

Reply to the Letter to the Editor by Sipila, Jussi

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ABSTRACT: This a Reply to the Letter to the Editor by Sipila, Jussi regarding our article titled: James LM, Georgopoulos AP. High Correlations Among Worldwide Prevalences of Dementias, Parkinson's Disease, Multiple Sclerosis, and Motor Neuron Diseases Indicate Common Causative Factors. *Neurosci Insights*. 2022 Aug 8;17:2633105522117598. doi: 10.1177/2633105522117598.

KEYWORDS: Motor neuron diseases, Parkinson's disease, Multiple Sclerosis, Dementia

We agree that fine-grain epidemiological information would be valuable in disentangling the complex interrelations among the pathogenetic mechanisms of motor neuron diseases (MND), multiple sclerosis (MS), Parkinson's disease (PD), and dementias of the Alzheimer's type (DEM). Such information would be particularly important in conjunction with additional information regarding potential biological and environmental insults to the brain as well as the genetic makeup of individuals regarding their immunologic makeup (Human Leukocyte Antigen [HLA] alleles) and their family history for these diseases. Our overarching hypothesis¹ is that these diseases arise as the result of (a) insults to the brain by a number of globally distributed biological and environmental factors, (b) the variable reaction of the

immune system to these insults, depending on the HLA genetic makeup of specific individuals, and (c) the differential vulnerability of different neural systems to the primary insults and/or the immune reaction (eg, autoimmunity), conferring the phenotypic signature of the diverse symptomatology of these diseases.

Our study¹ was based on counts of disease cases in 195 countries worldwide, without any information on within-country regional distributions of cases. It is remarkable that the percentage of disease cases per country population (disease prevalence) increased exponentially from MND to MS to PD to DEM. Examples from 6 different countries, arbitrarily chosen, with populations ranging from 200 000 (American Samoa, in 2016) to 1 378 000 000 (China) are

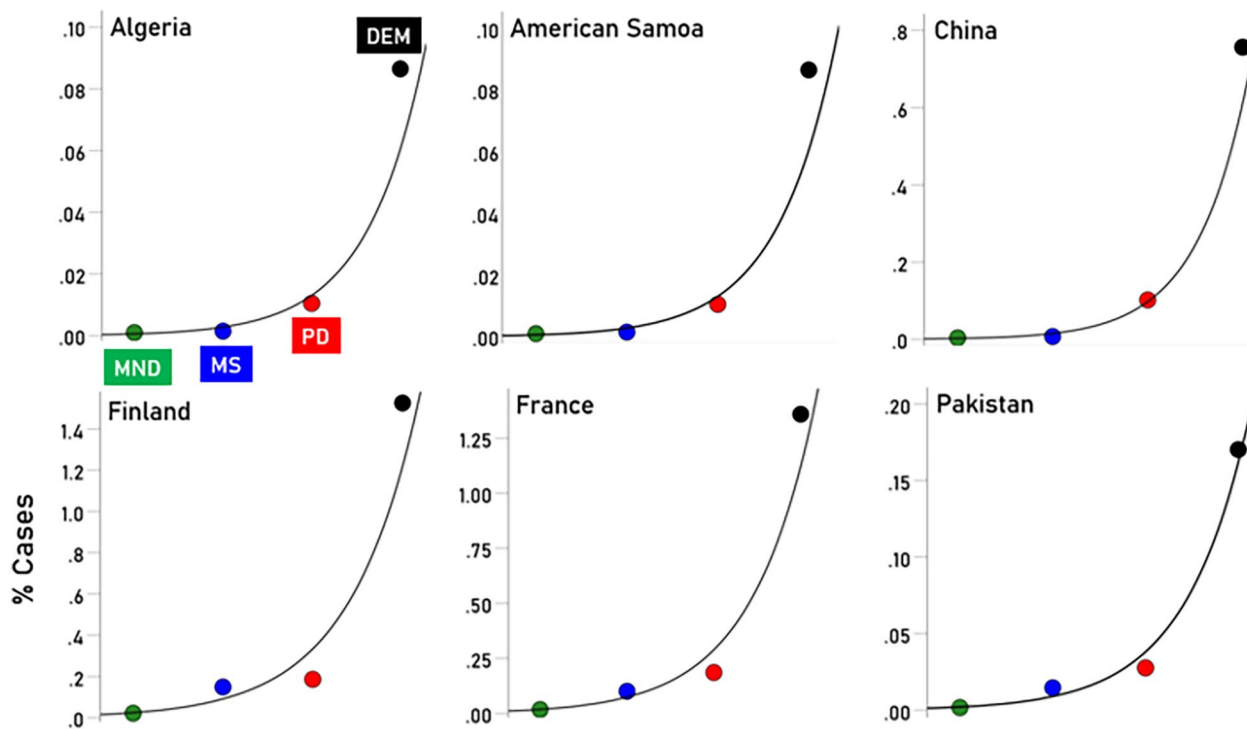


Figure 1. The percentage of cases (prevalence) of the four color-coded diseases is shown for 6 countries at different global locations and with widely varying populations to illustrate the close similarity of the exponential increase from MND to MS to PD to DEM. All coefficients of determination (r^2) of the exponential fits shown were very high (>0.9 ; range: 0.928–0.966).



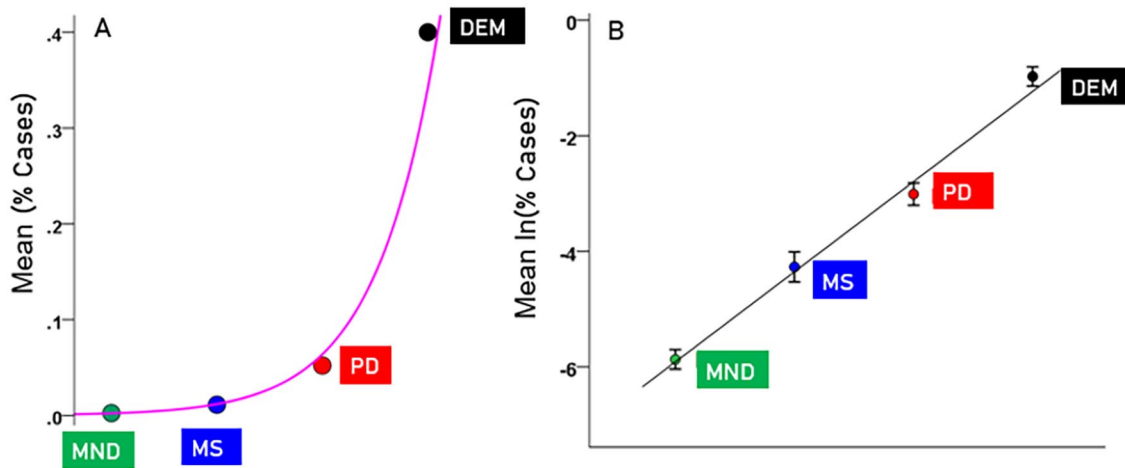


Figure 2. A, the mean percent of disease cases (prevalence, $N=195$ countries worldwide¹) is plotted in the original scale to illustrate the exponential fit. B, the mean percent of natural-log transformed disease cases is plotted to illustrate the linear increase of disease prevalence in the log-scale, as predicted by the exponential fit (A).

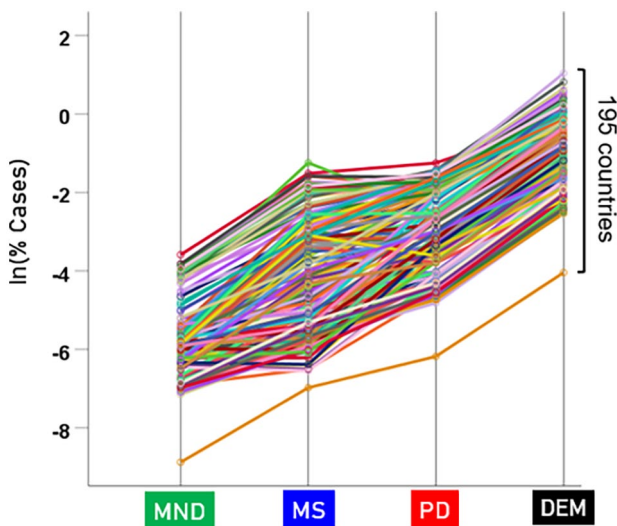


Figure 3. The log-transformed percent of cases in all 195 countries are shown to illustrate the similarity of linear increase in log-prevalence across countries and the wide (~ 4 -fold in the log-scale) range of overall disease prevalence among countries.

shown in Figure 1. The average prevalences over all 195 countries we analyzed in our study are shown in Figure 2A, and the average natural-log transformed prevalences are shown in Figure 2B; given the tight exponential fit of the raw data, the log-transformed data lie on a line. Figure 3 plots the log-transformed data of all 195 countries to illustrate (a) the basic linear, within-country, increasing trend in the log-transformed prevalences, from MND to MS to PD to DEM, and (b) the substantial range (~ 4 -fold in the log-scale) in the overall disease prevalence across countries.

These results stem from a whole-country, integrative level (“bird’s eye view”) of analysis and, as such, did not address issues of regional, within-country distributions of disease cases, which, as mentioned above, is an important

aspect regarding the identification of external (biologic, dietetic, environmental, etc.) and internal (genetic) factors influencing the manifestation of the disease. Whereas much work has been done with respect to external factors (geographic location, vitamin D, viral infections, etc.), very little effort has been expended on genetic factors, especially on the role of genetic HLA makeup in disease development. This is especially relevant, since different HLA makeup has been found to partially account for local variation in disease prevalence, with respect, for example, to malaria in Africa^{2,3} (protective role of HLA B*53, DRB1*13:01, and DRB1*13:02), pediatric autoimmune hepatitis following hepatitis A infection in Argentina⁴ (susceptibility role of DRB1*13:01 and protective role of DRB1*13:02) and MS in Norway⁵ (susceptibility role of DRB1*15). Given the very large polymorphism of the HLA genes in chromosome 6 (in fact, the most polymorphic set of genes in the human genome) and the frequently observed regional variation in HLA Class I and Class II individual makeup, it would be valuable to assess the role of this factor in shaping the regional distribution of the MND, MS, PD, and DEM. Ideally, we need a standard epidemiological grid design where, for each grid, (a) the number of disease cases per grid population, and (b) the HLA makeup of the cases and of a representative sample of healthy people, are determined. Informative results from such an immunogenetic approach at the across-country level have been published for MND⁶, MS⁷, PD⁸, and DEM⁸, paving the methodology for assessing data from much needed within-country disease-HLA association studies.

Author Contributions

LMJ and APG contributed to data retrieval and writing the manuscript. APG contributed to data analysis and

drafted the figures. LMJ and APG reviewed and approved the paper.

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