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Review Article

A Short Review on Predisposing Environmental Exposures and Related Methodological Approaches in Pediatric Multiple Sclerosis

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ABSTRACT

Pediatric Multiple Sclerosis (PedMS) is a rare but highly informative disease whose etiology is currently unknown but likely due to a complex interaction between genetic and environmental factors. Considering the overall MS population, pediatric onsets are reported to be around 3%-10% with some discrepancies derived by considering different age-range among studies. The lack of cultural-validated and published tools for collecting environmental exposures in PedMS has limited knowledge on etiology. The availability of comprehensive and validated questionnaires could improve PedMS modern research in providing reliable, repeatable, cross-cultural evidence on the topic. This brief review describes the main methodological approaches on the study of environmental risk factors involved in determining PedMS.

Keywords: Pediatric multiple sclerosis; Questionnaires; Environmental exposures; Risk factors

INTRODUCTION

Multiple Sclerosis (MS) is a chronic, inflammatory, and immune-mediated disease of the Central Nervous System (CNS) and represents the first cause of neurological disability in young adults aged between 20-40 years. Pediatric onset of Ms (PedMS) is reported to be 3%-10% among the overall MS population [1]. By considering studies from North America, Europe, the Middle East, and Asia, a recent meta-analysis estimated an overall incidence of 0.05 to 2.85 per 100,000 pediatric MS patients and an overall prevalence of 0.69 to 26.92 per 100,000 in MS children [2]. Currently, the definition of PedMS is widely debated in terms of age range in which the disease occurs. Although in some countries, such as Germany and UK, pediatric MS patients are aged 15 years and younger, the most widely adopted definition for PedMS is an onset in individuals aged less than 18 years [3].

The etiology of PedMS is unknown. Nevertheless, the most credited hypothesis points to a complex interaction between genetic and environmental factors, many of which are shared with the adult form of MS such as Epstein Barr Virus (EBV) infection, second-hand smoke exposure, low serum levels of vitamin D, obesity as well as increased body mass index [4-6]. PedMS is considered a rare form of disease onset, and this represents the main limitation for appropriate studies, both on the epidemiological and therapeutic aspects. However, PedMS etiological investigation is of particular relevance for several reasons. Firstly, MS pediatric form is burdened by a more turbulent disease course in terms of higher relapse rate, larger volume of MRI lesions, and more disabling cognitive impairment rate than the adult MS [7]. Identification of specific risk factors could lead to the implementation of preventive strategies and subsequent improvement in children's quality of life

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as well as intellectual performance. Moreover, as PedMS occurs–by definition–temporally closer to potential risk exposures and as such exposures are more reliably collected than among adults, living children in a more homogeneous environmental context, the identification of such etiological factors would have important implications in also better understanding the etiology of adult MS.

This brief review describes the main existing methodological approaches used to investigate environmental determinants of PedMS.

LITERATURE REVIEW

Studies designed to validate tools for collecting information on environmental exposures in PedMS are scarce. In the Pediatric MS Tool-Kit, in order to enhance comparable exposure measurement in PedMS, Magahlaes and colleagues validate a measurement framework on three exposures: cigarette smoking habit, vitamin D and sunlight exposure [8]. Building from this background and in the context of an Italian multicentre case-control study (the PEDiatric Italian Genetic and enviRonment ExposurE, PEDIGREE study) designed to investigate environmental exposures and related genetic interactions in young MS patients, the PEDIGREE Questionnaire was launched PEQ-IT [9]. PEQ-IT also stems from a tool used in previous studies on PedMS in the US population [10-13]. After a back-to-back translation process, the Italian questionnaire was tested on a small court of pediatric patients affected by various chronic non-inflammatory demyelinating CNS diseases and healthy controls. Specifically, 67 children (27 patients and 40 healthy controls) and 66 respective parents recruited from five Italian sites were assessed for environmental exposures occurred in different life stages. Based on reference methodology, participants responded for feasibility and acceptability of each question, with subsequent re-testing for reliability at 2-week interval [14]. After substantial revisions based on scores and comments provided by participants, a final version was obtained, and self-administration of PEQ-IT is currently ongoing in the study at large (the PEDIGREE Study). PEQ-IT represents a tool to assess environmental risk factors in PedMS in an Italian population.

In the US population a comprehensive environmental Questionnaire was adapted by Drs. Waubant and Barcellos and used in a number of studies on etiological aspects in PedMS [10-13,15]. The Questionnaire, also capturing exposure to pregnancy and perinatal factors, was administered to 265 parents of children with MS and 412 healthy controls enrolled at 16 American MS Centres by Graves and colleagues [10]. Significant results adjusted for age, sex, race, ethnicity, and socioeconomic status, reported that paternal gardening-related occupation or any use in household of pesticide-related products were both associated with children's 2-fold risk of developing pediatric MS [10]. A subsequent American case-control study conducted using the same methodology included a population of 326 children with MS or clinically isolated syndrome and 506 healthy controls. Findings showed that exposures to rodenticides, weed control products, plant/tree insect or disease control products during childhood increased risk for PedMS by 2-3-fold [11]. In addition, a third study analysed the role of putative exposures in determining MS in children by using the Questionnaire and on the same cohort. In this case, only questions relevant to infectious exposures in the first five years of life were included in the analyses but no associations between antibiotic use and PedMS were found [12]. Lastly, a study found that high county-level ozone may increase MS in children and that the risk is higher in those with DRB1*15 genotype, suggesting an additive interaction [13]. The Questionnaire was used to collect data on places of residence and pollutants exposure during childhood and county-level-modelled ozone data were acquired from the Centres for Disease Control and Prevention (CDC's) Environmental Tracking Network. In all cases, information was collected through self-completion of the Questionnaire by parents.

After literature review process, we found no references to validation projects within studies exploring environmental exposures in PedMS except for one case. Mikaeloff and colleagues tried to assess parental smoke exposure by comparing 129 MS children with age at onset lower than 16 years and 1038 healthy controls matched for age, sex and area of residence. Information about parental smoking habit at home during childhood was obtained from parents by an ad-hoc question previously validated for its clarity in an unpublished pilot qualitative study. Participants were asked "whether one or both parents had ever smoked inside the home before the index date (the precise date was given)". The results evidenced a significant role of parental smoking in increasing MS risk in children [16]. Another milestone in etiological research of PedMS is the study carried out by Gianfrancesco and collaborators who reported on the role of overweight in determining PedMS in females [17]. Participants (986 adult patients with pediatric onset and 585 healthy controls) completed a Computer-Assisted Telephone Interview (CATI) administered by trained staff interviewers and comprising questions related to various exposures. Data on educational level, smoking habit, sun exposure at 10 years of age, residence at birth and age 10 years, birth weight, having been breastfed, mother and father's body size at 30 years of age, history of infectious mononucleosis as a proxy for pre-MS EBV serostatus, current weight and height, weight during their 20s and 30s as well as information on MS features were collected. Examples of questions are as follows: ""Have you ever smoked at least one cigarette per day for one month or more?"; "At 10 years of age, how often did you sunbathe in the summer (lay in the sun with a bathing suit on between the hours of 10 am–2 pm)?" and possible answers were as: ""almost every day", "2–5 days per week", "at least once per week", "1–2 times per month" and "never"; "Overall, as a young girl/boy at 10 years of age you were:" with possible responses being "not physically active", "a little physically active", "moderately physically active" and "very physically active". Despite the interesting evidence from this study, some limitations such as inaccuracy in recalling body weight and selection bias could have been anticipated and blunted by validating the questions for acceptability, feasibility, and especially reliability (test-retest process) in a small pilot study.

DISCUSSION

Major investigations on environmental exposures in PedMS are based on case-control studies aimed at exploring a limited number of risk factors simultaneously. In the past, survey tools typically consisted of one or a few ad hoc questions formulated as part of follow-up physician visits or *via* telephone.

The recent availability of a comprehensive tool for exploring environmental exposures in PedMS has met with much acclaim among researchers in the field, as evidenced by the modest flourishing of publications mentioning it. In the light of such enthusiasm and in the context of an Italian multicentre study (the PEDIGREE Study), the PEDIGREE Questionnaire was launched and currently represents the first published tool tested for acceptability, feasibility, relevance, and reliability available for Italian MS researchers interested on the topic.

The development of common means to investigate a rare but highly informative disease would increase the transparency and strength of evidence and reduce the opportunity to insert research bias. In addition, adapting the same tool into different multi-ethnic research settings would result in more consistent and comparable results and substantial savings in time and research costs [8,17]. Another key problem in modern research is the frequent absence or approximate description of the means used in carrying out the experiment. In fact, if researchers fail to report the reliability of their measurements, not only suboptimal observations would be obtained in quantifying phenomena, but their reproducibility would be also affected. We hope that this effort might serve as a future track focused on improving consistency, precision, repeatability, and trustworthiness of evidence in etiological research.

CONCLUSION

Despite different attempts at investigating putative environmental risk factors involved in the etiology of PedMS, validated tools capable of capturing various exposures are poorly reported even if an exception is represented by the PEQ-IT. A sound and consistent shared methodological approach is necessary to ensure reliable evidence in epidemiological research and especially in multifactorial rare diseases, such as PedMS. The availability of new comprehensive questionnaires might substantially simplify and homogenize different methodological approaches and results in the field of etiological research in PedMS in a vision of saving resources. Further national validation studies are necessary to ensure the availability of the existing tool across countries.

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CONFLICT OF INTEREST

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