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ORIGINAL RESEARCH

Routine Blood and Cerebrospinal Fluid Markers in Newly Diagnosed Idiopathic Intracranial Hypertension: An Exploratory Case–Control Study

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Background: Idiopathic intracranial hypertension (IIH) is an enigmatic syndrome of raised intracranial pressure and papilledema with metabolic underpinnings, although the exact etiology remains obscure. We aimed to evaluate routine blood and cerebrospinal fluid (CSF) markers covering several organ systems in newly diagnosed IIH and compared to controls.

Methods: We registered the results of routine blood and CSF analyses in patients consecutively included in a prospective cohort by clinically suspected IIH. We compared females with confirmed IIH (2013 criteria) to "IIH mimics" in whom IIH was refuted (controls). We excluded patients with secondary pseudotumor cerebri syndrome, pregnancy, IIH relapse, age >50 years, male sex, other significant disease, or use of medications associated with multiorgan biochemical abnormalities with a prevalence of >1%.

Results: We compared 139 females with IIH to 78 controls of similar sex, age, and body mass index (BMI). In IIH, we found relatively higher plasma levels of leukocytes (p=0.02), neutrophils (p=0.04), and alkaline phosphatase (p=0.03), and lower levels of plasma urea (p=0.04) and CSF protein (p=0.02). Leukocytes and neutrophils correlated with lumbar opening pressure and were significantly higher in severe papilledema. Findings were not explained by BMI, smoking, or statistically influential covariates.

Conclusion: In a well-defined prospective cohort of newly diagnosed IIH restricted by careful censoring of secondary cases and confounding factors, we found relatively increased systemic inflammation in plasma which correlated with markers of more severe IIH disease activity. IIH is likely a heterogeneous and complex disease in which inflammation seems to be involved.

Plain Language Summary: Idiopathic intracranial hypertension (IIH) is a poorly understood neuro-metabolic disorder in which adiposity is somehow related to raised intracranial pressure (ICP) causing optic nerve swelling. To explore possible indices of pathophysiology and comorbidity, we compared results of routine blood and cerebrospinal fluid (CSF) analyses obtained from individuals with newly diagnosed IIH (hence, naïve to ICP-lowering treatment) to results from healthy control patients disproven of IIH. Analyses covered multiple organ systems. We carefully censored individuals with conditions or drugs that could confound biomarker analyses. We included 139 individuals with IIH and 78 controls of similar age, BMI, and sex. In IIH, we observed relatively higher levels of blood leukocytes, neutrophils, and alkaline phosphatase, and lower levels of urea and CSF protein. Elevation of leukocytes was not explained by BMI, or active smoking, was associated with severe optic nerve edema and correlated with lumbar opening pressure, a surrogate measure of ICP. These findings support established hypotheses of a role of inflammation in IIH and confirms previous observations of lower CSF protein, possibly related to altered CSF flow. Lower urea may reflect disrupted amino acid metabolism and warrants further study.

Keywords: pseudotumor cerebri syndrome, inflammation, urea, protein, amino acid metabolism, biomarkers

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Introduction

Pseudotumor cerebri syndrome (PTCS) is characterized by optic disc edema caused by raised intracranial pressure in the absence of structural cerebral lesions and abnormal cerebrospinal fluid (CSF) content. A range of conditions and drugs can induce PTCS, in which case the term *secondary* PTCS (*s*PTCS) is used. Secondary causes include systemic diseases (kidney, rheumatological, inflammatory, hormonal disorders, neuro-sarcoidosis, anemia), sleep apnea, and several pharmacological agents,[1,2] When known causes of PTCS are ruled out, a diagnosis of idiopathic PTCS (idiopathic intracranial hypertension (IIH)) is given. Although IIH is considered a complex metabolic disease, the exact etiology remains obscure – hence the term "idiopathic". Nevertheless, disruption of multiple organ systems is reported in IIH, including neuro-psychiatric,[3–5] inflammatory,[6–10] coagulation,[10–14] cardiovascular,[2,15] renal,[16] adipose,[16] and endocrinological[11,17–22] systems, and recent omics studies have revealed extensive metabolic perturbation.[16,23,24] Heterogeneity and inconsistency in previous literature with regard to disease stages studied, reporting of body mass index (BMI), comparison to BMI-matched controls, and ambiguous distinction between IIH and *s*PTCS limit interpretability and comparability. Also, most previous studies of biomarkers in IIH have had an organ-specific focus. With the present study, we aimed to cover these gaps by providing an updated evaluation of a broad range of routine biochemical markers based on current nosology. Differences in blood and CSF in IIH could potentially give insights into its pathophysiology or associated comorbidity. After all, *idiopathic* intracranial hypertension must have a cause, albeit probably multifactorial, heterogeneous, and complex. With restrictive censoring of *s*PTCS and confounders we minimize "noise" and explore the true idiopathic cases as of 2025.

Finally, experts have discussed whether or not a basic lab work-up is needed – to evaluate secondary causes for PTCS and to enable longitudinal monitoring during medical treatment of confirmed IIH.[25] With this study of a large IIH population, we also provide a reference for the biochemical profile to expect in newly diagnosed IIH.

Method

Setting and Study Participants

At two tertiary headache centers in Denmark (Danish Headache Center, Rigshospitalet, and Department of Neurology, Odense University Hospital) patients suspected of having IIH are consecutively enrolled in a prospective cohort approved by the Regional Committees on Health Research Ethics for Southern Denmark (ID: S-20170058) and adhering to the Helsinki Declaration and Danish data laws. Written informed consent is obtained from all participants. Within this cohort, we compared patients with confirmed IIH (including definite IIH, probable IIH, IIH without papilledema (IIHWOP), and suggested IIHWOP; *IIH* hereafter) to those, in whom IIH was initially suspected but disproven constituting a non-matched control group.

IIH was diagnosed according to 2013 criteria[26] in agreement between specialists in neurology and neuro-ophthalmology. The diagnostic pathway and work-up have been described previously;[27–30] detailed in the supplementary material 1).

Papilledema was confirmed and graded by an experienced neuro-ophthalmologist according to the Modified Frisén Scale[31] (MFS), and categorized into mild (MFS grade 1), moderate (MFS grade 2–3) or severe (MFS grade 4–5). We performed lumbar puncture with manometric OP measurement with the patient in an out-stretched relaxed lateral decubitus position. Neuroimaging (cerebral MRI and venography by CT or MRI) was done to exclude space-occupying and other lesions, hydrocephalus, and cerebral venous sinus thrombosis.

Exclusion Criteria

Of all patients enrolled in the cohort, we excluded those with pregnancy, IIH relapse, *s*PTCS, male sex, age >50 years (to avoid menopausal heterogeneity), known disorders associated with abnormal blood tests (endocrinological-, kidney-, liver-, hematological- and autoimmune disorders, congenital syndromes, cancer, neuro-inflammation, or neuro-infection), and patients prescribed medications known to cause IH or known to potentially disrupt multiple organ systems with a prevalence of ≥1%.

We omitted elevated liver markers if the patient had an alcohol consumption that exceeded officially advised maximum levels (≥10 units of alcohol weekly); this applied to one patient with elevated alkaline phosphatase (ALP).

Patients with leukocytosis were excluded from analysis of inflammatory markers in case of an explaining inflammatory or infectious condition as evidenced by pre-existing diagnoses, anti-inflammatory or -microbial therapy, symptoms, patient history, or clinical/paraclinical findings at time of diagnostic investigation. This applied to four patients (recent knee surgery, coughing, recent mild head trauma, allergic rhinitis in relevant season, leukocyte range 9.00–9.70 × 10^9/L).

Blood and Cerebrospinal Fluid Analyses

We included the results of all routine blood analyses performed at the time of IIH diagnostic clarification (±6 weeks). Blood tests were sampled routinely, hence, not standardized regarding time of the day or fasting status. We calculated and report plasma osmolality as 2x[Na]+[glucose]+[urea], and platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) as platelet- and neutrophil-count relative to lymphocyte count, respectively. We also registered results of routine analysis of CSF drawn at the diagnostic lumbar puncture. Biochemical analyses of blood and CSF are termed "biomarkers" hereafter. For geographical reasons, different laboratories performed the sample analyses. Assays and reference ranges are similar for all analyses presented.

Statistics

R studio 4.4.1 was used for analyses. We compared patients with confirmed IIH to controls and assessed differences of categorical variables with chi-square or Fisher's test. We handled the combined proportions of patients with an abnormal test result (below or above the reference range) as a binary variable (yes/no). Distribution of numeric data was inspected visually for normality and confirmed with Shapiro–Wilks test. We report normally distributed variables by mean and standard deviation (SD) and compared groups using independent two-tailed *t*-test, or Welch's *t*-test in case of unequal variance as evidenced by Bartlett's test of variance. We report non-normally distributed variables by median and interquartile range (IQR) and compared groups using Mann–Whitney *U*-test. Missing data were omitted within each separate analysis and reported. We corrected for multiple testing of differences in biomarkers by IIH status using Benjamini-Hochberg's method of false discovery rate (FDR).

Biomarkers that differed significantly between groups by $p<0.05$ in the uncorrected initial analysis were subject to the following tests: As a confirmatory measure, we did multiple linear regression analysis of the biomarkers depending on IIH status adjusting for BMI, age, and smoking. We then performed logistic regression, yielding the odds of having IIH depending on the biomarker in question adjusting for age, BMI, and smoking as a reversed test of association. Finally, we analyzed the association between biomarkers and indicators of active IIH disease: OP and papilledema severity. We used Spearman correlation analysis to assess the association between biomarkers and OP. Subsequently, we adjusted for influential covariates identified through backwards elimination in linear regression analyses (Model 1). We further added adjustment for smoking and BMI in analyse of leukocytes, neutrophils, and alkaline phosphatase given its plausible biological confounding effects. We report the degree of explained variance by unadjusted r-squares.

Difference in biomarker and OP distribution across papilledema severity was assessed with multiple regression, unadjusted and adjusted for influential covariates identified through backwards elimination (model 2), and subsequently additionally adjusted for smoking (Model 3), and OP (Model 4) to exclude a mediating effect, since OP is significantly higher in patients with severe versus mild papilledema.[32] We evaluated lumbar OP in different papilledema grades using Kruskal-Walli's test after testing variance homogeneity with Levene's test. Due to significant findings, Dunn's test was applied to assess which papilledema grades had significantly different levels of OP.

Results

Of 327 patients enrolled in the cohort due to clinically suspected IIH in the period 2018–2022 (OUH) and 2018–2024 (DHC), we included 217 participants for analysis (Figure 1). We diagnosed 139 patients with *IIH* (definite IIH n=124; probable IIH n = 7; IIHWOP n = 0, suggested IIHWOP n = 8). IIH was refuted in 78 patients serving as controls; they received a final diagnosis of a primary headache disorder (n=47), pseudo-papilledema (n=13, of which 12 also had a primary headache disorder), sleep apnea not causing PTCS (n=4), non-arteritic anterior ischemic optic neuropathy (NA-AION, n=2), secondary headaches (n=2; post-traumatic headache and headache due to chronic rhinosinusitis), idiopathic abducens palsy (n=1), and healthy or no final diagnosis (n=9). Demographic details are given in Table 1. Controls were

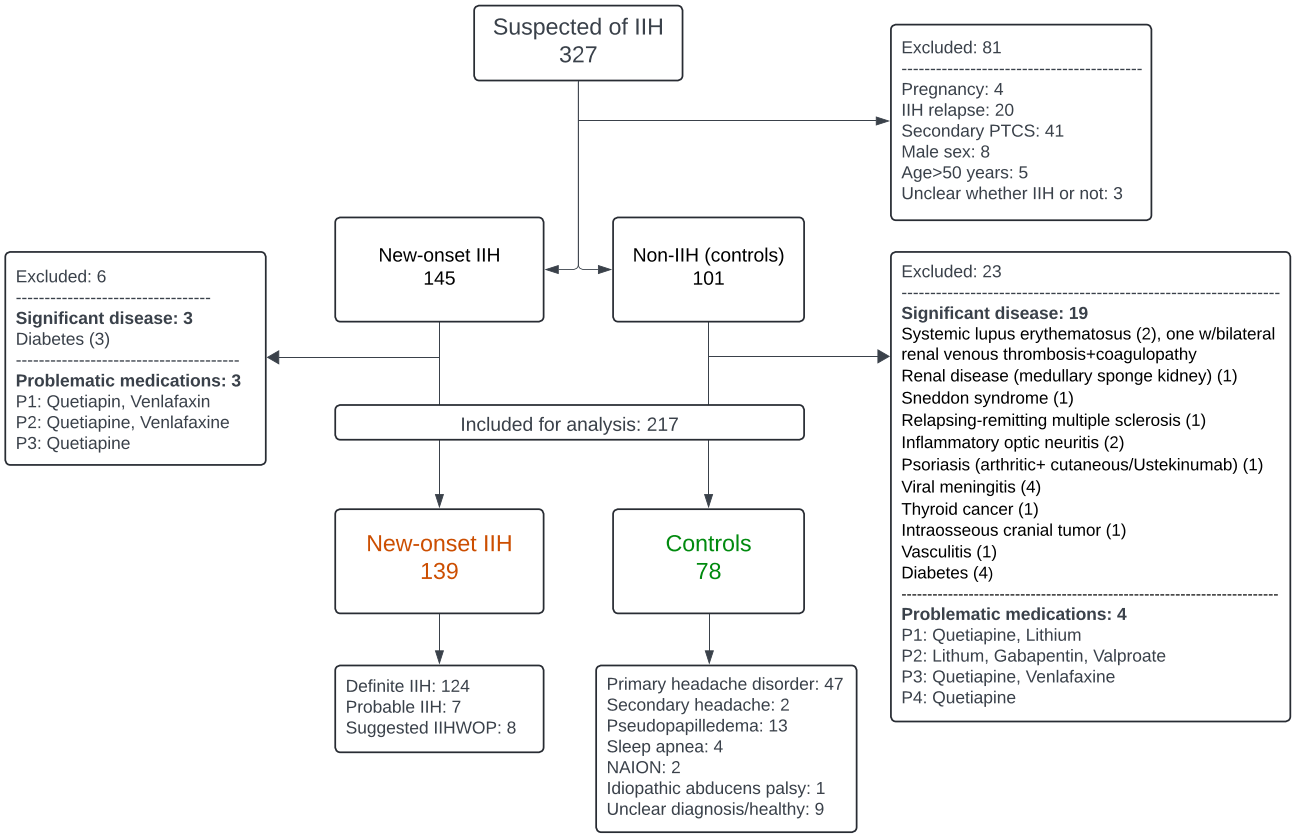

Figure 1 Flowchart of the selection of patients included for analysis, reasons for exclusion, and final diagnoses. Flowchart of the selection of patients included for analysis, reasons for exclusion, and final diagnoses.

slightly older than patients with IIH statistically (p=0.02), but the difference not clinically meaningful (median (IQR age 28 (23–34) vs 30 (26–37) years). Median (IQR) BMI was similar in IIH (35 (31–41)) and controls (38 (31–42), p=0.50), but more patients with IIH were actively smoking (40% versus 25% of controls, p=0.04) whereas fewer with IIH had headache (91% versus 99% of controls, p=0.03). We excluded 110 patients (Figure 1, including details of patients excluded due to medications and other diseases).

Table 1 Characteristics of Study Participants

	IIH	Controls	p-value
n	139	78	-
Female sex, n (%)	139 (100)	78 (100)	-
Age, years[§]	28 (23–34)	30 (26–37)	0.02
Body Mass Index [§]	35 (31–41)	38 (31–42)	0.50
Active smoking, n (%)	54 (40%)	19 (25%)	0.04
Headache (yes/no), n (%)	126 (91%)	77 (99%)	0.03
Lumbar opening pressure, cm CSF[§] [range]	37.0 (30.3–45.0) [18.0–66.0]	24.0 (20.0–30.5) [11.0–51.0]	<0.0001

(*Continued*)

Table 1 (Continued).

	IIH	Controls	p-value
Papilledema, MFS grade 0, n	7	76	-
Papilledema, MFS grade 1, n	30	0	-
Papilledema, MFS grade 2, n	45	2	-
Papilledema, MFS grade 3, n	32	0	-
Papilledema, MFS grade 4 or 5, n	12	0	-
Hormonal contraceptives, n (%)	55 (40)	38 (49)	0.24
Antihypertensive*, n (%)	9 (6)	7 (9)	0.59
Antidepressant*, n (%)	15 (11)	9 (12)	1

Notes: Missing data: BMI 5 (IIH: 3, nonIIH: 2), OP 11 (nonIIH), papilledema grade 13 (IIH: 13, due to unavailable ophthalmic imaging from time of diagnosis. The two controls with grade 2 papilledema were diagnosed with non-arteritic anterior ischemic optic neuropathy (NA-AION)); smoking 5 (3 IIH, 2 nonIIH); headache 1 (control). § median and interquartile range, test of comparison: Mann Whitney *U*-test; *Antihypertensives and antidepressants are reported regardless of indication (could also be prescribed for headache prevention).
Abbreviation: MFS, modified Frisén scale.

Difference in Biomarker Levels by IIH Status

Initial unadjusted biomarker analyses are given in Table 2. We found higher levels of leukocytes (p=0.01), neutrophils (p=0.04), and ALP (p=0.03), and lower levels of plasma urea (p=0.04) and CSF protein (p=0.009) in patients with IIH compared to controls. All mean/median values were within normal range. Findings were statistically insignificant after FDR correction. Through backwards elimination we identified the following influential covariates: For leukocytes and neutrophils: BMI and hormonal contraception; ALP: BMI; urea: antidepressants; CSF protein: age; OP: BMI and antidepressants. Adjusting for these relevant covariates and subsequently smoking as a biologically plausible confounder, leukocytes remained significantly elevated in IIH by 10% (95% CI 2–19%, p=0.01), and neutrophils by 12% (95% CI 0–25%, p<0.0), Table 3.

Table 2 Biochemical Markers in Blood and Cerebrospinal Fluid Comparing IIH with Controls

Organ System Profile	Reference value	Number of Observations (IIH/nonIIH)	IIH (n=139)	Control (n=78)	p-value[§]
INFLAMMATORY					
Leukocytes (10^9/L) [¤]	3.5–8.8	177 (117/60)	8.3 (7.4–10.2) 16↑ (14%)	7.8 (6.3–9.6) 8↑ (13%)	**0.01** (0.18) *1.00*
Neutrophils (10^9/L) [¤]	1.60–5.90	148 (101/47)	5.5 (4.5–6.5) 36↑ (36%)	4.8 (3.7–6.3) 16↑ (34%)	**0.04** (0.29) *1.00*
Lymphocytes (10^9/L) [ϒ]	1.00–3.50	165 (112/53)	2.5 ±0.7 5↓ (4%) 7↑ (6%)	2.3 ±0.7 -3↑ (6%)	**0.25** *0.39*
Monocytes (10^9/L) [¤]	0.20–0.80	164 (112/52)	0.55 (0.47–0.70) 25↑ (22%)	0.54 (0.42–0.68) 9↑ (17%)	**0.37** *0.60*

(*Continued*)

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Table 2 (Continued).

Organ System Profile	Reference value	Number of Observations (IIH/nonIIH)	IIH (n=139)	Control (n=78)	p-value[§]
Eosinophilocytes[¤] (10^9/L) [¤]	0.01–0.50	162 (110/52)	0.15 (0.10–0.20) 1↓ (1%) 4↑ (4%)	0.13 (0.08–0.23) 4↓ (8%) 1↑ (2%)	**0.75** *0.29*
C-Reactive Protein (CRP)	<10	167 (111/56)	27↑ (24%)	10↑ (18%)	*0.45*
Neutrophil-to lymphocyte ratio [¤]		144 (99/45)	2.2 (1.8–2.7)	2.3 (1.6–2.7)	**0.85**
Platelet-to-lymphocyte ratio [¤]		162 (109/53)	124 (107–159)	149 (112–177)	**0.20**
HEMATOLOGY					
Hemoglobin (mmol/L) [¤]	7.3–9.5	183 (118/65)	8.4 (7.9–8.8) 6 ↓ (5%) 6 ↑ (5%)	8.6 (8.2–8.9) 2 ↓ (3%) 4 ↑ (6%)	**0.11** *1.00*
Erythrocytes (10^{12}/L) [¤]	3.94–5.16	101 (68/33)	4.7 (4.4–4.9) 3↓ (4%) 8↑ (12%)	4.8 (4.5–5.0)- 4↑ (12%)	**0.17** *0.77*
Erythrocyte volume [¤]	0.35–0.46	136 (90/46)	0.41 (0.39–0.43) 1 ↓ -	0.42 (0.40–0.44) – 	**0.05**-
Mean corpuscular volume (MCV) (fL)[¤]	82-98	158 (102/56)	87 (83–90) 12 ↓ (12%) -	88 (84–90) 5 ↓ (9%)-	**0.42** -
Mean Corpuscular Hemoglobin (MCH) (fmol)	1.7–2.1	87 (56/31)	1.8 (1.7–1.9) 7↓ (13%) 1↑ (2%)	1.8 (1.7–1.9) 5↓ (16%) -	**0.42** *1.00*
Mean Corpuscular Hemoglobin Concentration (MCHC) (mmol/L) [ϒ]	19.7–22.2	156 (102/54)	20.5 ±0.8 14↓ (14%) 1↑ (1%)	20.6 ±0.6 4↓ (7%) 1↑ (2%)	**0.45** *0.45*
Platelets (10^9/L) [ϒ]	145-390	179 (115/64)	316 ±66 12↑ (10%)	312 ±74 10↑ (16%)	**0.72** *0.35*
KIDNEY					
Creatinine (μmol/L) [¤]	50-90	187 (122/65)	64 (58–74) 5 ↓ (4%) 4 ↑ (3%)	66 (59–74) 3 ↓ (6%) 1 ↑ (2%)	**0.62** *1.00*
Sodium (mmol/L) [¤]	137-144	186 (122/64)	140 (138–141) 7 ↓ (6%)	140 (138–141) 3 ↓ (5%)	**0.79** *1.00*
Potassium (mmol/L) [¤]	3.5–4.4	187 (122/65)	3.9 (3.7–4.0) 7 ↓ (6%)-	3.9 (3.7–4.0) 4 ↓ (6%) 2 ↑ (3%)	**0.86** *0.39*
Calcium, free (mmol/L)	1.18–1.32	136 (91/45)	1.24 (1.21–1.27) 4 ↓ (4%) 4 ↑ (4%)	1.23 (1.21–1.27) -3 ↑ (7%)	0.76 *1.00*
Albumin (g/L) [¤]	36-45	108 (74/34)	43 (39–44) 1 ↓ (1%) 5 ↑ (7%)	43 (38–45) -1 ↑ (3%)	**0.72** *0.43*

(*Continued*)

Table 2 (Continued).

Organ System Profile	Reference value	Number of Observations (IIH/nonIIH)	IIH (n=139)	Control (n=78)	p-value[§]
Urea (mmol/L) [¤]	2.6–6.4	126 (88/38)	3.8 (3.2–4.4) 7 ↓ (8%) 3 ↑ (3%)	4.1 (3.7–5.3) 4 ↓ (11%) 2 ↑ (5%)	**0.04** (0.29) *0.56*
Plasma osmolality		115 (81/34)	288.6 ±4.2	289.0 ±3.5	**0.57**
METABOLIC					
Hba1c (mmol/mol) [ϒ]	<48	145 (95/50)	35 ±3	34 ±3	**0.36**
Glucose (mmol/L) [¤]	4.2–6.3	168 (109/59)	5.6 (5.3–6.1) 1↓ (%) 25↑ (23%)	5.3 (5.0–5.9) -8↑ (14%)	**0.06** *0.17*
Cholesterol, total (mmol/L) [ϒ]	<5.0	129 (85/44)	4.7 ±0.8 30↑ (35%)	4.7 ±0.9 16↑ (36%)	**0.84** *1.00*
LDL cholesterol (mmol/L) [ϒ]	<3.0	129 (85/44)	2.9 ±0.8 39↑ (46%)	2.8 ±0.8 13↑ (30%)	**0.36** *0.11*
HDL cholesterol (mmol/L) [¤]	>1.0	129 (85/44)	1.1 (1.0–1) 30↓ (34%)	1.2 (1.1–1.3) 7↓ (18%)	**0.12** *0.04*
VLDL cholesterol (mmol/L) [¤]	<0.9	68 (47/21)	0.6 (0.5–0.9) 13↑ (28%)	0.8 (0.5–1.0) 9↑ (47%)	**0.54** *0.27*
Triglyceride (mmol/L) [¤]	<2.0	139 (93/46)	1.4 (1.0–2.0) 22↑ (24%)	1.5 (1.1–2.0) 13↑ (28%)	**0.89** *0.70*
HEPATIC		128 (82/46)			
ALT (U/L) [¤]	10-45	113/62	23 (18–32) 1 ↓ 5↑ (4%)	24 (20–31) -7↑ (11%)	**0.37** *0.12*
APTT (s) [ϒ]	25-37	57 (39/18)	31 ±4 5↓ (13%) 2↑ (5%)	30 ±4 2↓ (11%) 1↑ (6%)	**0.41** *1.00*
Bilirubin (μmol/L) [¤]	5-25	107 (78/29)	6.0 (4–8) 25↓ (32%)	7 (5–12) 5↓ (17%)	**0.22** *0.15*
Gamma-Glutamyl Transferase (U/L) [¤]	10-45	79 (52/27)	27 (20–34) 7↑ (13%)	24 (18–31) 3↑ (11%)	**0.63** *1.00*
Alkaline phosphatase (U/L) [¤]	35-105	168 (109/59)	75 (63–89) 12↑ (11%)	67 (59–79) 3↑ (5%)	**0.03** (0.29) *0.26*
LDH (U/L) [ϒ]	105-205	130 (90/40)	183 ±31 19 ↑ (21%)	189 ±28 11 ↑ (28%)	**0.28** *0.50*
Amylase (U/L) [¤]	25-120	30 (22/8)	63 ±20-	66 ±26 1↓	**0.73**

(*Continued*)

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Table 2 (Continued).

Organ System Profile	Reference value	Number of Observations (IIH/nonIIH)	IIH (n=139)	Control (n=78)	p-value[§]
CEREBROSPINAL FLUID					
CSF glucose (mmol/L) [¤]	2.2–3.9	165 (111/54)	3.3 (3.1–3.6) -9↑ (8%)	3.3 (3.0–3.5) 1↓ 3↑ (6%)	**0.93** *1.00*
CSF protein (g/L) [¤]	0.15–0.50	162 (109/53)	0.25 (0.22–0.33) 3↓ (3%) 4↑ (4%)	0.30 (0.25–0.36) 1↓ (2%) 2↑ (4%)	**0.009** (0.18) 1.00

Notes: §Unadjusted p-value in BOLD comparing biomarker level in IIH versus controls; FDR-adjusted p-value in brackets () are shown for significant findings in the initial analysis; p-value (*italics*) for testing difference in the proportion of patients with abnormal blood tests. [ϒ]Mean and standard deviation, *t*-test applied. [¤]Median and interquartile range, Mann–Whitney *U*-test applied. ↑ = number (%) of patients with levels above upper normal range limit; ↓ = number (%) of patients with levels below lower normal range limit.

Table 3 Stepwise Linear Regression of Biomarkers in IIH versus controls – With and Without Adjustment for Potentially Influential Covariates

	Leucocytes	Neutrophils	Alkaline Phosphatase	Urea	CSF Protein
Model 1	1.11 (1.03; 1.20), p<0.01, R^2 0.04 N=117/60	1.14 (1.03; 1.28), p=0.016, R^2 0.04 N=101/47	1.08 (1.00; 1.17), p=0.061, R^2 0.02 N=109/59	0.92 (0.82; 1.03), p=0.143, R^2 0.02 N=88/38	0.90 (0.81; 1.00), p=0.0558, R^2 0.02 N=108/53
Model 2 Covariate	1.11 (1.03; 1.20), p<0.01, R^2 0.17 N=117/60 BMI, hormonal contraceptives	1.12 (1.01; 1.25), p=0.029, R^2 0.19 N=101/47 BMI, hormonal contraceptives	1.08 (1.00; 1.17), p=0.049, R^2 0.07, N=107/57 BMI	0.93 (0.83; 1.04), p=0.206, R^2=0.06, N=88/38 Antidepressant	0.93 (0.83; 1.03), p=0.161, R^2 0.08, N=108/53 Age
Model 3 Covariate	1.10 (1.02; 1.19), p=0.01, R^2 0.19 N=115/58 BMI, hormonal contraceptives, smoking	1.12 (1.00; 1.25), p=0.042, R^2=0.19 N=99/45 BMI, hormonal contraceptives, smoking	1.06 (0.98; 1.15), p=0.139, R^2=0.08 N=104/55 BMI, smoking	– –	– –

Notes: Model 1: Unadjusted estimate. Model 2: Adjusted for influential confounder(s) identified through backwards elimination. Model 3: Adjusted for influential confounder(s) identified through backwards elimination and biologically plausible confounder(s).

Six patients (5%) diagnosed with IIH were mildly anemic (hemoglobin range 9.7–11.0 g/dL), whereas PTCS was considered secondary to more pronounced anemia (hemoglobin range 6.0–9.7 g/dL) in seven patients excluded from analyses. Had we diagnosed these patients with IIH regardless of anemia severity, the anemia prevalence in IIH increased from 5% to 9%, but compared to the 3% prevalence in controls, between-group difference remained insignificant (p=0.15), as did hemoglobin levels (median 8.4 (7.9–8.9) in IIH versus 8.6 (8.2–9.0) in controls, p=0.05).

Association Between Biomarkers and Active IIH Disease Markers

Lumbar Opening Pressure

Association between biomarkers and OP is shown in Figure 2 and Table 4. Unadjusted, OP correlated with leukocytes (ρ 0.27, p<0.001) and neutrophils (ρ 0.21, p=0.01) and inversely with CSF protein (ρ-0.17, p=0.03). In adjusted analyses, OP remained significantly increased by 4% (95% CI 1–7%, p<0.001, R^2 0.18) per one unit (10^9/L) increase in leukocytes and by 4% (95%

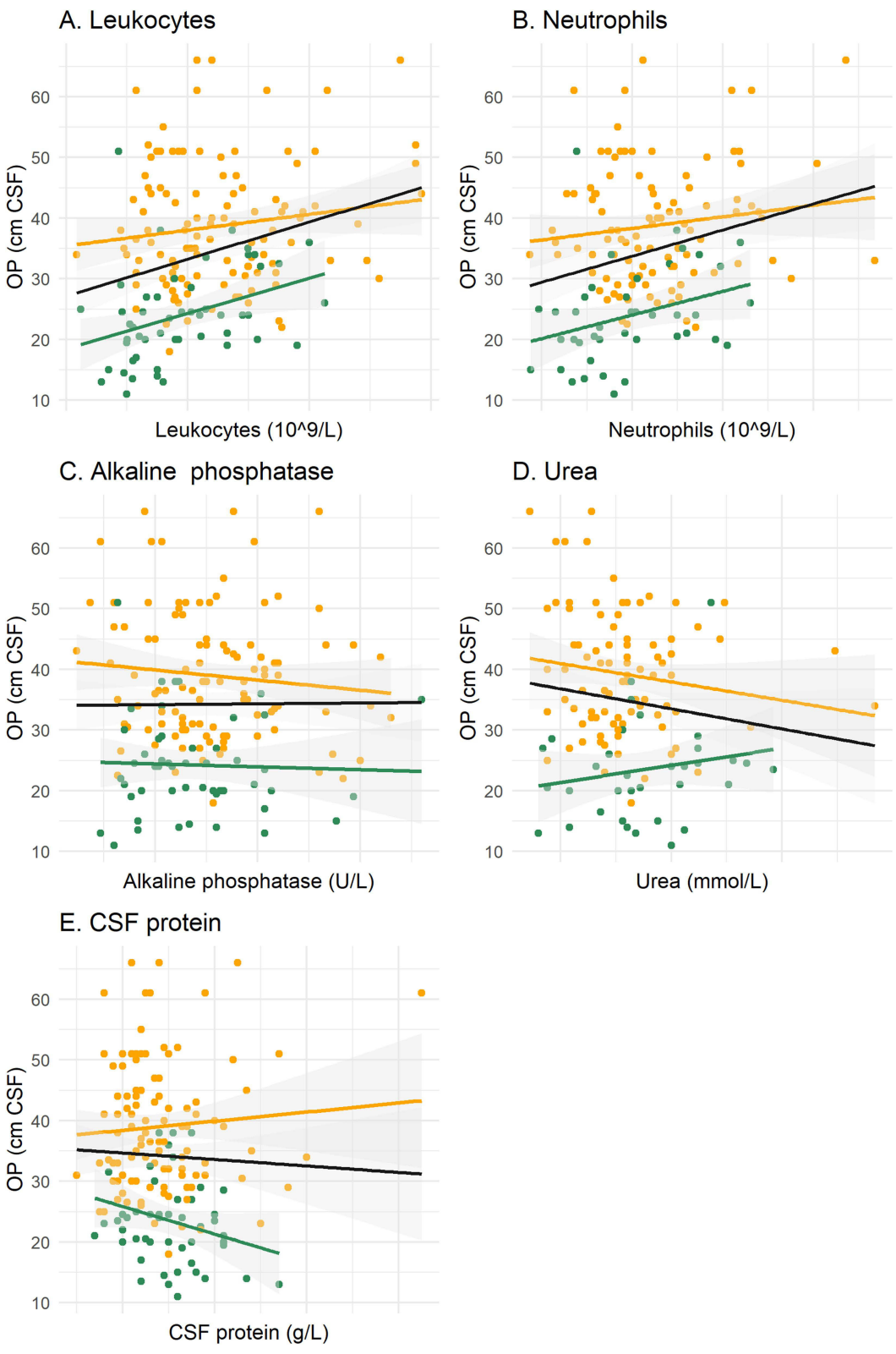

Figure 2 Biomarkers and lumbar opening pressure. Scatter plot of the unadjusted relationship between lumbar opening pressure (OP) and (**A**) leukocytes, (**B**) neutrophils, (**C**) alkaline phosphatase, (**D**) urea, and (**E**) CSF protein with least square regression lines. IIH (yellow), controls (green) and overall estimate (black).

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Table 4 Association Between Lumbar Opening Pressure and Biomarkers

	Leukocytes % Change (95% CI) in OP per 1 unit Change in Leukocytes	Neutrophils % Change (95% CI) in OP per 1 unit Change in Neutrophils	Alkaline Phosphatase % Change (95% CI) in OP per 1 Unit Change in Alkaline Phosphatase	Urea cm Change (95% CI) in OP per 1 Unit Change in Urea	CSF Protein % Change (95% CI) in OP per 1 Unit Change in CSF Protein
OP					
Spearman correlation[P]	**ρ 0.27, p<0.001, N=117/51**	**ρ 0.21, p=0.01, N=101/41**	ρ 0.03, p=0.68, N=109/51	ρ −0.14, p=0.12, N=88/35	**ρ −0.17, p=0.03, N=107/49**
Model 1	1.05 (1.03–1.08) R^2 0.10, p<0.0001 N=117/51	1.06 (1.02; 1.09) R^2 0.07, p<0.001 N=101/41	- *	−1.32 (−2.99; 0.35) R^2 0.02, p=0.12 N=88/35	0.72 (0.40; 1.30) R^2 0.01, p=0.27 N=108/49
Model 2	1.05 (1.02–1.08) R^2 0.14, p<0.001 N=115/50	1.05 (1.05; 1.09) R^2 0.13, p<0.01 N=99/40	1.00 (1.00; 1.00) R^2 0.04, p=0.82 N=107/57	−1.08 (−2.78; 0.61) R^2 0.08, p=0.21 N=87/34	0.77 (0.42; 1.39) R^2 0.05, p=0.38 N=106/48
Model 3	1.04 (1.02–1.07) R^2 0.18, p<0.001 N=112/49	1.04 (1.01; 1.08) R^2 0.16, p=0.01 N=98/39	1.00 (1.00; 1.00) R^2 0.08, p=0.61 N=104/55	-	-

Notes: Results in BOLD are statistically significant. Multiple linear regression analyses of significantly different biomarkers in initial analyses predicted by lumbar opening pressure. [P]Unadjusted. Model 1 Unadjusted linear regression of lumbar opening pressure (dependent variable) and biomarker (predictor); Model 2: Linear regression adjusted for covariates that were significantly influential on lumbar opening pressure as identified through backwards elimination (BMI, antidepressants); Model 3: Further adjusted for smoking. IIH was included as a covariate in the backwards elimination. Lumbar opening pressure was log-transformed in analyses of leukocytes, neutrophils, alkaline phosphatase, and CSF protein, so these estimates should be interpreted as the percentage change in OP per one unit increase in the predictor (biomarker), for example is OP increased by 5% (2–8%) per 1×10^9 increase in leukocytes in model 2. OP was not log-transformed in analyses of urea, wherefore this estimate should be read as OP change in cm per one unit change in urea, for example a decrease of 1.08 cm CSF per mmol/L increase in urea in model 2. *omitted since the linear model did not meet model assumptions.

CI 1-(%, p=0.01, R^2 0.16) per one unit (10^9/L) increase in neutrophils. In adjusted analyses, CSF protein no longer correlated with OP, and ALP and urea did not in any model. In subanalyses comparing IIH (n=139) to the subset of non-IIH with normal OP (OP<25 cm CSF, n=39), inflammation remained significantly increased in IIH (leukocytes 1.19 (1.09; 1.29, p<0.0001), and neutrophils 1.18 (1.04; 1.35, p=0.02) adjusted for BMI and hormonal contraception).

Papilledema Severity

Both unadjusted and adjusted for various covariates, we found consistently increased leukocytes and neutrophils in severe papilledema compared to no papilledema (Table 5, mean (95% CI) increase leukocytes: 1.24×10^9/L (1.06; 1.44), p<0.01; neutrophils 1.32×10^9/L (1.08; 1.62, p<0.01)). These findings were not mediated through increased OP since they remained significant in OP-adjusted analyses (model 4). Unadjusted, lower plasma urea associated with severe

Table 5 Biomarker Levels by Papilledema Severity

	Model	No Papilledema	Mild Papilledema	Moderate Papilledema	Severe Papilledema
Model 1					
Leukocytes	1	Ref. N=66	1.04 (0.92–1.17), p=0.550, N=22	**1.09 (1.00; 1.18), p=0.046**, N=70	**1.29 (1.09; 1.51), p<0.01**, N=10
	2	Ref. N=64	1.02 (0.91; 1.14), p=0.76, N=22	**1.11 (1.02; 1.20), p=0.01**, N=68	**1.25 (1.08; 1.46), p<0.01**, N=10
	3	Ref. N=64	1.01 (0.90; 1.13), p=0.88, N=22	**1.10 (1.01; 1.19), p=0.03**, N=66	**1.24 (1.06; 1.44), p<0.01**, N=10
	4		1.00 (0.89; 1.13), p=0.98	1.08 (0.98; 1.20), p=0.12	**1.19 (1.00; 1.43), p<0.05**

(*Continued*)

Table 5 (Continued).

	Model	No Papilledema	Mild Papilledema	Moderate Papilledema	Severe Papilledema
Neutrophils	1	Ref. N=52	1.04 (0.88; 1.23), p=0.63 N=19	1.09 (0.97; 1.23), p=0.14, N=61	**1.40 (1.13; 1.74), p<0.01**, N=10
	2	Ref. N=50	1.01 (0.87; 1.18), p=0.91 N=19	1.10 (0.99; 1.23), p=0.09, N=59	**1.33 (1.09; 1.62), p<0.01**, N=10
	3	Ref. N=49	1.00 (0.86; 1.17), p=0.97 N=19	1.09 (0.97; 1.22), p=0.13, N=58	**1.32 (1.08; 1.62), p<0.01**, N=10
	4	Ref.	0.99 (0.83; 1.18), p=0.93	1.08 (0.93; 1.24), p=0.31	**1.28 (1.00; 1.62), p<0.05**
Alkaline phosphatase	1	Ref. N=64	1.11 (0.99; 1.26), p=0.08, N=22	1.04 (0.95; 1.13), p=0.40, N=63	1.15 (0.97; 1.35), p=0.11, N=10
	2	Ref. N=62	1.12 (0.99; 1.26), p=0.06, N=22	1.05 (0.96; 1.14), p=0.31, N=61	1.14 (0.97; 1.35), p=0.11, N=10
	3	Ref. N=60	1.10 (0.98; 1.25), p=0.11, n=22	1.03 (0.94; 1.12), p=0.57, N=59	1.13 (0.95; 1.33), p=0.16, N=10
Urea	1	Ref. N=41	0.99 (0.84; 1.16), p=0.86, N=18	0.96 (0.85; 1.09), p=0.56, N=51	**0.74 (0.60; 0.91), p<0.01, N=10**
	2	Ref. N=41	1.11 (0.98; 1.25), p=0.09, N=18	1.04 (0.95; 1.13), p=0.41, N=51	1.14 (0.97; 1.35), p=0.12, N=10
CSF protein	1	Ref. N=59	**0.75 (0.65; 0.87), p<0.001, N=21**	0.94 (0.84; 1.05), p=0.26, N=63	0.92 (0.76; 1.12), p=0.39, N=11
	2	Ref. N=59	**0.78 (0.67; 0.91), p<0.01, N=21**	0.97 (0.87; 1.08), p=0.54, N=63	0.96 (0.79; 1.16), p=0.65, N=11

Notes: Results in BOLD are statistically significant. Stepwise linear regression. Model 1: Linear regression of biomarker (dependent variable) by papilledema grade (independent variable) without adjustment; Model 2: with adjustment of covariates identified through backwards elimination (leucocytes and neutrophils: BMI, hormonal contraceptives; alkaline phosphatase: BMI; Urea: Antidepressants; CSF protein: Age); Model 3: with further adjustment for smoking when biologically plausible; Model 4: with further adjustment for OP.

papilledema (0.74 (0.60; 0.91, p<0.01), model 1), however, not after adjustment for covariates. Lower CSF protein associated with mild papilledema versus no papilledema (0.78 (0.67; 0.91, p<0.01)) but this was not seen for moderate and severe papilledema, which may be driven by the few outliers of CSF protein that were markedly higher than the remaining majority in the IIH population (Figure 3E). Likewise, few outliers of high levels of urea could explain why the tendency of lower urea in moderate and mild papilledema did not reach statistical significance (Figure 3D).

Papilledema Severity, Opening Pressure, and BMI

OP strongly associated with papilledema severity (Figure 4): Comparing to no papilledema, OP increased by 9.0 cm (5.0–12.9, p<0.0001) in mild papilledema, by 13.4 cm (10.4–16.5, p<0.00001) in moderate papilledema, and by 22.3 cm (16.7–28.0, p<0.0001) in severe papilledema. Overall, BMI did not correlate with OP adjusted for age and smoking (1.00 (1.00–1.01), p=0.19), nor in IIH alone (1.00 (0.99–1.01), p=0.79), but we found a significant association between OP and BMI in controls (1.02 (1.01–1.03)), p=0.002) (Figure 5).

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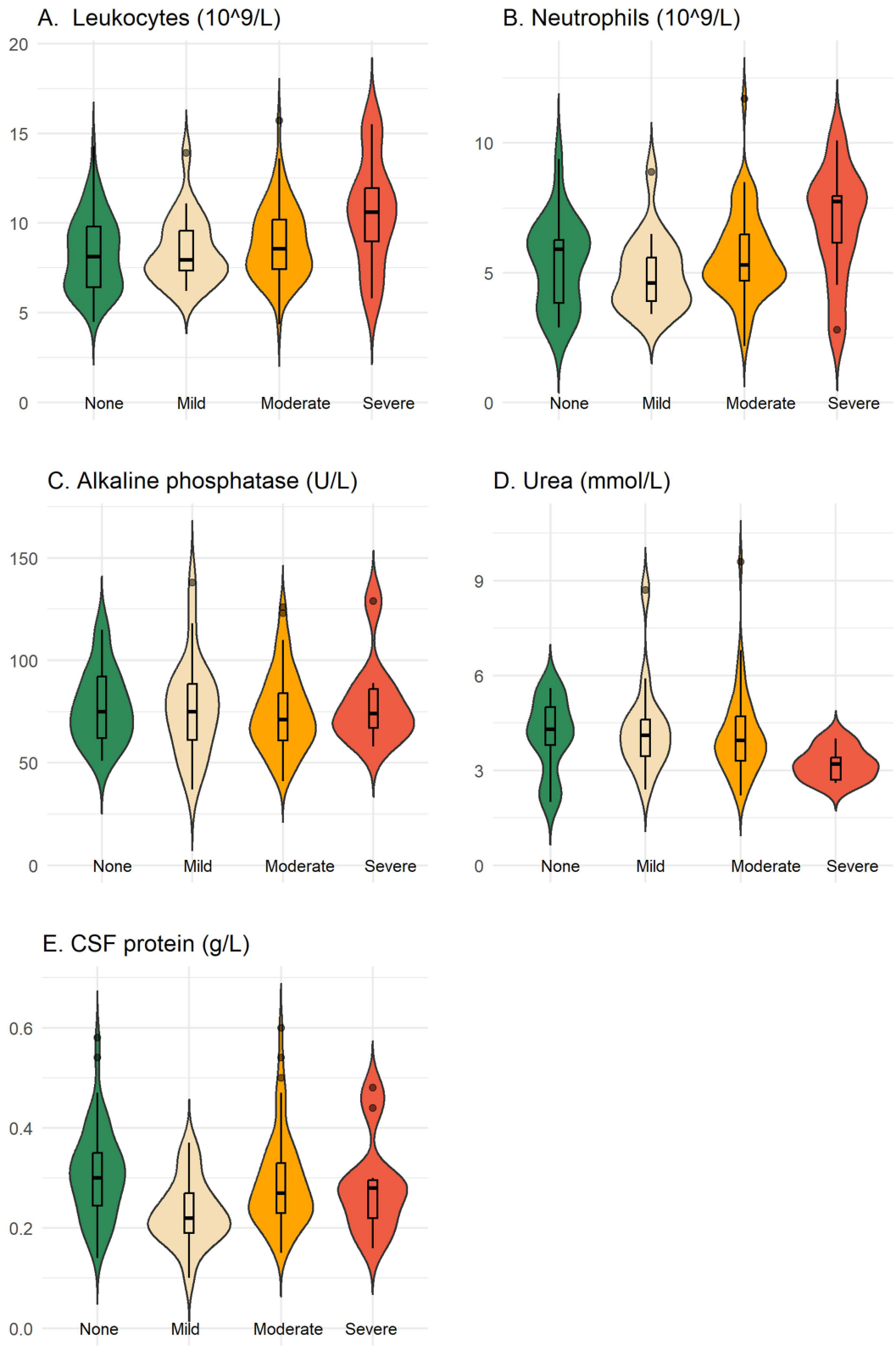

Figure 3 Biomarkers by papilledema severity. Unadjusted distribution of (**A**) leukocytes, (**B**) neutrophils, (**C**) alkaline phosphatase, (**D**) urea, and (**E**) CSF protein, each by papilledema severity: Green=no papilledema, yellow=mild papilledema, Orange=moderate papilledema; red=severe papilledema. The number of observations in each violin plot is for none, mild, moderate, and severe papilledema, respectively, as follows: Leucocytes: n=85, 30, 77, 12; neutrophils: n=20, 17, 59, 9; alkaline phosphatase: n=21, 20, 61, 9; urea: n=34, 27, 75, 12; CSF protein: n=85, 29, 75, 12.

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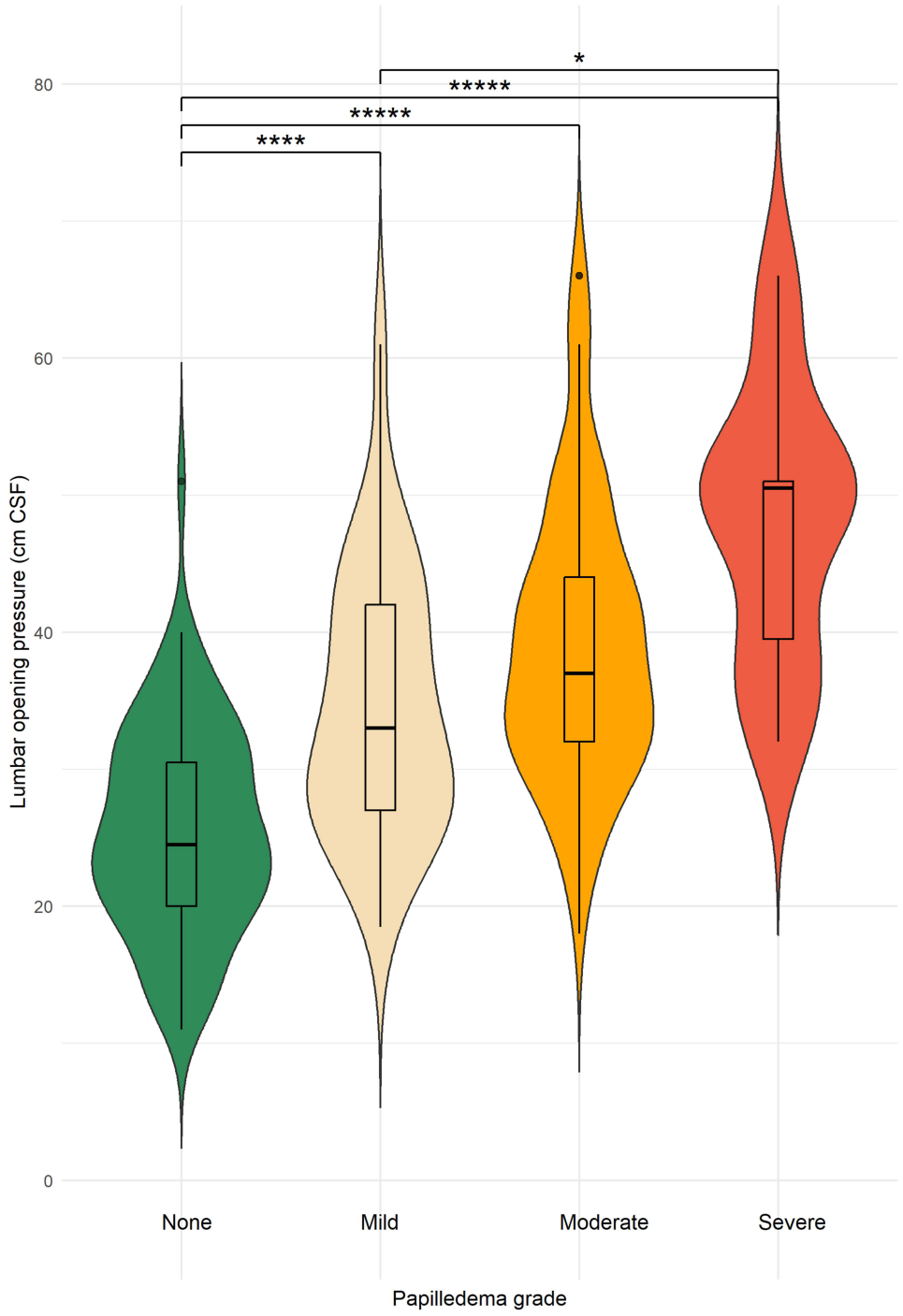

Figure 4 Lumbar opening pressure and papilledema severity. Unadjusted distribution of lumbar opening pressure (cm CSF) by papilledema grade. No papilledema=green (n=74), mild papilledema=yellow (n=30), moderate papilledema=Orange (n=77), severe papilledema=red (n=12); * p<0.05, **** p<0.0001 Kruskal-Walli's and Dunn's test with in-build Bonferroni correction.

Discussion

Inflammation

The major finding of this study is relatively increased systemic inflammation in IIH exceeding what can be explained by BMI and smoking.

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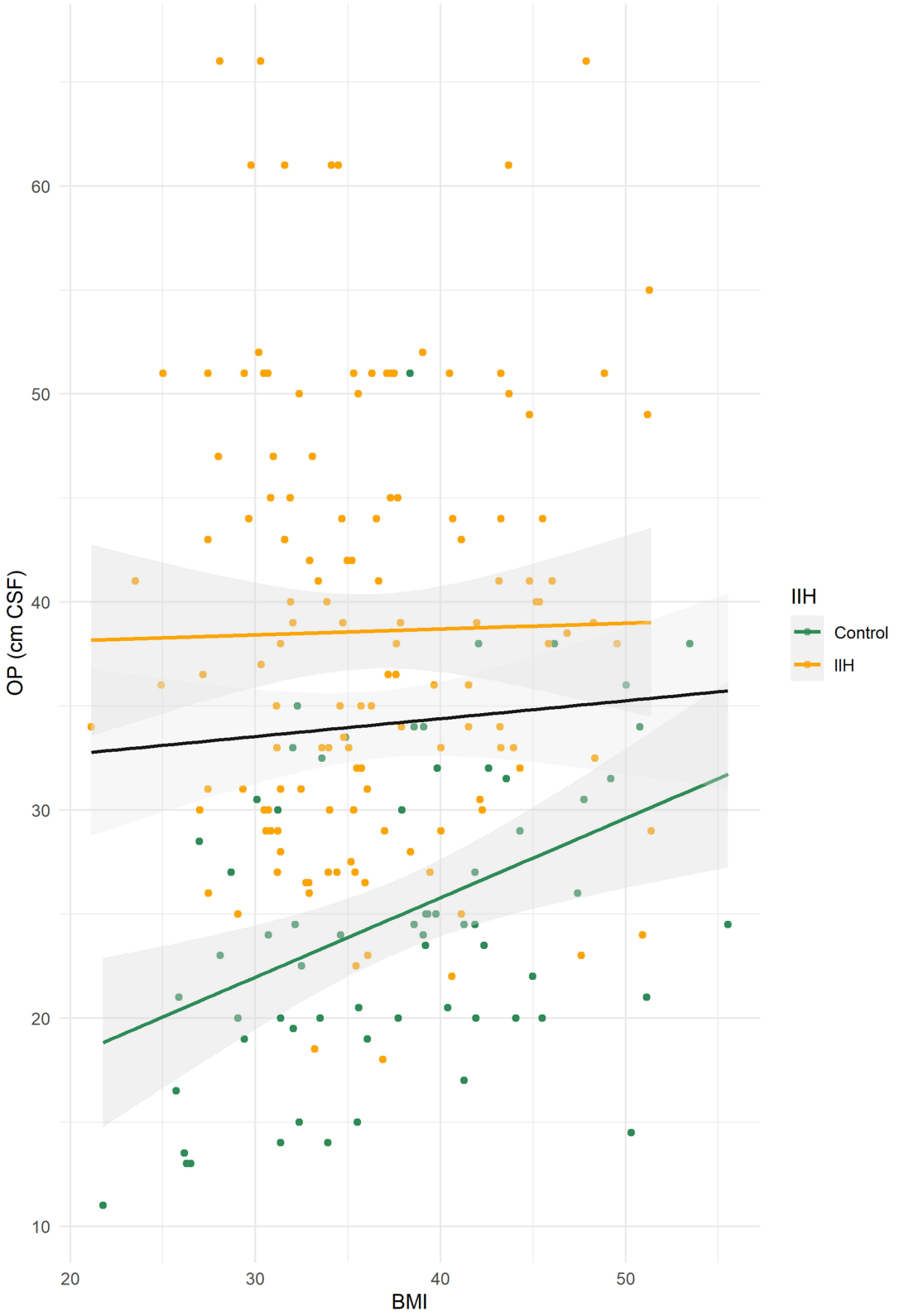

Figure 5 Lumbar opening pressure and BMI. Correlation between BMI and lumbar opening pressure overall (black) and in patients with IIH (yellow) and controls (green); ns = not significant. Unadjusted linear regression analysis.

We observed relatively increased leukocytes driven by neutrophils in IIH; median values of both were within the normal range, though, with equally many IIH and non-IIH, respectively, having values above the upper normal limit. Both leucocytes and neutrophils positively correlated with lumbar OP and severe papilledema and the latter was not explained by OP. The prevalence of leukocytosis is similar to previous observations in IIH.[33] Several triggers of leukocytosis (stress from hospitalization, invasive procedures, pain, high BMI) applied to both our patient groups, and other potential confounders (smoking, BMI) were adjusted for.

A previous large register-based study found the odds of having an infectious or inflammatory disorder and treatments hereof significantly increased in patients with IIH in the year preceding IIH diagnosis compared to controls with obesity and the general population.[34,35] The effect was more pronounced in closer temporal relation to IIH diagnosis suggesting possible causality. Despite the exclusion of such patients with *explained* leukocytosis in our study, relatively increased inflammation remained, corroborating an independent unexplained inflammatory state in IIH.

We observed elevated CRP in IIH in 26% in opposition to a previous report of 51% in which it correlated with less improved visual fields.[33] Another study reported higher CRP compared to controls,[7] where CRP correlated with BMI and OP, but a BMI of <25 in controls may have explained the between-group difference. PLR and NLR, used as inflammatory measures, were previously found elevated in IIH compared to age-, sex-, and BMI-matched controls, and correlated with worse visual status,[6] but BMI >30 was an exclusion criterion in that study. In our study, in which all participants had a median BMI >30, PLR tended to be *lower* and NLR similar in IIH versus controls. Hence, our observation of increased neutrophils in IIH was not reflected in elevated NLR in our cohort.

We observed that leucocytes correlated with lumbar OP. Inflammation in the central nervous system is well known to potentially induce intracranial hypertension, but the relationship between systemic inflammation and governance of ICP homeostasis is less studied. Several causes for *s*PTCS are characterized by systemic inflammation such as systemic lupus erythematosus, Behçet's disease, cystic fibrosis, granulomatosis with polyangiitis, and infectious diseases (Lyme disease, syphilis, HIV).[36] In IIH, pro-inflammatory cytokines are reported in blood[9] and CSF[8,9,37,38] and proteomics have revealed dysregulation of inflammatory proteins in the CSF.[10] Furthermore, IIH is associated with several inflammatory conditions, including PCOS,[39] elevated leptin levels in serum[19] and CSF,[18] metabolic syndrome, truncal adiposity,[16,40] and increased 11-beta hydroxysteroid dehydrogenase type 1 (11β-HSD1) activity,[20] which is associated with central obesity,[41] and whose inhibition correlates with reduced CSF pressure[42] and decreased ALP[43] in IIH. A common denominator in these mentioned conditions is obesity, which interplays with immunological functions.[44]

Acute and chronic inflammation is intricately linked to the enzyme 11β-HSD1.[45] 11β-HSD1 shapes inflammatory cell differentiation and function and is also linked to dysfunctional metabolic states, adipocyte function and morphology.[45] The latter deviates in IIH as compared to simple obesity.[16] Activity of 11-β-HSD1 is increased in IIH[20] and may be related to the inflammatory state. With the present observational cross-sectional study design, we cannot conclude on causality or detailed relationships. Prospective longitudinal studies investigating inflammatory profiles in parallel with changes in IIH disease activity would address this uncertainty more properly. It is an important limitation in many previous studies suggesting inflammation in IIH that controls were non-obese or BMI was not reported.[7–9,37,38] In our study, inflammation in IIH was not explained by BMI. The ability of BMI to reflect adiposity is controversial.[46,47] A more accurate measure of pathological adiposity, such as quantification of truncal versus peripheral fat mass, is preferable in understanding the source of inflammation in IIH but was unavailable in this study. IIH manifests a distinct obesity sub-phenotype as suggested by previous adipocyte phenotyping[16] and metabolomics studies[23,24,48] showing divergent metabolic signatures in IIH compared to BMI-matched controls. Similarly, although we found total cholesterol to be comparable in IIH and controls, HDL cholesterol was more frequently subnormal in IIH (p=0.04) indicating a more adverse lipid profile in IIH. Taken together, inflammation being independent of BMI in this study does not equal independence of adiposity.

Urea

We found relatively lower within-normal plasma urea in IIH compared to controls in initial analyses, but between-group differences were not statistically significant after adjusting for influential covariates. Urea correlated inversely with the

risk of severe papilledema. Patients were naïve to ICP-lowering treatment, so lower urea was not explained by inhibited hepatic synthesis or increased renal excretion caused by Acetazolamides inhibition of carbonic anhydrases.

Ureagenesis occurs in the mitochondria and cytoplasm of hepatocytes. It disposes the body of nitrogen from mainly amino acids (AA). Hence, urea reflects AA metabolism including intake, endogenous synthesis, metabolism, and urinary excretion. Glutamate is an important nitrogen donor in the synthesis of non-essential AA and serves a vital role in keeping the urea cycle running. In patients from our cohort, we previously showed 0.44-fold lower ($p<0.0001$) levels of serum glutamate in newly diagnosed IIH.[24] We speculate whether this links to lower plasma urea and to the disrupted AA metabolism previously suggested in IIH based on metabolomics studies[24,48] with indications of branch-chain AA being pooled into lipid biosynthesis.[16] The urea cycle also depends on mitochondrial function, which may be impaired in IIH, functionally[23] and structurally,[49] although it is unknown if this applies to hepatic mitochondria. Increased renal loss of urea is unlikely. Although renal function was previously found to be impaired in IIH, it was within the normal range,[16] and we observed no differences in renal markers.

Serum urea in patients with active IIH (some were acetazolamide-treated) was previously reported similar to BMI- and sex-matched healthy controls,[16,23] but urea was lower in CSF and urine, correlated with OP and headache, and increased with disease resolution.[23] The authors proposed that urea with its hyperosmolar properties acted as a compensatory mechanism counteracting ICP elevation by a reduction of the CSF:serum ratio. Osmosis would drive water movement from the CSF space to the blood and decrease ICP. Water movement across the blood-cerebrospinal fluid-brain-borders involve several mechanisms beyond osmosis,[50] though, and we previously reported similar plasma osmolality in IIH and controls.[51] Lower CSF and urine urea may also simply reflect globally lower levels in line with the lower plasma levels shown here. We found worse papilledema in patients with lower plasma urea. Adhering to the proposed mechanistic explanation, this may reflect an inability to compensate sufficiently by lowering the CSF:serum urea ratio. Unfortunately, we lacked CSF urea data to calculate this ratio. Discrepancy of the findings may be explained by differences in disease stages, as serum urea is dynamic throughout the IIH disease course[23] with the caveat that acetazolamide is influential.

Alkaline Phosphatase

We observed increased but within the normal range ALP in IIH compared to controls as observed by others.[16] Increased ALP was explained by obesity in our model, though, and we saw no consistent association with disease activity markers, except from an association with severe papilledema in model 2. Being an enzyme found in all cells of the body, ALP is highly unspecific. Oral contraceptives may cause slight increases; we did not correct for this, but the prescription of contraceptives was similar in IIH and controls. Increased ALP is seen in non-alcoholic fatty liver disease (NAFLD), and particularly in females with NAFLD, this can be the only elevated hepatic marker.[52] NAFLD is expected to be frequent in IIH due to comorbid obesity. Any involvement or significance of the liver and/or ALP in IIH remains uncertain, and the finding may be spurious.

Cerebrospinal Fluid Protein

We found decreased concentration of CSF protein in IIH compared to controls in line with previous findings[53,54] where CSF protein increased with ICP-lowering treatment.[53] A proposed explanation is increased CSF flow "washing out" the protein content. This opposes theories of impaired CSF resorption where a blockage of CSF flow presumably would result in unchanged or increased CSF protein. An inverse relationship between CSF protein and OP is also reported,[54,55] which we confirmed in the unadjusted correlation analysis. Adjusting for age, BMI, and smoking, statistical significance disappeared, maybe due to loss of statistical power, which may also explain why lower CSF protein is associated with mild but not moderate/severe papilledema.

Anemia

Anemia is proposed causal for PTCS,[56] but it remains controversial whether and by which threshold anemia in the context of papilledema should be termed primary or secondary PTCS. A meta-analysis reported a higher relative risk of anemia in IIH compared to controls (RR 1.44 [1.08–1.92]).[57] Iron deficiency anemia (<10.5 g/dL) is more incident in

the year preceding IIH diagnosis,[2] and anemia was independently associated with having IIH in a large register-based study.[58] Reported prevalences of anemia in IIH range from 10% to 32%.[33,57,59–62] In our practice, papilledema in the context of moderate-to-severe anemia is perceived as sPTCS, in particular when anemia correction is immediately followed by disease remission.[36] When we included patients with any severity of anemia in the IIH group, between-group differences of anemia and hemoglobin levels remained insignificant, but anemia prevalence approached that of previous reports. The absence of an agreed severity cut-off and formal criteria for anemia being interpreted as sPTCS results in heterogeneous classification of IIH populations but could not explain why we found similar hemoglobin levels in IIH in our population.

Lumbar Opening Pressure

We confirmed previous findings showing a strong relationship between OP and papilledema severity[32,63] which fits the mechanistic explanation of papilledema being caused by mechanical forces compressing the optic nerve axons and compromising blood supply to the nerve head.[64] We also replicated observations of BMI being associated with OP in nonIIH only, but not in IIH[40,65] as we have reported previously in this cohor*t*.[28]

Strengths and Limitations

Within a large, well-defined prospective cohort of consecutive treatment-naïve patients with newly diagnosed IIH diagnosed at two highly specialized centers, we broadly profiled several organ systems by routine biochemical analyses. The comparison to demographically similar "IIH mimics" as controls was a strength since i) they constitute the real-world dilemma of segregating IIH from mimics, and ii), although non-matched, they were rather healthy, equally obese, and young females. However, the IIH mimics were not entirely healthy headache-free controls, this would likely skew findings towards false-negative rather than false-positive conclusions.

Statistical significance of initial exploratory tests disappeared after FDR correction. Since i) our findings support previous knowledge, ii) correction for multiple testing increases the risk of type II errors, and iii) significance of leukocytes, neutrophils, and CSF protein was sustained in subsequent adjusted regression- and correlation analyses, we addressed initial findings as valid with the caveat of false positivity. Also, we provide transparency of how estimates were affected by our statistical method through a stepwise approach without and subsequently with adjustment for both statistically significant covariates identified through backwards elimination and biologically plausible influential covariates. This approach serves to minimize model overfitting. There are other methodological limitations. Blood sampling was done for clinical diagnostic purposes and therefore not standardized (time of the day, fasting status, laboratory facility). Timing in relation to disease onset could affect results of transiently altered markers such as acute-phase reactants. Our strict censoring could introduce selection bias towards a homogenous healthier group not representative of the entire span of PTCS and *mimics*. It may explain our fewer observations of deviating biomarkers compared to previous literature and implies a risk of overlooking real associations with diseases and medications. However, we aimed to find trends in the purely idiopathic form as stated in the introduction. Our approach is broad and based on analyses of blood and CSF that are widely implemented in daily clinical routine. This limits the "resolution" of potential discoveries but is, on the other hand, accessible and thus straightforward to replicate in other IIH patient populations.

Conclusion

We found increased systemic leukocytes driven by neutrophils and lower plasma urea and CSF protein in a large cohort of newly diagnosed IIH compared to IIH mimics. Findings were not explained by age, BMI, or smoking. IIH is likely a heterogeneous disease with elements of inflammation and perturbed metabolism. Decreased CSF protein may reflect hydrodynamic changes in CSF flow. We encourage replication and more detailed phenotyping in IIH cohorts with similar rigorous patient selection as well as in the entire spectrum of PTCS.

Abbreviations

CSF, cerebrospinal fluid; BMI, body mass index; IIH, idiopathic intracranial hypertension; IIH-WOP, idiopathic intracranial hypertension without papilledema; PCOS, polycystic ovarian syndrome; PTCS, pseudotumor cerebri

syndrome; *s*PTCS, secondary pseudotumor cerebri syndrome; LP, lumbar puncture; OP, opening pressure; ICP, intracranial pressure; MFS, modified Frisén score; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation; IQR, interquartile range; ALP, alkaline phosphatase; OR, odds ratio; RR, relative risk; AA, Amino acid; NAFLD, non-alcoholic fatty liver disease.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

This study was approved by the local ethical committee (Region of Southern Denmark, ID: S-20170058), followed the Helsinki Declaration and Danish data laws. Written informed consent was obtained from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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