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Review

Toward an immune-mediated subtype of autism spectrum disorder

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ARTICLE INFO

Article history:
Accepted 20 September 2014
Available online 13 November 2014

Keywords:
Autism spectrum disorder
Autoimmune disorders
Neuroimaging
Post-mortem
Animal models
Psychopharmacology
Pathophysiology
Immunology

ABSTRACT

A role for immunological involvement in autism spectrum disorder (ASD) has long been hypothesized. This review includes four sections describing (1) evidence for a relationship between familial autoimmune disorders and ASD; (2) results from post-mortem and neuroimaging studies that investigated aspects of neuroinflammation in ASD; (3) findings from animal model work in ASD involving inflammatory processes; and (4) outcomes from trials of anti-inflammatory/immune-modulating drugs in ASD that have appeared in the literature. Following each section, ideas are provided for future research, suggesting paths forward in the continuing effort to define the role of immune factors and inflammation in the pathophysiology of a subtype of ASD.

This article is part of a Special Issue entitled SI: Neuroimmunology in Health And Disease.

Contents

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http://dx.doi.org/10.1016/j.brainres.2014.09.048
0006-8993/

1. Introduction

A role for immunological involvement in autism spectrum disorder (ASD) has long been hypothesized. Although Kanner (1943) (Fig. 1) did not specifically address this in his initial description of the syndrome, a detailed review of the original 11 patient cases reveals some potentially important and pertinent observations and comments. In 10 of the 11 case descriptions, clinical information was provided that could represent, in part, immune dysregulation. For example, one patient required frequent changes of formula. Another had large and ragged tonsils and adenoids. Another patient had an attack of diarrhea and fever following small pox vaccination at 12 months. This patient also had large tonsils and adenoids which were removed. Feeding formulas were changed frequently for another patient with little success and he vomited a great deal during the first year of life. This patient also had his tonsils removed when he was 3 years old. Another patient quit taking any kind of nourishment at 3 months and was subsequently tube fed five times daily until one year of life. One patient vomited all food from birth through the third month of life. For another patient, for the first two months of life, the feeding formula caused considerable concern and he was kept in bed often because of colds, bronchitis, chickenpox, streptococcus infection, impetigo and rheumatic fever. Hypothyroidism was suspected in another patient and he was given thyroid extract. Feeding problems necessitated frequent hospitalizations for another patient and bilateral myringotomy tube placement was needed for him as he suffered from repeated colds and otitis media. A young girl experienced a febrile illness at 13 months and her subsequent increasing difficulties were interpreted as possible post-encephalitic behavior disorder. She was also given anterior pituitary and thyroid preparations, and her father was described as "one of those chronically thin persons, nervous energy readily expended".

A number of review papers have summarized results of studies investigating immunological factors in ASD (Van Gent et al., 1997; Ashwood and Van de Water, 2004; Stigler et al., 2009). These reviews have addressed the role of cellular and humoral immunity, bacterial and viral infections, peripheral and central immune measures, immunogenetics, and immunotherapy relative to ASD. The reviews have also highlighted that explorations of possible immune abnormalities in ASD have been limited by small sample sizes, the inclusion of heterogeneous groups of subjects, inadequate standardized clinical characterization of subjects, the lack of appropriate controls, and at times, inadequate study design.

The diagnosis of ASD is currently based on observable clinical characteristics, along with historical information, rather than objective biomarkers. There are likely to be distinctive, biologically-based subgroups of patients with ASD. Given the clinical and biological heterogeneity of ASD, it is not surprising that results from many of the studies investigating immunological factors have been inconsistent. A number of potentially important biological findings may be nullified by unknowingly including multiple etiologic