



Diagnostic Error in Neuro-ophthalmology: Avenues to Improve

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Accepted: 14 February 2022 / Published online: 23 March 2022

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Abstract

Purpose of Review To highlight potential avenues to reduce preventable diagnostic error of neuro-ophthalmic conditions and avoid patient harm.

Recent Findings Recent prospective studies and studies of patient harm have advanced our understanding. Additionally, recent studies of fundus photography, telemedicine, and artificial intelligence highlight potential avenues for diagnostic improvement.

Summary Diagnostic error of neuro-ophthalmic conditions can often be traced to failure to gather an adequate history, perform a complete physical exam, obtain adequate/appropriate neuroimaging, and generate a complete, appropriate differential diagnosis. Improving triage and identification of neuro-ophthalmic conditions by other providers and increasing access to subspecialty neuro-ophthalmology evaluation are essential avenues to reduce diagnostic error. Further research should evaluate the relationship between misdiagnosis and patient harm, and help identify the most impactful potential targets for improvement.

Keywords Neuro-ophthalmology · Diagnostic error

Introduction

Medical error is estimated to be the third most common cause of death in the USA [1], with about one in twenty experiencing preventable harm as a result [2]. Medical error has a significant economic impact, costing the USA about \$19.5 billion in 2008 [3]. Diagnostic errors are the most common, expensive, and dangerous medical errors among malpractice claims [4]. An estimated 12 million Americans experience diagnostic error each year [5]. However, a recent survey of safety professionals in the US healthcare system showed that while a majority agree that diagnostic error is common and preventable, a minority had taken action to

combat the issue, reflecting the need for further investigations into potential areas of improvement[6].

As demonstrated by the prevalence of misdiagnosis of stroke [7] and multiple sclerosis [8], neurology remains susceptible to diagnostic error, arguably due to the complex and varied clinical presentations of neurologic disorders [9, 10]. Neuro-ophthalmic conditions in particular have been shown to have high rates of misdiagnosis [11–18, 19••] that can result in preventable harm to patients [19••]. The typically complicated diagnoses and detailed clinical examination required to correctly diagnose neuro-ophthalmic conditions make them susceptible to misdiagnosis [20], but may also may shed light on opportunities for intervention.

This article is part of the Topical Collection on *Neuro-Ophthalmology*

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Laying the Groundwork: Prior Studies Showed High Rates of Misdiagnosis of Neuro-ophthalmic Conditions

Prior studies on diagnostic error in neuro-ophthalmology have been limited (Table 1). Studies have been primarily descriptive [13, 14, 16–18, 21, 22, 23•, 24•, 25], almost exclusively retrospective [13, 16–18, 21, 23•, 24•], and mostly limited in scope—either to a single condition [13,

Table 1 Studies characterizing rates and causes of diagnostic error in neuro-ophthalmic conditions

Authors, Publication Year	Design	Population	Condition(s)	Outcome(s) of interest	Misdiagnosis rate	Summary
Dillon et al., 1994 [21]	Retrospective review	588 patients	Optic neuropathy, diplopia, ptosis, proptosis	Appropriateness of diagnostic testing prior to neuro-ophthalmic consultation	N/A	For optic neuropathy, diplopia, and ptosis, rate of unnecessary testing ranged from 16–26%, resulting in excessive costs. For proptosis, testing was appropriate, but 56% of neuroimaging studies were sub-optimal to answer clinical question
Elmalem et al., 2010 [16]	Retrospective review	17 patients	3rd nerve palsy due to compression by Pcomm aneurysm	Missed diagnoses on noninvasive imaging	47%	Neuroradiology training and providing specific clinical information to radiologists was associated with diagnostic accuracy
McClelland et al., 2012 [14]	Prospective cohort study	84 patients	Multiple	Appropriate diagnostic imaging prior to neuro-ophthalmic consultation	69%	38% had suboptimal neuroimaging prior to neuro-ophthalmic consultation, and 29% required additional neuroimaging
Fisayo et al., 2016 [17]	Retrospective review	165 patients	IIIH	Misdiagnosis rate and causes	40%	24% had delayed alternative diagnosis. Unnecessary procedures were common, including LP in 80% of misdiagnosed patients. Most errors were due to inaccurate examination or inaccurate weighing of differential
Stunkel et al., 2018 [13]	Retrospective cross-sectional study	122 patients	Optic neuritis	Misdiagnosis rate and causes	60%	16% had unnecessary LP and 11% received unnecessary IV steroids. Most errors were due to inaccurate weighing of differential or inaccurate examination
Blanch et al., 2019 [26]	Prospective cohort study	198 patients	Papilledema	Misdiagnosis rate for papilledema using fundus photographs	21%	Sensitivity was close to 100% across all specialties (neuro-ophthalmology, neurology, ophthalmology and emergency medicine). Specificity ranged from 43–100% depending on specialty
Hartmann et al., 2019 [25]	Retrospective review	16 patients	Intracranial hypertension due to compression of dural venous sinus by meningioma	Delayed diagnosis	63%	40% had a poor visual outcome in the setting of delayed diagnosis. Most errors were due to misinterpretation of or failure to obtain sufficient imaging

Table 1 (continued)

Authors, Publication Year	Design	Population	Condition(s)	Outcome(s) of interest	Misdiagnosis rate	Summary
Kahraman-Koytak et al., 2019 [18]	Retrospective review	35 patients	Optic nerve sheath meningioma	Misdiagnosis rate and causes	71%	64% had a poor visual outcome in the setting of delayed diagnosis. 24% received unnecessary treatment with steroids, 20% receiving unnecessary lumbar puncture. Most errors were due to weighing of differential or inaccurate imaging interpretation

N/A not applicable. *P.com* posterior communicating artery. *IIH* idiopathic intracranial hypertension. *LP* lumbar puncture. *IV* intravenous

16–18, 24•, 26] and/or a single institution [13, 14, 16–18, 21, 23•]. Prior studies including multiple neuro-ophthalmic conditions found misdiagnosis rates up to 69% prior to neuro-ophthalmology consultation [14, 23•]. Similarly high rates of misdiagnosis have been seen in prior studies focusing on a single neuro-ophthalmic condition—up to 60% for optic neuritis [13] and 71% for optic nerve sheath meningiomas [18]. Several studies attempted to identify the cause of these diagnostic errors, and common themes were inadequate history [13, 16, 17, 22], inaccurate performance of the physical examination or inaccurate interpretation of the examination findings [13, 17, 24•], failure to obtain appropriate imaging to answer the clinical question [14, 22, 25], incorrect interpretation of imaging findings [13, 14, 16, 17, 21, 22, 23•, 25], and generation of a flawed or incomplete differential diagnosis [13, 22].

Notably, there was a dearth of prospective studies and research into whether these diagnostic errors lead to harm to patients. Similarly, all of these studies have focused on diagnostic label failure—the assignment of an incorrect diagnostic label [27]—and there has been little research into other errors involving the overall diagnostic process—diagnostic process errors [27]—such as failure to obtain a timely work-up to rule out possible critical diagnoses with appropriate urgency.

Recent Investigations: Further Characterizing the Diagnostic Process and Patient Harm

More recently, additional studies have examined patient harm from diagnostic error and errors in the diagnostic approach (Table 2). Recently, a multisite, prospective study examining all consecutive new patients referred to neuro-ophthalmology [19••] found that the referral diagnosis was incorrect in almost half (49%) of the 496 examined cases. Although the majority of patients (88%) had been referred appropriately, those with an inappropriate referral to neuro-ophthalmology were more likely to have been misdiagnosed prior to referral (76% vs 45% respectively). Neuro-ophthalmic consultation was impactful—in 2% of cases, neuro-ophthalmology consultation directly saved the patient’s life or vision. Surprisingly, even in cases that were referred inappropriately, neuro-ophthalmology had an impact on patient care through both avoiding unnecessary tests (61%) and avoiding harmful treatment or providing an appropriate urgent referral (17%). Causes of diagnostic error were primarily due to inaccuracies in history taking, physical exam, differential diagnosis, and interpretation of testing. Those who were misdiagnosed were more likely to have received inappropriate management prior to referral (34% vs 13%). Twenty-six percent of misdiagnosed patients were harmed

Table 2 Recent investigations characterizing the diagnostic process and patient harm

Authors, Publication Year	Design	Population	Condition(s)	Outcome(s) of interest	Misdiagnosis rate	Summary
Stunkel et al., 2020 [15]	Retrospective review	300 patients	Multiple	Analysis of neuro-ophthalmology referrals, misdiagnosis rate	49%	Delay of care or mismanagement occurred prior to neuro-ophthalmology consultation in 28% of cases
Schroeder et al., 2020 [24•]	Retrospective review	78 patients	3rd nerve palsy	Misdiagnosis rate and causes	22%	Most errors were due to inaccurate examination
Bacorn et al. [37]	Case series and literature review	2 patient case series, review of papers describing 25 patients	Facial nerve palsy	Misdiagnosis related to physical examination, history, and rare presentations	N/A	Use of term “Bells palsy” as shorthand for facial nerve palsy prior to ruling out alternative etiologies can contribute to misdiagnosis
Alshuler et al., 2021 [33]	Retrospective case-control	39 MRI images	Nonadenomatous sellar lesions and adenomas	Correct diagnosis based on MRI images	61%; 38%	61% of nonadenomatous cases and 38% of adenoma cases were incorrectly diagnosed by at least one reader. Most errors were avoidable
Stunkel et al., 2021 [19••]	Prospective cross-sectional study	496 patients	Multiple	Patient harm due to misdiagnosis	49%	26% of misdiagnosed patients experienced harm, with 97% of the harm likely preventable by earlier referral to neuro-ophthalmology. 23% received inappropriate management before referral
Chung et al., 2021 [28•]	Retrospective cross-sectional study	110 patients	3rd nerve palsy	Rate and causes of delay in arterial imaging, patient harm related to delay	N/A	36% of patients received urgent (within 24 h) arterial imaging. Median delay was 24 days from symptom onset and 12.5 days from initial medical contact. 25% of referring providers had not documented a complete examination. 1 patient was harmed

Table 2 (continued)

Authors, Publication Year	Design	Population	Condition(s)	Outcome(s) of interest	Misdiagnosis rate	Summary
Chan et al., 2021 [29●●●]	Retrospective cohort	181 patients	CRAO	Timing and characteristics of presentation, management	N/A	Only 34% presented within 24 h of vision loss. Presenting later was associated with lower likelihood of receiving adequate stroke work-up. Of 21 patients presenting within 4.5 h, only 3 received IV thrombolysis and 9 had misdiagnosis or delayed diagnosis
Mileski et al., 2021 [30]	Retrospective survey	1916 Optometrists	CRAO/BRAO	Optometric practice patterns for CRAO/BRAO	N/A	More than half of optometrists refer to outpatient ophthalmology rather than ED. Most are located within 30 min of ED with stroke center
Eldweik 2021 [35]	Retrospective review	29 patients	IIH	Frequency of misdiagnosis in patients who refused lumbar puncture	18%	All misdiagnosed patients had pseudopapilledema. Significant association between confirmed diagnosis and positive MRI/MRV findings. TVOs and pulsatile tinnitus only reported in the true IIH group
Yuan et al., 2021 [34]	Retrospective review	54 patients	IIH	Frequency of misdiagnosis and alternative diagnoses	22%	Most errors were due to laboratory or radiology testing errors
Zheng et al., 2021 [38]	Retrospective case series	23 patients	Extraocular tumors	Ocular symptoms associated with extraocular tumors	N/A	6 cases of initial misdiagnosis were made by a less experienced, less specialized ophthalmologist

N/A not applicable. MRI magnetic resonance imaging. CRAO central retinal artery occlusion. IV intravenous. BRAO branch retinal artery occlusion. ED emergency department. IIH idiopathic intracranial hypertension. LP lumbar puncture. MRV magnetic resonance venography. TVOs transient visual obscurations

due to the misdiagnosis or delayed diagnosis, with harms including adverse effects of unnecessary medications, progression of permanent vision loss, and death (due to delay in diagnosis of a diffuse leptomeningeal glioneuronal tumor). In most of these patients (97%), the harm would potentially have been prevented by earlier access to neuro-ophthalmology. Although this study required somewhat subjective assessments, including what constitutes harm and the preventability of harm, it established a significant relationship linking misdiagnosis and harm to patients.

Chung et al. [28•] evaluated whether patients referred for suspicion of or with a final diagnosis of third nerve palsy underwent urgent imaging (defined as within 24 h of initial encounter) to rule out an intracranial aneurysm as the cause. This study primarily focused on a diagnostic process error [27]—the failure to obtain imaging in a timely manner—rather than a failure to assign the correct diagnostic label—in this case third nerve palsy. The majority of patients (64%) had not received arterial imaging within 24 h. Although a third nerve palsy was correctly suspected by the referring provider in 82% of cases, less than half (39%) of those patients received urgent imaging. Similarly, 25% of providers failed to document at least one cardinal physical examination component necessary for diagnosing a third nerve palsy, which may have contributed to misdiagnosis, as a prior study of the misdiagnosis of third nerve palsies found that misinterpretation of the physical examination was a common cause of diagnostic error in this condition [24•]. There was a median delay of 24 days between symptom onset and arterial imaging. Although rare, this can leave a patient susceptible to a potentially fatal aneurysmal rupture. This study also specifically evaluated patient harm, and found a case of delayed diagnosis of a metastasis in the cavernous sinus [28•]. This study showed that whether or not the correct diagnostic label is assigned, the correct diagnostic process may not be followed, leaving patients vulnerable to potential harm.

Chan et al. [29••] and Mileski et al. [30] also focused on a diagnostic process error [27]—failure of patients with central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) to receive an urgent stroke workup. Chan et al. retrospectively reviewed 181 patients diagnosed with an acute CRAO who had presented to either the emergency department (ED) or outpatient ophthalmology clinic at a single institution. Only 12% presented within 4.5 h of vision loss; 23% presented between 4.5 and 24 h of vision loss, and 62% presented over 24 h after vision loss. Fewer patients presenting after 24 h received an appropriate stroke workup or were admitted. Only three patients received thrombolysis. Notably, of the patients who presented within 4.5 h, nine were affected by misdiagnosis or a delayed diagnosis in the ED. As thrombolysis has the potential to improve visual outcome [31], these diagnostic errors may

have led to patient harm. The authors advocate educational campaigns, implementing institutional protocols, and making use of stroke and fundus photography to speed accurate diagnosis of CRAO and improve access to treatment within the critical window.

Mileski et al. [30] surveyed 1916 optometrists and found that more than half of outpatient optometrists fail to send patients with CRAO/BRAO to the ED, and instead refer to outpatient ophthalmology, despite 77% being located within 30 min of an ED with an associated stroke center. In a related survey from 2009, only 35% of ophthalmologists referred patients with acute CRAO to the ED, compared to 86% of neuro-ophthalmologists and 73% of neurologists [32]. Improved education of both the general public and health care professionals is needed to help patients with acute CRAO/BRAO present earlier to the ED and receive an appropriate stroke workup.

Altshuler et al. [33] examined errors in distinguishing pituitary adenomas versus nonadenomatous lesions on magnetic resonance imaging (MRI) as interpreted by two neurosurgeons and two neuroradiologists. Sixty-one percent (11/18) of nonadenomatous cases and 38% (8/18) of adenoma cases were incorrectly diagnosed by at least one reader. Of misdiagnosed cases, 5 of the 11 misdiagnoses of nonadenomatous and 7 of the 8 misdiagnoses of adenoma cases were due to avoidable errors, further emphasizing interpretation of imaging as a potential cause of misdiagnosis, consistent with prior studies of diagnostic error in neuro-ophthalmology [13, 14, 16, 17, 21, 22, 24•], and suggesting that these errors could potentially be improved.

Yuan et al. performed a retrospective review [34] of pediatric patients with suspected idiopathic intracranial hypertension (IIH). Out of 54 patients, 22% (12/54) were misdiagnosed. Alternative diagnoses were inflammatory/infectious etiologies, malignancy, craniosynostosis, benign tumor, hydrocephalus, and retinitis pigmentosa. Missing these potential serious alternative diagnoses has the potential to lead to patient harm, although patient harm was not specifically evaluated by this study. In the majority of misdiagnosed cases (8/12), the errors were related to laboratory or radiology testing.

A retrospective cohort study [35] found a misdiagnosis rate of 17% for 29 patients who had refused lumbar puncture and been diagnosed with IIH. This study emphasized the importance of a proper clinical examination, as pseudo-papilledema was the correct diagnosis in all misdiagnosed cases. The study also called attention to the importance of taking an accurate history, as transient visual obscurations and tinnitus correlated with a true IIH diagnosis, and also emphasized the importance of the correct interpretation of imaging, as 3 out of 4 cardinal radiographic features of IIH on MRI [36] correlated with an accurate IIH diagnosis (Table 1).

A combined case series of two patients and literature review of 25 patients who were initially misdiagnosed with Bells palsy [37] found that alternative etiologies of facial nerve paralysis, including multiple cranial neuropathies, may be missed. Factors associated with misdiagnosis included misinterpretation of history, failure to perform or misinterpretation of examination findings, and the underlying diagnosis being a rare disease or unusual presentation. The authors emphasize that inaccurate use of the nomenclature of “Bells palsy”—without confirming that the facial nerve palsy is in fact isolated—could potentially contribute to misdiagnosis, as it implies to downstream providers that a comprehensive work up has been performed to rule out other causes.

Although not designed as a study of misdiagnosis, Zheng et al. [38] described sources of delayed diagnosis in a series of 23 patients who presented with ocular symptoms (such as vision loss, proptosis, and diplopia) and were found to have extra-ocular tumors. Six patients were initially misdiagnosed—three patients with intracranial tumors were initially misdiagnosed as having primary optic atrophy, two patients with choroidal metastases were initially misdiagnosed as having central serous chorioretinopathy and exudative retinal detachment, and one with nasopharyngeal carcinoma was initially misdiagnosed as having optic neuritis. In all six cases, the initial misdiagnosis was noted to have been made by a less experienced, less specialized ophthalmologist, and subsequently corrected by a more experienced specialist. Although identifying the cause of misdiagnosis was not the focus of this study, potential sources of error were discussed, including choice of imaging modality, mild or atypical visual field patterns (only one patient had a typical symmetric homonymous hemianopia due to a suprachiasmatic aneurysm, with 3 patients having monocular hemianopia and 6 patients with incomplete hemianopia, irregular visual field defect or tunnel vision), and the provider lacking specialized knowledge in neuro-ophthalmology.

Avenues for Combating Diagnostic Error

Currently, the best avenue for reducing diagnostic error remains unclear [6, 39–41] (Table 3). Based on existing data about the causes of diagnostic error of neuro-ophthalmic conditions, potential methods to reduce misdiagnosis include improving providers’ ability to gather a complete history and perform a complete and accurate physical examination to rule out serious diagnoses, in particular performing a thorough pupillary examination prior to dilation and improving ophthalmoscopy skills, providing radiologists with salient clinical information to emphasize specific areas to focus on, appropriate use of visual field testing and optical coherence tomography, expanding access to specialized providers such

as neuro-ophthalmologists and neurologists, education campaigns targeted at general providers and at the public, and creating institutional protocols for how to approach specific complaints or conditions [11, 12, 29••, 30, 42].

A recent prospective study [43] highlighted the power of gathering a history. An attending neuro-ophthalmologist was able to identify the correct diagnosis in 88% of 115 consecutive patients presenting to an outpatient neuro-ophthalmology clinic based on history and chief complaint alone. (Each patient subsequently underwent an appropriate, full neuro-ophthalmology evaluation to determine the true final diagnosis.) Although this study may not be generalizable, as this was a highly experienced neuro-ophthalmology specialist, it demonstrates the pivotal role of history for correctly diagnosing neuro-ophthalmic conditions.

Although experience improves a clinician’s acumen, there is no established feedback system in place to inform providers of cases they have misdiagnosed, meaning that even over years of experience, learning directly from one’s own misdiagnoses is rare [6, 44, 45], and physicians may have poor insight into whether their diagnoses are accurate [46]. To provide a standardized setting in which providers can, in a sense, learn from experience to avoid diagnostic error, one group has begun to design case-based computer simulations using a library of real patient encounters with systematic, sensory-derived clinical exams, in this case AVERT (Acute Video-oculography for Vertigo in Emergency Rooms for Rapid Triage) [45].

Fundus Photography

Accurate detection of optic disc edema is essential to generate an accurate differential diagnosis and triage patients before referral to neuro-ophthalmology. As discussed above, inaccuracies in the physical examination, including inaccurate assessment for papilledema, has consistently been shown to be an important source of diagnostic error [17, 35]. Many providers, particularly neurologists, primary care providers, and ED providers, need accurate information about whether papilledema is present for optimal medical decision-making. Although ideally direct ophthalmoscopy would be performed in these settings, in practice it is often not attempted, not performed accurately, or the findings are not interpreted correctly [47–51], and in these settings providers may not have access to tools such as dilating drops, indirect ophthalmoscopy, or slit lamp ophthalmoscopy, to improve accurate diagnosis of papilledema. Extensive prior research has demonstrated both the feasibility of incorporating nonmydriatic fundus photography into the ED evaluation, and that it improves detection of relevant findings [48, 49, 52–55], but until recently little was known about its feasibility in other care settings.

Table 3 Studies assessing interventions or technological advances relevant to diagnostic error of neuro-ophthalmic conditions

Authors, Publication Year	Design	Population	Outcome of interest	Summary
Newman-Toker et al., 2017 [6]	Survey	61 safety professionals from US hospitals and health systems	Assessment of awareness, interest, perceived barriers, and interventions to reduce diagnostic error	98% agreed diagnostic error is common, but less than half (40%) of institutions were seeking to address it within the following 6 months. Top perceived barriers to reducing diagnostic errors were lack of awareness, measures, and feedback
Bursztytn et al., 2018 [57•]	Retrospective review	109 patients (206 eyes)	Sensitivity and specificity of nonmydriatic fundus camera for optic disc edema detection	Sensitivity of the photos for detecting optic disc edema versus clinical exam by a neuro-ophthalmologist ranged from 72–92% among 4 graders, with specificity ranging from 82–95%
Bioussé et al., 2020 [65•]	Retrospective review	800 eyes	Comparison between DLS and neuro-ophthalmologists in classification of optic disc appearance (normal, papilledema, other disc abnormalities)	DLS correctly classified 85% of fundus photographs based on optic disc appearance, compared with 84% and 80% by the neuro-ophthalmologists. Sensitivity and specificity was comparable to 2 neuro-ophthalmologists
Bourdon et al., 2020 [73]	Prospective cohort study	500 patients	Effectiveness of teleconsultation to safely triage ophthalmic emergencies	Teleconsultation is effective to triage ophthalmic emergencies, reducing need for physical consultation, with 96% sensitivity and 95% specificity to properly evaluate need for physical consultation and only 1% misdiagnoses that led to delayed care. Neuro-ophthalmic emergencies received care within 1 day, and 7 out of 8 were correctly diagnosed via telemedicine
Irani et al., 2020 [58]	Prospective cross-sectional	206 patients (505 eyes)	Feasibility of using nonmydriatic fundus camera in an outpatient neurology clinic setting, prevalence of clinically relevant findings	It was feasible to obtain high quality photos in a short time (average of 2 min) by an operator with minimal training (15 min). 21% of patients had an abnormal finding, in 73% of cases neurologically relevant. When provider did not request photos, 20% of patients had an abnormal finding
Liu et al., 2020 [64•]	Retrospective review	576 eyes	Detection of disc laterality by DLS	DLS detected disc lateral with sensitivity of 96% and specificity of 98%, even for eyes with abnormal optic discs
Sharma et al., 2020 [59]	Prospective cohort	79 patients	Association of fundus abnormalities and clinical outcomes in acute SAH	Fundus abnormalities were not found to be an independent predictor of clinical outcomes
Kohli et al., 2021 [60]	Prospective	49 patients	Sensitivity and specificity of OUS to differentiate papilledema from pseudopapilledema	Ocular ultrasound was 68% sensitive for papilledema and 54% specific for pseudopapilledema
Vasseneix et al., 2021 [66]	Retrospective review	965 patients (2103 eyes)	Accuracy of DLS for classification of severity of papilledema	DLS had a high rate of accuracy (84%), sensitivity (91%), and specificity (73%) when classifying severity of papilledema based on fundus photos, comparable to 3 neuro-ophthalmologists

Table 3 (continued)

Authors, Publication Year	Design	Population	Outcome of interest	Summary
Conway et al., 2021 [70•]	Retrospective survey	159 patients	Patient satisfaction, challenges, and comfort, and physician's ability to gather clinical information via telemedicine visit during COVID-19 pandemic	Most (87%) of neuro-ophthalmologists surveyed reported having performed an examination that provided enough information for medical decision-making, but certain examination elements were limited. Most patient (65%) were satisfied with the visit

US United States. DLS deep learning system. min minutes. photos photographs. SAH subarachnoid hemorrhage. OUS ocular ultrasound. COVID-19 coronavirus disease 2019

Bursztyn et al. [56•] demonstrated that a handheld non-mydratic camera does not require extensive training, can be operated by a provider without previous training or prior experience as an ophthalmic photographer (in the study, a medical assistant, optometrist, and resident), and can produce high quality photographs with high sensitivity for detecting optic disc edema when interpreted by fellowship-trained neuro-ophthalmologists. The full clinical examination by a neuro-ophthalmologist was used as the standard for a diagnosis of true optic disc edema. The overall sensitivity of the photographs for detection of papilledema ranged from 71.8 to 92.2% among four graders. There were few photographs (0–8.3% per grader) that were considered ungradable, with some variation among graders, and none were thought to be ungradable by all graders. This is a promising avenue for expanding access to neuro-ophthalmology, as obtaining good-quality photographs did not require specialized training. However, in the study, the photographs were interpreted by fellowship-trained neuro-ophthalmologists, which may not be feasible in all practice settings.

Irani et al. [57•] evaluated the feasibility of incorporating nonmydratic fundus photography into an outpatient neurology clinic. A neurologist who had received just 15 min of training with the camera obtained 505 nonmydratic fundus photographs in 206 patients, and found that the vast majority (91%) were high quality, allowing for exclusion of subtle optic nerve and posterior pole abnormalities when graded by fellowship-trained neuro-ophthalmologists. Photographs were obtained quickly (requiring 2 min on average) with an overall high rating of ease, comfort, and speed by patients. The most common chief complaint was headache (74%), followed by known multiple sclerosis (14%), and idiopathic intracranial hypertension (IIH) (5%). Twenty-one percent of patients had an abnormal finding in at least one eye, 73% of which were neurologically relevant (optic disc pallor, edema, or drusen). The treating neurologist had the option to request photographs to incorporate into their clinical decision-making, but notably there were abnormalities found in $\geq 20\%$ of cases whether or not providers had requested the photographs. When requested, 24% had abnormal findings, and when not requested, 20% had abnormal findings. When photographs were not requested, around half also did not have a direct ophthalmoscope examination documented, and when documented, only 22% of abnormal findings had been correctly identified. Twelve of the 13 treating neurologists agreed that optic disc assessment is essential to the neurological exam, with about half citing high confidence in their ability to detect relevant abnormalities via direct ophthalmoscopy. Notably, all preferred the non-mydratic fundus photographs over direct ophthalmoscopy at the end of the study.

Sharma et al. [58] prospectively examined the use of fundus photography in the neurological intensive care unit.

In 79 patients with acute subarachnoid hemorrhage, fundus photographs were assessed for association between fundus abnormalities and poor outcome, length of neurological intensive care unit (ICU) stay, and hospital admission length. Twenty-nine had fundus abnormalities; 20 had intraocular hemorrhage. They found a significant association between intraocular hemorrhage and length of ICU stay, but not poor clinical outcome, and fundus photography in the intensive care unit was not found to outperform subarachnoid hemorrhage-specific clinical metrics already in use.

Ocular Ultrasound

A prospective study [59] evaluating the sensitivity and specificity of ocular ultrasound (OUS) called attention to the potential limitations of ocular ultrasound for differentiating papilledema from pseudopapilledema. Kohli et al. used an optic nerve sheath width of over 3.3 mm and a decrease of the optic nerve sheath width by 10% on abduction of the eye by at least 30° to define a positive OUS. The authors found OUS to be 68% sensitive and 54% specific for detecting papilledema versus pseudopapilledema. Notably, this was less sensitive and specific than previous studies showing 85–90% sensitivity and 63–79% specificity [60, 61]. The difference is likely due to how the investigators defined true papilledema—Kohli et al. defined a true diagnosis of papilledema as a change in optic disc appearance on fundus photographs between initial and follow-up visit, as evaluated by a masked neuro-ophthalmologist, with the intention of reducing bias. In contrast, the prior studies [60, 61] defined true papilledema using the full clinical impression. Overall, isolated use of ocular ultrasound may not be sufficient for accurate diagnosis of optic disc edema. For example, Carter et al. found 10% of patients with symptomatic papilledema had normal optic nerve sheath width, and Kohli et al. found that around 33% of patients with true papilledema had a negative OUS. Accurate diagnosis is likely best achieved through use of the full clinical picture.

Artificial Intelligence

Use of artificial intelligence is another potential avenue for combating diagnostic error [62]. Liu et al. [63•] developed a deep learning system (DLS) that could detect eye laterality with a high accuracy (98.78%), in photographs with various neuro-ophthalmic conditions, including congenital anomalies of the optic disc, optic disc hypoplasia, optic disc drusen, optic disc infiltration, morning glory disc, nonglaucomatous cupping, papilledema, tilted disc, optic atrophy, anterior ischemic optic neuropathy, compressive optic neuropathy, toxic optic neuropathy, hereditary optic neuropathy, and optic nerve sheath meningioma, suggesting a proof of concept that it could perform well in a neuro-ophthalmology

context, especially as blurred disc margins did not significantly affect accuracy. Biousse et al. [64•] compared the diagnostic performance of artificial intelligence deep learning—using the Brain and Optic Nerve Study with Artificial Intelligence (BONSAI) DLS—versus neuro-ophthalmologists in assessing optic disc appearance (normal disc, papilledema, and other disc abnormalities) on ocular fundus photographs, and found that the accuracy, sensitivity, and specificity of the DLS was similar or better than two neuro-ophthalmology experts. Most recently, Vasseneix et al. [65•] evaluated the ability of a DLS to specifically classify the severity of papilledema against three neuro-ophthalmologists, and found that the DLS had high rates of accuracy, sensitivity, and specificity (84%, 92%, and 74%, respectively), comparable with the neuro-ophthalmologists, and found a higher agreement score between the DLS and neuro-ophthalmologist than among the three neuro-ophthalmologists themselves.

Telemedicine

The advent of telemedicine also provides potential opportunities to improve access to neuro-ophthalmology [66]. Prior to the onset of the coronavirus disease 2019 (COVID-19) pandemic, studies had demonstrated both the breadth of potential uses of telemedicine within the field of ophthalmology [67] and that telemedicine could be used to appropriately triage ophthalmic emergencies [68]. After the onset of the COVID-19 pandemic, the use of telemedicine in ophthalmology in general [69], as well as neuro-ophthalmology specifically [70•, 71], expanded due to sudden necessity. So far, available data suggest that it is safe and sustainable [69, 72••]. A prospective study [72••] examining the first 500 patients requesting emergency teleconsultation during the beginning of the COVID-19 lockdown in France demonstrated that teleconsultation can effectively manage ophthalmic emergencies. Eight of the 500 (1.6%) patients had a neuro-ophthalmic emergency, with less than a day of average delay from symptom onset to teleconsultation. All eight patients were referred to the nearest tertiary care center for physical consultation, and all but one was confirmed to have had the correct diagnosis identified via teleconsultation. Challenges of using telemedicine in neuro-ophthalmology have been noted to include technological challenges for both the patient and the provider, inability to perform IOP checks, inability to assess some of the more subtle aspects of the extra-ocular motility examination, and inability to perform fundusoscopic examinations [66, 69, 70•]. Overall, telemedicine has the potential to expand access to neuro-ophthalmic consultation even outside the specific circumstances of the COVID-19 pandemic [66], which has the potential to improve diagnosis of neuro-ophthalmic conditions through more effective and accessible triage.

Conclusions

Misdiagnosis is prevalent and leads to preventable patient harm, but so far there is limited data characterizing patient harm due to diagnostic error of neuro-ophthalmic conditions. Recent studies have documented patient harm in misdiagnosed patients [19••, 28•], and showed that the harm may be largely preventable by earlier access to neuro-ophthalmology.

To combat diagnostic error of neuro-ophthalmic conditions, improving access to trained subspecialists and neuro-ophthalmology consultation by incentivizing and producing more neuro-ophthalmologists would be ideal [73]. The growth of telehealth in the setting of the COVID-19 pandemic provides a nontraditional avenue for improving patient access to subspecialty trained neuro-ophthalmologists. Additionally, educational campaigns and institutional protocols to address common diagnostic process errors has the potential to improve care, and creating alternative avenues for outside specialties to obtain vital clinical data may improve diagnosis of neuro-ophthalmic conditions. Access to technology such as nonmydriatic fundus photography (fundus photographs that can be quickly and easily taken in the ED or an outpatient setting) and artificial intelligence augmented by deep learning are potential avenues to improve diagnosis of neuro-ophthalmic conditions in areas with limited access to neuro-ophthalmologists. Finally, development of standardized methods of improving physicians' diagnostic skills, such as case-based learning incorporated with real patient scenarios, has the potential to address diagnostic error throughout medicine. Of course, reducing misdiagnosis is not limited to the use of new technologies. Obtaining a proper history and clinical examination have consistently been shown to be a factor in accurate diagnosis.

Further studies investigating harm due to misdiagnosis of additional neuro-ophthalmic conditions are needed, both to improve awareness and identify potential avenues of improvement. Additional studies will better establish the rate of patient harm due to misdiagnosis of neuro-ophthalmic conditions, and direct appropriate interventions and allocation of resources. Studies measuring the financial costs of diagnostic error of neuro-ophthalmic conditions may also demonstrate potential benefits of improving access to neuro-ophthalmology.

Declarations

Conflict of Interest The author/s do/es not have existing conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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