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Review

Neuroanatomic observations of the brain in autism: a review and future directions

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Abstract

Infantile autism is a behaviorally defined disorder associated with characteristic cognitive, language and behavioral features. Several postmortem studies have highlighted areas of anatomic abnormality in the autistic brain. Consistent findings have been observed in the limbic system, cerebellum and related inferior olive. In the limbic system, the hippocampus, amygdala and entorhinal cortex have shown small cell size and increased cell packing density at all ages, suggesting a pattern consistent with development curtailment. Findings in the cerebellum have included significantly reduced numbers of Purkinje cells, primarily in the posterior inferior regions of the hemispheres. A different pattern of change has been noted in the vertical limb of the diagonal band of broca, cerebellar nuclei and inferior olive with plentiful and abnormally enlarged neurons in the brains of young autistic subjects, and in adult autistic brains, small, pale neurons that are reduced in number. These findings combined with reported age-related changes in brain weight and volume, have raised the possibility that the neuropathology of autism may represent an on-going process.

Keywords: Brain; Neuroanatomy; Limbic system; Cerebellum; Large brain; Neurochemistry

Contents

It has been just over 60 years since Kanner (1943) first described an intriguing disorder in which children exhibit a significant disturbance in cognition and behavior in the absence of obvious physical or brain dysmorphology. For a period of time, parenting and environmental factors were believed to be responsible for the impaired language, social aloofness, perseverative and stereotypic behaviors and obsessive need for sameness that characterize this disorder. Gradually, however, with the observation that many of those affected had abnormalities on their electroencephalograms (Small, 1975), and a higher than expected incidence of seizures (Deykin and MacMahon, 1979), evidence for a neurological basis for the disorder began to unfold.

Given the complexity and variety of symptoms with which autistic individuals present, it has been difficult to conceptualize a defining cohesive neurological mechanism that might underlie the core features of this disorder. Some of the earliest efforts to address this question utilized neurophysiologic technology, with resulting studies reporting abnormalities of auditory-nerve and brainstem-evoked responses (Student and Schmer, 1978; Tanguay et al., 1982) and rapid eye movement sleep patterns (Tanguay et al., 1976). Although more recent investigations have failed to confirm these original observations (Rumsey et al., 1984; Courchesne et al., 1985), they nonetheless played an

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important role in initiating the path toward further neurobiologic research in autism.

Among biological abnormalities so far described in autism, neuroanatomic observations provide some of the strongest evidence. Results from postmortem and imaging studies have implicated the involvement of many major structures of the brain including the limbic system, cerebellum, corpus callosum, basal ganglia and brainstem. However, despite a growing body of data implicating the involvement of multiple sites and differing types of abnormalities, questions remain about many of these findings. Moreover, there is little direct information regarding the autistic brain during early development since most of the postmortem studies have been limited to investigations involving older children and adults. Nonetheless, available data provides evidence for a prenatal onset of at least some of the neuroanatomic abnormalities reported in the autistic brain.

Identification of the underlying neuroanatomic substrate in the autistic brain remains an ongoing challenge, compromised largely by the dearth of human pathological material of reasonable quality for study, technical limitations and the lack of an animal model. One of the first neuropathologic studies of an autistic brain was published by Aarkrog (1968) who described "slight thickening of the arterioles, slight connective tissue increase in the leptomeninges, and cell increase" in a right frontal lobe biopsy. Some years later, in 1976, Darby published a review of 33 cases of childhood psychosis in which he suggested a relationship between limbic system lesions and the affective features of autism, but no specific pathology was described (Darby, 1976). Subsequently, in 1980, Williams et al. examined autopsy material obtained from four individuals with autistic features, looking primarily for cell loss and gliosis (Williams et al., 1980). No consistent abnormalities were observed.

In 1985, observations of the brain of a 29-year-old well-documented man with autism was reported, studied in comparison with an identically processed age and sex-matched control, using the technique of whole brain serial section (Bauman and Kemper, 1985). Both brains were examined by means of a comparison microscope, multiple sections being studied side by side in the same field of view. The most significant findings were confined to regions of the limbic system and cerebellar circuits. No abnormalities were found in any regions of the cortex, an observation further supported by a detailed analysis of cortical neuronal and glial cell counts in another autistic brain by Coleman et al. (1985) and by repeated surveys of the original and subsequent whole brain serial section material (Kemper, personal communication). It should be noted, however, that Bailey et al. (1998) have noted neocortical malformations to be a prominent feature in their autopsy material. In four out of their six cases, they found evidence of thickened cortices, areas of increased neuronal density, irregular laminar patterns, increased number of neurons on layer I, and abnormally oriented pyramidal cells. In addition, more recently, Casanova et al. (2002) have reported that, in comparison to controls, the cerebral cortex in the autistic brain demonstrates more numerous minicolumns, and that these minicolumns were found to be smaller and more compact in configuration in the three cortical areas studied. Thus, at this point, the presence, consistency and significance of cerebral cortical abnormalities in the autistic brain remains uncertain. How these observational differences relate to the clinical heterogeneity of the subjects studied and to the disorder in general will be an important focus of future research.

Since the 1985 report, eight additional clinically well-documented cases have been similarly studied using the same methodology (Kemper and Bauman, 1996). None of these cases have shown any gross abnormalities. Patterns of myelination have appeared to be comparable to that of controls in all cases. Examination of the cortex has likewise been unremarkable when compared with controls with the exception of small neuronal cell size and increased cell packing density in the anterior cingulate gyrus in all brains, an observation not appreciated in the original case. Only two microscopic cortical malformations have been noted in this series of cases. A small heterotopic lesion on the infra-orbital region in one hemisphere was found in a child with a history of a severe seizure disorder, and multiple heterotopic cells were observed in the cerebellar molecular layer in a second autistic child with significant developmental delay (Kemper and Bauman, 1998). Systematic examination of the forebrain, hypothalamus, and basal ganglia in these cases have failed to show any differences from controls.

Areas of the forebrain that have been found to be abnormal have included the hippocampus, subiculum, entorhinal cortex, amygdala, mammillary body, anterior cingulate gyrus and septum, structures which comprise a major portion of the limbic system. In comparison with controls, these areas showed reduced neuronal cell size and increased cell packing density (increased numbers of neurons per unit volume) bilaterally (Bauman and Kemper, 1994). Golgi analysis of CA1 and CA4 pyramidal neurons has shown decreased complexity and extent of dendritic arbors in these cells (Raymond et al., 1989). In the amygdala, the most significant increase in cell packing density was noted in the most medially placed nuclei. With the exception of a single child of normal intelligence, the lateral nucleus has appeared to be uninvolved.

Small neuronal size and increased cell packing density was also observed in the medial septal nucleus (MSN). However, in the nucleus of the diagonal band of Broca (NDB) of the septum, a different pattern of abnormality was noted. In this nucleus, the neurons were adequate in number but were unusually large in the brains of all of the autistic children less than 13 years of age when compared to controls. In contrast, the cells of the NDB in all of the autistic brains older than 21 years of age were small and pale and markedly decreased in number (Kemper and Bauman, 1998). Unfortunately, no whole brain serial sections from autistic adolescents have been available for study and thus, it

is unknown when and how rapidly these changes might occur over this period of time.

Outside of the limbic system, the most apparent and consistent abnormalities have been confined to the cerebellum and related inferior olive. All the autistic brains reported to date, regardless of age, sex or cognitive abilities have shown a significant decrease in the number of Purkinje cells, primarily effecting the posterolateral neocerebellar cortex and adjacent archicerebellar cortex of the cerebellar hemispheres (Arin et al., 1991). Similar anatomic findings have been reported by Ritvo et al. (1986) and more recently by Bailey et al. (1998), thus making the presence of reduced numbers of Purkinje cells the most reproducible pathological observation in the autopsied autistic brain. Despite reports of hypo- and hyperplasia of the vermis with magnetic resonance imaging (MRI) (Courchesne et al., 1994), we have found no change in Purkinje size or cell number in this cerebellar region (Bauman and Kemper, 1996). Reduced numbers of Purkinje cells in the cerebellar hemispheres have been observed in both childhood and adult cases, in individuals with and without a history of seizures or medication usage and appear to be unrelated to cognitive function. With few exceptions, there has been an absence of glial hyperplasia (Bauman and Kemper, 1996; Bailey et al., 1998) suggesting that the cerebellar lesions have been acquired early in development. Animal studies have shown a progressively decreasing glial response after cerebellar lesions occurring at increasingly earlier ages (Brodal, 1940).

In addition to the presence of reduced number of Purkinje cells, abnormalities have also been observed in the fastigeal, globose and emboliform nuclei in the roof of the cerebellum, which like the NDB, appear to alter with age. In these three nuclear groups, all the adult brains have shown small pale neurons that are significantly decreased in number. In contrast, in all the childhood brains (ages 5–13 years), the neurons in these same nuclear groups, in addition to those of the dentate nucleus, have been found to be enlarged and plentiful in number (Bauman and Kemper, 1994).

A similar pattern of change in cell size has also been observed in the inferior olive of the brainstem but the number of neurons has been found to be preserved. Given the known close relationship of the olivary climbing fiber axons to the Purkinje cell dendrites (Holmes and Stewart, 1908), the preservation of the olivary neurons in the face of a significant reduction in Purkinje cell number strongly supports a prenatal origin for the cerebellar abnormalities. Studies in the fetal monkey indicate that the olivary climbing fiber axons synapse with the Purkinje cells dendrites in a transitory zone beneath the Purkinje cells called the lamina dessicans, thus forming a single unit (Rakic, 1971). In the human fetus, this zone is no longer present after 28–30 weeks gestation (Rakic and Sidman, 1970). Thus, given the resulting tight bond between the olivary neurons and the Purkinje cells after this time, loss or damage to the cerebellar Purkinje cells results in an obligatory retrograde loss of olivary neurons (Holmes and Stewart, 1908; Norman, 1940; Greenfield, 1954). Since, in the autistic brain, the number of the olivary neurons is preserved, it is likely that whatever event resulted in the reduction of the Purkinje cells in these cases has to have occurred before this tight bond has been established, and thus before 28–30 weeks gestation.

Abnormalities in the brainstem have also been observed in a small number of cases. Rodier et al. (1996) have described dysgenesis of the facial motor nucleus and agenesis of the superior olivary nuclei in a single case with autism and Moebius syndrome. The nature and location of these findings would suggest an onset during the first 4 weeks post-conception, during the time of neural tube closure. Bailey et al. (1998) have described the presence of ectopic neurons lateral to the olives bilaterally in one case and malformation of the olive in three cases, thus providing further pathological evidence for a prenatal onset of this disorder. A review of our own material has yielded olivary nuclear malformations, similar to those reported by Bailey et al. (1998) in some cases. A more systematic analysis of serially sectioned brainstem material from autistic subjects and age and sex-matched controls is now in progress.

1. Directions for future research

Based on the findings in the cerebellum, combined with brainstem and cerebral cortical abnormalities in some cases (Rodier et al., 1996; Bailey et al., 1998), there appears to be reasonable evidence to suggest that least some of the brain abnormalities observed in the autistic brain are of prenatal origin. In addition, however, there is a growing body of data that indicates that the underlying neurobiological processes involved in autism may be on-going and that postnatal factors may also be important. It has been observed, for example, that overall brain weight in children with autism is statistically heavier than that of age and sex-matched controls, while the weight of the autistic adult brain tends to be lighter than that of controls (Bauman and Kemper, 1997). More recently, imaging studies have indicated increased brain volume in autism, most prominent between the ages of 2 and 4.5 years of age, a feature which later appears to plateau during adolescence (Courchesne et al., 2001). In addition, microscopic observations of enlarged cells in some brain regions in autistic children and small pale cells that are reduced in number in these same areas in adults strongly indicate changes with age. Clinically and pathologically, this process does not appear to a degenerative one and may reflect the brain's attempt to compensate for its atypical circuitry over time. Future research will need to address the timing and pathogenesis of these changes and to consider how the resulting findings may impact on the clinical features of the disorder.

The observation of postnatal brain enlargement is intriguing and a number of hypotheses have been posed to explain its origins. Clinically, the head circumference of the autistic child has been said to be either normal or slightly small at birth but later increases in size during early

to mid-childhood (Lainhart et al., 1997; Courchesne et al., 2003). A number of possible neurobiological mechanisms have been proposed to explain this apparent early brain "overgrowth" including increased neurogenesis, decreased neuronal cell death, increased production of non-neuronal brain tissues (i.e. glial cells), decreased synaptic pruning and abnormalities of myelin. At this point, there is no firm pathological evidence to support any of these suggested hypotheses. Finding the answer to these questions may go a long way toward advancing our understanding of the underlying pathogenesis of this disorder.

Immunohistochemical studies utilizing autopsy brain material obtained from autistic subjects have been increasingly reported in the literature in recent years. Blatt et al. (2001) noted reduced binding of GABAa receptors in the hippocampus in the brains of four autistic adults studied in comparison to controls, but found no significant changes in kainate, cholinergic or serotonergic receptors. Perry et al. (2001) found a decrease in nicotinic receptors in tissue obtained from autistic frontal and parietal cortex, with a decrease in M1 receptors only in the parietal cortex. Although the basal forebrain failed to show similar findings, this region showed a marked increase in brain-derived neurotrophic factor (BDNF). More recently, this same research group has noted a decrease in three of the four nicotinic receptors in the cerebellum but no abnormalities of either M1 or M2 receptors or in choline acetyltransferase activity in this same area (Lee et al., 2002). Studies such as these are just beginning to expand our knowledge base about the neurobiology of autism and future investigations should continue to explore the underlying neurochemistry of the autistic brain with a particular focus on those regions known to be anatomically abnormal.

2. Conclusion

Our understanding of the neurobiology of autism has advanced substantially over the past 20 years but there is still much to be learned. There is an urgent need for an animal model to address numerous questions, which, because of the limited availability of suitable human autopsy material and the technical limitations involved in the study of the human brain, cannot be adequately addressed at this time. It is hoped that advancements in technology coupled with a better definition of the genetic, neurochemical and neuroanatomic profile of autism and its broader phenotype, will result in a more detailed understanding of the pathogenesis and neurobiology of the disorder, and ultimately to earlier identification and more effective interventions and treatment.

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