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ANATOMY AND NEUROBIOLOGY OF AUTISM

Neuropathology of infantile autism

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The neuropathology of infantile autism has been reviewed in several recent publications.[1,2] We have examined the whole brain serial sections of nine well documented cases of infantile autism in comparison with identically processed age- and sex-matched controls. In these brains comparable anatomic areas of the forebrain, brain stem and cerebellum were viewed side by side at the same magnification in the same field of view. Anatomic areas identified as abnormal by this technique were then subjected to further qualitative and quantitative analysis. Consistent findings were evidence of a curtailment of maturation in the forebrain limbic system, abnormalities in the cerebellar circuits, and an unusual pattern of change of postnatal brain size.

In the forebrain, many components of the limbic system show unusually small neurons that are more closely packed together than those of the age- and sex-matched controls, a pattern similar to that seen at an earlier stage of brain development. The most consistently involved areas were the amygdala, the hippocampal formation and its closely related entorhinal cortex and the mammillary body. The only exception to this pattern of pathological change was found in the septum, in a part of this area that projects to the limbic forebrain, the nucleus of the diagonal band of Broca. In the younger autistic individuals (less than 12 years of age), the neurons in this part of the septum were unusually large but adequate in number and in the older individuals (more than 21 years of age), they were unusually small and decreased in number. All of these limbic areas are key parts of the brain circuitry involved in memory and emotionality,[3] disturbances of which are prominent clinical features of infantile autism. Inconsistently noted in the forebrain were malformations of the neocortex. In our material these have been inconspicuous and present in only an occasional brain. However, Bailey *et al*[4] have found them to be a prominent feature in their autopsy material. It is difficult to say at what period of brain development the curtailed maturation arose. However, the presence of malformations in the cerebral cortex indicates a pathology dating to the period of fetal development. The cytoarchitecture of the remaining cerebral cortex showed no abnormality when compared to controls. Thus, the limbic system abnormalities in the forebrain represent a consistent, selective, apparently isolated change in the forebrain.

A different pattern of neuropathology was noted in the cerebellar circuits. Here there was a decrease in the number of Purkinje cells in the cerebellar cortex in all the autistic brains, a finding that was similar at all ages. The Purkinje cells are the projection cells of the cerebellar cortex, projecting to the deep cerebellar nuclei. In these deep cerebellar nuclei the neurons in the younger brains were abnormally large whereas in the older brains these neurons were abnormally small and in some nuclei decreased in number. A similar pattern of change in cell size was noted in the inferior olive in the brain stem with unusually large neurons in the younger brains and neurons smaller than expected in the older brains. In contrast to the deep cerebellar nuclei, these cellular changes in the inferior olive occurred without evidence of neuronal loss. The changes in the inferior olive were most evident in that part of the inferior olive that projects to the area of the cerebellar cortex with the most marked decrease in number of Purkinje cells, the posterior-lateral part of the lateral lobes of the cerebellum. The age-related changes noted in our material in the deep cerebellar nuclei and the inferior olive are an unusual neuropathology. During normal development the axons of the inferior olivary neurons form a tight synaptic relationship with a relatively few cerebellar Purkinje cells, a relationship that is established at about 28 weeks of gestation.[5] This relationship is sufficiently committed so that at later stages of development, inferior olivary neurons are lost when the related Purkinje cells are destroyed. These observations thus suggest that the decrease in number of Purkinje cells dates to a prenatal period of brain development before the establishment of this tight synaptic inter-relationship. The postnatal changes in cell size and number in the cerebellar nuclei and in cell size in the inferior olive are an unusual pathology that is not readily understood. Elsewhere[6] we have speculated that these changes may reflect the persistence of a fetal circuit that is related to the decrease in number of Purkinje cells. These postnatal age-related changes in neuronal size in the cerebellar nuclei and in the inferior olive, like those noted in the septal nuclei, provide evidence for an active pathological process that continues into the postnatal period. A clinical correlate of these cerebellar abnormalities is not readily apparent. An inconsistent finding in our brains, and in many others reported in the literature (see review[7]), is atrophy of parts of the cerebellar vermis. Bailey *et al*[4] have reported in the brain stem unusually prominent arcuate nuclei and malfor-

Correspondence: TL Kemper, Dept of Anatomy & Neurobiology, Boston University School of Medicine, 715 Albany St, W701, Boston, MA 02118, USA. E-mail: tkemper@bu.edu

mations of the inferior olive in some cases and Rodier *et al*[8] in a case with a clinical diagnosis of Moebius syndrome, reported a decreased number of neurons in the facial nerve nucleus and superior olive together with a shortening of the distance between the trapezoid body and the inferior olive.

The final change noted in the autistic brain is an unusual pattern of age-related alteration in brain weight (size). In our autopsy brains we have noted that the brain weight of our younger autistic individuals was significantly greater than comparable controls, a finding commensurate with the initial observation of Kanner[9] of increased head circumference. Sequential measurements of head circumference measurements have indicated that the abnormal increase in head circumference occurs at about 18 months (M Bauman, unpublished observations). The recent study of Courchesne *et al*[10] has provided further documentation of this in a MRI study of autistic individuals 2–16 years of age. In this study the abnormally large brain size was already present at 2 years and was followed by a striking deceleration of brain growth in the older autistic individuals.

Taken together these observations provide evidence for an evolving pathological process in the autistic brain that extends from the fetal period of brain development to adulthood. One of the most striking correlates of these age-related changes is that the usual time of onset of clinically recognized autistic behavior corresponds approximately to the timing of the onset of the accelerated brain growth, which is noted at about one and one half years of age.

TL Kemper[1] and ML Bauman[2]
[1]Dept of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, USA; [2]Children's Neurology Service, Massachusetts General Hospital, Harvard Medical School, MA, USA

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