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Clinical Value of Perfusion Abnormalities of Brain on Technetium-99m HMPAO Single-Photon Emission Computed Tomography in Children With Sydenham Chorea

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Abstract

We evaluated whether perfusion brain abnormalities by single-photon emission computed tomography (SPECT) imaging improves diagnostic and prognostic assessment in Sydenham chorea. Twenty-three children with acute autoimmune chorea underwent technetium-99m hexamethylpropyleneamine oxime brain SPECT imaging. In 16 children, SPECT was repeated during the follow-up. A pattern of basal ganglia hyperperfusion was observed in 20 (87%) patients. In 4 of 10 patients with generalized chorea, perfusion was comparable in right and left striatum and right and left thalamus. In 13 patients with hemi-chorea and in 3 with generalized chorea, unilateral hyperperfusion was detected. Three patients with generalized chorea had normal perfusion. Tracer uptake of basal ganglia of the patients at the acute phase was higher than at the follow-up ($P < .001$). SPECT seems a useful noninvasive tool in pediatric patients with Sydenham chorea to support the clinicians during the acute phase of disease and to monitor the course of autoimmune chorea.

Keywords

autoimmune chorea, functional imaging, perfusion imaging, brain SPECT, pediatric patients

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Sydenham chorea is a movement disorder, characterized by rapid, uncoordinated jerking movements primarily affecting the face, hands, and feet.[1] It results from childhood infection with β-hemolytic streptococcus and is one of the major diagnostic criteria of acute rheumatic fever. Molecular mimicry between streptococcal and basal ganglia antigens underlies an autoimmune response determined by antibodies against striatal antigens, however the exact pathophysiological mechanisms remain obscure.[2] The disease is usually latent, occurring up to 6 months after the acute infection and is more common in females. Sydenham chorea is characterized by the abrupt onset of neurologic symptoms, including chorea, dysarthria, and gait disturbance, loss of fine and gross motor control, headache, and hypotonia. Patients affected by this disease also present many psychological and psychiatric manifestations such as depression, anxiety, personality changes, emotional lability, obsessive-compulsive disorder, and attention deficit disorders. Nonneurologic manifestations of acute rheumatic fever are carditis, arthritis, erythema marginatum, and subcutaneous nodules.[3,4] A long time may elapse between the streptococcal infection and the onset of chorea and, therefore, laboratory tests might not confirm the streptococcal infection.[5] Morphologic imaging studies performed during the acute phase of Sydenham chorea demonstrated that computed tomography findings are normal, whereas magnetic resonance imaging (MRI) can sometimes reveal abnormalities in the basal ganglia.[1,6-9] Functional imaging by nuclear medicine procedures is a useful approach to evaluate basal ganglia perfusion and metabolism. Single-photon emission computed tomography (SPECT) studies in children with Sydenham chorea documented brain perfusion

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Table 1. Clinical Characteristics and SPECT Findings at Baseline of the Patient Population.

Patient	Sex	Age (y)	Localization of chorea	Arthritis	Carditis	Valvulophaty	SPECT
1	Male	13	L = R	+	−	−	Hyperperfusion (L = R)
2	Male	7	L = R	+	−	−	Normal perfusion
3	Female	8	L > R	+	+	+	Hyperperfusion (R > L)
4	Male	7	L = R	+	−	−	Hyperperfusion (L = R)
5	Female	10	L = R	+	+	+	Hyperperfusion (L = R)
6	Female	8	L = R	−	+	+	Normal perfusion
7	Male	10	R > L	+	−	−	Hyperperfusion (L > R)
8	Female	10	L > R	+	−	−	Hyperperfusion (R > L)
9	Male	11	R > L	−	+	+	Hyperperfusion (L > R)
10	Female	9	L = R	+	−	−	Hyperperfusion (L = R)
11	Female	12	R > L	+	−	−	Hyperperfusion (L > R)
12	Female	8	L > R	+	−	−	Hyperperfusion (R > L)
13	Female	12	R > L	+	+	+	Hyperperfusion (L > R)
14	Female	8	L = R	+	+	+	Hyperperfusion (R > L)
15	Female	9	R > L	+	+	+	Hyperperfusion (L > R)
16	Female	11	L > R	+	−	−	Hyperperfusion (R > L)
17	Male	15	L = R	+	−	−	Hyperperfusion (L > R)
18	Female	7	L = R	+	−	−	Normal perfusion
19	Male	8	R > L	+	−	−	Hyperperfusion (L > R)
20	Male	12	R > L	+	+	+	Hyperperfusion (L > R)
21	Female	10	L > R	−	+	+	Hyperperfusion (R > L)
22	Male	13	L = R	+	+	+	Hyperperfusion (R > L)
23	Male	8	L > R	+	+	+	Hyperperfusion (R > L)

Abbreviations: L, left; R, right; SPECT, single-photon emission computed tomography.

abnormalities mainly as hyperperfusion in infectious chorea or, more rarely, as hypoperfusion in degenerative chorea.[4,10-12] Although SPECT imaging is able to describe regional cerebral perfusion patterns in patients with Sydenham chorea, its clinical value in the diagnostic and prognostic evaluation of this condition is still unclear. The objective of this study was to evaluate whether perfusion brain abnormalities detected by SPECT imaging improves diagnostic and prognostic assessment in children with Sydenham chorea.

Methods

Participants

Twenty-three patients, who received a clinical diagnosis of acute chorea from 2004 to 2015, were retrospectively selected from medical records of the Department of Pediatrics of the University of Naples Federico II. The inclusion criteria were the presence of choreic movements with acute autoimmune etiology and age from 5 to 15 years. Thirteen patients were female and 10 male, mean age was 9.8 $\pm$ 2.1 years (age range, 7-15 years). All patients first had a full physical examination including a rheumatologic and neuropsychiatric assessment. According to its localization, chorea was defined as generalized or hemichorea. Routine laboratory tests included complete blood count, C-reactive protein, erythrocyte sedimentation rate, liver and kidney functions, dosages of antibodies of streptolysin-*O*, and autoantibodies. Cardiac and electroencephalographic evaluations were also performed. A group of 9 subjects of comparable age and sex, who underwent a brain perfusion SPECT study for another cause (ie, epilepsy, headache) and evaluated as normal, constituted the control group. All legal guardians gave informed consent, and children assented prior to participation in accordance with the guidelines of the Helsinki Declaration.

Imaging Studies

All patients underwent brain MRI and SPECT imaging 3 weeks within diagnosis (baseline studies). In 16 patients, a second SPECT scan was performed 8 to 12 months later during the recovery phase of the disease (follow-up studies). MRI was performed using a 1.5-Tesla scanner. Spin-echo T1-weighted images, T2-weighted images, and fluid-attenuated inversion recovery images were used for the analysis. T1-weighted sequences were also obtained after the administration of intravenous paramagnetic contrast (gadolinium). A neuroradiologist visually evaluated brain MRI.

SPECT imaging was performed according to the procedural guidelines of the European Association of Nuclear Medicine.[13] An intravenous line was established and each patient received 51.8 MBq/kg of technetium-99m hexamethylpropyleneamine oxime (HMPAO) while lying in the supine position with the eyes closed in a dimly lit, quiet room. Thirty minutes after tracer injection, brain SPECT was performed using a dual-head gamma camera equipped with a general-purpose, low-energy, parallel-hole collimator (E-cam; Siemens Medical Systems). Images were acquired with a 128 $\times$ 128 matrix for 360-degree evaluation with circular orbit. A total of 60 frames were taken at 6-degree intervals of 30 seconds for each and a total acquisition time of 30 minutes. Scatter correction and back-projection with a Butterworth filter (cutoff frequency 0.50 cycle/min, order 10) were performed. Attenuation correction of transaxial images was performed by Chang's method,[14] and coronal and sagittal slices were calculated with the original transaxial images.

Two experienced nuclear medicine physicians, blinded to clinical diagnosis and MRI findings, evaluated SPECT images by visual and

semiquantitative analyses. Using the cortical activity as reference, they visually established whether the subcortical structures were normoperfused, hyperperfused, or hypoperfused, and the conclusion was reached by consensus. Semiquantitative analysis was made comparing tracer uptake in the basal ganglia with that of a region unaffected by the disease. Cerebellar activity was used as reference for the calculation of the relative perfusion ratio. A set of 6 predefined regions of interest (ROIs) was placed using a 2-mm brush tool of a commercial biomedical image processing software (Osirix 5.6 Pixmeo, Geneva, Switzerland) on basal ganglia and cerebellum bilaterally at the transaxial planes. The mean count density per pixel of each right and left basal ganglia and thalamus region of interest was proportioned to the mean count density per pixel of the two cerebellar regions of interest and the basal ganglia–cerebellar ratio was calculated.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation and categorical data as percentage. Continuous data were compared by paired or unpaired *t* test and categorical data by chi-square test, as appropriate. A P value $<.05$ was considered statistically significant. Statistical analysis was performed with SPSS version 19.0 (SPSS, Inc, Chicago, IL).

Results

Patients Characteristics

Demographic data and clinical characteristics of the 23 patients are summarized in Table 1. Twenty patients with a previous streptococcal infection had a diagnosis of acute rheumatic fever based on Jones modified criteria whereas 3 children had a diagnosis of Sydenham chorea based on exclusion criteria. Eleven patients had echocardiographic alterations of valvulopathy and associated rheumatic carditis and 3 of them had a family history of acute rheumatic fever. At presentation, chorea was generalized in 10 patients (43%) and localized in 13 (57%), with subsequent generalization in 2 of them. In addition to chorea, 6 subjects showed decreased verbal fluency and personality changes and 1 of them a left hemiparesis. Tests of liver and kidney functions, antinuclear antibody, and anti-DNA were normal in all patients. All patients were treated with haloperidol or pimozide during the symptomatic phase of the disease but were out of therapy during the follow-up. In the 16 patients who underwent a second neurologic physical examination between 6 and 12 months by the acute phase, there were no choreic movements and, according to the pediatric neurologist, 3 of the 6 subjects who had behavioral symptoms during the acute phase of disease were definitely improved, whereas in 3 patients there was a persistence of neuropsychiatric disorders.

Imaging Findings

MRI performed during the acute phase of the disease was normal in 21 patients, whereas in 2 there were small foci of white matter gliosis, without important clinical value. Baseline SPECT findings are reported in Table 1. A pattern of basal ganglia hyperperfusion was observed in 20 (87%) patients. In

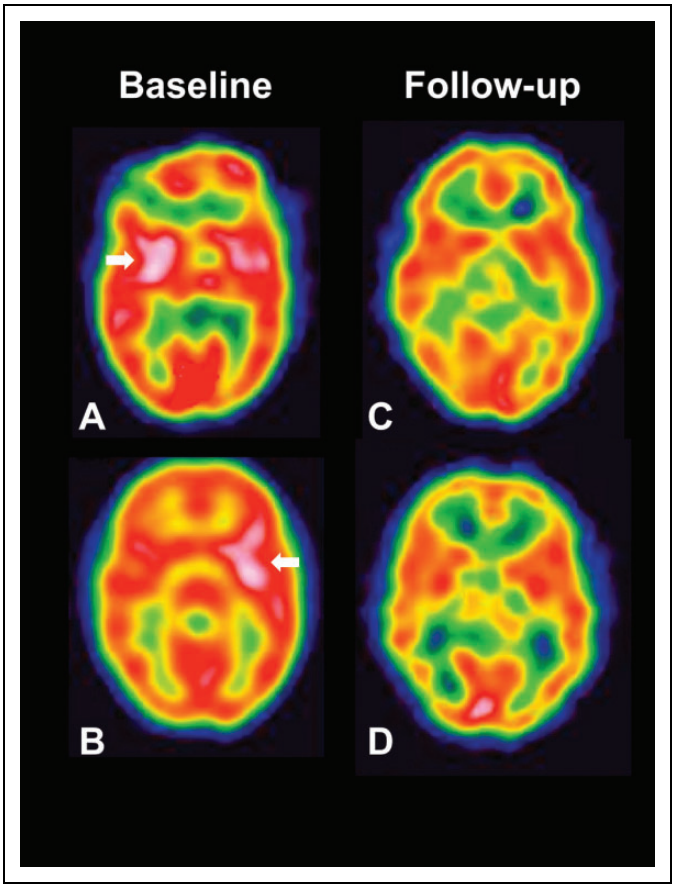

Figure 1. Examples of brain SPECT imaging in 2 patients (patient 1: A and C and patient 2: B and D) demonstrating hyperperfusion (arrows) in the right (A) and left (B) striatum during the acute phase of Sydenham chorea with normalization of the perfusion pattern during follow-up (C and D). SPECT, single-photon emission computed tomography.

4 of the 10 patients with generalized chorea, tracer uptake was comparable in right and left striatum and right and left thalamus. In 13 patients with hemi-chorea and in 3 with generalized chorea, a pattern of unilateral hyperperfusion was detected. Three patients with clinical manifestations of generalized chorea had normal perfusion. Examples of abnormal perfusion patterns at SPECT imaging during the acute phase of the disease are depicted in Figure 1. At semiquantitative analysis, patients' basal ganglia–cerebellar ratio was increased to 16% for the striatum and 13% for the thalamus (both $P<.05$) compared with control subjects.

In the 16 patients undergoing a second SPECT scan during follow-up (from patient 8 to patient 23 in Table 1), visual and semi-quantitative analyses of SPECT images demonstrated the reversibility of the perfusion abnormalities observed during the acute phase of the disease. Examples of normalization of perfusion pattern during follow-up are illustrated in Figure 1. Basal ganglia–cerebellar uptake ratios (% activity) in patients undergoing SPECT during the acute phase of the disease and at follow-up and in control subjects are reported in Table 2. At follow-up, the basal ganglia–cerebellar ratio was significantly

Table 2. Basal Ganglia–Cerebellar Uptake Ratio (% Activity) in Patients with Sydenham Chorea Undergoing SPECT Imaging During the Acute Phase of the Disease and at Follow-up and in Control Subjects.

	Patients (n = 16)		
	Acute phase	Follow-up	Control subjects (n = 9)
Right striatum	1.01 ± 0.13	0.74 ± 0.08[a]	0.85 ± 0.09[b]
Left striatum	1.01 ± 0.16	0.73 ± 0.08[a]	0.88 ± 0.09[b]
Right thalamus	0.96 ± 0.14	0.74 ± 0.08[a]	0.86 ± 0.09
Left thalamus	0.98 ± 0.14	0.76 ± 0.08[a]	0.85 ± 0.09[b]

Abbreviation: SPECT, single-photon emission computed tomography.
[a]$P < .001$ vs acute phase.
[b]$P < .05$ vs follow-up.

reduced compared with the acute phase ($P < .001$), with an average decrease of 27% in the striatum and of 22% in the thalamus (Figure 2).

Discussion

The results of the present study suggest that SPECT might be a useful noninvasive tool in pediatric patients with Sydenham chorea to support the clinicians during the acute phase of disease and to monitor the course of acute autoimmune chorea.

During the acute phase of the disease, most patients (87%) had striatum and/or thalamus hyperperfusion pattern. In 4 patients, tracer uptake was higher than cerebellar activity but without differences between the right and left hemispheres, whereas in 13, unilateral hyperperfusion was observed, which corresponded to the side of hemichorea. Kienzle et al.[2] hypothesized that molecular mimicry between streptococcal and basal ganglia antigens underlies an autoimmune response determined by antibodies against striatal antigens, resulting in blood-brain barrier disruption and edema. This might probably explain the increased metabolism in basal ganglia, seen as hyperperfusion in SPECT imaging. Therefore, hyperperfusion in the basal ganglia, seen in 20 of 23 patients in our study, seems to be a sign of the acute phase of disease. Three patients with generalized chorea showed unilateral hyperperfusion at visual analysis. However, 2 of these had bilateral hyperperfusion at semiquantitative analysis. These findings further support the use of this latter approach to overcome some of the limitations of the visual SPECT imaging analysis. Moreover, physical examination could be unable to detect the hemichorea side or that involuntary patient motion during image acquisition had barely modified SPECT images. Other 3 patients had normal cerebral perfusion with clinical manifestations of generalized chorea. Although previous studies reported the possible absence of vasculitis despite the presence of chorea,[12] the possibility of a molecular process without SPECT changes cannot be excluded.

All children who underwent a second SPECT study during the follow-up showed a normalization of basal ganglia perfusion pattern, which matched with the resolution of neurologic symptoms in the large majority of the patients. Previous studies described persistent chorea in about 50% of patients[15] and residue neuropsychiatric features even in treated patients.[16] These findings suggest that the follow-up of our study might miss residual minor chorea or attention and emotional issues that are not rare and might be missed in the absence of a standardized assessment. In a randomized study, Walker et al[16] compared the outcomes of 10 children treated with standard management alone to 10 who received additional intravenous immunoglobulin. The outcomes were assessed using a clinical rating scale, brain SPECT, and the duration of symptomatic treatment. Noteworthy, all three tools found improved outcomes in the group that received intravenous immunoglobulin. These results confirm that a normalization of SPECT images often match with resolution of symptoms.[17] On the contrary, Beato et al[18] in 12 adult women with Sydenham chorea in remission observed a modest albeit statistically significant ($P = .02$) pattern of hyperperfusion in the left putamen compared with age- and sex-matched control subjects. These latter findings suggest that perfusion abnormalities of the basal ganglia may persist even after the remission of abnormal movements in patients with Sydenham chorea and confirm that the follow-up of our study might miss residual minor chorea.

Using semiquantitative analysis, we also found that during the acute phase of Sydenham chorea patients had a higher striatum and thalamus tracer uptake compared to the same subcortical structures during the recovery phase, including 3 patients with apparently normal perfusion pattern. Two patients with clinical manifestations of generalized chorea and unilateral basal ganglia hyperperfusion at visual analysis had a bilateral hyperperfusion pattern at semiquantitative analysis. These results are in agreement with those of prior studies demonstrating that hyperperfusion of the basal ganglia observed during the acute phase of Sydenham chorea may disappear at follow-up.[10,11] Therefore, estimating perfusion ratios between subcortical structures and cerebellum may improve the accuracy of the analysis.

We also found that during the acute phase of Sydenham chorea, but not at follow-up, basal ganglia tracer uptake in patients was higher than that of control subjects. At the best of our knowledge, this finding during the recovery phase of disease has not been previously reported. During the acute phase, SPECT images appear quite heterogeneous with both hyperperfusion and hypoperfusion of the basal ganglia.[10,12,13,17]

Perfusion abnormalities can be related to the time of the imaging study because autoimmune process can evolve from inflammatory to a neuronal dysfunction state. The initial basal ganglia hyperperfusion seems to be a sign of the acute phase of Sydenham chorea. This pattern can be explained by blood-brain barrier abnormalities induced by the inflammatory process[12,19] and chorea originated from increased dopaminergic activity in the projections from the substantia nigra to the striatum, resulting in decreased γ-aminobutyric acid (GABA)-ergic projection from the striatum to the globus pallidus[20] or increased glutamatergic corticostriatal input.[11,21] On the other

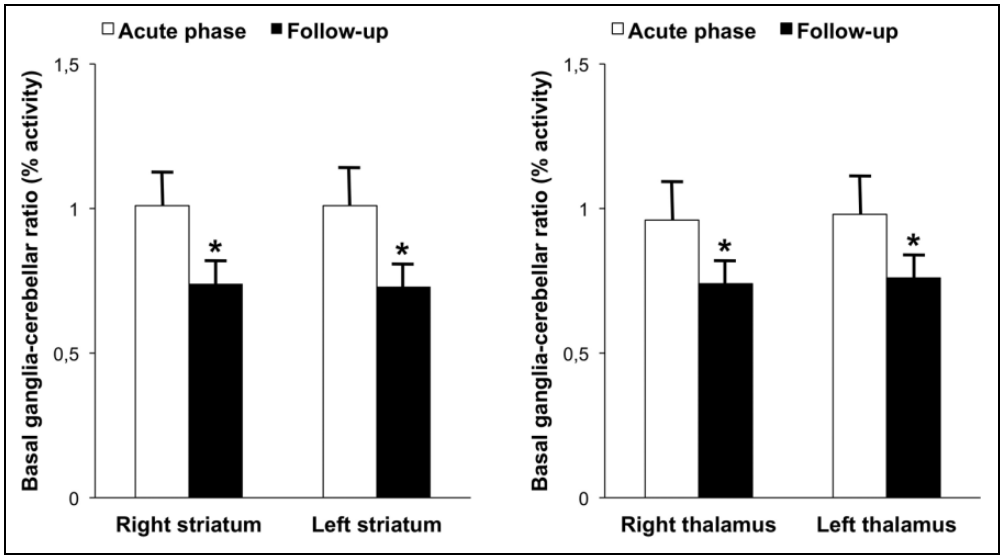

Figure 2. Basal ganglia–cerebellar uptake ratio (% activity) in the 16 patients with Sydenham chorea undergoing SPECT imaging during the acute phase of the disease and at follow-up. SPECT, single-photon emission computed tomography.

hand, hypoperfusion of striatum and thalamus, less frequently observed, may be explained by a different stage of the disease, considering that neurodegenerative disorders of basal ganglia causing chorea are characterized by striatal hypoperfusion and hypometabolism.[22] Therefore, SPECT perfusion pattern during the follow-up might also represent a sign of more permanent dysfunction of basal ganglia, which can follow the hyperperfusion observed during the acute phase.[18]

In the present study, all patients who underwent follow-up were out of therapy at the time of the second SPECT scan, and neuroleptic therapy, which could have decreased the hyperactivity of the dopaminergic system, was discontinued. It can be hypothesized that these patients had a transient hyperperfusion of the striatum and thalamus during the acute phase and the repeated scan showed a mild basal ganglia hypoperfusion pattern, which was not related to a permanent neuronal damage. It cannot be excluded that if these patients had undergone a third SPECT study after a longer follow-up, they would have a normal basal ganglia perfusion patterns with no difference with the control group. The small and heterogeneous control group represents another limitation of our study. Therefore, studies with a greater number of patients are needed to establish more firmly the relationship between the time to remission of Sydenham chorea and normalization of basal ganglia perfusion.

Conclusion

The results of this study suggest that better definition of cerebral perfusion patterns of the subcortical structures by SPECT imaging can support clinicians during the acute phase of Sydenham chorea and could be used to monitor the course of the disease. The resolution of the hyperperfusion at the recovery phase provides further support for the diagnosis of the disease and can support the clinicians to treat patients with antibiotic prophylaxis, to prevent a recurrence of acute rheumatic fever.

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Author Contributions

SMAG and FG performed the literature search. MGC, GR, AR, and EV were responsible for acquisition of the data. SMAG, MGC, FG, GR, AR, and EV worked on analysis and interpretation of data. MGC, MA, and AC worked on the conception and design. SMAG drafted the article. MGC prepared the manuscript. AC, EV, and MA revised and approved the final version for publication.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

All legal guardians gave informed consent and children assented prior to participation in accordance with the guidelines of the Helsinki Declaration.

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