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Research paper

Investigating the association between eye colour and the Neurological Pupil index

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ABSTRACT

Introduction: Brown or dark brown eyes make it difficult to distinguish the contrast between a black pupil and the surrounding iris, which may result in clinical assessment errors. The pupillometer can be used to derive an indexed value, the Neurological Pupil index™ (NPi) for pupillary light reflex. However, there are limited data associating the NPi and iris colour. We examine the NPi and eye colour association.
Methods: Data were pooled from the Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care (END-PANIC) Registry. The analysis includes 14,168 observations collected from 865 patients with neurological conditions who were admitted to the intensive care unit. Summary statistics and statistical models were developed to examine the association using Statistical Analysis Software (SAS) summary procedure.
Results: The mean age of the cohort was 56 years (standard deviation = 17). Eye colour included dark brown (n = 339), blue (n = 234), brown (n = 173), green (n = 82), and other (n = 37). There was significant differences ($p < 0.0001$) between mean NPi values by eye colour [blue = 4.08 (0.92), brown = 3.34 (1.45), dark = 3.71 (1.33), green = 4.08 (0.67), other = 3.76 (1.25)]. However, a further random-effects mixed model after controlling for confounding variables revealed no significant difference in NPi values among different eye colour groups.
Conclusions: The pupillary light reflex, when assessed using the pupillometer, is not dependent on the eye colour. Practitioners are not required to consider eye colour as a confounder when they perform pupillary assessment for examining patients with neurological conditions.

1. Introduction

Practioners routinely assess the pupillary light reflex (PLR) when assessing patients and evaluating for neurologic injury.[1,2] Assessment of the PLR in patients with acute brain injury has been historically performed using a penlight or flashlight.[3–5] Using this method, the PLR is classified as brisk, sluggish, or nonreactive (fixed).[6] However, subjective PLR assessment is unreliable, and this method is prone to inaccuracy in measurement[7] and poor inter-examiner reliability.[8,9] Automated hand-held pupillometry provides objective and reproducible measures for pupil size, constriction and dilation velocities, and latency.[10,11] The NeurOptics NPi®-200 (NeurOptics Inc., Irvine CA USA) is a commercially available pupillometer used in multiple clinical settings to provide an objective score for assessing pupillary reactivity.[11,12] This

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pupillometer also uses a proprietary algorithm to derive an indexed value called Neurological Pupil index™ (NPi), grading the pupil assessment on a scale of 0–5, in which NPi < 3 is considered abnormal and an NPi value greater than or equal to 3 is considered normal.[13] The parameters of the NPi algorithm includes pupil size, constriction velocity, dilation velocity, and latency.[13,14]

Automated pupillometry technology is becoming increasingly incorporated as a standard in clinical practice in neuroscience, neurosurgical, and neurocritical care practices across the globe.[12,15–17] As such, it is important to examine the impact of different variables on the NPi. The colour of the iris is one such variable that has been reported in a few studies to influence pupil size reactivity.[18,19] Historically, pupil size was considered to be larger in blue eyes than in dark eyes;[20] however, these findings were questioned when still photography was used to measure pupil size,[21] leading the authors to suspect that subjective assessment (penlight or flashlight) may have resulted in difficulty of in precisely identifying the pupil margin for individuals with brown or dark brown eyes.[21] However, others have not found the size of the pupil to be affected by the colour of the iris.[22] To our knowledge, the association between the NPi and iris colour has not been previously studied. Therefore, in this study, we examined the association between the NPi (PLR) and iris colour (eye colour).

2. Background

Quantifying the PLR is particularly important for patients with neurological disorders because changes in pupil size and reactivity to light can be a marker for a neurologic deficit. Modern neurological imaging such as brain computerised tomography (CT) scan can detect cerebral oedema but cannot be performed very frequently because of cost, radiation exposure, and the risks associated with patient transport.[23,24] Quantitative pupillometry is a noninvasive procedure that is being adopted in hospitals all over the world.[25] It can be used to serially monitor the PLR and serve as an early indicator of worsening intracranial dynamic such as uncal herniation of increasing intracranial pressure. Moreover, pupillary assessment is inexpensive compared with other expensive techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans.

The PLR examines the functional status of two cranial nerves: the optic nerve (CN-II) and oculomotor nerve (CN-III). The PLR is considered an important noninvasive assessment of the neurological condition of CN-II and CN-III.[26] Dysfunction of the PLR is linked to horizontal or vertical shift of the intracranial structures and increased risk of central brain herniation with or without increased intracranial pressure (ICP).[27] When light enters the pupil, it is converted to an electrical signal at the retina. This signal is carried along afferent axons through the pretectum to the Edinger–Westphal nucleus (EWN), which propagates an efferent parasympathetic signal along bilateral CN-III axons and initiates constriction of the pupil.[27–29]

Manual pupillary assessment, using a penlight, has been a mainstay for physicians and nurses despite limited interrater reliability. This limited reliability is partially attributed to external factors such as ambient lighting conditions, disparate levels of experience and skills among practitioners, and different visual acuity.[30,31] Clinicians have reported that darker eye colours are notoriously more difficult to assess and may increase the chances of an unreliable pupil reading. Previous research has shown that darker pupils have a greater contraction velocity (CV) than lighter coloured eyes.[18] Pupillometry is considered a reliable method to assess patients' pupils through NPi readings, independent of eye colour, but objective data in this area are lacking. More specifically, the automated pupillometer uses infrared technology and should be suitable even for patients with dark eye colours. The aim of this analysis is to investigate the association between NPi values and eye colour.

3. Methods

Data were pooled from the Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care (END-PANIC) registry.[32] The END-PANIC registry is a multicentre prospective registry of all pupillary readings of patients admitted to the intensive care units because of specific neurological conditions such as traumatic brain injury (TBI), acute ischaemic stroke (AIS), brain tumour, hemorrhagic stroke, spinal injury, and other neurological injury. This registry has four data collection sites located in California, Ohio, Texas, and Pennsylvania. Data from each site are shared with investigators from the University of Texas Southwestern Medical Center which is the primary coordinating centre for this registry. The methods of the END-PANIC registry were described in detail previously.[32]

The study was conducted following institutional review board (IRB) regulations. The END-PANIC registry contains data on more than 2500 individuals. Only individuals with documented eye colour were included in this planned secondary analysis. This analysis includes 14 168 observations collected from 865 patients who were admitted to the intensive care unit at one of the collaborating centres. All individuals were admitted with a neurological or neurosurgical diagnosis. Statistical analysis was performed using the SAS, version 9.4 (SAS Institute, Cary NC, USA), for Windows. This project is funded by NeurOptics, Inc., with grant number NCT02804438.

3.1. Statistical analysis

Frequencies and percentages were used to describe demographic data obtained at baseline: age, sex, race, Glasgow Coma Scale (GCS), primary diagnosis, and eye colour. Primary diagnosis was categorised as TBI, acute ischaemic stroke (AIS), haemorrhagic stroke, brain tumour (neoplasm), spinal injury, and other. Eye colour was scored as blue, brown, dark brown, green, and other. The dependent variable NPi and PLR data were analysed as continuous variables.

Summary statistics and statistical models were developed using SAS PROC summary to estimate the mean NPi and other PLR values (e.g., constriction velocity, latency, size) by eye colour while taking into consideration the repeated nature and clustering of the data. Statistical models were developed with age dichotomised as <65 or ≥65 years; race dichotomised as Caucasian or other, and GCS score as mild (GCS score = 13–15), moderate (GCS score = 9–12), or severe (GCS score = 3–8). A random-effects model (mixed model) without controlling for confounders was first constructed to explore for differences in the NPi and PLR readings by eye colour. Finally, similar mixed models were constructed while controlling for other variables; age, race, gender, GCS score, and primary diagnosis that were hypothesised to affect the outcome. In this model, we have determined a specific category within each confounding variable as a reference: other for primary diagnosis, mild for GCS score, other for race (after dichotomising race into Caucasian or other), and blue for eye colour.

4. Results

Demographics from the 865 individuals are provided in Table 1. The mean age was 56 years (standard deviation = 17); of these, 558 (64.51%) aged <65 years. A total of 433 (50.06%) were female, 587 (67.86%) were Caucasian, 165 (19.08%) African American, 31 (3.58%)

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Table 1
Descriptive statistics.

Variable	N (%)
Age	
Less than 65 years	558 (64.51%)
65 years or older	307 (35.49%)
Sex	
Female	433 (50.06%)
Male	432 (49.94%)
Race	
Caucasian	587 (67.86%)
African American	165 (19.08%)
Asian	31 (3.58%)
Other	51 (5.9%)
Missing	31 (3.58%)
Eye colour	
Blue	234 (27.05%)
Brown	173 (20.00%)
Dark brown	339 (39.19%)
Green	82 (9.48%)
Other	37 (4.28%)
Glasgow Coma Scale	
Severe	124 (14.34%)
Moderate	116 (13.41%)
Mild	621 (71.79%)
Missing	4 (0.46%)
Primary diagnosis	
Traumatic brain injury	3 (0.35%)
Acute ischaemic stroke	155 (17.92%)
Haemorrhagic stroke	194 (22.43%)
Tumour (neoplasm)	223 (25.78%)
Spinal injury	31 (3.58%)
Other	199 (23%)
Missing	60 (6.94%)

Asian, 51 (5.9%) other, and 31 did not report race. Eye colour included blue (n = 234, 27.05%), brown (n = 173, 20%), dark brown (n = 339, 39.19%), green (n = 82, 9.48%), and other (n = 37, 4.28%). The GCS scores were primarily classified as mild (n = 621, 71.79%), followed by moderate (n = 116, 13.41%) and severe (n = 124, 14.34%). Primary diagnosis included neoplasm (n = 223, 25.78%), haemorrhagic stroke (n = 194, 22.43%), AIS (n = 155, 17.92%), spinal injury (n = 31, 3.58%), and TBI (n = 3, 0.35%).

There were 14,168 paired PLR readings obtained from the 865 individuals. The readings for the left and right eyes were combined to give 28,336 observations, taking into consideration the repeated nature of the data. As shown in Table 2, the NPi values (mean, standard deviation) by eye colour for blue (4.08, 0.92), brown (3.34, 1.45), dark brown (3.71, 1.33), green (4.08, 0.67), and other (3.76, 1.25) had statistically significant difference ($p < 0.0001$). Similarly, we estimated other clinically relevant PLR values (latency, constriction velocity, size, dilation velocity) by eye colour (Table 2).

A random-effects mixed model indicated a significant difference in pupil size by eye colour ($p < 0.0001$), with a similar p-value ($p < 0.0001$) for constriction velocity, dilation velocity, and latency values by eye colour as well. However, a further random-effects mixed model after controlling for confounding variables (age, gender, race, GCS score, and primary diagnosis) reveals no significant difference in NPi values among different eye colour groups ($p > 0.05$). Table 3 provides estimates from models constructed to examine clinically associations. The effect of severe brain injury (GCS score of 3–8) versus mild brain injury (GCS score of 9–12) was significant (standard error: -0.51; $p < 0.0001$); however, no other confounding variables were found to be statistically significant.

5. Discussion

This is the largest known sample of critically ill patients to include eye colour as a variable of interest. The finding of no association between PLR and eye colour contributes significantly to clarify conflicting conclusions from prior studies. In 1994, Winn et al.[22] found that age, but not eye colour, predicted PLR change in size. A 1998 study of healthy volunteers found that CV, but not size or latency, was influenced by eye colour.[18] Few studies examined the association between eye colour and ocular diseases such as cataract, myopia, and intraocular pressure.[33–35] Therefore, before these results, it may have been considered clinically relevant to attend to eye colour when examining patients with neurological conditions.

The results from our study are consistent with those from the study by Winn et al.[22] and Bradely et al.[19] that the NPi is not associated with different eye colours. However, Bergamin et al.[18] found that eye colour is correlated with pupillary contraction and redilation velocities as they were greater in brown colour eyes. That study suggested that eye colour might be considered during pupillary assessment.[18] However, the study had 50 individuals and it compared two eye colour groups only, blue vs brown, and they used a specific software algorithm to measure the pupil response, while our study includes 865 patients and we used NeurOptics NPi® 200-pupillometer (NeurOptics Inc., Irvine CA USA) to measure the PLR which is increasingly being incorporated in routine clinical practice in neurological and neurosurgical intensive care units.

To fully explore the data, we examined common clinical variables and subject attributes. Given that pupil size and amplitude of pupillary light constriction decreases in elderly patients,[22,28,36,37] age was controlled in the multivariate mixed model as a confounder. We also controlled for gender as the association of gender and pupillary light reflex is controversial.[19,22,38] A few studies have examined the association between eye colour and the PLR. Most of those reports examined this association in a dark-adapted status.[18,19] One of the limitations of dark-adapted pupil diameter (DAPD) is that in clinical practice, one does not usually examine DAPD. In addition, ocular tonic and resting accommodations are not the same for individuals in the dark and they are changing with age.[39] Furthermore, studying the effect of eye colour on the PLR was not detailed in those studies and the size of subjects was small.[18,22] Only one study used the NeurOptics pupillometer device.[19]

Table 2
Pupillary light reflex values[a] by eye colour.

Variable (unit)	Eye colour					
	Blue mean (SD)	Brown mean (SD)	Dark mean (SD)	Green mean (SD)	Other mean (SD)	P-value
NPi (0–5)	4.08 (0.92)	3.34 (1.45)	3.71 (1.33)	4.08 (0.67)	3.76 (1.25)	<0.0001
Pupil size (mm)	3.55 (1.11)	3.91 (1.33)	3.81 (1.31)	3.63 (1.04)	4.24 (1.18)	<0.0001
Constriction velocity (mm/s)	1.63 (0.8)	1.53 (0.96)	1.73 (0.95)	1.60 (0.85)	2.02 (1.03)	<0.0001
Dilation velocity (mm/s)	0.70 (0.36)	0.66 (0.45)	0.80 (0.43)	0.70 (0.39)	0.91 (0.49)	<0.0001
Latency (seconds)	0.27 (0.11)	0.27 (0.07)	0.26 (0.07)	0.25 (0.05)	0.26 (0.05)	<0.0001

SD, standard deviation.
[a] Without controlling for age, gender, race, Glasgow Coma Scale and primary diagnosis.

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Table 3
Multivariate mixed model (by NPi).

Variable (effect)	Estimate (SE)	P-value
Eye colour		
Other vs blue	−0.12 (0.14)	0.38
Brown vs blue	−0.07 (0.08)	0.37
Dark brown vs blue	−0.08 (0.07)	0.24
Green vs blue	0.07 (0.10)	0.51
Age		
Less than 65 years vs above or equal to 65 years	−0.02 (0.06)	0.72
Race		
Caucasian vs other	0.01 (0.06)	0.84
Gender		
Male vs female	0.10 (0.05)	0.07
Glasgow Coma Scale		
Severe vs mild	−0.51 (0.08)	<0.0001
Moderate vs mild	−0.15 (0.08)	0.06
Primary diagnosis		
Traumatic brain injury vs other	0.34 (0.43)	0.44
Acute ischaemic stroke vs other	0.07 (0.08)	0.37
Haemorrhagic stroke vs other	−0.002 (0.07)	0.98
Brain tumour vs other	−0.01 (0.07)	0.90
Spinal injury vs other	0.14 (0.14)	0.35

SE, standard error.

6. Limitations

Several medical conditions such as low cardiac output are hypothesised to affect the PLR,[40] and it is a recognised limitation in this study that we did not control for other medical history. However, we did examine primary diagnosis and found no association. In addition, pupillary reflex can be altered by medications that impact the sympathetic and parasympathetic pathways such as opioids leading to fluctuation in pupil size, termed pupillary unrest, dancing pupil, or hippuss.[41] Such medical conditions are considered to be confounders, and they were not controlled for in our study. Another limitation is the subjective categorisation of eye colours. We did not test interobserver and intraobserver reliability in correctly classifying eye colour which may be affected by practitioner's experience. There are many factors that could affect the data analysis related to that matter such as equipment used at our hospital, specific training of our staff, and medications given to our patients that could be different from the ones used in other hospitals. However, we had a large sample size using advanced technology to assess the PLR which can eliminate the effect of those confounders.

7. Conclusion

The PLR, when measured by automated pupillometry, is not dependent on eye colour. Automated pupillometry could be incorporated into routine practice when assessing for neurological change without consideration of eye colour.

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Conflict of interest

F.A., S.S., V.A., and D.M.O. received salary support from NeurOptics Inc., for the research study. S.A-.O. has no conflicts of interest.

CRediT authorship contribution statement

Sameer Al-Obaidi: Conceptualization, Formal analysis, Data curation, Writing - original draft. **Folefac Atem:** Conceptualization, Formal analysis, Data curation, Supervision, Methodology, Writing - review & editing. **Sonja E. Stutzman:** Resources, Writing - original draft, Project administration. **Venkatesh Aiyagari:** Investigation, Writing - review & editing. **DaiWai M. Olson:** Investigation, Conceptualization, Writing - original draft, Supervision, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aucc.2019.10.001.

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