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Cerebellar abnormality in autism: a nonspecific effect of early brain damage ?

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Abstract. Cerebellum may be a common site of developmental abnormalities due to its protracted course of maturation. Recent studies have implicated morphological deviations of the cerebellum as responsible for specific behavioral and cognitive manifestations of autism. We investigated neuropsychology and quantitative MRI of the cerebellum in both high functioning subjects with autism and survivors of childhood leukemia treated with radiation and intrathecal chemotherapy. The results of neuropsychological testing revealed different patterns of cognitive deficits for the two groups, while the abnormal cerebellar morphology was similar for both groups. Since it is suggested that the cerebellum contributes to motor-attentional subsystems, the present data provide support for a cerebellar role in the governance of higher cognitive functions, found to be abnormal in both groups. However, the abnormal macromorphology of the cerebellar vermis described here appears to be non-specific to autism.

Key words: autism, acute lymphoblastic leukemia, MRI, hypoplasia, cerebellum, neuropsychology

Since various brain areas differ in their speed of ontogenetic course, it has been suggested that those with a protracted course of maturation may be more profoundly affected by brain insult than others (Ciesielski et al., in press). Among structures with protracted development are the hippocampus (Kolb 1989, Altman and Bayer 1990), the cerebellum (Ito 1984) and due to a prolonged period of myelination and synaptogenesis - the prefrontal cortex (Huttenlocher 1979, 1982). The neural make up of the cerebellum is not completed at birth and the process of neural migration is longer in this structure than in other brain areas. Cerebellum will be particularly prone to damaging insult. Cerebellum may therefore be a common site of abnormalities in many developmental disorders and disorders originating prenatally or early in life, and as such cerebellar abnormalities may not be specific to any particular developmental disorder.

Significant attention and controversy have been raised by *in vivo* planimetric magnetic resonance imaging (MRI) of the cerebellum. Hypoplasia of the cerebellar vermis and hemispheres has been described by Courchesne et al. (1988) and by Gaffney et al. (1988). Courchesne (1988) suggested that the morphological deviation in the neocortical posterior cerebellum, lobuli VI - VII is specific to autism. Aberrant connections from the neocerebellum and deep cerebellar nuclei may therefore underlie the various behavioral and cognitive manifestations of autism. This proposal was appealing as on one side it seemed to contribute to the understanding of the neuropathogenesis of autism and on the other it provided support for viewing the cerebellum as a modulator of higher neurologic functions, including motor-sensory, language, memory and emotional states. The latter view of the cerebellum is still in the midst of scientific debate and focuses on the significance of the dentate nucleus which has enlarged vastly in the course of human brain development (Leiner et al. 1993). Its primary site of connections with the frontal cortex in human have been used as evidence that the cerebellum may have significant influence on processess associated with human language and judgement (Leiner et al. 1986). Others see the major role of the cerebellum as one concerned with motor learning and not with purely cognitive processes (Glickstein 1993).

With this in mind, before any causal relationship between cerebellar abnormality and autism should be drawn, two questions need to be answered: (1) is the abnormal cerebellar morphology of VI-VII lobuli, if found specific to autism, and (2) is the pattern of pathology in cerebellum of autistic subjects correlated with cognitive, emotional and social manifestations of autism.

Quantitative MRI studies of the cerebellum completed in our laboratory on high functioning autistic subjects and survivors of childhood leukemia provided negative answers to both questions (Ciesielski et al., submitted). The cerebellar hypoplasia of VI-VII lobuli may not be unique to autism. Survivors of childhood leukemia treated with radiation (2,400 rads) and intrathecal chemotherapy (Methotrexate) before the age of five, showed a pattern of macromorphological changes in the cerebellum similar to autism. Statistically significant decrease of cerebellar vermis within both anterior and posterior cerebellar areas was found when compared to carefully selected normal controls. More dramatic decreases in lobuli I-V were observed in the autism group than in the leukemia group. Therefore, the cerebellar morphology of decreased VI-VII lobuli does not appear to be specific to autism. Observed *in vivo* abnormal macromorphology of the cerebellum does not appear to be related to behavioral manifestations of autism. Thus, the suggestion of such pathology of the cerebellum as a marker for autism should be reconsidered.

In contrast to morphological abnormalities common in both groups, the pattern of cognitive deficits was strikingly different between groups. A comprehensive battery of neuropsychological tests (including selected Halstead-Reitan battery tests, Wisconsin Card Sorting, Wechsler Intelligence Scale-R for Children, Halstead Category Test, Luria Simultaneous Reversal, etc.) revealed in subjects with autism predominant deficits in functions of conceptual and motor selective inhibition related to the prefrontal cortices. Their visual spatial per-

ception and memory, as indicated by Benton Visual Retention test, Complex Osterrieth Figure test and subtests from the Wechsler Memory scale were relatively preserved. The leukemia survivors, however, showed only secondary deficits related to frontal dysfunctions. They had major difficulties in visual-spatial and motor-coordination tasks commonly related to right hemisphere brain functions. In many cases, their language and speech abilities were within normal limits for age norms as determined by verbal reasoning, vocabulary and verbal conceptualization. The above between-group cognitive differences are reflected in distinctly different patterns of social-emotional interactions. Clinical interviews, observation and Pediatric Behavior Scale (PBS; Lindgren and Koeppl 1987) showed poor communication skills, loneliness and high anxiety in subjects with autism, while survivors of leukemia revealed an increased need for interpersonal contacts, social acceptance, and continuous emotional attachment. The children surviving leukemia displayed no autistic features. Abnormalites of the cerebellum have been reported in other clinical populations with and without autistic features such as in cases with schizophrenia and bipolar affective disorder (Lippman et al. 1982, Nasrallah et al. 1991), Joubert syndrome, alcoholism and in Fragile-X (Reiss et al. 1991).

Autopsy studies in autism revealed multiple abnormalities in the hippocampal formation, subiculum, amygdala, mamillary bodies and medial septal nucleus. Purkinje and, to a lesser degree, granule cell loss was reported in the cerebellum (Bauman and Kemper 1985, Bauman 1991). The preservation of neurons in the inferior olive, the multiple areas of the brain with increased cell packing density with reduced neuronal cell size and the absence of gliosis are consistent with the neocerebellar cell loss in autism occuring prior to birth. The etiology of this cell loss is, at the moment, unclear. To our knowledge, there are no autopsy studies of the central nervous system in survivors of childhood leukemia; the nature of the changes on the cellular level in these children is currently unknown. However, the time of the toxic insult by radiation and chemotherapy in leukemia subjects occurs at the time of life (between 2 to 5 years) when the cerebellum is still in a dynamic process of development. Purkinje cells continue their development, their dendritic arborization, and their formation of axonal connections and synaptogenesis. It is possible that these processes are halted by the toxic process and the normal cerebellar size never develops; in this case, as in possibly prenatal demage in autism, we may be dealing with the effects of hypoplasia rather than atrophy.

The abnormal neuronal make up of the cerebellum may, on the one hand, stem from early (possibly prenatal in autism and early postnatal in leukemia) genetic, viral or toxic insult. On the other hand, it may be exacerbated by the decreased learning experience in both groups of children, resulting from their cognitive deficiency and social isolation. Abnormalities of selective attention have been implicated among major cognitive deficits in subjects with autism (Rimland 1964, Ornitz 1979, Ciesielski et al. 1990) and in survivors of childhood leukemia (Brouwers et al. 1985). Attention which involves a difuse network of connected brain structures may be more readily disrupted and associated with such a pattern of structural cerebellar abnormalities. Selective attention has been thought to be highly associated with the need to make coherent motor responses to the environment. Allport has termed this sort of attentional mechanism "selection-for-action" (Allport 1990). Other investigators (Mesulam 1981, 1990, Posner et al. 1990) have suggested that the attentional system may consist of an integrated network of linked regions involving, posterior parietal lobes, superior colliculus, thalamus, anterior cingulate and frontal cortex. Petersen, Frith and their colleques (1988) have suggested that response/target selection or "selection-for-action" may be mediated by the anterior cingulate cortex. The cerebellum has rich connections to these areas as well as to prefrontal brain. Cerebellum is mostly functionally related to motor control and may be among the fundamental structures which contribute to attention-motor interactions. Therefore, our studies provide some support for a possible cerebel-

lar role in governance of the higher cortical, cognitive functions in humans. The cerebellar damage may as well be responsible for some of the cognitive, attentional deficits in autism. However, this cerebellar damage as evidenced by *in vivo* macromorphology is nonspecific to autism.

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