BIRTH DEFECT RISK FACTOR SERIES: HYDROCEPHALY

DEFINITION

Hydrocephaly is an enlargement of the head caused by an abnormal accumulation of cerebrospinal fluid (CSF) in the cranium due to an imbalance between the production and absorption of CSF. This forces the ventricles to enlarge (ventricular dilatation or ventriculomegaly), which in turn exerts pressure on the surrounding brain tissue, causing the brain tissue to shrink and the head to enlarge (Schrander-Stumpel 1998, Buyse 1990, Vintzileos 1983).

Congenital hydrocephaly is one of the most common central nervous system anomalies. This generally refers to a condition that exists prenatally and excludes other neural tube defects (Fernell 1987); this condition usually develops by the twentieth week of gestation (Stoll 1992), and defect can occur either alone, in association with spina bifida, or as part of a greater syndrome, such as Dandy-Walker Syndrome.

There are various types or classifications of congenital hydrocephaly. Aqueductal stenosis is a type of hydrocephaly that results from narrowing of the aqueduct of Sylvius, an opening connecting the third and fourth ventricles in the brain. It is the most common form of hydrocephaly. Dandy-Walker syndrome is a group of defects consisting of enlargement of the fourth ventricle of the brain, complete or partial absence of the cerebellar vermis (the middle area between the two cerebral hemispheres), cysts of the posterior fossa (internal base of the skull), and hydrocephaly. The hydrocephaly associated with Dandy-Walker syndrome may not be present at birth but develop later (Buyse 1990). Dandy-Walker syndrome accounts for 5-12% of hydrocephaly cases (Vintzileos 1983).

ETIOLOGY

Congenital hydrocephaly is heterogeneous in origin. This defect can occur as a result of a chromosomal abnormality, a prenatal infection, or a non-genetic structural defect. Maternal infection with toxoplasmosis and cytomegalovirus (CMV) can both result in hydrocephaly (Partington 2001). These infections can cause structural problems in the fetus, specially, cranial lesions that may cause hydrocephaly. Unexpectedly, these lesions are less likely to form in children born to mothers that experienced a delay in treatment or were not treated at all. It is unclear if this is due to lack of exposure to pyrimethamine-sulfadiazine treatments (Gras 2001).

The defect can be associated with chromosomal abnormalities (trisomy 13, trisomy 18, triploidy, etc.) and other syndromes (Walker-Wardburg syndrome, Meckel syndrome, Smith-Lemli-Opitz syndrome, chondrodystrophies, etc.). About one-quarter of the infants with hydrocephaly also have spina bifida; conversely, approximately 80% of children with spina bifida also have hydrocephaly. Hydrocephaly can also be secondary to central nervous system anomalies (encephalocele, holoprosencephaly, neoplasms, etc.). The majority of congenital hydrocephaly cases have other additional birth defects such as congenital heart disease and cleft lip and/or palate (Schrander-Stumpel 1998, Stoll 1992, Buyse 1990, Drugan 1989, Hudgins 1988, Vintzileos 1983, Chervenak 1985).

One specific gene that has been associated with this defect is L1, which is located on the Xq28 region. Mutations to the L1 cell adhesion molecule can manifest as a variety abnormalities and developmental delays (Partington 2001). Multiple syndromes are associated with this mutation, including MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs) syndrome and CRASH (corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus) syndrome. This indicates that mental retardation associated with hydrocephaly may not be related to the reduced-size of the ventricles, but related to an underlying genetic disorder (Partington 2001).

Non-genetic structural defects can occur for a variety of reasons. Hydrocephaly is positively associated with spina bifida. This defect is often caused by a lack of folate/folic acid in the maternal diet (Partington 2001). Prepregnancy multivitamin supplementation has also been shown to reeduce the risk of isolated hydrocephaly (Goh 2006).

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

No clear **racial** differences in congenital hydrocephaly risk are recognized (Stoll 1992, Wiswell 1990). One study completed in Brooklyn, New York indicated that there were increased rates of hydrocephaly among Puerto Rican mothers; however, the rates for African-American and Caucasian mothers were not significantly different (Sherman 1981).

A **secular trend** for congenital hydrocephaly has been reported by one study, where a decline in prevalence over time was found, paralleling the decline in neural tube defect prevalence (Stone 1989). However, another investigation observed no trend (Wiswell 1990). There does not appear to be any **seasonal variation** in congenital hydrocephaly prevalence (Stoll 1992, Castilla 1990, Wiswell 1990).

Hydrocephaly (ventriculomegaly) can be detected prenatally by ultrasonography (Fadel 1989, Vinzileos, 1987). Studies from various birth defects surveillance systems have found that, in regions where elective termination is allowed, prenatal diagnosis and elective termination reduce the birth prevalence of congenital hydrocephaly (Stoll 1992, Stone 1989, Drugan 1989, Hudgins 1988, Chervenak 1985).

Low socioeconomic status is a risk factor for all non-genetic defects, including hydrocephaly (Vrijheid 2000). Maternal residence near a landfill or solid waste incinerator is not a risk factor for this defect (Cordier 2003, Harrison 2003).

Congenital hydrocephaly prevalence does not appear to be influenced by **geographic location** (Stoll 1992). However, one study found a reduction in hydrocephaly risk with **higher altitudes** (Castilla 1999).

Maternal obesity has been positively associated with increased risk of isolated hydrocephaly (Anderson 2005).

Parental age does not seem to affect risk of having a child with hydrocephaly (Stoll 1992). In a different study, young maternal age was associated with a higher risk of hydrocephaly. However, the authors felt that this may be due to the fact that younger mothers are not subjected to prenatal testing to the same extend as older mothers. This may lead to more younger mothers carrying an affected infant to term (Reefhuis 2004).

A woman who has had one child with congenital hydrocephaly has a **recurrence risk** of 1-5% of having another affected child. If the hydrocephaly is associated with an inherited disorder, the risk is higher (Schrander-Stumpel 1998, Buyse 1990). Hydrocephaly rates have been reported to be higher for **consanguineous parents** (Rajab 1998, Stoll, 1992).

Infant sex does not appear to influence congenital hydrocephaly risk; males and females are equally affected (Stoll 1992, Buyse 1990). However, one study did report predominance among males (Wiswell 1990). **Plurality** has not been linked to congenital hydrocephaly risk (Stoll 1992).

FACTORS IN LIFESTYLE OR ENVIRONMENT

Maternal prenatal **infection** (toxoplasmosis, syphilis, cytomegalovirus, rubella) has been strongly associated with increased hydrocephaly prevalence (Schrander-Stumpel 1998, Stoll 1992, Vintzileos 1983). One investigation failed to find any effect on hydrocephaly risk for maternal **diabetes**, **epilepsy**, **x-rays**, **hypertension**, **fever**, **antihistamine exposure**, or **occupational exposure** (Kallen 2002, Stoll, 1992). Another study found no relationship between parental occupation of **farmer** and hydrocephaly prevalence; however, the study suggested increased hydrocephaly risk with parental **pesticide** exposure (Kristensen 1997).

Several studies have evaluated the relationship between maternal **multivitamin use** and congenital hydrocephaly risk. The studies found a slight reduction in risk; however, this reduction was not considered to be significant (Werler 1999, Czeizel 1993). This reduction is most likely correlated to the reduced risk of neural tube defects, specifically spina bifida, associated with multi-vitamin use. Most infants effected with spina bifida manifest hydrocephaly as well.

One study indicated that there was an increased risk of hydrocephaly and other defects associated with maternal exposure to **anesthesia** (Sylvester 1994). This study was limited, but the correlation was strongest when maternal exposure was in the first trimester.

Exposures to human **lymphocytic choriomeningitis virus** (a rodent borne-illness) during the first or second trimesters of pregnancy can cause hydrocephalus (Promed 2005). This illness is generally contracted through direct contact with domestic rodents, including mice, rats, hamsters, and gerbils (Promed 2005).

Maternal **thyroid disease** (hyperthyroidism or hypothyroidism) when treated did not increase the risk for hydrocephaly (Khoury 1989). Maternal exposure to **chemotherapy** during the second and third trimesters of pregnancy does not increase the risk of this defect (Cardonic 2004); nor does the use of **marijuana** (Fried 2000), **fluoxetine (**Prozac™) (Chambers 1996) or **cortico-steroids** (Park-Wyllie 2000).

PREVALENCE

The hydrocephaly prevalence rate in Texas for 1999-2003 deliveries was 7.07 cases per 10,000 live births (Texas Department of State Health Services 2006). Birth prevalence in the United States for hydrocephaly without spina bifida ranges from 0.35-15.34 per 10,000 live births (National Center on Birth Defects and Developmental Disabilities 2006). Differences in prevalence may be due to differences in case inclusion criteria.

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Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information. This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.*

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