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Review Article

Neuropathology and Animal Models of Autism: Genetic and Environmental Factors

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Autism is a heterogeneous behaviorally defined neurodevelopmental disorder. It is defined by the presence of marked social deficits, specific language abnormalities, and stereotyped repetitive patterns of behavior. Because of the variability in the behavioral phenotype of the disorder among patients, the term autism spectrum disorder has been established. In the first part of this review, we provide an overview of neuropathological findings from studies of autism postmortem brains and identify the cerebellum as one of the key brain regions that can play a role in the autism phenotype. We review research findings that indicate possible links between the environment and autism including the role of mercury and immune-related factors. Because both genes and environment can alter the structure of the developing brain in different ways, it is not surprising that there is heterogeneity in the behavioral and neuropathological phenotypes of autism spectrum disorders. Finally, we describe animal models of autism that occur following insertion of different autism-related genes and exposure to environmental factors, highlighting those models which exhibit both autism-like behavior and neuropathology.

1. Introduction

Autism is a heterogeneous neurodevelopmental disorder with multiple causes and a great range in the severity of symptoms [1, 2]. As described by Kanner in 1943, individuals with autism have four core features: (i) impairments in reciprocal social interactions, (ii) an abnormal development in the use of language, (iii) repetitive and ritualized behaviors, and (iv) a narrow range of interests [3]. These symptoms range from mild to severe as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) [4] (Figure 1). In addition to the core features, people with autism often have comorbid neurological disorders such as mental retardation and epilepsy [5]. The prevalence of mental retardation with autism is ~60%, but in the broader autism spectrum disorders (ASDs), the number is closer to 30% [6]. Epilepsy has been long associated with autism although estimates of the occurrence of seizure disorder vary from 5% to 44% [7]. Anxiety and mood disorders are very common in autism [8]. There is also a substantial heterogeneity in the onset of autism. Impairments in some children manifest before 18 months of age; however, 25%–40% of children with autism initially demonstrate near normal development until 18–24 months, when they regress into autism that is generally indistinguishable from the early onset form of the disorder [8]. The early onset versus regressive phenotypes of autism suggest different neuropathological mechanisms.

Neuropathological observations that have emerged over the past decade point towards early pre- and postnatal developmental abnormalities that involve multiple regions of the brain, including the cerebellum, cortical white matter, amygdala, brain stem, and cerebral cortex. However, since 1980, only 120 postmortem brains from people with autism have been studied [9]. Thus, the neuropathology literature is neither extensive nor rigorous, and there are several areas that remain open to further investigation. In the present review, we have highlighted neuropathological features of the areas that may play an important role in the pathology of autism.