



Alexandra Sinclair: Easing the pressure

Young women who are obese are at risk of idiopathic intracranial hypertension (IIH), which can cause crippling headaches and result in permanently impaired vision or even blindness. Alexandra Sinclair, a neurologist who studies IIH at the University of Birmingham, UK, spoke to *Nature* about new drugs for treating the disorder, and how these could allow astronauts to go beyond the Moon.

What is IIH?

IIH is a condition driven by raised fluid pressure around the brain for which we can find no structural cause. This pressure can swell the optic nerve and impair vision. It has devastating consequences for some people. Disabling chronic headaches, with intermittent or constant pain similar to a migraine, are the most common symptom, but up to 25% of people with IIH will experience permanent visual impairment.

Who does IIH typically affect?

More than 90% of those affected by IIH are women, and most are also obese. The disease used to be regarded as rare, but its incidence is increasing alongside that of obesity. Between 2005 and 2017, the rate of IIH in women in the United Kingdom more than tripled to about 9 per 100,000 people. Countries with high obesity rates, of which the United Kingdom is one, have a higher incidence and prevalence of IIH.

The cause is still largely unknown. Elevated intracranial pressure was initially noticed in the sixteenth century in Arctic explorers, who ate large amounts of seal and polar-bear livers, which contain a lot of vitamin A. In those quantities it's toxic, and it raised their brain pressure, much like in IIH. But IIH is not driven by ingesting high levels of vitamin A — there's no single obvious cause like that.

How do you treat IIH?

There are three main aspects to this. First, we give advice on weight management for all patients. There is evidence that weight loss can put IIH into remission and reduce headaches by lowering intracranial pressure.

We are currently concluding a clinical trial looking at how much weight loss is needed and how best to help people maintain a healthy weight.

Second, we must be attentive to any loss of sight. Vision can fall away rapidly — a person can become permanently blind in less than a month. For these patients, we can offer surgery such as cerebrospinal fluid (CSF) diversion, known as shunting, to rapidly lower intracranial pressure. But about one-third to one-half of shunts fail within a year, so this is not a long-term management strategy.

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We also look at medical management, but at present there are no drugs specifically designed for IIH. The most common drug we prescribe is the diuretic acetazolamide, which is used to stave off altitude sickness. But although evidence suggests that this drug improves vision in people with mild IIH, many have to stop taking it because of adverse side effects. So we are looking for better pharmaceutical options.

What other drugs are in the pipeline?

I am the chief scientific officer of Invex Therapeutics, where we are repurposing a glucagon-like peptide 1 (GLP1) receptor agonist that is moving through clinical trials. This class of drug is already widely used to treat type 2 diabetes and has anti-obesity effects. People with IIH do not tend to have diabetes, but in 2017 we found that a drug called exenatide directly reduces CSF secretion in rats by activating GLP1 receptors in the choroid plexus — the part of the brain where most CSF is produced. It helped reduce intracranial pressure by about 45%.

Why is NASA interested in your work?

Astronauts suffer from increased intracranial pressure in microgravity that can lead to symptoms very similar to those of IIH. It usually

affects astronauts who spend more than three months in space — their intracranial pressure builds over time. Constant pressure over a long period can damage the brain and optic nerve, so this is a particular concern for anyone planning a lengthy space flight, such as a mission to Mars — it would take at least a year to do a round trip. So in 2019, NASA came to talk to us about the potential use of GLP1 receptor agonists to reduce intracranial pressure in astronauts. We are currently discussing how to reduce the risk of visual impairment and headache associated with this kind of a journey.

How is your understanding of IIH changing?

The link to androgen excess is new and important — it's the first pathogenic pathway associated with IIH to be found. In 2019, we found that women with IIH have higher levels of testosterone in their blood and CSF than do women who are obese and women with polycystic ovarian syndrome — another condition associated with obesity in young women. We also found that women with IIH are twice as likely to develop cardiovascular disease as are other women, irrespective of their weight. And we've shown that abdominal fatty tissue is the primary correlator with intracranial pressure. These are all markers of metabolic disease. This suggests that IIH might not be idiopathic after all, but rather a systemic metabolic condition that manifests as raised pressure.

What lies ahead for people with IIH?

The future looks pretty bright. When I was a junior doctor, I saw a young woman with headaches, a swollen optic nerve and normal brain scans. Over the course of a weekend, she had gone from having normal vision to being able to see no more than a hand waving in front of her face. Back then there was a lack of knowledge and options, but things are improving. We are on the cusp of having new drugs for this condition.

Interview by Julianna Photopoulos

This interview has been edited for length and clarity.