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A systematic review of the risks factors associated with the onset and natural progression of hydrocephalus

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ABSTRACT

The purpose of this study was to systematically assess and synthesize the world literature on risk factors for the onset and natural progression of hydrocephalus, thereby providing a basis for policy makers to identify appropriate risk management measures to mitigate the burden of disease in Canada. Evidence for risk factors was limited for both onset and progression. Two meta-analyses that examined a risk factor for onset met the inclusion criteria. One found a significant protective effect of prenatal vitamins among case control studies, but not cohort/randomized controlled trials (RCTs). The second found maternal obesity to be a significant risk factor for congenital hydrocephalus. Significant risk factors among 25 observational studies included: biological (multiple births, maternal parity, common cold with fever, maternal thyroid disease, family history, preterm birth, hypertension, ischemic heart disease, ischemic ECG changes, higher cerebrospinal fluid protein concentration following vestibular schwannoma); lifestyle (maternal obesity, high-density lipoprotein (HDL) cholesterol, maternal diabetes, maternal age), healthcare-related (caesarean section, interhospital transfer, drainage duration following subarachnoid hemorrhage, proximity to midline for craniectomy following traumatic brain injury); pharmaceutical (prenatal exposure to: tribenoside, metronidazole, anesthesia, opioids); and environmental (altitude, paternal occupation). Three studies reported on genetic risk factors: no significant associations were found. There are major gaps in the literature with respect to risk factors for the natural progression of hydrocephalus. Only two observational studies were included and three factors reported. Many risk factors for the onset of hydrocephalus have been studied; for most, evidence remains limited or inconclusive. More work is needed to confirm any causal associations and better inform policy.

1. Introduction

Hydrocephalus is a condition in which excess cerebrospinal fluid (CSF) builds up inside the cavities of the brain (known as ventricles). Under normal conditions, CSF bathes the Central Nervous System (CNS, referring to the brain and spinal cord) and provides protection through cushioning and support; it brings nutrients to the brain, removes waste, and helps regulate intracranial pressure (National Institute of Neurological Disorders and Stroke, 2011; Spina Bifida & Hydrocephalus Association of Ontario, 2013; Spina Bifida & Hydrocephalus Canada, 2007; Princeton Brain & Spine Care, 2012). CSF is continually being produced, cycled through the CNS, and reabsorbed by the bloodstream. Hydrocephalus occurs when the rate of production of CSF is greater than the rate of re-absorption, and/or when drainage pathways are blocked. When this happens, the excess CSF accumulation may cause swelling and/or abnormal widening of the ventricles, which can create potentially harmful pressure on surrounding tissue.

Symptoms of hydrocephalus can vary with age. During infancy there may be vomiting, sleepiness, and the head circumference can increase to accommodate the extra fluid, which can be a visible change (National Institute of Neurological Disorders and Stroke, 2011). Hydrocephalus in older children and adults can have symptoms such as headaches, vomiting, balance problems, urinary incontinence and even memory loss (National Institute of Neurological Disorders and Stroke, 2011). Diagnosis of hydrocephalus may require a neurological exam, a computed tomography (CT) or magnetic resonance imaging (MRI) exam (National Institute of Neurological Disorders and Stroke, 2011).

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Hydrocephalus can be congenital (CHC) (developed prior to birth) or acquired (AHC) (developed during or after birth) and can occur at any age. Congenital hydrocephalus typically results from specific genetic abnormalities or developmental disorders (e.g., neural tube defects such as spina bifida), while acquired hydrocephalus is more often attributed to illness, injury, environmental or other factors. A closer examination of both of these subtypes is the purpose of the present review (National Institute of Neurological Disorders and Stroke, 2011; Spina Bifida and Hydrocephalus Association of Ontario, 2013; Spina Bifida & Hydrocephalus Canada, 2007; Princeton Brain & Spine Care, 2012).

Hydrocephalus can also be categorized as communicating or non-communicating (obstructive) according to the presence and/or location of a blockage. In communicating hydrocephalus, CSF is free to flow (i.e., communicate) between the ventricles, as no blockage occurs within the ventricular system. In obstructive hydrocephalus, a blockage occurs within the ventricular system, often within one or more of the narrow pathways that connect the ventricles (Princeton Brain & Spine Care, 2012). There are two additional related conditions, which do not clearly fit into either of these categories: hydrocephalus ex-vacuo and normal pressure hydrocephalus (NPH). Hydrocephalus ex-vacuo is not truly a form of hydrocephalus; it occurs when a stroke or traumatic injury leads to brain tissue loss or shrinkage, and, in turn, results in a compensatory widening of ventricular space (National Institute of Neurological Disorders and Stroke, 2011). This condition is outside the scope of the current review. NPH is characterized by enlarged cerebral ventricles with only intermittently elevated cerebrospinal fluid pressure; this type is often diagnosed based on a common set of symptoms including gait disturbance, loss of control of bladder function, and dementia (Pyykko et al., 2012). Predisposing factors for NPH may include: increasing age, subarachnoid hemorrhage, head trauma, infection, tumor, meningitis, and/or complications of surgery (National Institute of Neurological Disorders and Stroke, 2011). Idiopathic NPH (INPH) is a specific subtype of NPH that characteristically develops in the absence of any such predisposing factors (Pyykko et al., 2012). A common complication with INPH is hyponatraemia (i.e., low plasma sodium concentration).

The most frequent method of treatment for hydrocephalus is the surgical insertion of a shunt system, which allows for improved drainage and CSF re-absorption (National Institute of Neurological Disorders and Stroke, 2011; Spina Bifida and Hydrocephalus Association of Ontario, 2013; Spina Bifida and Hydrocephalus Canada, 2007; Princeton Brain & Spine Care, 2012). One measure of disease progression in hydrocephalus, particularly in infants, is whether the hydrocephalus is acute and resolves without surgical intervention or persists such that a shunt is required.

The incidence and prevalence of hydrocephalus is linked to etiology. Incidence of congenital hydrocephalus is estimated at about 3 per 1000 live births in the US; overall prevalence is estimated at 0.5% (Spina Bifida and Hydrocephalus Canada, 2007). On the other hand, the total incidence of acquired hydrocephalus is much harder to estimate because it is due to many and varied factors, including illness, injury, environmental and other unknown factors. However, it is noteworthy that about 100,000 shunts are implanted each year in developed countries (Spina Bifida and Hydrocephalus Canada, 2007). NPH is estimated to affect more than 1 in 200 adults over age 55 years (Spina Bifida and Hydrocephalus Association of Ontario, 2013).

The epidemiological characteristics of hydrocephalus on the whole are not well understood. Although considerable research exists into various individual risk factors for hydrocephalus onset, given the complexity of the disorder and its many potential etiologies, a combination of genetic and environmental factors may be at play for any or all subtypes (National Institute of Neurological Disorders and Stroke, 2011). Far less is known about the factors that affect progression. In light of these problems, effort is required to elucidate and gain a better understanding of the varied risk factors for both onset and progression of hydrocephalus and to integrate them into a more unified picture. The first step towards this objective was to systematically evaluate the published literature, including systematic reviews, meta-analyses and observational studies on the subject.

2. Rationale and objectives

2.1. Rationale

The purpose of this study was to systematically assess and synthesize the world literature on risk factors for the onset and progression of hydrocephalus, thereby providing a basis for policy makers to identify appropriate risk management measures to mitigate the burden of disease in Canada. This systematic review will provide a comprehensive summary of currently available evidence on risk factors for disease onset and progression, including biological, lifestyle, socioeconomic, environmental, and psychosocial factors. In addition, this study will provide a platform to identify potential modifiable risk factors for the onset and progression of hydrocephalus, as well as etiological data gaps that need to be filled.

2.2. Objectives

The primary objectives of this study are as follows:

1. Conduct a comprehensive, systematic literature review for the onset and progression of hydrocephalus with respect to a wide range of risk factors, including biological, lifestyle, socioeconomic, environmental, and psychosocial factors and possible mechanisms of action. Genetic risk factors will also be considered.
2. Assess and summarize the available evidence on the determinants of onset and progression of hydrocephalus and describe the strengths and weaknesses of the current scientific literature.

3. Methods

3.1. Criteria for considering studies for this review

The following is a brief description of the methodology used for selecting both non-genetic and genetic association studies. A complete description of methods and approach used in this study has been published in a separate paper (Hersi et al., 2017).

3.1.1. Types of studies

All eligibility criteria were established *a priori*. To be included in this study, the article had to meet each of these inclusion criteria: evaluate at least one etiological risk factor for the onset or natural progression of hydrocephalus; be a systematic review, meta-analysis, case-control study, cohort study, genome wide association study or candidate gene study; involve human subjects; report a measure of risk (including odds ratio, relative risk, etc.); published in English or French.

Studies were excluded if they met any of these criteria: published prior to 1950; the study only evaluated the association between variables and not the cause and effect relationship; risk factor under review was a form of intervention or treatment for the disease and therefore not impacting the natural progression of disease.