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Evolving Central Hypothyroidism in Children with Optic Nerve Hypoplasia

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ABSTRACT

Background: **Children with optic nerve hypoplasia (ONH) are at high risk for early-onset congenital central hypothyroidism (CH); however, reports of evolving, late-onset CH are rare and poorly documented.**

Aim: **To examine the clinical and biochemical data of children with ONH who developed CH after documented normal thyroid function tests at an earlier age.**

Patients and Methods: **Children who developed late-onset CH were selected for review from an observational study (n = 214) that examined clinical risk factors for endocrinological abnormalities in children with ONH.**

Results: **Eight patients with ONH developed CH between the ages of 20-51 months. One child at age 28 months developed CH within 4 months of prior normal thyroid function tests. There were no associations among clinical, neuroradiographical, vision, and/or pituitary outcomes.**

Conclusions: **Children with ONH may develop CH over time, and surveillance thyroid function tests may be necessary as frequently as every four months.**

KEY WORDS

optic nerve hypoplasia, central hypothyroidism, evolving, acquired, hypopituitarism

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INTRODUCTION

Central hypothyroidism (CH) is generally rare with historical estimates of prevalence ranging between 1:68,200 and 1:100,000 infants[1,2]. However, more recent studies approximate the prevalence of CH to be 1:16,404 to 1:20,263 live newborns[3,4]. Thus, CH may be more common than previously thought. Children with optic nerve hypoplasia (ONH) are at high risk for CH. Among this group of children, 43% are hypothyroid[5]. In addition, children with ONH are born with an increased risk for poor neurocognitive and vision outcomes. Early detection and treatment of CH are crucial so as not to further impair normal postnatal growth and development.

The early identification of CH poses a troublesome clinical challenge. Most newborn screening programs are not designed to detect congenital hypothyroidism due to hypothalamic or pituitary disease, and, therefore, CH may not be identified until after clinical symptoms of hypopituitarism become apparent[6]. Additionally, CH may evolve with time and the diagnosis may not be accompanied by readily discernible symptoms. Survivors of traumatic brain injury[7] and childhood cancer[8,9] have demonstrated that CH may occur months to years after the initial cranial insult and that surveillance blood tests are necessary to reveal occult neuroendocrine deficits. Progressive pituitary dysfunction has also been reported to evolve postnatally in children born with congenital causes, such as mutations of hypothalamic-pituitary transcription factors[10-12] and structural brain malformations[13-15]. However, longitudinal reports that characterize evolving CH as a dynamic developmental process among children with ONH are rare and poorly docu-

mented, even though ONH is now recognized as a growing cause of childhood blindness[16]. It is important to better understand the evolution of late-onset CH in this population given that hypothyroidism is associated with poor neurodevelopment[5] and vision outcomes (unpublished data) in children with ONH.

PATIENT SERIES

From a prospective study (n = 214) aimed at characterizing the endocrinological abnormalities among children with ONH[17], eight patients were observed to develop CH between the ages of 20-51 months after documented normal thyroid function tests earlier in life. Herein we report the salient clinical and radiographical features, vision assessments, and biochemical data for these patients (Table 1). Institutional laboratory values defined abnormal results.

Patient #1

A male term infant was born with normal birth weight and length. He had recurrent perinatal hypoglycemia during the first day of life and he required phototherapy for neonatal jaundice. The constellation of symptoms, including nystagmus, poor vision, and developmental delay, led to funduscopic examination and the diagnosis of bilateral ONH at age 7 months. Computed tomography of the brain revealed hypoplasia of the corpus callosum, absent septum pellucidum, and a normal pituitary gland. Thyroid function tests were normal at ages 17 and 26 months, but he developed CH by age 32 months at which time thyroid hormone (TH) replacement therapy was initiated. He was diagnosed with growth hormone (GH) deficiency at age 19 months and he had mild hyperprolactinemia. His cortisol response [1793 nmol/L (65 μg/dL)] during a febrile illness at age 19 months was robust, but a random cortisol was below the lower level of detection at age 47 months. This prompted a low-dose adrenocorticotropic hormone stimulation test in which the peak serum cortisol level was only 193 nmol/L [7 μg/dL (normal >497 nmol/L or >18 μg/dL)][18].

Patient #2

A female term infant had down-beating nystagmus and poor vision at age 7 months. Brain magnetic resonance imaging (MRI) revealed small optic nerves and absence of the septum pellucidum, infundibulum, and pituitary gland. Her diagnosis of bilateral ONH was confirmed via funduscopic examination at age 10 months. Low blood glucoses prompted provocative hormone testing at age 12 months, which revealed GH deficiency, but normal cortisol responses. Thyroid function tests were normal at age 11 months, but she developed CH by age 20 months, following which thyroxine replacement was initiated. However, her TH levels remained low through age 35 months secondary to poor compliance with medication administration. She also had mild hyperprolactinemia.

Patient #3

A male term infant with a history of neonatal jaundice, developmental delay, and nystagmus was diagnosed with ONH at age 9 months. A brain MRI revealed hypoplastic optic nerves and chiasm, but his central nervous system anatomy was otherwise normal. He had normal thyroid function tests at age 9 months, but, starting at age 36 months, he had low TH levels that persisted through age 53 months at which time he was referred to a pediatric endocrinologist and thyroxine replacement was initiated. The GH stimulation test (using glucagon as the secretagogue) at age 50 months was uninterpretable as he was hypothyroid during the test, but the patient's peak stimulated serum cortisol level was normal. Mild hyperprolactinemia was also present.

Patient #4

A male infant born after 36 weeks of gestation was hospitalized for two weeks in the neonatal intensive care unit (NICU) for respiratory distress syndrome. He had neonatal jaundice, but no hypoglycemia. Concerns regarding his vision prompted ophthalmic evaluation and ONH was diagnosed at age 8 months. He had complete blindness in both eyes. A brain MRI showed bilaterally small optic nerves and chiasm, and a

TABLE 1

Children with optic nerve hypoplasia who developed central hypothyroidism

Patient	Gender	Vision assessment at age >48 months	Other endocrinopathies	Age (months)	TSH (mU/L)	Free T4 (pmol/L)[1] [Total T4 (nmol/L)[2]]
1	M	OD: Reaches for 6-inch toy at 1-foot away; OS: No LP	GHD; CI (evolved); Hyperprolactinemia	17 26 32 38* 45* 47*	2.83 4.85 3.37 *5.04 H* 2.79 0.93	16.7 [91.4] **[84.9 L]** **8.9 L** **8.2 L** 14.4
2	F	OD: 1/200; OS: 1/30	GHD; Hyperprolactinemia	11 20 24 30* 35*	3.87 3.65 	16.7 **9.5 L** **[83.7 L]** **9.4 L** **9.9 L**
3	M	OD: Reaches for 1-inch toy at 1-foot away; OS: Motion perception	Hyperprolactinemia	9 36 50 53 67*	1.14 	18.7 **11.8 L** **9.7 L** **[72.1 L]** 13.1
4	M	OD: No LP; OS: No LP	Hyperprolactinemia	8 32 37 41	2.87 3.04 3.58 	10.3 **10.2 L** **12.0 L** **11.1 L**
5	F	OD: Fix and follow 1-inch toy at 1-foot away; OS: No LP	GHD (likely); Hyperprolactinemia	19 51 60* 69*	2.2 4.32 3.09 3.65	16.7 **7.5 L** **6.4 L** **9.0 L**
6	F	OD: Fix and follow 1-inch toy at 1-foot away; OS: LP	Partial CI; Hyperprolactinemia	4 47 48	 4.17	10.3 **6.3 L** **6.2 L**
7	F	OD: 20/40; OS: 20/30	GHD; Hyperprolactinemia	1 8 24 28 32 36 40 44* 46*	4.71 1.98 	9.9 12.1 12.9 **8.9 L** **8.8 L** **9.8 L** **9.0 L** 12.5 15.4
8	F	OD: No LP; OS: LP	GHD; Hyperprolactinemia	2 6 24 26 29* 33 34*	4.95 	9.8 12.9 **9.8 L** **9.5 L** 11.6 **7.9 L** 15.4

GHD = growth hormone deficiency; CI = cortisol insufficiency; OD = right eye; OS = left eye; LP = light perception.
H = high (in italics); L = low (in bold).
* On TH replacement therapy.
[1]To convert free T4 from pmol/L to ng/dL, divide pmol/L by 12.87.
[2]To convert total T4 from nmol/L to µg/dL, divide nmol/L by 12.87.

left-sided choroidal fissure cyst; the pituitary gland, septum pellucidum, and corpus callosum appeared normal. Surveillance thyroid function tests at age 8 months were normal, but the patient developed CH by age 32 months. Due to an unstable social situation, TH replacement was not started immediately and his free thyroxine (fT4) level remained low through age 41 months. Poor linear growth prompted GH stimulation testing at age 32 months, but the results were uninterpretable given the presence of hypothyroidism during the test. He had mild hyperprolactinemia and normal serum cortisol levels.

Patient #5

An ex-36-week premature female infant was born with acute respiratory distress. She required intubation for several weeks and she had neonatal jaundice; there was no hypoglycemia. A brain MRI at age 3 months revealed hypoplastic optic nerves and chiasm, thin corpus callosum, ectopic posterior pituitary gland, and normal septum pellucidum. A suspected diagnosis of ONH was confirmed by funduscopic examination. She was euthyroid at age 19 months, but surveillance thyroid function tests at age 51 months revealed a very low fT4 level and, despite initiation of thyroxine replacement, fT4 levels remained low at ages 60 and 69 months. A GH stimulation test was attempted at ages 35, 36, and 45 months, but all were unsuccessful due to problems with intravenous access. Her short stature (-2.19 SDS) and low serum levels of insulin-like growth factor (IGF)-I [<1.3 nmol/L or <10 ng/mL (normal 9.7-26.4 nmol/L or 74-202 ng/mL)] and IGF-binding protein (IGFBP)-3 [0.6 mg/L (normal 0.8-3)] were consistent with a diagnosis of GH deficiency. She had mild hyperprolactinemia and normal serum cortisol levels.

Patient #6

This female infant was born at term with neonatal hypoglycemia, hypothermia, and jaundice during the first two weeks of life. Abnormal ocular movements at age one month prompted funduscopic examination and the diagnosis of bilateral ONH was made at age 4 months. An MRI demonstrated small optic nerves and chiasm, a partially absent septum pellucidum and a small pituitary gland. Her fT4 was normal at age 4 months, but thyroid function tests were not rechecked until age 47 months at which time the patient was growing poorly and the fT4 was very low. She failed GH stimulation testing (while hypothyroid) at age 47 months and her peak stimulated serum cortisol level was 334 nmol/L [12.1 μg/dL (normal >497 nmol/L or >18 μg/dL)]. Mild hyperprolactinemia was also present.

Patient #7

This female infant was delivered at 42 weeks via Caesarian section secondary to a decreased fetal heart rate. She was hypotonic with poor respiratory effort at birth and had hypoplasia of the corpus callosum, cortical heterotopia, and a large retrocerebellar cyst on brain MRI. Mild bilateral ONH was diagnosed by funduscopic examination. While in the NICU, the patient had seizures, hypoglycemia, and poor feeding. Surveillance for possible hypopituitarism at age one month revealed no significant abnormalities, aside from mild hyperprolactinemia. Fasting hypoglycemic seizures were noted between her first and second birthdays prompting re-evaluation of the patient's hypothalamic-pituitary axis. She was found to have isolated GH deficiency at age 24 months and treatment with GH decreased the frequency of the hypoglycemic seizures. Surveillance thyroid function tests were rechecked at age 28 months revealing a low fT4 level. Her TH levels remained low repetitively until thyroxine replacement therapy was initiated at age 40 months.

Patient #8

A female infant was born at term via Caesarian section secondary to fetal distress. There was meconium aspiration at birth as well as neonatal jaundice. At age 2 months, she was hypotonic and had poor vision. Ophthalmic evaluation revealed bilateral ONH and a brain MRI showed a hypoplastic corpus callosum and absence of the septum pellucidum, in addition to small optic nerves and chiasm. She had normal thyroid function tests at ages 2 and 6 months, but, by age 24 months, she had developed CH. Her

growth was poor during the 10 months prior to the diagnosis of CH, although she was also GH-deficient. She had a normal serum cortisol level and mild hyperprolactinemia.

DISCUSSION

Early treatment of hypothyroidism is unequivocally imperative for normal growth and development in children. However, classical symptoms of hypothyroidism of central origin do not generally manifest acutely and this can remain an occult clinical diagnosis. In its early development, CH may be detectable only biochemically and the natural progression leading up to the diagnosis of late-onset CH in children with ONH is not well described. We report eight children with ONH in whom CH evolved within the first five years of life. It is reasonable to believe that older children with ONH may continue to be at risk for CH later in life.

Among our reported patients, the average age of diagnosis of CH was 33.8 months (range 20-51). However, there was a significant amount of time (mean 20.4 months) that elapsed between the last normal and first abnormal set of thyroid function tests. Thus, it is possible that biochemical hypothyroidism would have been evident at an earlier age if thyroid function tests were checked more frequently. Given that one of the children (patient 7) developed hypothyroidism within four months of documented normal thyroid function tests, this suggests that surveillance for evolving CH in young children with ONH may be necessary as often as every four months.

In addition to late-onset CH, one child (patient 1) was also noted to 'acquire' cortisol insufficiency. He clearly had a documented cortisol level that was above the accepted threshold of normal at age 19 months. However, after follow-up stimulation testing at age 47 months, he had a subnormal response. The symptoms of cortisol insufficiency may be vague and generally indistinguishable from those associated with more common ailments. In addition, occult cortisol deficiency can have dangerous consequences during severe illness. This case suggests that cortisol insufficiency may also evolve with time and that children with ONH require close monitoring and surveillance for diminishing cortisol responsiveness.

Our longitudinal study of children with ONH was not intended to study the evolution of 'acquired' CH and/or cortisol insufficiency; thus, their actual prevalence and natural progression still need to be determined. However, our observations demonstrate that normal TH and robust stimulated cortisol levels in early life do not preclude evolving deficiencies. In addition, there were no apparent associations between clinical symptoms, vision assessments, brain MRI findings, existing hypopituitarism, and/or evolving pituitary dysfunction; thus, the early detection of evolving hypopituitarism may not be feasible using clinical information alone. For these reasons, surveillance hormone testing is paramount to detect early evolving hormone deficiencies.

In conclusion, children with ONH are at risk for progressive thyroidal dysfunction of central origin. CH may evolve as early as four months after documented normal thyroid function tests. Given the importance of normal TH levels during early childhood and the non-specific signs and symptoms of early hypothyroidism, we suggest that children with ONH be evaluated for evolving CH as frequently as every four months during early childhood. Our report of a patient with ONH who also developed cortisol insufficiency over time is important, but it would be unreasonable to propose general screening guidelines based on a single observation. More rigorous prospective studies are necessary to validate our observations and to examine improved ways to manage evolving hormone deficiencies in children with ONH.

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