OBSERVATION

Serial Brain SPECT Images in a Case of Sydenham Chorea

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Background: The pathophysiological nature of Sydenham chorea (SC) has been presumed to be an autoimmune-mediated inflammatory process. Positron emission tomography in SC has revealed a striatal hypermetabolism that might explain the transient neuronal dysfunction. However, any focal hyperperfusion in the striatum or its related structures has not been demonstrated in previous single photon emission computed tomographic (SPECT) imaging studies, which raised a concern about the pathogenesis of the striatal hypermetabolism.

Objective: To investigate the cerebral perfusion patterns of the subcortical structures by using serial technetium Tc 99m–ethyl cysteinate dimer SPECT in a case of SC, which may provide a clue for the pathophysiological mechanisms.

Design: A case report and serial SPECT studies.

Case Presentation: A girl aged 4 years 3 months showed severe generalized choreic movements with concomitant signs of acute pharyngitis. Results of a laboratory study taken 7 days after the onset of chorea showed elevated antistreptolysin O titer, C-reactive protein levels, and erythrocyte sedimentation rate. Other laboratory data, throat culture, echocardiography, brain magnetic resonance imaging, and electroencephalography did not reveal any abnormalities. Five days after treatment with haloperidol and penicillin, the chorea began to improve slowly, and completely resolved in 2 months.

Results: Three serial SPECT images and semiquantitative analysis of cerebral perfusion were obtained. Cerebral perfusion in the striatum and thalamus was markedly increased bilaterally during the stage of active chorea and then returned nearly to its baseline level during the convalescent phase. These cerebral perfusion patterns were concordant with semiquantitative analysis.

Conclusions: Hyperperfusion in both the striatum and thalamus in our patient may reflect the subcortical inflammatory processes in SC. The unequivocal SPECT findings in our patient are difficult to reconcile with the negative findings of previous SPECT studies but may suggest the heterogeneity of the perfusion patterns in SC.

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SYDENHAM CHOREA (SC) is a movement disorder of childhood usually associated with β-hemolytic streptococcal infection. The pathophysiology of SC is still unclear; however, the cross-reactivity of a streptococcal antibody with basal ganglionic neurons[1] and the demonstration of brain cross-reactive epitopes of streptococcal M protein[2] caused an autoimmune-mediated inflammatory process. Recent investigations using positron emission tomography (PET) or single photon emission computed tomography (SPECT) revealed variable imaging features in a few cases of SC. Positron emission tomographic studies[3,4] showed isolated striatal glucose hypermetabolism, which suggested that SC was a striatal disease. However, it is still unknown whether the striatal hypermetabolism reflects the striatal neuronal dysfunction related to the focal inflammatory process or the enhanced neuronal activities resulting from the enhanced glutamatergic corticostriatal inputs. In SPECT studies, Hill et al[5] did not find any perfusion abnormalities in a case of SC, but Heye et al[6] reported a hypoperfusion in the basal ganglia in another case. These SPECT features were somewhat difficult to reconcile with the PET results. We conducted a serial SPECT imaging study using technetium Tc 99m–ethyl cysteinate dimer (99mTc-ECD) in a patient with SC.

REPORT OF A CASE

A girl aged 4 years 3 months without any history of antenatal or perinatal illnesses

MATERIALS AND METHODS

After sedation with intravenous injection of lorazepam, 99mTc-ECD was given intravenously and SPECT images were obtained with a brain-dedicated annular crystal gamma camera equipped with low-energy, high-resolution, parallel-hole collimators (Digital Scintigraphics Inc, Waltham, Mass). We acquired 120 projections using a 128 × 128 matrix for 20 minutes. Scatter correction and backprojection with a Butterworth filter (cutoff frequency 1.1 cycle/min, order No. 10) were performed. Attenuation correction of transaxial images (slice thickness = 1.67 mm) was performed by Chang's[7] method, and coronal and sagittal slices were calculated with the original transaxial images.

The first SPECT was undertaken 3 months previously as a baseline workup for the rehabilitation therapy of cerebral palsy, when the patient was free of any involuntary movements. It revealed slightly decreased cerebral perfusion in the left striatum and thalamus (**Figure**, SPECT 1). The second SPECT was undertaken on the 11th day of chorea when active choreic movements were continuing. At that time, 99mTc-ECD was injected while she was on the ward at the rehabilitation facility 10 minutes after the complete disappearance of chorea, which resulted from the intravenous injection of lorazepam used to put her to sleep. The second SPECT image showed a marked hyperfixation of radioligand in both striatum and thalamus bilaterally compared with SPECT 1 (Figure, SPECT 2). Two months later, the third SPECT image was taken when the chorea had disappeared completely, which revealed the return of striatothalamic hyperperfusion to the baseline level (Figure, SPECT 3).

We also conducted a semiquantitative analysis. In consideration of normal cerebellar perfusion in baseline SPECT and of the structure least relevant to chorea, we chose a cerebellar activity as the reference for the calculation of the relative perfusion ratio. A region of interest was manually drawn over the cerebellum and mean pixel counts were obtained. The region of interest was drawn over the right striatum and thalamus of SPECT 2 with the same region of interest mirrored to the contralateral side and in the same area of SPECT 1 and SPECT 3. The lesion-cerebellar ratio of each SPECT image was calculated, and the changes in perfusion relative to the SPECT 1 scan were obtained (**Table**). Semiquantitative analysis revealed a definite perfusion increase in the bilateral striatum and thalamus by 18% to 21% in the SPECT 2 image with only minimal perfusion changes between the SPECT 1 and SPECT 3 images.

was referred to our neurology department for evaluation of continuous involuntary movements of 6 days' duration. There was no family history of such disorders. Her motor development had been delayed; she sat up at age 15 months, crawled at age 20 months, and stood at age 24 months. Seven months prior to our evaluation, a transient episode of abnormal involuntary movements developed in association with an acute pharyngitis and fever. The episode lasted for 2 days and then disappeared. The description of the movements in that episode was similar to those of this most recent event.

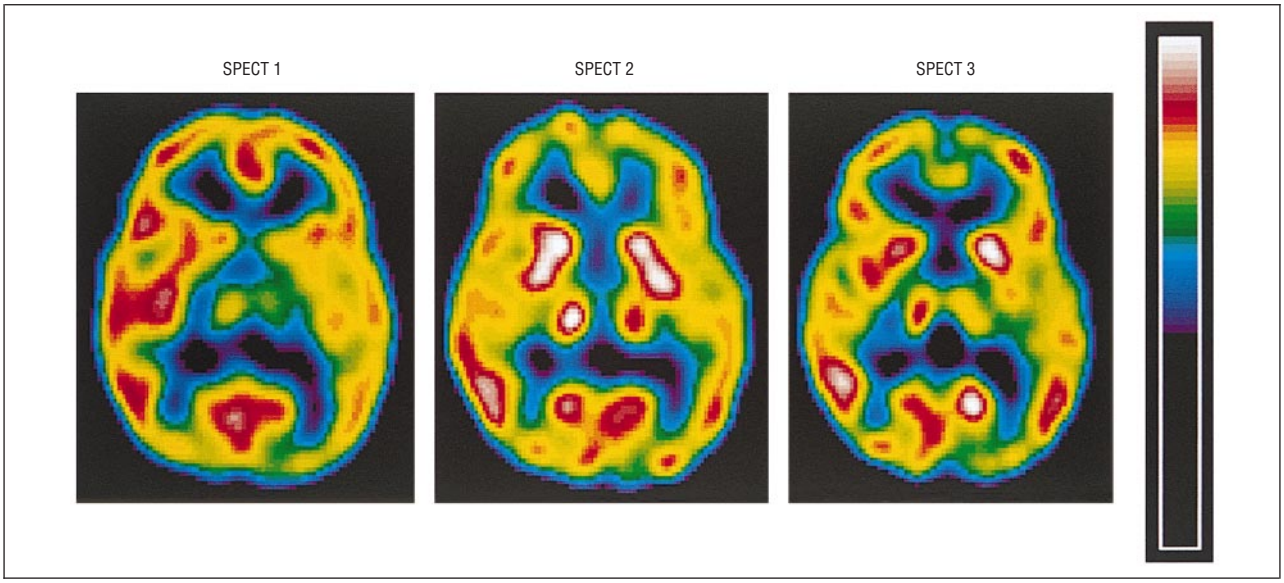
Three months prior to our seeing her, the patient had been admitted to the rehabilitation center for evaluation of delayed development. Examination revealed a moderate spastic diplegia with increased tendon reflexes, extensor plantar reflexes, and delayed developmental milestones. Motor and psychomotor development index values were both lower than 50 on the Bayley scales (motor normal, ≥102; psychomotor normal, ≥158). Results of brain magnetic resonance imaging and laboratory studies, including a chromosomal study and amino acid analysis, were normal. She was diagnosed as having cerebral palsy and enrolled in the rehabilitation program for treatment of the spastic diplegia. During the course of the rehabilitation program, she developed an acute pharyngitis with fever and swollen and infected tonsils. The involuntary movements developed shortly thereafter and gradually worsened. Her condition was treated with antibiotics and intermittent administration of sedative drugs for 6 days before her referral to us.

At the time of examination, her body temperature was 38.5°C and her tonsils were swollen and infected. A mild, diffuse hypotonia was noted with extensor plantar reflexes; deep tendon reflexes were mildly decreased. The involuntary movements consisted of irregular, unpredictable, flowing, and large-amplitude activities that involved all 4 extremities as well as the face. The clinical feature of involuntary movements was consistent with chorea intermixed with athetoid components. The chorea persisted only during waking periods and spontaneously disappeared during sleep.

Results of laboratory studies taken 7 days after the onset of chorea revealed that antistreptolysin O titer was 217 IU/mL (normal, < 200 IU/mL), C-reactive protein was 1.25 mg/dL (normal, < 0.8 mg/dL), and the erythrocyte sedimentation rate was 50 mm/h. The results of other routine blood chemistry, antiphospholipid antibody, lupus anticoagulant antibody, serum copper, and ceruloplasmin tests, as well as tests for thyroid function, rheumatic factor, antinuclear antibody, and mycoplasma antibody were all normal. Throat culture and peripheral blood smear were negative for organisms, and her echocardiogram showed no abnormalities. Results of brain magnetic resonance imaging and electroencephalography were normal. Diagnosis of SC was made, and treatment with haloperidol and penicillin was started on the ninth day. Five days after the start of treatment with medication, the chorea gradually began to diminish and completely disappeared in 2 months.

COMMENT

The serial SPECT images and semiquantitative analysis in our case clearly demonstrated a reversible focal hyperperfusion in the striatum and thalamus bilaterally during the active phase of SC, which suggested that increased cerebral blood flow (CBF) of the whole thalamostriatal circuitry was responsible for the genesis of chorea. However, our results were quite different from



The first single photon emission computed tomographic image, SPECT 1, taken when the patient was free of any involuntary movements, reveals mildly decreased cerebral perfusion in the left striatum and thalamus. The second image, SPECT 2, was taken 3 months later during active chorea, and shows marked hyperperfusion in both the left striatum and thalamus. The third image, SPECT 3, taken during the convalescent phase, shows the return to nearly baseline level of the hyperperfused area observed in the SPECT 2.

the previous reports of SPECT and PET in SC, which showed either no abnormalities or hypoperfusion in the striatum in SPECT[5,6] and an isolated striatal hypermetabolism with normal thalamic metabolism in PET.[3,4] These discrepancies between our results and others are quite difficult to explain. In fact, our patient had cerebral palsy, and the baseline SPECT study (Figure, SPECT 1) revealed left striatothalamic hypoperfusion, which might be responsible for the different cerebral perfusion pattern observed in the previous cases. Cerebral palsy is associated with diverse perfusion patterns in SPECT, and the SPECT features in our patient were not unusual in cerebral palsy in our experience.[8] However, cerebral palsy is a static process and may not have any interactions with the pathogenesis of SC. In addition, the SPECT 3 scan revealed a perfusion pattern similar to that seen in SPECT 1, which had confirmed that the chorea was reversible and independent of the underlying cerebral palsy.

We used 99mTc-ECD as radioligand for CBF, but others used technetium Tc 99m–hexylmethylpropylene amineoxine. All these radioligands have been recognized as reliable CBF agents, and the use of different radioligands is quite unlikely to be responsible for the different results. However, a comparative trial of different radioligands in SC may be required to resolve this issue.

The other possibility would be the movement-related hyperperfusion in the thalamostriatum. However, the voluntary movement-related hyperperfusion usually involves both striatum and motor cortex to the same degree.[9] In addition, we intentionally avoided such choreic movements by putting the patient to sleep using intravenous lorazepam before the injection of radioligand for the second SPECT study. We were not able to find any technical errors involved with the SPECT studies in this patient.

The striatal hyperperfusion in our patient agrees well with the isolated striatal hypermetabolism noted in previous PET studies in cases of SC.[3,4] Striatal hypermetabolism and hyperperfusion clearly suggest the presence of striatal neuronal dysfunction related to either the direct consequence of underlying pathogenesis of SC, a probable autoimmune-mediated inflammatory process, or secondarily enhanced striatal neuronal activities due to increased corticostriatal synaptic activities. However, the thalamic hyperperfusion in our patient was difficult to reconcile with the normal metabolism in PET. In fact, this was unexpected because thalamic metabolism was reduced in an experimental model of chorea probably due to the reduced pallidothalamic afferents.[10] Recently, experimental data[11,12] revealed that the organization of basal ganglia is more complex than that of simple direct and indirect loops. The paradoxical effect of pallidotomy in dyskinesia[13] and increased thalamic metabolism in choreic Huntington disease,[14] which was the opposite of what would be expected from the traditional model, also clinically supported this complexity. As pointed out by Weeks

Mean Pixel Count Ratio Seen in the SPECT Images—ROI: Whole Cerebellum—and Perfusion Differences From SPECT 1 ROI Revealed in Subsequent Images*

	ROI:Cerebellum†			Change in Relative Perfusion, %	
ROI	SPECT 1	SPECT 2	SPECT 3	SPECT 2/ SPECT 1	SPECT 3/ SPECT 1
Right basal ganglia	1.01	1.20	1.05	19	4
Left basal ganglia	1.00	1.20	1.06	20	6
Right thalamus	0.99	1.17	0.97	18	–2
Left thalamus	0.91	1.10	0.95	21	4

**SPECT indicates single photon emission computed tomography; ROI, region of interest.*

†*These data are expressed as a ratio of mean counts per pixel in ROI relative to whole cerebellum.*

et al,[14] it is possible that generalized chorea with bilateral thalamic hyperperfusion in our patient may be related to the increased pallidothalamic activities instead of decreased activities.

A few pathologic studies of SC [15,16] have reported the presence of inflammatory lesions involving the striatum, thalamus, and cortex. It seems possible that the active inflammatory brain lesions are associated with focal hyperperfusion. Juhler and Paulson[17] demonstrated that the areas of focal inflammation in the model of experimental allergic encephalomyelitis were associated with a focal increase of CBF. Also, there was ample SPECT evidence of regional hyperperfusion in various inflammatory diseases such as herpes encephalitis[18] and toxoplasmosis.[19] Thus, it is possible that the striatal and thalamic hyperperfusion in our SPECT 2 scan might represent the abnormally increased CBF that is related to the active inflammatory process in these structures, and chorea might be secondary to the striatothalamic neuronal dysfunction.

Another possibility for the discrepancies may be the heterogeneity in the pathomechanisms of chorea. Previous pathological investigations of patients with chorea did not identify any specific structural lesions common to the development of chorea,[20] which suggested that the lesion responsible for the genesis of chorea might be located anywhere in the basal ganglia circuitry. Although the pathophysiological characteristics of the underlying disease are different, hyperperfusion in both the striatum and thalamus contralateral to the side of hemichorea was also reported in a patient with hyperglycemia.[21] Therefore, it is likely that the functional imaging findings may be variable in different patients with chorea even in the cases of SC. Unfortunately, the number of cases of SC investigated by either SPECT or PET is still too limited to draw any firm conclusions. However, the unequivocal SPECT findings of striatothalamic hyperperfusion in our patient, contradictory to the previously normal SPECT results, clearly suggest that the variable perfusion patterns are seen in SC.

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