Unraveling the Link Between Optic Nerve Hypoplasia and Endocrine Dysfunction

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Introduction

Optic Nerve Hypoplasia (ONH) is a congenital abnormality of the optic nerve

ONH is the leading cause of blindness in children

The etiology of ONH is multifactorial: genetic[1], prenatal factors[2]

Some children with ONH develop pituitary hormone deficiency (PHD)[3]

All children with ONH are followed with frequent screening for PHD

Objectives

Primary:

Identify the type and timing of pituitary hormone deficiency (PHD) in children with ONH to help guide the necessity for and frequency of testing for pituitary function

Secondary:

Identify MRI, ophthalmologic, prenatal and neurobehavioral factors that predict the development of PHD in patients with ONH

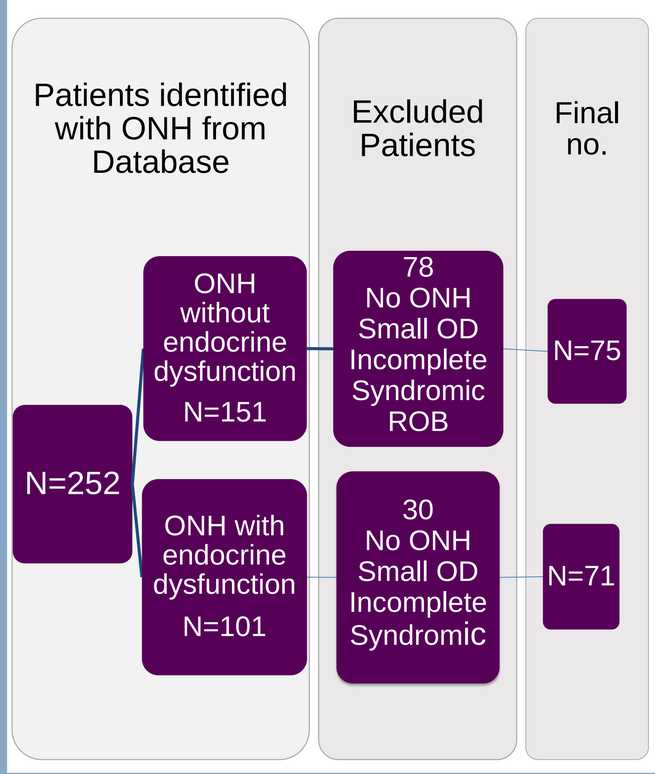
Methods

Retrospective cohort study

ONH diagnosed between 1975 and 2014 queried in the Endocrinology & Diabetes Unit clinical database at BC Children's Hospital, BC, Canada

All patients were followed up to monitor the development of PHD
Chart reviews were conducted for all patients with confirmed ONH and demographic data, prenatal, neurobehavioural, radiologic, hormonal and ophthalmologic factors were collected

Descriptive statistics were used (means, medians, proportions)
Multivariable Cox proportional hazard (PH). The model was used to identify the predictors of PHD.



Results

Of the children with ONH, 49% developed hormone dysfunction
Most common PHD were: GH (63%), TSH (63%), ACTH (58%)

Table 1: Patients Characteristics:

Characteristics	PHD (N= 71)	No PHD (N=73)	Characteristics	PHD (N= 71)	No PHD (N=73)
Demographics (%):			**Neurological**		
Age at ONH Diagnosis (yrs); median (IQR)	2.03 (0.57 - 7.53)	12.1 (5.3 - 28.47)	Developmental delay	44 (61.97)	31 (42.47)
Female	38 (53.5)	42 (57.52)	Seizures	17 (23.94)	11 (15.07)
Prenatal Factors:			**MRI Findings:**		
	30 (42.25)	18 (24.66)	Abnormal posterior pituitary	26 (36.62)	2 (2.74)
Prematurity	3 (4.23)	12 (16.44)	Absent pituitary stalk	10 (14.08)	2 (2.74)
Ophthalmologic:			Hypoplastic Anterior Pituitary	18 (25.35)	1 (1.37)
Bilateral ONH	59 (83.1)	48 (65.75)	Absent Corpus Callosum	13 (18.31)	4 (5.48)
Blindness	23 (32.94)	7 (9.59)	Absent Septum Pellucidum	13 (18.31)	6 (8.22)

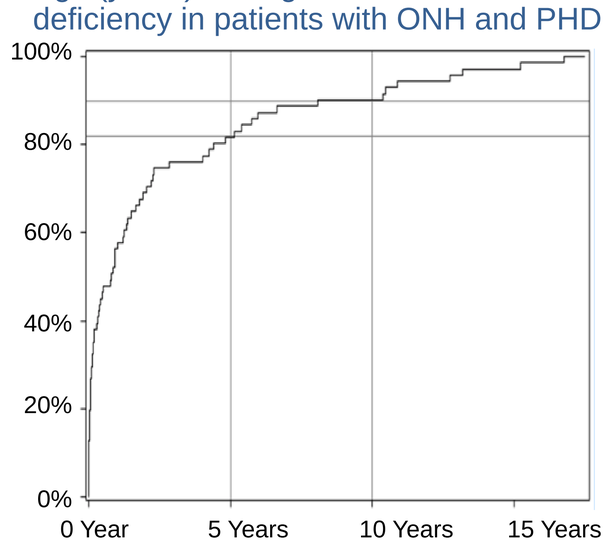
Table 2: Unadjusted Hazard Ratio estimates of PHD on patients with ONH

Characteristics	Hazard Ratio (95% CI)	p-value
Age at ONH Diagnosis	0.93 (0.83, 1.05)	0.24
Female	0.79 (0.5, 1.26)	0.33
Any substance abuse	**1.84 (1.14, 2.95)**	**0.01**
Prematurity	**0.27 (0.08, 0.86)**	**0.03**
Bilateral ONH	1.67 (0.9, 3.11)	0.11
Blindness	**2.08 (1.26, 3.42)**	**0.004**
Developmental delay	1.48 (0.91, 2.39)	0.11
Seizures	1.29 (0.75, 2.23)	0.36
MRI: Abnormal posterior pituitary	**5.04 (3.03, 8.38)**	**<0.0001**
MRI: Absent pituitary stalk	**2.42 (1.23, 4.75)**	**0.01**
MRI: Hypoplastic/absent anterior Pituitary	**3.52 (2.04, 6.08)**	**<0.0001**
MRI: Absent Corpus Callosum	**2.22 (1.21, 4.07)**	**0.01**
MRI: Absent Septum Pellucidum	1.85 (1.01, 3.38)	0.05

Table 3: Adjusted Hazard Ratio estimates of PHD on patients with ONH

	Model 1		Model 2	
Characteristics	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age at ONH Diagnosis	0.98 (0.87, 1.1)	0.7	0.96 (0.84, 1.09)	0.48
Female	0.75 (0.46, 1.22)	0.25	0.8 (0.49, 1.29)	0.36
Any substance abuse	1.51 (0.91, 2.48)	0.11	1.61 (0.99, 2.63)	0.06
Prematurity	**0.33 (0.1, 1.07)**	**0.06**	**0.26 (0.08, 0.86)**	**0.03**
Blindness	**1.72 (1.03, 2.86)**	**0.04**	**1.85 (1.1, 3.09)**	**0.02**
MRI: Abnormal posterior pituitary	**3.8 (2.01, 7.18)**	**<0.0001**	**-**	**-**
MRI: Absent pituitary stalk	1.02 (0.47, 2.23)	0.96	1.37 (0.62, 3.03)	0.44
MRI: Hypoplastic/absent anterior pituitary	**-**	**-**	**2.52 (1.29, 4.91)**	**0.01**
MRI: Absent corpus callosum	1.28 (0.65, 2.53)	0.48	1.79 (0.93, 3.44)	0.08
MRI: Absent septum pellucidum	1.14 (0.6, 2.16)	0.69	0.99 (0.5, 1.95)	0.98

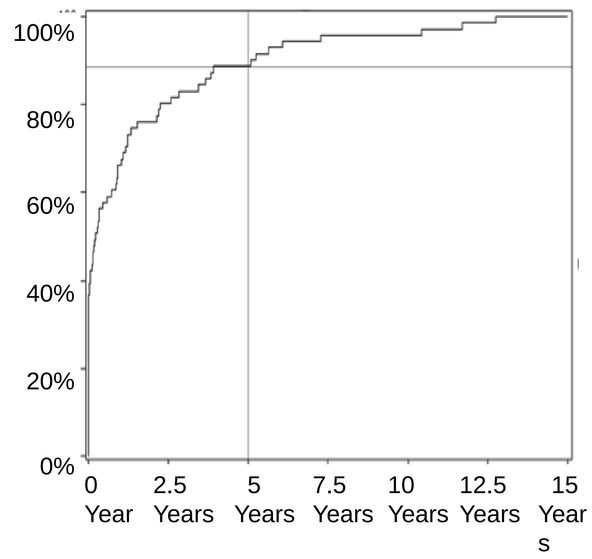
Age (years) of diagnosis of 1st Hormone deficiency in patients with ONH and PHD



82% developed their 1st PHD by age 5 years

90% developed their 1st PHD by age 10 years

Time (years) from diagnosis of ONH to 1st hormone deficiency in patients with ONH



By 5 years after diagnosis of ONH, **88.6%** developed their 1st PHD

Conclusions

To our knowledge, this study reports on the largest cohort of patients with ONH with the longest follow-up period.

Among patients with ONH who go on to develop pituitary hormone deficiency:

- By age 5, 80% of children will have developed their 1st hormone deficiency
- By 5 years after ONH diagnosis, 90% of children will have developed their 1st hormone deficiency

Risk factors for developing PHD include structural abnormalities of the pituitary gland and blindness. Other CNS structural abnormalities (i.e. of the corpus callosum/septum pallucidum) were not predictive of PHD. A novel finding was prematurity as a protective factor.

Limitations included incomplete records (11 cases) as well as different approaches to the frequency of screening for PHD and brain imaging.

Future directions will include developing a predictive model for PHD and validating it against a larger sample of patients with ONH. Also, further research into prematurity as a protective factor is warranted.

References

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Conflict of interest:

None of the authors have any conflict of interest.