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Prenatal determinants of optic nerve hypoplasia: Review of suggested correlates and future focus

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Abstract

Optic nerve hypoplasia (ONH), a congenital malformation characterized by an underdeveloped optic nerve, is a seemingly epidemic cause of childhood blindness and visual impairment with associated lifelong morbidity. While the prenatal determinants of ONH are unknown, early case reports have led to a longstanding speculation that risky health behaviors (e.g. recreational drugs, alcohol) are a likely culprit. There has yet to be a systematic review of the epidemiology of ONH to assess the common prenatal features that may help focus research efforts in the identification of likely prenatal correlates. A review of the past 50 years of epidemiologic research was conducted to examine the prenatal features linked with ONH and provide direction for future research. There are select prominent prenatal features associated with ONH: young maternal age and primiparity. Commonly implicated prenatal exposures (e.g., recreational or pharmaceutical drugs, viral infection, etc.) were rare or uncommon in large cohort studies of ONH and therefore unlikely to be major contributors to ONH. Familial cases and gene mutations are rare. The preponderance of young mothers and primiparity among cases of ONH is striking, although the significance is unclear. Recent research suggests a potential role for prenatal nutrition, weight gain, and factors of deprivation. With the rapidly increasing prevalence of ONH, future research should focus on investigating the relevance of young maternal age and primiparity and exploring the recently suggested etiologic correlates in epidemic clusters of ONH.

Introduction

The birth defect known as optic nerve hypoplasia (ONH) has emerged as the leading single ocular cause of childhood blindness and visual impairment in the United States and Europe.^{7; 23; 28; 54} Underdevelopment of the optic nerve in one or both eyes is the defining feature (Figure 1); however, the diagnosis of ONH is rarely limited to visual impairment alone.⁸ Hoyt et al described cases of ONH associated with hypopituitarism, some of which also were missing the septum pellucidum. They incorrectly attributed recognition of this association to Georges de Morsier.³⁵ De Morsier described "septo-optic dysplasia" post-

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mortem report in an 84-year-old woman with normal vision, but a vertically rotated optic tract, along with an absent septum pellucidum.¹⁷ He, in fact, did not report optic nerve hypoplasia, nor recognize a syndrome that encompassed other midline brain anomalies. Nonetheless, a definition of septo-optic dysplasia (SOD) has evolved that includes optic nerve hypoplasia associated with midline brain malformations (radiographically absent septum pellucidum, hypoplastic corpus callosum, or pituitary abnormalities) and/or hypopituitarism. A detailed history of the evolution of our understanding of the clinical associations of ONH is reported elsewhere.⁹ It is now clear that isolated ONH is uncommon, even when neuro-imaging is normal.²¹

Fewer than 30 cases of ONH were reported prior to 1970.¹⁷ In the subsequent 30 years, the prevalence of ONH increased six-fold to 1.1 per 10,000 children.⁵³ The rise in prevalence occurred amidst declines in other causes of childhood visual impairment.⁷ While some degree of increased surveillance for ONH is probable, this is unlikely to account for this rapid rise.

Despite the progress of clinical research in understanding the profound impact of ONH on childhood development, the etiology of ONH remains largely unknown although numerous prenatal determinants have been suggested. Early case reports^{32; 33; 34; 43; 45; 63; 73} (lowest level of evidence) incited a long-standing speculation that parental risky health behaviors (e.g. recreational drugs, alcohol) may be to blame, yet larger cohort studies (higher level of evidence)²⁵ fail to confirm this. These prenatal exposures are not likely to be major contributors to ONH and thus, we must look beyond these factors in epidemiologic research on ONH.

We review the literature of the past 50-years to examine the evidence for the prenatal factors purported to predispose offspring to ONH.

Results of Literature Review

Risk Factors based on Anecdotal Reports

Table 1 delineates the proposed prenatal correlates of ONH based on anecdotal reports. Of these, recreational and prescription drug use and viral infection are the most pervasive throughout the literature.

Recreational drug use was first introduced as a potential etiologic correlate by Hoyt in a case report of gestational exposure to LSD.³⁴ Since then there have been three additional reports of cases of ONH with prenatal exposure to recreational drugs.^{32; 48} In a report on 48 cases of ONH, Margalith et al described maternal prenatal use of LSD, marijuana, heroin, or psilocybin in five.⁴³ Orrico et al described a case of ONH and digital anomalies with prenatal multidrug exposure to heroin and cocaine.⁵² Patel et al reported a history of unspecified drug exposure in one of 87 cases of ONH.⁵³ In total, among the 159 cases with relevant data reviewed in the literature, there are eight cases (5%) with prenatal drug exposure.

Prescription drugs implicated in ONH include abortifacients, anti-convulsants, and anti-depressants. McKinna¹³ and Amatyakul et al²⁰ reported cases in which there was prenatal exposure to quinine as an abortifacient.^{2; 45} Hoyt and Billson described seven cases, out of their 67, with prenatal exposure to anti-convulsants, including phenytoin, phenobarbital, and diazepam.³³ Subsequently there were two case reports of in utero exposure to carbamazepine⁷³ and valproic acid.⁴⁶ Hellstrom et al²² and Birkabaek et al²³ each reported first trimester exposure to anti-depressants in two of their cases in cohorts of, respectively, 26 and 55 cases of ONH.^{5; 29} In a series of 100 cases, Tornqvist et al had one case with

documented prenatal use of an anti-depressant.⁶⁹ Collectively, there are 14 cases (6% of the 252 total in the reports cited) with prenatal exposure to potentially teratogenic drugs.

Infectious agents have also been linked to ONH. In 1976, Hittner et al presented two cases of ONH with gestational exposure to cytomegalovirus (CMV).³⁰ Subsequently, Margalith et al and Burke et al reported single cases of prenatal CMV exposure in their retrospective cohorts of 51 and 46, respectively, using highly selective testing for viral infection.^{12; 43} Two other cases of ONH with CMV exposure have been described in a prospective cohort of 204 cases of ONH.²¹ The rarity of CMV exposure was further demonstrated when a systematic search for virus DNA using metabolic screening cards on 26 cases of ONH and found no positive results for CMV.¹⁹

Risk Factors based on Case Series or Epidemiologic Studies

Purported risk factors borne out of sixteen case series or epidemiologic reports include young maternal age, primiparity, gender predisposition, prenatal complications including maternal diabetes, and prenatal exposure to alcohol and smoking (Table 2).

Presumed to constitute all of the cases of ONH in British Columbia, Jan et al found 20 cases in the 30 years up to 1977. Considered an emerging ocular disease, the clinical documentation of prenatal and birth characteristics were compared to cases of optic atrophy and national birth statistics. There was an apparent female predisposition (1.5:1) and a toxemia prevalence four times higher than the general population (20% vs 5%).³⁷ Margalith et al extended the analysis with an additional 31 cases of bilateral ONH.⁴³ New findings highlighted a predominance of adolescent (52% vs 11%) and primiparous (54% vs 36%) mothers, compared to the general population. Similar to Jan et al, the prevalence of toxemia was three times higher than that of the general population (15% vs 5%). Incidental findings of prenatal exposures, identified in the previous section, included recreational drug exposure.⁴³ Robinson and Conry further studied the British Columbia cohort to assess an association of maternal age relative to other birth defects that shared a similar gestational window of vulnerability – cerebral palsy and fetal alcohol syndrome. The average maternal age of the ONH cohort was significantly lower (mean 22.4 years) than the comparison groups (24.6 years and 28.7 years, respectively).⁶⁰

Kim et al reported on a unique form of ONH, superior segmental ONH, in which the superior portion of the optic nerve head is underdeveloped, and found gestational diabetes in all 10 cases.⁴⁰ Superior segmental ONH, however, is clinically distinct from typical ONH with presentation in older children and adults with isolated visual field defects. Phenotypic differences raise concern about the validity of generalizing these findings to ONH overall. Only isolated cases of gestational diabetes have been identified in epidemiologic studies employing systematic, standardized assessments of typical ONH.^{21; 69}

Two cross-sectional studies of ocular abnormalities in children with fetal alcohol syndrome (FAS) suggest that prenatal alcohol exposure is an etiologic correlate of ONH. Stromland and Ribiero et al compared findings from FAS cohorts of similar size (approximately 30 cases) to a control of non-FAS children. Respectively, ONH was detected in 48% (14/30) and 25% (8/32) of cases of FAS but not in the control group.^{57; 63} Although ONH may be common in children with FAS, prenatal alcohol exposure was infrequently identified in other studies on ONH (Table 2).^{12; 19; 59} including two epidemiologic studies using standardized assessment compared to population birth data.^{21; 47; 69}

In 1990, Roberts-Harry et al examined 40 consecutive cases of ONH to distinguish the maternal features of 34 bilateral, and six unilateral cases. They found that maternal age was not remarkably young and that two cases (6%) of bilateral ONH had prenatal exposure to

alcohol.⁵⁹ Burke et al reviewed the prenatal features of 46 consecutive cases of bilateral ONH and reported an association between preterm births and toxemia in three cases, twin-twin transfusion syndrome in two cases, and maternal anemia in one case. In term infants with ONH, they found prenatal alcohol exposure in one case.¹² In a Scottish study, Murray et al compared the maternal features of 26 cases of ONH seen in an endocrinology clinic to the general population. Mothers of affected cases were statistically significantly younger overall (median 21 years vs 27 years) and more likely to be primiparous (73% vs 54%). Decreased maternal age persisted after restricting the analysis to primiparous mothers: median 20 years compared to 25 years.⁵¹ Haddad and Eugster also found decreased maternal age (mean 20.2 years) and 74% primiparity in 56 cases of ONH (equal gender distribution) in an endocrinology clinical cohort of ONH cases.²⁷ In 100 consecutive cases (males 1.8:1) of ONH, Garcia et al. found prenatal alcohol exposure in nine (9%), gestational diabetes in six (6%), and cocaine exposure in one (1%).²² McNay et al reported decreased maternal age compared to cases with isolated hypopituitarism in a large cohort of ONH (25.1 ± 1.6 years vs 29.0 ± 1.9 years) and documented prenatal alcohol exposure in seven (2%) cases.⁴⁷

To date, there have been two epidemiologic studies that assessed the maternal and prenatal features associated with ONH in comparison to a control group. The first, in Sweden, was a study of prenatal risk factors of ONH identified from a population-based registry of visually impaired (VI) children.⁶⁹ Population birth data during the same time period comprised the comparison group. For cases of ONH, VI registry data provided information on prenatal complications. Standardized surveys gathered data on exposure to smoking and recreational or prescription drugs in the first trimester. Of the 125 cases of ONH in the study population, of which prenatal exposure data were available for 100. Using a weighted analysis, odds ratios (OR) were estimated for maternal age, parity, and prenatal smoking. This revealed an increased risk with decreasing maternal age and primiparity. Specifically, mothers between 20–24 years of age were at greatest risk (OR: 1.5; 95% CI: 1.02, 2.21). The OR dropped below 0.88 for women 25 years and older until age 40 years when the risk appeared to rise. Primiparous women were at greatest risk with an OR of 1.73 (95% CI: 1.16, 2.58). Early prenatal smoking was associated with an increased risk and appeared to be a proportional dose-response relationship. Toxemia was found in four cases. Incidental prenatal exposures noted in this study were addressed in the preceding sub-section. A strength of this study is the thorough prenatal documentation of complications and exposures to smoking and drugs. This study was limited by the restriction of exposure data to a single (variable) time point in the first trimester.⁶⁹

In a prospective registry study of near consecutive cases with ONH, Garcia-Filion et al retrospectively analyzed the prenatal histories for 204 cases of ONH in comparison to national birth data. A systematic maternal questionnaire collected details on the entire prenatal course for 105 cases: index pregnancy characteristics; complications; maternal weight; exposure to smoking, alcohol, and prescription and illicit drugs; and reproductive and family history. There was an apparent racial/ethnic predilection for Caucasians and protection for Hispanics and Asian-Pacific Islander populations. Young maternal age and primiparity were identified as independent correlates. Gestational diabetes (eight cases), toxemia (eleven cases), and viral infection (two cases with CMV) were rare. The use of alcohol, smoking, and prescription and illicit drugs was isolated to a few cases. The prenatal histories were remarkable for a high frequency of preterm labor in the second trimester, vaginal bleeding in the first trimester, and low maternal weight gain or weight loss in the first to second trimesters. Consequently, the authors suggested a potential role for prenatal nutrition and weight gain in ONH.²⁰

The epidemiologic focus shifted from individual level analyses with an area based study of cases of ONH. In northwest England, Patel et al examined the geographic distribution, based

on the residential address at the time of first clinical presentation, of 87 cases of ONH to identify spatial clusters and demographic risk factors. Standardized incidence ratios (SIRs) of census districts were estimated and correlated with district measures of socio-demographic factors. Overall, SIR estimates were positively correlated with the frequency of unemployment, low income households, and teenage pregnancy. Three apparent clusters were identified: elevated SIRs 167 – 198%. Each cluster, compared to all of northwest England, had a higher frequency of teenage pregnancy (8.9 vs 6.3 per 1000 females 13–15 years of age), unemployment (13.6% vs 8.8%) and low-income households (26.9% vs 14.2%). Incidental prenatal exposures noted in this study were described previously. Patel et al concluded that there was an association of ONH with social deprivation, suggesting that the increased risk of ONH reflects an underlying tendency towards unhealthy behaviors and/or environmental exposures. Maternal demographics in this cohort are unknown. Additionally, the residential address at the time of first clinical presentation is subject to multiple secondary factors that may not reflect the maternal prenatal socio-demographics and exposures. Nevertheless, this is the first study to address the presence of disease clusters.⁵³

Evidence for a genetic linkage

Familial Cases—There are sporadic reports of familial cases of ONH^{1; 4; 6; 13; 14; 26; 41; 49; 65; 70}, suggesting a genetic causative factor. These cases are commonly described under an umbrella diagnosis of septo-optic dysplasia, with the criteria of ONH plus hypopituitarism and/or midline brain defects. There are only five reports that identify ONH in the affected cases. Three of these were available for review and are described here.

A set of monozygotic twins with mild unilateral segmental ONH in opposite eyes and no endocrine or developmental problems provides strong evidence of genetic predisposition since the monozygotic twinning event precedes formation of the retinal ganglion cells.¹³ This report also suggests that the pathogenic mechanism for segmental ONH may be the result of local failure of retinal ganglion cell differentiation under genetic control or to a simultaneous environmental effect, whereas more severe ONH associated with systemic problems may be related to more generalized dysregulation of neuronal path finding or apoptosis.

Hackenbruch et al described three females with ONH from different generations of a non-consanguineous family. No systemic or developmental problems were described, and the funduscopy photographs suggest optic atrophy rather than optic nerve hypoplasia. Two deceased male members of the family were possible cases of ONH owing to visual impairment, but there was no supporting ophthalmologic evidence.²⁶

Benner et al described two siblings, both with ONH, hydrocephalus, partial agenesis of the corpus callosum, seizures, and possible hypopituitarism.⁴ There are two other case reports of suspected familial ONH that were unavailable for review.^{41; 49}

The paucity of familial cases and lack of monozygotic twins with definite ONH argue against a primarily hereditary cause. Prenatal environmental risks would be expected to occasionally impact multiple members of the same family. Conversely, a genetic cause remains possible until a case of discordant monozygotic twins is reported.

Many researchers have noted a phenotypic overlap of ONH with other isolated or combined CNS abnormalities (e.g. agenesis of the corpus callosum, holoprosencephaly, combined pituitary hormone deficiency). The overlap led to loosening the term septo-optic dysplasia to represent a continuum in which ONH was no longer required.^{16; 44; 47; 55; 56; 71}

Consequently, the error noted in reported familial ONH is misclassification of cases with hypopituitarism and/or midline brain malformations without hypoplastic optic nerves as “septo-optic dysplasia”. In a report entitled, “Evidence for possible Mendelian inheritance of septo-optic dysplasia”, Wales and Quarrel presented a brother and sister born of consanguineous parents who had hypopituitarism and absent corpus callosum and septum pellucidum.⁷⁰ Ophthalmologic examination was normal in both cases. Despite this, they were incorrectly considered to have ONH in their clinical phenotypes of “septo-optic dysplasia” in subsequent genetic reports.^{10; 16; 38; 39; 44; 72} Thomas et al also described familial “septo-optic dysplasia” in two male siblings (nonconsanguineous parents) with isolated hypopituitarism. One sibling had normal optic nerves and vision. The other sibling had “dysplastic” optic discs with normal vision, and dysmorphic features of the face and limbs.⁶⁷ These cases were incorrectly characterized in subsequent literature^{44; 71} as having ONH. Other familial events described in the literature involved clinical phenotypes of hypopituitarism and/or midline defects in multiple members, only one of whom also had ONH.^{1; 6}

Genetic Mutations—Numerous genes have been ascribed pathogenic linkage to ONH because of the phenotypic overlap with CNS abnormalities previously described. The highly conserved embryonic development of the forebrain, pituitary, and ocular structures between mice and humans encourages the translational potential for identifying a common gene mutation leading to defects in humans. Research on murine models found that mutations in HESX1¹⁶, SOX2⁶⁶, SOX3⁵⁸, OTX2³, FGF8¹¹, and PROKR2⁶⁴ disturb morphogenesis of the forebrain, midline brain, hypothalamus, pituitary gland, olfactory and/or ocular structures resulting in phenotypes similar to some human congenital defects.^{15; 39; 44; 55; 56; 72; 74} Although these models have enhanced our understanding of prosencephalic development, the observed ocular abnormalities of anophthalmia, microphthalmia and retinal dystrophy are distinct from ONH, in which the only ocular defect is absence of retinal ganglion cells.

In a recent review, by McCabe et al of the gene mutations linked with “septo-optic dysplasia”, nearly all mutations were detected in cases with hypopituitarism and/or midline malformation without ONH.⁴⁴ Isolated cases of ONH with genetic mutations exist in the literature, however.

In 1998, Dattani et al described the first genetic mutation (HESX1) in a study of 20 cases [familial (n=2) and sporadic (n=18)] of “septo-optic dysplasia”. A homozygous HESX1 mutation (R160C) was identified in the familial cases (male and female siblings from a consanguineous family) that Dattani et al. described as having “ONH”,¹⁶ the same cases previously described by Wales and Quarrel as having normal optic nerves and vision.⁷⁰ No mutations were found in the sporadic cases.¹⁶ Subsequent research by this group led to identification of four additional cases with mutations in the HESX1 gene associated with “ONH” in their “SOD” phenotype. The four patients in whom the two additional HESX1 gene mutations (S170L^{10; 67}, E149K⁴⁷) were identified did not have ONH. Thomas et al described a HESX1 mutation (S170L) in male siblings (described above) with isolated growth hormone deficiency.⁶⁷ Their clinical phenotypes have been incorrectly described as including “ONH”.⁴⁴ Another case, presented by Brickman et al, had a similar HESX1 genetic mutation (S170L) with isolated growth hormone deficiency and no ocular abnormalities.¹⁰ In a cohort study (n=861) of “septo-optic dysplasia” (n=357) and hypopituitarism, McNay et al found a HESX1 mutation (E149K) in a patient identified as “septo-optic dysplasia” with a clinical phenotype of hypopituitarism, midline pituitary defects, supernumerary digits, but no ocular abnormalities. Within this same study, at least 8% of patients described as “septo-optic dysplasia” had no ocular abnormalities. None of the above patients with a HESX1 mutation exhibited ONH. This, combined with the rarity of

mutations in a large series of cases, led McNay et al to conclude that the HESX1 mutation is an unlikely culprit in ONH.⁴⁷

There are, however, two cases with presumed ONH (suspected by MRI only) with novel HESX1 mutations. The first, described by Tajima et al, was a HESX1 mutation (306/307Ins AG) in a patient with hypopituitarism, midline brain defects, and unilateral ONH.⁶⁵ In the second, Cohen et al identified a HESX1 mutation (d.1684delG) in a case with bilateral vision impairment and evolving growth hormone deficiency. They showed that this mutation of HESX1, which is expressed exclusively in Rathke's pouch, down regulates the subsequent expression of PROP1 through DNA heterodimerization.¹⁴ PROP1 expression regulates pituitary secretory cell differentiation. No mechanism by which HESX1 could impact retinal ganglion cell differentiation or apoptosis has ever been demonstrated.

Human cases with a SOX2, SOX3 or OTX2 mutation have clinical phenotypes of hypopituitarism, midline defects, and/or ocular malformations including anophthalmia or microphthalmia and rarely coloboma.⁴⁴ Disruptions of SOX2 and OTX2 preclude normal development of the optic vesicle and optic cup, with affected individuals having anophthalmia or microphthalmia.^{24; 66} The optic nerves in such cases may be technically hypoplastic, but such ocular abnormalities are not part of the ONH syndrome. A recent case report by Gorbenko del Blanco et al, however, describes an OTX2 mutation in a case of hypopituitarism with a MRI finding of a single small optic nerve.²⁴ Ocular malformations have not been reported in patients with a SOX3 mutation.

Recently, Raivio et al described novel mutations of three genes associated with "septo-optic dysplasia"—FGFR1, FGF8 and PROKR2. None of the patients with a FGFR1 or FGF8 mutation exhibited ONH. A heterozygous mutation in PROKR2 was identified in a patient with ONH.⁵⁶

Analysis

Past research collectively produced a broad spectrum of prenatal factors which may predispose offspring to ONH. With the exception of the persistent finding of young maternal age and primiparity, heterogeneous prenatal histories of cases of ONH render the pathogenic factors largely unknown. The suggested prenatal correlates can be categorized into maternal factors, prenatal exposures, and genetic factors.

Maternal Factors

The preponderance of youth and primiparity in the majority of cases is striking although the significance of these maternal features to ONH is unclear. Young maternal age emerged as a unique feature among cases of ONH in 1978. Immediately following the first report, two research groups reported in letters to the editor, decreased maternal age among their cases of ONH.^{18; 42} Although initially suggested as a coincidence³⁶, evidence that mothers of children with ONH tended to be younger grew quickly. Maternal age may be a surrogate for multiple health and demographic factors that drive prenatal risks. While mothers of offspring with ONH tend to be younger on average, it is unclear in past research whether there were other etiologic factors present (e.g. socioeconomic factors, nutritional status). The remarkably high prevalence of primiparity could simply be an effect of young maternal age. This confounding hypothesis was refuted by results from the studies by Tornqvist et al, Murray et al and Garcia-Filion et al, that reported parity as an independent risk factor after adjusting for maternal age. Young maternal age and primiparity are the most persistent correlates of ONH.^{20; 69}

Many reports speculate that the young maternal age can be linked to increased risk of unhealthy behavior and poor preconceptional health.^{47; 51; 53; 59} The speculation has been predicated on anecdotal or case reports, the lowest level of evidence. This hypothesis is complicated by a dearth of findings of risky behavior in epidemiologic studies employing standard assessment methods with a control group (a higher level of evidence).²⁵

Prenatal Exposures

The occurrence of ONH has long been linked to recreational or prescription drugs, viral infection, maternal diabetes, and smoking and alcohol use during pregnancy. These are generally based on isolated exposures or case reports, and provide the lowest level of evidence.²⁵ Maternal diabetes may be unique to a subset of cases with segmental ONH, but is otherwise sporadic among cases of ONH. Smoking as a risk factor as reported by Tornqvist et al⁶⁹, first suggested by Murdoch and Zeki in a letter to editor,⁵⁰ is challenged by the finding of infrequent exposure to smoking, measured by a standard interview, in a cohort study by Garcia-Filion et al. Alcohol as a risk factor remains questionable. If indeed ONH comprises up to half of the cases of FAS as suggested by Stromland, then the prevalence of ONH should far exceed the current estimate of 1 per 10,000. The high frequency of prenatal alcohol exposure reported by Stromland and Ribiero et al is more likely a reflection of a focus on cases of FAS.^{57; 63} The purported contributory role of recreational or prescription drugs, viral infection, smoking and alcohol, factors pervasively reported in publications on ONH, is based on weak evidence. These are unlikely to be major contributors based on higher level of evidence; however, in rare defects with heterogeneous prenatal histories, one cannot entirely dismiss the likelihood of a combination of factors that may include these or other unmeasured exposures.

Genetic factors

Genetic mutations in cases of ONH are rare, and a specific genotype/phenotype correlation has yet to be found to explain the majority of cases. A genetic link is suggested by findings of gender predisposition^{22; 37; 40; 43; 57; 60}, heritability^{4; 13; 26; 41; 49}, and sporadic reports of genetic mutations.^{14; 24; 56; 65}

Murine mutant models have revealed the role of many genes in development of the diencephalon, globe and retina.^{3; 11; 16; 58; 64; 66} Some of these genes are likely involved in the development of ONH. Thus far, however, all murine mutant models have more extensive ocular and retinal dysgenesis than is seen with human ONH.

The majority of the reports on associated genetic mutations in humans either dismissed ONH as a requisite feature of septo-optic dysplasia or were incorrect classifications of ONH.⁴⁴ Without ONH, such cases do not fit the diagnostic criteria and more likely reflect a different etiology. We did, however, find documentation of mutations in four cases with suspected ONH by MRI: two cases with a HESX1 mutation, one case with an OTX2 mutation and one case with a PROKR2 mutation.^{14; 24; 56; 65}

The etiology of ONH is likely multifactorial involving a gene-environment interaction, whereby gene variants modify susceptibility to a toxic or beneficial product that influences the biologic response. Attributing ONH to a single genetic mutation is unlikely, but remains possible. The pathogenesis of ONH more likely reflects a combination of factors that disrupt the temporally and spatially dependent cascade of genes required for early neuronal genesis during a gestational window of heightened vulnerability.

Limitations of Past Research

Reports addressing prenatal determinants of ONH are subject to methodological limitations not unique to epidemiologic investigations of rare birth defects. The selection of case samples and retrospective nature of data collection inject the greatest likelihood of bias. Cases often originated from a single clinic source that may represent a subset for which the prenatal characteristics may differ from population of ONH overall. This is best exemplified by the selection of cases based on alcohol exposure status in the studies by Stromland and Ribiero et al.^{57; 63} The likelihood of information bias is high owing to the retrospective ascertainment of prenatal exposures from medical records or parental report. Exposures typically are not captured systematically in the prenatal period and absence of documentation cannot be as absence of exposure. Additionally, there is the likelihood that mothers of affected children recall a potentially adverse prenatal exposure more often than mothers of children without a birth defect. This may be exacerbated by increased disease severity or a diagnostician probing for an explanation of the birth defect. Standardized assessments may alleviate these limitations. To date, there have been two epidemiologic studies employing an assessment questionnaire in addition to a control group^{21; 69}, one of which lacked an ideal control group.²¹

Future Research Directions

After 50 years of epidemiological research, there has been little progress in the identification of etiologic correlates of a seemingly epidemic birth defect associated with a profound lifelong morbidity. We describe and summarize the prenatal features linked with ONH to provide direction for future research. Collectively, there are select prominent features: young maternal age and primiparity. Commonly implicated prenatal exposures (i.e., recreational or pharmaceutical drugs, viral infection, etc.) are uncommon and, thus, are not likely to be major contributors to ONH. Research efforts should redirect the focus on these uncommon exposures and investigate other potential factors for which young maternal age and primiparity may be a surrogate.

Early reports speculated that the decreased maternal age in ONH was a proxy for unhealthy behavior involving recreational drugs and alcohol. There is little evidence for this hypothesis. Rather, young maternal age and primiparity are likely proxies for multiple other underlying health and demographic factors that may drive risk for ONH but are unexplored as of yet.

Only one other birth defect has been associated with young maternal age - gastroschisis.³¹ In gastroschisis, the increased risk of decreased maternal age has been correlated with inadequate prenatal nutrition⁶⁸ and low body mass index (BMI)⁶¹. From a prospective cohort study of ONH, the findings of low prenatal BMI, inadequate weight gain and first or second trimester weight loss in early gestation suggest a similar association for ONH.²⁰ This inverse correlation of increased risk with low prenatal weight status is in sharp contrast to published reports linking obesity to congenital anomalies⁶² and highlights a unique opportunity to examine the role of prenatal weight and nutritional status in ONH. Methods should focus on the assessment of prenatal weight status (preconception, weight gain, and weight loss), nutritional status (preconception and early gestation), demographics, and interaction with maternal age.

Until recently, epidemiological research of ONH has focused on the individual prenatal profile of offspring with ONH. The rapid rise in prevalence of ONH, our anecdotal clinical observations of spatial clusters (unpublished), and a recent report of spatial clusters in an urban area of England suggests there may be another unexplored epidemiological feature of ONH – spatial clustering. From an ecological study, Patel et al reported an association of

spatial clusters of ONH with population factors of deprivation.⁵³ While these are crude indicators of deprivation, this report provides evidence that poor health status may be a contributing factor to the development of ONH. The existence of disease clusters of ONH and an underlying association with population characteristics in other countries is unknown and should be studied. Such research may aid epidemiologic efforts by identifying geographic areas with a high density of cases and unique demographics for individual level study designs.

Conclusion

Researchers have not identified the etiologic correlates that predispose offspring to ONH. Throughout the past 50 years, the only persistent prenatal features of ONH have been young maternal age and primiparity. Research in recent years identified a potential role for prenatal nutrition, weight gain, and population factors of deprivation. The interaction of these factors with young maternal age and primiparity is unexplored. Future endeavors should concentrate on elucidating the surrogate role of decreased maternal age and primiparity, employing methodology designed to tackle the challenges of birth defect research.

Methods of Literature Search

The authors searched the MEDLINE database for articles published between 1915 and 2010. Search words used included optic nerve hypoplasia, etiology, prenatal, cause of, septo-optic dysplasia, epidemiology, and risk factors. Additional references of key articles were examined and only those articles judged to be of clinical importance were included. Studies were excluded if they were reports of isolated cases with clinical characteristics beyond those commonly seen with ONH.

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Figure 1a.

Figure 1b.

Figure 1.
Figure 1a. Normal optic nerve. Dashed lines indicate the perimeter of the optic disc, which is filled entirely by the optic nerve.

Figure 1b. Hypoplastic optic nerve. The dashed line circle indicate the perimeter of the optic disc. The arrow indicates the optic nerve, which incompletely fills the optic disc.

Table 1

Suggested risk factors based on anecdotal reports

Prenatal Correlate	1st Author, Year
Intrauterine growth restriction	Hellstrom, 1999; Birkabaek, 2003
Threatened abortion	Roberts-Harry, 1990
Twin-twin transfusion syndrome	Burke, 1991
History of birth defects in multiparous women	Tornqvist, 2002
Recreational drugs	Hoyt, 1978; Hotchkiss, 1979; Michaud, 1982; Margalith, 1984; Orrico, 2002; Patel, 2006
Antidepressants	Hellstrom, 1999; Tornqvist, 2002; Birkebaek, 2003
Anticonvulsants	Hoyt, 1978; McMahon, 2001; West, 1990
Anti-emetics	Roberts-Harry, 1990
Antifungal agents	Tornqvist, 2002
Infertility treatment	Tornqvist, 2002
Quinine	McKinna, 1966; Amatyakul, 2007
Prenatal Complications	Reidl, 2002
Viral Infection	Hitner, 1976; Burke, 1991; Bistner, 1973; Margalith, 1984; Hellstrom, 2000
Anemia	Roberts-Harry, 1990; Burke, 1991
Trauma	Margalith, 1984

Table 2

Prenatal correlates arising from case series or epidemiologic studies

1 st Author, Year	Country	N	Study Population	Prenatal Exposure Studied	Data Source	Comparison Group	Results		
							Maternal	Prenatal Exposures	Birth Findings
Jan, 1977	Canada	20	Population cohort of cases in B.C. ^a	Documented prenatal exposures	Medical record	Population birth statistics – B.C.		Toxemia	Females ^b
Margalith, 1984	Canada	51	B.C. cohort + bilateral cases (neurology) ^a	Maternal factors and noted prenatal exposures	Medical record	Population birth statistics – B.C.	Young maternal age; primiparity	Toxemia; gestational viral bleeding; viral infection; alcohol abuse (n=1)	Females ^b
Robinson, 1986	Canada	54	B.C. cohort + bilateral cases born in B.C. (neurology) ^a	Maternal age	Birth registry	Population sample of cases of CP and FAS (B.C.)	Young maternal age		Females ^b
Kim, 1989	USA	10	Superior segmental ONH	Gestational diabetes	Medical record	None		Gestational diabetes in 100%	Females
Siromland, 1985/ Ribiero, 2001	Sweden Portugal	30 32	Cases of ONH with FAS	Alcohol use	Medical record	None		Alcohol abuse Alcohol abuse	Males
Roberts-Harry, 1990	England	40	Clinic cohort	Documented prenatal exposures	Medical record	None		Alcohol abuse (n=2)	
Burke, 1991	Ireland	46	Bilateral ONH	Documented prenatal exposures	Medical record	None		Toxemia (n=3), twin-twin transfusion syndrome (n=2), maternal anemia (n=1), alcohol use (n=1)	
Hellsrom, 2000	Sweden	117	Clinic cohort	Documented prenatal exposures	Medical record	None		Alcohol use (n=25), CMV (n=2)	SGA (12 cases)
Tomqvist, 2002	Sweden	125	Population cohort of bilateral ONH (1979–1997)	Maternal factors; smoking; and noted prenatal exposures	Birth registry; medical record survey data (up to 12 weeks)	Population births	Young maternal age; primiparity	Smoking ↑OR; antidepressants (n=3), infertility treatment (n=2), recreational drugs	SGA
Fahnhelm, 2003	Sweden	28	Bilateral ONH	CMV infection	Birth registry	Cases of optic nerve coloboma		Smoking	
Murray, 2005	Scotland	30	Clinic cohort	Maternal age; parity	Medical record	Population birth statistics	Young maternal age; primiparity		
Haddad, 2005	USA	56	Clinic cohort	Maternal factors; noted prenatal exposures	Medical record	None	Young maternal age; primiparity		
Garcia, 2006	USA	100	Clinic cohort	Documented prenatal exposures	Medical record	None		Alcohol use (n=9); gestational diabetes (n=6)	Males
McNay, 2007	England	314	International cohort of ONH	Genetic mutations; maternal factors; noted exposures	Medical record	Cases of hypopituitarism	Young maternal age; primiparity	Alcohol use (n=7)	HESX1 mutation (n=1)
Patel, 2006	England	86	Population cohort	Socio-demographic correlates	Medical record	Population socio-demographic statistics	Area correlation with low maternal age,	Gestational diabetes (n=1); recreational drug use (n=1)	

1 st Author, Year	Country	N	Study Population	Prenatal Exposure Studied	Data Source	Comparison Group	Results		
							Maternal	Prenatal Exposures	Birth Findings
Garcia-Filion, 2010 ^c	USA	204	Clinic cohort/registry	Maternal factors and exposures	Registry data; standard survey	Population birth data	unemployment, low income. Young maternal age; primiparity; low weight gain; weight loss; gestational vaginal bleeding	Gestational diabetes (n=8); prenatal infections (n=8); habitual alcohol use (n=2); recreational drug use (n=11)	Preterm labor; single case among 5 sets of twins & 1 set of triplets

^aThe original B.C. cohort (Jan et al. 1977) expanded to conduct research specific questions.

^bFinding shared between the three B.C. cohorts.

^cDetails on the full prenatal course available for 105 cases.