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A five-year longitudinal study of the regional cerebral metabolic changes of a schizophrenic patient from the first episode using Tc-99m HMPAO SPECT

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Abstract This is a naturalistic study of the relationship between cerebral metabolic activity, clinical symptoms and treatment response in a schizophrenic patient for 5 years from the onset of her illness. Serial technetium-99m-HMPAO brain SPECT was used to measure regional cerebral metabolism. The Cambridge Neurological Inventory and neuropsychological tests (WAIS-R verbal subscales, Wisconsin Card Sorting Test, semantic verbal fluency, logical memory in Weschler Memory Scale) were used for neurocognitive assessment. Under-activity of the left temporal area was observed in the course of patient illness despite remission of the psychotic symptoms. Bilateral prefrontal metabolic under-activity was noted at the emergence of negative symptoms, executive neurocognitive dysfunction and the treatment-resistant state. After response to clozapine, the right prefrontal activity returned to a normal level. Our findings suggested that persistent left temporal under-activity detected by SPECT despite clinical remission may indicate a vulnerability for further relapses and development of a treatment-resistant state. Treatment-resistant state, negative symptoms and executive neurocognitive deficit may involve abnormal prefrontal metabolic activity and can be alleviated in clozapine-responsive patients.

Key words Schizophrenia · Treatment resistant · SPECT · Clozapine

Introduction

Functional neuroimaging is important for delineating the relationship between schizophrenic symptoms, treatment response and regional cerebral metabolic activity. Findings from cross-sectional studies include correlation between temporal lobe over-activity and positive symptoms (Kurachi et al. 1985), correlation between prefrontal under-activation, negative symptoms (Volkow et al. 1987; Andreasen et al. 1992) and frontal cognitive impairment (Paulman et al. 1990). An unresolved issue in this field is whether the identified patterns of regional cortical activity represent transient variables co-occurring with symptoms, or whether they are more persistent features. Previous longitudinal studies reported transient changes (e.g. hypofrontality, increased left or right temporal activity) associated with active psychotic symptom which normalised after symptom remission (Matsuda et al. 1989; Notardonato et al. 1989; Hawton et al. 1990; Suzuki et al. 1993). In addition, several studies observed persistent frontal under-activity (Wolkin et al. 1985), laterality (right vs left hemispheric metabolism) and a steeper subcortical to cortical gradient (Gur et al. 1987) as compared to normal subjects on repeated scanning after medication. These reports are constrained by the relatively short follow-up periods (longest 18 months). We report a patient with first episode schizophrenia on whom serial Single Photon Emission Computerised Tomography (SPECT) was used to monitor cortical function for more than 5 years (62 months).

Subjects and methods

A 19-year-old right-handed female student previously led an active social life and average academic performance presented with a six-month history of auditory and visual hallucination, delusion of persecution and control. No evidence of a seizure disorder, substance abuse nor other significant medical problem was noted. Physical examination was unremarkable. Laboratory investigations including full blood count, liver, renal and thyroid function tests were normal. Electroencephalogram showed no evidence of seizure activity or focal abnormalities. Contrast computerised tomography brain scan and magnetic resonance imaging showed no structural abnormality. In particular, they revealed no temporal lobe abnormality. She was diagnosed to be suffering from paranoid schizophrenia (F20.09), based on ICD-10 (World Health Organization 1992) criteria for schizophrenia by a panel of two senior psychiatrists.

The patient was followed up for 5 years. The clinical symptoms were assessed by the 18-item Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) and High Royds Evaluation of Negativity Scale (HEN; Mortimer et al. 1989). Neurocognitive assessment was conducted using the Cambridge Neurological Inventory (Chen

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et al. 1995), Wechsler Adult Intelligence Scale-verbal subscales (WAIS-R-HK, Revised Cantonese Version; The Hong Kong Psychological Society 1989), Wisconsin Card Sorting Test (Heaton 1981), logical memory in Wechsler Memory Scale (Wechsler 1987; adapted for Cantonese speaking patients, C.W. Wong, personal communication) and semantic verbal fluency test (Chen et al. 1996).

Serial brain SPECT imaging was performed at different stages of her illness. Consent was obtained from the patient for each scanning. During each of the brain SPECT scans, 20mCi of Tc-99m HMPAO (except the fifth scan in which Tc-99m ECD was used because Tc-99m HMPAO was unavailable) was injected into an antecubital vein while the patient was resting with eyes open, in a softly lit, quiet room for 15 minutes. Thirty minutes later, the patient was placed supine using a soft head restraint to minimize motion. SPECT was performed with a rotating gamma camera equipped with high resolution collimators (Elscint Apex 409 for first and second scan and Elscint Apex Helix for subsequent scans). Data acquisition time was approximately 30 minutes per scan. Semiquantitative regional blood flow analysis was performed according to the method by Catafau et al. (1994). Briefly, eight standardized 9-mm thick oblique slices were taken from the frontocerebellar direction. Fourteen irregular regions of interest (ROIs) were automatically drawn initially on the left hemisphere then mirrored to the right hemisphere (software is available from the authors upon request). Each ROI was drawn on two consecutive slices, and mean count values per pixel were obtained. For each hemisphere, the prefrontal relative perfusion index was calculated as: prefrontal index = 100 X mean counts per pixel of prefrontal ROIs / mean counts per pixel of all ROIs drawn. Anterior temporal indices were also obtained from the same formula. SPECT acquisition and subsequent semiquantification were performed by one of the authors throughout the whole study period. We used published perfusion indices of eight healthy right-handed women of age 24.6 (± 3.0) for comparison (Catafau et al. 1994). A difference of more than 2 standard deviations from the normal control was considered to be statistically significant.

Results

The longitudinal course of the patient's illness with clinical symptoms, neurocognitive functions and SPECT findings is summarised in Table 1. In the first episode, she achieved full clinical remission after two weeks of haloperidol. Her maintenance medication was changed to sulpiride (100 mg per day) because of extrapyramidal side effects from haloperidol. She was asymptomatic and working well as a secretary while she was on maintenance medication. She suffered a relapse 44 months after the onset of her psychotic illness because of poor drug compliance. She responded well to sulpiride (400 mg per day) and her psychotic symptoms subsided completely after three weeks of treatment. There was no evidence of negative symptoms nor social functioning impairment. She continued to perform successfully in a secretarial job. Six months later (52 months after onset), she had a relapse again. Her condition deteriorated with emergence of negative symptoms including blunted affect, impoverishment of thought, social withdrawal, poor volition and occupational impairment. In addition there were impairments in neurocognitive functioning. This time she was resistant to conventional antipsychotics (trifluoperazine up to 53 mg per day and haloperi-

Table 1 The 5 year course of the clinical assessment, treatment response and cerebral metabolism of a schizophrenic patient

Months from onset of illness				6	10	40	44	56	62
Clinical status				1st Episode	Remission	Remission	2nd Episode	3rd Episode	Remission
SPECT§	Rt PF	Control†	98.2 (1.6)	95.8	95.6	99.1	97.9	90.2*	95.5
	Lt PF		98.9 (1.1)	94.0*	93.4*	98.8	98.2	91.8*	91.6*
	Rt AT		99.8 (3.2)	100.4	95.1	95.4	98.1	93.8	97.6
	Lt AT		98.3 (3.4)	84.0*	92.7	90.2*	86.6*	85.4*	84.1*
BPRS	Global score			31	18	18	28	51	22
	Positive symptoms score			14	3	3	11	16	3
	Negative symptoms score			3	3	3	3	11	3
HEN	Summary score			0	0	0	0	10	0
VF	Correct items			n.a.	n.a.	n.a.	17	16	27
	Inappropriate items			n.a.	n.a.	n.a.	0	22	0
WCST	Category completed			n.a.	n.a.	n.a.	6	1	6
	Total error			n.a.	n.a.	n.a.	11	57	3
	Perseverative error			n.a.	n.a.	n.a.	2	8	1
	Non-perseverative error			n.a.	n.a.	n.a.	8	22	2
	Unclassified error			n.a.	n.a.	n.a.	1	27	0
LM	Immediate recall			n.a.	n.a.	n.a.	14	1.5	18.5
	30 min delayed recall			n.a.	n.a.	n.a.	14.5	0	18
Soft neurological signs				n.a.	n.a.	n.a.	None	FT Op/Tap	None
Anti-psychotic drug (dosage, mg)				Halo (10)	Sulp (100)	Sulp (100)	Sulp (400)	Halo (43)	Cloz (300)

§ Relative perfusion index; † Mean relative perfusion index (standard deviation) of 8 female contral subjects from Catafau et al. (1994); * Below 2 standard deviations from control

Rt PF Right prefontal; *Lt PF* Left prefrontal; *Rt AT* Right anterior temporal; *Lt AT* Left anterior temporal; *SPECT* Single photon emission computerised tomography; *BPRS* Brief psychiatric rating scale; *HEN* High Royds evaluation of negative scale; *VF* Verbal fluency; *WCST* Wisconsin card sorting test; *LM* Logical memory; *FT Op/Tap* Finger thumb opposition and taping; *Halo* Haloperidol; *Sulp* Sulpiride; *Cloz* Clozapine; *n.a.* Not available

dol up to 55 mg per day for 8 weeks each). She responded well to clozapine at a dose of 300 mg per day. Her psychotic symptoms subsided completely and cognitive function normalised two months after treatment. She continued to work as a secretary.

Brain SPECT imaging was performed on six occasions during the course of her illness (Table 1). The first scan was performed one week after starting haloperidol (5 mg) when the patient still had active positive symptoms. Left anterior temporal lobe was found to have under-activity in the first scan, but returned to normal in the second scan during clinical remission. Left prefrontal under-activity was also noticed in the first and second scan. In the third scan, left anterior temporal lobe under-activity emerged again despite clinical remission. The fourth scan during the second psychotic episode showed left anterior temporal under-activity. In the fifth scan when the patient was treatment-resistant with the emergence of negative symptoms and neurocognitive impairment, significant under-activity of both prefrontal lobes and persistent left anterior temporal under-activity were noted. When the patient was clinically remitted after clozapine treatment at the sixth scan, the right frontal under-activity returned to normal but not the left side. Left anterior temporal under-activity persisted. Throughout the 5 years course, the right anterior temporal lobe activity remained normal.

Discussion

The longitudinal course of our patient's schizophrenic illness included remission, relapse and development of treatment-resistance. Left temporal under-activity was found irrespective of clinical relapse or remission while right temporal activity remained normal. The left temporal under-activity detected during clinical remission might reflect the presence of the underlying disease process which might be at risk for further relapses and treatment-resistant state. The perfusion asymmetry between the left and right temporal lobe in our patient is relevant to the large body of research about lateral dysfunction in schizophrenia which was initially observed from the association between schizophrenia-like symptoms in epilepsy and left-sided temporal lobe focus (Flor Henry 1969) and was subsequently confirmed by neuropsychological, neurophysiological and neuroimaging studies (reviewed by Gruzelier 1996). Although neuroimaging studies consistently localised abnormalities in temporal lobes, the findings for specific types of abnormalities are inconsistent. Positive psychotic symptoms were not only reported to be associated with over-activity at the left temporal lobe (Matsuda et al. 1989; Liddle et al. 1992; Suzuki et al. 1993) but also right temporal lobe (Notardonato et al. 1989). Our current findings are more consistent with a recent study by Russell et al. (1997). They used SPECT to find that schizophrenic patients had significant left temporal hypoperfusion as compared to controls.

An interesting finding was the significant reduction of bilateral prefrontal activity when negative symptoms, excecutive dysfunction and treatment resistant state emerged. It is consistent with previous findings on the association of SPECT hypofrontality with negative symptoms (Volkow et al. 1987; Wiesel et al. 1987; Andreasen et al. 1992; Schroder et al. 1995) and neurocognitive impairment (Paulman et al. 1990). Notedly, after subsequent response to clozapine, the right prefrontal metabolic activity was reversed to the previous state. Rodriguez et al. (1996), using SPECT found that a clozapine responder had significantly higher before-clozapine perfusion than the non-responder in thalamic, left basal ganglia, and right prefrontal regions with subsequent reduction of perfusion in the preceeding two areas without any change of the frontal region. In our patient, we could not quantify the metabolic change in the basal ganglia and the thalamus because of the technical problems, such as partial volume effect and attentuation correction. The difference in the change of frontal lobe perfusion may be due to the difference in the reference area for the perfusion index calculation. Rodriguex et al. used cerebellum while we took all ROIs as the reference standard. Moreover, the duration of illness of Rodriguex and coworker's patients (19 years for responders and 24 years for non-responders) was longer than that of our patient (5 years). This may be due to a progressive change of underlying neurobiological abnormalities over time. Clozapine is effective in treatment-resistant schizophrenia for the improvement of positive, negative and neurocognitive domains. However, the exact mechanism is not known. Our findings may lend support to the assumption that clozapine can improve the metabolic activity at frontal lobes probably more obvious in patients with shorter duration of illness when many of the abnormalities may still be reversible.

All six SPECT scans were performed when the patient was taking antipsychotic medication. Thus medication may be a potential confounding factor for the SPECT findings. The effect of antipsychotics on cerebral blood perfusion has been studied in the past. Goldman et al. (1996) found that normal subjects, but not schizophrenic patients, demonstrated a significant increase in global cerebral perfusion three hours after adminstration of haloperidol. Jibiki et al. (1992) showed from their SPECT study that two of the five schizophrenic patients had a conversion of relative frontal hypoperfusion to hyperperfusion after intramuscular haloperidol injection. Concerning the effect of sulpiride, Wik et al. (1989) found an increased metabolic rate in the right lentiform nucleus as the only brain region altered by sulpiride. These findings did not support a significant medication effect on temporal lobe metabolic activity. Moreover, haloperidol is unlikely to be a significant confounding factor on the bilateral frontal lobe under-activity detected at the 5th SPECT scan because from the study of Jibiki et al. (1992), haloperidol produced increased frontal perfusion.

We used a different gamma camera for SPECT imaging from the third scan onward because of the regular upgrading of medical equipment in our hospital. Moreover, Tc-99m EDC was used instead of Tc-99m HMPAO at the fifth scan due to unavailability of the latter. In the quantitation of regional cerebral perfusion, we compared the up-

take of radiotracer from one region with the average uptake from all regions in the same scan. Theoretically, the ratio would not be affected by the camera resolution and sensitivity as well as radiopharmaceutical. Thus, these changes would not substantially affect the intepretation of our findings. Similarly, it should be acceptable, though not ideal, to use the normal reference from Catafau et al. (1994) for comparison although they used a different scanner and scanning protocol and we adopted the same semiquantitative regional blood flow analysis.

Our study suffers from the limitations of a single case report. The effect of anti-psychotics on SPECT findings cannot be totally excluded in this naturalistic study, but as argued above their effects are unlikely to distort our interpretation of the major findings. It is also important to note that with functional neuroimaging one cannot distinguish between cause and effect in the changes in cerebral metabolism and symptoms. Some of the issues can be addressed in a large scale longitudinal study.

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