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A Decrease in the Size of the Basal Ganglia in Children with Fetal Alcohol Syndrome

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Magnetic resonance imaging was conducted on six children and adolescents with fetal alcohol syndrome and seven matched normal controls. Detailed volumetric analyses demonstrated significant reductions in the cerebral vault, basal ganglia, and diencephalon in the children with fetal alcohol syndrome, compared with control children. In addition, the volume of the cerebellar vault was smaller than controls in 4 of the 6 children with fetal alcohol syndrome, although the group difference did not reach significance. When the basal ganglia were divided into the caudate and lenticular nuclei, both of these regions were significantly reduced in the children with fetal alcohol syndrome. Finally, when the overall reduction in brain size was controlled, the proportional volume of the basal ganglia and, more specifically, the caudate nucleus was reduced in the children with fetal alcohol syndrome. These results may relate to behavioral findings in both humans and animals exposed to alcohol prenatally.

Key Words: Prenatal Alcohol Exposure, MRI, Basal Ganglia, Caudate, Cerebellum.

THE FIRST report of structural brain damage after prenatal alcohol exposure was in an infant with fetal alcohol syndrome (FAS) who died shortly after birth.[1–3] This autopsy revealed extensive brain abnormalities, including microcephaly, migration anomalies, callosal dysgenesis, and a "massive" neuroglial, leptomeningeal heterotopia covering the left hemisphere. A second infant, born to a binge drinker, was reported soon after the first.[3] This child died at 10 days of age, and an autopsy revealed severe hydrocephalus, as well as a thinned corpus callosum, extremely small cerebellum, and a large neuroglial, leptomeningeal heterotopia. Since these first two accounts, other reports of structural central nervous system defects in children heavily exposed to alcohol during gestation have included brainstem and cerebellar anomalies, migration errors, absent olfactory bulbs, hydrocephalus, meningomyelocele, and porencephaly.[4–7] Currently, reports of 25 autopsies appear in the literature. These are summarized elsewhere.[8] Briefly, a wide range of neuropathologies, from anencephaly to migration anomalies, has been observed in children with FAS. On the basis of these reports, it has been surmised by some (e.g., Refs. 6 and 9) that the nature of the brain damage resulting from prenatal alcohol exposure is extremely variable.

Recently, studies using magnetic resonance imaging (MRI) have provided further information and new directions for the study of prenatal alcohol exposure. To date, MRI results have been included in case reports of 10 children with FAS or prenatal exposure to alcohol [(PEA) used herein to refer to children with known histories of significant ethanol exposure, but without all of the requisite signs to qualify for a diagnosis of FAS].[10–15] Four of these reports[10–12,14] provided only descriptive information regarding the MRI results. In addition, two of the children in these reports later died, one at 8 days and the other at 2.5 months of age, both after persistent medical problems.[11,12] The other two articles[13,15] used detailed volumetric analysis and comparison to normal controls, and suggested that the basal ganglia were especially sensitive to prenatal alcohol exposure. In the first of these reports, two children with FAS were evaluated, and microcephaly, enlarged ventricles, and reduced volumes in the cerebellum, basal ganglia, and diencephalic structures were documented. In addition, both of these children displayed abnormalities of the corpus callosum, with complete agenesis in one case. Furthermore, the MRIs of a small group of children with Down Syndrome, who were equally mentally retarded and microcephalic, were included for comparison. The basal ganglia and diencephalic structures of the FAS children were reduced, compared with both the Down Syndrome group and normal control children. More recently, Mattson et al.[15] examined two additional cases of children with histories of heavy prenatal alcohol exposure and behavioral disturbance, but who did not meet the criteria for a diagnosis of FAS. These two PEA cases also had small cerebral and cerebellar vaults and small basal ganglia, although the diencephalic structures were within normal limits when overall brain size was taken into account. The decrease in basal ganglia volume in the absence of the features for a diagnosis of FAS suggests that this group of structures may be

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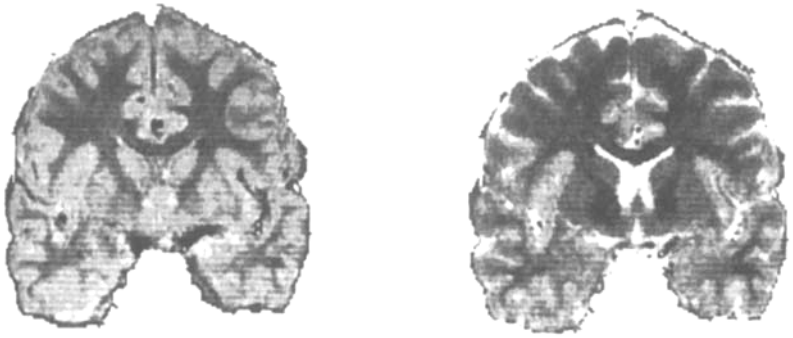

Fig. 1. Example of the two image sets: (right) proton density-weighted image and (left) T_2-weighted image.

extremely sensitive to a prenatal alcohol insult. The purpose of the current study was to replicate and extend our previous findings concerning the basal ganglia in children with FAS.

METHODS

Subjects

Six children and adolescents with histories of prenatal alcohol exposure were evaluated in this study. They were all diagnosed as having FAS on the basis of craniofacial, physical, and behavioral features, and ranged in age from 8 to 19 years (mean age = 13.0 years). All six of these subjects have been followed in our laboratory and have received extensive neuropsychological testing. The results of these tests indicated intelligence quotients (IQs) from <40 to 87. Excluding the child with an IQ below 40, the mean IQ for the FAS group was 81.6. There were 4 males and 2 females; 5 of the subjects were Caucasian and 1 was African-American. None of these subjects were included in our previous reports of basal ganglia reductions.[13,15]

MRI data for control subjects were obtained from a large, multidisciplinary neurodevelopmental research project at University of California at San Diego (UCSD). Seven control subjects within an appropriate age range had technically adequate imaging results at the time of the current study. They ranged in age from 8 to 18 years (mean age = 12.3 years). Limitations in the number of control subjects existing in the UCSD project at the time of this study prevented one-to-one age and gender matching to the FAS subjects. However, the subjects did not significantly differ as a group for age ($p > 0.1$) or gender ($p > 0.1$). Six of the control subjects were male, and all were Caucasian. All control subjects were screened for history of serious medical illness or developmental or intellectual difficulties. All MRI examinations were conducted without sedation.

Procedure

Imaging Protocol. Magnetic resonance imaging (MRI) was performed with a 1.5 Tesla superconducting magnet (Signa; General Electric, Milwaukee, WI) at one of two locations: either UCSD/AMI Magnetic Resonance Institute or Scripps Clinic and Research Foundation. The same imaging protocol was used at both locations. A fast spin-echo acquisition yielded two separate image sets: a proton density-weighted image (TR = 3000, TE = 17, ET = 4) and a T_2-weighted image (TR = 3800, TE = 102, ET = 8). Examples of these images can be seen in Fig. 1. Section thickness was 4 mm, with no gaps between successive sections in all instances. A 256 × 256 matrix and 24 cm field of view were used. For the following discussion of image analysis, the term pixel will be used to refer to a single picture element (or signal value) from the image matrix. All image analysis was done by a trained operator, who was blind to subject age, gender, and group membership.

Image Analysis. Volume estimates were obtained for the supratentorial cranium, infratentorial cranium (cerebellum), caudate nucleus, lenticular nuclei (putamen, globus pallidus, and claustrum), and the diencephalon (thalamic and septal nuclei). Because the nucleus accumbens is contiguous with both the caudate nucleus and the diencephalic structures, some accumbens is contained in the diencephalic region, although most is in the caudate measure. In addition, the caudate and lenticular nuclei were summed and are referred to as the basal ganglia in some of the statistical analyses. These estimates were obtained by first isolating intracranial areas, discarding other pixels from the images, and then applying a high-pass digital filter to reduce artifactual signal drift due to field inhomogeneities. Next, the supratentorial and infratentorial cranial regions were separated, and pixels within each region were summed across all sections. Visually determined thresholds were then used, first, to separate cerebrospinal fluid from brain tissue, and next, to separate gray from white matter. These thresholds were not used to "segment" tissue for the entire brain section, but rather, a rectangular polygon was drawn to circumscribe only the subcortical region of interest. Thus, the visual distinction between tissues was simplified, because the decision-making process in the thresholding task was more focused and applied only to the small subcortical region (Fig. 2). The subcortical nuclei measured herein were not traced, but rather pixels classified as gray matter that were visually determined to be within the caudate nuclei, lenticular nuclei, or diencephalic structures were circumscribed. Estimates of the volumes of these structures were made by summing the designated gray matter pixels across all sections. Fully processed images are displayed in Fig. 3.

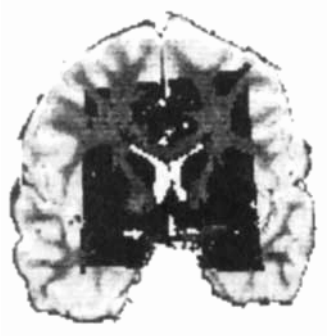

Fig. 2. Rectangular polygon circumscribing only the region of interest highlighting the pixels classified as gray matter.

RESULTS

Because of small sample sizes (n's = 6 and 7) and the likelihood of nonnormal distributions, nonparametric Mann Whitney U tests were used to analyze all MR data (Fig. 4). Children in the FAS group had significantly smaller cerebral vaults ($U = 7.0$, $p < 0.05$). This result is consistent with early descriptions of microcephaly in children with FAS[1] and similar reductions in overall brain size from our previous reports.[13,15] The cerebellar vault was

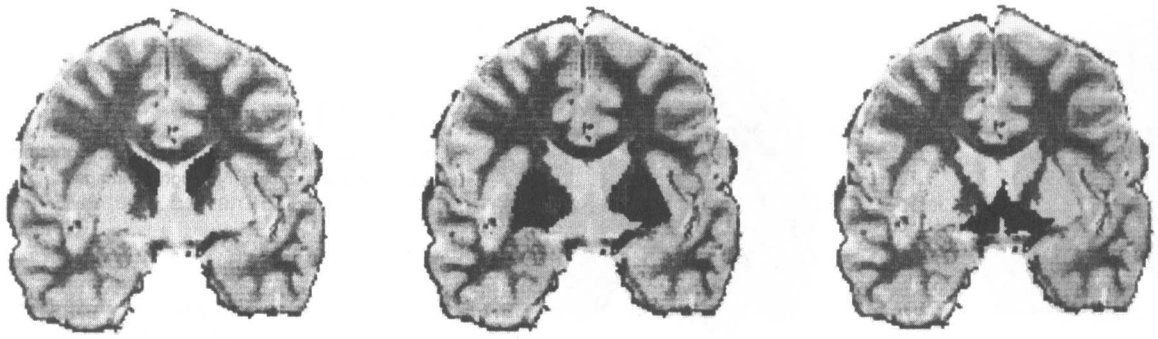

Fig. 3. Examples of fully processed images showing caudate (left) and lenticular (center) nuclei and diencephalon (right).

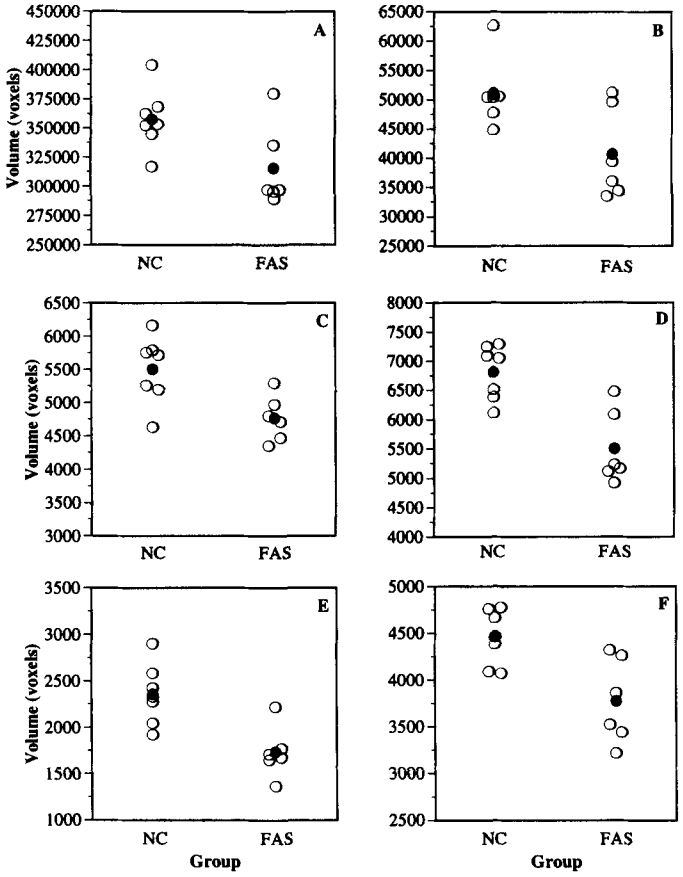

Fig. 4. Results of volumetric analyses of select brain regions of children with FAS and matched normal controls (NC). The regions of interest are: (A) cerebral vault; (B) cerebellar vault; (C) diencephalon; (D) basal ganglia; (E) caudate nucleus; and (F) lenticular nuclei. Volumes are presented as raw data in voxels (i.e., the three-dimensional volume units from which the pixel values derive). Filled circles represent group means.

also smaller in the alcohol-exposed group; however, this difference was only marginally significant ($U = 8.0$; $p < 0.07$). Our previous reports suggested that the overall volume of the cerebellum,[13,15] as well as the area of the midsagittal anterior vermal region,[16] is reduced after prenatal alcohol exposure. An examination of the current data (Fig. 4b) reveals that 4 of the 6 alcohol-exposed subjects had cerebellar vault volumes out of the range of the normal controls. The volumes for the other two individuals, however, were well within the normal range.

In light of our previous findings of basal ganglia reductions in children with FAS and PEA, we again evaluated this brain region in this new group of children with FAS. Once again, the volume of the basal ganglia was reduced in the FAS group, compared with the normal controls ($U = 2.0$; $p < 0.01$). Furthermore, we divided the basal ganglia into its component parts: the caudate and lenticular nuclei. Both the caudate ($U = 2.0$; $p < 0.01$) and the lenticular nuclei ($U = 4.0$; $p < 0.02$) were reduced in the FAS group, compared with controls. Lastly, the volume of the diencephalon was evaluated. Again, the FAS group displayed reductions in comparison with controls ($U = 6.0$; $p < 0.05$).

Because of the reductions in overall cerebral volume, each brain region was re-evaluated as a proportion of overall brain size. As with the raw values, the proportional volume of the basal ganglia was reduced in the FAS group ($U = 3.0$; $p < 0.02$), as was the proportional volume of the caudate nucleus ($U = 6.0$; $p < 0.05$). However, neither the lenticular nuclei ($U = 13.0$; $p > 0.1$) nor the diencephalon ($U = 20.0$; $p > 0.1$) were reduced in volume when overall brain size was taken into account. These data are presented in Fig. 5.

Because of the differential results concerning the caudate and lenticular nuclei, an additional nonparametric test of interaction (Group × Region) was conducted on the proportional volumes of the two nuclei. The Adjusted Rank Transform technique was selected based on a review of nonparametric tests of interaction.[17] The results of this analysis revealed that, even though in independent analyses the caudate, but not the lenticular nucleus, was significantly smaller in the FAS group than in the NC group, the interaction was not statistically significant [$F(1,22) < 1.0$].

DISCUSSION

In this group of children with FAS, volumetric analysis of MR images indicated that the cerebrum, basal ganglia, and diencephalon were reduced in volume, compared with normal controls. Given that microcephaly is so prevalent in FAS, and the finding of significant decreases in overall brain volume in this group, it is not surprising that the

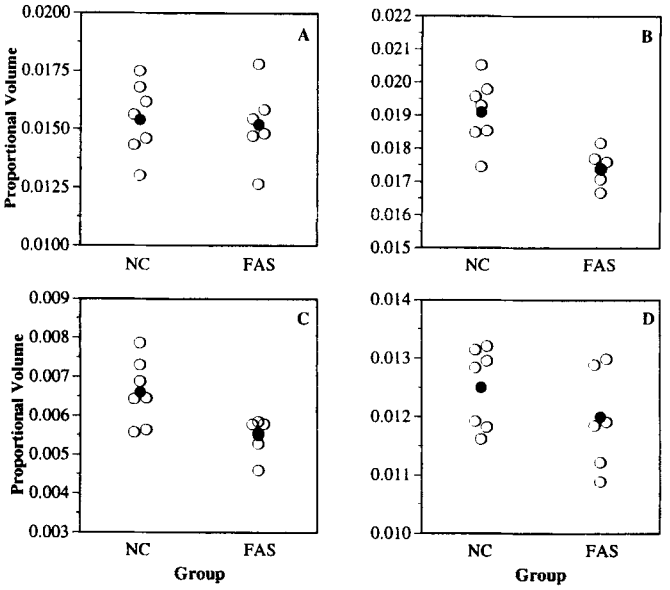

Fig. 5. Proportional volumes of select brain regions of children with FAS and matched normal controls (NC). Proportions are calculated using individual cerebral volumes (Fig. 1). The regions of interest are: (A) diencephalon; (B) basal ganglia; (C) caudate nucleus; and (D) lenticular nuclei. Filled circles represent group means.

subcortical structures measured herein are reduced. As such, when overall brain size was controlled, the diencephalon was not reduced in the FAS subjects. However, the basal ganglia were disproportionately smaller in the FAS group than in the control group when brain size was accounted for. Furthermore, when the components of the basal ganglia (caudate and lenticular nuclei) were analyzed separately, only the proportional volume of the caudate nucleus was significantly smaller in the FAS group. However, it must be stressed that the nonparametric test of interaction did not support a statistically significant interaction between alcohol exposure and basal ganglia region. Thus, the suggestion that the caudate might be particularly sensitive to prenatal alcohol exposure must be considered speculative at this time.

Although when compared with controls, the volume of the cerebellum was reduced in 4 of the 6 FAS subjects, the overall group difference approached but did not reach statistical significance ($p < 0.07$) using nonparametric analyses. Despite this result, it may be that the cerebellum is indeed affected after prenatal alcohol exposure. Including subjects from our previous studies, a total of 10 children have been examined thus far. Eight of these ten had cerebellar vault volumes out of the range of normal controls. There is also evidence for cerebellar abnormalities in humans[4,6,7,16,18] and rats exposed to alcohol during the perinatal period.[19–22]

This study replicates our previous report of basal ganglia reductions in children with FAS. In addition, there is some suggestion that the caudate nucleus might be more affected by prenatal alcohol exposure than the lenticular region, although the lack of a statistically significant interaction between alcohol exposure and brain region prevents any firm conclusions at this time. Importantly, these data were obtained with different subjects, a different imaging protocol, and different image analysis methods than were used in our previous preliminary report. Yet, the results presented herein are similar, adding strength and verifying the reliability of these findings, even though the sample size is still relatively small.

The reduction in the volume of the basal ganglia may relate to some of the behavioral disturbances noted in children with FAS. The basal ganglia's role in behavior may involve a partial segregation of function, whereby the putamen carries out motor functions, whereas the caudate is primarily responsible for cognitive functions. Structurally and functionally, the basal ganglia have connections throughout the cortex, and the areas of the cerebral cortex that connect to the striatum (caudate and putamen) do so in such a way that the topographic organization of the cortex is preserved.[23] Specifically, the caudate receives input from frontal eye fields and association areas of the frontal and parietal lobes, whereas the putamen (part of the lenticular nuclei) is innervated by neurons from the primary motor, premotor, supplementary motor, and somatosensory cortices.[24,25] Furthermore, the putamen's efferents primarily innervate the premotor cortex, whereas the caudate's efferents are directed to the prefrontal cortex.[24] As such, we might expect that behavioral deficits associated with caudate reductions might encompass deficits similar to those of patients with frontal system dysfunction, whereas putamen or lenticular reductions might result in deficits in the area of motor skills.

Most information on the role of the basal ganglia in cognition comes from the study of patients with illnesses related to the basal ganglia, such as Parkinson's disease (PD) or Huntington's disease (HD). Both of these disorders involve neuropathology of the basal ganglia, and both have cognitive features in addition to the obvious motor symptoms. Along with those of a few other disorders, the cognitive features of PD and HD have been termed "subcortical dementia,"[26,27] and have been extensively detailed in the neuropsychological literature. Subcortical dementia is characterized by memory deficits (primarily a retrieval problem), bradyphrenia, personality and affective changes, attentional impairments, and deficits in executive functioning (e.g., planning). Other deficits have been noted after basal ganglia lesions in animals and humans. In animals, caudate lesions produce deficits in spatial memory, perseveration, as well as difficulty shifting responses.[24,28] In humans, focal striatal lesions have been associated with deficits in language and attentional processes.[27]

There is evidence to suggest that behavioral deficits similar to those evidenced after caudate damage exist following significant prenatal alcohol exposure. Similar to HD patients, children and/or animals exposed to alcohol prenatally show deficits in spatial learning,[29,30] evidence of kinetic tremor,[31] attentional disorders,[32–34] and perseverative

behavior.[35,36] In addition, deficits in explicit memory have also been reported in children exposed to alcohol prenatally in the absence of full-blown FAS[37] and in children with FAS.[36] Finally, deficits in executive functioning, similar to those evidenced in patients with frontal systems dysfunction, have been noted in children with FAS or PEA.[38,39]

In addition, other key features of the effects of prenatal alcohol exposure may be consistent with caudate dysfunction. Many of the behavioral/cognitive deficits after caudate damage (e.g., perseveration and response set shifting) are consistent with a deficit in response inhibition. Riley et al.[40,41] have proposed that prenatal alcohol exposure causes a response inhibition deficit such that children and animals exposed to alcohol in utero are unable to inhibit responses or behaviors.[35] For example, rats prenatally exposed to alcohol were less able to perform a passive avoidance task in which they simply had to stay in one location to avoid shock.[42] Prenatally exposed rats also show increases in activity[43,44] and exploratory behavior,[45] decreases in spontaneous alternation, and deficits in reversal learning[41,46] that are consistent with a response inhibition deficit.

Children who have been exposed to alcohol prenatally also demonstrate some behavioral deficits that might be consistent with a lack of response inhibition. For example, hyperactivity and impulsivity are hallmarks of FAS.[47] In addition, these children demonstrate increases in intrusion, perseveration, and false-positive errors on verbal recall.[36] On measures of attention, they make an increased number of errors of commission.[32,33]

In summary, this study documents volumetric reductions in the brains of children with FAS. Specifically, reductions were noted in the cerebral vault, the basal ganglia, and the diencephalon. Furthermore, when brain size was controlled, the proportional volume of the basal ganglia and, more specifically, the caudate nucleus was reduced in the FAS group. We believe that these specific reductions in brain are related to behavioral abnormalities seen in children with FAS.

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