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In response to: Fargen KM et al. "Idiopathic" intracranial hypertension: An update from neurointerventional research for clinicians. *Cephalalgia* 2023; 43. DOI: 10.1177/03331024231161323.

Dear Sir,

We read with interest the article by Fargen et al (1) questioning whether idiopathic intracranial hypertension (IIH) is indeed idiopathic, and their proposal that venous sinus stenosis (VSS) is a central to the underlying pathophysiology of raised intracranial pressure (ICP). The majority of women diagnosed with IIH are people living with obesity. Population studies have observed the increased incidence and prevalence of IIH in those with an increased body mass index (BMI) (2,3), and have found an elevated BMI to be directly associated with greater risk of a diagnosis of IIH (2). Furthermore, a relationship between BMI and visual outcomes has been established where severe papilloedema was noted in IIH patients with BMI $>40 kg/m^2$ and with every $10 kg/m^2$ increase in BMI observed the odds of severe visual loss was increased by 1.4 times (4).

The literature evidences other potential pathophysiological drivers for IIH, omitted from Fargen et al.'s review (1). Primarily, systemic hormonal dysregulation has been noted in IIH with a distinct profile of androgen excess identified. Hyperandrogenism, in particular testosterone, has been shown to be elevated in women with IIH compared to age, sex, and BMI matched women with polycystic ovarian syndrome and also age, sex and BMI matched women living with obesity. Testosterone is known to be a driver of the Na^+/K^+-ATPase pump in the choroid plexus which directly increases cerebrospinal fluid (CSF) production (5). Secondly, metabolic disturbances suggesting a global metabolic dysregulation have been found to be evident in the CSF, serum and urine of people with IIH using proton nuclear magnetic resonance spectroscopy, in comparison to an age, sex and BMI matched control group. The CSF:serum urea ratio was observed to be altered with urea being shown to be lower in the CSF of IIH participants compared to controls; this was in correlation with ICP and headache severity. The CSF:serum urea ratio was found to be greatest in the acute phase during high ICP potentially as a compensatory mechanism to drive fluid out of the CSF (6). Finally, it has been observed that IIH has unique disease features which are not explained by obesity alone. In big data studies, where obese controls have been comparators, people with IIH have been shown to have a doubled risk of cardiovascular disease (2) and insulin resistance (7). People with IIH have been demonstrated to have reduced birth rates, increased incidence of gestational diabetes and pre-eclampsia as compared to controls (8).

Reduction of ICP is one of the therapeutic aims in IIH. This has been successfully achieved, as evidenced through randomised control trials (RCT), with the carbonic anhydrase inhibitor acetazolamide (9), bariatric surgery (10), and most recently reported the Glucagon-like peptide-1 (GLP-1) receptor agonist, Exenatide (11). While dural VSS (DVSS) (12), and indeed CSF shunting (13) have been shown to reduce ICP, none have been subject to the rigor of an RCT. Indeed, interventions to reduce the ICP alone have not been shown to alter the metabolic phenotype of truncal adiposity, insulin resistance, hyperleptinemia, fertility and pregnancy complications which typically remain if body weight is not lost. Consensus in IIH management has previously recommended interventional procedures are reserved for the specific indication of impending sight loss, where rapid resolution of raised ICP is required (14,15).

Over the past two decades many authors, including Fargen et al. (1), have documented the presence of

cerebral VSS in people with raised ICP (12). The evidence suggests that extramural (extrinsic) venous stenosis occurs in IIH secondary to a positive feedback loop which is initiated by raised ICP (12). There is currently no direct evidence confirming that venous hypertension is the primary cause for raised ICP in IIH. We strongly believe cerebral VSS (CVSS) reflects a consequence of the increased ICP rather than the casual driver of raised ICP in the vast majority of people with IIH. Intracranial venous hypertension syndrome may apply better to a small subset of people with intracranial hypertension, rather than the defining cause of all IIH cases. We postulate this may include patients who have not documented recent weight gain, those not living with obesity, and potentially those living with connective tissue disorders, such as Ehlers-Danlos syndrome.

In a condition managed by neurologists, ophthalmologists, neurosurgeons and now interventional radiologists, each specialist may see a different angle of the disease. However, it is important for all health care professionals to be mindful of the metabolic phenotype encompassing the spectrum of systemic manifestations of IIH. These are not addressed by lowering the ICP through intracranial interventions. In the United Kingdom there is genuine equipoise for a RCT comparing dural VSS and CSF shunting in those deemed to be at high risk of visual loss. High quality evidence is required to understand the indication for DVSS in IIH and to enable DVSS to become a universally accepted treatment paradigm.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MT and GT do not have conflicts of interest.

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SPM has received Honoria from Novartis for speaking on fundoscopy, but within a national headache network meeting (2019); Chiesi (2020,2021), Heidelberg Engineering (2019, 2020,2021), and Teva (2019, 2021). She has served on advisory boards for Invex Therapeutics, Janssen, and Gentech. She has received payment for consultancy work for Invex therapeutics (2020, 2021).

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