NeuroToxicology 61 (2017) 266–289

Contents lists available at ScienceDirect

NeuroToxicology

Determinants of neurological disease: Synthesis of systematic reviews

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ARTICLE INFO

Article history:
Received 3 April 2017
Accepted 3 April 2017
Available online 12 April 2017

Keywords:
Systematic reviews
Meta-analyses
Neurological conditions
Onset
Progression
Modifiable
Risk factors

ABSTRACT

Systematic reviews were conducted to identify risk factors associated with the onset and progression of 14 neurological conditions, prioritized as a component of the National Population Health Study of Neurological Conditions. These systematic reviews provided a basis for evaluating the weight of evidence of evidence for risk factors for the onset and progression of the 14 individual neurological conditions considered. A number of risk factors associated with an increased risk of onset for more than one condition, including exposure to pesticides (associated with an increased risk of AD, amyotrophic lateral sclerosis, brain tumours, and PD; smoking (AD, MS); and infection (MS, Tourette syndrome). Coffee and tea intake was associated with a decreased risk of onset of both dystonia and PD. Further understanding of the etiology of priority neurological conditions will be helpful in focusing future research initiatives and in the development of interventions to reduce the burden associated with neurological conditions in Canada and internationally.

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http://dx.doi.org/10.1016/j.neuro.2017.04.002
0161-813X/

Burden of neurological disease
Intervention
Mitigation

1. Introduction

With population aging, it is projected that various forms of cognitive impairment will have the highest economic, social, and health care burden of all diseases in Canada over the next 25 years (Elmslie, 2015). Neurological conditions represent one of the leading causes of disability in Canada (CIHI, 2007), having high psychosocial impacts and causing daily challenges to affected individuals and their caregivers. The concomitant economic burden of neurological disease, including both direct and indirect costs, is significant. The total cost for 11 major neurological conditions was estimated by the Public Health Agency of Canada (PHAC) to be approximately $8.8 billion annually, representing 6.7% of the total attributable cost of illnesses in Canada in 2000–2001. This growing impact of neurological conditions both on Canadians and the Canadian health care system underscores the need for an in-depth understanding of the determinants and impacts of neurological disease to inform future public health policy development.

This paper provides a synthesis of the findings of the systematic reviews on the determinants of 14 important neurological conditions conducted as part of a three year National Population Health Study of Neurological Conditions (NPHSNC), jointly coordinated by the Neurological Health Charities Canada (NHCC) and the Public Health Agency of Canada (PHAC). The specific objectives of this study were to systematically assess and synthesize the scientific literature on risk factors for the onset and progression of priority neurological conditions, including biological, lifestyle, socioeconomic, environmental, and psychosocial factors, as well as co-morbid conditions. The 14 priority neurological conditions studied included: spina bifida, hydrocephalus, cerebral palsy, muscular dystrophies, Tourette syndrome, epilepsy, dystonia, Huntington's disease, amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, primary brain tumors, multiple sclerosis, and neurotrauma. Following Little et al. (2017), the ordering of the 14 conditions involves four conditions in which substantial proportion of cases are congenital (spina bifida, hydrocephalus, cerebral palsy, and muscular dystrophies); three disorders that occur primarily in young people (Tourette syndrome, epilepsy, and dystonia); two rare disorders with poor prognosis (Huntington's disease and amyotrophic lateral sclerosis); and four more common disorders (Parkinson's disease, Alzheimer's disease, primary brain tumors, multiple sclerosis, and neurotrauma). A comprehensive review of the genetic risk factors for these conditions can be found in Little et al. (2017). The systematic reviews were conducted by teams of investigators at five Canadian centres, including the University of Ottawa (the lead centre), University of Toronto, University of Calgary, University of British Columbia, and the Newfoundland and Labrador Centre for Health Information (NLCHI).

An overview of the National Population Health Study of Neurological Conditions is provided by Gaskin et al. (2017). The core protocol for the conduct of the systematic reviews is described by Hersi et al. (2017); modifications to the core protocol adopted in conducting systematic reviews for specific conditions are noted by the authors of these reviews (Barakat-Haddad et al., 2017; Donnan et al., 2017a,b; Martino et al., 2017; McKay et al., 2017; van Lieshout et al., 2017; Walsh et al., 2017a,b; Wang et al., 2017; Chao et al., 2017; Hersi et al., 2017). A synthesis of genetic risk factors for the 14 neurological conditions is provided in the companion paper by Little et al. (2017).

The predominant measures for determining the association between exposure and outcome (onset of neurological disease or progression of neurological disease were the odds ratio (OR) and relative risk (RR)). Few studies reported an attributable risk (AR): in the case of multiple sclerosis, or instance, no study reported an AR (McKay et al., 2017). While ORs and RR estimate the strength of an association, the AR estimates proportion of the disease burden that is attributable to the exposure (Rothman et al., 2008). The OR and RR are important for inferring causality and represent valuable measures in etiologic studies. The limited use of an AR across all systematic reviews makes it challenging to estimate the potential public health impact of various exposures. Further, many studies within each systematic review reported only a *p*-value, without any measure of disease risk (e.g., OR, RR, or AR). A *p*-value indicates the statistical significance of an association, but does not specify the strength of that association (Rothman et al., 2008) making inferences about the clinical importance of these results even more challenging. To circumvent these challenges, findings from the systematic reviews project were subjected to review by clinical experts specializing the neurological diseases of interest to assess the clinical and public health significance of any identified risk factors.

Based on a comprehensive systematic review followed by a series of expert consultations with clinicians for each of the 14 neurological conditions, an attempt has been made to prioritize the identified risk factors affecting onset and progression of these neurological conditions based on the weight of evidence provided by the systematic reviews. This provided a basis of identifying the most important modifiable risk factors that could be targeted for intervention to help alleviate the burden of these conditions.

Following Wigle et al. (2008), the weight of evidence that a specific risk factor was causally associated with a specific neurological condition was identified as sufficient, limited, or inadequate (further details on the classification of risk factors can be found in the methodology paper) (Hersi et al., 2017). These three categories of evidence are based on the quality and the quantity of the evidence, and are defined below.

(i) Sufficient evidence [S]: at least one systematic review rated of moderate/high quality has reviewed the available evidence and published a peer-reviewed report indicating there is a credible relationship.
(ii) Limited evidence [L]: evidence is suggestive of an association between the agent and the outcome but is limited (and may or may not represent a credible relationship) because chance, bias and confounding cannot be ruled out with confidence, e.g., at least one high-quality study shows a credible association, but the results of other studies are inconsistent.
(iii) Inadequate evidence [I]: available studies are of insufficient quality (e.g., available studies have failed to adequately control for confounding or have inadequate exposure assessment), consistency or statistical power to permit a conclusion regarding the presence or absence of an association or no studies exists that examine the relationship.

For genetic risk factors identified using information from the Alzgene and Pdgene databases, and from replicated GWA studies, evidence was considered sufficient when clear association with gene regions was specified by the SNPs discovered and replicated. No attempt was made to document the potential for increase or decrease risk for genetic risk factors.