physicians consider a patient’s history and diagnose by process of elimination, says Prab Prabhakar, a paediatric neurologist at Great Ormond Street Hospital and University College London.

But children don’t always have the vocabulary to explain their symptoms, and even when they do, their symptoms can differ from those in adults. Whereas adults generally describe a migraine headache as a pounding, one-sided head pain, children – especially those younger than eight – often say that their headaches span the entire forehead.

To improve diagnostic accuracy, some research suggests that clinicians should turn to coloured pencils. In the 1990s, Carl Stafstrom, a neurologist at Johns Hopkins Medicine in Baltimore, Maryland, started asking children to draw their headaches. He quickly noticed patterns, including the depiction of objects that can cause pain, such as lightning bolts, hammers and even a high-heeled shoe pounding on a head.

In a 2002 study, he and his colleagues analysed headache images drawn by 226 children and found that the drawings accurately predicted a migraine diagnosis around 90% of the time². “If a kid says I have a bad headache, then typically a clinician writes ‘severe headache’ in the chart,” Stafstrom says. “But if the child

draws a picture of his head exploding like a volcano, that gives you a whole other insight into the level of pain.” Stafstrom has now collected thousands of images and is using them to explore whether headache drawings are equally accurate for older and younger children. He is also assessing whether the drawings of parents who experience migraines are similar to those of their children.

Health-care providers might also need to look for signs earlier in life, says Amy Gelfand, a paediatric neurologist at the University of California, San Francisco. Early in her career, she was struck by similarities between babies with colic, who demonstrate inconsolable crying and fussiness, particularly in the evenings, and adults with migraines, who describe feeling overwhelmed by lights, sounds and other stimuli.

Digging through the literature, she found a couple of papers linking colic in infancy with childhood migraines, as reported by their parents. In two subsequent survey-based studies^{3,4}, she and her colleagues found that mothers with migraines are more than twice as likely to report having babies with colic than were those who did not have the condition.

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Although colic is often attributed to gastrointestinal issues, Gelfand suspects that some babies might have sensitive brains that are overwhelmed by a bright, loud world. Colic peaks during a time of rapid development for the visual system, she adds. She is planning to use machine learning to calculate how much babies cry, to test the link more objectively.

If the colic connection pans out, Gelfand says, reducing overstimulation might be a better treatment for colic than the dietary changes that are currently recommended. Pregnant women with migraines could also prepare for the potential of having a baby with colic and look out for signs of migraines as their children grow up.

Colic isn’t the only potential manifestation of migraines in very young children, Prabhakar says. Migraines have been linked to torticollis (a kind of muscular neck kink in babies), abdominal pain and cyclical vomiting syndrome (recurring sequences of nausea, vomiting and lethargy). Researchers have tended to extrapolate what they know about migraines from adults to children, he says, but the evidence for early signs suggests that they need

to flip their approach. “The research is upside down,” Prabhakar says. “We need to study what migraine is in young children.”

Placebo power

Once a child is diagnosed with migraine, guidelines⁵ released by the American Headache Society last year recommend that they be treated with over-the-counter non-steroidal anti-inflammatories and painkillers, such as naproxen, ibuprofen and paracetamol. A class of medications called triptans is also advised in some cases, as is avoiding lifestyle factors such as missing meals or under-sleeping.

In the past decade, several new classes of medications have become available for treating and preventing adult migraines, including gepants (calcitonin gene-related peptide (CGRP) receptor antagonists), ditans (5-HT_{1F} receptor agonists) and anti-CGRP monoclonal antibodies. Most target different pathways from triptans, and trials are now under way in young people, although providers already prescribe the drugs off-label, Gelfand says. “There are so many things that I use in my everyday practice now that weren’t available even a couple of years ago,” she says.

Non-pharmaceutical treatments are in the works, too, including a wearable neuro-modulation device called Nerivio. Approved for acute treatment in adults, the device is wrapped around the upper arm, where it stimulates nerves to inhibit pain signals and end migraine attacks. The results of trials in children aren’t yet available, but Gelfand says that some children and teenagers who have tried it in her practice have liked it because it seems to cause fewer side effects. Other neuro-modulation devices are in various phases of development and testing with both adults and children, adds Serena Orr, a paediatric neurologist and headache specialist at the University of Calgary in Canada.

Evidence that current preventive medications have similar effects to placebo has, however, continued to build since the CHAMP trial reported the finding in 2016. In a meta-analysis published this year⁶, researchers looked at more than 2,200 patients from 23 studies. They found some evidence for a small benefit of the prophylactic medications propranolol and topiramate in the first five months of treatment, but in the longer term the drugs performed no better than placebo. In another study this year⁷, an injected medication called onabotulinumtoxin A was also found to work no better than placebo in adolescents. And in an as-yet-unpublished analysis, Powers’s group found that three years after the CHAMP trial ended, young people who got better during the study tended to stay better,



Scott Powers (right) found that placebos work as well as drugs in preventing some migraines.

no matter whether they received the medication or a placebo.

The power of placebo at preventing migraines in young people has presented clinicians with a conundrum, Powers says. There seems to be no need to prescribe a treatment with the potential for side effects, but doctors cannot prescribe sugar pills to their patients. Instead, some suggest that their patients take vitamins or supplements such as riboflavin, magnesium and coenzyme Q₁₀, which have essentially no risk and might help on their own or through the pill-taking effect. Doctors have also become more willing to recommend that people stop taking medications if they don't like the side effects, recognizing that the benefits might not be worth it.

The evidence that placebo works just as well as medication for preventing migraines in young people has led to fresh approaches to migraine management, including psychological techniques. Cognitive behavioural therapy (CBT) is showing particular promise. In a study of 135 young people who kept a daily headache diary for 20 weeks⁸, Powers and his colleagues found that CBT was more effective than headache education when the two were used in combination with amitriptyline. Headache education included lessons on what a migraine is and how to develop habits that might prevent attacks, such as regular eating, sleeping and exercise. At the end of the trial, 47% of the CBT group reported four or fewer migraine headaches each month and 32% reported three or fewer. By comparison, 20% of the headache education group reported four or fewer headaches each month and 16% reported three or fewer.

CBT seems to alter brain functioning in areas that control emotion and pain, which are different from those affected by pill-taking, Powers's team reported in June⁹.

As evidence accumulates to support non-pharmacological options for preventing migraine in children, one remaining hurdle is that not enough practitioners are trained to deliver the most beneficial types of relaxation exercises, Powers says. He wants to develop a plan to teach nurses, paediatricians and family doctors how to recognize migraine in young people and offer psychological care that can make a difference.

"What I'd like to see before I retire is that if I had daughter or son who started getting migraines at age 10, we'd be much better at diagnosing faster," Powers says. Diagnosis should happen within six months, he says, not after four years – then there would be a clear plan about using relaxation skills first, and medication only if required.

Changing trajectory

For a large fraction of children with migraines, no approach seems to help alleviate their pain. In the CHAMP trial, about 40% of patients did not get better through medication or placebo. To help these children, researchers need a deeper understanding of what paediatric migraine is.

In a study at the University of Calgary, researchers used magnetic resonance spectroscopy to show that young people who experience migraines exhibit a different pattern of cortical excitation and inhibition in their brains from adults with migraines¹⁰. In the thalamus, sensorimotor cortex and visual cortex of children

with migraines, levels of the neurotransmitters GABA and glutamate varied depending on how long the child had been experiencing migraines and how close they were to the next attack. A better understanding of this brain chemistry could lead to improved treatments.

For some children, research suggests that improvement might come from the way physicians, parents and kids talk about migraines. A study¹¹ of 95 young people with chronic pain earlier this year found that certain well-intentioned parental behaviours – notably, excusing children from activities, paying more attention to them when they were in pain, and frequently asking about the pain – were associated with worse pain in the children.

There might be ways of intervening to help parents alter those patterns, Orr says, and health-care providers could be part of the solution. Research suggests that response to placebo can vary depending on how providers talk about treatment options to patients¹². This means that doctors might be able to enhance the placebo effect by talking up the potential of the treatment.

Those working in the field think that improving the diagnosis and treatment of migraines in children is hugely important, because intervening early could modify the pathways of brain development and pain perception for the better for the rest of their lives. "Five years of follow-up data suggest that kids who get better while children tend to stay better, and are less likely to become adults with uncontrolled migraines," Powers says. "They still have the disease and they still have to find ways to cope with it. But we believe we're actually bending that curve of their lifetime experience."

It's possible that the brain can learn to have frequent migraines or to avert them, Gelfand adds, and that management in childhood might make a difference. "The brain learns from its own behaviour," Gelfand says. "By treating early, we can change the trajectory of the disease."

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1. Powers, S. W. et al. *N. Engl. J. Med.* **376**, 115–124 (2017).
2. Stafstrom, C. E., Rostasy, K. & Minster, A. *Pediatrics* **109**, 460–472 (2002).
3. Gelfand, A. A., Thomas, K. C. & Goadsby P. J. *Neurology* **79**, 1392–1396 (2012).
4. Gelfand, A. A. et al. *Headache* **59**, 988–1001 (2019).
5. Oskoui, M. et al. *Neurology* **93**, 487–499 (2019).
6. Locher, C. et al. *JAMA Pediatr.* **174**, 341–349 (2020).
7. Winner, P. K. et al. *Headache* **60**, 564–575 (2020).
8. Kroner, J. W. et al. *Headache* **56**, 711–716 (2016).
9. Nahman-Averbuch, H. et al. *Headache* **60**, 1165–1182 (2020).
10. Bell, T. et al. Preprint at bioRxiv <https://doi.org/10.1101/2020.04.14.041616> (2020).
11. Neville, A. et al. *Pain* **161**, 1072–1082 (2020).
12. Peerdeman, K. J. et al. *Pain* **157**, 1179–1191 (2016).