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Pharmacotherapy and Regional Cerebral Blood Flow in Children with Obsessive Compulsive Disorder

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While regional cerebral blood flow (rCBF) studies on adults involving the caudate, prefrontal, orbitofrontal, and cingulated areas have been reported, no such published data on children exist. In this study, we aimed to determine the significance of pre- and post-treatment regional cerebral blood flow (rCBF) differences in children with obsessive compulsive disorder (OCD) and compared them with healthy controls. Eighteen drug-free obsessive compulsive children, aged 11 to 15, without comorbid states except for anxiety disorders - participated in this study. The control group consisted of 12 children, aged 11 to 15, with no medical or psychiatric illnesses. Using SPECT (Single Photon Emission Computerized Tomography) scans with Technetium-99m-HMPAO-hexamethly propyleneamine oxime (Tc99mHMPAO), the rCBF was calculated in 15 regions of the control group according to a standard protocol, while in the study group, it was measured at baseline and after 12 weeks of treatment with a fixed dose of paroxetine (20 mg qd). We compared the resulting pre- and post-treatment CBF values for the control group and study group. The right and left caudates, right and left dorsolateral prefrontals, and cingulate had significantly higher rCBF in children with obsessive compulsive disorder than in the control group. These areas, in addition to the right anteromedial temporal, showed significant rCBF reduction after treatment with paroxetine. The mean percentage of change in obsession scores during the treatment correlated significantly with the baseline and post-treatment rCBF level of the right caudate, post-treatment left caudate, and baseline left caudate. Our findings on children are consistent with adult studies and support the theory of a cortical-striatal-thalamic-cortical loop disturbance in OCD.

Key Words: SPECT, Tc-99M-HMPAO, obsessive compulsive disorder, child, treatment, paroxetine

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INTRODUCTION

Obsessive compulsive disorder (OCD) is characterized by recurrent, persistent, and intrusive thoughts, impulses, or images along with repetitive, purposeful, and intentional behaviors (e.g. washing, cleaning, and checking) to allay overwhelming anxiety.[1] About one in every 200 children or adolescent develops obsessive compulsive disease (OCD) that causes significant functional loss in the educational, social and occupational domains.[1] OCD is phenomenologically and biologically distinct from other anxiety disorders and is now accepted to be a neurobiological disorder with a variety of etiologic factors, including genetic susceptibility, neurophysiological aberrations, regional brain dysfunction, and poststreptococcal autoimmunity.[2,3]

While many studies have attempted to identify the pathophysiology of OCD-for instance, through the use of structural and functional brain imaging-most of these studies were conducted on adults. Structural imaging studies using CT and MRI failed to show a consistent pattern in OCD.[4]

On the other hand, there has been a considerable lack of imaging studies on children with OCD; the few that do exist are structural imaging studies that reported the pathology of the ventral frontal cortex, thalamus, and basal ganglia.[4] A growing body of functional brain imaging studies (cerebral blood flow, cerebral glucose metabolism, and functional-MRI) on OCD have implicated specific regions of the brain with some consistency.[4,5] Studies mostly done with SPECT, and rCBF (regional cerebral flow) were reported to differ

between resting OCD patients and healthy controls, and between pre- and post-treatment adult OCD patients.[4-9] The only SPECT study on early-onset OCD was performed on adults and revealed significant decrease of cerebral blood flow in several brain regions when compared to late-onset OCD patients and healthy controls.[10]

The limited data suggested that adult OCD patients have abnormalities in the frontal lobe - in particular, the orbito-frontal cortex, and the basal ganglia (specifically the caudate nuclei, which normalized with pharmacological treatment).[4,5] Although there has been significant interest in the pharmacotherapy of OCD in children, there is no published data on children that focuses on the cerebral blood flow before and after treatment.

In this study, we aimed to compare, using 99mTc-HMPAO SPECT, the rCBF of 18 children suffering early-onset OCD (study group) with the rCBF of 12 healthy subjects (control group) as well as compare the rCBF of the study group before and after treatment with a fixed dose (20 mg qd) of paroxetine for 12 weeks. We also sought to compare rCBF between patients who responded to the treatment and those that did not, and assess the correlation of rCBF with obsessive compulsive symptoms and depressive symptoms.

MATERIALS AND METHODS

Study individuals

Eighteen right-handed children (11 boys, 7 girls), ranging from ages 11 to 15 (mean age was 13.17 ± 1.59), participated in this study. Each child had OCD before age 12. The control group consisted of 12 right-handed children (7 boys, 5 girls), from 11 to 15 years old (12.50 ± 1.38). The Ethical Committee of Cukurova University's Faculty of Medicine approved the study and treatment protocol. Parents and children were informed about the study protocol and alternative treatment options. All subjects were outpatients of the University's Child and Adolescent Psychiatry Department. Both the parents and children gave written consent regarding the study and data publication.

The criteria for the study group were as follows: between 9 and 15 years of age, a DSM-IV (Diagnostical and Statistical Manual for Mental Disorder-IV) diagnosis of OCD[11] (agreed by two certified child psychiatrists after clinical interviews), high scores (>19) on the Maudsley Obsessive Compulsive Questionnaire for Children (MOCQ),[12] above-70 IQ, and written consent of both the parents and the subjects. The Global Assessment of Relational Functioning (GARF) Scale, according to DSM-IV, was used to evaluate global functioning. Children with OCD had GARF scores between 41 and 60, which indicated moderate to severe difficulties. The control group was from the Child Nephrology Department of Cukurova University and consisted of 12 children (7 boys, 5 girls) with no medical or psychiatric illness (based on normal neurologic and psychiatric examinations and lab work-ups). Along with clinical interviews, the Conners Parent Questionnaire[13] and Conners Teacher Questionnaire[13] were used for screening. Subjects were excluded from the study and control groups according to the following criteria: previous medication history for any psychiatric disorder, comorbidity of any kind of psychiatric disorder (including affective disorders, mental retardation, attention deficit hyperactivity disorder, tic disorders, and pervasive developmental disorders except for comorbid anxiety disorders), diagnosis of pediatric autoimmune neuropsychiatric disorder associated with streptoccic infection (PANDAS), any medical conditions that required medication, abnormal findings on neurological examination, EKG and EEG, history of seizure disorders, any abnormal laboratory findings on whole blood count, blood biochemistry analysis (Na, K, Cl, Ca, BUN, creatinine, glucose, bilirubine, blood iron level, and lipid profile) liver function tests (SGOT, SGPT), urinalysis and urine screening.

Pharmacological treatment and follow up

After completion of all diagnostic and clinical work-ups, all patients were given a daily paroxetine dosage of 10 mg for one week. This dosage was raised to a total of 20 mg per day for the rest of the 11 weeks thereafter. No patient received additional medication or therapeutic interventions. Patients were also checked by a child

psychiatrist every two weeks. There were no severe side effects and no drop-outs during the study.

Following the clinical interviews, the obsessive-compulsive symptoms were rated on the Maudsley Obsessive Compulsive Questionnaire (MOCQ), which is a self-report scale that was the sole standardized measurement of obsessive-compulsive symptoms in Turkish children and adolescents at the time of the study. The score is between 0 and 37 on MOCQ where higher scores correlate to higher severity.[12] Depressive symptoms were assessed with the Depression Inventory for Children (CDI), which was modified from the Beck Depression Inventory, the validity and reliability of which has been studied in Turkish children and adolescents. The score is between 0 and 54 on CDI where higher scores correlate to higher severity.[13] Before (baseline) and after treatment (at 12th week), MOCQ and CDI were administered to the children at the child and adolescent psychiatry clinic early in the day before SPECT imaging. We defined "the responders" as those with equal to or more than a 30% drop on the MOCQ at the end of the study. "The non-responders" were defined as children who had less than a 30% drop on the MOCQ.

SPECT imaging protocol and evaluation

SPECT scans were conducted according to a standard protocol. Technetium-99m-HMPAO-hexamethly propyleneamine oxime (Ceretec, Amersham International U.K.) was prepared according to the product information. This a neutral and lipid- soluble complex that crosses the blood brain barrier and is distributed in proportion to regional cerebral blood flow.[14] First pass extraction is high (85%), and the compound is retained in the brain for four hours. This allows sufficient time for imaging with a gamma camera. A Tc-99m-HMPAO dose of 7.4 MBq (200μCi) per kg body weight was intravenously administered to the patients during rest, with eyes open and ears unplugged. All of the patients were cooperative during the study and rested in a quiet, dark room for 20 minutes before injection. All the patients were able to tolerate the time of image acquisition without obsessions or compulsions. The acquisition was started 30 min after tracer injection. The tomographic planar data was collected on a large field-of-view gamma camera (Starcam 4000i, GE Medical Systems) fitted with a low energy, high-resolution parallel-hole collimator. A circular orbit was employed to acquire 64 planar images of 360(at 30 sec per frame on a 64x64 matrix. Scatter correction and back projection with a Butterworth and Ramp filter were performed. The head of the patient was aligned parallel to the orbitomeatal (OM) line with the aid of a head holder. Coronal, sagittal and transaxial slices parallel to the orbitomeatal line were generated. Each slice was on average 12.6 mm thick. All images were reconstructed and analyzed by the same physician on the Starcam 4000i computer system. The images were analyzed qualitatively and quantitatively. A region of interest (ROI) method was used as similarly described by Yazici, et al.[15] to describe the regions of the brain and the entire brain cortex on transaxial slices. ROIs were placed manually over fifteen brain regions and the cortex (Fig. 1). The ratios of the individual regions to the cortex were calculated in 15 regions (right and left caudate, right and left dorsolateral prefrontal, right and left orbitofrontal, right and left anteromedial temporal, right and left posteromedial temporal, visual cortex, cingulate, mid- cerebellum, right and left cerebellum) as described in other literatures.[9]

Because the uptake varied among the subjects, each subject's uptake values were normalized to the area of mean cerebellar uptake (mean of mid-, right-, left-cerebellum) in order to perform statistical comparisons (mid-cerebellum + right cerebellum + left cerebellum/3=x, rCBF=raw uptake value in a particular region/x). As in other studies,[16,19] we used cerebellum for normalization, given that it is proposed to be less likely involved in the neuropathology of OCD than the cerebrum. Excluding the cerebellum, all of the 12 ROIs were expressed as intra-subject ratios to the visual cortex (Table 1). The nuclear medicine specialist who analyzed the images did not see the patients and did not know any specific clinical details about them.

Statistical analysis

Data were analyzed using the Statistical

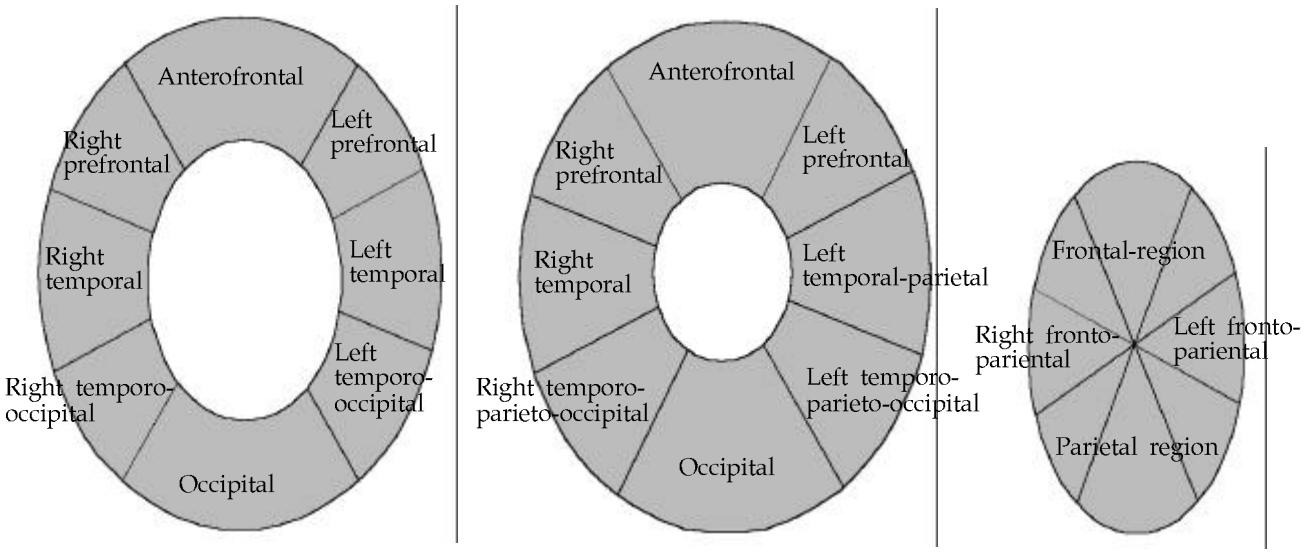


Fig. 1. The cerebral regions of interest drawn on the transaxial slices.

Package for the Social Sciences (SPSS) 10.0. The paired t-test was used to determine the rCBF differences in OCD patients before and after treatment. We compared the rCBF of the responders and the non-responders separately using the paired t-test. Using student t-tests we compared the study group and control group rCBF scores, pre- and post-treatment rCBF scores, baseline depression (on CDI) scores, percentage of mean change in depression scores, and baseline obsession (on MOCQ) between the responders and the non-responders in the study group. In the study group, correlation of each region's mean cerebral blood flow and obsession scores on MOCQ, depression scores on CDI, and the percentage of change at the end of the study from baseline [(baseline score-12th week score)/baseline score] on MOCQ and CDI was calculated with Pearson's correlation (r values). We also searched for rCBF correlations between brain regions in the study group, in the treatment responders as well as in the non-responders. We set a threshold of $p<0.05$ for statistical significance.

RESULTS

In contrast to the control group (7 boys and 5 girls, aged 12.50(1.38), children with obsessive compulsive disorder (11 boys and 7 girls, 13.17 ± 1.59) had significantly higher rCBF scores in the right and left caudate, right and left dorsolateral prefrontal, and cingulate (Table 1).

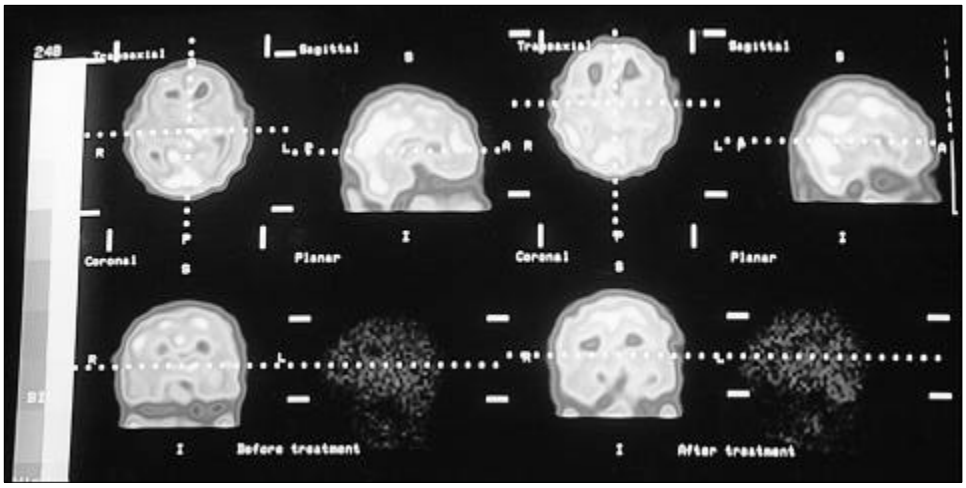
There were 12 responders (equal to or more than 30% decrease on the MOCQ score at the end of the study) and 6 non-responders (less than 30% decrease on the MOCQ score) in the study group. In the study group, the mean obsession score significantly changed from 21.27 ± 5.48 (at baseline) to 15.82 ± 8.84 (at the end) (t=2.03, p=0.05), and the mean depression score was reduced from 18.45 ± 12.08 (at baseline) to 15.88 ± 14.44 (at the end) without statistical significance (t=1.23, p=0.25). Scores showed no statistical significance between the responders and the non-responders on baseline CDI (14.86 ± 8.53 vs. 25.40 ± 13.99; t=-1.63, p=0.134) and on baseline MOCQ (21.71 ± 5.47 vs. 22.20 ± 6.61; t=-0.14, p=0.892).

There was a reduction in cerebral blood flow in all brain regions after treatment. The right and left caudate, right and left dorsolateral prefrontal, right anteromedial temporal, and cingulate showed significant rCBF reduction after paroxetine treatment (Table 2). In the responders, the right caudate, right anteromedial temporal, and left posteromedial temporal showed significant rCBF reduction after treatment. In the non-responders, only the left dorsolateral prefrontal

Table 1. Comparison of Mean Values and Standard Deviation in Each of the 12 Regions Expressed as Ratio to Cerebellum between OCD Group and Control Group

Regions	OCD	Controls	t-value	p^a
	Mean ± SD	Mean ± SD		
Right caudate	0.825 ± 0.08	0.745 ± 0.08	2.47	0.02*
Left caudate	0.778 ± 0.07	0.702 ± 0.04	3.46	0.002‡
Right dorsolateral prefrontal	0.908 ± 0.21	0.727 ± 0.06	2.95	0.007‡
Left dorsolateral prefrontal	0.869 ± 0.11	0.766 ± 0.07	2.80	0.010†
Right orbital frontal	0.786 ± 0.12	0.768 ± 0.08	0.47	0.642
Left orbital frontal	0.753 ±0.12	0.774 ± 0.11	0.47	0.641
Right anterior medial temporal	0.782 ± 0.07	0.739 ± 0.03	1.87	0.08
Left anterior medial temporal	0.762 ± 0.08	0.733 ± 0.87	0.86	0.40
Right posterior medial temporal	0.787 ± 0.08	0.751 ± 0.05	1.38	0.180
Left posterior medial temporal	0.767 ± 0.06	0.731 ± 0.03	1.87	0.08
Visual cortex	1.040 ± 0.05	0.935 ± 0.25	1.49	0.07
Cingulate	0.885 ± 0.09	0.795 ± 0.12	2.17	0.04*

a, two tailed t-test; OCD, Patient group with obsessive compulsive disorder; Controls, Control group; SD, standard deviation.
*$p<0.05$.
†$p=0.01$.
‡$p<0.001$.



R: right, L: left, A: anterior, P: posterior. Pre-treatment: transaxial, sagittal, and coronal images before pharmacotherapy which are presented on the left side of the picture, post-treatment: transaxial, sagittal, and coronal images after 12 weeks of pharmacotherapy with an antidepressant (paroxetine 20 mg qd) which are presented on the right side of the picture.

Fig. 2. Pre- and post-treatment cerebral blood flow findings in an 11-year-old boy with obsessive compulsive disorder who improved more than 30% on the obsession scale with psychopharmacology, as shown by transaxial, sagittal, and coronal images.

region was significantly reduced after treatment. Both before the treatment and after the treatment, there was no significant rCBF difference in all brain regions between the responders and the non-responders.

Fig. 2. shows global hypoperfusion in the transaxial, coronal, and sagittal images of an 11-year-old boy with OCD who improved with psy-

Table 2. Comparison of Mean Regional Cerebral Blood Flow (rCBF) and Pre- and Post-treatment rCBF between the Study Group, Responders, and Non-responders

Regions		Study group N=18 Mean ± SD	Respondersa N=12 Mean ± SD	Non-responders N=6 Mean ± SD
R. Caudate	At baseline	0,825 ± 0,08[a]	0,846 ± 0,06[c]	0,795 ± 0,10
	After treatment	0,758 ± 0,05[a]	0,779 ± 0,06[c]	0,730 ± 0,03
L. Caudate	At baseline	0,778 ± 0,07[c]	0,791 ± 0,05	0,759 ± 0,09
	After treatment	0,707 ± 0,05[c]	0,727 ± 0,06	0,679 ± 0,04
R. Dorsolateral Prefrontal	At baseline	0,908 ± 0,21[d]	0,969 ± 0,25	0,822 ± 0,11
	After treatment	0,749 ± 0,08[d]	0,774 ± 0,09	0,713 ± 0,06
L. Dorsolateral Prefrontal	At baseline	0,869 ± 0,11[b]	0,888 ± 0,12	0,842 ± 0,10[c]
	After treatment	0,785 ± 0,09[b]	0,813 ± 0,08	0,745 ± 0,09[c]
R. Orbitofrontal	At baseline	0,786 ± 0,12	0,814 ± 0,10	0,747 ± 0,13
	After treatment	0,741 ± 0,08	0,766 ± 0,08	0,706 ± 0,07
L. Orbitofrontal	At baseline	0,753 ± 0,12	0,780 ± 0,11	0,716 ± 0,13
	After treatment	0,684 ± 0,09	0,714 ± 0,09	0,642 ± 0,06
R. Anteromedial Temporal	At baseline	0,782 ± 0,07[e]	0,804 ± 0,08[d]	0,751 ± 0,06
	After treatment	0,734 ± 0,07[e]	0,735 ± 0,05[d]	0,731 ± 0,10
L. Anteromedial Temporal	At baseline	0,762 ± 0,08	0,775 ± 0,08	0,743 ± 0,08
	After treatment	0,717 ± 0,09	0,736 ± 0,07	0,690 ± 0,10
R. Posteromedial Temporal	At baseline	0,787 ± 0,08	0,804 ± 0,07	0,762 ± 0,09
	After treatment	0,751 ± 0,06	0,744 ± 0,06	0,760 ± 0,07
L. Posteromedial Temporal	At baseline	0,767 ± 0,06	0,795 ± 0,06[e]	0,727 ± 0,05
	After treatment	0,740 ± 0,05	0,730 ± 0,03[e]	0,754 ± 0,06
Visual Cortex	At baseline	1,040 ± 0,05	1,060 ± 0,05	1,021 ± 0,05
	After treatment	0,965 ± 0,28	0,880 ± 0,34	1,084 ± 0,06
Cingulate	At baseline	0,885 ± 0,09[f]	0,910 ± 0,06	0,851 ± 0,12
	After treatment	0,798 ± 0,10[f]	0,816 ± 0,13	0,774 ± 0,07

Similar superscripts in the same column or row represent rCBF significance between brain regions; [a] and [b] represent $p \leq 0.01$ and [b c d e], , , , and [f] represent $p < 0.05$.
R, Right; L, Left; SD, Standard deviation. Paired t-test was used to compare treatment response, student t-test was used for comparison between the responders (equal to or more than 30% reduction on obsession score) and the non-responders.

chopharmacology. The reduction in cerebral blood flow can be more easily observed in the frontal parts (anterior sides in the picture) of the brain.

There were no significant correlation between rCBF and baseline scores of depression and obsession (Table 3). The mean percentage of change in depression scores during the treatment correlated significantly with the rCBF of baseline left dorsal prefrontal, post-treatment left anteromedial prefrontal, and post-treatment left posteromedial temporal. The mean percentage of change in obsession scores during the treatment correlated significantly with the rCBF of baseline and post-treatment right caudate, post-treatment left caudate, and baseline left caudate.

In the responders, the rCBF of baseline right

Table 3. Correlation of Cerebral Blood Flow with Depression, Obsession, and Change in Depression and Obsession Scores

Regions		Depression at baseline r values	Change in depression r values	Obsession at baseline r values	Change in obsession r values
R. Caudate	At baseline	-0.1208	0.3906	0.2118	0.6533*
	After treatment	-0.2802	-0.2777	-0.1520	0.6549*
L. Caudate	At baseline	-0.2133	0.5848	0.2165	0.1944
	After treatment	0.3534	-0.0668	-0.1032	0.6774*
R. Dorsolateral Prefrontal	At baseline	-0.3250	0.3777	0.3163	0.4441
	After treatment	0.0087	-0.0029	-0.2866	0.3623
L. Dorsolateral Prefrontal	At baseline	0.2075	0.6448*	0.5001	0.3834
	After treatment	0.1797	0.2877	0.1663	0.5305
R. Orbitofrontal	At baseline	-0.2084	0.0407	-0.0871	0.5275
	After treatment	0.2260	0.4598	0.2743	0.5302
L. Orbitofrontal	At baseline	-0.1149	0.0246	-0.1871	0.4435
	After treatment	0.0677	0.3657	0.0753	0.4826
R. Anteromedial Temporal	At baseline	-0.1762	0.0669	-0.2528	0.4878
	After treatment	0.1383	0.5238	-0.0370	0.2283
L. Anteromedial Temporal	At baseline	-0.0648	0.1790	-0.0167	0.4634
	After treatment	-0.1500	0.6911*	0.0495	0.4532
R. Posteromedial Temporal	At baseline	-0.1902	0.2838	-0.1895	0.4543
	After treatment	0.4826	0.5335	0.3634	0.0605
L. Posteromedial Temporal	At baseline	-0.1378	0.1617	-0.0685	0.5070
	After treatment	0.0869	0.6026*	-0.1553	-0.0121
Visual Cortex	At baseline	-0.0920	0.0884	-0.1188	0.0778
	After treatment	0.2260	-0.3494	-0.2522	-0.2328
Cingulate	At baseline	-0.2598	0.2247	0.3582	0.7780†
	After treatment	0.0193	0.0207	-0.1913	0.3769

Pearson's correlation was used.
* represent $p<0.05$.
† represent $p\leq0.01$ and Paired t-test was used to compare treatment response. R, Right; L, Left.

caudate correlated significantly with only baseline right dorsolateral prefrontal (r=,652, p=0.02), whereas post-treatment right caudate correlated significantly with the post-treatment left caudate (r=,9221, p=0.003) and post-treatment right dorsolateral prefrontal (r=,8302, p=0.02) regions. In the non-responders, the post-treatment right caudate correlated significantly(r=,948, p=0.02) with only the post-treatment left caudate region. No other significant rCBF correlation was found between brain regions in the study group, in treatment responders, and in non-responders.

DISCUSSION

This is the first study of cerebral blood flow and pre- and post-treatment SPECT on OCD in children, and the fact that the study group consisted of early-onset (onset before age 12), drug-free, and pure OCD without any comorbidity (except for anxiety disorders) strengthens the implications of our results. We found a significant difference in rCBF between our study group (higher rCBF scores) and control group (lower rCBF scores) in the caudate, cingulate, and prefrontal regions.

Moreover, we also detected significant change (reduction) in the caudate, cingulate, prefrontal, and temporal regions of the study group after 12 weeks of treatment with paroxetine. Although some of the children had high depression scores on the CDI, none clinically diagnosed with depression, which would have made interpretation of the results more difficult.

Some studies on adults, including the study that assessed childhood-onset OCD, report decreased rCBF in OCD patients when compared to healthy controls,[10,16] while some others report increased rCBF.[6,8,9,17,18] The increased rCBF we obtained in children with OCD is the first report of its kind, and considering the conflicting results in adults,[5,9,10,14,16-18] our finding needs confirmation through further studies. Post-treatment SPECT studies revealed decreased cerebral blood flow after treatment.[6-9] Similar to most of the treatment studies we found a reduction in all rCBF after treatment.

The rCBF in the right and left caudate was significantly higher in the study group than in the control group, and reduced significantly after treatment in our study group (n=18). The right caudate also decreased significantly after treatment in the responders (n=12) and was positively correlated with the mean obsession score change both at the baseline and at the end. The left caudate after treatment correlated positively with the change in obsession scores. While some authors report decreased HMPAO uptake in the caudate in OCD adults,[9,10,14,16] others reported no difference[17,18] or increased[5] rCBF in the caudate when compared to healthy controls. Functional imaging studies after treatment in adult OCD patients showed significant rCBF reduction in the right and left caudate,[19,20] mediofrontal,[7] orbitofrontal,[9,20] right prefrontal,[6] and temporal[6] regions. The increased glucose metabolism rates (in the left orbitofrontal, bilaterally in the prefrontal, and in the anterior cingulate) in early-onset adult OCD patients[21] were reported to have decreased after treatment (significantly in the orbitofrontal region).[22] Our findings of reduced post-treatment rCBF in the right and left caudate, right and left dorsolateral prefrontal, right anteromedial temporal, and cingulate of the subjects in the study group are consistent with most of the previous studies (see Table 2).

We found no statistically significant rCBF difference between the responders and the non-responders in all brain regions at baseline and at the end the treatment. However, the responders showed significant rCBF reduction in three regions (right caudate, left posteromedial temporal and right anteromedial temporal regions) after treatment, whereas the non-responders showed significant reduction only in the left dorsolateral prefrontal (see Table 2). Benkelfat, et al.[20] reported that the treatment responders showed a significant decrease in cerebral glucose metabolism in the left caudate in contrast to poor-responders. Baseline rCBF was also reported to be higher in the prefrontal region, cingulate, and basal ganglia for the responders than for the non-responders.[6]

It was reported that the severity of OCD symptoms correlated positively with the left orbitofrontal rCBF in early-onset OCD,[10] but similar to Machlin, et al.[18] we found no connection between rCBF and severity of obsessions. However, we found that the change in obsession correlated significantly with the pre- and post-treatment right caudate, pre-treatment cingulate, and post-treatment right caudate (see Table 3). In addition, we found that change in depression was closely linked to the left dorsolateral prefrontal (at baseline), left anteromedial temporal (after treatment), and left posteromedial temporal. The correlation of post-treatment rCBF with the change in depression should be further investigated in controlled studies for a better understanding of rCBF changes in OCD subjects.

Studies on adult OCD patients revealed significant correlation between the caudate and orbitofrontal cortex blood flows before treatment, but not after treatment.[9,19] Before treatment, there was a positive correlation between the right caudate and the right prefrontal cortex in the responders, but not in the non-responders. No notable rCBF correlation was present between these brain regions after treatment. The post-treatment right caudate showed significant correlation with the left caudate and right dorsolateral prefrontal in the responders, while it corresponded significantly with the left caudate in the non-responders. The degree of correlation between the caudate and frontal regions (either before and

after treatment) in the treatment responders, and not in the non-responders, should be further studied in an attempt to understand whether these correlations can predict a better response to treatment or even relapse in the long-run in children with OCD.

Statistical parametric mapping (SPM) is a powerful technique for comparing functional imaging data sets among groups of patients and is currently the most widely used method for analysis of functional activation images.[23] While this technique has been widely applied in studies on adults, it has rarely been applied to studies on children, due, in part, to the lack of validation of the spatial normalization procedure in children of different ages.[24] However, in preliminary studies, SPM analysis showed that children over 6 years of age appear to display the same pattern of glucose utilization as adults,[24] and this method can be of interest in SPECT studies in children.

It is important to take into consideration the limitations of this study before drawing any conclusions. Our sample size is small, and overgeneralization of our findings to all OCD in children may result in erroneous conclusions. We included no medicated control group in the study, and we drew our conclusion by analyzing the study sample in two groups based on their treatment response. We used a fixed dose of paroxetine (20 mg qd), which was reported to be effective in OCD in children in a 12-week open-label study.[25] The non-responders might be a heterogeneous group, and given that we used a fixed drug dosage, there might be some patients in the non-responders who responded to the treatment slowly (slow-responders) or only partially, and were in need of higher doses of paroxetine to respond well to the treatment.

Taken together, functional imaging studies, including this study, provide converging evidence implicating prefrontal cortex, cingulate, and caudate dysfunction in OCD. Our findings in children are consistent with adult studies and support the theory of a cortical-striatal-thalamic-cortical loop disturbance in OCD.[4,5,9] However there are some discrepancies with previous studies, which may be due to various factors: different technological tools, different scanning environment, different methods for analyzing and comparing regions, difference in subject demographics, illness severity and comorbidity, and size of the subject pool. We need further functional imaging studies on a larger sample of OCD children that are compared with well-matched controls to better evaluate short- and long-term pharmacological and cognitive-behavioral therapy responses.

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