Clinical Characteristics of Idiopathic Intracranial Hypertension in Patients Over 50 Years of Age: A multicenter clinical cohort study

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• PURPOSE: To characterize the clinical features of idiopathic intracranial hypertension (IIH) in patients >50 years of age compared to the typical IIH population and existing data for this older cohort.

• DESIGN: Retrospective, clinical cohort study.

• METHODS: Medical records of 65 patients >50 years of age at first diagnosis of IIH were reviewed based on the Modified Dandy Criteria from 4 academic centers. Each center provided randomly selected controls from IIH patients <50 years of age for each study patient at their location. Data recorded included patient demographics, presenting symptoms, medications, coexisting medical conditions, cerebrospinal fluid (CSF) opening pressure, treatments, and neuro-ophthalmic data from initial and final visits.

• RESULTS: Compared to controls, the older cohort showed the following characteristics: fewer females (n = 51 [78.5%] vs. controls: n = 60 [92.3%]; P = .045), fewer headaches (n = 33 [50.8%] vs. controls: 52 [80.0%]; P = .001), more frequent incidental discoveries of papilledema (n = 19 [29.2%] vs. controls: 7 [10.8%]; P = .015), and lower CSF opening pressure [median: 33 cm H_2O [range: 21-58 cm H_2O] vs. the median for controls: 34 cm H_2O [range: 24-67 cm H_2O; P = .029).

• CONCLUSIONS: Patients with IIH diagnosed at >50 years of age were less often female and had lower CSF opening pressure, fewer headaches, a higher chance of incidentally identified papilledema, and body mass index similar to that of younger IIH patients. Older IIH onset was not associated with worse visual outcome. (Am J Ophthalmol 2021;224:96–101. © 2020 Elsevier Inc. All rights reserved.)

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IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH) IS A rare syndrome (0.9 of 100,000 persons) of increased intracranial pressure of unknown cause.[1] Some authors prefer the term "pseudotumor cerebri syndrome" to encompass IIH and intracranial hypertension from a known secondary cause.[2] More than 90% of the patients affected are obese women at a mean age of 30 years old at the time of diagnosis.[1] Symptoms of IIH can include transient or permanent vision loss, headaches, binocular diplopia, and pulsatile tinnitus.[1] Few studies have investigated the clinical features of patient conditions diagnosed as IIH later in life, and the authors are unaware of any studies describing a large cohort of older patients. Previous findings from studies with a small subset of older patients with IIH suggest this population may have fewer headaches, more visual disturbances at presentation, and better visual outcomes than younger patients.[3–5] Further characterization of this older patient population would advance understanding subtleties in clinical manifestations and help with diagnosis and management of this rare disorder. Therefore, a large cohort of IIH patients >50 years of age at time of diagnosis were studied.

SUBJECTS AND METHODS

THIS MULTICENTER, RETROSPECTIVE, CLINICAL COHORT study was conducted at the Mayo Clinic, University of Minnesota, Rochester, the Washington University in St. Louis, and the University of Oklahoma. Approval was obtained from the local governing Institutional Review Board (IRB) at each site. Due to the retrospective nature of the study, the IRBs approved a request to waive consent. Data from patients who had opted out of research were not included. The study adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act in addition to all federal, state, and local laws.

• STUDY POPULATION: All patients whose electronic medical records contained billing codes International Classification of Diseases, Ninth revision (ICD9) 348.2 or ICD10 G93.2 (tenth revision) were identified. Data were gathered from patients >50 years of age at the time their

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condition was first diagnosed with IIH based on the following Modified Dandy Criteria used in the Idiopathic Intracranial Hypertension Treatment Trial: 1) the presence of signs and symptoms of increased intracranial pressure; 2) the absence of localized findings on neurologic examination, except for those known to occur from increased intracranial pressure; 3) the absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased cerebrospinal fluid (CSF) pressure (>20 cm H_2O). Abnormal neuroimaging except for empty sella turcica, optic nerve sheath with filled out CSF spaces, and smooth-walled, non–flow-related venous sinus stenosis or collapse should lead to another diagnosis; 4) the awake and alert patient; 5) no other cause of increased intracranial pressure was present.[6] The cutoff age of 50 was chosen as it approximates 2 standard deviations (SD) above the mean age of IIH diagnosis.[5] In total, 65 cases were evaluated: 29 from the University of Minnesota, 17 from the Mayo Clinic, 11 from the University of Oklahoma, and 8 from Washington University in St. Louis. Additionally, each center provided a randomly selected IIH patient <50 years of age as a control for each study patient. To select control patients, all IIH patients <50 years of age in each institution's database were assigned a number. A list of random numbers equal to the number of study patients from each institution was generated, and those patients <50 years of age whose assigned number was generated were selected as controls.

Recorded data included demographics (age, sex, self-reported race, body mass index [BMI], and CSF opening pressure), presenting symptoms (pre-diagnosis duration of symptoms, headache, subjective vision change, pulse synchronous tinnitus, diplopia, transient visual obscurations, no or incidental finding of papilledema), potentially contributing coexisting medical conditions (sleep apnea, anemia, systemic hypertension, polycystic ovary syndrome, diabetes mellitus, thyroid disease), use of contributing medications (-cycline type antibiotics, vitamin A derivatives, cyclosporine), treatments (medications, diet modification, cerebrospinal fluid shunt, optic nerve sheath fenestration [ONSF]), and data from initial and final neuro-ophthalmic visits (visual acuity, Frisen optic disc grade, automated perimetry mean deviation, mean retinal nerve fiber layer thickness). Although the same optical coherence tomography device was not used between institutions, each institution used either a Spectralis unit (Heidelberg Engineering, Franklin, Massachusetts, USA) or Cirrus unit (Zeiss, Dublin, California, USA). The difference in retinal nerve fiber layer measurements between these devices is approximately 5 μm.[7] Although this likely plays a role in subtle changes, for larger differences such as in the setting of papilledema, this difference is relatively minor. Controls and cases were measured on the same device, making comparisons among groups and the difference in initial and final retinal nerve fiber layer reasonable. All images were reviewed for quality (signal strength 7+ on the Cirrus and Q value 28 on the Spectralis units).

• **STATISTICAL ANALYSIS:** Data for the cases and controls were summarized using frequencies and percentages for categorical items. Medians and interquartile ranges (IQR) were used for continuous or ordered variables. Analytical methods included Fisher exact test and Wilcoxon rank sum test to compare differences in characteristics, risk factors, treatments, and outcomes of patients with IIH >50 years of age compared to patients <50 years of age for their worse eye. For each patient, the worse eye was defined as the eye with higher grade of papilledema at the initial visit. If the 2 eyes were the same, 1 eye was randomly selected. Nonparametric statistical methods were used due to skewness in the distributions of outcome variables. Data analysis was conducted using SAS version 9.4 software (SAS Institute, Cary, North Carolina, USA). All statistical tests were two-sided and P values <.05 were considered statistically significant.

RESULTS

THERE WERE 65 PATIENTS IN EACH GROUP. FOR METRICS where data were unavailable, the number of patients studied is provided. The median age of the older IIH cohort was 54 years (IQR: 51, 60) and 30 years (IQR: 24, 34) for the control cohort (Table). Compared to the control cohort, patients in the older cohort were less often female (n = 51; 78.5% vs. control cohort: 60; 92.3%; P = .045), had fewer headaches at presentation (n = 33; 50.8% vs. control 52 cohort: 80.0%; P = .001), and were more frequently asymptomatic with incidentally discovered papilledema when seeking unrelated eye care (n = 19; 29.2% vs. control cohort: 7; 10.8%; P = .015). In addition, IIH patients >50 years of age demonstrated slightly lower CSF opening pressures (n = 33 [IQR: 27, 39] vs. control: n = 34 [IQR: 31, 42] cm H_2O; P = .029) (Figure 1) and more commonly showed coexisting medical conditions including hypertension (n = 45 [69.2%] vs. control n = 5; 7.7%; P <.001), diabetes mellitus (n = 21; 32.3%; vs. younger cohort: 4 [6.2%]; P <.001), and thyroid disease (n = 12 [18.5%] vs. control n = 2; 3.1%; P = .009). Also, IIH patients >50 years of age were less likely to use cycline-type antibiotics than patients <50 years of age (n = 0 [0%] vs. older cohort n = 7; 10.8%; P = .013).

Older age (≥50) at the time of diagnosis did not appear to be associated with worse outcomes as shown by insignificant differences in automated perimetry mean deviation at first −2.63 [−7.04 to −1.19] n = 60 vs. −1.94 [−4.33 to −0.84]) n = 57; P = .316) and final (−2.64 [−5.01 to −0.78] n = 49 vs. −1.16 [−4.10 to −0.47] n = 53; P = .190) visits, need for surgical treatment with CSF shunt (4 of 62 [6.5%] vs. 5 of 65 [7.7%]; P >.999) or optic nerve

TABLE. Characteristics of Patients ≥50 Years Old With Idiopathic Intracranial Hypertension Compared to Patients <50 Years Old for Their Worse Eye

Variable	< 50 Years Old (n = 65)[a]		≥50 Years Old (n = 65)		P^b
	Median n	% or IQR	Median n	% or IQR	
Demographics/risk factors					
Age at diagnosis, y	30.0	24, 34	54.0	51, 60	
Females	60	92.3	51	78.5	.045
Whites	54	83.1	48	73.9	.286
Body mass index	36.8	32.2, 44.1 (n = 54)	36.1	30.9, 42.5 (n = 52)	.600
Cerebrospinal fluid pressure, cm H_2O	34	31, 42	33	27, 39	.029
Vitamin A derivatives	0	0.0	0	0.0	>.999
Cycline antibiotics	7	10.8	0	0.0	.013
Cyclosporine	0	0.0	1	1.5	>.999
Sleep apnea	11	16.9	21	32.3	.066
Anemia	3	4.6	2	3.1	>.999
Hypertension	5	7.7	45	69.2	<.001
Polycystic ovary syndrome	5	7.7	0	0.0	.058
Diabetes	4	6.2	21	32.3	<.001
Thyroid disease	2	3.1	12	18.5	.009
Presenting symptoms					
Pre-diagnosis duration, weeks	8.0	2, 22 (n = 58)	12.0	0, 24	.654
Headache	52	80.0	33	50.8	.001
Vision change	33	50.8	27	41.5	.379
Pulse synchronous tinnitus	21	32.3	13	20.0	.162
Diplopia	8	12.3	7	10.8	>.999
Transient visual obscurations	19	29.2	19	29.2	>.999
Incidental papilledema finding	7	10.8	19	29.2	.015
Initial visit					
First visual acuity, LogMAR	0	0, 0.1	0	0, 0.1 n = 64	.070
Papilledema, Frisen scale	3.0	1.0, 3.5	2.0	2.0, 3.5	.955
Humphrey visual field analyzer, mean deviation	−1.94	−4.33 to −0.84 (n = 57)	−2.63	−7.04 to −1.19 (n = 60)	.316
Mean retinal nerve fiber layer thickness	172	126, 278 (n = 42)	161	108, 224 (n = 39)	.168
Treatment					
Medication	63	96.9	63	96.9	>.999
Diet modification	55 (n = 63)	87.3	39 (n = 53)	73.6	.095
Shunt	5	7.7	4 (n = 62)	6.5	>.999
Optic nerve sheath fenestration	4 n = 64	6.3	7 (n = 62)	11.3	.360
Final visit					
Visual acuity, LogMAR	0	0, 0 (n = 64)	0	0, 0.2 (n = 59)	.001
Papilledema, Frisen scale	0	0, 0 (n = 55)	0	0, 0 (n = 59)	.808
Humphrey visual field analyzer, mean deviation	−1.16	−4.10 to −0.47 (n = 53)	−2.64	−5.01 to −0.78 (n = 49)	.190
Mean retinal nerve fiber layer thickness	104	89, 110 (n = 41)	96	82, 111 (n = 32)	.314
Follow-up duration, weeks	76.1	47.8, 160.4 (n = 62)	55.9	27.9, 155.1 (n = 60)	.171
Change in visual acuity, LogMAR	0	−0.05, 0 (n = 64)	0	0, 0 (n = 58)	.097

IQR = interquartile range.

[a]For metrics where data were unavailable for all patients, the number of patients studied (n) are provided.

[b]*P* values were derived from Fisher exact test or Wilcoxon rank sum test.

sheath fenestration (4 of 64 [6.3%] vs. 7 of 62 [11.3%]; $P = .360$). Both groups demonstrated similar BMI (36.1 [30.9-42.5] n = 52 vs. 36.8 [32.2-44.1] n = 54 $P = .600$), similar optic disc grade at first (2.0 [2.0-3.5] vs. 3.0 [1.0-3.5]; $P = .955$) and final (0 [0-0] vs. 0 [0-0]; $P = .808$) visits, and were followed for a similar number of weeks (55.9 [27.9-155.1] n = 60 vs. 76.1 [47.8-160.4] n = 62; P = .171). The final visual acuity was worse in the older cohort (0 [0-0.2] n = 59 vs. 0 [0-0] n = 64; $P = .001$ (Figure 2), but there were no significant differences in the change

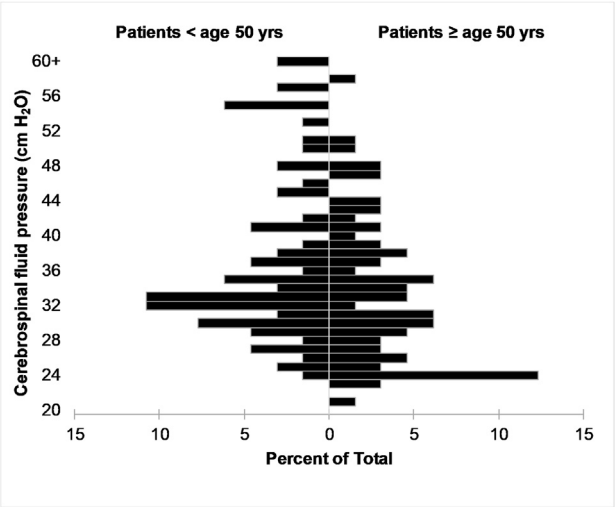

FIGURE 1. Distributions of cerebrospinal fluid opening pressure in 65 patients with idiopathic intracranial hypertension who were older than 50 years of age and in controls 65 controls < 50 years of age at presentation.

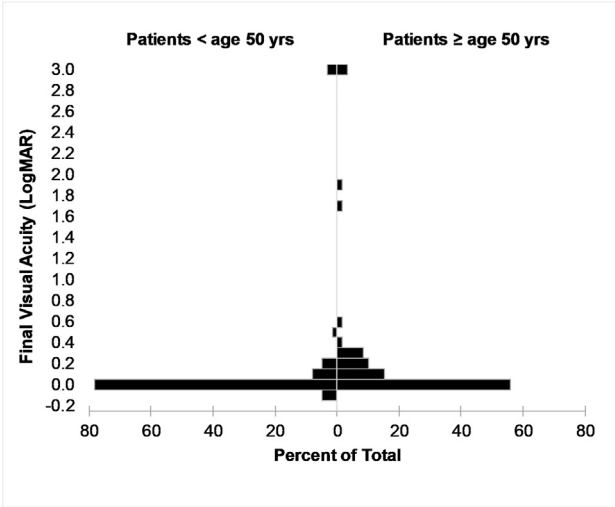

FIGURE 2. Distributions of visual acuity in patients with idiopathic intracranial hypertension who were 50 years old and older (n = 59) and in a control population younger than 50 years old (n = 64) at final visit.

between initial and final visits (0 [0-0] n = 58 vs. 0 [−0.05-0] n = 64; P = .097) (Figure 3). There were few quantitative data for weight loss and this could not be assessed among groups. Multiple variable analyses did not identify any additional significant associations between study endpoints and the combination of age group and other covariates.

DISCUSSION

TO THE BEST OF THE AUTHORS' KNOWLEDGE, THIS IS THE largest series of IIH patients >50 years of age. Previous retrospective studies of older IIH patients have included 14 patients >44 years of age, 19 patients >50 years of age, and 23 patients >40 years of age.[3–5] The rarity of IIH in this population has made it difficult to study, and differences between older IIH patients and their typical younger counterparts have not been fully clarified. This present study showed demographic differences in line with previous studies but also showed no significant differences in visual outcomes compared to controls.

Patients with IIH diagnosed at >50 years of age were less often female (78.5%) than patients <50 years of age (92.3%). This is similar to 2 prior retrospective studies of older IIH patients, including 14 patients >44 years of age and 19 patients >50 years of age, but this was not found in a study of 23 patients >40 years of age.[3–5] Although 2 of those studies found older IIH patients to be more often white and less obese, both of the present cohorts >50 years of age and <50 years of age were predominantly white (73.9%, 83.1%, respectively) and obese (median BMI: 36.1 and 36.8, respectively) without statistically significant differences between groups.[3,5] The differences between the authors' present and previous studies may be due in part to differences in the size of study populations or selected age cutoff.

Few of the present patients in either group were taking medications associated with IIH.[8] No patients used vitamin A derivatives, and similar numbers of patients >50 years of age and <50 years of age used cyclosporine therapy. Patients >50 years of age used cycline-type antibiotics less often than those <50 years of age, which is likely explained by its usage for acne treatment in younger patients.[9] We did not find significant differences in the rates of sleep apnea, anemia, or polycystic ovary syndrome between the 2 cohorts. Although the present patients >50 years of age were significantly more likely to have co-existing hypertension, diabetes mellitus, and thyroid disease, these differences were likely confounded by age alone rather than by differences in IIH presentation.[10–12]

Both cohorts reported experiencing symptoms for a similar time period before diagnosis (median: 8 vs. 12 weeks). A previous retrospective review of IIH >50 years of age supports this timeline, reporting a median of 8 weeks.[5] Patients >50 years of age in the present study were less symptomatic at presentation with 29.3% vs. 10.8%, respectively, presenting with incidentally discovered papilledema. Both cohorts had similar frequency of complaints of subjective vision change, pulse synchronous tinnitus, and diplopia, and the same rate of transient visual obscurations at presentation. A previous study of IIH in 19 patients >50 years of age found similar rates of visual complaints in patients >50 years of age (42%), but unlike the present study, that previous study found a much lower rate in their patients < 50 (21%).[5] Frequency of headaches

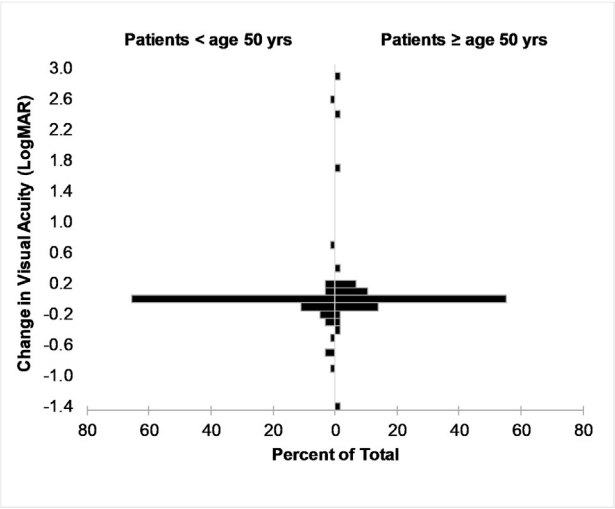

FIGURE 3. Distributions of visual acuity changes in patients with idiopathic intracranial hypertension who were 50 years old and older (n = 58) and in a control population 50 years old and younger (n = 64) between first and final visits.

at presentation in older patients IIH have been noted to range from 26% to 65%.[3–5] Our study confirms the findings of those prior studies that older patients with IIH present less often with headaches than the typical population (50.8% vs. 80%, respectively). Additionally, IIH patients in the present study diagnosed >50 years of age presented with lower CSF opening pressures than patients <50 years of age. Older patients diagnosed with IIH could represent new recognition of longstanding IIH, where these patients did not seek earlier care due to having relatively mild symptoms. This could account for lower rates of headache and more frequent presentation with incidental papilledema on routine examination.

Patients in both cohorts were most often medically managed with acetazolamide and/or loop-diuretics. The second most frequent intervention in both groups was diet modification. Although 1 study found patients >50 years of age required lower rates of both surgical (ONSF 11% vs. 18%, CSF shunt 11% vs. 17%, respectively) and medical treatment (74% vs. 91%, respectively), difference between the need for surgical treatment with either CSF shunting (6.5% vs. 7.7%, respectively) or ONSF (11.3% vs. 6.3%, respectively) were not found between our cohorts.[5] The duration of follow-up was similar between the cohorts in the present study (median: 55.9 weeks vs. 76.1 weeks, respectively) and ranged from 6 weeks to 2 years in prior reviews.[3,5]

It has been suggested that visual prognosis in older IIH patients may be similar or better than the typical IIH patient based on visual field improvement, recovery of visual acuity, reduced rate of severe visual loss, and less need for treatment.[3–5] The authors found that patients >50 years of age at the time of diagnosis had similar visual outcomes as shown by insignificant differences in either automated perimetry mean deviation at first and final visits or need for surgical treatment with CSF shunt or ONSF. Additionally, optic disc grade at first and final visits were also similar. Although the final visual acuity was worse in patients >50 years of age (LogMAR 0 [0-0.2] vs. 0 [0-0], respectively) there were no significant differences in the change between initial and final visits between cohorts, and worse acuity in older patients are likely attributed to non-IIH age-related ocular pathology such as lenticular changes.

The main limitations of this study are the low incidence of patients >50 of age diagnosed with IIH, which limits the number of patients available for analysis, its retrospective design, and the lack of consecutive controls. Despite these constraints, the authors believe the findings presented improve on the current understanding of the clinical characterization of this older subset of IIH patients. Overall, it was found that older patients with IIH experience presentation, clinical course, treatment, and visual outcome similar to that of younger patients and should be managed similarly. Given that older patients have fewer symptoms of intracranial hypertension, this could suggest these patients represent delayed recognition of longstanding IIH.

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