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Review article

Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: A systematic review and meta-analysis

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ABSTRACT

Background: Accumulating evidence suggests a positive association between exposure to non-agricultural pesticides and childhood brain tumors (CBT).
Objective: (1) To conduct a systematic review and meta-analysis of published studies on the association between residential/household/domestic exposure to pesticides and childhood brain tumors. (2) To clarify variables that could impact the results.
Methods: Publications in English were identified from a MEDLINE search through 28 February 2017 and from the reference list of identified publications. Risk estimates were extracted from 18 case-control studies published between 1979 and 2016 and study quality assessments were performed. Summary odds ratios (mOR) were calculated according to fixed and random-effect meta-analysis models. Separate analyses were conducted after stratification for study quality, critical exposure period, exposure location, specific exposures, pesticide category, application methods, type of pest treated, type of CBT, child's age at diagnosis and geographic location.
Results: Statistically significant associations were observed with CBT after combining all studies (mOR: 1.26; 95% CI: 1.13–1.40) without evidence of inconsistency between study results or publication bias. Specifically, increased risks were observed for several groupings and more particularly for gliomas and exposure involving insecticides. Statistical significance was also reached for high quality studies, for all exposure periods, for indoor exposure and, more particularly, during the prenatal period for all stratifications involving insecticides (except for outdoor use), for pet treatments, for flea/tick treatment, for studies from USA/Canada and studies from Europe (borderline) as well as for data from studies including children of up to 10 years at diagnosis and of up to 15 years.
Conclusions: Our findings support an association between residential exposure to pesticides and childhood brain tumors. Although causality cannot be established, these results add to the evidence leading to recommend limiting residential use of pesticides and to support public health policies serving this objective.

1. Introduction

Descriptive epidemiology of childhood brain tumor (CBT) has recently been reviewed (Johnson et al., 2014). In the United States and Canada, brain and central nervous system (CNS) tumors are the most frequent solid tumors and the second leading cause of cancer-related death in children and adolescents 0 to 19 years of age (Kaderali et al., 2009; Siegel et al., 2013). In Europe, primary tumors of the CNS are the second most common (after leukemia) and the most lethal childhood tumors in children 0 to 14 years old (Gatta et al., 2014; Steliarova-Foucher et al., 2004). CBT include several histologic subtypes, each with a different incidence rate according to age (higher incidence rates observed in children 0 to 4 years of age in USA and Europe), country (overall incidence varies from 1.12 cases to 5.26 per 100,000 persons in Kuwait and in USA), gender (more common in males) and ethnicity (for review, see Johnson et al., 2014). The higher incidence rate of childhood brain tumors occurring before the age of 5 suggests that both prenatal and early postnatal exposures may be especially important.

Improved survival after a diagnosis of CNS tumor recorded over the past 40 years can mainly be attributed to earlier detection and advances in treatment (e.g., surgical techniques, rational use of postoperative radiation and chemotherapy) (Arndt et al., 2007; Wells and Packer,

Abbreviations: ASTRO, astroglial brain tumors; CBT, childhood brain tumor; CNS, central nervous system; CYPs, cytochrome P450s; 95% CI, 95% confidence interval; 2,4-D, 2,4-dichlorophenoxy acetic acid; ICCC, international classification of children cancer; ICD, international classification of diseases; MA, meta-analysis; mOR, summary odd ratio estimate; OC, organochlorine; OP, organophosphorus; OR, odds ratio; PNET, primitive neuroectodermal tumors; SE, standard error; 95% UI, 95% uncertainty interval

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2015).

However, despite these medical progresses and decades of epidemiological research, the etiology of CBT remains largely unclear. A multifactorial process involving genetic and environmental factors is the most likely explanation. It has been suggested that associations with parental exposure to toxicants during pregnancy may differ with polymorphisms in genes metabolizing these toxicants. As an example, positive associations were observed between both paternal and maternal smoking during pregnancy and childhood brain tumors such that children with a greater PAH activation genotype were at a higher risk relative to children with wild type genotype (Barrington-Trimis et al., 2013). Dubuc and collaborators recently reviewed major cytogenetic and genomic aberrations associated with the most common pediatric brain tumors (medulloblastoma, ependymoma, supratentorial primitive neuroectodermal tumors, and pilocytic astrocytoma) and described advances in the understanding of the epigenetics of brain tumors (Dubuc et al., 2010, 2012). Established CBT risk factors are limited to ionizing radiation exposure and to some cancer syndromes including neurofibromatosis types 1 and 2, tuberous sclerosis, nevoid basal cell carcinoma, Turcot, Cowden, hereditary retinoblastoma and Rubinstein-Taybi syndromes. Many potential risk factors have been studied with inconclusive results, including anthropometric factors (birth weight, birth length, head circumference, maternal age), developmental and birth characteristics (birth defects, premature birth, parity, single or multiple birth, as examples), parental exposures during pregnancy (smoking, alcohol, vitamin intake, folic acid intake, medication, dietary N-nitroso compounds), parental occupational exposures (electromagnetic fields, pesticides), head injuries, allergic conditions (atopy), infectious exposures (Johnson et al., 2014; Vienneau et al., 2016).

For years, pesticides have been specifically scrutinized in this respect. Several literature reviews on pesticide exposure and childhood cancer have been published the last ten years (Infante-Rivard and Weichenthal, 2007; Infante-Rivard, 2008; Nasterlack, 2006, 2007; Turner et al., 2010; Van Maele-Fabry et al., 2010, 2011, 2013; Wigle et al., 2009, as examples). Environmental exposure to pesticides is of particular concern for children as they are particularly vulnerable due to physiological and behavioral characteristics (greater food or fluids intake per body weight, “hand-to-mouth” activity, as examples) that can increase the dose and toxicity as compared to adults (Karr et al., 2007; Moya et al., 2004; Roberts et al., 2012). Children can be exposed to pesticides indirectly from parental pesticide exposure via occupational and para-occupational (“take-home”) exposure. Two meta-analyses (MA) suggest some support for a positive association between paternal and parental occupational exposure to pesticides and childhood brain tumors, respectively (Van Maele-Fabry et al., 2013; Vinson et al., 2011). Children can also be directly exposed to pesticides from residential/household/domestic uses. The main sources of such pesticide exposures include professional pest control services, indoor uses (in homes, schools, and other buildings), outdoor uses (in garden, public areas, agricultural application drift), handling treated or contaminated pets or others (use of insecticidal shampoos for lice infestation, as examples) (Zahm and Ward, 1998). Indoor broadcast applications can leave lingering residues in the air, carpet, toys and house dust (Deziel et al., 2015). The present work analyzes the possible association between residential/household/domestic exposure to pesticides and childhood brain tumors.

While most epidemiological studies on the relationship between childhood pesticide exposure and brain cancer were considering parental occupational exposures, there were fewer studies assessing residential exposures. Several were of small size and the results were inconsistent. Recently, three MA combined results on childhood brain tumors following residential exposure to pesticides (Chen et al., 2015; Kunkle et al., 2014; Vinson et al., 2011). Two of which examined the association with several childhood cancers, including brain cancer (Chen et al., 2015; Vinson et al., 2011) and one focused on childhood brain cancer with regard to parental farm-related pesticide exposure during pregnancy (Kunkle et al., 2014). Very few results from Vinson et al. (2011) related CBT to residential exposures, most of them focusing on occupational exposures and occupational or residential exposures combined. The MA of Chen et al. (2015) concerned exclusively postnatal exposure (children as exposure group); and in the MA of Kunkle et al. (2014), only scarce data for non-agricultural exposure are reported.

The purpose of our study is to systematically review and to meta-analyze the available epidemiological data on the relationship between residential pesticide exposure and childhood brain tumors. We aim to enhance our understanding of the potential involvement of residential exposure in the etiology of CBT by exploring several variables as potential sources of heterogeneity in results: the quality of the studies, the sources of pesticide exposure and exposure location, critical exposure periods, specific pesticide category, application methods, type of pest treated, specific exposures, type of CBT, child age at diagnosis and geographic location.

2. Materials and methods

The systematic review and MA was conducted according to the protocol described in details in previous publications by our group (Van Maele-Fabry et al., 2010, 2011, 2013) and followed the available guidelines, including PRISMA (Liberati et al., 2009) and PRISMA-P (Moher et al., 2015) statements for reporting systematic review and MA. It has to be stressed that these guidelines do not cover all the complexities associated with reporting systematic reviews in the pediatric population. A study protocol for the development of guidelines for conducting and reporting of systematic reviews and MA in newborn and child health research (PRISMA-Children [C] and PRISMA-Protocol for Children [P-C]) is being developed and the final statements are expected to be published in 2017 (Kapadia et al., 2016).

2.1. Study identification and selection

2.1.1. Study identification

The search strategy was designed to identify all English-language observational studies on childhood brain tumors and residential pesticide exposure published in the open literature in peer-reviewed journals. An electronic search on MEDLINE (National Library of Medicine, Bethesda, MD) was conducted for the period 1966 to 28 February 2017 using “(pesticides OR herbicides OR insecticides OR fungicides) AND ((children OR childhood) AND brain tumors) AND (residential OR domestic OR household)”. This was supplemented by single or multiple combinations of the words pesticide(s), herbicides, insecticides, fungicides, child, children, childhood, infant, newborn, preschool child, adolescent, youth, teenage, tumors, cancer, neoplasm, astroglial, astrocytomas, glial, primitive neuroectodermal, embryonal, intracranial, residential, household, domestic, indoor, outdoor with no restriction of publication type or publication date. The reference lists of the relevant publications and review papers were also checked for additional studies.

2.1.2. Study selection

Studies using a cohort and a case-control design, that referred to children exposed to pesticides from residential use (indoor or outdoor), with (subtypes of) brain tumors as the outcome were considered eligible. Studies not published in English, published in the grey literature, that did not report original results (reviews, MA, case-reports, comments, letters, editorials, and abstracts), experimental and ecological studies, focusing only on genetic data, that clearly examined a specific cancer type other than brain cancer as well as those dealing with no residential exposure, e.g. exposure resulting from agricultural drift or those reporting data for farm-related exposures were excluded.

The screening step was performed by evaluating the titles and abstracts of the studies identified by the electronic search. The full text of