Commentary: The role of inflammation in idiopathic intracranial hypertension

The manuscript titled "Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as inflammation markers in patients with papilledema due to idiopathic intracranial hypertension" investigates the role of inflammation in the pathogenesis of idiopathic intracranial hypertension (IIH).[1] It has also provided a novel and a simple method of using hemogram as a marker of inflammation in IIH.

IIH, otherwise known as pseudotumor cerebri, is a chronic debilitating condition seen predominantly in overweight individuals particularly in women of reproductive age group. It is characterized by elevated intracranial pressure (ICP) in the absence of any space-occupying lesion in the brain and in the presence of normal cerebrospinal fluid (CSF) composition. Diagnosis is made by using the modified Dandy's criteria.[2] The primary pathogenesis of IIH remains unknown but several mechanisms have been proposed to explain the raised CSF pressure such as increased CSF production,[3] impaired CSF absorption at arachnoid granulations and or lymphatics,[4] cerebral edema[5], and elevated cerebral venous pressure[6] from aberrant venous pressure gradients.[7]

It has been hypothesized that inflammation may play a role in IIH.[8-10] Obesity is proposed as a risk factor for IIH; thus, adiposity might have a causative role in IIH, but the mechanisms by which obesity predisposes to the condition have not been fully elucidated. Human fat is an active endocrine tissue, secreting numerous neuroendocrine molecules that could potentially play a role in IIH. Few studies have evaluated the mechanisms by which hormones and adipokines exert their effects on ICP regulation in IIH.

Obesity is known to cause a chronic proinflammatory state in the body,[11-13] and this may be strongly associated with IIH development.

Several mechanisms have been proposed by which an inflammatory process could be involved in IIH pathogenesis, partly to explain the strong association of obesity and IIH. The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11b-HSD1)), a modulator of glucocorticoids, may have a potential role in IIH by regulating CSF secretion. It has been shown to be dysregulated with increased activity in both obesity and IIH.[14] In humans, 11b-HSD1 increases local cortisol levels. Long-standing high cortisol levels have been shown to increase secretion of pro-inflammatory mediators[15] and possibly to increase the production of CSF by affecting sodium transporters in the choroid plexus.[14] Weight loss and lower ICP values have been shown to reduce 11b-HSD1-levels in IIH patients.[14]

A first phase II randomized controlled trial in IIH evaluated the *in vivo* efficacy of 11b-hydroxysteroid dehydrogenase type 1 inhibitor AZD4017 compared with placebo. They demonstrated reduction in serum cortisol: cortisone which correlated with decreased intracranial pressure.[16]

The possible role of proinflammatory cytokines and apokines such as leptin, IL-2, IL-10, IL-12, IL-17, and TNF-α have been studied in IIH. Several studies have demonstrated increased or decreased levels of these inflammatory mediators indicating again that proinflammatory activation could plausibly be involved in the pathogenesis of IIH.[9,17-19] Adipokines such as leptin, could act directly on the choroid plexus or arachnoid granulation tissue, or indirectly via peripheral mechanism with consequent secondary central effects that modify CSF secretion and absorption. But the role it may have in disease development requires further investigation.

Chronically increased circulating or CSF cytokines in an obese individual may result in fibrotic changes or lead to a hypercoagulable state causing blockage of the arachnoid granulations and, therefore, reducing drainage of CSF.

Exposure to an infectious or inflammatory disorder in the year preceding IIH diagnosis was significantly associated with increased odds of developing IIH supporting the hypothesis that a major inflammatory activation could act as a trigger factor to IIH development.[20]

The authors of this paper looked at the neutrophil-to-lymphocyte ratio NLR (neutrophil count divided by lymphocyte count) and platelet-to-lymphocyte ratio PLR (platelet count divided by lymphocyte count) as inflammatory markers in IIH. This is because platelets and neutrophils are mediators of inflammatory responses. The NLR and PLR have been studied as inflammatory markers in other systemic and ocular inflammatory diseases and also in non-arteritic anterior ischemic optic neuropathy.[21] But has not been studied in IIH previously, hence this seems like a novel concept that has thrown additional perspective on the role of inflammation in IIH. Interestingly this paper found that NLR and PLR were higher in patients with IIH than controls ($P < 0.05$), higher in patients with papilledema ($P < 0.05$) in the IIH group and were found to be associated with worse visual acuity. The authors certainly have provided a simple and easy to obtain blood test that could be further explored prospectively as an inflammatory marker in IIH. As cited in their manuscript, prospective studies are needed to study the correlation of NLR and PLR with the previously defined inflammatory markers in IIH to truly understand their role in ICP regulation.

Padmaja Sudhakar

Department of Ophthalmology and Neurology,
University of Kentucky, Lexington, KY, USA

Correspondence to: Dr. Padmaja Sudhakar,
Department of Ophthalmology and Neurology,
University of Kentucky, 740 S. Limestone, Lexington,
KY 40536, USA.
E-mail: sudhapaddy@yahoo.com

References

1. Ceylan OM, Yılmaz M, Yilmaz H, Çelikay O, Köylü MT, Turan A. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as inflammation markers in patients with papilledema due to idiopathic intracranial hypertension. Indian J Ophthalmol 2021;69:1499-505.
2. Friedman DI, Jacobson DM. Diagnostic criteria for idiopathic intracranial hypertension. Neurology 2002;59:1492-5.
3. Quincke H. Über Meningitis serosa: Sammlung linische Vortra 67. Inn Med 1893;23:655-94.

4. Johnston I. Reduced CSF absorption syndrome. Reappraisal of benign intracranial hypertension and related conditions. Lancet 1973;2:418-21.
5. Sahs AL, Joynt RJ. Brain swelling of unknown cause. Neurology 1954;6:791-803.
6. King JO, Mitchell PJ, Thompson KR, Tress BM. Cerebral venography, and manometry in idiopathic intracranial hypertension. Neurology 1995;45:2224-8.
7. Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: Mechanisms, management, and future directions. Lancet Neurol 2016;15:78-91.
8. Sinclair AJ, Ball AK, Burdon MA, Clarke CE, Stewart PM, Curnow SJ, *et al*. Exploring the pathogenesis of IIH: An inflammatory perspective. J Neuroimmunol 2008;201-202:212-20.
9. Markey KA, Uldall M, Botfield H, Cato LD, Miah MA, Hassan-Smith G, *et al*. Idiopathic intracranial hypertension, hormones, and 11beta-hydroxysteroid dehydrogenases. J Pain Res 2016;9:223-32.
10. Samanci B, Samanci Y, Tuzun E, Altıokka-Uzun G, Ekizoğlu E, İçöz S, *et al*. Evidence for potential involvement of pro-inflammatory adipokines in the pathogenesis of idiopathic intracranial hypertension. Cephalalgia 2017;37:525-31.
11. Mancuso P. The role of adipokines in chronic inflammation. ImmunoTargets Ther 2016;5:47-56.
12. Andersen CJ, Murphy KE, Fernandez ML. Impact of obesity and metabolic syndrome on immunity. Adv Nutr (Bethesda, Md) 2016;7:66-75.
13. Apostolopoulos V, de Courten MP, Stojanovska L, Blatch GL, Tangalakis K, de Courten B. The complex immunological and inflammatory network of adipose tissue in obesity. Mol Nutr Food Res 2016;60:43-57.
14. Sinclair AJ, Walker EA, Burdon MA, van Beek AP, Kema IP, Hughes BA, *et al*. Cerebrospinal fluid corticosteroid levels and cortisol metabolism in patients with idiopathic intracranial hypertension: A link between 11beta-HSD1 and intracranial pressure regulation? J Clin Endocrinol Metab 2010;95:5348-56.
15. Verma M, Kipari TMJ, Zhang Z, Man TY, Forster T, Homer NZM, *et al*. 11beta-hydroxysteroid dehydrogenase-1 deficiency alters brain energy metabolism in acute systemic inflammation. Brain Behav Immun 2018;69:223-34.
16. Markey K, Mitchell J, Botfield H, Ottridge RS, Matthews T, Krishnan A, *et al*. 11β-Hydroxysteroid dehydrogenase type 1 inhibition in idiopathic intracranial hypertension: A double-blind randomized controlled trial. Brain Commun 2020;2:fcz050.
17. Edwards LJ, Sharrack B, Ismail A, Tench CR, Gran B, Dhungana S, *et al*. Increased levels of interleukins 2 and 17 in the cerebrospinal fluid of patients with idiopathic intracranial hypertension. Am J Clin Exp Immunol 2013;2:234-44.
18. Dhungana S, Sharrack B, Woodroofe N. Cytokines and chemokines in idiopathic intracranial hypertension. Headache 2009;49:282-5.
19. Altiokka-Uzun G, Tuzun E, Ekizoglu E, Ulusoy C, Yentür S, Kürtüncü M, *et al*. Oligoclonal bands and increased cytokine levels in idiopathic intracranial hypertension. Cephalalgia 2015;35:1153-61.
20. Sundholm A, Burkill S, Waldenlind E, Bahmanyar S, Nilsson Remahl AIM. Infectious and inflammatory disorders might increase the risk of developing idiopathic intracranial hypertension-A national case-control study. Cephalalgia 2020;40:1084-94.
21. Polat O, Yavaş GF, İnan S, İnan ÜÜ. Neutrophil-to-Lymphocyte ratio as a marker in patients with non-arteritic anterior ischemic optic neuropathy. Balkan Med J 2015;32:382-7.

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_252_21

Cite this article as: Sudhakar P. Commentary: The role of inflammation in idiopathic intracranial hypertension. Indian J Ophthalmol 2021;69:1506-7.