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Letter
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Autism, Autoimmune Disease and Socioeconomic Status

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Autism has been positively associated with high socioeconomic status (SES) in at least eight epidemiological studies from different populations and in different ethnic backgrounds [1-8], while two Scandinavian studies did not find that association [9,10]. Similarly, other related population based studies in autism have investigated parental educational levels [11] or geographical clustering of autism [12]. Although the causal basis for these associations with autism are unclear, many autism studies have suggested that they may be related to access to health resources, in the context of higher income and/or education, influencing increasing autism diagnosis [11,13]. Other explanations for geographical clustering of autism have been suggested including clustering due to information related occupations [14], as well as rainfall [15].

Autism has also been increasingly associated with altered immunity and autoimmune disease [16-18] with multiple independent lines of molecular evidence including; antibodies found against brain proteins [19-21], cytokine aberrations [22-27], immune activation in the brain [28,29], transcriptional activation of immune pathways in the brain [30], gastrointestinal inflammation [31,32], and population based genetic associations [33]. Recently, brain reactive antibodies against GAD65, an autoantigen commonly found in type 1 diabetes [34] have been noted in autistic children [35]. In addition, non-molecular similarities between autism and autoimmune and inflammatory conditions have been noted, including similar male gender bias in both autism and pediatric autoimmune disease [36], associations with maternal and paternal age [37-39], and interbirth interval [40,41].

Importantly, multiple population based epidemiological studies from different countries have found an increase in autoimmune disorders in families with autistic children, suggesting shared etiological factors, with type 1 diabetes and autoimmune thyroiditis [42] shown to be increased [43-48]. An increase in cases of different autoimmune and inflammatory disorders in families with an index case of a given autoimmune disease is a consistent finding in many autoimmune disorders [49], and suggests a shared genetic etiology [50,51] of immune dysregulation.

Curiously, some autoimmune and inflammatory disorders, in particular type 1 diabetes, autoimmune thyroiditis, and asthma have been positively associated with high SES, and the study of SES and geographical clustering parallels that found in autism. Associations of type 1 diabetes and high SES have been found in diverse populations from the Unites States [52,53], Scotland [54], Sweden [55], Norway [56], Chile [57], and Australia [58]. Associations of high SES with asthma in Israel [59] and thyroid autoimmunity [60] in Russia versus Finland have also been reported. Moreover, in both autism [3,4] and autoimmune disease [58,59,61] a similar increasing *dose dependent* relationship with increasing SES has been reported. In contrast, type 2 diabetes has been associated with low SES, mediated by high body mass index [62].

Unlike autism, the positive correlation of SES with autoimmunity is frequently attributed to biological etiological factors rather than differential diagnosis of disease in the context of access to health care resources. This often focuses on factors modulating the developing prenatal and neonatal immune system. For example, the "hygiene hypothesis" [63] is often invoked to explain the positive correlation with SES in autoimmune disease [52,56,58-60]. The hygiene hypothesis incorporates a number of features of the westernized lifestyle including; a decreased exposure to infectious agents during pregnancy or neonatal life, small family size, high antibiotic use, and good sanitation which are thought to result in a skewing of early immune development toward a proinflammatory state, predisposing the developing immune system to atopic and inflammatory disorders [64,65]. This phenomenon has also been invoked to help explain the dramatic or "epidemic" rise in autoimmune and allergic disorders since approximately 1980 [66-68].

Thus, if you consider the overlapping aspects of autism and autoimmune disease, it raises the suggestion that the positive association of high SES and autism may have similar origins in factors affecting early immune dysregulation. Moreover, this scenario is consistent with differences in access to health care playing a role in autism, given that greater access to prenatal and neonatal health care often leads to decreased rates of bacterial infection, viral infection, and environmental pathogenic exposure, as well as higher antibiotic use, which in turn may be associated with higher levels of inflammation leading to increased autoimmune disease.

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