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Technetium-99m HMPAO brain SPECT in children with attention deficit hyperactivity disorder

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Attention deficit hyperactivity disorder (ADHD) is a developmental, neurobehavioral syndrome with an onset in childhood. The aim of this study was to investigate the existence of regional perfusion changes in ADHD by means of Tc-99m HMPAO brain SPECT. Thirteen children with a diagnosis of ADHD and 7 healthy, age-matched controls were included in this study. Hypoperfusion was observed on the right temporal cortex in 9, and on the left temporal cortex in 3 children. The distribution of the lesions showed right lateral temporal cortex involvement in 3, right medial temporal cortex in 9 and left medial temporal cortex in 8 children. Asymmetric perfusion was seen on the caudate nucleus in 4, on the thalamus in 3 and on the frontal cortex in 6 children. There was a significant difference between children with ADHD and controls in right medial temporal cortex: cerebellum and right lateral temporal cortex: cerebellum ratios. Hypoperfusion in the right medial temporal cortex was significantly and inversely correlated with Du Paul teachers' questionnaire rating scale ($r = -0.71$, $p = 0.006$). It has been postulated that difficulty in self regulating response to stimuli in ADHD is mediated by underfunctioning of the orbital frontal cortex and subsequent connection to the limbic system. Decreased temporal cortex perfusion may dysfunction of the limbic system or the orbito-frontal-limbic axis.

Key words: ADHD, technetium-99m HMPAO, brain SPECT

INTRODUCTION

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is one of the most prevalent disorders that child and adolescent psychiatrists treat. Prevalence of ADHD in the general population is approximately 5% of school-age children.[1] ADHD is characterized by a developmentally inappropriate poor attention span or age-inappropriate features of hyperactivity and impulsivity or both. To meet the DSM-IV diagnostic criteria, the disorder should be present for at least 6 months, cause impairment in academic or social functioning, and occur before the age of 7 years. ADHD appears to be heterogeneous, with a variety of known etiologies such as head trauma, intrauterine exposure to toxins, and infections,[2] but in the majority of cases no etiology has been determined.

A neurobiological basis for ADHD has been proposed since the earliest descriptions of this disorder.[3] In recent studies, the possible neurobiological factors in ADHD have been investigated by evaluating the functional activity of the brain. Though the precise nature of ADHD is not clearly understood, involvement of the frontal-striatal system may play an important role. *In vivo* imaging studies of ADHD with positron emission tomography (PET) and single photon emission computed tomography (SPECT) have analyzed the patterns of cerebral blood flow (rCBF), demonstrating decreases in brain metabolism, especially in the premotor cortex and the superior prefrontal cortex, and hypo-perfusion of striatal and periventricular structures with sensorimotor cortical hyperperfusion.[4–7] The aim of this study was to investigate the existence of regional perfusion changes in

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children with ADHD by means of Tc-99m D,L-hexamethylpropylene amine oxime (HMPAO) brain SPECT.

MATERIALS AND METHODS

Subjects and Study Protocol

Thirteen children with a diagnosis of ADHD (mean = 9.5 ± 1.6, 9 male and 4 female) and 7 healthy, age-matched controls (mean = 8.8 ± 1.9, 5 male and 2 female) were included in this study. The diagnosis of ADHD was established according to DSM-IV criteria. A clinical interview was performed both with children and parents. Each child with ADHD was also assessed by Conners teachers questionnaire rating,[8,9] Du Paul parents and teachers questionnaire rating.[10] An estimated full-scale intelligence questionnaire (IQ) was obtained with Wechsler Intelligence Scale for Children-Revised (WISC-R).[11] An IQ below 80, a history of head injury or neurologic illness, developmental delay, existence of Tourette's syndrome, tic disorder, or any other axis I psychiatric disorder, except for other disruptive behavior disorders such as conduct disorder, oppositional defiant disorder or learning disability (LD), were accepted as exclusion criteria. None of the children had been treated with stimulant therapy previously. Magnetic resonance imaging (MRI) was performed in all patients to exclude an anatomical lesion. The control group consisted of age matched children referred to our clinic for SPECT imaging but had normal electroencephalography (EEG), magnetic resonance imaging (MRI) and brain SPECT findings.

The study protocol was approved by the institutional ethical committee. Written informed consent was obtained from parents of all the children. The study was explained to the parents and children in detail.

Table 1 Clinical data in children with ADHD

Clinical Data	ADHD
Age	9.5 ± 1.6
Sex	9 male, 4 female
Additional Clinical Information	
* ODD	3 children
* ODD + LD	2 children
* LD	2 children
* LD + C	1 child
Conners Teachers Rating Scale	T index
† Hyperactivity	75 ± 11
† Inattentive and Passive	64 ± 6
† Conduct	74 ± 11
† Hyperactivity/Restlessness Conners 10 item	78 ± 10
Du Paul Teachers Rating Scale	33 ± 4
‡ Inattention/Hyperactivity	19 ± 3
‡ Impulsivity/Hyperactivity	19 ± 3
Du Paul Parents Rating Scale	32 ± 5
‡ Inattention/Hyperactivity	19 ± 3
‡ Impulsivity/Hyperactivity	21 ± 3

* ODD: Oppositional Defiant Disorder, DB: Conduct Disorder, LD: Learning Disability.

† Subgrous of Conners questionnaire rating scale. On a scale of 55 to 100, scale of 65 or greater is considered clinically significant. Two or more subgroups elevated above 65 indicates ADHD.

‡ Subgroups of Du Paul questionnaire rating. A score greater than 14 indicates ADHD.

Imaging Procedure

Tc-99m HMPAO (Ceretec®, Amersham Medical Limited, England) was prepared by adding 1110 MBq of freshly eluted Tc-99m pertechnetate to 5 m*l* of saline solution. The solution was administered to the children no more than 30 minutes after preparation. Radiochemical purity exceeded 90% when tested by instant thin-layer chromatography. 296–407 MBq of Tc-99m HMPAO was injected intravenously in a dimmed and quiet room. Imaging was performed at least 30 minutes after the injection, with a three headed gamma camera (Neurocam, GE, Medical Systems, Horsholm, Denmark) equipped with high-resolution collimators. A total of 128 frames were obtained in 64 × 64 digital matrices, 35 s/frame and over 360° (each pixel 4 × 4 mm). These data were preprocessed with a modified Metz filter (based on a Gaussian line spread function with FWHM = 11 mm, order of 4) and were reconstructed by filtered back-projection with a ramp filter. The commercially supplied Sorenson method (GE Medical systems, Star 4000 computer, Milwaukee, WI) was used for attenuation correction. Coronal and sagittal plane slices were obtained after reconstruction of 2-pixel-thick (8 mm) slices in a transaxial plane parallel to the orbitomeatal line. Transaxial slices were transformed into temporal plane images, which were parallel to the longitudinal axis of the temporal lobes to evaluate lateral and medial temporal cortices.

Images were evaluated visually and semiquantitatively. Visual evaluation of the images was done independently by two nuclear physicians. Irregular regions of interest (ROIs) were drawn for semiquantitative evaluations. Four standardized 8-mm-thick oblique slices corresponding to symmetrically identical right and left cortical regions were used. The ROI boundaries were drawn along the outside surfaces of the brain and internally followed the division between the gray and white matter. The cortex: cerebellum ratios were obtained with the mean counts.

For each region, ADHD patients were divided into two groups according to the presence of hypoperfusion in visual evaluation (as with and without hypoperfusion) and compared with symptom rating scales to investigate whether decreases in rCBF were associated with symptom rating scales.

Statistical Analysis

Mann Whitney-U test was used to compare differences in the cortex: cerebellum ratios of the children with ADHD and normal controls and to determine differences in symptom rating scales for each region. All results were expressed as the mean ± 1 s.d. p values < 0.05 were considered statistically significant. A linear relationship was searched for only in regions with decreased rCBF with the symptom rating scales by calculating the Pearson correlation coefficients.

RESULTS

The children with ADHD and controls were well matched for age and sex. Eleven children with ADHD were right-handed and 2 children left-handed. Six controls were right-handed and one was left-handed. Table 1 shows clinical data, Conners teachers questionnaire rating, and the Du Paul parents and teachers questionnaire rating in children with ADHD. All children had normal physical and EEG examination results with no gross anatomical abnormality on MRI images. Four children had mild enlargement of the right temporal horn and 2 children had reversal of normal ventricular asymmetry on MRI images. Full scale IQ was not used in all the children. A difference of 15 points between the verbal test and performance test which are subgroups of WICS-R, established a diagnosis of LD. Verbal test scores were low in 5 children with LD so their full scale IQs were lower than 80; but performance test results were higher than 80 so these patients were included in this study.

In visual evaluation, hypoperfusion was observed on the right temporal cortex in 9 and on the left temporal cortex in 3 children. The distribution of the lesions showed right lateral temporal cortex involvement in 3, right medial temporal cortex in 9 and left medial temporal cortex in 8 children. Asymmetrical perfusion was seen on the caudate nucleus in 4, on the thalamus in 3 and on frontal cortex in 6 children (Fig. 1). In semiquantitative evaluation, there was a significant difference between children with ADHD and controls in the right medial temporal cortex: cerebellum (RMT/C) and right lateral temporal cortex: cerebellum (RLT/C) ratios (Table 2). After the exclusion of 5 children with LD, RMT/C and RLT/C ratios were calculated to investigate whether there was any effect of this disorder on the temporal cortex ratio. RMT/C and RLT/C ratios were found as 0.83 ± 0.08 and 0.87 ± 0.04, respectively, which were still significantly different (p = 0.03, p = 0.02, respectively). No significant difference between children with ADHD and controls was observed in the other cortical regions.

The correlation coefficient for RMT/C and Du Paul teachers questionnaire rating was r = –0.71 (p = 0.006). No correlation was found between the other cortical regions with decreased rCBF and the symptom rating scales.

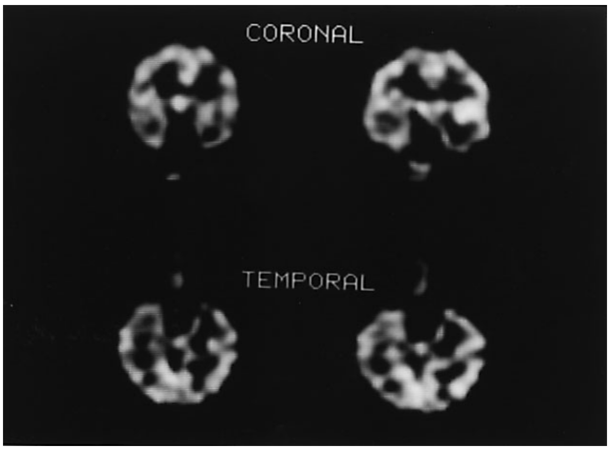

Fig. 1 Tc-99m HMPAO SPECT images of an 8 year-old child with ADHD and oppositional defiant disorder and a scale of 37 for Du Paul teachers questionnaire rating in total show hypoperfusion in the bilateral temporal cortex and left frontal cortex. Hypoperfusion in the left medial temporal cortex is more marked than right medial temporal cortex.

Table 2 Statistically significant differences in rCBF between ADHD and controls

	ADHD	Control	p
RMT/C*	0.83 ± 0.07	0.93 ± 0.07	0.01
RLT/C†	0.87 ± 0.05	0.93 ± 0.05	0.03

* RMT/C = Right medial temporal cortex: cerebellum ratio.
† RLT/C = Right lateral temporal cortex: cerebellum ratio.

Table 3 Symptom rating scales and semiquantitative cortex/cerebellum ratios of right medial and lateral cortices classified according to the presence and absence of hypoperfusion in visual evaluation

Cortical Regions	Cortex: Cerebellum Ratios and Scales	Hypoperfusion (+)	Hypoperfusion (−)	p
Right Medial	RMT/C*	0.78 ± 0.04	0.90 ± 0.02	0.003
Temporal Cortex	Du Paul Teachers Rating Scale (Total)	35 ± 3	29 ± 3	0.006
Right Lateral	RLT/C†	0.82 ± 0.03	0.90 ± 0.03	0.006
Temporal Cortex	Hyperactivity/Restlessness Conners 10 item	86 ± 10	73 ± 7	0.05

* RMT/C = Right medial temporal cortex: cerebellum ratio.
† RLT/C = Right lateral temporal cortex: cerebellum ratio.

Compared to children with no hypoperfusion in visual evaluation, children with hypoperfusion in the right medial temporal cortex and right lateral temporal cortex had significantly higher symptom rating scales on the Du Paul teachers questionnaire rating in total and hyperactivity/restlessness Conners 10 item test (Table 3). For the Du Paul teachers rating scale, the ADHD group with hypoperfusion in the right medial temporal cortex had a scale equal to or more than 32, and the ADHD group with no hypoperfusion had a scale lower than 32 except one patient with a scale 33. We propose that if children with ADHD have a scale of greater than 32 on the Du Paul parents questionnaire rating, decreases in rCBF can be observed by SPECT.

DISCUSSION

Comorbidity is a major problem in patients with ADHD. Frequent comorbidity of conduct disorder, oppositional defiant disorder and learning disability has been reported.[12,13] Therefore, children with these disorders in addition to ADHD were not excluded in this study. Similar patient selection was also performed in several previous studies.[5,14]

Though several studies have been done previously, the neurobiological basis of ADHD has not been fully understood. PET studies had recently provided many insights into the field of ADHD. Zametkin et al. investigated differences in cerebral glucose metabolism in adults with histories of ADHD and demonstrated significant decreases in brain metabolism by using F-18 fluorodeoxyglucose. The greatest reductions in glucose metabolism were at the premotor cortex and the superior prefrontal cortex. There were also decreases in several other regions, including the right thalamus, right caudate and right hippocampus.[4] In their later study, Zametkin et al. demonstrated lower metabolism in six of 60 specific regions including the left anterior frontal lobe, left thalamus and right hippocampus in adolescents with ADHD while performing an auditory-attention test.[5] Amen et al. investigated Tc-99m HMPAO brain SPECT findings at rest and during intellectual stress in children and adolescents with ADHD. Sixty-five percent in the ADHD group revealed decreased perfusion in the prefrontal cortex with intellectual stress.[15]

Because we have noticed that hypoperfusion in the temporal cortex was more frequent than in the frontal cortex, thalamus and caudate nuclei in visual evaluation of the SPECT images, we decided to assess the lateral temporal cortex and medial temporal cortex more closely. In semiquantitative evaluation of the temporal slices, we demonstrated significant rCBF differences between children with ADHD and controls in the right medial temporal cortex and right lateral temporal cortex. No significant rCBF differences were found in the other cortical regions. Amen et al. previously reported temporal lobe dysfunction in a percentage of children and adolescents with ADHD.[15] Focal cerebral dysfunction was demonstrated in the developmental LD.[16] There were also significant rCBF differences in the right medial temporal cortex and right lateral temporal cortex ratios after excluding five children with accompanying learning disability. It has been suggested that right hemisphere lesions producing inappropriate motor activity might play a role in the understanding of ADHD.[17] In our study, hypoperfusion in the right cortical regions was more frequently seen than in the left cortical regions both in visual evaluation and semiquantitative evaluation.

The significant correlation between the left anterior frontal brain metabolism and severity of symptoms was observed previously.[5] In our study, decreased rCBF in the right medial temporal cortex and right lateral temporal cortex was associated with more severe symptoms. Decreased rCBF in the right medial temporal cortex was significantly and inversely correlated with the Du Paul parents and teachers questionnaire rating scale.

Casey et al. investigated the relationship between specific frontostriatal structures (prefrontal cortex and basal ganglia) and response inhibition deficits observed in children with ADHD. Significant correlations were found between the task performance and the anatomical measures of the prefrontal cortex and caudate nuclei, predominantly in the right hemisphere. These findings suggested that right frontostriatal circuitry may play a role in response inhibition and ADHD.[18] A new unified theory suggests that the symptoms of ADHD are most accurately explained by an impairment in response inhibition, which results in difficulty in the self-regulating response to stimuli. This impaired responding is mediated by under-functioning of the orbital frontal cortex and subsequent connections to the limbic system.[19] The ROI of the medial temporal lobe consists of some parts of the limbic system, such as the hippocampus, the parahippocampal gyrus, and amygdala.[20] Interconnections between the limbic system and striatum[19–21] may account for differences in rCBF in our study.

CONCLUSION

According to our knowledge, this is the first study that demonstrated significant hypoperfusion in the right medial temporal cortex and right lateral temporal cortex in ADHD. Decreased temporal cortex perfusion may reflect dysfunction of the limbic system, or the orbito-frontal-limbic axis. Studies investigating the temporal cortex in ADHD may provide new insights into the pathophysiology of ADHD.

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