Brain Perfusion SPECT in Juvenile Neuro-Behçet's Disease

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Regional cerebral blood flow was evaluated by ^{99m}Tc-hexamethylpropyleneamine oxime SPECT in 7 patients (age range, 7–18 y; mean age, 9.1 y) affected with Behçet's disease and signs or symptoms of central nervous system involvement at different times of their clinical history. **Methods:** Three patients suffered from seizures, 3 patients were affected with severe persistent headache that was refractory to common analgesic and nonsteroidal antiinflammatory drugs, and 1 patient had recurrent episodes of acute intracranial hypertension. Electroencephalography was performed on all patients, MRI on 5 patients, and CT on 1 patient. Brain SPECT was performed using a high-resolution, brain-dedicated camera. After conventional visual analysis by 2 expert readers, 2 transaxial sections were drawn parallel to the bicommissural line: the first across the thalami and the second across the temporal lobe at the level of the mesiotemporal structures. Cortical regions of interest were drawn automatically on the cortical ribbon on the 2 sections, whereas other regions of interest were drawn by hand around the basal ganglia, the thalami, and the mesiotemporal structures. Asymmetry analysis was then applied, and hypoperfusion was considered when the asymmetry value was >10%. **Results:** Hypoperfusion was observed in all patients by visual and asymmetry analyses; this finding was localized mainly in the basal ganglia, the thalami, and the temporal cortex, including its mesial portion. Temporal hypoperfusion was found primarily in patients with seizures, and hypoperfusion of deep gray nuclei was found mainly in the other patients. Electroencephalography disclosed brain functional impairment in 5 of 6 patients, whereas MRI showed multiple bilateral white matter lesions in 1 patient suffering from persistent headache. **Conclusion:** As in adults, perfusion SPECT seems to be very sensitive in disclosing brain abnormalities in children and adolescents with Behçet's disease and signs or symptoms of central nervous system involvement, even with negative findings on brain MRI.

Key Words: juvenile Behçet's disease; brain SPECT; neuro-Behçet's disease; pediatrics; regional cerebral blood flow

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Behçet's disease (BD) is a systemic vasculitis characterized by recurrent oral and genital ulcerations and relapsing uveitis. Together with these typical features, virtually any organ or system, including the central nervous system (CNS), may be affected to some extent.

The diagnosis of BD is made on the basis of clinical criteria established in 1990 by the International Study Group (ISG) for BD (*1*); criteria for the diagnosis of juvenile BD (JBD) still remain to be validated. Moreover, no widely accepted criteria are available to define adult and juvenile neuro-BD (n-BD). JBD actually has an insidious relapsing–remitting course and often is oligosymptomatic at the early stage, so that incomplete forms are commonly found in children (*2*,*3*).

CNS involvement may be caused by either primary parenchymal lesions or vascular damage, and signs or symptoms attributable to CNS involvement have been reported in 10%–50% of the adult BD population and in as high as 35% of the pediatric BD population (*4*). It is likely that most of this variability depends on different criteria used to define the CNS disease (*2*,*5*). In fact, the range of clinical manifestations related to CNS impairment is extremely wide and is not always easily recognized. Whereas clinical presentations such as motor hemisyndromes, meningeal syndrome, seizures, and cranial nerve palsies usually do not represent a diagnostic problem, other more subtle or even equivocal syndromes related to CNS involvement, such as mild cognitive deterioration and headache, may lead to misinterpretation and contribute to underestimation of the actual prevalence (*2*).

The diagnostic challenge of n-BD is, therefore, particularly relevant, and neuroimaging procedures have been used successfully in suspected n-BD patients in recent years. In adults, MRI has been reported to show lesions mainly in the brain stem, the basal ganglia, and the white matter in a portion of patients with clinically diagnosed n-BD (*6*,*7*); in other cases, MRI was found to be normal (*8–11*). Recently, magnetic resonance angiography has been used to detect venous and arterial involvement in BD patients (*12*). Regional cerebral blood flow studies by SPECT have repeatedly shown perfusional deficits in patients with symptomatic

n-BD with or without pathologic MRI findings (*8–11, 13,14*) and even in patients without clinically evident n-BD (*13*), a finding leading to the suspicion of subclinical brain involvement. MRI studies have been sporadic as far as pediatric n-BD is concerned (*2*), showing similar findings as in adults, and no SPECT data are available as yet.

In this study, we report on a group of 7 patients affected with JBD or incomplete JBD and suffering from neurologic complaints, who underwent brain perfusional SPECT examination using a brain-dedicated camera at different times during their clinical history. Electroencephalography (EEG) and MRI were also performed in most cases.

MATERIALS AND METHODS

Seven Italian boys who showed clinical features that suggested the diagnosis of BD were studied. The local ethics committee approved the study, and each patient's relatives gave informed consent. The main clinical characteristics are summarized in Table 1.

Five patients matched the criteria of the ISG for BD (*1*) before the age of 16 y. Although the remaining 2 boys (patients 4 and 6) did not meet the ISG criteria, they complained of recurrent oral aphthosis plus 1 of the other criteria proposed by the ISG. On the basis of these data, they were defined as having incomplete BD according to the suggestion of other authors (*2*). It is noteworthy that patient 4 was the brother of patient 3, and their mother also was affected with BD (*15*).

The heralding clinical manifestations developed when the patients were between 6 and 12 y old (median, 8.3 y old). The time interval between the onset of symptoms and the definite clinical diagnosis in the 5 patients with BD ranged from 1 to 5 y (median, 3 y). In the 2 patients with incomplete BD, the first symptom ensued 2 y before being referred to our institute.

Patients 3–5 have 1 parent affected with BD. Moreover, patient 1 has a positive family history (cousin) of oral aphthosis.

All 7 boys displayed recurrent buccal aphthosis with oral ulcers. Patients 2 and 7 had recurrent genital aphthosis, which occurred after buccal aphthosis. Patient 7 also had perianal aphthosis. Various skin lesions were present in all patients: papulopustular lesions (patients 3–7), erythema nodosum (patients 1 and 2), and necrotic folliculitis (patient 2). A pathergy test was positive in 2 boys (patients 1 and 5). Arthralgias or enthesitis (or both) was present in 5 boys (patients 1, 2, and 4–6) and was associated with low back pain in 2 boys.

Six patients suffered from nonspecific gastrointestinal symptoms, such as recurrent abdominal pain and diarrhea. No cardiac, nephrourologic, pulmonary, or macrovascular manifestations were observed during the observation time. In 2 patients, ocular changes are described together with CNS involvement. HLA B51 antigen was present in 2 of the 7 patients (patients 2 and 5).

Brain ^{99m}Tc-HMPAO SPECT

The SPECT equipment used in this study (CERASPECT; Digital Scintigraphics, Waltham, MA) acquires brain perfusion images of ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) using a camera equipped with a stationary NaI(Tl) annular crystal and an array of 63 photomultipliers built outside the crystal. The cylindric, low-energy, high-resolution lead collimator is the only moving piece during the acquisition at 15 s per stop over 120 stops, with the head of the patient positioned inside. In this way the system optimizes the trade-off between spatial resolution and counting statistics. The sensitivity of the collimator with a point source in air is 190 counts per second (cps)/MBq (7.0 cps/μCi), with a spatial resolution for the 140 keV of ^{99m}Tc $<$8.5 mm at the center of rotation and 6.3 mm in peripheral regions (full width at half maximum). The geometry of the holes built in the collimator is equivalent to a triple-head rotating gamma camera, in that 3 different regions of the detecting crystal contribute to the acquisition of counts during each angular position. Dedicated hardware and software procedures average these 3 different sinograms into sinograms equivalent to those generated by a single-head camera (*16*).

All SPECT acquisitions were obtained 30–90 min after intravenous injection of 7.4–11.1 MBq/kg freshly prepared ^{99m}Tc-HMPAO (Ceretec; Amersham Medical, Ltd., Amersham, U.K.) according to the procedure guideline for brain perfusion SPECT (*17*). Sensory input was minimized while injecting the tracer in a quiet, dimly lit room, with the patient lying on a reclining chair (eyes closed and ears unplugged). All boys met these requirements.

Sixty-four axial slices parallel to the anterior commissure–posterior commissure (AC–PC) line, 1.67-mm thick, were reconstructed on a 128 × 128 matrix (1 pixel = 1.67 mm) using a 2-dimensional Butterworth-filtered backprojection (cutoff, 0.80 cm; order, 10) according to a previously described method (*18*).

TABLE 1
Clinical Features of 7 Patients with Behçet's Disease and Signs or Symptoms of CNS Involvement

Patient no.	Age at onset (y)	Sex	Pathergy test	HLA B51	Aphthosis		Eye	Skin	Gastrointestinal
					Oral	Genital			
1	8	M	+	−	+	−	−*	+	+
2	12	M	−	+	+	+	−	+	+
3	9	M	−	−	+	−	−*	+	+
4	7	M	−	−	+	−	−	+	−
5	8	M	+	+	+	−	−	+	+
6	11	M	−	−	+	−	−	+	+
7	9	M	−	−	+	+	−	+	+

*Retinal vasculitis.

Two skilled readers performed visual interpretation of the SPECT images. Semiquantitative evaluation was performed on 2 transaxial sections parallel to the AC–PC line (8.3-mm thick: 5 slices summed together), as identified by the guide of a widely used anatomic atlas (*19*), which included brain areas in which perfusion deficits had been found by visual analysis in all patients. The first (upper) section was constructed by summing the 5 most intermediate of all slices, which included the thalami. The second (lower) section was identified by summing 5 slices across the mesiotemporal structures (hippocampal formation, including the hippocampus and the parahippocampal gyrus). In each section, the cortical ribbon was delimited automatically and was then divided into twelve 30° sectors to identify 12 regions of interest (ROIs) in the upper section and 10 ROIs in the lower section (in this section the most anterior ROIs are drawn on midline deep nuclei or outside the brain). Moreover, irregular but symmetric ROIs were drawn by hand around the thalami, the lenticular nuclei, and the head of the caudate nuclei in the upper section and around the mesiotemporal structures in the lower section. Thus, 30 ROIs were identified in each examination: 22 in the superficial cortex, 2 in the mesiotemporal cortex, and 6 in the deep nuclei (Fig. 1A). Asymmetries between homologous ROIs were computed as $([R - L]/[R + L] \times 0.5) \times 100$, where R is mean counts per pixel in the right ROI and L is the corresponding value in the left ROI. Hypoperfusion was considered when ROI asymmetry was >10% (*20*). Asymmetry analysis was chosen because of the rather symmetric perfusional pattern of the normal brain, especially in young people (*21*), and because of the impossibility of obtaining normal reference values in such a young age range.

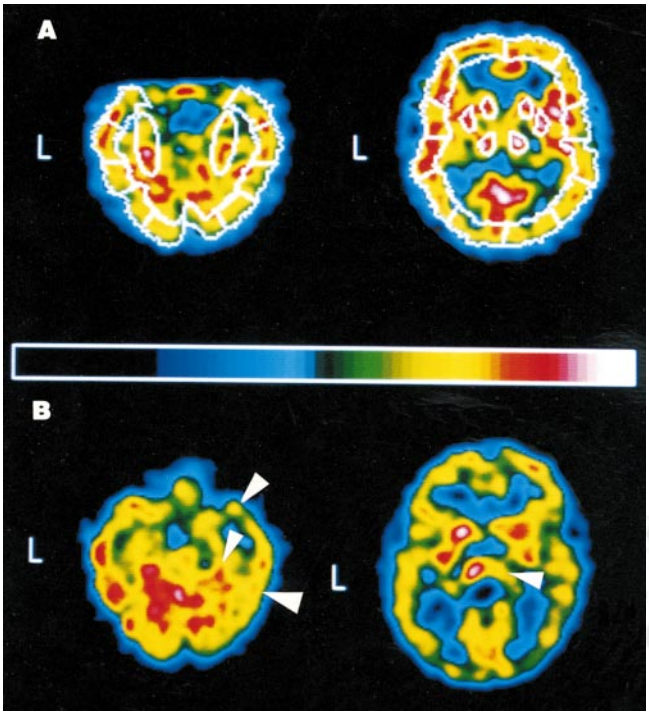

FIGURE 1. (A) ROIs drawn over 2 transaxial sections parallel to bicommissural line. ROIs were drawn automatically around superficial cortex by software option; symmetric ellipsoid ROIs are drawn by hand around mesiotemporal cortex (left), and symmetric irregular ROIs are drawn by hand around thalami and basal ganglia (right). (B) Examples of brain hypoperfusion in 2 boys with BD. (Left) Cortical hypoperfusion of right mesio- and laterotemporal cortex (arrowheads) in patient 2 (second SPECT examination); patient also had hypoperfusion of head of right caudate nucleus. (Right) Hypoperfusion of right thalamus (arrowhead) (asymmetry of head of caudate nucleus did not reach cutoff asymmetry value of 10%) in patient 1 (first SPECT examination). ^{99m}Tc-HMPAO uptake values are expressed according to common color scale. L identifies left side of brain.

MRI

MRI was performed on 5 patients (patients 2–4, 6, and 7) using 1.5-T superconductive equipment with the following parameters: bicommissural paraxial planes; protonic density (repetition time/echo time [TR/TE] = 2,000/30), T1-weighted (TR/TE = 660/20), and T2-weighted (TR/TE = 2,500/120) sequences; sixteen 5-mm-thick slices with a 1-mm gap; 2 or 4 excitations; 26.1-cm field of view; and 256 × 256 matrix. The T1-weighted sequences were obtained also after intravenous injection of 0.15 mmol/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany).

EEG

EEG was recorded on paper by 16 leads positioned over the scalp of each patient according to the 10-20 International System (according to the guidelines of the International Federation of Clinical Neurophysiology). The EEGs were read by a pediatric neurologist with expertise in EEG who was blind to the SPECT and MRI results.

RESULTS

Brain Data

Table 2 summarizes the results of brain examinations, including visual and semiquantitative SPECT analysis, EEG, and MRI. Asymmetry data of individual patients are detailed in Table 3.

Clinical Findings

The main clinical features and the neuroimaging findings of the 7 patients follow; SPECT results are based on expert visual diagnosis.

Patient 1. During the first year of the clinical course of the disease, at 8 y of age, he developed severe intracranial hypertension with papilledema, headache, and horizontal diplopia. Contrast-enhanced brain CT findings were negative. EEG disclosed diffuse, high-voltage, slow waves, especially over the right centroposterior region. Ophthalmologic evaluation revealed exudative retinal lesions, and fluorescein angiography showed retinal vasculitis. No signs of meningeal irritation were found. The clinical picture was attributed to acute vasculitis of the brain. High-dosage (5 mg/kg/d) methylprednisolone intravenous pulse therapy was administered for 3 d, followed by oral prednisone (1 mg/kg/d) for the following days. The clinical signs of intracranial hypertension improved significantly, and the prednisone dosage was then tapered slowly and maintained at a minimal dose of 5 mg every other day. Cyclosporine was added at a dose of 3 mg/kg/d. The first brain SPECT examination was performed 1 y after this episode and showed hypoperfusion of the right thalamus and the head of the right caudate nucleus (Fig. 1B, right). At this time, the patient suffered from severe headache, regularly relapsing

TABLE 2
Brain Examination Findings of 7 Boys with Behçet's Disease and Neurologic Complaints

Patient no.	Examination	SPECT analysis		EEG*	MRI*
		Visual	Semiquantitative		
1	First	R caudate, R thalamus	R thalamus	+	NA†
	Second	L laterofrontal	L laterofrontal, L mesiotemporal	+	NA†
2	First	Normal	Normal	−	NA
	Second	R latero- and mesiotemporal	R latero- and mesiotemporal, R caudate	+	−
3		L caudate, L polar temporal	L caudate, L polar temporal	+	−
4		L mesiotemporal	L mesiotemporal	+	−
5		L caudate	L caudate	−	NA
6		L polar temporal, L thalamus	L polar temporal, L thalamus, R mesiotemporal	+	−
7		L laterofrontal	L laterofrontal	+	+

*− = normal; + = altered.
†Normal contrast-enhanced brain CT.
Caudate = head of caudate nucleus; NA = not available.

on the day without prednisone administration. Thus, prednisone (5 mg) was given every day, with substantial headache relief.

Another less severe flare-up of cerebral vasculitis relapse occurred 2 y after the first one, with similar presentation as the first flare-up. A new course of high-dose intravenous corticosteroid was given for 3 d, followed by prompt clinical improvement. SPECT examination was repeated 1 wk after the onset of symptoms, showing hypoperfusion of the left lateral frontal cortex. Contrast-enhanced CT findings were again negative. Azatioprine (1 mg/kg/d) was added to therapy.

Patient 2. He developed recurrent episodes of diffuse headache at 18 y of age, 6 y after the onset of the disease, while being treated with low-dose oral prednisone. At this time, EEG and brain SPECT findings were normal. Headache improved with a mild, transient increase of corticosteroid dosage. One year later, he suffered from an apparently primary generalized tonic–clonic seizure. EEG disclosed diffuse discharges of high-voltage, sharp waves, whereas brain MRI findings were negative. At this time, brain SPECT showed hypoperfusion of the right mesio- and laterotemporal cortex (Fig. 1B, left). No antiepileptic treat-

TABLE 3
Semiquantitative Brain SPECT Data of 9 Examinations on 7 Boys with Behçet's Disease

ROI	Patient 1		Patient 2		Patient				
	First*	Second*	First*	Second*	3	4	5	6	7
Temporal polar	−3.2	−4.9	−5.4	−8.6	**15.0**	−5.5	−1.2	**10.1**	4.7
Temporal anterior	6.9	−3.5	2.3	−7.4	5.0	−5.4	3.4	3.7	−5.0
Temporal lateral	0.2	7.8	2.1	**−10.8**	−4.4	−5.6	7.0	5.0	−3.2
Temporooccipital	7.7	−0.3	2.9	−8.3	2.4	4.1	−4.4	−2.2	−2.3
Occipital	−3.7	−9.0	9.7	2.1	4.2	2.5	−5.8	−1.3	0.9
Temporal mesial	3.1	**14.8**	8.3	**−11.3**	−3.5	**10.5**	2.5	**−10.4**	4.4
Frontal polar	−1.8	−6.6	1.3	4.4	2.7	4.3	−1.2	1.9	−5.2
Frontal anterior	−3.9	2.5	−3.9	−4.3	0.9	−0.1	−3.2	7.0	5.0
Frontal lateral	−3.7	**11.1**	−3.0	0.8	−2.6	−4.6	−3.4	−2.5	**11.5**
Parietal	−0.7	1.1	−3.0	3.0	4.6	1.2	−4.5	0.5	−2.7
Parietooccipital	0.1	3.1	−0.9	0.0	−0.9	2.2	−1.4	−1.7	−0.5
Occipital	6.0	8.1	5.3	5.3	5.8	−0.2	4.9	2.9	1.5
Caudate nucleus	−7.8	−4.9	4.4	**−10.4**	**10.8**	7.5	**11.8**	−6.3	−3.7
Lenticular nucleus	3.1	1.2	4.0	−2.7	−2.9	−2.8	2.0	−4.4	1.0
Thalamus	**−10.7**	−5.0	6.0	−3.5	3.4	0.6	3.7	**11.9**	−4.2

*Examination.
Semiquantitative asymmetry data indicate percentage asymmetry for couples of homologous ROIs in 2 hemispheres; boldface type indicates values >10%.

ment was administered. Prednisone dosage was increased to 0.5 mg/kg/d; EEG findings were normal 2 mo later, and the patient no longer suffered from neurologic complaints.

Patient 3. The first clinical manifestation was a generalized seizure (loss of consciousness with diffuse hypotonia) at 6 y of age. At this time, EEG disclosed spikes and waves over the left centrotemporal region with sporadic diffusion to the whole brain, whereas brain MRI findings were negative. Sodium valproate therapy was started at the dosage of 20 mg/kg/d. EEG was repeatedly positive in the following years, always showing abnormalities over the left central and temporal regions, but the patient no longer suffered from seizures. At 9 y of age, meningeal syndrome ensued. Examination of cerebrospinal fluid revealed pleocytosis, represented mainly by lymphocytes, normal protein and glucose levels, and negative cultures for bacteria. Ophthalmologic examination disclosed retinal vasculitis. Brain MRI findings were again negative. A diagnosis of aseptic meningitis was made and prednisone (1 mg/kg/d) was administered, followed by full recovery in 2 wk. Brain SPECT was performed 6 mo after recovery of aseptic meningitis, while the patient was seizure free, and showed hypoperfusion of the left temporal polar cortex and caudate nucleus. Neuropsychologic evaluation did not disclose any cognitive deficit.

Patient 4. This patient was the brother of patient 3 and had incomplete BD. At 7 y of age, he presented with complex sleep disturbances with the features of somnambulism. In the same period, he began to experience recurrent episodes of throbbing headache in both frontotemporal regions. Parents and teachers reported inadequate school performance, and a moderate deficit of attention and learning was shown by neuropsychologic evaluation. Diurnal sleep EEG recording showed high-voltage, sharp waves and spikes over both frontal regions, sometimes involving the whole brain. MRI findings of the brain were normal. The child received carbamazepine (200 mg/d), which resulted in strong improvement of sleep disturbances and wake and sleep EEG changes. Mucocutaneous and systemic manifestations ensued approximately 1 y later, when brain SPECT disclosed hypoperfusion in the left mesiotemporal region. Because of the worsening of sleep episodes, the dosage of carbamazepine was doubled 1 y later, with new improvement. Follow-up was extended to 18 mo, with the patient receiving nonsteroidal antiinflammatory drugs (NSAIDs) and the same dosage of carbamazepine and still not meeting the full ISG criteria for complete BD.

Patient 5. Recurrent episodes of diffuse headache started at 6 y of age. At this time, EEG findings were negative. Because of the relapsing–remitting course of headache, the patient received common analgesic drugs and no specific investigation was performed. Two years later, at 8 y of age, mucocutaneous manifestations of the disease ensued, whereas headache worsened significantly. Hence, the patient was admitted to our institute. On the basis of the clinical history and the mucocutaneous syndrome, the diagnosis of complete BD was made. Before starting specific therapy, brain SPECT examination was performed, which showed hypoperfusion of the head of the caudate nucleus in the left hemisphere. Neuroradiologic examination was planned but the parents refused to continue any diagnostic procedure and asked for the patient's discharge. Treatment of the headache with low-dose prednisone (0.2 mg/kg/d) had begun, but the observation period was too short to judge the clinical response. The patient was no longer referred to our institute.

Patient 6. This patient had incomplete BD. Systemic and mucocutaneous symptoms ensued at 11 y of age, together with episodes of bilateral, frontal headache with nausea and photophobia, which failed to respond to common NSAIDs but improved significantly after corticosteroid administration. At 13 y of age, his headache worsened significantly and the patient was admitted to our institute. EEG findings were normal, whereas brain SPECT showed hypoperfusion of the left thalamus and polar temporal region. The patient received regular low-dose prednisone therapy, with improvement of symptoms. Taking into consideration the improvement of systemic manifestations and headache, the prednisone dosage was tapered 2 mo later. He developed a flare-up a few months later and, again, the headache promptly worsened. At this time, EEG showed sporadic sharp waves over both centroparietal regions, especially of the left hemisphere. MRI findings of the brain were normal. Brain SPECT was planned but was not feasible because of logistic difficulties. The prednisone dosage was increased again and was followed by full clinical recovery. After 1 y of follow-up, the patient still is in clinical remission with daily oral low-dose prednisone therapy and without having developed the complete form of BD.

Patient 7. One year after the onset of mucocutaneous symptoms (at 9 y of age), the patient began to experience severe, subcontinuous bilateral frontal headaches. EEG showed diffuse slow waves and sporadic sharp waves over both frontotemporal regions. Brain MRI findings were negative. His headache was substantially unresponsive to NSAID therapy but improved greatly during corticosteroid administration. At 11 y of age, the patient came to our attention. His headache and the general clinical picture had worsened. EEG showed diffuse slow waves and brain MRI disclosed mild, diffuse hyperintensity of the periventricular white matter and centrum semiovale of both hemispheres and a small area of hyperintensity in the left cerebral peduncle. Brain SPECT showed hypoperfusion of the left laterofrontal cortex. The patient received a course of oral prednisone (1 mg/kg/d) with improvement of his headache and the general condition.

DISCUSSION

This study reports a cerebral perfusion deficit in a group of boys with BD and central neurologic symptoms. Brain SPECT findings supported the clinical diagnosis in all

cases; moreover, therapeutic changes that were made on 4 patients also took into account the SPECT report.

In fact, the first SPECT examination was performed on patient 1 during a period of severe headache and showed hypoperfusion of the right thalamus and the head of right caudate nucleus, which led to an increase in prednisone dosage. A second SPECT study was performed on the same patient 1 y later, during recurrence of cerebral vasculitis, and showed hypoperfusion of the left laterofrontal cortex with negative findings on brain CT. Clinical relapse and SPECT findings supported the addition of azathioprine to corticosteroids, which was followed by clinical remission. The changing pattern of hypoperfusion in this patient is in keeping with PET (*5*) and SPECT (*8*) studies, which showed fluctuation of deficits in patients with n-BD either after adequate therapy or during relapse of the disease. Patient 2 suffered a generalized seizure after a long-lasting headache; brain SPECT showed hypoperfusion of the right mesio- and laterotemporal cortex, whereas EEG disclosed diffuse discharges of high-voltage, sharp waves and MRI findings were normal. Again, SPECT findings guided corticosteroid therapy with disappearance of the seizures. In patient 5, who suffered from refractory headache, prednisone administration was started after SPECT showed hypoperfusion of the left caudate nucleus, although the follow-up was too short to evaluate the response to therapy. Finally, in patient 6, brain SPECT disclosed hypoperfusion of the left thalamus and temporal pole during chronic headache 2 mo before EEG showed mainly left-sided changes, and guided corticosteroid administration led to clinical remission.

SPECT was performed on patients 3 and 4 during neurologic remission, and SPECT findings were related to EEG changes. In patient 3, who had suffered from seizures and 1 episode of aseptic meningitis, hypoperfusion of the left temporal polar cortex and caudate nucleus matched with EEG changes over the left centrotemporal region. In patient 4, who had presented sleep disturbances with bilateral frontal headache, SPECT disclosed hypoperfusion in the left mesiotemporal region, whereas EEG showed bilateral frontal changes.

Patient 7 was probably the most intriguing one, showing multiple, bilateral white matter changes on MRI, diffuse EEG changes, hypoperfusion of the left frontal cortex, and only headache at clinical presentation. Headache has been regarded as a possible lone clinical manifestation of pediatric n-BD (*2*,*3*,*22*,*23*), and recent neuroimaging findings in adulthood are in line with this interpretation (*5*,*6*). In fact, isolated headache, which is observed frequently, is not always taken into right account to define n-BD (*2*). Although a recent assessment of interobserver agreement about detection of n-BD symptoms has given encouraging results (*24*), agreement is still lacking on this issue (*25*), and whether headache must be considered a risk factor for developing more serious neurologic involvement in the long term is still debated (*26*,*27*). Features of headache in this series were the rather diffuse localization, the continuous or subcontinuous temporal pattern, and the poor response to common analgesics and NSAIDs.

Brain perfusional SPECT was very sensitive in this series of children with n-BD by disclosing brain functional abnormalities in all cases, even in the 5 patients with negative brain structural examinations. Therefore, perfusional SPECT may be used to confirm the clinical diagnosis of n-BD and to guide therapeutic choice, as happened in 4 of 7 patients of this series. In this context, EEG, though lacking spatial resolution, also appeared to be very sensitive to brain involvement, by showing abnormalities in most cases, as reported recently for brain-stem auditory evoked potentials (*28*).

As far as SPECT data analysis is concerned, perfusional deficit was first assessed by visual analysis and then by asymmetry analysis (10% cutoff), with good agreement between the 2 methods (Table 2). Cerebral perfusion has been reported to be rather symmetric in healthy humans by several techniques, including quantitative ^{133}Xe (*29*) and semiquantitative ^{99m}Tc-HMPAO SPECT (*21*). Perfusion symmetry is more obvious in healthy young people, in whom SDs of asymmetry values were found not to exceed 3.4% for gray matter (*21*), thus pointing to values $>$7% as a potentially abnormal asymmetry. A threshold of this order is in keeping with the findings that good interobserver agreement is reached in recognizing artificial lesions in the cerebellum when counts are reduced between 5% and 10% in either of the 2 hemispheres (*20*). Moreover, if a range of interhemispheric difference between 10% and 13% is regarded as significant in acute stroke, where definite structural lesions exist (*30*,*31*), a threshold of 10% seems to be an acceptable choice in a series of patients with normal structural brain examinations in 5 of 6 instances.

Similar to the findings of several studies that have reported brain perfusional deficit in n-BD of adulthood in the last decade (*8–11*,*13*,*14*), explanation of SPECT results in children is not univocal because different mechanisms have been suggested for the pathophysiology of n-BD. During n-BD, focal brain lesions are found more commonly in the brain stem, basal ganglia, and hemispheric white matter, but pathologic changes are widespread and may involve virtually any part of CNS, including the spinal cord (*25*). Lesions in the cortex are very sparse and, for unknown reasons, the cerebellum is seldom involved (*32*). Vasculitis of the CNS is the most frequently invoked mechanism and, indeed, it has been proven in some studies (*32–34*), but other factors have been suspected to play a role. Cerebral vein thrombosis seems to be responsible for only part of the cases (*22*), whereas the presence of chemical mediators that may cause cerebral damage, such as the interleukin-6 and oligoclonal IgA and IgM, awaits further confirmation (*13*). Finally, some authors suspect that the main cause of cerebral damage is not of vascular origin (*26*,*35*), and an emblematic case of neutrophilic and eosinophilic inflammation of brain tissue without vasculitis has been described recently (*36*). On the other hand, according to a recent view (*25*), brain

parenchymal involvement in n-BD would be the result of a combination of focal lesions in classical sites (i.e., upper brain stem, basal ganglia, and white matter) and relatively low-grade, diffuse inflammation of CNS, as shown by Scott (*37*). This character of histopathology would explain the discrepancy between the most typical sites of lesion by MRI and clinical and perfusional findings, which point to frequent involvement of the cerebral cortex, as a likely result of disseminated inflammation. In our series, the finding of hypoperfusion of basal ganglia and thalami in patients suffering from diffuse headache seems in line with this interpretation. Moreover, probably because of the relatively infrequent focal involvement of the cerebral cortex in pathologic series (*27*,*32*), cortical hypoperfusion has also been interpreted as a result of cortical deafferentation from deeper gray structures that are frequently impaired. The finding that cortical hypoperfusion responds with a higher blood flow increase to administration of acetazolamide than do areas with normal perfusion suggests a preserved cortical microcirculation and would support the hypothesis of diaschisis (*38*).

CONCLUSION

Similar to reports in adults, brain perfusional SPECT is a very sensitive method to detect brain involvement in pediatric patients with n-BD syndromes and may support the clinical diagnosis of n-BD, especially in children with negative findings on brain structural examinations. The polymorphous clinical presentation of n-BD and differences between adults and children in the clinical picture require a consensus to better define the clinical and instrumental diagnosis of CNS involvement.

REFERENCES

1. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet*. 1990;335:1078–1080.
2. Koné-Paut I, Chabrol B, Riss J-M, Mancini J, Raybaud C, Garnier J-M. Neurologic onset of Behçet disease: a diagnostic enigma in childhood. *J Child Neurol*. 1997;12:237–241.
3. Koné-Paut I, Yurdakul S, Bahabri SA, et al. Clinical features of Behçet's disease in children: an international collaborative study of 86 cases. *J Pediatr*. 1998;132: 721–725.
4. Akman-Demir G, Serdaroglu P, Tasci B. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients—The Neuro-Behçet Study Group. *Brain*. 1999;122:2171–2182.
5. Weiner SM, Otte A, Schumacher M, et al. Neuro-Behçet's syndrome in a patient not fulfilling criteria for Behçet's disease: clinical features and value of brain imaging. *Clin Rheumatol*. 2000;19:231–234.
6. Jager HR, Albrecht T, Curati-Alasonatti WL, Williams EJ, Haskard DO. MRI in neuro-Behçet's syndrome: comparison of conventional spin-echo and FLAIR pulse sequences. *Neuroradiology*. 1999;41:750–758.
7. Kocek N, Islak C, Siva A, et al. CNS involvement in neuro-Behçet syndrome: an MR study. *AJNR*. 1999;20:1015–1024.
8. Markus HS, Bunker CB, Kouris K, Costa DC, Harrison MJ. rCBF abnormalities detected, and sequentially followed, by SPECT in neuro-Behçet's syndrome with normal CT and MRI imaging. *J Neurol*. 1992;239:363–366.
9. Watanabe N, Seto H, Sato S, et al. Brain SPECT with neuro-Behçet disease. *Clin Nucl Med*. 1995;20:61–64.
10. Trotta F, Bajocchi G, Colamussi P, et al. Cerebral hypoperfusion detected by SPECT in early neuro-Behçet syndrome. *Nucl Med Commun*. 1998;19:777–780.
11. Oshima M, Kikuchi Y, Furui S. Cerebral perfusion impairment with normal magnetic resonance imaging findings in a patient with neuro-Behçet disease. *Clin Nucl Med*. 2000;25:156–157.
12. Danaci M, Akpolat T, Koyuncu M, Unal R, Belet U. The advantages of MRI and MRA for diagnosing Behçet's disease and internal jugular vein thrombosis. *Comput Med Imaging Graph*. 2000;24:121–124.
13. Garcia-Burillo A, Castell J, Fraile M, et al. Technetium-99m-HMPAO brain SPECT in Behçet's disease. *J Nucl Med*. 1998;39:950–954.
14. Kao H, Lan J-L, ChangLai S-P, Chieng P-U. Technetium-99m-HMPAO SPECT and MRI of brain in patients with neuro-Behçet's syndrome. *J Nucl Med*. 1998;39:1707–1710.
15. Koné-Paut I, Geisler I, Wechsler B, et al. Familial aggregation in Behçet's disease: high frequency in siblings and parents of pediatric probands. *J Pediatr*. 1999;135:89–93.
16. Genna S, Smith AP. The development of ASPECT, an annular single crystal brain camera for high efficiency. *IEEE Trans Nucl Sci*. 1988;35:654–658.
17. Juni JE, Waxman AD, Devous MD, et al. Procedure guideline for brain perfusion SPECT using technetium-99m radiopharmaceuticals. *J Nucl Med*. 1998;39:923–926.
18. Rodriguez G, Nobili F, Copello F, et al. ^{99m}Tc-HMPAO SPECT and quantitative electroencephalography in Alzheimer's disease: a correlative study. *J Nucl Med*. 1999;40:522–529.
19. Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain*. New York, NY: Thieme Medical; 1980.
20. Stapleton SJ, Caldwell CB, Leonhardt CL, Ehrlich LE, Black SE, Yaffe MJ. Determination of thresholds for detection of cerebellar blood flow deficits in brain SPECT images. *J Nucl Med*. 1994;35:1547–1555.
21. Catafau AM, Lomena FJ, Pavia J, et al. Regional cerebral blood flow pattern in normal young and aged volunteers: a ^{99m}Tc-HMPAO SPET study. *Eur J Nucl Med*. 1996;23:1329–1337.
22. Bahabri SA, Al-Mazyed A, Al-Balaa S, El-Ramahi L, Al-Dalaan A. Juvenile Behçet disease in Arab children. *Clin Exp Rheumatol*. 1996;14:331–335.
23. Krause I, Uziel Y, Guedj D, et al. Childhood Behçet disease: clinical features and comparison with adult-onset disease. *Rheumatology*. 1999;38:457–462.
24. Bhakta BB, Brennan P, James TE, Chamberlain MA, Noble BA, Silman AJ. Behçet's disease: evaluation of a new instrument to measure clinical activity. *Rheumatology*. 1999;38:728–733.
25. Serdaroglu P. Behçet's disease and the nervous system. *J Neurol*. 1998;245:197–205.
26. Akman-Demir G, Baykan-Kurt B, Serdaroglu P, et al. Seven-year follow-up of neurologic involvement in Behçet syndrome. *Arch Neurol*. 1996;53:691–694.
27. Serdaroglu P, Yazici H, Ozdemir C, Yurdakul S, Bahar S, Aktin E. Neurologic involvement in Behçet's syndrome: a prospective study. *Arch Neurol*. 1989;46: 265–269.
28. Stigsby B, Bohlega S, McLean DR, Al-Kawi MZ. Transcranial magnetic stimulation in Behçet's disease: a cross-sectional and longitudinal study with 44 patients comparing clinical, neuroradiological, somatosensory and brain-stem auditory evoked potential findings. *Clin Neurophysiol*. 2000;111:1320–1329.
29. Devous MD Sr, Strokeley EM, Chehabi HH, Bonte FJ. Normal distribution of regional cerebral blood flow measured by dynamic single-photon emission tomography. *J Cereb Blood Flow Metab*. 1986;6:95–104.
30. Giubilei F, Lenzi GL, Di Piero V, et al. Predictive value of brain perfusion single-photon emission computed tomography in acute ischemic stroke. *Stroke*. 1990;21:895–900.
31. Rango M, Candelise L, Perani D, et al. Cortical pathophysiology and clinical neurologic abnormalities in acute cerebral ischemia. *Arch Neurol*. 1989;46: 1318–1322.
32. Rubinstein LJ, Urich H. Meningoencephalitis of Behçet's disease: a case report with pathological findings. *Brain*. 1963;86:151–160.
33. Kawakita H, Nisimura S, Satoh Y, Shibata N. Neurological aspects of Behçet's disease: a case report and clinicopathological review of the literature in Japan. *J Neurol Sci*. 1967;5:417–439.
34. Lakhanpal S, Tani K, Lie JT, Katoh H, Ishigatsubo Y, Ohokubo T. Pathological features of Behçet's syndrome: a review of Japanese autopsy registry data. *Hum Pathol*. 1985;16:790–795.
35. Wolf SM, Shotland DL, Phillips LL. Involvement of nervous system in Behçet's syndrome. *Arch Neurol*. 1965;12:315–325.
36. Hadfield MG, Aydin F, Lippman HR, Sanders KM. Neuro-Behçet's disease. *Clin Neuropathol*. 1997;16:55–60.
37. Scott D. Mucocutaneous-ocular syndrome (Behçet's syndrome) with meningoencephalitis: report of case with autopsy. *Acta Med Scand*. 1958;161:397–400.
38. Pupi A, Sestini S, De Cristofaro MTR, et al. Use of technetium-99m hexamethylpropylene amine oxime single-photon emission tomography for the study of cerebral blood flow reactivity after acetazolamide infusion in patients with Behçet's disease. *Eur J Nucl Med*. 2000;27:700–706.