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Diagnostic process, misdiagnosis and bias in suspected idiopathic intracranial hypertension: a retrospective observational cohort study

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ABSTRACT

Background Misdiagnosis of idiopathic intracranial hypertension (IIH) is prevalent and potentially harmful. We evaluated the diagnostic process of IIH and the impact of implementing a National Guideline (NG) on IIH management to improve patient care.

Method In this observational retrospective study, we retrieved data on diagnostic investigations, duration, errors and causes for suspecting IIH from patients referred to the Danish Headache Center by suspected new-onset IIH from January 2020 to September 2022. We compared outcomes by final diagnosis (true vs disproven IIH) and the period before and after implementation of the NG. Level of significance was Bonferroni adjusted to p<0.002.

Results 96 patients were referred. We confirmed IIH in 27 (28%) and disproved IIH in 69 (72%) whose final diagnoses were predominantly headache disorders (70%) and pseudo-papilloedema (12%). True IIH was discovered by optic disc oedema (n=25, none detected by neurologists); neuroimaging indicating elevated intracranial pressure (n=1) or a typical clinical phenotype (n=1) aided little but often elicited IIH suspicion suggesting anchoring bias with premature closure. Misdiagnosis affected 11% (n=11). Diagnostic workup was more comprehensive and faster in true IIH (p<0.001). Mismanagement dropped by implementation of the NG (from 44% to 20%, p=0.02).

Conclusion Optic disc oedema is the most predictive determinant of true IIH; neuroimaging and phenotype alone have poor diagnostic value and introduce bias. Fundus exam is urgent and decisive in suspected IIH and should guide diagnostic strategy to mitigate unnecessary investigations and preserve vision. An NG reduced diagnostic errors and optimised the diagnostic process.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Misdiagnosis in idiopathic intracranial hypertension (IIH) is prevalent. Overdiagnosis may entail unnecessary medication with significant side effects and invasive procedures including neurosurgery. Underdiagnosis implies risk of visual loss. Guidelines exist on IIH management once papilloedema is diagnosed but the diagnostic journey preceding and beyond this finding is not well described.

WHAT THIS STUDY ADDS

⇒ We provide insights into current clinical practice in the diagnostic process of IIH in Denmark and evaluate the impact of implementing a National Guideline. Clinicians seem to be unfamiliar with the diagnostic criteria of IIH, be influenced by cognitive biases and underestimate the importance of immediate optic nerve head assessment in possible IIH.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We propose implementation of optic nerve head screening tools in non-specialist settings to optimise the diagnostic process and unburden tertiary care.

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is an unsolved conundrum of elevated intracranial pressure (ICP). Despite a tremendous increase in prevalence,[1–3] the disease remains uncommon, with the most recent Western prevalence ranging from 4.7/100 000[1] to 76/100 000.[2] The patient phenotype is remarkably homogeneous: predominantly females of fertile age with obesity[1]—the latter termed a current pandemic. IIH is a great mimicker of primary headache disorders,[4] which are common too. Neuro-ophthalmologists report 'flooding' with 'rule-out' referrals of suspected IIH[5] of which only a minority has it. False-positive misdiagnosis of IIH is prevalent[6 7] inflicting unnecessary invasive procedures, off-label medication with heavy side effects and postponed true diagnosis. False-negative misdiagnosis may cause irreversible visual impairment.

Historically, IIH has been a diagnosis of exclusion, hence the term '*idiopathic*', with diagnostic criteria characterised by negative findings (normal neurological examination, neuroimaging and cerebrospinal fluid (CSF) content). Diagnostic criteria have

moved towards more positive findings (papilloedema, opening pressure (OP) ≥25 cm CSF, neuroimaging indicating elevated ICP and abducens palsy).[8] Unfortunately, interpretation of the optic disc can be difficult even for experienced ophthalmologists, OP is subject to various sources of error, and no consensus exists on quantitative measures of abnormality regarding neuroimaging indicating IIH. This leaves clinicians with a limited toolbox in the diagnostic process, particularly non-specialists, and several cognitive biases have been observed in the diagnostic process of IIH.[6]

In 2018, two international guidelines on the management of IIH were independently published.[9 10] These guide management once the diagnosis is settled, but the oftentimes cumbersome and faulty process preceding diagnosis[5 11] calls for evidence-based guidance. The first National Guideline (NG) of IIH management in Denmark was published in May 2021.[12] A key aim was to direct a uniform multidisciplinary strategy with clear organisation and timely diagnostic workup (DWU). After recommending that all patients with suspected IIH should be referred to tertiary care the annual referral rate to the Danish Headache Center (DHC) doubled.[11] It has recently been shown that a specialised multidisciplinary approach at tertiary level improves patient outcomes,[13] satisfaction,[14] and health economic and societal costs.[15] Whether it improves the diagnostic process is yet unclear.

We aimed to describe current IIH diagnostic practice leading to tertiary headache care in terms of cause of discovery, DWU, diagnostic accuracy and mismanagement. Second, we aimed to evaluate the impact of the NG.

METHOD

We retrospectively evaluated charts of patients referred to the DHC from January 2020 to September 2022, with suspected or newly diagnosed IIH. Exclusion criteria were IIH relapse and secondary pseudotumour cerebri syndrome (PTCS). IIH was diagnosed according to the revised 2013 diagnostic criteria[8] and final diagnosis categorised as IIH (IIH confirmed) or non-IIH (IIH disproven).

Setting

The DHC is a tertiary outpatient headache clinic specialised in IIH management in close collaboration with neuro-ophthalmologists from the Department of Ophthalmology. Patients may be referred to neuro-ophthalmologists and/or the DHC when IIH is initially suspected or diagnosed. In the DHC, non-mydriatic fundus photography and automated perimetry has been implemented since May 2020, allowing screening and longitudinal follow-up of the optic disc and visual fields complementary to ophthalmology care; the interpretation competence of DHC staff was recently validated.[16] The initial entry to DWU is heterogeneous and includes opticians, emergency departments, primary, secondary and tertiary care specialties, in particular ophthalmologists and neurologists, but also other specialties and in any possible sequence depending on presenting symptoms, patient help-seeking behaviour and interpretation by health professionals. Patients referred to the DHC are triaged in a three-level system within eight working days from referral; IIH is handled as category 1 (most urgent) without exact cut-offs for waiting time.

After publication in May 2021, the NG was launched at scientific meetings, the Danish Medical Journal and within the societies that prepared the guideline (Neurology, Neurosurgery, Neuroradiology, Ophthalmology and the Danish Headache Society). The NG stresses initial urgent ophthalmic evaluation, neuroimaging including venography within 48 hours, identification of secondary causes and lumbar puncture (LP), encourages expert consultation and recommend specialised centres for management.

Outcomes

We registered diagnostic accuracy (proportion of patients in whom we confirmed IIH), number of patients diagnosed with IIH and/or prescribed ICP-lowering treatment before referral, mean time from first documented consideration of IIH to final diagnosis (diagnostic duration) and from referral to first visit at the DHC, details of the DWU including fundus and visual field exam, neuroimaging and invasive procedures (LP, neurosurgical interventions) and specialties involved. We categorised causes eliciting IIH suspicion according to first-mention of possible IIH in charts as follows: (1) suspected optic disc oedema (ODE) with no indication that IIH was considered before this finding; (2) neuroimaging: When IIH was not suspected until the radiologist noted signs indicating IIH; (3) clinical presentation: phenotype (young, obese, female) and/or symptoms frequently seen in IIH (headache, visual disturbances, pulsatile tinnitus) and (4) any other reason.

The number and type of errors were categorised by a medical doctor experienced in IIH management (NSH) according to the Diagnostic Error Evaluation and Research (DEER) tool.[17] We assessed mismanagement as any kind of inappropriate diagnostic process/workup preceding final diagnosis. Several DEER categories could apply to one individual. In case of uncertainty, a senior IIH specialist was consulted (RHJ). We considered LP as 'mismanagement' if performed by irrelevant IIH suspicion and not indicated otherwise. We evaluated whether patients with ODE had neuroimaging with venography performed before referral to the DHC to exclude venous sinus thrombosis and space-occupying lesions.

A patient was considered false-positively misdiagnosed if (1) IIH was diagnosed and/or (2) ICP-lowering medication prescribed by the outside provider before referral despite sufficient diagnostic evidence to already exclude IIH or IIH without papilloedema (IIHWOP). A false-negative misdiagnosis was registered if the patient did fulfil diagnostic criteria of IIH/IIHWOP, but the diagnosis was rejected in the DHC without argumentation as per chart review.

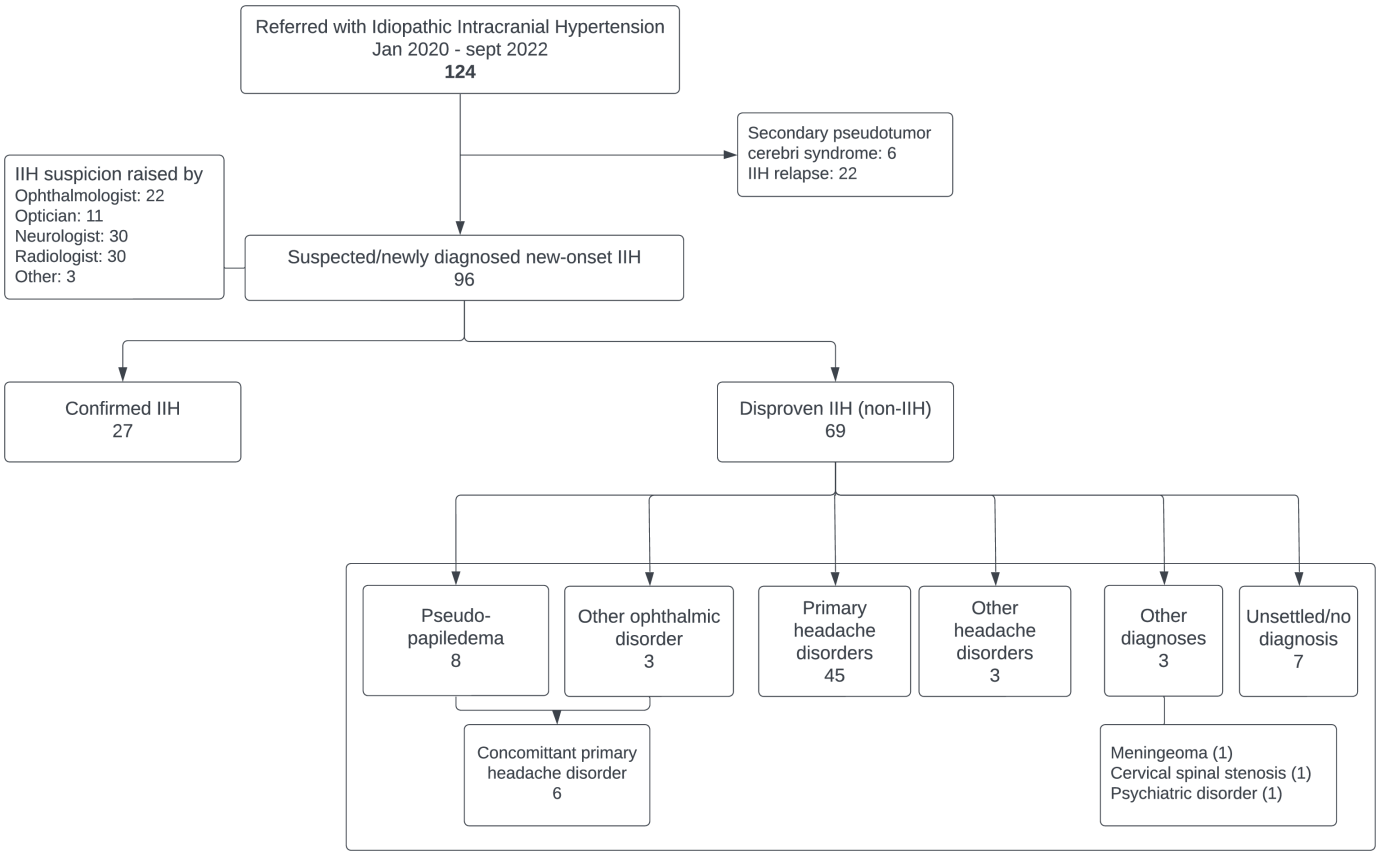

Figure 1 Flow chart of patients included for analysis, reasons for exclusion and final diagnoses. IIH, idiopathic intracranial hypertension.

Finally, we evaluated how urgently patients with suspected IIH and an unknown optic nerve status were evaluated ophthalmologically.

Statistical analysis

We compared outcomes by final diagnosis (IIH vs non-IIH) and by period (before the publication of the NG (January 2020–May 2021) and after (June 2021–Sept 2022)). We report proportions of categorical outcomes and between-group differences using χ^2 test or Fisher's exact test. Continuous variables are given as mean and SD (normally distributed) or median and IQR (non-normally distributed), and between-group differences are calculated by a two-sided t-test or Mann-Whitney U test. Significance level was Bonferroni corrected to adjust for multiple testing and set at p<0.002 (0.05/23 tests). Missing data were omitted from the given analysis.

RESULTS

Final diagnoses

The DHC received 124 referrals by 'IIH' (figure 1). Omitting secondary PTCS (n=6) and IIH relapse (n=22) left 96 patients with supposed new-onset IIH. We confirmed IIH in 28% (n=27): 26 patients had definite IIH, one had probable IIH; none were diagnosed with IIHWOP. We disproved IIH in 72% (n=69) whose final diagnoses were headache disorders in 70% (n=48), pseudo-papilloedema in 12% (n=8) and others in 20% (n=14) (figure 1). Patients with confirmed IIH versus non-IIH were similar regarding female sex (p=0.19), mean body mass index (p=0.69), obesity (p=0.16) and age (p=0.017) (table 1).

Initial reason for suspecting IIH

IIH was suspected equally frequent by neurologists (n=30), ophthalmologists/opticians (n=22/11) and radiologists (n=30); in few cases by another specialty (bariatric surgery clinic (n=1), neurosurgery (n=1), general practitioner (n=1)).

ODE as the initial cause for considering IIH as per chart documentation led to the discovery of 93% of true IIH cases, yielding a positive predictive value (PPV) of 0.74 in opposition to PPV 0.03 for neuroimaging and PPV 0.04 for clinical phenotype (figure 2). These causes for IIH suspicion significantly segregated IIH from non-IIH (p<0.0001).

In confirmed IIH, ODE was discovered by an ophthalmologist (n=16) or an optician (n=9), none by neurologists. In one young female with morbid obesity, headaches and visual complaints, the clinical phenotype alone caused IIH discovery. In another patient, IIH was discovered by three neuroimaging signs of intracranial hypertension.

Among non-IIH, 39% (n=27) were investigated due to clinical phenotype. Neuroimaging elicited IIH suspicion in 45% (n=31), mostly due to partial empty sella (n=27;

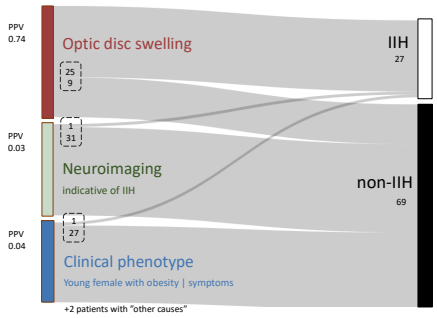

Figure 2 The figure shows the initial causes that made clinicians suspect IIH (left side): impression of optic disc oedema, neuroimaging indicating increased intracranial pressure or clinical presentation. The numbers of patients eventually confirmed to have IIH are shown (right side). p<0.0001 for a difference in initial causes and final diagnosis. IIH, idiopathic intracranial hypertension; PPV, positive predictive value.

in 12 of these this was the only sign indicating elevated ICP) and distended optic nerve sheaths (n=17), whereas flattening of the posterior aspect of the globe (n=5), complete empty sella (n=3) and venous sinus stenosis (n=5) were less prevalent. Eight non-IIH had≥3/4 neuroimaging signs, none had ODE. At least two may be missed IIHWOP (see below), whereas the remaining had no LP since not considered clinically likely to have IIHWOP.

'Other factors' (n=2) causing IIH suspicion included familial predisposition to IIH (n=1), and OP of 28 cm CSF in suspected subarachnoid haemorrhage which was ruled out (n=1); neither had IIH.

We confirmed papilloedema in 74% (25/34) of those with suspected ODE; the remaining were diagnosed with optic neuritis (n=1), eye disease from systemic disease (n=1), pseudo-papilloedema (n=5) and primary headache disorder with normal optic nerves (n=2).

DWU before referral

Patients with confirmed IIH were seen by a median of 3 specialties (IQR: 2–3), non-IIH by a median of 2 specialties (IQR: 1–2) before referral. Patients with confirmed IIH had a more thorough DWU before referral compared with non-IIH (table 1) regarding cerebral venography (81% vs 20%, p<0.0001), LP (85% vs 29%, p<0.0001), fundus (93% vs 45%, p<0.0001) and visual field examination (59% vs 25%, p=0.002).

Mean lumbar OP was higher in IIH versus non-IIH (36.4±9.5 cm CSF vs 26.4±7.2 cm CSF, p<0.0001). ICP-lowering treatment (21% vs 12%, p<0.0001) and a diagnosis of IIH before referral (18% vs 5%, p<0.0001) were more frequent in IIH than in non-IIH. Equally many had had CT or MRI neuroimaging (96% and 90%, p=0.43). Fewer patients with IIH needed further investigations in the DHC compared with non-IIH (44% vs 77%, p=0.004, table 2). Re-evaluation with MRI was necessary in 4% of IIH and in 22% of non-IIH (p=0.04). Re-LP was considered necessary by diagnostic indication in the DHC in four patients, but this did not change the diagnostic conclusion, and in only one case did it change whether the OP was above or below the diagnostic threshold of 25 cm CSF.

Timeliness of the diagnostic process

Median diagnostic duration was 88 days (IQR 28–173, range 0–539 days); it was shorter in IIH (7 days (IQR 2–47) compared with non-IIH (102 (IQR 75–189, p<0.0001, table 2). Median time from referral to first outpatient visit in the DHC was 46 days (IQR 29–76 days, range 1–278) with no difference between IIH and non-IIH (p=0.97). Median time to first ophthalmic evaluation in patients with unknown optic nerve status when IIH was suspected was 36 days (IQR 16–67, range 1–146 days).

DIAGNOSTIC ERROR

Misdiagnosis and mismanagement

False-positive misdiagnosis affected nine patients. They were prescribed ICP-lowering treatment by the outside provider despite ODE already being ruled out by an ophthalmologist. Seven of these patients had OP≥25 cm CSF (range 26.5–44.5 cm CSF, two had no LP), but all had <3 neuroimaging signs of elevated ICP and none had abducens palsy, hence, excluding IIHWOP. We corrected the erroneous IIH diagnosis within a mean time of 128 days (range 34–323 days).

Another two young females with overweight were prescribed ICP-lowering treatment before referral. ODE was ruled out, but both had elevated OP/ICP and four neuroimaging signs indicating elevated ICP. IIH was rejected by the DHC in favour of a primary headache disorder and ICP-lowering treatment terminated. These patients could have had suggested IIHWOP and are considered possibly false-negatively misdiagnosed by the DHC. Chart review revealed no details of why IIHWOP was not considered likely.

Mismanagement was found in 30% of IIH (n=8) and 29% of non-IIH (n=20, p=1) (table 3). Several DEER categories were oftentimes problematic within the same patient. The most prevalent error was failure in weighing the urgency (n=20) including delayed referral after verified ODE and preterm referral to neurosurgery before ophthalmic examination. Failure in ordering/performing tests included unnecessary LP (36% of those suspected of IIH by clinical phenotype and 25% of those suspected by neuroimaging) and lack of cerebral venography in patients with ODE.

Impact of NG on IIH management

Comparing referrals before (n=39) and after (n=56) the publication of the NG, diagnostic accuracy decreased numerically but not significantly (38% before vs 21% after, p=0.11), opposite of the rate of misdiagnosis (8% before vs 14% after, p=0.52). The mean monthly referral rate was 2.3 patients before and 3.5 patients after the NG.

Table 1 Demographic details and pre-referral diagnostic workup in patients referred to tertiary centre by suspected idiopathic intracranial hypertension, overall and by final diagnosis

	Total	IIH confirmed (IIH)	IIH disproven (non-IIH)	P value
n (%)	96 (100)	27 (28)	69 (72)	–
Female sex, n (%)	89 (93)	27 (100)	62 (90.0)	0.19
Obese, n (%)	70 (79)	24 (89)	46 (74)	0.16
BMI, mean (SD)	36.0 (±8.0)	36.5 (±7.8)	35.8 (±8.2)	0.69
Age, mean (SD)	36.6 (±11.3)	32.1 (±9.0)	38.3 (±11.6)	0.017
Number of specialists seen prior to referral, median (IQR)	3 (1–3)	3 (2–3)	2 (1–2)	–
Neurosurgical intervention*, n (%)	3 (3)	1 (4)	2 (3)	–
Referred before National Guideline, n (%)	39 (41)	15 (56)	24 (35)	0.11
Diagnostic workup before referral to the Danish Headache Center				
Seen in emergency department, n (%)	27 (30)	10 (37)	17 (27)	0.45
Seen by an ophthalmologist, n (%)	64 (67)	27 (100)	37 (54)	**<0.0001**
Fundus photo, n (%)	57 (59)	25 (93)	32 (46)	**<0.0001**
Automated perimetry, n (%)	34 (35)	16 (59)	18 (26)	0.004
Cerebral venography, n (%)	36 (38)	22 (81)	14 (20)	**<0.00001**
Cerebral CT or MRI, n (%)	88 (92)	26 (96)	62 (90)	0.43
Lumbar puncture (yes/no), n (%)	43 (45)	23 (85)	20 (29)	**<0.0001**
Number of lumbar punctures, mean (SD) (range)	0.7 (±0.7) (0–3)	1.2 (±0.4) (1–2)	0.6 (±0.7) (0–3)	
Lumbar puncture opening pressure, cm CSF (SD) (range)	31.1 (±9.7) (17–60.0)†	36.4 (±9.5) (22–60)	26.4 (±7.2) (17–45)	**<0.0001**
Pressure-lowering treatment initiated before referral, n (%)	33 (35)	21 (81)	12 (17)	**<0.0001**
Diagnosis of IIH given before referral, n (%)	23 (24)	18 (69)	5 (7)	**<0.0001**

Total: All patients referred to the Danish Headache Center by suspected or newly diagnosed 'Idiopathic Intracranial Hypertension', which was eventually confirmed or disproven. Level of significance is set at 0.002.
Missing data: BMI/obesity 7 NA (non-IIH); IIH diagnosis already given 2 NA (1 IIH, 1 non-IIH); pressure-lowering treatment initiated before referral: 1 NA (IIH); LP: 3 NA (1 IIH, 2 non-IIH); neurosurgical intervention 5 NA (2 non-IIH, 3 IIH).
*Invasive intracranial pressure monitoring.
†One patient was diagnosed with probable IIH, hence, there was one OP<25 cm CSF.
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BMI, body mass index; CSF, cerebrospinal fluid; LP, lumbar puncture; OP, opening pressure.

Overall, mismanagement was registered in 44% (n=17) before vs 20% (n=11) after the NG (p=0.022). Equally many patients were seen by an ophthalmologist (69% before vs 59% after, p=0.42), prescribed ICP-lowering medication (41% before vs 31% after, p=0.43) and had an LP (56% before and 38% after, p=0.11). Diagnostic duration was similar (121 days vs 111 days, p=0.55), as was mean grade of papilloedema (2.4 vs 1.7, p=0.25) before and after the NG, respectively.

DISCUSSION

We describe the diagnostic process in suspected new-onset IIH leading to tertiary headache care in Denmark. We confirmed IIH in a minority only (28%) in line with 27% observed in an American tertiary neuro-ophthalmology clinic (NOC).[18] We disproved IIH in 72% of which 13% (n=9) were false-positively misdiagnosed. This is much lower than previously observed (40% false-positively misdiagnosed) in American tertiary NOC.[6] Misdiagnosis may inflict patient harm and unnecessary spending of resources, although costs directly related to IIH misdiagnosis are unknown.[19] Our observation that ICP-lowering treatment was maintained by the referring clinician despite sufficient DWU to rule out IIH before referral may reflect lack of confidence with IIH diagnostic criteria or uncertainties about how to interpret isolated elevation of OP including the inherent flaws of OP measurements. As observed in IIH previously,[6 19] this could represent anchoring bias or representativeness heuristic with premature closure, where the clinician fixates on

Table 2 Postreferral diagnostic evaluation

	Total	IIH confirmed (IIH)	IIH disproven (non-IIH)	P value
n (%)	96	27 (28)	69 (72)	–
Diagnostic error				
False-positive misdiagnosis, n (%)	–	–	9 (13)	–
Possible false-negative misdiagnosis, n (%)	–	2 (7)	–	–
Postreferral diagnostic workup				
Relumbar puncture ordered by the DHC, n (%)	5 (5)	2 (7)	3 (4)	0.62
Re-MRI ordered by the DHC, n (%)	16 (17)	1 (4)	15 (22)	0.04
Further investigations needed in the DHC, n (%)	65 (68)	12 (44)	53 (77)	0.004
Still followed in DHC (September 2023), n (%)	50 (52)	21 (78)	29 (43)	0.004
No need for medication/in remission, n (%)	33 (34)	17 (63)	16 (26)	0.002
Initial cause of IIH suspicion				
Suspected optic disc oedema, n (%) (ophthalmologist (n)/optometrist (n))	34 (35) (23/11)	25 (93) (15/10)	9 (13) (8/1)	
Neuroimaging findings, n (%)	32 (33)	1 (4)	31 (45)	–
Clinical phenotype and/or symptoms, n (%)	28 (29)	1 (4)	27 (39)	
Other reason, n (%)	2	0	2 (3)	
≥3/4 neuroimaging signs, n (%)	14 (15)	6 (23)	8 (12)‡	0.20
Timeliness of diagnostic process*, Median number of days (IQR) (range)				
IIH suspicion to ophthalmic evaluation†	36 (16–67) (1–146)	26 (14–39) (1–51)	36 (17–75) (2–146)	–
IIH suspicion to final diagnosis (diagnostic duration)	88 (28–173) (0–539)	7 (2-47) (0–287)	102 (75–189) (6–539)	**<0.0001**
Referral date to first visit in the DHC	46 (29–76) (1–278)	49 (33–63) (12–87)	46 (26–76) (1–278)	0.97

Total: All patients referred to the Danish Headache Center by suspected or newly diagnosed 'Idiopathic Intracranial Hypertension', which was eventually confirmed or disproven. Level of significance is set at 0.002.
Missing data: date of referral: 1 NA (non-IIH); days from suspicion to first DHC visit: 3 NA (2 non-IIH, 1 IIH); still a patient in the DHC 1 NA (non-IIH); in remission 8 NA (non-IIH); neuroimaging signs 3 NA (1 IIH; 2 non-IIH); seen in ED 7 NA (non-IIH).
*Median number of days from raised IIH suspicion to given outcome (IQR) (range).
†Patients in whom 'entrance to investigation' was an ophthalmologist (n=39) and those already evaluated ophthalmologically before IIH was suspected (n=3) are omitted (22 NAs), leaving n=2 in the IIH group and n=29 in the non-IIH group.
‡Possibly false-negatively misdiagnosed IIH without papilloedema (IIHWOP, n=2), the remaining (n=6) were considered clinically unlikely to have IIHWOP (older age, male sex, more likely explanations).
DHC, Danish Headache Center; IIH, idiopathic intracranial hypertension.

IIH by vague indications, for example, pattern recognition (young female with obesity, headache and indicative neuroimaging) but refrains from differential diagnostic considerations despite subsequent contradicting information (ruling out ODE). Fortunately, misdiagnosed did not undergo surgical interventions but pronounced acetazolamide side effects,[20] presumed sick days and absenteeism, discomfort of LPs,[21] and being (erroneously) diagnosed with a serious disease burdened these patients.

False-negative misdiagnosis possibly affected at least two patients, in whom IIHWOP may have been underdiagnosed by tertiary specialists. Although poorly understood[22] and seemingly rare,[23] IIHWOP is expected to appear in a period of >2.5 years in a tertiary headache facility. Since ODE was ruled out and patients were treated according to headache phenotype in line with consensus guidelines,[10] therapeutic implications seem ignorable, though.

A predominant cause of previously reported false-positive IIH misdiagnosis was erroneous interpretation of the optic disc.[6] Further demonstrated, 32% of those referred to tertiary NOC by 'papilloedema' had it confirmed.[18] In contrast, we confirmed papilloedema in 74% of suspected ODE, of which only two had non-anomalous optic nerves. ODE in our setting was suspected exclusively by opticians/ophthalmologists using specialised equipment (fundus photography, optical coherence tomography (OCT)), whereas documented utilisation of direct ophthalmoscopy among Danish neurologists was rare.

ODE initiates a cascade of predefined expedited investigations which explains the shorter diagnostic

Table 3 Diagnosis error evaluation and research

	IIH (n=27)		Non-IIH (n=69)	
	Before NG (n=15)	After NG (n=12)	Before NG (n=24)	After NG (n=44)
1. Access/presentation	2	0	1	2
Failure/delay in presentation	2	–	1	–
Failure/denied care access	–	–	1	2
Number of patients with no errors	13	12	23	42
2. History	0	1	1	0
Failure/delay in eliciting critical piece of history data	–	1	–	–
Inaccurate/misinterpretation	–	1	–	–
Failure in weighing	–	–	1	–
Failure/delay to follow-up	–	–	–	–
Number of patients with no errors	15	11	23	44
3. Physical examination	0	0	0	0
Failure/delay in eliciting critical examination finding	–	–	–	–
Inaccurate/misinterpreted	–	–	–	–
Failure in weighing	–	–	–	–
Failure/delay to follow-up	–	–	–	–
Number of patients with no errors	15	12	24	44
4. Tests	2	1	5	8
Failure/delay in ordering needed tests	2	1	1	4
Failure/delay in performing ordered tests	–	–	3	–
Error in test sequencing	–	–	–	–
Ordering of wrong tests	–	–	–	3
Tests ordered wrong way	–	–	–	–
Sample mixup/mislabeled	–	–	–	–
Technical error/poor processing of specimen/test	–	–	–	–
Erroneous lab/radiology reading of test	–	–	–	–
Failed/delayed reporting of result to clinician	–	–	–	–
Failed/delayed follow-up of (abnormal) test result	1	–	–	–
Error in clinical interpretation of test	–	–	1	3
Number of patients with no error	13	11	19	36
5. Assessment	3	2	10	9
Failure/delay in considering the diagnosis	–	1	1	2
Too much consideration/weight given to the diagnosis	–	–	2	4
Too little weight on competing/coexisting diagnosis	–	–	–	2
Failure/delay to recognise/weigh urgency	3	1	8	2
Failure/delay to recognise/weigh complications	–	–	–	–
Number of patients with no error	12	10	14	35
6. Referral/consultation	3	2	2	2
Failure/delay in ordering referral	2	2	1	2
Failure/delay obtaining/scheduling ordered referral	1	–	1	–
Error in diagnostic consultation performance	–	–	–	–
Failed/delayed communication/follow-up of consultation	–	–	–	–
Number of patients with no error	12	10	22	42
7. Follow-up	0	1	1	1
Failure to refer patient to close/safe setting/monitoring	–	1	–	1

Continued

Table 3 Continued

	IIH (n=27)		Non-IIH (n=69)	
	Before NG (n=15)	After NG (n=12)	Before NG (n=24)	After NG (n=44)
Failure/delay in timely follow-up/rechecking of patient	–	–	1	–
Number of patients with no error	15	11	23	43
Overall				
Number of errors	11	8	22	25
Error rate (number of errors per month)	0.65	0.50	1.29	1.56
Number of patients with diagnostic error	5	3	12	8
Number of patients without any diagnostic error	10	9	12	36

Prevalence of diagnostic errors in patients with confirmed versus disproven IIH. Grey boxes: Number of patients with/without diagnostic error within the given category. White boxes: Number of errors within that category. The total number of patients with any diagnostic error within each category may be lower than the accumulated number of errors because several diagnostic errors can happen in one patient. Date of referral: 1 NA (non-IIH).
IIH, idiopathic intracranial hypertension; NG, National Guideline.

duration and more extensive DWU in confirmed IIH versus non-IIH. Non-IIH was seen by fewer specialties and more often required further investigations including reimaging which probably indicates less clarified and/or more complex cases unmanageable in primary and secondary care. Ophthalmic examination probably could have spared several of these referrals. It is important to stress that consideration of IIH may be relevant, but the lack or delay of eye examination is criticisable. The NG recommends ophthalmic assessment before neuroimaging and LP. Ignorance of or non-adherence to this sequence may explain why time to ophthalmic assessment was similar before and after the NG. An immediate funduscopic and visual field examination is decisive in IIH. It is concerning that 33% of our patients were not evaluated ophthalmologically before referral to the DHC with a potentially sight-threatening condition. Fortunately, none of these had IIH confirmed. Nevertheless, there was a considerable delay from IIH suspicion to first ophthalmic evaluation (mean 45 days (±40 SD)) in fundus evaluation-naïve patients. Likewise, only 35% of our patients had visual fields examined before referral similar to observations in tertiary NOC.[6 18] These observations encouraged our ambition to optimise our fast-track with expedited fundus photography and automated perimetry in fundus evaluation-naïve individuals referred by 'IIH' as suggested.[5 6] Other screening tools are transorbital sonography[24] and OCT imaging[25] candidating as solutions to timely assess ODE. This will aid clinicians keep the balance of spend of resources versus gain from a cost-benefit and a 'do-no-harm' perspective. Optimised fast-track may also expedite and prioritise time-to-first-visit in the DHC to align better with the quality assurance framework for triage of new-onset/suspected IIH proposed by neuro-ophthalmologists.[26]

Although under-reported,[18] neuroimaging indicating intracranial hypertension is common incidental findings,[27] in particular empty sella. At least three specified neuroimaging signs of elevated ICP have a sensitivity of 59.5%–85.2% and a specificity of 93.5%–100% in diagnosing IIH[28–30] but their usefulness is hampered by lack of consensus definition of abnormality. Also, radiological evaluation of IIH signs is sensitive to rater experience and referral information.[31] Neuroimaging was a major reason for suspecting IIH (33%). Similarly, in tertiary NOC, IIH was suspected due to neuroimaging in 27%,[18] of which 12% (8/66) had papilloedema opposed to 3% (1/32) in our setting confirming the unreliability of isolated IIH-suspicious neuroimaging.[27] A note from the radiologist reading 'possible IIH' could prompt the unexperienced clinician to proceed with unnecessary DWU contributing to the mentioned anchoring bias.

Impact of NG

Implementation of the NG hopefully increased IIH awareness. This possibly introduced availability heuristic. The referral rate, but not the diagnostic accuracy, increased following NG implementation. Maybe the NG reinforced reluctancy to diagnose IIH outside of tertiary care. More frequent consideration of IIH and earlier outreach for expert evaluation could be at the expense of diagnostic accuracy but could also explain the observed reduction in overall mismanagement. We cannot conclude whether the NG improved non-specialist management or resulted from increased specialist-driven management. Being an uncommon disorder, a high proportion of confirmed IIH in suspected cases (high diagnostic hit-rate) would raise concern about missed cases. Hence, the goal is not a high diagnostic hit-rate but a low mismanagement and misdiagnosis rate. The accumulated number of errors was stable but may be misleading because several errors oftentimes were registered in a single individual, and due to small sample size, each error had a significant impact on statistics. Previous evaluation with the DEER tool in IIH[6] exclusively covered misdiagnosed patients and reported the one major cause. These different methodologies

limit comparison. Nevertheless, we confirmed challenges regarding suboptimal weighing/prioritising. Our observations disagreed by inaccurate or misinterpreted physical examination: we had few of these as opposed to tertiary NOC[6] since Danish neurologists rarely did ophthalmoscopy.

We observed LP in 29% of non-IIH—less frequent than 79% observed in tertiary NOC.[6] However, we lack information about patients having an LP by suspected IIH but never referred. This explains the high OP in non-IIH: patients with normal OP would rarely be referred by IIH. Notably, re-LP did not change the final diagnosis, so therapeutic consequences of such should be carefully considered.

Limitations

We were limited by our own ability to diagnose correctly. We did not observe patients not referred to tertiary care, nor patients referred to the DHC in whom IIH was not suspected by referral, but who eventually were diagnosed with it. This disabled a realistic evaluation of false-negatively misdiagnosed and introduced spectrum bias[32] since non-IIH constituted a very selected 'IIH mimicry' population. Referral patterns are indeed biased by initial DWU, working diagnosis and by complexity. This likely explains why the main cause for IIH suspicion in true IIH was impression of ODE and emphasises the value of funduscopy. Undocumented consideration of IIH before ophthalmic evaluation is possible, which could flaw our reports on causes for discovery of true IIH (reporting bias). In patients referred by neuro-ophthalmologists, IIH suspicion is well founded, whereas patients referred by non-specialist represents more heterogeneous clinical practices. Mapping referral patterns of suspected IIH in tertiary NOC and primary and secondary care would complement the picture of the diagnostic journey these patients traverse. It is unlikely that patients with ODE and normal neuroimaging are seen in neuro-ophthalmology only, as the DHC manages ICP-lowering treatment in these– regardless of headache. Conversely, patients with ODE due to other pathologies are not seen in the DHC.

Notably, predictive values of the causes for IIH suspicion (ODE, neuroimaging and clinical phenotype) reflect clinicians' diagnostic behaviour, not the intrinsic diagnostic abilities (sensitivity and specificity) of these factors.

The retrospective nature and dependence on chart information of the study is another important limitation.

CONCLUSION

Primary headache disorders in females with overweight and neuroimaging showing empty sella are common reasons for suspecting IIH, but few have it. We encourage urgent eye examination as a 'gate-keeper' and guide in the investigational strategy of suspected IIH to preserve vision and mitigate unnecessary DWU, for instance, by use of fundus photography in non-specialist settings. Diagnostic biomarkers are needed to counteract the current cognitive-biased approach. We recommend NGs to reduce mismanagement and improve patient care.

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