

Neuroradiological Correlates of Abnormal Pupillary Light Reflex Findings Among Patients in the Neuroscience Intensive Care Unit

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ABSTRACT

BACKGROUND: Changes in pupil reactivity secondary to cerebral mass effect are traditionally linked to compression of the oculomotor nerve by the uncus or by horizontal midbrain displacement. The neurological pupil index (NPI) is a metric to assess the pupillary light reflex. This study explores the relationship of midline shift, cisternal, and sulcal effacement or ventricular compression in patients with a new finding of abnormal pupillary light reflex. **METHODS:** This retrospective study identified adult patients with serial pupillometer readings between 2018 and 2023 who had a baseline head computed tomography (CT) scan, subsequent new-onset NPI worsening from normal to abnormal, and a repeat CT scan within 2 hours of the NPI changes. Those with NPI worsening were compared with those with no NPI change. **RESULTS:** Among 77 patients (27 with NPI worsening, 50 without), those with NPI worsening exhibited a higher incidence of midline shift on the repeat CT. Regression models revealed a significant correlation between midline shift change and abnormal NPI ($r = 0.2260$, $P < .001$). However, NPI worsening was not linked to changes in ventricular compression, nor sulcal or cisternal effacement. **CONCLUSION:** Midline shift, rather than cisternal or sulcal effacement, is associated with abnormal NPI values.

Keywords: cisternal effacement, hydrocephalus, midline shift, neuroscience ICU, pupil metrics, uncal herniation

The assessment of pupil size and light reflex mechanisms is a critical portion of the evaluation and treatment of patients in neuroscience intensive care units (NSICUs) globally.¹ Serial monitoring of pupil metrics in patients with neurological injury is typically performed by frontline nurses and provides clinically relevant information.^{2,3} In the NSICU, this ongoing assessment is vital for the early identification of neurological deterioration.⁴⁻⁷ Serial monitoring of pupil reactivity and size by nurses can detect subtle changes that may indicate worsening intracranial

pressure or other neurological emergencies, allowing for timely interventions that can be lifesaving.⁸ Subjective manual assessment of the pupillary light reflex (PLR) with a flashlight has high variability and can lead to error.⁹ In contrast, quantitative pupillometry (QP) provides objective serial measurements with high reliability using a standardized light stimulus.⁴ Nurses using QP can enhance assessment accuracy and promote early intervention as a vital part of the multidisciplinary team. The use of QP reduces interobserver variability and enhances the precision of neurological assessments, which is critical in the NSICU.

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A normal PLR requires intact signal transduction via the afferent and efferent fibers, including proper nuclear and internuclear communication in the pupillary light pathway.¹ Early clinical observations and experimental studies in the 19th century led to the conclusion that a light-fixed and dilated pupil indicated an expanding intracranial process or raised intracranial pressure.¹⁰ In the last century, emphasis was placed on the role of medial temporal lobe (uncal) herniation compressing the oculomotor nerve as the cause of pupil dilation.^{10–12} However, with the advent of computed tomography (CT), recent studies conclude that horizontal displacement of the midbrain—rather than uncal herniation—seemed to be associated with abnormal PLR findings.^{13,14}

Providing nurses with tools to identify the presence and degree of mass effect may guide determination of the need for transporting patients to obtain confirmatory imaging to guide management.^{15,16} Previous studies examining the relationship of neurological pupil index (NPi) values with radiological findings on a CT scan lack a control population.^{17,18} Using registry data, this retrospective study analyzes and compares radiographic findings among patients with an abnormal change in NPi with those among patients without an abnormal NPi change.^{19,20}

Methods

This study used a retrospective design to identify cases and controls among patients admitted to a single medical center's NSICU, using pupil data obtained from an international registry that has been approved by the institutional review board. The data collection processes and collection of pupil readings have been previously detailed.²¹ This analysis was conducted only on patients admitted to the NSICU at a tertiary medical center in the Southwestern United States because CT scans from other centers in the registry were not available. We identified patients with a normal NPi on admission who had at least 2 head CT scans 6 hours apart, with QP readings associated with each head CT. Patients without a baseline head CT upon admission or without a second CT scan obtained <2 hours after recording an abnormal NPi were excluded. The intervention cohort was those with a change in NPi who had both a baseline CT scan and a second CT conducted ≤2 hours after the NPi change was detected. Controls were those with a baseline head CT on admission and a subsequent CT scan but no change in NPi values associated with either CT scan.

We reviewed radiographic images for differences in the degree of midline shift, cisternal and sulcal effacement, and changes in ventricular size. All scans were reviewed by a radiologist and reported in the medical record. For this study, all imaging studies in the axial and coronal planes were also reviewed by 2

individual investigators (J.L.M. and V.A.) using a standardized protocol. The lateral shift of the septum pellucidum and pineal gland was measured using the Philips IntelliSpace enterprise software (Philips Healthcare). The presence of ventricular, sulcal, or basal cisternal effacement and the side of effacement were noted. Effacement of the perimesencephalic cistern was used to identify uncal herniation.

Statistical analyses were performed with SAS v9.4 for Windows (SAS Institute). Baseline characteristics were reported as frequency (percentage) for nominal and ordinal data, and as mean (standard deviation) for continuous data. To compute whether there was a difference in midline shift in patients who had an NPi change versus those who did not, we conducted a χ^2 analysis to see whether there was a difference in worsening of midline shift between the 2 groups. We repeated this analysis if there was a difference in either group to a midline shift of the pineal gland of 3 to 6, 3 to 8, or ≥8 mm, or a midline shift of the septum pellucidum to 3 to 8, 8 to 13, or ≥13 mm. These thresholds were chosen because they have been shown to correlate with level of sensorium (drowsy, stupor, and coma).²² Finally, we used a mixed model regression analysis controlling for age, sex, race, and diagnosis to identify an association between the change in NPi and the change in midline shift. A subanalysis was also conducted to see whether there was an association with ipsilateral or contralateral NPi changes for both a right- and left-sided midline shift using a mixed effect linear regression model. A McNemar test was conducted to compare the presence of basal cistern, ventricular, and sulcal effacement in each group. Throughout the study, the type I error was maintained at 5%. Among the patients who had a change in NPi, we used a paired *t* test to compare their Glasgow Coma Scale (GCS) scores before and after the NPi change, and a mixed effect linear regression model to assess the correlation between NPi change and GCS scores.

Results

Of 77 patients meeting inclusion criteria, 50 had no change in NPi and 27 had either a unilateral or bilateral change in NPi to a value < 3.0 (abnormal pupil response). The patients had a mean age of 60.8 (17.7) years, 41 (53.3%) were male, 51 (66.2%) were White, and 71 (92.2%) were non-Hispanic (Table 1). Comparison of patients based upon the degree of midline shift showed a greater degree of midline shift on the second CT for patients with an NPi change as compared with those without an NPi change (Supplementary Tables 1A and 1B, <http://links.lww.com/JNN/A590>). Among patients who did not have a change in NPi, there were no patients with an increase in midline shift in the second CT compared with the first. However, among patients who went on to manifest an abnormal NPi, 6 patients

TABLE 1. Demographic Data for All Patients

Variable	Level	Overall (N = 77)	Patients With an NPi Change (n = 27)	Patients Without an NPi Change (n = 50)	P
Sex	Male	41 (53.25%)	15 (55.56%)	29 (58.00%)	.3393 ^a
	Female	36 (46.75%)	12 (44.44%)	21 (42.00%)	
Race	Black	13 (16.88%)	5 (18.52%)	8 (16.00%)	.6934 ^a
	Asian	5 (6.49%)	2 (7.41%)	3 (6.00%)	
	White	51 (66.23%)	16 (59.26%)	35 (70.00%)	
	Other/unknown	8 (10.39%)	4 (14.81%)	4 (8.00%)	
Ethnicity	Hispanic	4 (5.19%)	0 (0.00%)	4 (8.00%)	.0470 ^a
	Not Hispanic	71 (92.21%)	25 (92.50%)	46 (92.00%)	
	Unknown	2 (2.60%)	2 (7.41%)	0 (0.00%)	
Age	Years ^b	60.78 (17.68)	55.55 (16.03)	63.6 (18.04)	.0378 ^c
Diagnosis	Ischemic stroke	29 (37.66%)	6 (22.22%)	23 (46%)	.001 ^a
	Hemorrhagic stroke	19 (24.68%)	10 (37.04%)	9 (18%)	
	Subdural hematoma	5 (6.49%)	3 (11.11%)	2 (4%)	
	Brain tumors	11 (14.29%)	2 (7.41%)	9 (18%)	
	Functional neurosurgery	4 (5.19%)	0 (0%)	4 (8%)	
	Other	9 (11.69%)	6 (22.22%)	3 (6%)	

Abbreviation: NPi, neurological pupil index.

^aFisher exact test.^bMean.^cKruskal-Wallis test.

had worsening of pineal gland shift, and 7 patients had worsening of septum pellucidum shift (Supplementary Tables 1A and 1B, <http://links.lww.com/JNN/A590>). After controlling for age, race, sex, and diagnosis, the regression model identified a significant correlation between change in midline shift and an abnormal NPi ($r = 0.2288$, $P < .001$). Additional regression analysis to examine whether right-sided versus left-sided shifts had any correlation with NPi changes in the ipsilateral eye NPi value indicated no significant correlation ($P > .05$). A similar regression analysis to identify correlations with the contralateral NPi value also indicated no significant correlation ($P > .05$).

Additional investigation of other CT characteristics indicated no significant differences in the incidence of reported ventricular, sulcal, or cisternal effacement in the group of patients with NPi changes compared with those without. Regression analysis did not indicate a significant correlation between GCS scores and NPi change ($r = 0.14195$, $P = .063$). However, the paired t test did show a significant difference between GCS scores of the eye, verbal, and total score component before and after the NPi change.

Discussion

By investigating the correlation of radiological findings with changes in NPi scores for patients in the

NSICU, our findings support and extend relatively recent views that pupillary changes secondary to expanding supratentorial lesions are more likely due to horizontal displacement and distortion of the midbrain than to mechanical compression of the oculomotor nerve.^{13,22} The ability of nurses to understand this relationship provides for early identification of neurological deterioration and timely escalation of care. Although, previously, uncal herniation was hypothesized as leading to compression or stretching of the extra-axial oculomotor nerve, lateral midbrain displacement and distortion could lead to dysfunction of the fascicular portion of the nerve leading from the Edinger-Westphall nucleus to the point of exit from the midbrain, thus impairing pupillary constriction.¹

Whereas previous studies have addressed dilated and nonreactive pupils secondary to intracranial mass effect,⁸ our study demonstrates that a finding of early pupillary abnormality as manifested by an abnormal NPi is more likely to be due to midbrain displacement. In a study of 204 patients with moderate to severe traumatic brain injury, midline shift, basal cisternal compression, and effacement were all associated with abnormal pupillary reactivity on univariate analysis.²³ However, logistic regression revealed no association between midline shift and PLR changes. Of note, this retrospective study did not use QP, and subjective PLR assessments conducted in the emergency department were recorded as

either normal, unilaterally unreactive, or bilaterally unreactive. The ability to rely on objective QP data rather than subjective assessments is critical in managing these complex patients. A study of the correlation of NPi and midline shift in 134 patients with stroke (94 ischemic and 40 hemorrhagic) found a significant correlation between horizontal shift of the septum pellucidum and NPi.¹⁷ The correlation between NPi and midline shift in patients with hemorrhagic stroke was confirmed in another series of 44 patients with cerebral hemorrhage. Others found no significant associations between pupil reactivity and radiographic markers of shift in a small series of 53 patients.¹⁴ However, there are potentially important relationships for the difference between right and left NPi change and the shift of septum pellucidum or pineal gland in patients with ischemic stroke.²⁴

None of these previous studies included a control sample of patients who did not have changes in NPi; therefore, it is difficult to accurately draw a conclusion between the relationship of NPi and midline shift from these studies. Our study benefits from including a control sample of patients who had 2 successive CT scans and various degrees of midline shift. We found that there was a significantly higher degree of midline shift in patients with an abnormal NPi compared with those with a normal NPi. In addition, other common radiographic findings such as cisternal effacement, and ventricular or sulcal effacement, which have not been thoroughly evaluated in the setting of NPi changes, were analyzed here to characterize further associations between CT findings and abnormal NPi values. We found that midline shift, but not the other markers of brain compression, had a significant correlation with an abnormal NPi.

We found that there are significant associations between the septum pellucidum and pineal gland midline shift and abnormal NPi values that can be detected by serial nursing assessment of QP. We identified a greater degree of midline shift on the second CT compared with baseline CT imaging in patients with NPi values < 3.0. This is consistent with previous studies that have indicated a correlation with midline shift and change in pupil reactivity.^{4,5} However, we found no associations between ipsilateral and contralateral NPi values and midline shift. The inability to provide a significant correlation with ipsilateral versus contralateral shift is consistent with a study that investigated midline shift in patients with intracranial hemorrhage.¹⁸ Our results support the hypothesis that objective measures of pupillary reactivity correlate with displacement of cerebral structures and can be a helpful indicator of worsening intracerebral pathology.

Cerebral edema resulting from various forms of brain injury can exert a mass effect that leads to midline structure displacement.²⁵ Midline shift has an association with worse patient outcomes,²² altered consciousness,²⁶

and neurological deterioration,²⁷ all conditions that neuroscience nurses monitor during their daily practice. Neuroimaging is critical for the assessment and early intervention of patients at risk for secondary brain injury.²⁸ However, patient transport is time consuming, requiring significant nursing coordination for critically ill patients, and has a potential risk for secondary injury to the patient.¹⁶ Recent research has focused on identifying noninvasive neuromonitoring tools, and the integration of QP in clinical practice may benefit neuroscience nursing by offering a noninvasive tool to monitor changes in midline shift and pupillary reactivity. Previous research showcased the positive mindset toward adopting QP in NSICU by patient care technicians and nurses.²⁹ Early identification of worsening conditions through QP can enhance timely intervention and improve patient outcomes for patients with neurological injury. Adopting advanced monitoring techniques provides neuroscience nurses an opportunity to provide more accurate, timely, and efficient care, ultimately improving the quality of patient management and enhancing recovery trajectories.³⁰

Limitations

A primary limitation is that all subjects were from a single hospital in the United States. In addition, the retrospective nature of this study and the limited ability to pair pupil data with CT scans within 2 hours of the pupil change reduced the total number of enrolled subjects. Because of the small sample size, it was also not possible to accurately match patients with controls for age, sex, diagnosis, and degree of midline shift on baseline CT scan. However, this must be balanced against the benefit of identifying a control group. Our data set also consists of patients with heterogeneous pathologies leading to midline shift, for which different interventions may have been conducted. These interventions could potentially influence midline shift in our study cohort. Because of the small sample size, varied pathology, and the retrospective nature of the study, we did not correct for potential confounders such as lesion volume and the use of osmotic agents. Finally, we only studied NPi and not other QP markers such as constriction and dilation velocity, absolute pupil size, and right-to-left NPi difference.

Conclusion

There is an association between midline shift and a change in NPi from normal to abnormal. Nurses recognizing the risk of midline shift through QP is essential in guiding clinical decisions that may prevent further deterioration. However, we did not find an association of a worsening NPi with ventricular compression, and sulcal or cisternal effacement. These results suggest that QP may prove to be a helpful tool for nurses to monitor worsening midline shift and support the hypothesis that pupillary changes due to expanding intracranial lesions are

more likely secondary to horizontal shift of the midbrain and distortion of the fascicular oculomotor fibers rather than mechanical compression of the oculomotor nerve by uncus herniation. Further research with larger sample sizes and prospective designs will be valuable in solidifying the role of pupil metrics in guiding earlier interventions to prevent worsening midline shift in critically ill patients.

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