Drug Therapy and Cerebral Perfusion in Obsessive-Compulsive Disorder

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Cerebral perfusion in a previously untreated patient with obsessive-compulsive disorder was studied qualitatively and semiquantitatively with SPECT before, during and 6 wk after treatment with clomipramine. The patient's symptoms disappeared while on medication and relapsed after drug withdrawal. At baseline, there was an increased perfusion ratio in the bilateral orbitofrontal, anterior cingular, frontotemporal and right caudate regions. These alterations disappeared during drug therapy. After treatment discontinuation and symptomatic relapse, the same pattern of hyperactivity was found. Semiquantitative measurements after treatment withdrawal showed a return to perfusion values similar to those observed before treatment in subcortical structures. In cortical areas, this level was not completely achieved. Subtraction SPECT images showed perfusion changes at the orbitofrontal, caudate and thalamic levels.

Key Words: obsessive-compulsive disorder; single-photon emission computed tomography; clomipramine; neuroimaging

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Obsessive-compulsive disorder (OCD) has been studied with different functional neuroimaging techniques. Rubin et al. (*1*) reported a significantly increased perfusion in the orbitofrontal and high dorsal parietal cortex bilaterally and in left posterofrontal cortex with SPECT. Reduced bilateral perfusion in the caudate nucleus head also was observed. Machlin et al. (*2*) found significantly increased medial-frontal perfusion.

Neuronal metabolism in OCD has been studied with PET. Baxter et al. (*3*) observed hypermetabolism of the orbitofrontal gyri and of the head of the right caudate nucleus. Swedo et al. (*4,5*) found a significant metabolic decrease in previously hyperactive orbitofrontal cortex. Martinot et al. (*6*), however, reported decreased frontal glucose metabolism in OCD patients.

The aim of the present study is to analyze the effects of the successful treatment of OCD on functional abnormalities in a patient who had received no previous therapy.

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CASE REPORT

Patient

The patient is a 31-yr-old woman who had not had previous treatment for OCD (DSM-III-R criteria). She did not meet any other psychiatric diagnostic criteria. Her symptoms (obsessions and compulsions about order and cleanliness) were evaluated with the Yale-Brown obsessive-compulsive scale; total score was 24. This scale covers a range from 0 to 40. Any value in between may be considered pathological if the subject meets OCD criteria.

Imaging Protocol

An Elscint APEX 409-A gamma camera with a high-resolution, low-energy collimator (model APC-4) was used to acquire the SPECT images. After resting for 20 min in the supine position in a semidark and silent room with eyes closed, 600 MBq ^{99m}Tc (HMPAO) were injected intravenously through a previously cannulated peripheral vein. Five to 10 min later, a total of 60 images per exploration were obtained in a 64 × 64 matrix with 360° complete rotation and continuous circular orbit. Total acquisition time was 25 min. Transaxial slices were reconstructed by filtered backprojection using attenuation correction with $\mu = 0.12$ cm and a Metz filter with coefficients 4.0 and 7.4. The transaxial slices of 1 pixel (7 mm) thickness were reoriented to sets of transversal (parallel to a line between the base of frontal and occipital lobes), coronal and sagittal, each of them 2 pixels.

Several regions of interest (ROIs) were defined (Fig. 1). The perfusion ratio between the corresponding region and the homolateral cerebellar hemisphere was calculated for each ROI. The ranges of values for a control group also were obtained (n = 28; 14 men, 14 women). In this group, the mean age was 37.4 yr (s.d. 17.5; range 19–72 yr) and the education level 14.7 yr (s.d. 4.7 yr). These subjects had no history or current evidence of central nervous system or psychiatric illness. They had a normal CT scan and did not receive any substance that could modify cerebral perfusion in the week before the SPECT scan. Their Mini-Mental Exam scores were over 26/30.

The OCD patient underwent SPECT imaging during three different conditions: pretreatment, after 6 wk of clomipramine (175 mg/day) treatment and no other therapy 6 wk after discontinuing this treatment.

Qualitative images for these conditions were obtained by identical reconstruction and imaging procedures. Subtraction images corresponding to the differences between the first and second and the third and second conditions, respectively, are presented, as

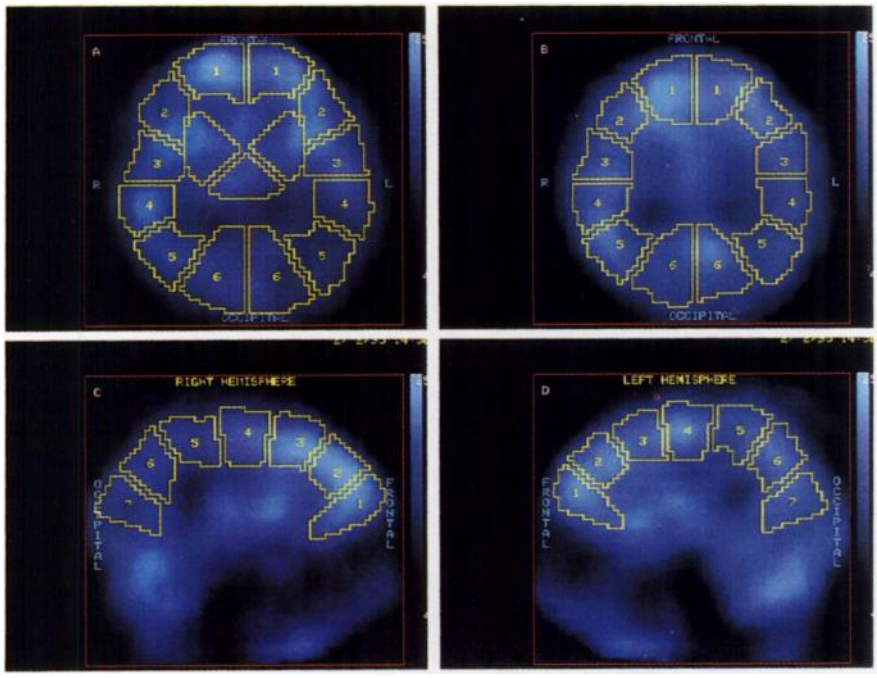

FIGURE 1. ROIs defined at basal and supraventricular transversal slices (A, B) and paramedian sagittal right and left (C, D) levels. Subcortical regions at transversal basal levels include two lateral (basal ganglia) and one posterior (thalamus) ROI.

well as the corresponding semiquantitative results. The subtraction images were created by superpositioning of the corresponding slices in the transversal plane at thalamic level and in the right paramedian sagittal plane.

Statistical Analysis

Semiquantitative perfusion values are presented for each ROI along with the same ratios obtained from the control group. For each ROI z scores (direct score minus group mean divided by s.d.) for perfusion values were calculated to compare the patient's values with those of the control group.

RESULTS

The images obtained before treatment showed increased activity in the orbitofrontal, dorsolateral prefrontal, medial frontal, anterior cingulate and frontotemporal regions bilaterally and right caudate and posterolateral temporal hyperactivity. While on clomipramine therapy, these alterations disappeared. After treatment withdrawal, right hyperactivity in the frontal anterior, anterior cingulate and temporal regions again was found. Although not so evident as before treatment, the right caudate also showed increased HMPAO uptake. In all three conditions, left parieto-occipital hypoactivity was detected.

The subtraction images (Fig. 2) depict important perfusion decrease in the orbitofrontal, caudate and thalamic areas bilaterally during treatment. In this image, the color scale corresponds to the percent perfusion changes. The original pattern was again observed after treatment.

Semiquantitative measurements also showed a similar pattern before and after treatment (Tables 1, 2 and 3).

The ROIs with z scores ≥ 3 before were: bilateral basal 1 (orbitofrontal area), left basal 2 (inferior prefrontal cortex), right supraventricular 1 and left supraventricular 2 (superior prefrontal cortex), right sagittal 2 and 3 (medial prefrontal and anterior cingulate cortex). These values (Tables 1–3) are similar to the pre- and post-treatment values. The ROIs with increased values after treatment were: right basal 1, bilateral supraventricular 1 and sagittal 2, including,

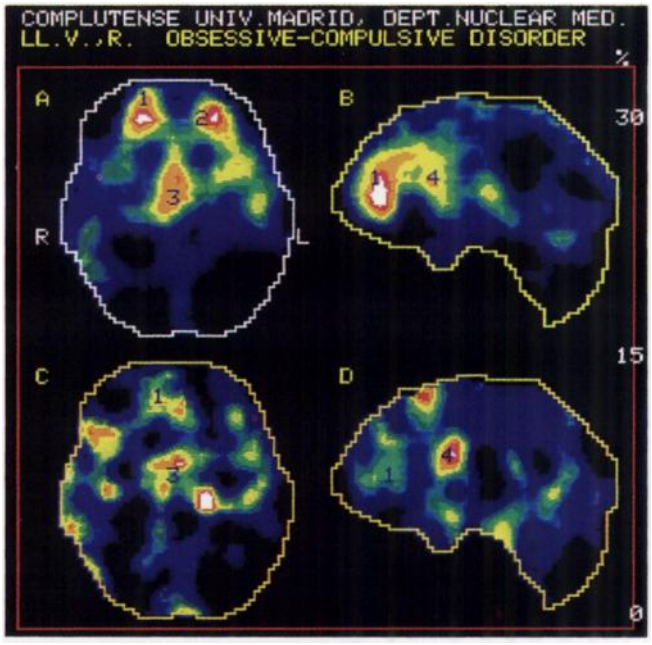

FIGURE 2. Subtraction SPECT images calculated at the basal ganglia in the transversal plane (A, C) and at right paramedian level in the sagittal plane (B, D). A and B represent the result of subtracting the second condition from the first condition of the study. C and D represent the result of subtracting the second condition from the third condition of the study. The color scale corresponds to percent perfusion changes. A significant perfusion decrease in the orbitofrontal (1 and 2), thalamic (3) and caudate nucleus (4) is apparent with treatment (A, B). A similar pattern was again observed after treatment withdrawal (C, D).

TABLE 1
Control Group Perfusion Ratios between Basal and Homolateral Cerebellum ROIs

ROIs	Controls	Before	During (%)	After (%)
		Right hemisphere		
Orbitofrontal	0.850 (0.05)*	1.05	0.842 (−20)	0.942 (−11)
Z score†		4.00‡	−0.16	1.84††
Prefrontal	0.880 (0.055)*	0.924	0.825 (−11)	0.962 (4)
Z score†		0.80	−1.00	1.49
Frontotemporal	0.910 (0.005)*	0.967	0.835 (−14)	0.944 (−2)
Z score†		1.14	−1.5	0.88
Middle temporal	0.910 (0.05)*	0.961	0.737 (−23)	0.936 (−3)
Z score†		1.02	−3.46§	0.52
Temporo-occipital	0.855 (0.005)*	0.933	0.818 (−12)	0.818 (−12)
Z score†		1.56	−0.74	−0.74
Occipital	0.910 (0.05)*	0.892	0.850 (−5)	0.881 (−1)
Z score†		−0.36	−1.00	−0.58
Thalamus	0.89 (0.07)*	0.855	0.710 (−17)	0.846 (−1)
Z score†		−0.5	−2.57**	−0.5
Basal ganglia	0.920 (0.06)*	1.00	0.829 (−17)	0.975 (−3)
Z score†		1.33	−1.51	0.91
		Left hemisphere		
Orbitofrontal	0.840 (0.05)*	0.993	0.820 (−17)	0.905 (−9)
Z score†		3.40§	−0.44	1.44
Prefrontal	0.890 (0.055)*	0.993	0.807 (−19)	0.958 (−3)
Z score†		2.06**	−1.66	1.36
Frontotemporal	0.900 (0.06)*	0.950	0.783 (−14)	0.938 (−2)
Z score†		0.83	−1.95††	0.63
Middle temporal	0.910 (0.04)*	0.866	0.753 (12)	0.870 (1)
Z score†		−1.1	−3.92‡	−1.00
Temporo-occipital	0.850 (0.05)*	0.822	0.797 (−4)	0.760 (−6)
Z score†		−0.56	−1.06	−1.80††
Occipital	0.915 (0.05)*	0.859	0.866 (1)	0.906 (6)
Z score†		−1.12	−0.98	−0.18
Thalamus				
Z score†				
Basal ganglia	0.875 (0.07)*	0.959	0.796 (−17)	0.910 (−5)
Z score†		1.20	−1.12	−1.28

*The perfusion ratios of the control group are presented as mean (s.d.). The during and after treatment perfusion values are accompanied by the percent changes with respect to the before treatment condition.

†Z scores result from the comparison of the before, during and after treatment values of the patient with the control group. Level of significance of Z scores: ‡$p < 0.00005$; §$p < 0.0003$; ¶$p < 0.001$; **$p < 0.01$; ††$p < 0.05$.

TABLE 2
Perfusion Ratios in Supraventricular ROIs

ROIs	Controls	Before	During	After
		Right hemisphere		
Prefrontal	0.855 (0.05)	1.04	0.854 (−18)	0.962 (−8)
Z score		3.7[§]	0.02	2.14[**]
Anterior frontal	0.865 (0.057)	0.955	0.844 (−12)	0.939 (−2)
Z score		1.57	−0.37	1.29
Posterior frontal	0.890 (0.05)	0.917	0.808 (−12)	0.920 (1)
Z score		1.08	−0.73	1.14
Anterio parietal	0.980 (0.05)	0.937	0.812 (−13)	0.897 (−4)
Z score		0.94	−1.56	0.30
Posterior parietal	0.870 (0.055)	0.938	0.776 (−17)	0.910 (−3)
Z score		1.23	−1.70[††]	0.72
Occipital	0.910 (0.055)	0.883	0.825 (−7)	0.925 (5)
Z score		−0.49	−1.54	0.27
		Left hemisphere		
Prefrontal	0.850 (0.057)	0.953	0.842 (−12)	0.981 (3)
Z score		1.80[††]	−0.14	2.29[**]
Anterior frontal	0.845 (0.057)	0.972	0.777 (−20)	0.939 (−3)
Z score		2.22	−1.19	1.64
Posterior frontal	0.880 (0.055)	0.896	0.745 (−17)	0.929 (4)
Z score		0.29	−2.45[**]	0.89
Anterior parietal	0.880 (0.055)	0.825	0.802 (−3)	0.865 (5)
Z score		−1.00	−1.56	−0.27
Posterior parietal	0.855 (0.06)	0.815	0.785 (−4)	0.820 (1)
Z score		−0.60	−1.16	−0.58
Occipital	0.910 (0.058)	0.890	0.839 (−6)	0.975 (10)
Z score		−0.34	−1.24	1.12

See Table 1 for definitions.

respectively, the orbitofrontal, dorsolateral premotor and anterior cingulate cortices.

Percent perfusion changes (Tables 1, 2 and 3) showed significant decreases in the bilateral anterior frontal, temporal and basal ganglia and right parietal regions during treatment. Values after treatment showed a return to pretreatment values, except in the orbitofrontal cortex.

DISCUSSION

In our patient, frontal, cingulate and basal ganglia hyperactivity were observed before and after treatment. Both perfusion abnormalities and symptoms disappeared during clomipramine therapy.

In the present study, cortical hyperactivity was predominantly frontal (medial and orbital), a finding in agreement with previous studies (*1–3*). Bilateral orbitofrontal and left dorsolateral prefrontal cortices were hyperactive before treatment. A similar but less marked perfusion pattern was observed after treatment. The difference may be partially due to the higher severity of symptoms before treatment. Anterior cingulate hyperactivity was also observed in this patient and is a pattern previously reported for OCD (*5,9*). By interrupting caudate-cingulate connections, anterior cyngulotomy is an effective treatment for refractory OCD (*10*).

In agreement with previous studies (*1,5,9*), a bilateral cortical involvement is supported by these results. The subtraction images showed significant perfusion decreases during treatment and perfusion increases after treatment at thalamic and right caudate levels, although the corresponding semiquantitative values were within the normal range. The caudate nucleus head has been reported to be prominent in OCD pathogenesis in different PET studies with better spatial resolution. The small size of the caudate head may account for the absence of quantitatively significant results. Right caudate hyperactivity, however, was observed on the qualitative images.

The observed frontal, cingulate and caudate hyperactivities are in agreement with the proposed circuit in OCD (*8*). In this model, caudate hyperactivity would lead to frontal and cingulate hyperactivity through pallidal and thalamic connections. The almost complete return to pretreatment levels of caudate and thalamic activity may support basal ganglia hyperfunction in this circuit in OCD. This is in agreement with the different correction rates for caudate and frontal hypermetabolism in OCD (*3,5*).

TABLE 3
Perfusion Ratios in Sagittal ROIs

ROIs	Controls	Before	During	After
		Right hemisphere		
Orbitofrontal	0.850 (0.05)	0.972	0.781 (−20)	0.877 (−10)
Z score		2.24**	−1.38	0.54
Anterior medial frontal	0.860 (0.05)	1.09	0.827 (−24)	0.946 (−13)
Z score		4.60§	−0.66	1.72††
Middle frontal	0.860 (0.056)	1.03	0.847 (−18)	0.948 (−8)
Z score		3.03¶	−0.23	1.57
Posterior medial frontal	0.890 (0.05)	0.934	0.797 (−15)	0.956 (2)
Z score		0.88	−1.86	1.32
Anterior medial parietal	0.870 (0.055)	0.864	0.797 (−8)	0.894 (4)
Z score		−0.10	−1.46	0.43
Posterior medial parietal	0.910 (0.055)	0.901	0.830 (−8)	0.900 (0)
Z score		−0.16	−1.45	−0.18
Medial occipital	0.910 (0.055)	0.850	0.798 (−7)	0.824 (−3)
Z score		−1.09	−2.03††	−1.56
		Left hemisphere		
Orbitofrontal	0.840 (0.04)	0.947	0.789 (−17)	0.815 (−14)
Z score		2.67**	−1.27	−0.625
Anterior medial frontal	0.850 (0.055)	0.993	0.826 (−17)	0.952 (−4)
Z score		2.60**	−0.43	1.85
Middle frontal	0.880 (0.055)	0.980	0.846 (−13)	0.933 (−4)
Z score		1.81	−0.61	0.963
Posterior medial frontal	0.880 (0.055)	0.920	0.834 (−9)	0.986 (7)
Z score		0.83	−0.83	1.93††
Anterior medial parietal	0.860 (0.065)	0.880	0.833 (−5)	0.986 (12)
Z score		0.36	−0.67	1.93††
Posterior medial parietal	0.915 (0.056)	0.928	0.849 (−9)	0.958 (3)
Z score		0.23	−1.17	0.76
Medial occipital	0.910 (0.05)	0.840	0.831 (−1)	0.840 (0)
Z score		−1.40	−1.58	−1.40

See Table 1 for definitions.

The parieto-occipital hypoactivity in this patient seems to be unrelated to the symptomatology, since it did not change through different conditions. Bilateral inferior temporal hypoactivity observed during treatment is probably a pharmacologic effect, since it only appears during clomipramine treatment (Table 1). Further studies are needed to clarify this point.

CONCLUSION

A close association was observed between OCD symptoms, perfusion and clomipramine treatment in this patient. Thus, SPECT confirmed the clinically observed efficacy of clomipramine and the need of long-term medication in the post-treatment study.

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