Cerebral Blood Flow Abnormalities in Children With Sydenham's Chorea: A SPECT Study

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Functional imaging studies in patients with Sydenham's chorea have suggested brain perfusional abnormalities. In this study, we aimed to investigate the cerebral perfusion patterns of the cortical/ subcortical structures by using Tc-99m hexamethylpropylenamine oxime single photon emission computed tomography in children with Sydenham's chorea, accompanied with magnetic resonance imaging and cranial Doppler studies. Brain MRI and Doppler studies of the all cases were normal. In the brain SPECT study, six patients were determined to have cerebral perfusion abnormalities. Although six patients responded well to the therapy, two girls who had hypoperfusion in the right frontal region as well as hypo- / hyperperfusion in the basal ganglia did not respond to therapy. While the chorea form of the patients who have cerebral perfusional abnormality was generalized, the clinical picture of the patients with normal cerebral perfusion was in the form of hemichorea.

Key words: *Brain SPECT, Sydenham's chorea, Tc-99m HMPAO.*

SYDENHAM'S chorea (SC) is one of the major diagnostic criteria of acute rheumatic fever (ARF), 80% of SC patients are children and adolescents in age group between 5-15 years and especially girls. Immunologic, genetic and personal characteristics are known to be responsible. These patients are supposed to have antibodies against subthalamic and caudate nucleus(1-3).

Vascular lesions in the basal ganglia and the substantia nigra and variations in the blood-brain barrier in the patients with SC are known(1,4). Furthermore, perfusion abnormalities in the basal ganglia of some patients with SC have been reported in the single photon emission computed tomography (SPECT) studies. These perfusion abnormalities sometimes may have prognostic value. Whereas hyperperfusion is a good prognostic symptom, hypoperfusion can be a bad one(3-7).

Brain scintigraphy using technetium-99m hexamethylpropyleneamine oxime (Tc-99m HMPAO) SPECT technique allows blood perfusion assessment of the brain. Tc-99m HMPAO is the first neutral-charged lipophilic Tc-99m chelate with rapid uptake and prolonged cortical retention. After intravenous injection, it can normally cross the intact blood-brain barrier and diffusely distribute throughout the cerebral cortex proportional to regional blood flow (rCBF). It has a great acceptance for routine neuro-SPECT imaging. Consequently, subsequent images indicate the defined neurophysiological state present at the time of injection(6,7). HMPAO brain SPECT has the ability to detect abnormal rCBF in patients

who may have normal appearing in the CT and MRI scans(5-7). The studies performed by SPECT for basal ganglia disorders indicate that SPECT is a useful method to evaluate basal ganglia functions including neuro-degenerative disorders(1,3-6).

With this background, we investigated brain perfusion abnormalities by using brain SPECT accompanied with brain MRI and cranial Doppler in patients with SC.

Subjects and Methods

Of the 14 patients who had acute rheumatic fever with chorea, eight patients (5 girls, 3 boys, aged between 7-15 years) whose SPECT study could be carried out were included in the study. Inclusion criteria were: presence of choreic movements with onset within the last six months, and age from 5 to 15 years. Informed consent was obtained from the parents and children before being enrolled. SC was diagnosed according to modified Jones criteria(1-3). Following tests and laboratory studies were carried out: whole blood count including white blood cell count (WBC), erythrocyte sedimentation rate (ESR), hepatic and renal function tests, anti- streptolysin O (ASO), C-reactive protein (CRP), serum and urine copper level, serum ceruloplasmine, urine/blood amino acid, *X*-ray chest, electro-cardiography and echocardiography. All laboratory and imaging (Doppler, MRI and SPECT) were completed within 24 hours of admission.

The cranial arterial Doppler was done using Toshiba Aplio. MRI studies were performed on a 0.3-T open Hitacy scanner. A 3-mm slice thickness was used. During cranial analysis, the following sequences were applied: Spin Echo T1, Proton Density and Fast Spin Echo T2. To evaluate the basal ganglia, 3D coronal spoiled gradient echo sequence was added. After obtaining sequences, the brain structures of the patients were evaluated visually.

In the scintigraphic study, half an hour before the radiopharmaceutical injection, an intravenous cannula was inserted to an appropriate peripheral vein of the patient. Then the patient relaxed under optimal conditions for the brain scintigraphy. An average 0.3 mCi/kg dose of Tc-99m HMPAO (Brain-SPECT, Medi-Radiopharma Ltd, Budapest, Hungary) was injected intra-venously to the patient in a quiet, dimmed room. Sedation of the patient, if necessary, was ensured with chloral hydrate (50-75 mg/kg/dose) and/or midazolam (0.05 mg/kg/dose) at least half an hour after the injection. Image acquisition started approximately at one hour postinjection. A single-head gamma camera (Toshiba GCA 602A) equipped with the general purpose, low-energy, parallel-hole collimator was used in the scintigraphic study. The patient was positioned supine on the imaging table under the gamma camera. Patient's head was fixed with a Velcro restraint and made motionless. Gamma camera acquisition parameters were used as following: totally 60 images each of which was 25 seconds duration, at 64 × 64 matrices, per 360 degree rotation. Then the data were reconstructed according to the predetermined protocol on the camera software. Images were applied × 2 magnification for a better visual evaluation. Two nuclear medicine specialists regarding hypo and hyperperfusion evaluated the obtained images at transaxial, coronal and sagittal tomographic slices visually.

SC patients were treated with medical therapy (penicillin prophylaxis and halo-peridol at a dose of 3 mg/day, b.i.d.). Two girl patients (cases no 2 and 6) who did not respond to both the haloperidol and the valproic acid therapy, underwent corticosteroid therapy(8).

Results

Summary of the clinical and laboratory features of SC patients are shown in *Table I*. Mean age of the patients was 10.8 ± 3.1 years (7-15 years). The majority of the patients (n = 5, 62.5%) consisted of the girls and streptococcal history existed only in half of the cases. The medium duration from onset to evaluation was 5.1 ± 2.8 (2-10) weeks.

While one of the patients (12.5%) had only chorea, the other seven (87.5%) patients had chorea accompanied with arthritis and/or carditis. The average values of the patients' acute-phase reactants were elevated moderately: CRP 15.3 ± 13.5 mg/L (0-5 mg/L), ASO 524 ± 348 Todd units (≤=166 Todd units), ESR 38.5 ± 14.6 mm/h (0-20 mm/h) and WBC 13.4 ± 5.6 × 10^3/μL (4.5-13.5 × 10^3/μL). ASO, CRP, WBC and ESR have been elevated in 7, 6, 5 and 6 patients, respectively. ESR was found in low level in two girls. Latent period of the disease was long and the SPECT findings were normal in these two children.

Brain MRI and cranial arterial Doppler study of all patients were normal.

Although six patients responded well to the therapy, two girl patients (no 2 and 6) did not respond to both the haloperidol and valproic acid therapy, and thereafter these patients underwent corticosteroid therapy(8). Corticosteroid protocol consisted of two phases. Phase 1 involves pulse-therapy with intravenous methyl-prednisolone, 25 mg/kg/day, for 5 consecutive days. For phase 2, after the completion of the pulse-therapy, the patients were discharged on oral prednisone (1 mg/kg/day) started on day 6. The oral form was gradually tapered down. Although the chorea findings of these patients decreased, they are still continuing.

In the brain SPECT study, six patients were detected to have abnormal rCBF (*Table I*): (*i*) Three patients had isolated left basal ganglia hypoperfusion, (*ii*) Three patients had hypoperfusion in the right (n = 2) and left (n = 1) frontal regions as well as hypoperfusion (n = 2) or hyperperfusion (n = 1) in the basal ganglia, (*iii*) Two patients had normal cerebral perfusion. There was no relationship between the severity of the hypoperfused areas and arthritis/carditis. Three patients had arthritis and chorea, and there was a strange co-existence between these major criteria. While the chorea form of the patients who had cerebral perfusional abnormality was generalized, the clinical picture of the patients with normal cerebral perfusion was in the form of hemichorea. The chorea findings of the patients who had perfusion abnormalities in the basal ganglia and the right frontal area were severe and these patients did not respond well to the therapy.

Discussion

SC is the most common acquired chorea of childhood and is the sole neurological manifestation of RF. SC occurs in 10-20% of patients with RF. Cardiac involvement in SC has been reported in 23-84%, whereas association with arthritis does not exceed 30% (3-5).

It has been known that in some infectious/inflammatory situations, the basal ganglia microcirculation and/or blood-brain barrier demonstrate changes (3,4,10). The primary pathologic finding is vasculitis of the cortical arterioles with round cell infiltration of the gray and white matter in the surrounding area, possibly the results of the cellular response to antineuronal antibodies. In the histological studies, it has been proved that in the patients with SC, vasculitis develops in the basal ganglia and this causes destruction in the blood-brain barrier. The perfusional changes

TABLE 1–*The Clinical and Laboratory Findings of the Patients.*

Case No	Sex	Age (years)	Anamnesis of Streptococcus infection	Duration from onset to evaluaion (weeks)	ASO/CRP/ WBC/ESR	Arthritis/ Carditis	Clinic	Chorea type	SPECT	Response to therapy
1	F	15	No	3	434 / 12 / 14 / 46	Arthritis	Trembling in hand, disarthry	Hemichorea (right)	Normal	Good
2	F	13	No	8	344 / 13 / 7 / 16	–	Severe generalized choreiform movements, hypoactive DTR, hypotonia, dismetry, disarthry, diadochinesis, walking apraxia	Generalized	Hyporperfusion in the right frontal region and hyperperfusion in the right basal ganglia	Not good
3	F	12	Yes	4	456 / 9 / 14 / 56	Arthritis	Hypoactive DTR, walking apraxia	Generalized	Hypoperfusion in the left basal ganglia	Good
4	M	11	Yes	2	267 / 22 / 19 / 54	Carditis	Clumsiness, choreiform movements in the hand and the arm	Hemichorea (right)	Normal	Good
5	M	7	Yes	3	126 / 16 / 22 / 42	Arthritis	Choreiform movements in the hands and arms	Generalized	Hypoperfusion in the left basal ganglia	Good
6	F	8	No	10	1120 / 3 / 9 / 20	Carditis	Choreiform movements in the arms and hands, emotional lability	Generalized (right> left)	Hyporperfusion in the right inferior frontal region and the right basal ganglia	Not good
7	F	7	No	5	994 / 3 / 16.3 / 34	Carditis	Disarthry, hypotonia	Generalized (left> right)	Hypoperfusion in the left basal ganglia	Good
8	M	14	Yes	6	455 / 45 / 6.5 / 40	Carditis & arthritis	Severe generalized choreiform movements, emotional lability	Generalized	Hypoperfusion in the left superior frontal gyrus and the right basal ganglia	Good

F: female M: male ASO: anti-streptolysin O (=166 Todd units) CRP: C-reactive protein (0-5 mg/L)
WBC: white blood cell count (4.5-13.5 x10^3/μL) ESR: erythrocyte sedimentation rate (0-20 mm/h) DTR: Deep tendon reflexes

Key Message

- Brain perfusion abnormalities can be found by brain SPECT imaging in children with generalized Sydenhams' chorea.

visualized in brain scintigraphy are the result of this destruction(1,4).

There are few reports about the brain SPECT in SC (1, 3,). Lee, *et al.* (10) reported a case, showing hyperperfusion of the basal ganglia and Dilenge, *et al.*(11) reported two cases, showing hyperperfusion. Alternately, Hill, *et al.*(5) reported a case showing no abnormality and Heye, *et al.*(4) reported a case showing hypoperfusion in striatum.

It has been known that there is a relationship between the basal ganglia perfusional changes in the brain SPECT studies and clinicopathological situation (3-7). There are studies proving that hypoperfusion in basal ganglia develops in degenerative cases, whereas hyperperfusion develops in the infectious/inflammatory situations (1,3-7).

There is streptococcal infection anamnesis in half of our patients. The duration time of the symptoms of SC is less than 1 month in 4 patients (50%). This period is less than the time interval reported in the literature(1-4). Because all of our patients were students, their teachers could notice abnormal movements earlier and/or the racial and geographical differences could be the reason of the short duration. Presentation of the brain SPECT as normal in two patients showing short latent period with active ARF can be interpreted being necessary a definite time for the visualization of the abnormal perfusion pattern in SPECT imaging.

We could not find any relation between the clinical picture and the isolated SC or SC accompanied with the major findings, and the rCBF findings. For example, clinical manifestations, response to therapy and SPECT findings of the patient 2 who had chorea alone and the patient 6 who had chorea with carditis were similar. We could not determine a significant difference about the SPECT findings between the girls and boys.

In our study, cranial Doppler study was found normal in the patients. We suppose that there was no gross cerebral blood-flow abnormality in the patients with SC. However, it will not be an honest attitude to interpret our MRI findings as exactly normal because of the low tesla (0.3 T) of existing MRI device. Such abnormalities were reported with more advanced MRI device(12). To design a study consisting more patients with more sensitive combined techniques (such as PET, diffusion-weighted imaging and proton MR spectroscopy, excitatory/inhibitory neurotransmitters and performance tests) may be more clarifying for all these possible relationships.

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REFERENCES

1. Barsottini OG, Ferraz HB, Seviliano MM, Barbieri A. Brain SPECT imaging in Sydenham's chorea. Braz J Med Biol Res 2002; 35: 431-436.
2. American Heart Association. Guidelines for the diagnosis of rheumatic fever: Jones criteria,

1992 update. JAMA. 1992; 268: 2069-2073.

3. Demiroren K, Tastekin G, Oran B. Diagnostic role of 99mTc hexamethyl-propyleneamine oxime brain single photon emission computed tomography in Sydenham's chorea. Pediatr Int 2004; 46: 450-455.

4. Heye N, Jergas M, Hotzinger H, Farahati J, Pohlau D, Przuntek H. Sydenham chorea: clinical, EEG, MRI and SPECT findings in the early stage of the disease. J Neurol 1993; 240: 121-123.

5. Hill A, Herkes GK, Roche P. SPECT and MRI findings in Sydenham's chorea. J Neurol Neurosurg Psychiatry 1994; 57: 763.

6. Netrakom P, Krasuski JS, Miller NS, O'Tuama LA. Structural and functional neuroimaging findings in substance-related disorders. Psychiatr Clin North Am 1999; 22: 313- 329.

7. Jacquier-Sarlin MR, Polla BS, Slosman DO. Oxido-reductive state: The major determinant for cellular retention of technetium-99m-HMPAO. J Nucl Med 1996; 37: 1413-1416.

8. Barash J, Margalith D, Matitiau A. Corticosteroid treatment in patients with Sydenham's chorea. Pediatr Neurol 2005; 32: 205-207.

9. Gerber AM. Group A Streptoccus. *In:* Behrman RE, Kliegman RM, Jenson HB (eds). Nelson Textbook of Pediatrics, 17th edn. Philadelphia: WB Saunders Company, 2004, pp 870-883.

10. Lee PH, Nam HS, Lee KY, Lee BI, Lee JD. Serial brain SPECT images in a case of Sydenham chorea. Arch Neurol 1999; 56: 237-240.

11. Dilenge ME, Shevell MI, Dinh L. Restricted unilateral Sydenham's chorea: Reversible contralateral striatal hypermetabolism demonstrated on single photon emission computed tomographic scanning. J Child Neurol 1999; 14: 509-513.

12. Davutoglu V, Kilinc M, Dinckal H, Soydinc S, Sezen Y. Sydenham's chorea-clinical characteristics of nine patients. Int J Cardiol 2004; 96: 483-484.

13. Weindl A, Kuwert T, Leenders KL, Poremba M, Grafin von Einsiedel H, Antonini A, *et al*. Increased striatal glucose consumption in Sydenham's chorea. Mov Disord 1993; 8: 437-444

14. Goldman S, Amrom D, Szliwowski HB, Detemmerman D, Goldman S, Bidaut LM, *et al*. Reversible striatal hypermetabolism in a case of Sydenham's chorea. Mov Disord 1993; 8: 355-358.

15. Ikuta N, Hirata M, Sasabe F, Negoro K, Morimatsu M. High-signal basal ganglia on T1-weighted images in a patient with Sydenham's chorea. Neuroradiology 1998; 40: 659-661.