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Original Article

Ophthalmic and Neuroimaging Associations In Optic Nerve Hypoplasia/Septo-Optic-Pituitary Dysplasia

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ABSTRACT: ***Background:*** Optic nerve hypoplasia (ONH) and septo-optic-pituitary dysplasia (SOD) are neurodevelopmental disorders associated with congenital visual impairment. Our aim was to investigate associations between several ophthalmic and neuroimaging features in patients with ONH/SOD. ***Methods:*** A retrospective chart and neuroimaging review was performed in patients with ONH/SOD. Ophthalmic signs (e.g., monocular best-corrected visual acuity [BCVA], nystagmus, and strabismus) and neuroimaging data were extracted and their associations were investigated. ***Results:*** There were 128 patients (70 males) with ONH/SOD who had neuroimaging. Their mean age at the end of the study was 13.2 (*SD*: 7.5) years. Ophthalmic data were available on 102 patients (58 males). BCVA varied from normal to no light perception. There were statistically significant associations between: (A) Reduced optic nerve or chiasm size on neuroimaging and more severely impaired BCVA and (B) laterality of the reduced optic nerve or chiasm size on neuroimaging and laterality of: (1) The eye with reduced BCVA, (2) small optic disc size, and (3) RAPD, if present ($p \leq 0.0002$ each). The presence of symmetrically small optic nerves on MRI was significantly more common in patients with nystagmus than when nystagmus was absent ($N = 96$, 75% vs. 38.6%, $p < 0.0001$). The presence of neuronal migration disorders, their type and laterality were not associated with BCVA and laterality of the reduced BCVA. ***Conclusion:*** The functional and structural associations in ONH are consistent with the impaired visual function that results from the hypoplastic anterior visual pathways. However, these associations were not perfectly concordant making prediction of adult BCVA challenging in these patients.

RÉSUMÉ : Associations observées en ophtalmologie et en neuro-imagerie dans l'hypoplasie du nerf optique et la dysplasie septo-optique accompagnée d'hypopituitarisme. ***Contexte :*** L'hypoplasie du nerf optique (HNO) et la dysplasie septo-optique (DSO) accompagnée d'hypopituitarisme sont des troubles neurodéveloppementaux associés à une déficience visuelle congénitale. L'étude visait à examiner les associations entre différentes caractéristiques ophtalmiques et en neuro-imagerie chez des patients atteints d'HNO et de DSO. ***Méthode :*** L'étude consistait en un examen rétrospectif de dossiers de patients atteints d'HNO et de DSO, et de caractéristiques observées en neuro-imagerie. Il y a d'abord eu une extraction de données sur des signes ophtalmiques (ex. : acuité visuelle corrigée maximale [AVCM) en monoculaire, nystagmus, strabisme) et en neuro-imagerie, puis une analyse d'associations. ***Résultats :*** L'équipe disposait de données en neuro-imagerie sur 128 patients (70 hommes) atteints d'HNO et de DSO. Leur âge moyen à la fin de l'étude était de 13,2 ans (écart-type : 7,5). Quant aux données en ophtalmologie, elles concernaient 102 patients (58 hommes). L'AVCM variait de normale à l'absence de perception de la lumière. Des associations statistiquement significatives ont été établies entre : A) une diminution de la grosseur du nerf optique ou du chiasma optique, observée en neuro-imagerie et le degré de gravité de la diminution de l'AVCM; et B) la latéralité de la diminution de la grosseur du nerf optique ou du chiasma optique, observée en neuro-imagerie et la latéralité : 1) de l'œil ayant une diminution de l'AVCM; 2) de la petite surface de la papille optique; et 3) du déficit pupillaire afférent relatif, si DPAR il y avait ($p \leq 0{,}0002$ chacun). La présence d'une diminution symétrique des nerfs optiques à l'IRM était significativement plus fréquente dans les cas de nystagmus que dans les cas d'absence de nystagmus (N = 96; 75 % contre 38,6 %; $p < 0{,}0001$). Par contre, il n'y avait pas d'association entre la présence de troubles de la migration neuronale, leur type et leur latéralité, et l'AVCM et la latéralité de la diminution de l'AVCM. ***Conclusion :*** Les associations établies entre les structures et leur fonctionnement dans l'HNO sont compatibles avec la déficience visuelle qui résulte de l'hypoplasie des voies visuelles antérieures. Toutefois, la concordance de ces associations n'était tout pas fait parfaite, ce qui rend difficiles les prévisions relatives à l'AVCM à l'âge adulte chez ces patients.

Keywords: Vision; MRI; Pituitary gland; Septum pellucidum; Neuronal migration disorders

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Introduction

Optic nerve hypoplasia (ONH) is a developmental abnormality of the optic nerve that may occur in isolation either unilaterally or bilaterally, and sometimes in association with hypopituitarism and/or absent septum pellucidum/corpus callosum abnormalities (Figs. 1 and 2).[1,2] The latter is commonly referred to as septo-optic dysplasia or more accurately septo-optic-pituitary dysplasia (SOD). ONH/SOD are one of the commonest causes of congenital visual impairment. The best-corrected visual acuity (BCVA) in patients with ONH/SOD varies from normal to no light perception.[1]

Many cases are thought to be due to an acquired in-utero insult,[3] while a genetic etiology is found only in a minority of cases.[4]

The province of Manitoba in Canada has a high incidence of ONH/SOD for unknown reasons.[2] Most of these patients have had years of follow-up by pediatric ophthalmologists, neurologists, and endocrinologists at the only Children's Hospital in the province. A prior study focusing on the ophthalmic features in our cohort of patients with ONH/SOD was published recently.[5]

There is a paucity of studies investigating the association of ophthalmic features in ONH/SOD with neuroimaging findings.[6,7]

Our primary hypothesis was that ophthalmic signs in patients with ONH/SOD are typically associated with neuroimaging abnormalities. The primary aim was to ascertain if BCVA, nystagmus, strabismus, laterality of the relative afferent pupillary defect (RAPD), and laterality of the small optic disc have associated neuroimaging abnormalities in patients with ONH/SOD.

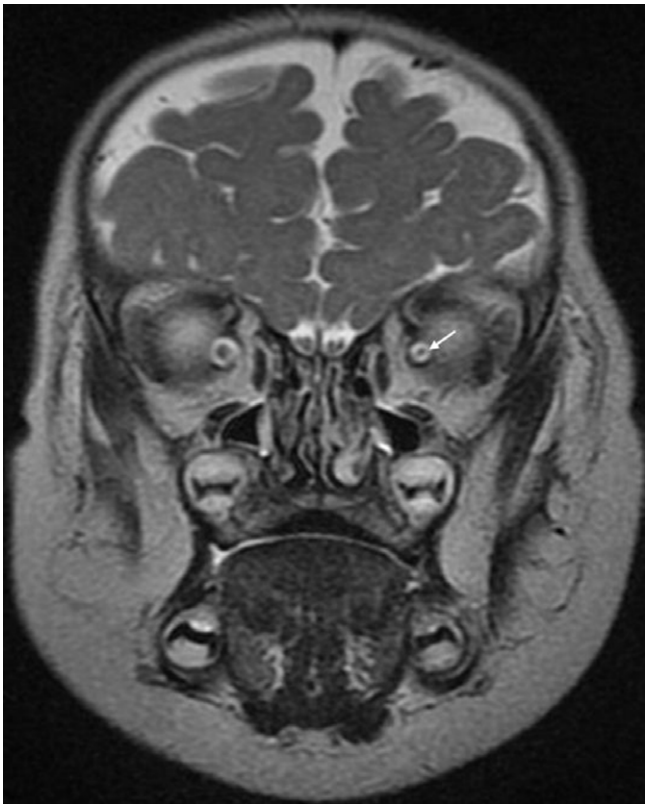

Figure 1: Brain MRI of a 9 month old female with suspected left optic nerve hypoplasia. The coronal T2-weighted image of the orbits shows the small size of the intraorbital portion of left optic nerve (arrow). The right optic nerve is normal in size.

Methods

Patients

Patients with ONH/SOD were identified from two sources. The first was through searching a database of all patients assessed by the section of pediatric endocrinology since 1986. The search terms "optic," "nerve." "hypoplasia," "septo," and "dysplasia" were used. The second source was through searching clinic letters available electronically from 1990 to August 2019, from the sections of pediatric neurology and pediatric ophthalmology using the same search terms. The diagnosis was verified by two of the authors (MSS and IHC). Both have clinical expertise in these disorders. A small optic disc or discs on ophthalmoscopy recorded in the ophthalmology clinic letters confirmed the diagnosis of ONH. When hypopituitarism and/or midline brain abnormalities on neuroimaging were present then the diagnosis was SOD. Only residents of Manitoba were included in this study. Ethics approval was granted by the Health Research Ethics Board, University of Manitoba.

Variables

Basic demographic, ophthalmic, and neuroimaging data were extracted from the patients' charts including sex, age at their clinic visits, and at the end of the study (30th June 2020), the first and last reliable monocular quantitative BCVA in each eye, laterality (unilateral/bilateral) and, if unilateral, the side (right/left) of the worse BCVA, strabismus and its type, nystagmus, RAPD presence and laterality, and optic disc size and laterality on funduscopy.

Patients whose BCVA could not be quantified by a monocular logarithm of the minimum angle of resolution (logMAR) acuity were excluded, e.g., patients labeled as having "central, steady, and maintained," "fix and follow" vision, or if they only had a binocular BCVA documented. Standardized VA tests based on the children's level of cooperation and developmental age were used. When BCVA data were not recorded in logMAR, they were converted to logMAR to facilitate analysis. The BCVA data were divided into two groups for each patient: The eye with the worse BCVA and the eye with the better or equally affected BCVA. Low, "off-chart" BCVA data were assigned the following logMAR values: Counting fingers: 2; hand motion: 2.3; light perception: 4; and no light perception: 4.5, as described in prior studies.[5,8–10]

Patients were then divided into four BCVA categories according to their logMAR values for the right and left eyes and most affected and lesser or equally affected eyes at the first and last clinic visits. The categories were Category 1 (BCVA within the normal range): logMAR ≤ 0.3; category 2: logMAR > 0.3–1; category 3: logMAR > 1–< 2; and category 4 (most impaired BCVA): logMAR 2–4.5, as described in our recently published study on the same cohort.[11] We based the categories on BCVA definitions of normal (20/40 or better), legal definition of blindness (20/200 or worse), and nonquantifiable BCVA on VA charts (i.e., counting fingers or worse) in a similar manner to another published paper on this topic.[6] The number and percentage of patients in each of these categories were calculated.

Neuroimaging data were obtained mostly from reviewing brain MRI scans as previously described in this cohort.[12] In instances where the scans were not available, the data were extracted from the MRI report. When MRI was not performed, a high-quality CT scan was used. Brain MRI was acquired on 1.5 or 3 T MRI scanner (GE). The minimal standardized protocol utilized sagittal T1-weighted,

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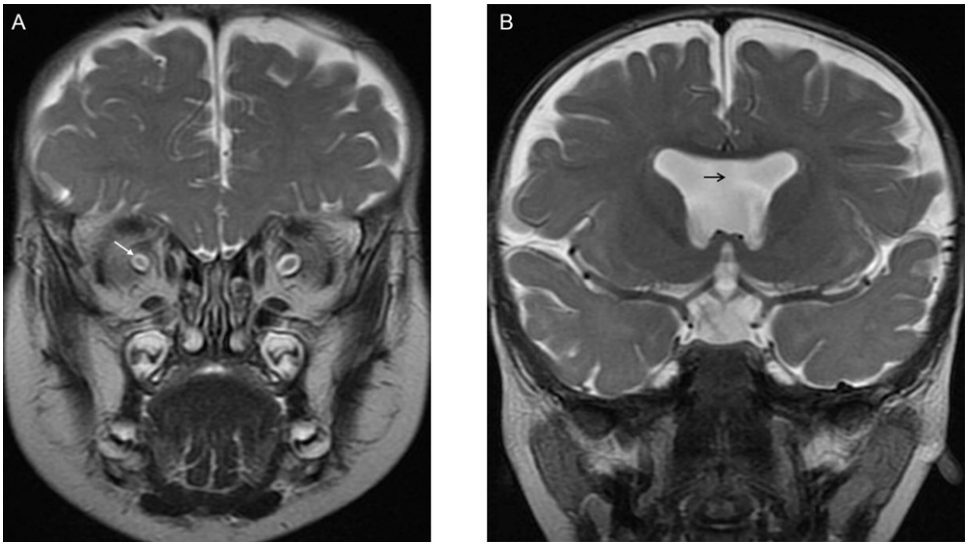

Figure 2: Brain MRI of a 10 month old male with suspected right optic nerve hypoplasia. (A) Coronal T2-weighted image of the orbits showing the significantly small size of the intraorbital portion of right optic nerve (arrow). (B) Coronal T2-weighted image of the brain demonstrating absence of septum pellucidum (arrow).

axial/coronal T2-weighted, and axial/coronal fluid-attenuated inversion recovery imaging sequences. Other sequences included susceptibility-weighted imaging, diffusion-weighted imaging, apparent diffusion coefficients maps, fast spoiled gradient echo imaging, and magnetic resonance angiography.

Additional images with dedicated orbital and pituitary gland views were reviewed, when available. Contrast with gadolinium was given at the discretion of the radiologist. All initial and subsequent brain MRI images available that were completed by June 2020 were reviewed by a pediatric radiologist with expertise in neuroimaging (KR).

The data extracted included age at the time of the neuroimaging scan(s), and structural abnormalities (laterality [unilateral/bilateral], side [right/left], shape, size, absence) of infra- and supratentorial structures including the white matter and cortex in particular neuronal migration disorders (NMD), deep gray matter, pituitary gland, septum pellucidum, corpus callosum, and optic nerves/chiasm. Visual inspection of each scan was undertaken to determine if there was a decrease in the size of the various aforementioned neuroimaging features. If there was doubt regarding the size, then comparison with published age-specific normative data was undertaken. The data were converted to numerical variables to facilitate statistical analysis. All extracted data were checked twice or more.

Statistical Analysis

All analyses were carried out using SAS/STAT® software, version 9.4 (SAS Institute Inc., Cary, NC). Chi-squared, Fisher exact, and Wilcoxon sign-rank tests were used to investigate the association between two or more categorical variables. Correlations were carried out on the combined ophthalmic and neuroimaging data ($N = 102$). ANOVA was used to compare the mean of continuous variables against categorical variables. Normality assumption of continuous variables was checked by Shapiro–Wilk test and presented as mean and standard deviation (SD) if they had a normal distribution, otherwise median, quartiles, minimum, and maximum values were reported. Logistic regression was used to investigate the univariate and multivariable (adjusted for other covariates) relationship among the variables. A p-value < 0.05 was used to assess statistical significance.

Results

There were 128 patients (70 males) with neuroimaging studies. Their mean age (SD) at study end was 13.2 (7.5) years. Their clinical and neuroimaging features have been published recently.[5,11–13] A summary is presented in Table 1.

Ophthalmic data were available on 102 patients (58 males). Ninety of the 102 patients were examined in clinic twice or more. Median age (interquartile range) in years at first clinic visit was 3.6 (2.2–5.1), last clinic visit 8.7 (5.8–11.5), and study end 12.5 (8.5–17.7) years. Median duration (interquartile range) of follow-up was 4.5 (3.0–7.2) years. At last clinic visit, BCVA was most severely affected on the right in 32, left in 38, and was equally affected in both eyes in 18 patients ($N = 88$). At last clinic visit, median (interquartile range) BCVA in the most affected eye was 1.3 (0.7–4.0, $N = 88$) and 0.4 (0.1–0.7, $N = 90$) in the least affected eye. At last clinic visit, the number of patients in each BCVA category in the most affected eyes was: 6 in category 1 (normal), 28 in category 2, 12 in category 3, and 42 in category 4 (most severe). Nystagmus was reported in 53 cases. Strabismus was reported in 87 cases (exotropia in 45, esotropia in 40, and other in 2) as described previously.[5]

Ophthalmic Findings and Optic Nerve/Chiasm Sizes on Neuroimaging

BCVA

The laterality (unilateral/bilateral) of the decreased BCVA was significantly associated and generally concordant with laterality of the reduced optic nerve ($N = 99$) and chiasm ($N = 98$) sizes on neuroimaging ($p < 0.0001$). Furthermore, the side (right/left) of the most affected BCVA on the first ($N = 92$ for optic nerve, 91 for optic chiasm) and last ($N = 85$ for optic nerve, 84 for optic chiasm) clinic visits were significantly associated and generally concordant with the side of the small/ or smaller optic nerve and chiasm on neuroimaging ($p < 0.0001$). However, these highly significant statistical associations were not perfectly concordant.

In addition, the categories of BCVA impairment for the right and left eyes at the first and last clinic visits were significantly associated with the side of the small/or smaller optic nerve and chiasm ($p \leq 0.0002$), whereby the more severe BCVA categories

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Table 1: Demographic and [‡]neuroimaging features in patients with optic nerve hypoplasia and septo-optic-pituitary dysplasia

Demographic/neuroimaging features	Number of patients (%)
Total number of patients with neuroimaging [males/females]	128 [70 (54.7)/58 (45.3)]
Mean (SD) age at study end, years	13.2 (7.5)
Mean age (SD) at first neuroimaging, years	3.61 (5.8)
Neuroimaging scans reviewed	
Total	116 (90.6)
MRI	114 (89.1)
Only CT	2 (1.6)
Data extracted from MRI reports	12 (9.4)
Total with>1 MRI	34 (26.6)
Optic nerve size on neuroimaging	
Small optic nerve(s) size	120 (93.8)
Borderline small optic nerve(s) size	5 (3.9)
Optic nerves not optimally seen	2 (1.6)
Not mentioned in MRI report (when MRI scan is not available)	1 (0.8)
Side of optic nerve involvement	
Bilateral symmetrical decrease in optic nerves size	79 (61.7)
Right optic nerve only is small	18 (14.1)
Left optic nerve only is small	17 (13.3)
Bilateral asymmetrical decrease in optic nerves size	11 (8.6)
Unknown	3 (2.3)
Optic chiasm size	
Small optic chiasm size	84 (65.6)
Small optic chiasm size on left	16 (12.5)
Small optic chiasm size on right	12 (9.4)
Borderline small optic chiasm size	5 (3.9)
Normal optic chiasm size	5 (3.9)
Unknown or not mentioned	6 (4.7)
Pituitary gland size	
Normal pituitary gland size	86 (67.2)
Small pituitary gland size	36 (28.1)
Unknown or not mentioned	6 (4.7)
Ectopic posterior pituitary gland	
No ectopic posterior pituitary gland	103 (80.5)
Ectopic posterior pituitary gland present	19 (14.8)
Unknown	6 (4.7)
Septum pellucidum	
Septum pellucidum present	74 (57.8)
Septum pellucidum absent	52 (40.6)
Unknown	2 (1.6)
Corpus callosum	
Normal corpus callosum size	116 (90.6)
Corpus callosum abnormalities (dysplastic, partial absence, and absence)	11 (8.6)
Unknown	1 (0.8)
Neuronal migration disorders (NMD)	
Total	26 (20.3)
Spatial distribution of NMD:	
Right	7/26 (26.9)
Left	6/26 (23.1)
Bilateral	13/26 (50.0)
Number of NMD types	5
Details of the NMD types:	Number of patients (% of all patients with NMD)
1. Schizencephaly	15 (57.7)
2. Heterotopia	12 (46.2)
3. Polymicrogyria	10 (38.5)
4. Cortical dysplasia	4 (15.4)
5. Lissencephaly	1 (3.8)
Number of all five types of NMD	42
Number of patients with one type of NMD	13/26 (50.0)
Number of patients with two types of NMD	10/26 (38.5)
Number of patients with three types of NMD	3/26 (11.5)

[‡]Adapted with permission from Table 1 in Salman et al.[12] Neuroimaging features in children with optic nerve hypoplasia and septo-optic-pituitary dysplasia. Can J Neurol Sci. 2023 Jul 26:1–9. doi: 10.1017/cjn.2023.263. and Table 3, in Salman et al.[13] Risk factors in children with optic nerve hypoplasia and septo-optic dysplasia. Dev Med Child Neurol. 2023;66:106–16. doi: 10.1111/dmcn.15678.

occurred on the side with the smaller optic nerve and chiasm sizes on neuroimaging.

Optic Disc

The laterality of the small optic disc size was significantly associated and generally concordant with the laterality of the small optic nerve and chiasm sizes on neuroimaging ($p < 0.0001$). The side with the small optic disc was also significantly associated and generally concordant with the side of the reduced optic nerve and chiasm sizes on neuroimaging ($N = 95$ and 94, respectively, $p < 0.0001$). However, these highly significant statistical associations were not perfectly concordant.

RAPD

The presence of RAPD was significantly associated with the laterality of the reduced optic nerve and chiasm sizes on neuroimaging ($N = 98$ for optic nerves and 97 for optic chiasm, $p < 0.0001$), i.e., RAPD presence was significantly associated with unilateral rather than bilateral cases and, when present, its side was significantly associated and generally concordant with the side that had the reduced optic nerve and chiasm sizes ($N = 49$ for optic nerves and 48 for optic chiasm, $p < 0.0001$). However, these significant statistical associations were not perfectly concordant.

Nystagmus

The presence of symmetrically small optic nerves on MRI was significantly more common in patients with nystagmus than when

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nystagmus was absent ($N = 96$, 75% vs. 38.6%, $p < 0.0001$). Similarly, a symmetrically small optic chiasm on MRI was significantly more common in patients with nystagmus than when nystagmus was absent ($N = 95$, 88.2% vs. 50%, $p < 0.0001$). However, each of these two covariates (i.e., optic nerves and chiasm reduced sizes) and the presence of neuronal migration abnormalities (see below) were not found to be statistically significant in the multivariable logistic regression model for nystagmus presence.

Strabismus

Strabismus presence and type were not significantly associated with the reduced sizes of the optic nerves or chiasm on neuroimaging ($p \geq 0.11$).

Ophthalmic Findings and Neuronal Migration Disorders on Neuroimaging

The presence of NMD, their types (schizencephaly, polymicrogyria, and heterotopia), and the number of types in each patient were not associated with the category of BCVA in the most affected eye on the first ($p \geq 0.68$) and last clinic ($p \geq 0.19$) visits. The presence of neuronal migration abnormalities was not associated with the laterality of the decreased BCVA ($p = 0.30$). The side of the neuronal migration abnormalities was not associated with: (1) The most affected side of the BCVA on the first ($p = 0.92$) or last ($p = 0.71$) clinic visits, (2) the side of the small optic disc ($p = 1.00$), or (3) the side of the small/ or smaller optic nerves and chiasm sizes ($p \geq 0.44$).

Nystagmus was not associated with any specific type of neuronal migration abnormalities ($p \geq 0.06$). Strabismus presence and type were not significantly associated with the presence and type of neuronal migration disorders ($p = 1.00$).

Ophthalmic Findings and Other Neuroimaging Abnormalities

Pituitary Gland Size

An abnormally small in comparison with normal pituitary gland size was significantly associated with: Nystagmus ($N = 95$, 85.2% vs. 41.2%, $p = 0.0001$), bilaterally decreased BCVA ($N = 98$, 85.2% vs. 40.9%, $p = 0.0002$), and bilaterally decreased optic disc size ($N = 94$, 92% vs. 50.7%, $p = 0.0003$). However, each covariate was not statistically significant in a multivariable logistic regression model.

Pituitary gland size was not associated with BCVA category of the most affected eye at first or last clinics visits, strabismus, or strabismus type ($p \geq 0.50$).

Ectopic Posterior Pituitary Gland

The presence of an ectopic posterior pituitary gland in comparison with a normal posterior pituitary gland location was significantly associated with: Nystagmus ($N = 95$, 82.4% vs. 47.4%, $p = 0.01$), bilaterally decreased BCVA ($N = 98$, 88.2% vs. 45.7%, $P = 0.006$), and bilaterally decreased optic disc size ($N = 94$, 87.5% vs. 56.4%, $P = 0.02$).

The presence of an ectopic posterior pituitary gland was not associated with BCVA category of the most affected eye at first or last clinics visits, strabismus, or strabismus type ($p \geq 0.31$).

Septum Pellucidum

Absence of septum pellucidum in comparison with its presence was significantly associated with: Nystagmus ($N = 98$, 70% vs. 43.1%, $p = 0.009$) and bilaterally decreased optic disc size ($N = 97$, 78.4% vs. 51.7%, $p = 0.009$).

There was a trend for the absence in comparison with the presence of septum pellucidum to be associated with bilaterally decreased BCVA ($N = 101$, 67.5% vs. 44.3%, $p = 0.07$). However, each covariate was not statistically significant in a multivariable logistic regression model.

The absence of septum pellucidum was not associated with BCVA category of the most affected eye at first and last clinics visits, strabismus, and strabismus type ($p \geq 0.33$).

Corpus Callosum

An abnormal corpus callosum was not associated with BCVA category of the most affected eye at first and last clinics visits, nystagmus, strabismus, strabismus type, bilaterally decreased BCVA, or optic disc size ($p \geq 0.12$).

Discussion

Several studies have investigated the associations between endocrine deficiencies, developmental delay, neurological abnormalities (e.g., cerebral palsy), and neuroimaging features in ONH/SOD.[14,15] However, we did not find studies with a large sample size that systematically investigated the associations between ophthalmic and neuroimaging features in ONH/SOD. More specifically, we are not aware of studies that reported on the associations of RAPD, nystagmus, strabismus with neuroimaging features in ONH/SOD. However, in few reports, it was noted that the reduced BCVA,[7,16] the laterality of the reduced BCVA,[7] and optic disc size[6,7,15] were either not concordant or only showed modest-moderate correlation with the laterality of the reduced optic nerves or chiasm sizes,[6,15] diameter,[16] or cross-sectional area[7] of the optic nerves on MRI. One study tabulated four BCVA functional categories in their patients with ONH/SOD according to the presence of normal versus abnormal neuroimaging structures (pituitary gland, SP, CC, and NMD), but statistical analysis was not reported likely due to the small sample size in the various subgroups.[6]

In our investigation, there were statistically significant associations between: (A) Reduced optic nerve or chiasm size on neuroimaging and more severe BCVA category and (B) laterality of the reduced optic nerve or chiasm size on neuroimaging and laterality of: (1) The eye with reduced BCVA, (2) small optic disc size, and (3) RAPD, if present ($p \leq 0.0002$ each). These functional and structural associations are consistent with the impaired visual function that results from the reduced size of the anterior visual pathways in ONH.[7,16]

However, despite our highly significant results, the associations were not perfectly concordant in some of our patients. Such discordance in findings has been reported anecdotally in a few studies, where a small optic disc on fundus exam was noted in only 13 of 17 patients with small optic nerve size on MRI,[6] or unilateral ONH on funduscopy that was discordant with the cross-sectional areas of the optic nerves on MRI in 2 of 6 patients,[7] or small "anterior visual pathways" on MRI in 38 of 40 patients with a clinical diagnosis of ONH,[13] and discordance between funduscopic versus neuroimaging diagnosis of ONH in 20% of 20 patients with unilateral ONH on funduscopy and 23.5% of 57 patients with bilateral ONH.[15] Similar examples in our investigation include a minority of our patients with small optic discs also had normal optic nerves or chiasm sizes on MRI, patients with unilaterally small optic disc had bilateral ONH on MRI, or patients with ONH on MRI had normal or near normal BCVA on the affected side. This discordance makes it challenging to predict the anticipated

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adult visual acuities in this cohort of patients. Perfect concordance is rare in clinical-radiological correlation studies in general, especially when there are a large numbers of subjects with varying ages. Yet, our highly significant results demonstrate that for the majority of patients, the results correctly show that an association exists between visual clinical features and neuroradiological abnormalities. The imperfect correlations may be due to subclinical abnormalities, subjectivity in some of the clinical assessments, and degree to which patients can cooperate with their clinical evaluation. With regard to imaging, the lack of concordance could be related to the subjectivity inherent in the radiologist's assessment, or the resolution limits inherent in MRI technology. For example, subtle decreases in optic nerve size could potentially be missed, especially in MRI scans that were performed with older technology as was the case for some of our subjects at the start of the study period.

The presence of NMD, their type, and laterality were not associated with the severity of BCVA and the laterality of the reduced BCVA suggesting that the two entities are independent features in this disorder.

Nystagmus was associated with bilaterally reduced optic nerve sizes and symmetrically small optic chiasm on MRI. Prior studies reported that bilateral reduction in BCVA is typically associated with nystagmus.[5,17] The significant associations between the presence of nystagmus and: Small pituitary gland size, the presence of an ectopic posterior pituitary gland, and absence septum pellucidum may have been due to confounding, since these structural abnormalities were commonly seen in patients with bilateral rather than unilateral reduction in BCVA among our patients. The categories of BCVA were not associated with any of these structural brain abnormalities and therefore their presence should not be used to prognosticate BCVA.

Study limitations: Our investigation is subject to the limitations of retrospective chart review. It is reliant on the accuracy of the extracted data. Missing information decreased the sample size and thus the power of the study to detect small differences between the groups. Our patients have all been verified by two of the authors to have ONH/SOD; we thus avoided misclassification of cases. However, only patients with monocular BCVA that could be quantified were included; patients who were designated as "fix and follow" or "central, steady, and maintained" were excluded. Hence, some patients and especially those who are younger are not represented in this investigation.

Assessing VA in young infants, toddlers, and children with or without developmental delay is not easy at times, with variable degrees of abilities based on developmental age and cooperation that may be different from one clinic visit to the next. Such factors add a degree of difficulty in obtaining consistently accurate measures of BCVA. However, this is unavoidable and represents the realities of routine clinical ophthalmology practise.

Children with low "off-chart" BCVA who are able to count fingers may have a quantifiable visual acuity that is on a continuous acuity scale rather than the single value of 2.0 we allocated to all of them on the logMAR scale. This is unavoidable since the BCVA data were collected retrospectively and not in the standardized manner that is usually done in prospective studies. Our assumption for the "counting fingers" category may potentially produce a weakness in the statistical test we used, which uses a ranking system to analyze the data. Finally, our dataset had a few or no observations in one or more categories of the response variables with other variables. Consequently, the likelihood function based on logistic regression failed to yield probability estimates.

Data availability statement. All data are displayed in the manuscript.

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Competing interests. The authors MSS, SH, EC, and KR report that there are no competing or conflict of interests to declare. ICH received payments as an expert witness for a case of bilateral retinoblastoma and also for a child with cerebral palsy. He is a long- time board member of the Canadian Orthoptic Council and also for DePICT RB (which is a not-for-profit retinoblastoma treatment electronic patient record). Neither of these are paid or result in any benefit.

Statement of authorship. MSS initiated and designed the study. He contributed to finding the patients, data collection, analysis, and interpretation. He wrote the first draft of the manuscript and edited subsequent drafts. SH performed the statistical analysis, checked and interpreted the results, and edited several versions of the manuscript. EC extracted and rechecked the data from the ophthalmology charts. She converted the visual acuity data into logMAR and checked the converted data. She interpreted the results and edited the paper. IHC helped with the literature search, ophthalmic data collection, auditing the dataset for accuracy, helping with interpretation of the results, and edited a few drafts. KR performed the imaging data collection, reviewed available MRI/CT, checked the accuracy of the imaging data, helped in neuroimaging data interpretation, and edited the manuscript. All authors approved the last version of the paper.

Ethics approval. Ethical approval for the study has been granted by the Research Ethics Board of the University of Manitoba.

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